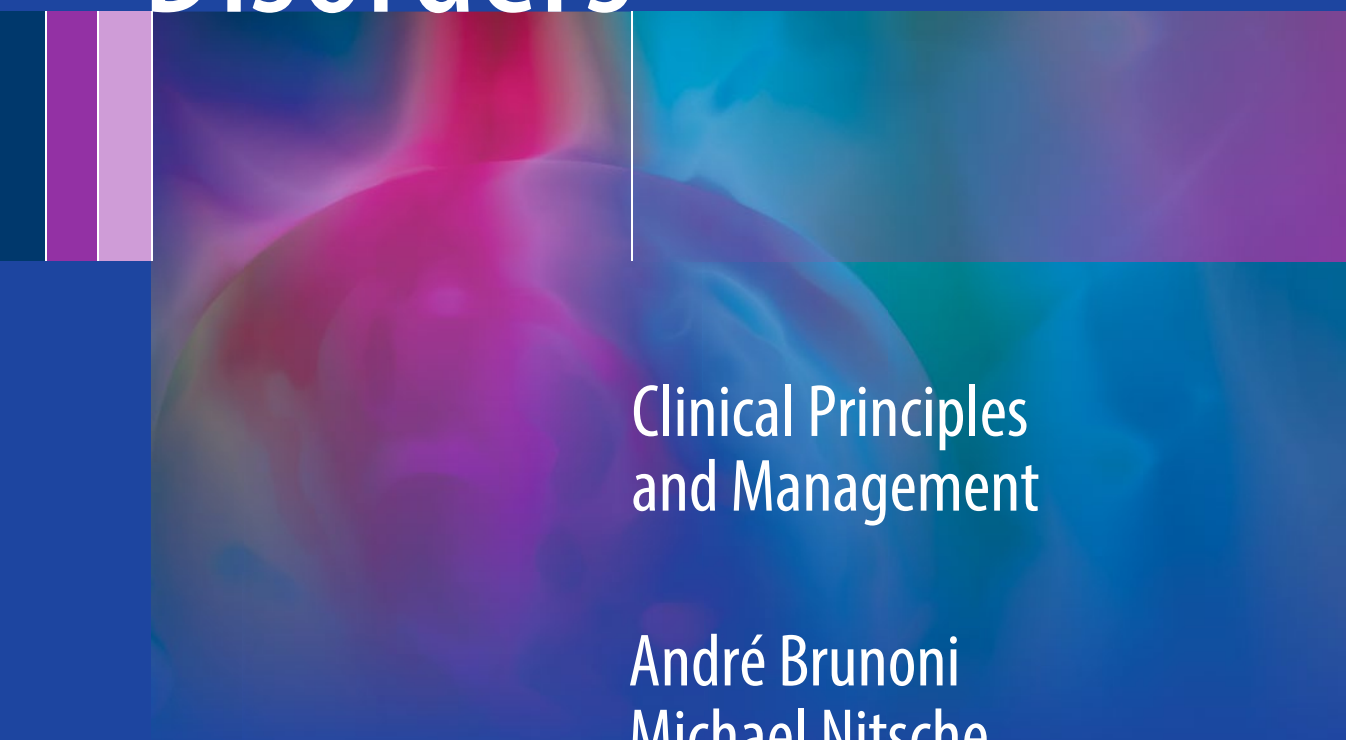
Transcranial Direct Current Stimulation in Neuropsychiatric Disorders



Clinical Principles and Management

André Brunoni
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Foreword

Why write a book on transcranial direct current stimulation (tDCS)? This question is especially relevant in the face of the rapidly increasing numbers of journals, open access publications, wikis and blogs. In parallel to the exponential spread of information sources, information and beliefs also tend to be found in shared virtual spaces, where they are amplified and reinforced. Critical reflection on concurrent and opposing opinions, or a synopsis of such opinions, is underrepresented in such "echo chambers". This is the case for the general public discourse and may also be true for the reception of scientific findings.

tDCS is a technically extremely simple method and easy to apply. Thus, people can be tempted to build the equipment themselves or try do-it-yourself (DIY) application without any expert guidance—numerous video clips for DIY tDCS on the web are just one form of public sharing of knowledge and convictions about this method that are echoed by other followers. People are also tempted to follow intuitive attitudes or convictions about tDCS, e.g. non-verified dose/parameter response assumptions, hypotheses on the functional anatomy of tDCS effects or a general idea of reinforcing brain functions with no side effects (cognitive enhancement). The 2016 paper "tDCS modulates neuronal activity and learning in pilot training" [1] is just one example where the title immediately and strongly suggests an application in real-world settings. Karl R. Popper's general rule, however, "that we are not to abandon the search for universal laws and for coherent theoretical system, nor ever give up our attempts to explain causally any kind of event we can describe" [2], which he proposed to be closely associated with the "principle of causality", should remind us to be careful about making assumptions. Admittedly, though, we often follow associative or correlative relations, particularly when applying insights from neuroscience to clinical situations.

Of course, a single book cannot counterbalance or overrule current trends in a scientific discussion. Moreover dispersed, "open access" pieces of data and information are also extremely valuable in a thorough discussion of scientific findings. Nevertheless, because this book combines a critical amount of data and hypotheses it allows the reader to appraise findings and theories on tDCS and its variants.

Andre Brunoni, Michael Nitsche, Colleen Loo and the other authors, all pioneers and leading experts in the field, have taken a brilliant approach to this endeavour and guide us through the state of the art in tDCS. The different chapters cover tDCS development, related technologies (e.g. transcranial

alternating current stimulation, tACS, or transcranial random noise stimulation, tRNS), physiology and translational research from animal experiments to preclinical studies in humans involving neurocognitive and neuropsychological approaches, electroencephalography and magnetic resonance imaging (MRI). Several chapters cover specific applications ranging from cerebellar and spinal tDCS to different applications in neuropsychiatric disorders. The final part of the book outlines and discusses safety-related, ethical and regulatory issues.

tDCS is part of the armamentarium of non-invasive brain stimulation (NIBS), which constitutes a growing array of techniques such as transcranial magnetic stimulation (TMS), paired associative stimulation (PAS) and transcutaneous vagal nerve stimulation.

Each NIBS technique, but also each variant of tDCS, is a neurophysiologically distinct method. The authors of this book are aware that tDCS is used as a non-focal approach on the most complex organ/system of the human body and that the differential action of tDCS on single neurons or neuronal circuits or glial cells is difficult to predict or target. Dose-response curves often show non-linear functions, which are currently not fully understood. Furthermore, dynamic effects of repeated tDCS administration, which are particularly important for therapeutic applications, still need to be elucidated. The combination of tDCS with psychotherapy and other interventions is currently being tested in pilot studies and is proving to be extremely challenging [3]. Such open methodological fields would provide a large experimental terrain for preclinical studies in cellular and animal models, but studies in this preclinical field are still underrepresented. Thus, the book may stimulate the transfer of research based on clinical or experimental data in humans to the preclinical field of cellular or animal research strategies (reverse translation).

This book is comprehensive and as such valuable. The task of preparing it motivated the editors and authors to move systematically through the field of research and to also cover topics which are not on the main track, e.g. the history of tDCS and ethical and regulatory issues. Consequently the content of chapters may overlap, as a reflection of different perspectives. This book allows the reader to jump between chapters to compare information, hypotheses and views. It is an excellent resource for senior and junior scientists, doctorate students and others to introduce them to this fascinating field of research.

Frank Padberg

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Preface

The clinical interest in non-invasive brain stimulation has grown exponentially over the past 25 years, with the development of non-pharmacological, neuromodulatory techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). TDCS, the youngest sibling of the brain stimulation family, is in fact a "new old technique". With anecdotal reports of the use of the torpedo fish to treat pain and headache via its electrical discharges during the ancient history, electricity was indeed used in the nineteenth and twentieth centuries to treat several neurologic and psychiatric ailments, usually with sparse scientific foundations. Although more recently, in the 1960s and 1970s, the treatment of some psychiatric disorders was investigated using brain polarization (a technique similar to modern tDCS), the research did not endure—perhaps due to the stigma of electroconvulsive therapy or the concomitant development of pharmacotherapy in that period. TDCS reappraisal only took place in 1998–2000, when two independent European groups showed that the electric currents applied over the motor cortex induced changes in brain excitability. From then onwards, tDCS has been increasingly investigated and has attracted considerable attention in both basic and clinical research settings.

In the present book we aimed to present the main advancements regarding the use of tDCS in neuropsychiatric disorders. The book is divided into three parts. The first part discusses the mechanisms of action of tDCS under different perspectives, which encompass neurophysiological, neuroimaging and neuropsychological studies as well as animal studies and computer-based models. In the second part, state-or-the-art evidence of tDCS use in several neurological and psychiatric disorders is presented. The third and last part of the book discusses different possibilities of the clinical and research use of tDCS, including safety, ethical and regulatory aspects.

This book would not have been produced without the invaluable contribution of leading researchers and scientists of the field. We are grateful and thank these authors for their time and effort in writing informative, insightful and up-to-date chapters. We are also grateful to Springer for supporting our project, particularly Gabriel Natan Pires, the Springer associate editor who encouraged us to edit this book, and Susan Westendorf, the Springer project coordinator responsible for this book production.

We believe that this book will be useful to neurologists, psychiatrists and physicians interested in the potential clinical applications of tDCS. This book will also be of interest for neophytes, who are looking for a primer in

non-invasive brain stimulation. More experienced researchers will also enjoy reading this book as it contains top-quality work written by several tDCS experts. We, the editors, are convinced that *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Clinical Principles and Management* will be a captivating bedside book for many researchers in the field—us included.

São Paulo, Brazil — Andre Brunoni
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Part I

Introduction and Mechanisms of Action

Historical Aspects of Transcranial Electric Stimulation

1

Stefano Zago, Alberto Priori, Roberta Ferrucci, and Lorenzo Lorusso

Abstract

The first clinical experience with electric fish, and a long history of application of electrotherapeutic techniques, started from the eighteenth century leading to the modern use of transcranial direct current stimulation (tDCS). This history had various degrees of success and the treatment of mental disorders using electricity followed a cyclical course throughout the centuries. In the beginning, clinicians approached transcranial electric stimulation with enthusiasm, treating numerous disorders such as neurasthenia, melancholia, mania, and hysteria, but also hallucinations, migraine, and dementia. This phase saw a lot of excesses and exaggerations, typical of early stages of the application of a new therapeutic technique. Later, at the end of the nineteenth century transcranial electric stimulation was considerably less used, After failing to produce consistent results. In the twentieth century, experimental data clearly demonstrated that using motor evoked potentials tDCS resulted in changes in motor-cortical excitability supporting a series of new experimental clinical evidence. Today, tDCS is recognized as being an effective technique in applying a direct current to the scalp, further demonstrating its ability to treat clinical conditions such as affective disorders, chronic pain and post-lesional cognitive disorders.

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Keywords
Transcranial direct current stimulation • History • Torpedo fish • Voltaic pile • Galvanic current • Faradic current

The First Clinical-Therapeutic Electrical Applications: The Electric Fish

The roots, beginnings, and first attempts at using transcranial electrical stimulation, as a medical cure, can be found in the Greco-Roman period when electricity generated from fish organs was used to cure pain, headaches, gout, arthritis, and paralysis of various parts of the body [1–4]. However, the powers of *electric fish* had been probably known well before Roman times for being able to produce an electric discharge, as indicated by some Egyptian archeological findings on tombs that showed images of the electric fish in this period and a therapeutic use cannot be excluded [1–5]. The ruins of Pompei also contained frescoes of this fish [4].

The fish certain record of electrical therapeutic application was set out by Scribonious Largus (c.1–c.50 A.D.), one of the first physicians in ancient Rome during the periods of Tiberius (14–37 A.D.), Caligula (37–41 A.D.) and Claudius (41–54 A.D.) who, in his text on therapeutics *De Compositionibus Medicamentorum* (see Fig. 1.1) reported a collection of drug compounds or recipes in use by physicians at that time, and mentioned the use of bioelectric phenomenon of certain fish (*Torpedo Torpedo* and *Torpedo Nobiliana*) for therapeutic ends [6–9].

These fish were known for being capable of producing an electric discharge and their scientific name comes from the Latin *torpere* to be stiffened or paralyzed but also to be numb, insensitive [4, 5, 10].

In particular, Scribonius Largus suggested a remedy for headaches by placing recently caught black torpedo fish on the cranial surface of patients, making the fish emit its electrical discharge. He observed:

> Headache even if it is chronic and unbearable is taken away and remedied forever by a live torpedo placed on the spot which is in pain, until the pain ceases. As soon as the numbness has been felt the remedy should to be removed lest the ability to feel be taken from the part. Moreover, several torpedos of the same kind should to be prepared because the cure, that is, the torpor which is a sign of betterment, is sometimes effective only after two or three. [1]

Two fundamental points emerge from these statements. On the one hand, the paralyzing shock does not provoke convulsions but instead a temporary state of dullness and relief of painful symptoms, presumably stunning the peripheral skin receptors, or affecting spinal or brain structures inducing an immediate and residual transient period of pain relief. On the other hand, in certain situations, it was necessary to use more than one fish to obtain the desired narcotic effect. Scribonius Largus did not provide any source for the basis of his therapeutic approach and it is probable that he would have developed such a method personally but perhaps with the suggestions of some fishermen [1, 9].

The electric fish continued to be used by physicians throughout the Greco-Roman period. For example, 30 years after the *Compositiones* of Scribonius Largus, the Greek physician Pedacii Discoridis Anazarbeo (44–90 A.D.) in his book *De Materia Medica* suggested using the torpedo in the treatment of headaches [11, 12]. It seems that also Plinio the Younger (61–113) reported the use of the electric ray fish to reduce labour pains; however the ancient Romans seem to have preferred using the dietary health properties of the fish rather than exploiting its electrical properties while alive [1, 3]. Galen of Pergamus (129–200 A.D.) criticized the dietary use of the torpedo denying its curative powers. He highlighted instead, the efficacy of the paralyzing shock given off by the live fish due to thermic reaction and proposed it as a treatment for epilepsy and

SCRIBONII LARGI
COMPOSITIONES
MEDICÆ.
IOANNES RHODIVS
recenſuit,
Notis illuſtrauit,
LEXICON SCRIBONIANVM
adiecit.

PATAVII, CIↃ IↃC LV.

Typis Pauli Frambotti Bibliopolæ.
SVPERIORVM PERMISSV.

Fig. 1.1 The *Compositiones medicamentorum of* Scribonius Largus, from 1655 Edition

headache and maintained it to be the most effective form of cure [1]. He wrote:

> The whole torpedo, I mean the sea torpedo, is said by some to cure headache and prolapsus ani when applied. I indeed tried both, and the torpedo should be applied alive to the person who has the headache, and that it could be that this remedy is anodyne and should free the patient from pain as do other remedies which numb the senses: this I found to be so, and I think that he who tried this did so for the above mentioned reason. [12].

Many other physicians, Roman, Arabic, and Medieval, continued to mention the therapeutic capacity of the electric fish. Marcellus Empericus (IV sec. d.C.), Aetius Amidenus (527–565), Alexander Trallianus (525–605), Paulus Aeginata (625–690), Avicenna (980–1037), Averroè (1126–1198), Ibn-Sidah (1007–1066), and Dawud al Antaki (1543–1599) were among those who promoted the benefits of electric shocks emitted by the electric organs of certain fish in the treatment of headaches, depression, epilepsy and arthritis [1, 12]. Electric fish were later used for the treatment of seizures, depression, and pain until the eighteenth century [1, 13].

Transcranial Electrical Stimulation: From Electrostatic Machines to Volta's Pile

In 1600, appears for the first time the term *electricus* in William Gilbert's *De Magnete* considering the attractant properties of substance like amber [14]. In the eighteenth century, sporadic attempts were made to treat mental diseases, using *artificial electric energy* derived from electrostatic machines and stored in capacitors such as glass globes, cylinders, brass, and silk threads or huge Leyden jars. These were in use in the mid-1700s as portable electric devices, and appear to have introduced a flourishing period in the medical use of electricity (see Fig. 1.2).

Kadosh and Elliott [15] underlined that from the 1740s onwards there was a widespread and commercial availability of transcranial electrical stimulation machines for personal and domestic use. During the Victorian and Edwardian period, electrical stimulation machines that dispensed static, frictional, faradic, or battery electrical current could be bought everywhere and some physicians, therapists, and patients claimed that transcranial electrical stimulation could generate feelings of euphoria and even improve mental performance [16]. This produced some promising clinical results, but technology and methodology were incomplete.

The German Christian Kratzenstein (1723–1795), then a student at the University of Halle, accomplished what was considered the first electrotherapy cure in 1744, healing a young woman of a contracted finger. He predicted that electricity would be useful not only in physical, but also mental patients, whose health worries and anxieties prevented them from sleeping, and could become a remedy for hypochondriasis and women with hysterical conditions. Kratzenstein published two clinical cases in *Abhandlung von dem nutzen der electricität in der arzneywissenschaft* (translated in Priestley's 1767 *History and present state of electricity*, p. 472) [14, 17].

The French physician Charles Georges Le Roy (1723–1789) (see Fig. 1.3) in 1755 reported in detail his cure of what today may be called a case of hysterical or psychogenic blindness [18]. He placed conducting wires around the patient's head and led one wire to his leg. The wires were connected to an array of Leyden jars and three shocks were administered in the hope that sight would be restored.

After the patient received his first electric stimulation, he reacted with convulsions of the eyes and he saw rays of light for the first time. When he received the third stimulation, somewhat stronger than the others, he screamed and fainted, as a result of this treatment he began to regain his eyesight. In another case with blindness along with the pain of the stimulation the patient did perceive vivid flashes of light (phosphenes) and underwent the treatment several times in the following days. Nonetheless, he remained blind. Figure 1.4 reports the application electrical therapeutic adopted by Le Roy.

The British lay preacher in Worcester Cathedral Richard Lovett (1692–1780), in 1755, demonstrated to have successfully treated some mental

Fig. 1.2 (**a**-**c**) Simple machines that harnessed electricity in 1700s and an example of central Galvanization technique

Fig. 1.3 Charles Georges Le Roy

afflictions with an electrostatic machine [19, 20]. In 1756, he published the book *The Subtil Medium Prov'd*, considered to be the first English manual for electro-medical applications. In 1774, Lovett published his text *The Electrical Philosopher, containing a new system of physics founded on the principle of a Universal Plenum of Elementary Fire*. His work impressed John Wesley (1703–1791), one of the founders of the reformist movement in the eighteenth century, who in 1759 wrote:

> I doubt not but more nervous disorders would be cured in one year by this single remedy than the whole of the English Materia Medica will cure by the end of the century. [21].

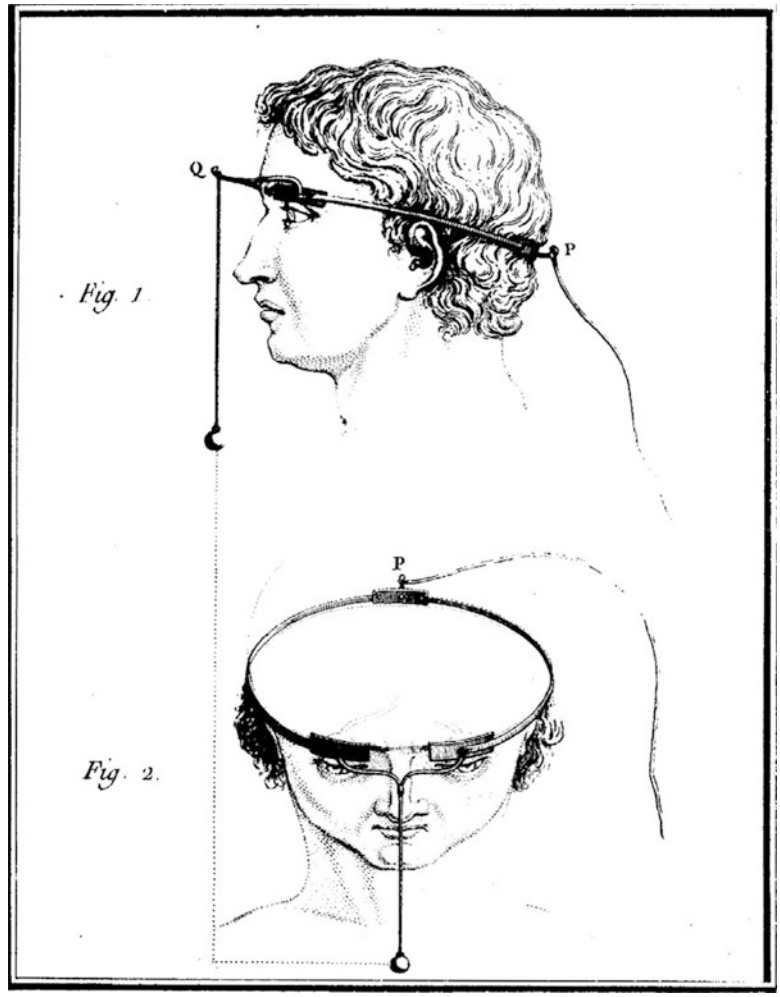

Fig. 1.4 The apparatus used by Dr Charles Le Roy in his attempt to cure blindness with electrical stimulation

In Lovett and Wesley's time nerves were considered to be fine tubes through which mysterious fluid flowed; Wesley hypothesized that: …*what if the electric ether is the only fluid in the universe fine enough to flow through them?* Regarding this physical and metaphysical mechanism and the general enthusiasm of that time, Wesley admitted to some limitation to electrical treatments because he had little results with longstanding paralysis and he also noted a characteristic inconsistency in the response to treatment, considered now as a typical placebo response [14].

In 1777, the Italian physicist Tiberio Cavallo (1749–1809) published *A complete treatise on electricity in theory and practice, with original experiments* in which he reported cures for epilepsy, paralysis, chorea, deafness and blindness [22]. In 1780, Cavallo, published *An essay on the theory and practice of medical electricity* [23], which, apart from some personal clinical observations, contained the interesting description of a patient affected by St Vitus dance and cured with electricity by the English physician John Fothergill (1712–1780). Fothergill, renowned for his support of Benjamin Franklin's publications on electricity contributed a preface for them.

Physicians of the period recommended that currents of no more than 5–10 mA should be applied to the head because higher currents could have risks of burning and shock. Some side effects were reported including: headaches, flashes of light, dizziness and nausea, especially

when connections were imperfect or broken. The consequences could be more serious. In 1783, the Dutch physician Jan Ingenhousz (1730–1799) knocked himself unconscious and amnestic when he carried out electrical experiments, and Benjamin Franklin (1706–1790) suffered retrograde amnesia after accidentally administering an electric shock to his head [24]. Including Franklin's experiments (1757) others physicians applied electricity treatment on functional symptoms, e.g., the Scots Robert Whytt and Andrew Duncan, respectively, in 1765 and 1784 [14].

At the end of eighteenth, and the beginning of the nineteenth century, we had a flurry of technological development with Leyden jars and rudimentary batteries developed by Luigi Galvani (1737–1798) and Alessandro Volta (1745–1827) between 1791 and 1800. In 1831, Faraday discovered the induction current, which provided the first continuous electrical current and quickly led to the production of practical machines for channeling mechanical energy into electrical. Many hospitals developed departments with electrical induction machines and this new technology was very quickly put into action [14].

Undoubtedly, with the invention of the electric battery in 1799 by Volta, experience on the effects of the electric current on humans became more systematic. The studies that led him to develop this revolutionary device began in 1792, after Volta read the work of Galvani on the existence of an intrinsic electricity in living organisms [25–29]. Volta himself, Galvani, and especially his nephew Giovanni Aldini (1762–1834), (see Fig. 1.5) started to use electric stimulation using the Voltaic pile on patients with depression, epilepsy, amaurosis and other diseases. Galvani interpreted epileptic disorders as electrical phenomena and used electro-medical applications, like Volta, who carried out short electrotherapeutic applications at the *Conservatorio delle Zitelle Povere* of Como with encouraging results [30, 31].

The most relevant contribution can we see in Aldini's publication, in 1804, *Essai Theorique et Experimental sur le Galvanisms*, in which after spreading and defending the work of his famous uncle, he recommended galvanism as "electric therapy" to aid mental ailments and even to revive the dead [32, 33].

Fig. 1.5 Giovanni Aldini

The core idea was that if nervous energy was by its nature electrical, then mental diseases could be interpreted as alterations of an electrical nature. The galvanic stimulation of nervous regions could help to correct such defects. Aldini applied galvanic currents to the crown of patients affected by depression after having experimented with the effect of the treatment on himself with electrodes in both ears, or in one ear and his mouth, or on the forehead and nose [34]. He experienced an unpleasant sensation due to the immediate shock on opening the circuit followed by a prolonged insomnia and by hyperactivity, which lasted several days [33, 34]. Passing the current between the ears produced violent convulsions and pain, but he claimed good results in patients suffering from melancholia. The most rigorous account of these applications involved Luigi Lanzarini, a 27 year-old farm worker, who was affected by a serious form of depression and who arrived at the *Ospedale Sant'Orsola* of Bologna, on 17th May 1801. Aldini began treatment using the Voltaic pile, containing 15 metal discs, increasing them in number so as to increase the intensity of stimulation during the treatment. The optimal effects were achieved when the patient held his hand at the base of the pile, while the arc

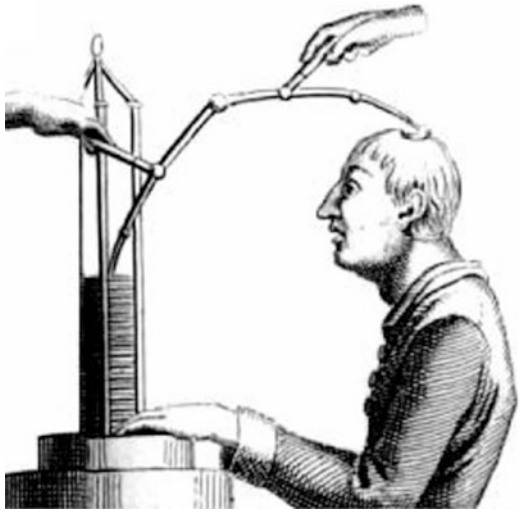

Fig. 1.6 Aldini's patient Luigi Lanzarini suffers from melancholia to whom galvanism is being applied in the head

emerging from the upper part of the apparatus was touching the appropriately shaven and lubricated superior parietal bone. Figure 1.6 shows the therapeutic procedure carried out on Lanzarini.

The depressive state of the patient progressively improved in the following days and after a brief observation period at Aldini's home, he was permitted to go back to his family in his hometown. Aldini applied his electrotherapeutic experiences also at the *Salpêtriere* in Paris where he met the renowned psychiatrist Philippe Pinel (1745–1826) who had heard word of Aldini's electrotherapeutic applications and was very curious to personally see the effects on his mentally ill patients. The results, however, were quite poor due to patients being often in a state of agitation and being quite frightened when faced with Aldini's strange apparatus. Aldini attempted to avoid this situation by putting each electric arc on the ears and even on the earrings of female patients. When Aldini left Paris, Pinel attempted several times to use Galvanism on some patients but no accounts in writing of these experiments were found [33]. Successively, Aldini became a sort of traveling showman, demonstrating the effect of application of current to cadavers in many European cities with particularly theatrical demonstrations. His experiments on the heads of executed criminals in London are well known [33].

In his therapies, Aldini lacked instruments to indicate the intensity of the current used and took into account only the number of copper and zinc discs in the voltaic pile that were indicative of a coarse gradation of stimulation delivered. Moreover, in the absence of a non-rational principle on the therapeutic effect of electric currents, Aldini merely pointed out that after the delivery a general rearrangement of brain function occurred, similar to what happened in violent trauma brain injury. This finding is more reminiscent of the practice of electroshock than that of a lasting modulation of the brain using transcranial direct stimulation at low voltage (tDCS or polarization). However, Aldini in this application used low current voltage for extended periods of time provoking a fleeting daze but neither seizures nor generalized symptoms such as apnea, cyanosis and amnesia [2, 32].

In the same period as Aldini, other European clinical researchers made use of galvanic current to treat mental disorders [3, 35]. In 1801 in Germany, Friedrich Ludwig Augustin (1776–1854) recounted a case of treatment using Galvanic current for a catalectic crisis with paralysis to one arm and leg with intermittent fever. After 3 weeks of treatment the paralysis disappeared and the patient appeared more alive with their humor much improved [36]. In the same year, again in Germany, Christian Heinrich Ernst Bischoff (1781–1861) pointed out that he treated depression, hysterical paralysis, and stupor with remarkable results using Volta's pile [37]. Figure 1.7 shows the depiction of the instruments used by Bischoff in his clinical practice.

The German Karl Johann Christian Grapeingiesser (1773–1813) reported the treatment of a young female with a 4-year history of hysterical aphonia using Galvanic current applied to blisters on the throat over a period of 5 days [38].

In Italy, in 1804, the psychiatrist Gian Pietro Tonelli described some clinical cases of transcranial galvanic stimulation in two patients who:

> … due to strong hemorrhage, terror, and other causes they were rendered cognitively impaired so that their faculties languished exceedingly, and the sense organs, especially vision, had lost much of their energy [31].

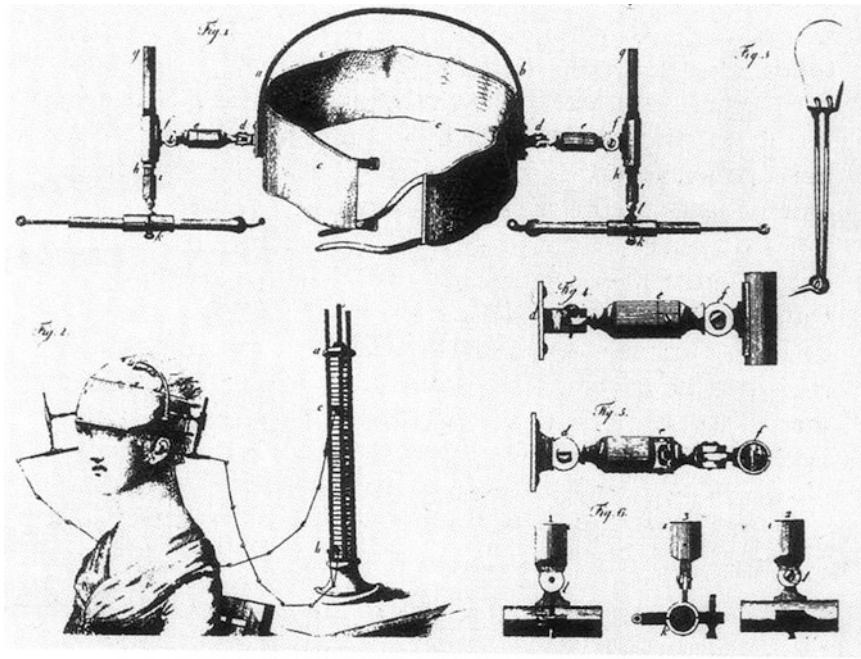

Fig. 1.7 Instruments used by Bischoff in his clinical practice of electric stimulation

After application of the galvanic current, patients claimed to feel much better:… *because it seemed to them they were internally washed by a life-giving fluid, which awakened the power of their spirit, and made the sensory organs pristine again*. Tonelli remarked that these effects also corresponded to: "… *a certain liveliness, and a more cheerful and relaxed attitudes which showed in the face and they testified to recognizing stronger images and greater mobility in the eye*" [31].

During the 1850s, electrotherapy came into use again as a therapeutic agent for neurological and psychiatric diseases in European, and North American asylums, in a form other than the indiscriminate use it had over the previous century [16]. There was a differentiation between galvanic and faradic electric currents, their various strengths, long or short-term application, etc. [39, 40].

Some illustrious neuroscientists, in the second half of the nineteenth and beginning of the twentieth centuries, embraced transcranial electrical stimulation for the treatment of psychiatric and neurological diseases. For example, in France, Francoise Magendie (1783–1855), Jean Martin Charcot (1825–1893), and Joseph Babinski (1857–1932) verified the effect of electricity respectively in patients with epilepsy, melancholia and hysterical conditions [41, 42]. In Germany, Jan Evangelista Purkinje (1787–1869) considered the application of electricity to cure neurological diseases and in Italy, Carlo Matteucci (1811–1862) reported in the treatment of neurological diseases such as chorea, neuralgias, and paralysis [43]. A name that is not famous but of particular interest is the Norwegian Christian Engelskjön who maintained that it was not the direction of the current which influenced the electrotherapeutic result but rather the differentiation between Galvanic (continuous) and faradic (interrupted) current. Therefore, depression and paralysis should be treated with an ascending Galvanic flux caused by the cathode, while mania and other excited states should be treated with descending Galvanic current caused by the anodal effect. Engelskjön used the two types of current in treating two kinds of migraine: one linked to vasoconstrictive damage and the other vasodilation: the faradic current was used as an anti-vasoconstrictor while the galvanic current was used to limit the pain due to vasodilation

[44, 45]. Also in this period other physicians treated migraine with electrotherapy [46].

In the same period, numerous medical practitioners, in Europe and North America, began applying electrical methods to their patients, warning in some cases against the then unwarranted application of electric stimulation to almost all the mentally ill [47–66].

Among the illnesses treated were neurasthenia, melancholia, mania, hysteria, but also hallucinations, migraine, and dementia. Patients with depressive symptoms or hysterical reactions were said to benefit most from this form of therapy [20]. The preferred technique was the application of one electrode to either the scalp or the rear of the neck, round about the second or third cervical vertebra, and another to a distant region of the body such as the hand or foot. Electricity was usually applied in daily or alternate daily sessions, lasting from 10 to 20 min [20]. Intensity was reported by investigators according to the number of battery cells used, between 20 and 35, and treatment varied in length, from seconds to minutes [35]. Several clinicians observed that electrical treatments, and more specifically galvanic therapy, were capable of inducing epileptic convulsions if too strong a current was used [67].

The most important contributor to this entire development, seems to be the German psychiatrist Rudolph Gottfried Arndt (1835–1900) (see Fig. 1.8) who, in a fascinating 130-page review, did the most to unveil the psychological and organic background of the role and influence of electricity with regard to neuro- and psychopathology [48–50, 68].

Arndt carried out studies on electric stimulating treatment in severe psychoses with depressive symptoms or even catatonia, hypochondriac delusion and melancholia, suggesting the use of faradic current (alternate current) as a stimulant against passivity, stupor, weakness, and manic-depressive disorder. On the other hand, direct current was to be applied in other forms of affective disorders, psychoses and psychotic symptoms. He reported that vertical, horizontal and diagonal galvanization on the head, with both electrodes attached to the cranial bone, sometimes supported by simultaneous galvanization of the sympathetic system (vagus nerve stimulation) and the cervical spinal cord was especially successful in fresh, recently developed psychoses and anxieties. He also recommended galvanization of the head and the auditory centre against acoustic hallucination. Arndt [69] also highlighted the difficulties connected with electrical stimulation in the treatment of mental disorders when he wrote:

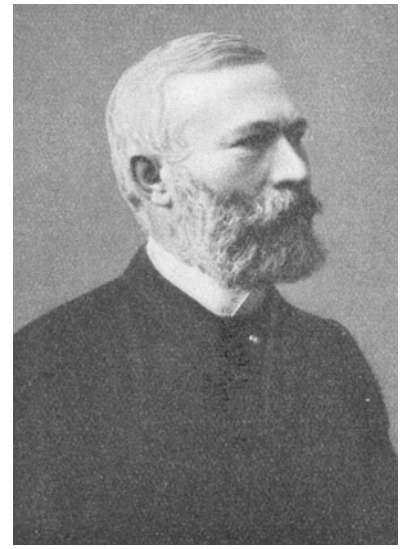

Fig. 1.8 Rudolph Gottfried Arndt

> The electric current is a two edged sword … it may aggravate some forms of mental derangement and even make them incurable … great care, patience and confidence are required, qualities only found in man convinced of the final effect of his treatment. Mere attendants, nurses or assistants, who simply do what they are told, and because it is their duty, will never have the success of a medical man convinced of the efficiency of electricity. [69]

In contrast to his colleagues, who described individual cases, another German psychiatrist Wilhelm Tigges (1830–1914) published studies on differential individual groups of patients with similar sickness or symptoms. His conclusions were that electric brain stimulation was effective with patients suffering from depression and hence should be used in those for whom conventional therapy could no longer help. He found that for patients whom we would now consider schizophrenic rich in positive symptoms, electrotherapy showed little or no effect [68, 70–72].

A repeated observation in these studies was that different polarities (cathodal or anodal) had different effects (sedative, stimulative, etc.) depending also on differences among individual patients and the type of electric current used. A sedative effect resulted when a negative pole was applied to the scalp. A sleep-inducing effect was also reported by the French physician Stéphane Leduc (1853–1939). He experimented with low intensity electrical stimulation periodically interrupted (100/200 times per second with 8–16 V and 2 mA) passed transcranially in animals. The result he obtained was the appearance of a state of astonished immobility progressively culminating in a state of inhibition comparable to chloroform narcosis [73]. Leduc called this condition electric sleep (and by later authors electronarcosis) and was obtained by applying electrodes in an axial direction on the forehead and to the rear of the head which, after a short period of excitement, was accompanied by vegetative phenomena [73–76]. He recommended transcranial electric stimulation in cases of cerebral neurasthenia.

It should be noted that there were in this phase plenty of excesses and exaggerations, typically found in the early stages of the application of a new therapeutic technique, which sometimes led to an excess of zeal. In addition to the reports of the successful use of electricity to treat mental illness some clinicians raised doubts about the efficacy of electricity in treating mental illness [67]. Electricity was also applied in a extreme way during the first World War (but also in the second World War) submitting traumatized soldiers to electric stimulation in order to discipline and return them to the front [77].

In the following years, incongruent results, or none at all, led to the gradual abandonment of electric therapy until the 1930s when electroconvulsive therapy was introduced. Electroconvulsive therapy (ECT) could be considered the first modern example of the therapeutic application of brain stimulation for the treatment of psychopathologies. The Italian psychiatrist Ugo Cerletti (1877–1963) relied on a young colleague Lucio Bini (1908–1964) for the development of an instrument able to ensure maximum safety in the application of electrical current. These original scientists used ordinary alternating current propagated in sine waves and in measured intensity as a means of producing convulsive seizures. However, they received harsh criticism about the project, which was presented by Bini at the *Congress of Neuropsychiatry of Munseigen* in 1937 on the treatment of schizophrenia. In March 1938, the method was introduced at the *Academy of Medicine* in Rome and in April 1938, the first real application of ECT was performed by Cerletti and Bini on a patient affected by an apathetic and abulic condition with diagnosed schizophrenia [78]. Figure 1.9 shows the apparatus used by Cerletti and Bini in their first ECT experience.

ECT fundamentally altered the management of mental illness and gave birth to the development of numerous electrostimulation instruments in Europe and the USA [79, 80]. The popularity of ECT greatly decreased in the 1960s and 1970s, due to the use of more effective neuroleptics and as a result of a strong anti-ECT movement [81]. However, ECT has recently come back into use for the treatment of serious cases of patients with

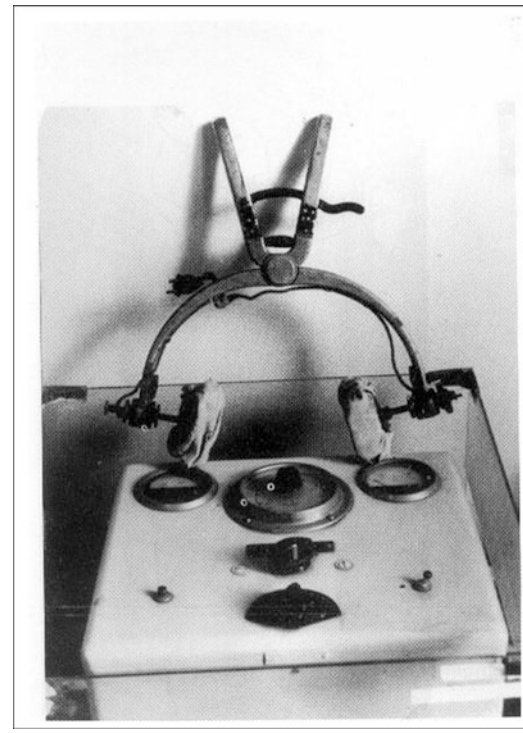

Fig. 1.9 Apparatus used by Cerletti and Bini in their first electroconvulsive experience

depression present with psychological and somatic symptoms [82].

It should be noted that in the 1950s in Italy, electroconvulsive therapy coexisted with prolonged transcranial low intensity electrical stimulation, as an alternative method deriving from the electroshock teraphy of Cerletti and Bini [83, 84]. For example, Corradini (1950) reported the analysis of the prolonged transcranial electrical stimulation at a low tension on 52 patients affected by psychosis or depression.

Clearly, transcranial direct current stimulation (i.e., tDCS) differs fundamentally from electroconvulsive therapy (ECT). While ECT consists of inducing convulsive activity with alternating current, tDCS induces modulation of the brain function with continuous current to produce physiological changes and spontaneously influence neuronal activity without seizures [85]. The current used in tDCS (typically 0.25–2 mA) is also of a much lower intensity than that used in modern ECT (800–900 mA). Although tDCS can barely excite silent cells, it is very effective in changing spontaneous cell firing [85]. Evidence suggests that unlike ECT, tDCS does not cause memory disturbances or loss of consciousness, nor does the patient need to be sedated or given muscle relaxants [86].

The Reappraisal of Transcranial Direct Current Stimulation (tDCS) from 1960 Onward

In the 1960s some studies on animals confirmed that anodal tDCS increases the spontaneous firing rate and excitability of cortical neurons by depolarizing the membrane, whereas chathodal tDCS leads to hyperpolarization of neuronal membranes and thus invokes decrease of the neuronal firing rate and excitability [87–89].

For example, Bindman et al. [88] showed that currents as low as 0.25 μA/mm^2 applied to the exposed pia via surface electrodes (3 μA from 12 mm^2 saline cup on exposed pia surface) could influence spontaneous activity and the evoked response of neurons for hours following just minutes of stimulation in rat preparations. See Fig. 1.10.

Purpura and McMurtry [89], showed similar effects in cat preparations for currents as low as 20 μA/mm^2 from cortical surface wick electrodes ranging in area from 10 to 20 mm^2. These scientists showed that currents, at magnitudes much lower than those necessary for the initiation of an action potential, could still lead to alterations in the level of neural excitability.

In the 1960s, more systematic studies in normal and clinical subjects with tDCS were performed. For example, Lippold and Readfearn [90], using very slow scalp tDCS up to 50–500 μA in 32 normal subjects, showing that scalp anodal currents stimulation induced an increase in alertness, mood and motor activity, whereas cathodal currents produced quietness and apathy. In a second study, with depressed patients, Redfearn, Lippold, and Costain (1964) [91] demonstated that direct anodal scalp current improved mood in more than half of their 26 patients. Herjanic and Moss-Herjanic [92], reported short but encouraging results in the use of tDCS on schizophrenic patients. These results were confirmed in further double-blind studies (e.g., [93–95]), but other studies failed to report significant effects in psychiatric patients [96–98].

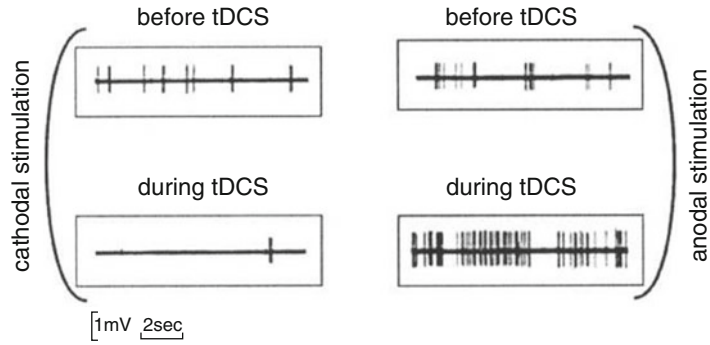

Fig. 1.10 The physiological mechanisms of anodal and cathodal tDCS on spike activity in rat preparation (modified by Bindman et al. 1964)

On the whole, these studies showed a clinical variability due probably to inaccurate and heterogeneous diagnostic criteria in recruiting psychiatric patients and in specifying the position of the electrodes. The latter is important as the earlier experiments were carried out using either one electrode over the scalp and another elsewhere on the body (often the knee), rather than both electrodes positioned on the scalp. This change in technique characterized the application of the method in neuropsychiatric disorders [99]. These incongruent results and the subsequent progress made in treating psychiatric disorders with drugs led to the abandonment of the tDCS [86].

However, by the end of the 1990s more precise and systematic observations were made about the efficacy of polarization on humans [100]. Priori and colleagues tested in normal subjects the functional effects of very weak DC (0.5 mA, duration <7 s) on the motor areas of the cerebral cortex, examining the modification in motor evoked potentials (MEPs) elicited in the small hand muscle of subjects by TMS. Four experiments were performed polarizing the cortex by using two electrodes placed on the scalp, one over the left motor cortex (7 cm lateral to vertex) and the other under the chin. These findings provided direct evidence that a very low electric field crosses the skull and may influence brain excitability (see Fig. 1.11).

The mechanism could be explained in two ways: one is that scalp anodal tDCS hyperpolarizes superficial excitatory interneurons in cortical motor areas. Another explanation is that anodal scalp tDCS depolarizes superficial inhibitory interneurons (facilitating activity) in the cortex.

Shortly after, Nitsche and Paulus established that prolonged (minutes) tDCS could produce

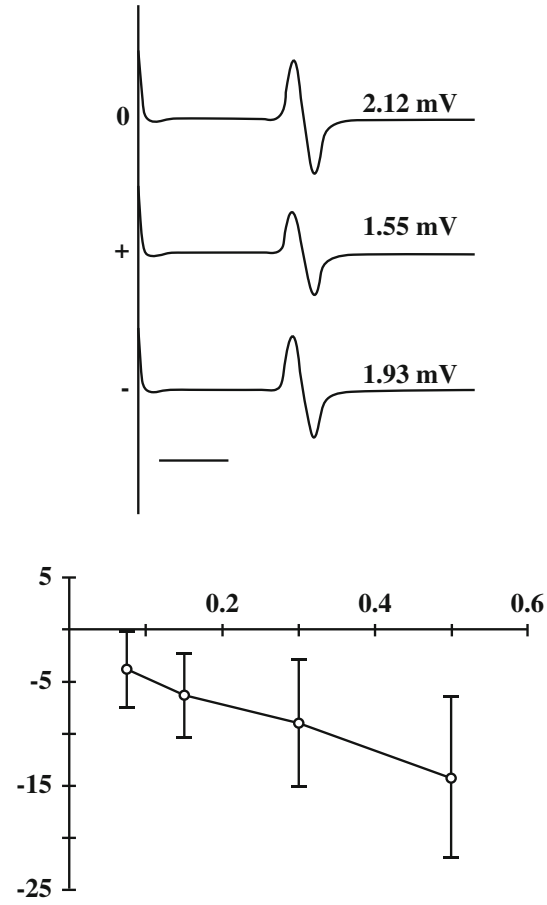

Fig. 1.11 The effect of weak scalp tDCS (0.3 mA, 7 s) on the motor potential evoked by transcranial magnetic brain stimulation in a subject in the study of Priori et al. [100]. In the upper panel: 0, control condition; +, anodal condition polarization; –, cathodal conditioning polarization

lasting and polarity specific changes in cortical excitability [101]. Cathodic polarization applied to the motor cortex can induce a considerable reduction in cortical excitability, while anodic polarization increases excitability [101]. There was a full re-evaluation of the use of electrical current stimulation of the brain with neurophysiological and therapeutic objectives.

Within the last decades, tDCS has seen a wide range of potential applications and can be used to explore basic aspects of neurosciences [102–106].

In 2000s, pilot clinical studies were performed for indications spanning depression [107], pain [108], epilepsy [109], spinal and cerebellar stimulation [110], and a broad range of neuropsychiatric [111] and neuropsychological disorders [112–114]. tDCS has also been explored for rehabilitation including after stroke [115]. Moreover, due to the perceived safety of tDCS it was initially validated for neurophysiological changes in healthy subjects and continues to be investigated in healthy individuals for changes in behavior and cognitive performance [116, 117].

Concluding Remarks

The first clinical experience with electric fish, and a four-century-long history of electrotherapeutic applications, has led to the modern use of tDCS. This history includes various degrees of success and the therapeutic value of electricity in the treatment of mental disorders followed a cyclical course throughout the centuries. Clinicians approached transcranial electric stimulation with great enthusiasm in the eighteenth century, only to abandon it at the end of the nineteenth century, when they failed to produce consistent results, raising doubts about the efficacy of electrotherapy [67, 118]. In the twentieth century, several experimental studies clearly demonstrated using motor evoked potentials that tDCS resulted in changes in motor-cortical excitability. Recently, with the adoption of more adequate protocols of experimentation, the ability of tDCS to treat a number of clinical conditions such as affective disorders, chronic pain conditions and post-lesional cognitive disorders has been demonstrated.

As pointed out by Bikson et al. [119], controlled investigation involving tDCS for treating psychiatric or cognitive disorders should not be compared with improvised devices or practices that apply uncontrolled electricity to the brain without reference to established protocols.

Today, tDCS is recognized as an effective technique in the application of direct current to the scalp, usually delivered by a small battery-driven stimulator, by attaching electrodes of different polarities to the skin and emitting a constant current. tDCS is an easy, noninvasive technique which causes minimal disturbance to the subject and is able to produce prolonged variations of cerebral excitability while influencing neuronal plasticity. The simplicity and economics of the technique, the minor nature of adverse effects, and the long-lasting results render tDCS a promising rehabilitative procedure.

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The New Modalities of Transcranial Electric Stimulation: tACS, tRNS, and Other Approaches

2

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Abstract

The most frequently used low-intensity transcranial electrical stimulation (tES) techniques are transcranial direct current (tDCS), alternating current (tACS), and random noise stimulation (tRNS). During tES, currents are applied with intensities ranging between 0.4 and 2 mA through the human scalp. It has been suggested that tACS interacts with cortical oscillations in a frequency-specific manner at single and using tRNS, at multiple frequencies. All techniques might affect homeostatic mechanisms or the signal-to-noise ratio in the brain. The aim of this review is to summarize basic aspects of tACS and tRNS, their possible neuronal mechanisms and clinical applications.

Keywords

Transcranial stimulation • Alternating current • Random noise • Brain oscillations

Introduction

Transcranial alternating current stimulation (tACS) is, to a certain extent, newer method than transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) and better suited to noninvasively modulate brain oscillations (see [1, 2]). Technically, its application is similar to tDCS, although the concept with regard to the underlying mechanism is substantially different. During one half cycle of an AC oscillation, one electrode serves as anode and the other one as cathode and the current strength increases and decreases following a half sine wave. During the other half cycle, the pattern reverses ensuring the zero sums. Therefore, the membrane potential, on average, is not affected, but the depolarizing or hyperpolarizing effect of the cycle is assumed to be strong enough to modify neuronal activity and to induce online effects.

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Of course, it is possible to combine tACS with a DC offset, which is described later.

TACS can be classified as a form of tES, usually involving application of sinusoidal current across the scalp [3–5]. Also other pulse shapes, such as rectangular, may also be applied (not further dealt with here), although some authors suggested that tACS should not include rectangular or any other than non-sinusoidal waveforms. The possible physical spectrum may be indefinite in any case; the sinusoidal waveform may be biased, biphasic components can vary in amplitude and frequency, a combination of sinusoids could be used, and many more possibilities exist. With conventional intensities being limited to a maximum 2 mA peak-to-baseline [6], the applied intensities during tACS are at least two orders of magnitude less than the intensities intended to induce seizures as part of the therapeutic outcome and thus, are regarded safe.

Out of the indefinite spectrum some frequencies and intensities have been chosen to investigate the direction and the duration of the online effects and aftereffects. Most of these investigations used tACS frequencies in the physiologic EEG-detectable range, especially, when the intended outcome is to interact or influence these oscillations frequencies or measure them by EEG [5, 7–9]. TACS is applied in clinical research most relevant in Parkinson's disease (PD) [10]. Further insight in how brain oscillations are connected to cognitive functions causally will certainly predict more optimized stimulation parameters in the future. Furthermore, Higher frequencies then those in the EEG range, such as 140 Hz, may draw links to the frequencies used in deep brain stimulation (e.g., [6]).

Recent reviews cover quite extensively the existing literature (see [1, 2]), therefore here, we would like to focus on basic methodologic aspects and possible clinical applications.

tACS: Intrusion with Brain Oscillation

It is suggested by several animal and human studies that the mechanism of tACS is based on entrainment of brain oscillations. Modulation of active Purkinje cell activity by AC fields was shown by Chan and Nicholson in 1988 [11]. Later Francis and colleagues [12] demonstrated that electric pulses of 140 μV/mm root mean square or 295 μV/mm peak amplitude were sufficient to increase the firing rate of single neurons in the rat hippocampal slices at the lower end of intensities. Nevertheless, in this study pulsed stimulation was used and not the classical sinusoidal tACS.

Entrainment of neuronal oscillations by weak electrical AC stimulation was shown first by Deans and colleagues for induced gamma frequencies [13] and at the same time at the single neuron spiking level by Radman et al. [14]. Later, Fröhlich, Ozen and Reato extended the existing concepts for slow-waves and gamma oscillations. Coupling constants, as defined how many mV of a neurons membrane is polarized per V/m electric field, were differed: the field gradient varied between 0.2 and 1 mV/mm, which might be due to the different experimental setups and animal types. Ozen and colleagues [15] attached stainless steel wires to the skull of anesthetized rats, stimulated them electrically with AC and simultaneously recorded intracranial activity. Here, an entrainment of ongoing neuronal activity at frequencies mimicking the frequency of cortical slow oscillations in the frequency range of 0.8–1.7 Hz was found in many cortical areas. Voltage gradients of 1 mV/mm in the extracellular space were sufficient to affect discharge probability of neurons. At the low intensity end with sinusoidal stimulation Reato and colleagues [16] performed electrical stimulation experiments in slices of rat hippocampus and also simulations on neuronal networks. Both experiments revealed a threshold of 0.2 mV/mm before an AC was able to modulate ongoing neural activity. Fröhlich and McCormick [17] applied AC fields to the cortical slices of ferrets. They were able to demonstrate that AC fields at 0.5 mV/mm were sufficient to modulate the ongoing neural activity.

Nevertheless, the results of the animal studies might not be directly translated to human experiments. Indeed, computer simulations of the current flow during tDCS using models of the human head have revealed that a significant amount of

the current may be shunted by the well conducting skin (~90 %), while less current reaches the brain [18]. Furthermore, at the case of tACS the frequency response of each type of conducting element between the electrodes and the brain should also be taken into account [19].

Modulating the Activity of the Human Brain Using tACS

Different outreads have been used to measure cortical modulation by tACS. An enhancement of the EEG alpha amplitude was seen at the posterior part of the brain after 10 Hz tACS [7] with aftereffects for 30 min after 10 min of stimulation [20]. The elevation of EEG amplitudes can correlate with behavioral outcomes: e.g., amplification of gamma oscillations (30–80 Hz) with 40 Hz tACS during sleep led to the induction of lucid dreaming [21]. Linear increases in stimulation intensity may have nonlinear effects on the affected neural tissue and the physiological or behavioral consequences with lower intensities inducing inhibition and higher intensities excitation [6].

The frequency of the brain oscillations can also be modulated by tACS. Animal studies have demonstrated that stimulating cortical tissue at a stimulation frequency below the frequency of intrinsic oscillations can slow down the brain oscillations, and stimulating at a frequency above the intrinsic oscillations can speeded it up [17]. In human studies a similar effect was observed as well. Helfrich and coworkers [7] found an increase of the EEG alpha peak during 10 Hz tACS over the visual cortex. However, we should note that entraining oscillations does not only affect oscillations at the frequency of stimulation, but also at harmonic multiples as well as subharmonics. Furthermore, certain frequencies can interact with others referred to as cross-frequency coupling [22, 23]. Therefore, it has to be assumed that entraining one frequency may affect other frequencies. Same argument states with regard to the anatomical location of the effect: long-range coupling of cortical oscillations will most certainly trigger changes within the whole functional network. Thus, modulation of brain oscillations by tACS will not be a linear process and the effect may not be limited to the given frequency or area of stimulation.

Modulation of the phase of the brain oscillations can also have physiological and behavioral relevance. When using more than two electrodes, it is possible to manipulate the phase of the stimulation, which refers to the angle of the sinusoid relative to different electrodes, enabling anti-phase or in-phase stimulation. Correspondingly, brain areas that exposed to the similar conditions by in-phase stimulation are expected to facilitate their communications with each other. For example changing the inter-hemispheric phase-coherence in the gamma range via 40 Hz tACS have led to altered perceptions of ambiguous motion stimuli [24–26]. In the auditory cortex using 10 Hz tACS resulted in altered perception of a near-threshold auditory stimulus [27]. Stimulating the left frontal and parietal cortex by 6 Hz tACS in phase, cognitive performance in a delayed letter discrimination task was improved, when stimulating out of phase it was worsened [28].

Using tACS on Another Way: tRNS

Transcranial random noise stimulation (tRNS) was developed with the intent to desynchronize pathological cortical rhythms [29]. The technical application of tRNS can be adapted from tDCS and tACS, such that the electrode-montages and the applied paradigms are the same or very similar. Here, the stimulation is conventional biphasic like at the case of tACS, with various forms of noise. In typical examples, during tRNS a white noise in a frequency spectrum between 0.1 and 640 Hz (full spectrum) or 101–640 Hz (high frequency stimulation) can be applied. During one embodiment of "random noise" stimulation, the probability function of the stimulation follows a Gaussian or bell-shaped curve with zero mean and a variance, where 99 % of all generated current levels were between ± 1 mA (when 1 mA stimulation intensity is used). It was observed that filtering of the high-frequency subdivision between 100 and 640 Hz of the whole tRNS spectrum is functionally

responsible for alteration of excitability, at least in the motor cortex [29].

The physiological mechanisms of tRNS are largely unexplored due to missing animal studies. Although higher frequencies (e.g., 140 Hz) have been shown to modulate brain activity, at least in the motor cortex, the neuronal membrane acts as a low-pass filter, and therefore, high frequencies that are applied during tRNS are supposed to polarize neurons only by a very small amount. Deans and colleagues [13] measured the polarization of neurons during AC stimulation and estimated the coupling constant between electric field and induced polarization (mV per V/m applied). They found that 100Hz AC stimulation gave a coupling constant of 0.050 mV per V/m. Therefore, 1 V/m in the brain at 100Hz can polarize a neuron by only 50 μV. This intensity is too small to modulate the single neuron activity. One possibility can be that many synaptically connected active neurons can provide an amplification mechanism of the basic stimulation effect [16, 17].

One potential online effect of tRNS might be associated with repetitive opening of Na+ channels, observed in rat hippocampal slices during the application of AC stimulation [30]. In humans a recent pilot study the Na+ channel blocker carbamazepine showed a tendency towards inhibiting the activity of the motor cortex post stimulation [31].

The effects of tRNS might be based on other mechanisms, it was suggested that tRNS may increase synchronization of neural firing through amplification of subthreshold oscillatory activity, which in turn reduces the amount of endogenous noise (e.g., [32]). However, it is not clear, how this process can induce long-term, neuroplastic-like changes in the human brain. For example Cappelletti and colleagues using the repeated bilateral parietal stimulation showed the increased numerosity discrimination ability [33] that last for several weeks. Another study reported that bifrontal application of tRNS for 5 days enhanced the speed of both calculation- and memory-recall-based arithmetic learning [34]. Six months later the behavioral effects in the stimulated group relative to sham controls were still present.

Other Types of Oscillatory tES: Oscillating Transcranial Direct Current Stimulation (o-DCS)

Oscillatory tDCS (o-tDCS, also abbreviated as so-tDCS or ts-DCS) is a form of tES using DC stimulation where waveform is typically monophasic square or monophasic sinusoidal wave stimulation. Slow oscillatory tDCS (so-tDCS) conventionally refers to a signal with a frequency below 1 Hz [35]. Transcranial Sinusoidal Direct Current Stimulation (ts-DCS) is a form of o-tDCS where the waveform is a monophasic, biased sinusoid. so-tDCS may also be used to describe protocols with sinusoids when the frequency is low [35, 36]. ts-DCS frequencies and intensities are similar to those used in tACS [3]. The duty cycle of o-tDCS and its derivatives can be varied (e.g., [36] 5 intervals with 1 min gap).

These forms of stimulation are not so frequently used in the research than the conventional tACS and many times they are described as tDCS. However, the distinction between o-tDCS and the conventional tDCS applied intermittently and repeatedly (repetitive tDCS: e.g., 15 s on/off tDCS, from [37]) is, that tDCS is probably effective during the sustained phase of the stimulation while o-tDCS is anticipated to produce changes during the alteration phase of the current when the current flow is nonstatic.

Clinical Applications

Many studies have indicated that both tACS and tRNS are effective at modulating brain activity and result in behavioral effects in human subjects; nevertheless, they are rarely applied in patient populations.

Tinnitus has been attributed to reduced activity in the alpha range in the auditory cortex [38]. For the reduction of the symptoms of tinnitus it has been shown that low frequency tRNS (0.1–100 Hz) was more effective than either tDCS or interestingly, tACS using the individual alpha frequency [39]. Another study reported a significantly more pronounced reduction in loudness and distress in pure tone tinnitus compared to

narrow band noise tinnitus when high frequency tRNS was applied [40]. Based on these results, tRNS over the auditory cortex is a promising treatment option for different types of tinnitus, nevertheless, there a clear mechanistic explanation for the different results obtained with different types of tRNS is still not exist. With regard to other disorders, in neuropathic pain one patient out of four responded to tRNS applied over the motor cortex [41].

tACS is probably suited to treat disorders, which are characterized by distorted brain oscillations, by restoring to their original function. It was found that tACS has the potential as a therapeutic application in PD. Oscillatory activity, which guides the motor cortex, originating from the globus pallidus internus is increased in patients suffering from tremor. Brittain and coworkers [10] applied tACS over the motor cortex in patients diagnosed with tremor-dominant PD. tACS was most effective at the individual tremor frequency for inducing cortical phase cancellation, presumably due to suppression of the resting tremor amplitude. This study used a closed loop stimulation setup: tremor frequency was measured online and the motor cortex stimulation parameters were adjusted according to the measured activity. It was proposed that closed-loop individually adjusted stimulation can considerably surpass the traditional approach.

In another study Krause and colleagues [42] studied the effects of 10 and 20 Hz as well as sham tACS in PD patients and healthy controls. The application of 20 Hz tACS reduced the cortico-muscular coherence amplitude in the beta band upon isometric contraction during fast finger tapping in PD patients, but not in healthy control subjects. These results suggest that tACS could probably entrain cortical oscillation in PD patients and opening a promising field in the therapy of movement disorders.

Repetitive transorbital alternating current stimulation (rtACS) as a tool for visual rehabilitation also demonstrated promising results. During this intervention, electrodes are positioned near the eye aiming to inject current to the eyeball, stimulating the retina. The active electrodes include two super-orbital electrodes, four active electrodes placed above and below the eye and one return electrode is positioned on the right upper arm or right shoulder [43, 44]. rtACS has been proposed to induce vision restoration by activating residual visual functions in patients with damage to the retina, optic nerve, or visual system.

There are other possibilities, e.g., epilepsy would be another disorder that can feasibly be treated by tACS. It was found that in epileptic patients shortly before a seizure an increased synchronization of gamma band oscillations occur [45]. Thus, multichannel tACS may induce enough desynchronization to restrain an upcoming epileptic event.

Bifrontal oscillatory currents in the theta range enhanced functional connectivity between the prefrontal components of working memory and retrospective monitoring in humans [46]. These results support the feasibility of utilizing tACS to treat theta-rhythm functional disconnectivity and related cognitive impairments, e.g., in schizophrenia. Nevertheless, there are no published clinical trials on this field yet.

Conclusions

Not many tACS studies exist so far, thus experience with the application of this type of stimulation is still limited. The so far insufficient duration of the aftereffects (except 140 Hz tACS) might be increased using longer stimulation duration or repetitive stimulation during days or weeks, or with optimized stimulation protocols, such as an intermittent short stimulation paradigm (8 s stimulation and 8 s pause) [47]. Another important question would be to clarify the exact neuronal mechanisms underlying the tACS effects. Many studies suggest that tACS can entrain and enhance cortical oscillations (see above), however, not excluding the possibility that tACS induces short term plasticity rather than entrainment [47].

Compared to tDCS, tACS and tRNS have a better blinding potential with regard to the cutaneous sensations, such as itching, tingling or burning [48]. Furthermore, absence of the polarity effect, typical for tDCS [49], and presence of

the oscillatory phase provide an additional degree of freedom during the experimental design. Nevertheless, phosphene perception during tACS in a wide frequency range (6–70 Hz), might affect the execution of the task and the understanding of results (e.g., by inducing shifts in arousal, compared to sham stimulation).

Due to the above-mentioned multiplicity of tACS parameters and paradigm, tACS experiments requires fixation of more factors, compared to tDCS. Also, clarification of physiological characteristics, e.g., which oscillations that associated with a given motor or cognitive process are going to be modified in a healthy or patient population, may optimize effects. It should be clear whether the frequency, amplitude, or phase would be modulated. Application of the multi-electrode arrays together with the electric field modeling allows for targeting more complex neuronal assemblies, such as the coherence between two or more brain regions. Control stimulation frequencies next to the sham stimulation or the stimulation of another brain area not being involved in a given task will improve significance of the results. Finally, the importance of the double-blinded placebo-controlled experimental design should not be underestimated.

tACS and tRNS supplement tDCS in research and in clinical practice. Development of hypothesis-driven approaches based on brain oscillations and behavior are expected to provide another perspective that can bring major progress in the near future.

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Physiology of Transcranial Direct and Alternating Current Stimulation

3

Min-Fang Kuo, Rafael Polanía, and Michael Nitsche

Abstract

Non-invasive brain stimulation with direct (transcranial direct current stimulation, tDCS) or alternating currents (transcranial alternating current stimulation, tACS) has been developed in neuroscience research in the last decades and since then has become an effective tool to induce neuroplasticity and modulate cognition and behaviour in humans. The primary effect of tDCS is a subthreshold modulation of resting membrane potentials, which results in alterations of cortical excitability and spontaneous cortical activity. Sufficiently long stimulation results in long-lasting neuroplastic after effects. Beyond these local effects, tDCS induces modifications of functional cortical and subcortical networks. On the other hand, tACS is presumed to primarily entrain oscillatory cortical activity, dependent on the frequency of stimulation, and has been widely applied to investigate motor and cognitive functions. Here we provide an overview about physiological mechanisms of tDCS and tACS, and review their potential application in studies of brain function and cognition.

Keywords

Non-invasive brain stimulation • tDCS • tACS • EEG • Neuroplasticity • Cortical excitability • Brain oscillation • Pharmacology • Functional connectivity • Focality

Introduction

Non-invasive brain stimulation (NIBS) techniques have generated renewed interest in recent decades as promising tools to explore human cerebral functions and to treat neurological and psychiatric diseases [1]. Apart from invasive stimulation paradigms such as deep brain and vagal nerve stimulation, non-invasive tools like

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transcranial magnetic stimulation (TMS) or transcranial electrical stimulation (tES), including transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), are attractive for use in humans, because they permit painless modulation of cortical activity and excitability through the intact skull [2]. This chapter gives an overview of the physiological effects of tES techniques. Their application and impact on brain functions and cognitive processes are also discussed.

tDCS

Tonic application of direct currents to the brain, although a relatively old method in strict terms, has regained increasing interest as a potentially valuable tool for the induction and modulation of central nervous system neuroplasticity. About 45 years ago it was demonstrated that in anesthetised rats direct currents, delivered by intracerebral or epidural electrodes, induce stimulation polarity-dependent activity and excitability alterations of the sensorimotor cortex, which can be stable for hours after the end of stimulation [3]. A few years later it was verified that also transcranial application of direct currents can induce an intracerebral current flow sufficiently large to achieve physiological and functional effects [4, 5]. The number of studies in humans in these early days was however limited. In one of the few neurophysiological studies, it was found that this kind of stimulation alters EEG patterns and evoked potentials at the cortical level in humans [6]. With regard to cognitive and behavioural effects, early clinical studies describe a mixed impact on depression and other psychiatric diseases [7–10], and improved performance in a choice reaction time task in healthy subjects [11]. In the following years, electrical stimulation of the human brain via transcranial application of direct currents as a tool to influence brain function was nearly forgotten, most probably due to mixed results of initial studies and limited options to explore physiological effects in humans. Nevertheless, in the last decade it has been re-evaluated following the development of methods that allow probing its neurophysiological effects (e.g. transcranial magnetic stimulation—TMS, functional magnetic resonance imaging—fMRI, and positron emission tomography—PET). tDCS developed into a technique that reliably induces and modulates neuroplasticity in the human cerebral cortex non-invasively, and painlessly in order to elicit prolonged—but yet reversible—shifts of cortical excitability [2, 12–15]. This section offers an overview of tDCS protocols, and their physiological effects.

tDCS Protocols and Effects

For tDCS, the direct current is usually applied via conductive rubber or metal electrodes embedded in a sponge soaked with saline. Alternatively, electrode-skin contact can be made by a sufficiently thick film of another electrolyte-based contact medium, such as conductive gel or cream. A medium NaCl concentration between 15 and 140 mM is reported to optimally minimise discomfort during stimulation [16]. The electrodes are connected to a stimulator delivering constant current which is essential for stable current strength to ensure reliable tDCS effects. Usually applied stimulation parameters range from 1 to 2 mA current intensity, from 3.5 to 100 cm^2 electrode size, and up to 20-min stimulation duration in most studies. These parameters are considered safe, as shown by behavioural measures, electroencephalography (EEG), serum neurone-specific enolase concentration, diffusion-weighted and contrast-enhanced MRI measures, and missing severe side effects in healthy and diseased humans, as well as in animal experiments [2, 12, 13, 17–20]. Electrode positions above cranial foraminae and fissures should be evaluated with caution or avoided because these could increase effective current density relevantly and thus have damaging effects. At the beginning of the stimulation most subjects will perceive a slight itching sensation, which normally fades with time [21, 22]. To avoid retinal phosphenes due to the tenfold higher sensitivity of the retina compared to the brain to electrical stimulation [23], as well as make and break effects, ramping up and down of current intensity for 8–30 s at both the start and end of stimulation is suggested [24].

The tDCS effects, including efficacy, direction, and focality of the excitability changes, are determined by *stimulation polarity/electrode position, current density (i.e. current strength/stimulated area), stimulation duration, electrode size, and configuration*. These parameters are discussed in the following sections.

Current Intensity/Density

In most of the studies, in which conventional tDCS is applied, current intensity is set at 1–2 mA, which results in about 0.03–0.06 mA/cm^2 current density. These stimulation intensities are sufficient to induce relevant excitability shifts in the human primary motor cortex (M1) and alter physiological, perceptual, and cognitive processes in prefrontal, parietal, temporal, and occipital cortices [2, 12, 14, 25, 26]. Increasing current density might increase efficacy of stimulation due to a larger membrane polarisation shift [14]. It might also affect additional neuronal populations because of a greater efficacy of the electrical field in deeper cortical layers and different sensitivities of specific neuronal populations to DC stimulation [27]. Moreover, because of physiologically based non-linearity of tDCS effects (see also below), more intensive stimulation can also convert directionality of the effects [28], and different populations might display altered sensitivity to tDCS [29].

Electrode Position/Configuration/Current Direction

Stimulation polarity determines the direction of cortical excitability changes elicited by tDCS. In most studies, both in humans and animals, anodal DC stimulation enhances cortical excitability and activity, whereas cathodal stimulation results in reversed effects [13, 14, 27]. However, deviating results have also been reported for subgroups of neurons [27, 30], hippocampal slice preparations [31], and specific return electrode positions [32]. One explanation for these heterogeneous effects is the fact that not so much the polarity of the electrode over the stimulated area per se is the decisive factor for the net effects of tDCS on excitability, but rather the direction of current flow relative to neuronal orientation: the respective current has to flow along the longitudinal axis of a given neuron to induce relevant effects on membrane polarity [33]. Polarisation of the soma and axon might determine the direction of the effects more than dendritic polarisation, because of higher receptor and ion channel density at the soma and axon level. Consequently, the position of the return electrode is critical for achieving the intended excitability shifts, because together with the stimulation electrode it determines the electric field orientation in relation to neuronal orientation. In accordance, the position of the return electrode had been shown to determine the direction of the effects, and efficacy of tDCS to induce cortical excitability alterations for motor, and visual cortex stimulation [14, 34, 35], and identical electrode arrangements result in opposite effects on cortical excitability in case of antagonistically oriented neurons [31]. Moreover, for motor cortex stimulation it was demonstrated that positioning of the return electrode at the shoulder or arm results in diminished efficacy, as compared to the "classical" bipolar electrode configuration with the return electrode positioned over the contralateral orbit [36]. On the other hand, too low inter-electrode distance results in massive shunting of current flow between electrodes via the skin. Thus, distance between electrodes is relevant for the efficacy of tDCS.

The "classical" tDCS protocols to induce neuroplastic excitability alterations involve stimulation with two relatively large electrodes (usual size between 25, and 35 cm^2) positioned on the head. These electrodes induce relatively non-focal effects of the underlying cortex, but also at remote areas, as shown experimentally for stimulation of the primary motor cortex [37, 38], and via modelling approaches [39]. Low focality is not necessarily a problem for each application of tDCS. In clinical syndromes, modulation of pathologically altered excitability of larger regions might be preferable, and in some cases, where the intended effects are thought to originate from an interaction of task- and stimulation-generated activity alterations, functional focality might result from this interaction. However, focality is crucial for basic studies aiming to explore the contribution of a specific area to brain

function. Thus new tDCS protocols suited to increase focality of stimulation have been developed. At least two factors contribute to the low focality of tDCS, the size of the relative large electrode positioned over the target area, and the physiological effects of the return electrode, if positioned at the scalp. Focality of tDCS over the target area can be enhanced by reducing electrode size, and keeping current density constant. By this modification of the stimulation protocol it has been shown for the motor cortex that a more selective alteration of excitability of specific hand muscle representations is accomplished [38]. Following the same rationale, increasing the size of the return electrode at constant current strength of 1 mA from 35 to 100 cm^2 makes this electrode functionally inefficient, most probably due to reduced current density, and thus results in an at least functionally monopolar stimulation [38]. Alternatively, the return electrode can be positioned at another location than the scalp, e.g. the neck, shoulder, arm, or knee [7, 32, 40]. However, this remote position of the return electrode might diminish the efficacy of stimulation [36], and it is unclear if other sets of neurons would be affected by these approaches due to different electrical field orientation.

Based on modelling of electrical field strength, alternative electrode configurations have been developed to optimise stimulation focality; the so-called high-density tDCS (HD-tDCS) is one of these approaches. Here relatively small electrodes are used, and a central stimulation electrode is surrounded by four return electrodes placed in the vicinity of the stimulation electrode [39]. Since the distance between the respective electrodes is relatively short, and thus shunting is enhanced relative to the more conventional electrode arrangements, current density has to be relatively high to obtain similar effects as with the large electrodes. Taking this into account, the cortical excitability alterations induced by this protocol seem to be similar to those elicited by conventional tDCS [41]. However, information about the physiological focality of these excitability alterations is not available so far. The functional efficacy of this electrode configuration has been demonstrated in some pilot studies, including pain perception [42]. Another optimising future strategy might be multi-electrode approaches, which show encouraging results in modelling [43, 44].

Stimulation Duration/Interval

Stimulation duration determines the occurrence and length of after effects of DC stimulation in animals and humans. In humans, a typical protocol to induce acute effects of tDCS on cortical excitability without generating after effects is applied with a stimulation duration of 4 s [14]. This stimulation protocol induces the respective excitability alterations only during stimulation. tDCS for more than 3 min seems necessary to induce cortical excitability and activity alterations, which outlast stimulation [14]. Hereby, at least within certain limits extended stimulation protocols induce prolongation of the resulting after effects. tDCS from 3 to 7 min results in polarity-specific excitability alterations for some minutes after the end of stimulation, whereas anodal tDCS for 13 min and cathodal tDCS for 9 min results in after effects lasting for about 1 h in the human motor cortex (Fig. 3.1) [13, 15]. This relationship between stimulation duration, and duration of after effects, is however not linear under all conditions: recently it was shown that anodal tDCS for 26 min results in excitability-diminishing, and not -enhancing, after effects, most probably caused by intraneuronal calcium overflow [45]. Thus for the induction of after effects lasting relevantly longer than 1 h after tDCS, which are desirable especially to achieve therapeutic effects in clinical studies, simply prolonging stimulation duration seems not to be the optimal strategy. One alternative might be the repetition of stimulation sessions. Indeed, repeating cathodal or anodal tDCS within a time window of 30 min increases and prolongs the after effects of both, anodal and cathodal tDCS relevantly, for anodal tDCS for more than 24 h after stimulation [45, 46]. On the other hand, tDCS-intervals of 3 and 24 h diminished the after effects of the second protocol in both studies. Thus specific timing is important for prolongation of tDCS effects on cortical excitability. Moreover, the results of these studies suggest that consecutive tDCS protocols

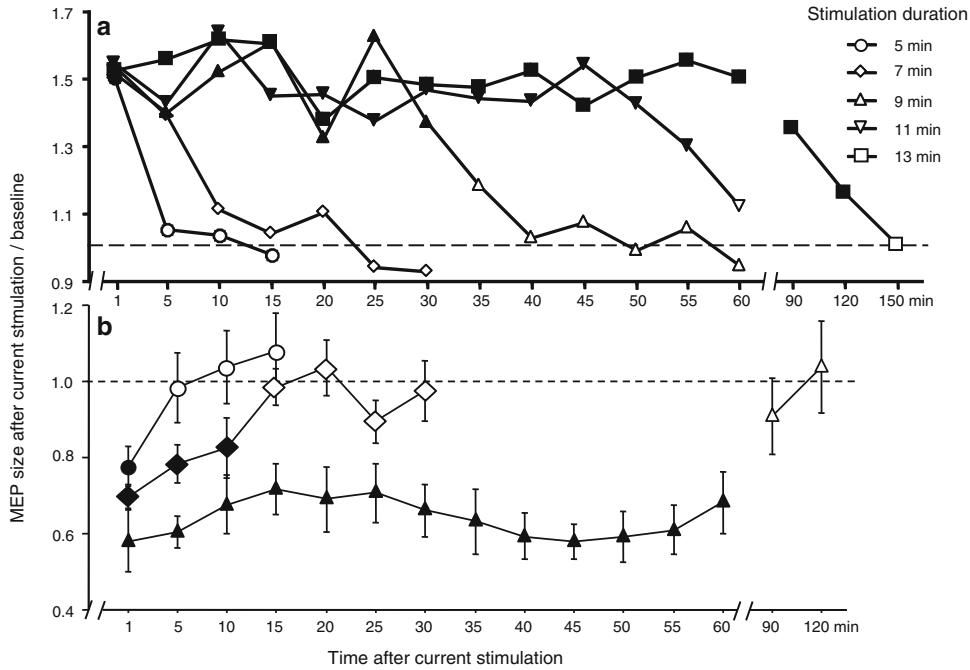

Fig. 3.1 After effects of transcranial direct current stimulation (tDCS) on motor cortical excitability. tDCS of the human motor cortex modulates TMS-elicited MEP amplitudes after stimulation for up to an hour, depending on stimulation duration. Anodal stimulation (**a**) enhances, while cathodal (**b**) diminishes cortical excitability. Note that 5–7-min stimulation result in short-lasting after effects, while prolonged tDCS increases the duration of the after effects over-proportionally ([13, 15], with permission of *Neurology* and *Clin Neurophysiol*)

might interact even when the overt impact on cortical excitability has vanished. Therefore, a sufficient interval between experimental sessions is recommended, when it is not intended to induce cumulative after effects.

Taken together, for tDCS various protocols are available, which differ with regard to stimulation polarity, current density, stimulation duration, as well as electrode size and locations. Dependent on these parameters, stimulation protocols can be customised at least to a certain extent to achieve the desired direction, strength, focality, and duration of effects on cortical activity and excitability. However, systematic studies about optimised physiological and functional effects are rare so far. For functional effects, the development of optimised protocols might have to take into account not only the impact of tDCS on cortical processes, but also the interaction between stimulation, and task-related cortical activity alterations, which might not be trivial in each case. Another future challenge might be the development of individually adapted stimulation protocols, which take inter-individual differences of anatomy and physiology into account. It should also be noted that given the large number of tDCS studies investigating the effects of different parameters, a one-to-one transferability of effects obtained by stimulation of different cortices cannot be taken for granted due to state dependency, anatomical differences, and other factors [47–50]. Therefore titration of stimulation parameters is recommended if no reference is available for a particular tDCS protocol [12, 49–51].

tDCS Physiology

A multitude of studies has been conducted to explore the physiological effects of tDCS in the last years, the majority with the motor cortex as model system initially. The primary motor hand area (M1) has been widely used as a model system in order to study modulation of cortical

excitability by tDCS, because it lies on the cortical convexity of the precentral gyrus with a minimal distance to the scalp surface and therefore can easily be reached with TMS pulses, by which usually excitability is monitored. Furthermore, specific stimulation protocols have been developed for the motor system to monitor different types of intracortical neurons as well as cortical output neurons [52]. Therefore, most of our knowledge about basic physiology of tDCS originates from studies in the human motor cortex. However, physiological effects of tDCS on other cortical areas have also been explored, and beyond TMS, evoked potential measures, EEG, and functional imaging have contributed to our understanding of the physiological background of tDCS. Whereas regional effects of tDCS were in the focus of investigations during the first years, the impact of tDCS on cortical network activity became a new topic of research recently.

Regional Effects of tDCS

Acute Change of Cortical Excitability

The primary mechanism of DC stimulation on the cerebral cortex is a subthreshold modulation of neuronal resting membrane potentials. Current has to enter and leave a given neuron to exert any physiological effects due to physical reasons; thus in any case DC stimulation—independent from the polarity of the electrode over a target area—will have de- and hyperpolarising effects on a given neuron. For the direction of the effects on cortical excitability and activity, it is relevant to acknowledge that the soma and initial axon segment of a neuron are more sensitive for the alteration of membrane potentials via weak electrical fields. Thus the physiological effects of DC stimulation might depend on alteration of these membrane segments [53]. In animal experiments anodal stimulation (i.e. results in an enhancement of cortical excitability, and activity, while cathodal stimulation has antagonistic effects [27, 30]. However, this polarity-dependent effect has to be qualified. As mentioned above, orientation of electrical field relative to neuronal orientation determines the direction of the effects. Accordingly, antagonistic effects of DC stimulation were described not only for subgroups of neurons, but also for specific preparations, such as hippocampal slice experiments [30, 31]. In humans, similar stimulation polarity-dependent effects have been shown for short stimulation durations of few seconds, which do not induce after effects. Anodal tDCS (i.e. stimulation with the anode placed over the target area) enhances cortical excitability, while cathodal stimulation diminishes it in the human motor cortex, as demonstrated by TMS. These effects are largely restricted to global parameters of corticospinal excitability, which are determined by ion channel conductivity, such as single pulse MEP amplitudes induced by medium TMS intensity and recruitment curves. They do not involve major alterations of intracortical facilitation, and inhibition, as monitored by TMS double-pulse stimulation protocols [14, 54]. Accordingly, blocking voltage-gated sodium and calcium channels abolishes the excitability enhancement accomplished by anodal tDCS, but block of glutamatergic NMDA receptors or enhancement of GABAergic inhibition does not affect the acute effects of tDCS [55, 56]. Thus, taken together, the primary effects of tDCS seem to involve polarity-specific membrane potential alterations, but no synaptic effects.

Sustained Change of Cortical Excitability and Activity

In experiments in anesthetised rats, Bindman and colleagues described prolonged enhancements of cortical activity and excitability lasting for hours after anodal stimulation, while cathodal DC stimulation had antagonistic effects, if stimulation was conducted for 5 min or longer [3]. Identically directed after effects of tDCS are accomplished when stimulation duration exceeds 3 min in humans. tDCS over the motor cortex for up to 7 min results in after effects of about 5–10-min duration, while longer stimulation durations for up to 13 min induce excitability alterations stable for about 60–90 min [13–15]. However, the duration of the after effects might differ between cortical regions, with somewhat shorter lasting effects induced by tDCS over the visual cortex [35, 57].

At the cortico-spinal level, tDCS elicits similar after effects as those accomplished during short stimulation. The slope of the recruitment curve is reduced after cathodal tDCS, but enhanced after anodal stimulation [54]. For intracortical effects, anodal tDCS enhances intracortical facilitation and reduces intracortical inhibition, whereas cathodal tDCS induces antagonistic effects [54]. Most probably, these effects are accomplished by combined modulation of motor cortical afferents and motor cortex output neurons with conventional large electrodes, since selective premotor stimulation induces only the above-mentioned intracortical effects in M1, while focal stimulation over M1 with a small electrode only resulted in the above-mentioned cortico-spinal effects [58]. Because block of glutamatergic NMDA receptors abolishes the after effects of tDCS, and the NMDA receptor agonist D-cycloserine prolonged the after effects of anodal stimulation [55, 59], it can be assumed that tDCS induces plasticity of the glutamatergic system, which is calcium-dependent. Calcium dependence of tDCS-induced plasticity has been demonstrated in another study [55]. These results are in accordance with animal experiments, in which it was shown that anodal tDCS enhances neuronal calcium content [60]. Beyond modulation of the glutamatergic system, it has recently been shown that both anodal and cathodal tDCS reduce free GABA in the cortical areas under the electrodes [61]. This result fits with an enhancing effect of both anodal and cathodal tDCS on TMS-induced I-wave facilitation, which is controlled by the GABAergic system [54]. GABA reduction has been shown to enhance glutamatergic plasticity in animal slice experiments, and could have a facilitating effect on tDCS-induced plasticity in humans as well. This might also explain why enhancement of GABAergic receptor activity by lorazepam had no effect on cathodal tDCS-induced plasticity however led to a rebound anodal excitation [56], because benzodiazepines only enhance efficacy of already active GABAergic receptors. It is worth to be mentioned that the induction of plasticity by tDCS seems to require spontaneous neuronal activity, as shown by Fritsch et al. [62]. This makes sense, because neuronal activity in the presence of subthreshold membrane depolarisation will enhance calcium influx relative to pure subthreshold depolarisation, or spontaneous activity alone, which in isolation might not suffice to open NMDA receptor channels (Fig. 3.2).

Beyond the "classic" tDCS protocols, which induce after effects of about 1-h duration, and thus early-phase plasticity, late-phase plasticity, which lasts for more than 24 h after intervention, can be induced by repeated tDCS within a critical time window of 30 min [45] similar to animal experiments [63]. Interestingly, continuous anodal tDCS with doubled stimulation protocol duration results in excitability-diminishing plasticity, and increasing the interval to 3 or 24 h duration diminished the efficacy of the stimulation protocol in the same study. The late-phase LTP-like effects of repeated anodal tDCS depend on the glutamatergic system. The excitability diminution induced by 26 min continuous stimulation might result from intracellular calcium overflow, since calcium channel block abolished this effect [45].

Taken together, it can thus be concluded that the after effects of tDCS depend on glutamatergic mechanisms, and that tDCS-induced reduction of GABA might serve as a "gating" mechanism.

Pharmacology of tDCS

Neuromodulators have a relevant impact on glutamatergic plasticity in animal models, and humans (Fig. 3.2) [64]. In accordance, monoamines and acetylcholine have a prominent impact also on tDCS-induced plasticity. For dopamine, physiological receptor activity is critical for the induction of after effects, because these are abolished by D2 receptor block [65]. Interestingly, increasing dopamine receptor activation by the non-selective precursor L-dopa has dosage-dependent non-linear effects on tDCS-generated plasticity. Whereas low- and high-dosage L-dopa abolish excitability-enhancing, and—diminishing plasticity, medium dosage prolonged the excitability-diminishing after effects of cathodal tDCS, and converted anodal tDCS-induced facilitation into inhibition [66, 67]. Similar effects were accomplished with the D2 agonist bromocriptine [68].

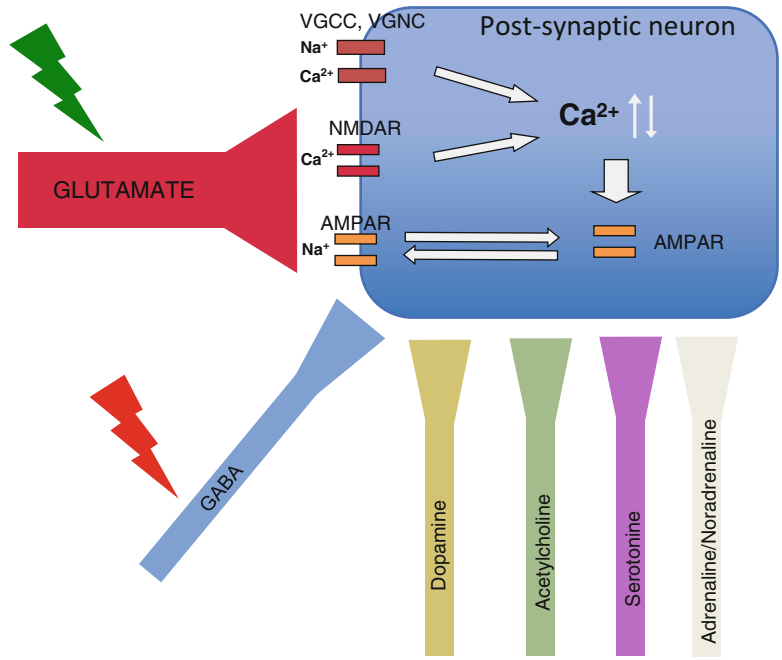

Fig. 3.2 Mechanisms and modulatory effects of tDCS-generated glutamatergic plasticity. In this figure, the main plasticity mechanism of glutamatergic synapses, and the modulatory impact of other neurotransmitters and ion channels are displayed. As far as explored, tDCS has an enhancing effect on glutamatergic neurons (*green arrow*) [55, 119], while several studies showed that they reduce GABA activity (*red arrow*) [61, 120]. The release of glutamate activates NMDA receptors, which have calcium (Ca^{2+}) channel properties, if it is sufficiently strong. Depending on the amount of the consecutive intraneuronal calcium increase, enzyme cascades are activated which result in postsynaptic insertion or removal of glutamatergic AMPA receptors. The amount of post-synaptic AMPA receptors determines if a given activation of a presynaptic neuron results in supra-threshold post-synaptic activation. Thus a modification of AMPA receptor density is the main basis for LTP and LTD. The activity of voltage-dependent calcium channels contributes to intracellular calcium alterations, and the activation of sodium (Na^+) channels to the resting membrane potential, which affects the probability that NMDA receptors are activated, and presynaptic activity results in a postsynaptic action potential. Various neurotransmitters such as GABA, dopamine, acetylcholine, serotonin, adrenaline, and noradrenaline influence these principle mechanisms of action in a complex, sometimes non-linear, way via their specific receptors, and they also have an impact on glutamatergic receptors and ion channels

In contrast, D1 receptor activation under D2 receptor block re-established tDCS-induced plasticity of both stimulation polarities dosage-dependency [69, 70]. Taken together, dopamine has prominent non-linear effects on tDCS-induced plasticity, which depend on dosage, and receptor subtype activity. For the cholinergic system, enhancement of global cholinergic activation resulted in a similar effect as medium-dosage L-dopa on tDCS-generated plasticity, i.e. a slight prolongation of cathodal tDCS-induced excitability diminution, and a conversion of anodal tDCS-induced after effects from facilitation into excitability reduction [71]. At least for anodal tDCS, these effects depend on activation of nicotinic receptors, since nicotine and the nicotinic α4β2 agonist varenicline had a similar effect on tDCS-induced plasticity [72, 73]. Furthermore, it was shown recently that this modulation depends on glutamate and calcium influx [74].

For serotonin, activation by a selective serotonin reuptake inhibitor (SSRI) facilitated and prolonged the after effects of anodal tDCS, and converted plasticity induced by cathodal stimulation into facilitation [75]. This effect was further enhanced after long-term application of SSRI [76]. So far, dosage-dependent effects of serotonin and acetylcholine/nicotine on tDCS-induced plasticity have not been explored. However, the results show a prominent and complex impact of

neuromodulators on tDCS-induced plasticity, which might e.g. be relevant for treatment of patients suffering from neurological and psychiatric diseases, where neuromodulator activity is often pathologically altered and counteracted upon by pharmacological intervention.

tDCS Effect on Cortical Regions Other Than M1

Most of the above-mentioned studies were performed in the human primary motor cortex, but the effects of tDCS are not restricted to this region. In the last years, numerous studies have been conducted, which show a similar functional or physiological impact of tDCS on a multitude of cortical regions. Neurophysiological effects have been demonstrated for the visual cortex, where anodal and cathodal tDCS have similar effects on cortical excitability as motor cortex stimulation, however antagonistic effects were also observed when the return electrode was positioned at the neck [32]. tDCS over the visual cortex results in shorter duration of the after effects, as compared to stimulation over M1. For tDCS of the somato-sensory cortex, anodal tDCS increased respective SEP amplitudes for at least 60 min after stimulation in one study [77], and cathodal tDCS reduced those in another one [78]. For auditory cortex stimulation, anodal tDCS over the temporal, and cathodal tDCS over the temporo-parietal cortex enhanced the respective evoked potentials [79]. Recent development of concurrent TMS-EEG recordings allows the investigation of physiological mechanisms of tDCS via direct monitoring of cortical excitability. Anodal tDCS increased mean field power of TMS-evoked cortical potentials both during and following tDCS over the posterior parietal cortex [80]. Such methodological advance will further contribute to the understanding of tDCS physiology into larger detail.

Inter-regional Effects of tDCS

Apart from the regional effects of tDCS under the stimulation electrodes, remote effects on topographically distant cortical and subcortical areas were described relatively early [37]. However, it was unclear whether those effects are caused by physiological spreading of cortical activity or by physical current spread. Simulation studies, although not physiologically validated so far, are in favour for at least a partial contribution of spread of current flow [39]. In addition, clear physiological effects of tDCS on remote areas have been described. Premotor anodal tDCS enhances intracortical facilitation of M1, most probably due to the activation of premotor-primary motor cortex afferents [58], and combined dorsal premotor and supplementary motor area (SMA) stimulation alters motor and somatosensory evoked potentials [81]. For parietal cortex stimulation, anodal tDCS enhanced, but cathodal tDCS reduced MEP amplitudes. Moreover, anodal tDCS over the posterior parietal cortex increased both, ipsilateral M1 intracortical inhibition and facilitation, as well as parietal-motor cortical connectivity [82]. Furthermore, anodal tDCS over the posterior parietal cortex increased cortico-cortical potentials elicited by TMS in both local and surrounding or contralateral regions [80].

Recently, functional connectivity approaches have been applied to explore cortical network alterations induced by tDCS. For motor cortex stimulation under resting conditions, a fMRI study revealed that nodal minimum path length increased after anodal tDCS over M1, which means that functional connectivity of this area with topographically distant regions of the whole brain significantly decreased. In contrast to this generally reduced whole brain connectivity of M1, functional connectivity was enhanced between the primary motor cortex on the one hand, and premotor and superior parietal areas on the other [83]. In another study, cathodal tDCS of the primary motor cortex increased functional connectivity between the stimulated M1, and the contralateral M1 and premotor cortices [84]. A similar effect of tDCS was described for anodal stimulation combined with motor practice in an EEG study, where functional connectivity was enhanced between primary motor, premotor, and sensorimotor areas in the high gamma band [85]. Moreover, anodal tDCS of the primary motor cortex alters cortico-subcortical connectivity of the motor cortex at rest. Specifically, it was

shown to enhance connectivity with the ipsilateral caudate nucleus, and thalamus [86]. Alterations of intrinsic motor cortex connectivity by tDCS have also been demonstrated: cathodal stimulation increased local connectivity, most likely due to cortical noise reduction accomplished by the respective excitability and activity diminution, while anodal tDCS enhanced long-distance connectivity within this area [87]. Therefore it can be concluded by the results of these studies that motor cortex tDCS alters the connectivity of large parts of the motor network.

Beyond tDCS of the motor cortex, stimulation of the dorsolateral prefrontal cortex has been demonstrated to induce widespread alterations of functional connectivity, including the default mode network, and attention-related networks in healthy subjects [88, 89].

To summarise, in addition to its regional effects under the stimulation electrodes, tDCS has prominent effects on functional networks at both cortical and subcortical levels. The relevance of these network alterations for cognition and behaviour needs to be explored in future studies.

tACS

tACS is a variant of tES, which modulates oscillatory brain activity via application of alternating currents. Beyond different current wave characteristics, other stimulation parameters, such as electrode arrangement and current intensity, are comparable to those of tDCS. tACS is presumed to affect neuronal membrane potentials by subthreshold (i.e. no action potential generation) oscillatory electrical stimulation with specific frequencies, and to interact with ongoing rhythmic cortical activities. Its main effect is a modulation and entrainment of ongoing rhythmic brain activity, and not induction of plasticity. However, for specific stimulation frequencies, also neuroplastic excitability modifications have been described [90–93]. By its modulating effect on task-related oscillatory brain activity, tACS is a useful tool to investigate the causality of physiological phenomena for cognition and behaviour.

tACS Protocols and Effects

The application of tACS employs a similar set-up as conventional tDCS, except for the polarity of stimulation. While anodal or cathodal stimulation in case of tDCS describes the constant polarity of an electrode during the whole intervention and determines the direction of effects, the polarity of the two electrodes in tACS alternates every half cycle. The efficacy of tACS is mainly determined by the intensity, frequency, and phase of the stimulation protocol, which results in modulation of cortical excitability and/or oscillations.

Physiological Effects of tACS

So far the number of studies exploring the neurophysiology of tACS remains limited. Similar to tDCS, tACS is assumed not induce cortical activity, but to modulate spontaneous activity via subthreshold membrane polarisation. One potential relevant effect is modulation of spontaneous oscillatory activity. In accordance, computational modelling suggests that external electric stimulation with relatively low amplitude, as applied in tACS, is indeed sufficient for synchronising oscillatory activity of neural networks. Animal studies demonstrated synchronisation of neuronal spike activity corresponding to the externally applied frequency of oscillations within different frequency bands [94, 95], a phenomenon termed entrainment. Similar effects were obtained in the human brain. When tACS was applied within the individual alpha frequency for 10 min over the occipital lobe, the corresponding spectral power was facilitated, and this effect outlasted the intervention [96, 97]. Likewise, it was shown that by prefrontal stimulation in the gamma frequency range, but not at other frequencies, during REM sleep, where gamma band activity is presumed to have important functional relevance, brain activity in these frequencies was enhanced (Fig. 3.3) [98]. Thus taken together, these studies deliver evidence for a modulatory effect of tACS on spontaneous cortical oscillatory activity.

Beyond its impact on oscillatory brain activity, tACS can also affect cortical excitability. These effects seem critically to depend on stimulation frequency, and differ between online and after

effects. For the primary motor cortex, online effects on cortical excitability were selectively obtained by 20 Hz stimulation, but not by tACS within other physiological frequency bands. Since 20 Hz is the predominant frequency in the resting motor cortex, this result fits nicely with the modulatory impact of tACS on oscillatory brain activity [99]. For after effects, even longer tACS durations (2–10 min) within similar frequency ranges showed no effect on MEPs [91, 100]. However, tACS over M1 with 140 Hz and 0.63 A/m^2 for 10 min significantly enhanced cortical excitability during and after stimulation [90]. In the same study, lower stimulation intensity with 0.25 A/m^2 resulted in a decrease of excitability. With even higher frequency stimulation between 2 and 5 kHz, tACS (0.2 A/m^2 for 10 min) induces MEP enhancements lasting for more than 1 h [101]. To summarise, tACS may non-linearly alter cortical excitability during and after intervention. The presence and direction of this effect depends on stimulation frequency, intensity, and duration.

tACS Effects on Cognition and Behaviour

The modulatory impact of tACS on oscillatory cortical activities has an impact on cognition and behaviour. A couple of studies were conducted for uni-regional tACS to explore the relevance of oscillatory activity of a specific area for performance. A couple of studies were performed in the visual domain. For visual perception, stimulation with beta or alpha frequency significantly reduced phosphene thresholds in illuminated or dark conditions respectively [102]. Since beta frequencies are predominant in illuminated surroundings, whereas alpha frequencies dominate under light deprivation, this study suggests that tACS can modulate visual perception via its impact on naturally occurring cortical oscillations. In another study with tACS over V1, contrast perception was enhanced under high gamma (60 Hz) frequency stimulation, while spatial attention remained unchanged [103], underscoring the region-specific effect of tACS. Beyond visual areas, other cortical modalities have been also shown to be affected by tACS. Somatosensory tactile perception was enhanced specifically with tACS over the sensory cortex in the alpha (10–14 Hz) and high gamma (52–70 Hz) range [104]. For the motor system, 20 Hz tACS slowed down voluntary movement but 70 Hz stimulation enhanced motor performance [105, 106], while another study showed increased behavioral variability following 10 Hz tACS [107]. tACS over M1 also facilitated motor sequence learning but only when applied at alpha frequency, which is associated with the inhibition of irrelevant stimuli during cognitive tasks [106]. In addition to relative elementary cognitive processes, tACS was employed to alter more complex functions. Working memory performance was altered by tACS in the theta frequency range (6.5 Hz) over the left DLPFC [108], and sleep-dependent consciousness levels were affected by tACS in the gamma frequency range (Fig. 3.3) [98]. Similarly, rhythmic stimulation with gamma frequency over the left middle frontal gyrus enhanced fluid intelligence in another study [109].

In the above-mentioned studies, tACS was applied with standard frequencies across subjects. However, individual alignment of stimulation parameters to physiological oscillations might be also a promising approach. Cecere and co-workers [110] explored the relevance of adjustment of tACS over V1 to individual oscillatory activity in a cross-modal sound-induced visual illusion task. tACS was applied with the individual alpha frequency or ±2 Hz . As compared to stimulation with individual alpha frequency, the deviating stimulation protocols enlarged or shrinkened the illusion perception time window, demonstrating a critical impact of specific alpha frequency on this perceptual process [110].

Furthermore, individually adjusted tACS also offers the potential to modulate peripheral and periodic motor movements such as tremor with individually adjusted frequency alignment [111]. In that study, stimulation was not only adjusted to individual frequency, but also phase-locked to oscillatory activity. tACS in phase with oscillatory activity enhanced, whereas antagonistic stimulation reduced tremor considerably, presumably via phase cancellation effects. Taken together, these studies show that tACS adjusted to physiological oscillations is able to modulate cognitive

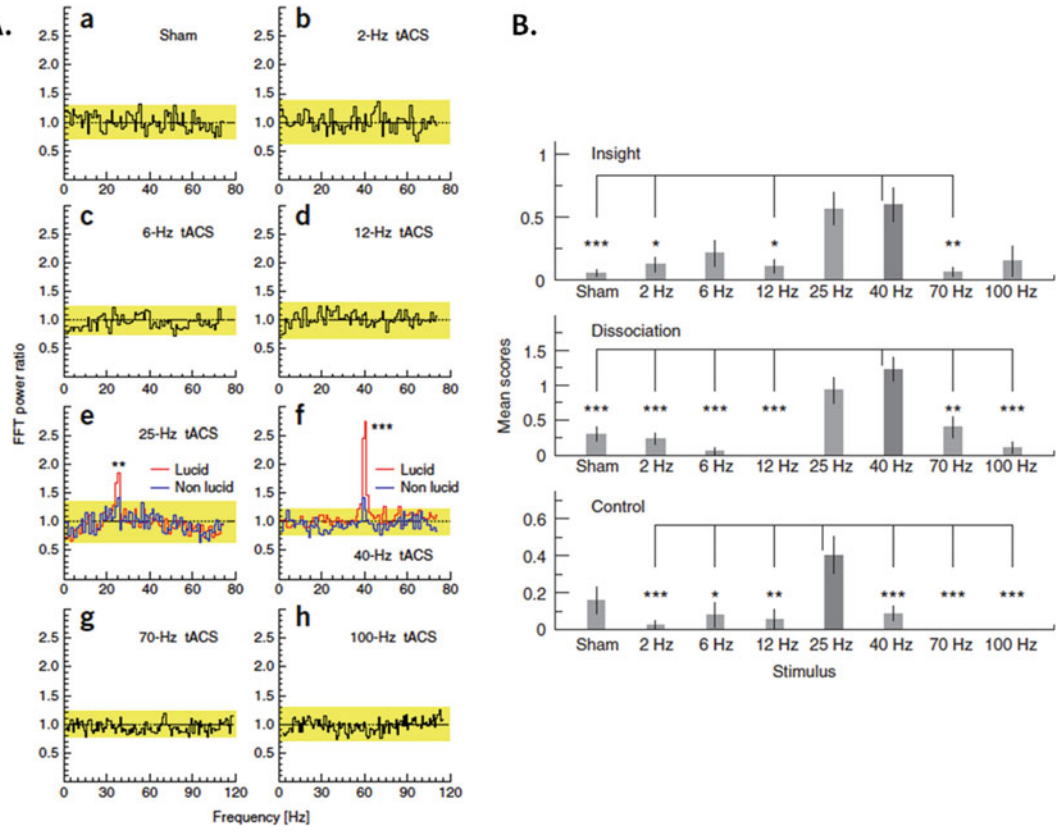

Fig. 3.3 Enhancing self awareness during dreaming with high-gamma tACS. (**a**) Grand average FFT power ratios of activity during (phase II) versus activity before stimulation (phase I) for the different stimulation conditions: sham, 2, 6, 12, 25, 40, 70, and 100 Hz. *Yellow* shading represents mean values ±2 s.e. Any excursions outside of this range are considered to be significant at least at the $P<0.05$ level. Note that, with 40 and 25 Hz stimulation, lucid dreams (*red line*) were accompanied by a significantly larger increase in the respective frequency band than non-lucid dreams (*blue line*). (**b**) Selected contrasts of mean scores (s.e.) for the LuCiD factors insight, dissociation, and control. The contrasts for insight and dissociation were strongest during stimulation with 40 Hz (40-Hz reference condition is *shaded*, *top* and *middle frame*). Control was increased most during stimulation with 25 Hz (25-Hz reference condition is *shaded*, *bottom frame*). ***$P<0.001$, **$P\leq0.01$, *$P\leq0.05$ (Voss et al. 2014, with permission of Nature Neuroscience)

processes of different complexity in different domains, and that sophisticated approaches like individual adjustment of tACS frequency and phase-locked stimulation are promising approaches to improve insight about the relevance of regional oscillations for performance.

Beyond exploration of regional effects, tACS is suited to explore the relevance of oscillatory brain activity for task-relevant interactions between cortical areas. Specifically, tACS offers the opportunity to explore the causal relevance of functional oscillatory connectivity for task performance via combined stimulation of distant, but functionally connected cortical areas. A couple of studies demonstrated this effect for perceptual tasks. Anti-phasic tACS over parietal and occipital areas in the alpha frequency range (6–10 Hz), which increases a presumed inhibitory alpha effect, reduced the performance of a visual detection task [112]. Moreover, a phase-specific tACS effect was observed by anti-phasic (180° difference) 40 Hz stimulation bilaterally over the parieto-occipital junction. Here, motion perception was altered possibly via modulation of interhemi-

spheric functional coupling in the gamma range [113, 114]. In the latter study, high-density tACS (HD-tACS), with the same electrode montage as HD-tDCS, was applied in order to separately adjust different phase angles of the electrodes placed over the two hemispheres. Beyond these elementary processes, also modification of more complex cognitive tasks was explored. For working memory performance, it was shown that parietal and frontal areas connect during task performance in the theta frequency range. In accordance with the hypothesis that synchronisation between both areas is causally relevant for task performance, synchronised stimulation with 6 Hz frequency improved reaction time, whereas antagonistic tACS diminished performance [115]. Likewise, interhemispheric anti-phase tACS over F3/F4 with slow-wave frequencies (0.75 Hz, current density 5.17 A/m^2) during a nap reduced activity in Delta-frequency bands, which was correlated with impaired memory recall [116]. Turning to examples at social cognitive processes, in an initial EEG study it was demonstrated that gamma phase-coupling between the medial fronto-polar and superior parietal cortex correlated with the accuracy of making decisions based on subjective preferences [117]. This correlative evidence was causally confirmed with multi-site tACS, where it was shown that transcranially inducing decoupling between the fronto-polar and parietal regions identified in the EEG study indeed impaired the ability of human participants to correctly choose between alternatives containing primary rewards [118].

Thus taken together, tACS is able to modulate cognitive functions, and beyond regional modulation of oscillatory activity, also specific network alterations are suited to modify functional connectivity and performance.

General Remarks

Since tDCS and tACS have been re-introduced as a tool to induce acute and neuroplastic alterations of cortical excitability and activity and to modulate cognitive processes, an increasing number of studies has been conducted to develop protocols enhancing the efficacy of stimulation, and to explore the physiological basics of the effects. For tDCS, the determinants of efficacy, such as stimulation intensity, duration, and repetition intervals have been identified, and protocols which allow a more focal stimulation have been developed. It has been shown that the dependence of tDCS efficacy on these stimulation parameters is not linear in each case. Future work should focus on further optimising stimulation protocols, which will be important especially for clinical applications, where stable alterations of cortical excitability and activity are needed. Moreover, given the partial non-linearity of the effects, exploring optimal combinations of stimulation with performance would be an important, but not trivial, topic of future research. Since most of the studies reported in this review were conducted in the primary motor cortex, the transferability of the respective results to other cortical areas has yet to be explored. With regard to the mechanisms of action, pharmacological, TMS, EEG, and functional imaging studies have revealed the main physiological mechanisms of tDCS, i.e. the primary effect of membrane polarisation, the dependence of the after effects from alterations of glutamatergic synapses, and the complex alteration of tDCS-induced plasticity by neuromodulators. Furthermore, it became increasingly clear recently that the effects of tDCS are not only restricted to the area under the electrodes. The stimulation also induces alterations of connectivity within cortical and cortico-subcortical networks. As for tACS, experiments in both animals and humans, as well as results from computational simulation increased insights into the basic physiology. However, the development of tACS protocols is still in a relatively early state as compared to tDCS. Further investigations including the combination of neurophysiological recordings and neuroimaging techniques will be desirable to improve our mechanistic understanding. Although knowledge about the physiological basis of tDCS and tACS is incomplete, respective studies provide a basis, which might also be important for evaluating new fields of application in future.

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Computer-Based Models of tDCS and tACS

4

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Abstract

Transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) are noninvasive neuromodulatory techniques that deliver low-intensity currents facilitating or inhibiting spontaneous neuronal activity. These techniques have a number of advantages that have been applied in clinical settings; in particular, tDCS/tACS dose in principle is easily customized by varying electrode number, position, size, shape, and current. However, the ability to leverage this customization depends on how tDCS/tACS dose modulate the underling brain current flow. This relationship is not simple and can benefit from the use of computational models of current flow, personalized to individual subjects and cases. Tools for modeling range from Finite Element Method models to stand-alone GUI based software for clinicians. Many software packages can load individual's MRI scans, allowing individualized therapy design. However, the challenge remains to design and interpret these models while remaining aware of their limitations. Current flow models alone cannot "make dose decisions," but rather inform the rational design of electrotherapy. This is evidenced in exemplary studies combining computer modeling and clinical data, several examples of which are outlined in this chapter. Though modeling software is now widely available, newer generations of algorithms promise more precision and flexibility, and thus it is predicted that with increased validation, dissemination, simplification and dissemination of modeling tools, computational forward models of neuromodulation will become useful tools to guide the optimization of clinical electrotherapy. Essential for this adoption and refinement is an appreciation by clinicians of the uses and limitations of computational models, and conversely understanding by engineers and programmers of what software functions are relevant to clinical practice.

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Overview of Computational Models of Noninvasive Neuromodulation

This chapter introduces the rationale and approach behind modeling tDCS/tACS as well as the technical development and limitations of models currently in use. This chapter is intended to provide a broad introduction for both clinical researchers and engineers interested in translational work to develop and apply computational models of customized tDCS/tACS. A central premise of this chapter is that models cannot "make decisions" about tDCS/tACS, but rather are tools that inform how protocols should be interpreted and optimized. As such, it is incumbent on clinical researchers to appreciate the function and limitations of models, and conversely for programmers to consider the goals of the end user (investigator) when deciding what functionality is relevant for their modeling software.

Conventionally, stimulation techniques can be grouped into two categories: protocols that *induce* activity of neurons (supra-threshold), and protocols that exert *modulatory* effects on ongoing neuronal activity and excitability (sub-threshold). For a complete historical context of terminology see ref. [1]. The first group includes high-intensity short-pulse transcranial electrical stimulation (TES), transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and paired associative stimulation (PAS). The second group, includes forms of low-intensity sustained tES including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial pulsed current stimulation (tPCS), and transcranial random noise stimulation (tRNS). The electric field intensities produced in the brain by supra-threshold techniques are two orders of magnitude above sub-threshold techniques [2–10] which allows for action potentials to be triggered [11]. However, it is important to recognize that supra-threshold techniques ultimately affect behavior by modulating endogenous networks while sub-threshold techniques can influence firing in the active system [12]. Based on the growing evidence that current delivered to specific brain regions can promote desirable plastic changes, stimulation techniques are emerging as promising tool in symptom management [13–15]. However, stimulation should be applied in a manner that is within safe and well-tolerated parameters. Complimentary to other brain stimulation approaches (Fig. 4.1), tDCS and tACS have been gaining considerable interest because they are well tolerated, can be used as add-on therapies, and have low maintenance costs [16]. This review focuses on low-intensity approaches and specifically tDCS and tACS (as they are most commonly used clinically); however, many of the conclusions of this chapter can be generalized.

In contrast to pharmacotherapy, noninvasive electrotherapy offers the potential for both anatomically specific brain activation and temporal control. Anatomical targeting can be achieved through the rational selection of electrode number, shape, and position. In training applications such as rehabilitation, neuromodulatory techniques such as tDCS/tACS can combine focal stimulation with specific training to reinforce a particular region of activation [17] including with "functional targeting" [18, 19]. Temporal control is possible due to the instantaneous delivery of electricity to the brain through the scalp. There is no electrical "residue" since the generated brain current disappears as soon as stimulation is paused. The tDCS/tACS dose can also be modeled for specific subjects and targeted in ways not possible with other interventions. Specifically, the "dose" of electrotherapy (see ref. [5] for definition) is readily adjustable by determining the location of electrodes (which

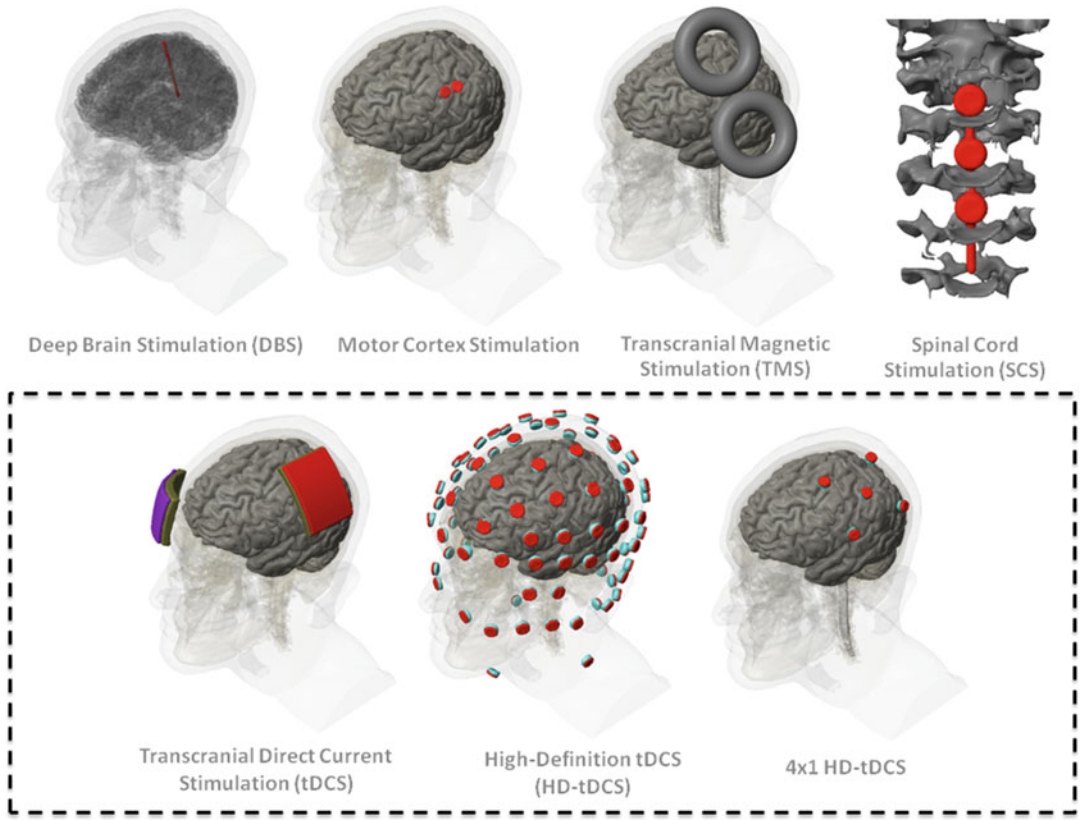

Fig. 4.1 Comparable stimulation techniques: deep brain stimulation, motor cortex stimulation, transcranial magnetic stimulation, and spinal cord stimulation (*top row*); classic transcranial direct current stimulation (tDCS) via sponge pads, optimized high definition-tDCS (HD-tDCS), and 4 × 1 HD-tDCS (*bottom row*). Transcranial direct current stimulation is an increasingly popular investigational form of brain stimulation, in part, due to its low cost, portability, usability, and safety. However, there are still many of unanswered questions. The number of potential stimulation doses is practically limitless. Stimulation can be varied by simply changing the electric current waveform and electrode shape, size, and position. These variations can thus be analyzed through computational modeling studies that have resulted in montages such as HD-tDCS and 4 × 1 HD-tDCS

determines spatial targeting) and selecting the stimulation waveform and intensity (which together determines the nature and timing of neuromodulation). Thus, a single programmable electrotherapy device can be simply configured to provide a diversity of dosages. Though this flexibly underpins the utility of neuromodulation, the myriad of potential dosages (stimulator settings and combinations of electrode placements) makes the optimal choice difficult to readily ascertain. The essential issue in dose design is to relate each externally controlled dose with the associated brain regions targeted (and spared) by the resulting current flow—and hence the desired clinical outcome. Computational forward models aim to provide precisely these answers (Fig. 4.2), and thus need to be leveraged in the rational design, interpretation, and optimization of neuromodulation.

The precise pattern of current flow through the brain is determined not only by the stimulation dose but also by the underlying anatomy and tissue properties. Thus, in predicting brain current flow using computational models, important to not only precisely model both the stimulation itself, but also the relevant anatomy upon which it is delivered on an individual basis. The latter issue remains an area of ongoing technical development and is critical to establishing the clinical utility of these models. For example, cerebral

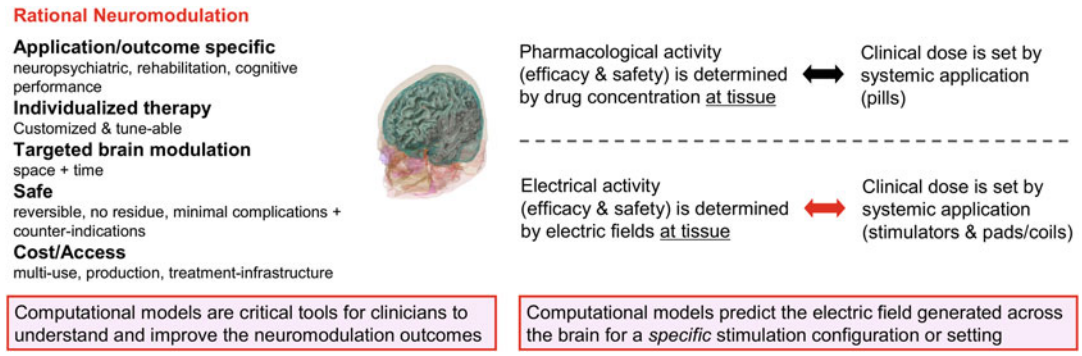

Fig. 4.2 Role of computational models in rational electrotherapy: (*left*) Neuromodulation is a promising therapeutic modality as it affects the brain in a way not possible with other techniques with a high degree of individualized optimization. The goal of computational models is to assist clinicians in leveraging the power and flexibility of neuromodulation (*right*). Computational forward models are used to predict brain current flow during transcranial stimulation to guide clinical practice. As with pharmacotherapy, electrotherapy dose is controlled by the operator and leads a complex pattern of internal current flow that is described by the model. In this way, clinicians can apply computational models to determine which dose will activate (or avoid) brain regions of interest

spinal fluid (CSF) is so highly conductive (a preferred "super highway" for current flow) that details of CSF architecture profoundly shape current flow through adjacent brain regions. Especially relevant for rehabilitative applications is the recognition that individual anatomical idiosyncrasies can result in significant distortions in current flow. This is especially apparent when skull defects and brain lesions occur.

Methods and Protocols in the Generation of Computational Forward Models of tDCS/tACS

This section outlines the technical steps and pitfalls of computational models for tDCS/tACS and so aimed primarily to the engineers and programmers developing these tools. However, clinicians and experimentalists interested in understanding the technical challenges and limitations of modeling will also benefit from these sections, consistent with our emphasis that these are tools to be used by experientialists and clinicians—and only by understanding the nature and limits of tools can they be applied meaningfully.

During tDCS/tACS, current is generated in the brain [20]. While there are intrinsic electric fields in the brain as recording during electroencephalogram (EEG), models of tDCS/tACS predict an induced electric field given a source (the stimulation electrodes). Solving for the induced fields from a known source and vice-versa is what technically differentiates stimulation models from source localization models used in EEG. These modeling methods are dubbed the "forward" and "inverse" models respectively.

Because different electrode montages result in distinct brain current flow, researchers and clinicians can, in principle, adjust the montage to target or avoid specific brain regions in an application specific manner. Though tDCS/tACS montage design often follows basic rules-of-thumb (e.g., "increased/decreased excitability" under the anode/cathode electrode for tDCS and "boost oscillating activity" under one electrode for tACS), computational forward models of brain current flow provide more accurate insight into detailed current flow patterns and in some cases, can even challenge simplified electrode-placement assumptions.

We note two common over-simplifications using rule-of thumb for tDCA/tACS dose design. For example, clinical tDCS studies are often designed by placing the anode electrode directly over the targeted region desired to be excited, while the cathode electrode is placed over a far removed region from the target to avoid unwanted

reverse effects. This region could be the contralateral hemisphere or in some cases even extracephalic locations like the neck, shoulder or the arm. However, the cathode remains active and an extracephalic location means extensive deep and mid brain current flow. More generally, all regions *between* electrodes are stimulated. As another example, researchers have used smaller stimulation electrode sizes and bigger reference electrode sizes to offset the focal limitations of tDCS/tACS; while clinical neurophysiology has established that electrode size can "shape" the pattern of current flow [21], the dispersion caused before current reaches the brain limits the role of electrode size [22, 23].

With the increasingly recognized value of computational forward models in informing tDCS/tACS montage design and interpretation of results, there has been recent advances in modeling tools and proliferation of technical publications, e.g., [6, 7, 10, 23–36]. At this stage, the limitations of computational models seem to rest largely in the clinical and experimental applications, including the continuing validation and refinement of modeling parameters (e.g., conductivities) and results. Nevertheless, careful consideration of the development of modeling techniques can provide insight on how models can be leveraged.

The work done by Miranda and Lomarev [32] was among the earliest numerical modeling efforts that specifically examined tDCS montages and intensities in the context of a "spherical head." Later, the focality of cortical electrical fields was compared across small electrode configurations proposed to achieve targeted modulation [29]. Wagner et al. (2006) was the first CAD (Computer Aided Design) rendered head model that analyzed current density distributions for various montages, including healthy versus cortical stroke conditions. The more recent modeling efforts have been mostly MRI derived. Oostendorp et al. [33] was the first to consider anisotropy in the skull and the white matter, specifically the conductivity of these tissues were a function of direction/fiber alignment. Datta et al. [27] built the first high-resolution head model with gyri/sulci specificity. Suh et al. [7] concluded that skull anisotropy causes a large shunting effect and may shift the stimulated areas. Sadleir et al. [35] compared modeling predictions of frontal tDCS montages to clinical outcomes. Datta et al. [28] studied the effect of tDCS montages on TBI and skull defects. Parazzini et al. [34] was the first to analyze current flow patterns across subcortical structures. Dmochowski et al. [37] showed how a multi-electrode stimulation can be optimized for focality and intensity at the target.

Recent efforts have focused to build patient-specific models and compare modeling predictions to experimental outcomes. In considering new electrode montages, especially in potentially vulnerable populations (e.g., skull damage, children), forward models are the main tool used to relate the externally controllable dose parameters (e.g., electrode number, position, size, shape, current) with resulting brain current flow. While the specific software applications can vary across groups, in general, the approach and workflow for model generation follow a similar pattern (Fig. 4.3).

The steps for generating high-resolution, anatomically specific, forward models of noninvasive neuromodulation are adapted from extensive prior work on computational modeling. These involve: (1) Demarcation of individual tissue types such as bone, cerebrospinal fluid, and brain from high-resolution anatomical data (e.g., magnetic resonance imaging slices obtained at 1 mm slice thickness) using a combination of automated and manual segmentation tools. Specifically, from the perspective of stimulating current flow, it is necessary to distinguish tissues by their resistivity; the majority of the effort that has gone into the development and implementation of models has involved this step (see also next section). The number and precision of the individual masks obtained is pivotal for the generation of accurate 3D models in order to capture critical anatomical details that may influence current flow. (2) Modeling of the exact physical properties of the electrodes (e.g., shape and size) and precise placement within the segmented image data (i.e., along the skin mask outer surface). (3) Generation of accurate meshes (with a high quality factor) from the tissue/electrode masks, whilst preserving resolution of subject anatomical data. The generation of meshes is a

process where each mask is divided into small contiguous 'elements' which allow the current flow to then be numerically computed—hence the term "Finite Element Method" stimulations. In modern efforts, the number of elements in tDCS models can exceed tn million. (4) Resulting volumetric meshes are then imported into a commercial finite element (FE) solver. (5) At this step, resistivity is assigned to each mask (every element in each mask) and the boundary conditions are imposed, including the current applied to the electrodes. (6) The standard Laplacian equation is solved using the appropriate numerical solver and tolerance settings. In modern efforts the degrees of freedom can exceed 14 million. (7) Data is plotted as induced cortical electric field or current density maps (Fig. 4.3).

Though each of the above steps is required for high-resolution modeling, they rely on personnel technical expertise and hence result in variation in protocols across groups and publications [6, 7, 10, 23–36, 38, 39]. These variations are relevant to clinical practice only in the sense that they change predictions in current flow that meaningfully effect dose decisions. The sources and impact of these variations are addressed in the next section.

Initial models of transcranial current flow assumed simplified geometries such as concentric spheres that could be solved analytically as well as numerically [29, 32]. Such concentric sphere models are useful to address generic dose questions such as the global role of inter-electrode distance, electrode montage, or the relationship between electrode and brain current density, precisely because they exclude regional anatomical differences. More realistic models started to include explicit representation of human anatomy [36]. Datta et al. [27] published the first model of tDCS with gyri resolution, illustrating the importance of anatomical precision in determining complex brain current flow. Addition of diffusion tensor imaging (DTI) incorporates anisotropic properties in the skull and the white matter regions [7]. Fine resolution of gyri/sulci lead to current "hotspots" in the sulci, thereby reinforcing the need for high-resolution modeling [6]. An open-source head model

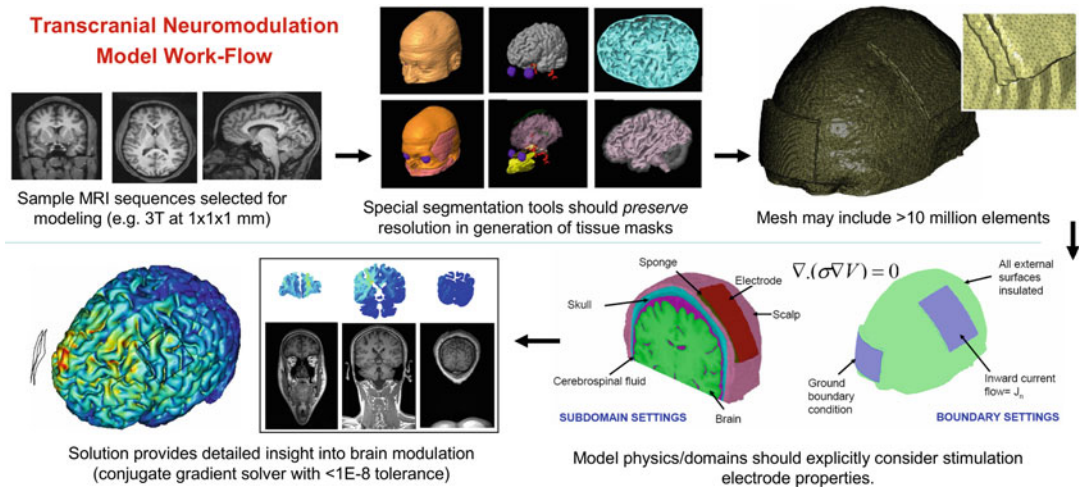

Fig. 4.3 Imaging and computational work-flow for the generation of high-resolution individualized models: Though the specific processes and software packages will vary across technical groups and applications, in each case high-resolution modeling initiated with precise anatomical scans that allow demarcation of key tissues. Tissues with distinct resistivity are used to form masks. These masks along with the representation of the physical electrodes are meshed to allow FEM calculations. The boundary conditions (generally simply reflecting how the electrodes are energized) and the governing equations (related to ohms law) are well established. The reproduction of the stimulation dose and the underlying anatomy thus allow for the prediction of resulting brain current. These current flow patterns are represented in false-color map and analyzed through various post-processing tools

comprising of several different tissue types was adapted to analyze current flow through cortical, subcortical, and brain stem structures [34]. Such models help determine whether current of sufficient magnitude reaches the deeper subcortical structures.

To this day, only a few studies have attempted to more directly link clinical outcomes and model predictions—and thus validate model utility. Clinical evaluation was combined with model predictions to investigate the effects of different montages on clinical disorders such as fibromyalgia [31]. Patient-specific models have been used to retrospectively analyze the therapeutic success of a given experimental stimulation montage [26] and compare model predictions with patterns of activation revealed by functional magnetic resonance imaging (fMRI) [30]. Postmortem "current flow imaging" has also used to validate general model prediction [40] and individualized tDCS models were validated with simultaneous scalp potential recordings [41]. In response to the anatomical localization problem of traditional tDCS, a more focal 4×1 high-definition tDCS was developed through computational models and then validated in a clinical neurophysiology trial [42]. The focal delivery of current using the 4×1 montage was further validated using suprathreshold TES) [43]; moreover, the models predicted individual variation in sensitivity to currents delivery among typical adults of >2×. These example applications open the door for potentially customizing tDCS on a subject-to-subject basis within the clinical setting [44].

In a subsequent section we describe avenues for clinicians to practically access computational modeling tools, but precisely because this is now a "standard" models approach, limitations of varied approaches need to be understood. If tDCS continues to emerge as an effective tool in clinical treatment and cognitive neuroscience, and concurrent modeling studies emphasize the need for rational (and in cases individualized) dose decisions, then it will become important for tDCS researchers to understand the applications (and limitations) of computational forward models [45].

Pitfalls and Challenges in the Application and Interpretation of Computational Model Predictions

Computational models of tDCS range in complexity from concentric sphere models, to biologically inspired synthetic shapes, to high-resolution models based on individuals MRI. The appropriate level of modeling detail depends on the clinical question being asked, as well as the available computational resources available. Whereas simple geometries (e.g., spheres) may be solved analytically [46], realistic geometries employ numerical solvers. Regardless of complexity, all forward models share the goal of correctly predicting brain current flow during transcranial stimulation to guide clinical therapeutic delivery. Special effort has recently been directed towards increasing the precision of tDCS models. However, it is important to note that increased model complexity does not necessarily equate with greater accuracy or clinical value.

To meaningfully guide clinical utility, attempts to enhance model precision must rationally balance detail (i.e., complexity) and accuracy. (1) Beginning with high-resolution anatomical scans, the entire model workflow should preserve precision. Any human head model is limited by the precision and accuracy of tissue segmentation (i.e., "masks) and of the assigned conductivity values. One hallmark of precision is that the cortical surface used in the final FEM solver should capture realistic sulci and gyri anatomy. Models incorporating gyri level resolution, starting with Datta [27], clearly show that current is "clustered" in local hot spots correlated with cortical folding. (2) Simultaneously, a priori knowledge of tissue anatomy and factors known to influence current flow should be applied to further refine segmentation. We believe that of critical importance are discontinuities not present in nature that result from limited scan resolution, notably both unnatural perforations in planar tissues (e.g., ventricular architecture, discontinuities in CSF where brain contacts skull, misrepresented skull

fissures,) and microstructures (e.g., incomplete or voxelized vessels) can produce significant deviations in predicted current flow. Moreover, because of the sensitivity of current flow to any conductivity boundary, increasingly detailed segmentation (e.g., globe of the eye and related structures, glands, and deeper midbrain structures) without reliable reported human conductivity values in literature (especially at static frequency) may also lead to errors. It is worth noting that the respective contribution of the automated/manual interventions also depends on: (a) sophistication of the particular database or automated algorithm employed since they are usually not optimized for forward transcranial modeling [26, 47] and (b) the need for identification of anomalies in suspect populations like skull defects, lesions, and shunts. Thus, addition of complexity without proper parameterization can evidently decrease prediction accuracy. An improper balance between these factors can introduce distortions in predicted brain current flow.

Having mentioned the importance of balancing increased complexity with clinical access to modeling, it is fundamental to emphasize a difference between the "value" of adding precision (complexity) as it is evaluated in engineering papers versus clinical translation. Increasingly detailed computational approaches have been proposed in recent years of varying anatomical and physiological detail [33, 34, 48]. These include whole body models, additional tissues and layers with and without anisotropic properties, and image derived conductivity values using effective medium approximations [9, 49–51]. At the same time, computational models indicate subject specific variability in susceptibility to the same dose [44, 52–54], indicating the value of individualized modeling, or at least modeling across a set of archetypes. Real clinical translational utility must balance the value of increased sophistication with the cost associated with clinical scanning, computational time, and human resources/intervention (manual correction/pre- and post-processing etc.). Thus the question is not if different models will yield different predictions (as must be posed in an engineering paper) but rather does increased complexity change model predictions in a way that is clinically meaningful. While this is a complex and application specific question, a first step toward systematizing value across a myriad of groups and efforts is to develop a metric of change versus a simpler approach, and then applying a threshold based on perceived clinical value and added cost.

It is simplistically assumed that added detail/complexity will enhance model precision and, if done rationally, model accuracy [5, 55]. Though an engineering group can devote extended resources and time to a "case" modeling study, the number of potential electrode combinations and variations across normal heads [44] and pathological heads means that in clinical trial design the exact models will likely not be solved for all subjects (e.g., 4×1 over FP3 in a female head). However, while different models will yield different predictions; practical dose decision is based on study specific criterion making a meaningful clinical difference. Therefore, additional complexity and detail is only clinical meaningful if it results in a different clinical decision being made as far as dose individualization—otherwise, the additional detail is purely academic. Two clinical applications of modeling are considered (1) Deciding across montages—namely which montage is expected to achieves the optimal clinical outcomes (safety/efficacy) in a given subject or on average across subjects; (2) Deciding on dose variation across subjects—namely if and how to vary dose based on subject specific anatomy. These aspects of using computational models in clinical practice are addressed in the next sections.

Assuming accurate and precise representation of all tissue compartments (anatomy, resistivity, anisotropy) relevant to brain current flow, it is assumed that by using modern numerical solvers, the resulting prediction is independent of the numerical technique used. Our own experience across various commercial solvers confirms this implicit assumption when meshes are of sufficient detail. That is, a precise description in methods (use of publically available programs) and representation of resulting mesh density and quality (in figures or methods) as well as tests

using various solvers provides explicit control for errors generated by the computation itself.

Literature regarding forward modeling, or more broadly the dissemination of modeling analysis to the clinical hands, introduces further issues in regard to (1) interpretability, reproducibility, and accuracy (tissue masks) and (2) graphical representation of regions of influence (degree of "activation). As there is no standard protocol for tissue imaging or segmentation, diversity in the resulting tissue masks will invariably influence predicted current flow. As such, it is valuable to illustrate each 3D tissue mask in a publication's methods and/or classified serial sections. In regard to representation of relative activation, studies employ either maps of current density (unit of A/m2) or electric field (unit of V/m)., but because the two are related linearly by local tissue resistivity, when plotting activation in a region with uniform resistivity (for example the cortical surface), the spatial profile is identical. When plotting activation across tissues (e.g., coronal section), current density may be advantageous to illustrate overall brain current flow. However, the electric field in the brain is directly related to neuronal activation (e.g., for varied resistivity, the electric field, but not current density, provides sufficient information to predict activation). Despite best efforts, figure preparation invariably restricts tissue mask perspectives and comprehensive display of volumetric current flow, which can be supplemented with online data publication (http://www.neuralengr.com/bonsai).

When interpreting simulation predictions, it is important to recognize that the intensity of current flow in any specific brain region does not translate in any simple (linear) manner to the degree of brain activation or modulation, even when considering current direction. Moreover, recent neurophysiological studies indicate changes in" excitability "may not be monotonic with stimulation [4]. For example increasing stimulation amplitude or duration can invert the direction of modulation, as can the level of neuronal background activity [56]. However, to a first approximation, it seems reasonable to predict that regions with more current flow are more likely to be affected by stimulation while regions with little or no current flow will be spared the direct effects of stimulation. As a first step to understand the mechanism of action of tDCS, a relationship between model predicted regional current flow and changes in functional activation has been recently demonstrated [30]. The "quasi-uniform" assumption considers that if the electric field (or current density) is uniform on the scale of a region/neuron of interest, then "excitability" may be modulated with local electric field intensity [57] (see discussion in refs. [29, 58]). Though efforts to develop suitably detailed biophysical models that consider the myriad of neurons with distinct positions and morphologies or 'continuum' approximations [59] of modulation are pending, the current state-of-the-art requires (implicit) application of the "quasi-uniform" assumption.

Forward modeling studies and analysis are often published as case reports with predictions only evaluated on a single head [6, 10, 31, 34]. The suitability of single subject analysis reflects limited available resources and the clinical question being addressed. For a given electrode montage and stimulation dose, the sensitivity of global brain current to normal variation in anatomy (including across ages, gender) is unknown. However, high-resolution modeling suggests gyri-specific dispersion of current flow, which could potentially account for individual variability. More generally, gross differences in tissue dimensions, notably skull thickness and CSF architecture, are expected to influence current flow; in some cases, modeling efforts specifically address the role of individual anatomical pathology, such as skull defects [28] or brain lesions [26]. It is precisely because these studies have shown the importance of specific defect/lesion details, that findings cannot be arbitrarily generalized. This in turn stresses the importance of individualized modeling as illustrated in the next section.

Though this section focused on the technical features of modeling, there is a broader concern in promoting effective collaboration between engineers and clinicians. For analogy, clinicians are generally aware of the challenges and pitfalls

in post-processing and feature selection of fMRI data—and indeed, are thus intimately involved in data analysis rather than blindly relying on a technician. For computational "forward" models of neuromodulation, where results may inform study design and patient treatment, it is as important to consider the uses and technical limitations of modeling approaches—and vigilance and skepticism on the part of clinicians will only enhance model rigor. Critically, for this reason, clinician/investigator experience and judgment supersedes all model predictions, even as these models form an important tool in dose design.

Use of Computational Models in Clinical Practice: Consideration for Efficacy

Before beginning our sections of consideration for clinical practice, we note that the ability of clinicians to leverage computational models is limited by access to modeling tools. For clinicians interested in using computational forward models to inform study design or interpretation, but who do not have the time and resources to establish an independent modeling program, several options are available. (1) A collaboration with a modeling group [10] or a company can allow for customized exploration of montage options; (2) referencing existing published reports or databases (www.neuralengr.com/bonsai); [60]) for comparable montages (with careful consideration of the role of individual variation and other caveats presented in the next section); (3) with some coding experience, using a novel process where a desired brain region can be selected and the optimized electrode montage is proposed within a single step has been developed [37]; (4) Graphical User Interface (GUI) based program to simulate arbitrary electrode montages in a spherical model is now available (www.neuralengr.com/spheres). GUI-based software using gyri-precise brain anatomy has now been developed as well [38, 39, 60]. This last solution illustrates an important trend: even as increasingly complex and resource expensive modeling tools are developed, parallel efforts to simplify and automate (high-throughput) model workflow are needed to facilitate clinical translation.

In regard to efficacy, it is typically the case that scientists and clinicians have identified one or more brain regions that they desire to modulate (e.g., based on fMRI and prior behavioral studies; [10, 61–64] and typically this modulation is expressed as a desire to enhance or inhibit function in the region. While this is a starting point for rational dose optimization using computational models, several additional parameters and constraints need to be specified.

A central issue relates to the concern, if any, about current flow through other brain regions. In one extreme, current flow through other regions outside of those targeted is considered unimportant for trial outcomes—and in such a case the optimization would be for intensity at the target while ignoring details of current flow through other brain regions. Conversely, it may be desired to minimize current flow through all other brain regions while maximizing current flow intensity in the targeted brain region—in such a case the optimization is for focality. The reason this distinction between optimization for intensity and optimization for focality is so critical is that produces highly divergent "best" dose solutions [37]. Optimization for intensity often produces a bipolar (one anode and one cathode) montage across the head, such montages typically produces broad current flow across both the target and other brain regions. Optimization for focality typically produces a "ring" montage (with one polarity surrounded by another, analogous to the HD-tDCS 4×1;[27]) that spares much of the brain regions outside of the target but also produces less relative current flow at the target then optimization for intensity. In practicality, though distinctions between optimization for intensity and optimization for focality must be made, the (iterative) process of dose optimization may be subtler. Certain brains regions outside of the target may be "neutral" as far as collateral stimulation, others may be "avoid" regions "and other may in fact be considered" beneficial "to the outcomes. A best montage therefore is highly dependent on both the trial design outcomes and the experimenter's opinion on how distinct brain regions are implicated.

Another critical parameter to consider in trial design is the desired electric field intensity at the target (s). As emphasized throughout this review, optimization based on electric field at the target is expected produce more consistent outcomes then optimization by external current intensity. None-the-less, an experimenter may choose to select a current level (e.g., 1 mA, 2 mA) simply because of historical experience and trends. It is important to emphasize that at least for neurophysiological measures (such as TMS) and likely for behavioral and clinical outcomes, the relationship between current and outcomes is not linear and not necessarily monotonic [65, 66]—meaning reversing current direction (at the level of electrodes and the brain) may not reverse the direction of change, and increasing current intensity may not increase, and can even reverse, the direction of change. The effects of stimulation may vary with the brain region (e.g., prefrontal may not response as motor) or the state of that region, for example is there is ongoing activity (due to a concurrent task) or pathology (due to injury or disease; [67]), in ways that remain poorly understood. In general, more is thus not more with stimulation intensity and thus the decision of what current intensity is desired is a complex and critical one for outcomes. The same challenges applied to selecting a desired brain electric field where higher electric field at a target may not produce increased neuromodulation or more of the type of change desired—moreover increasing electric-field intensity at the target by increasing applied current will increase electric field intensity at every other brain region proportionally. Finally the orientation of the electric field at the target may be critical and depending on the orientation different montages may be considered.

Though the above paints an increasingly complex picture of dose optimization in tDCS it may be unwise to simply ignore these issues and use "historical" montages (e.g., whatever is popular in the literature) and not leverage computational models to the extent possible to optimize dose. In the face of complexity (and risk), experimenters may feel a desire to simply revert to using what has already been reported successful in the literature, but such an approach seems inconsistent with broader efforts to advance the field especially when these previous approach were not optimization (and indeed a very limited set of montages are used across highly disparate indications). None-the-less, given the complexity and unknowns, historical montages do represent a good starting point for dose optimization. Practically, we recommend the optimization process can begin by simulated previously used successful and unsuccessful montages to consider the brain current flow patterns generated in each case, it is against these standards montages that any optimized montage can be compared.

Use of Computational Models in Clinical Practice: Consideration for Safety

Computational models also provide a tool to support assessment of safety. tDCS is considered a well-tolerated technique [16] but vigilance is always warranted with an investigational tool; moreover, given that most montages produce current flow through many brain regions, combined with the desire to explore increasing intensities and durations/repetitions of treatment, as well as stimulation in susceptible subjects (e.g., children), computational models, though only predictions, provide quantitative methods to increase confidence and identify hazards.

We distinguish effects at the skin (which relate largely to electrode design/electrochemical issues and electrode current density) from effects at the brain (which relate to electric fields in the brain) [68]. Computational models predict current flow at both the skin and the brain. Often dose design simply avoids crossing (or even approaching) a threshold for intensity in any given region both inside and outside the target. This threshold is often based on historical approaches. Here the distinction between dose optimization based only on stimulation parameters (e.g., total current) verses brain electric field (with leverages computational models) is evident. Maintaining applied current (e.g., 1 mA) but changing electrode montage and/or subject inclusion (e.g., skull defects) may profoundly change current density/electric field in the skin and brain. Computational models are thus useful to relate new montages/approaches

against historically safe ones. It is often the case that even when current density/electric field is predicted, the experimenter still applied the upper limited of applied current. Thus maximum current density/eclectic field and maximum current intensity become constraints in the efficacy optimization process.

Use of Computational Models in Clinical Practice: Consideration for Individual Dose Titration

There are two general uses for computational models in designing rational experiments and clinical trials. The first is the selection of the best generic dose as discussed above. The second "if" to consider is if and how to customize dose to individual subjects. Even across normal healthy adults there is a twofold difference in the electric field generated in the brain for a given applied current [43, 44, 49]. This variation is potentially profoundly significant when considering that twofold changes in applied current can invert the direction of change (see above). Therefore, anatomical differences, even across healthy adults may explain some of the know variation in existing tDCS studies and normalizing for brain electric field across subjects, by leveraging computational models, may in part correct for individual differences.

When considering extremes of age [52, 53] or body mass [9] or the presence of variable brain or skull injuries [28], the potential for individual differences to influence current flow increases [63]. While it is not unusual for tDCS montages to be changed based on individual disease etiology (e.g., stroke location) this is often done using basic rules of thumb (e.g., position the "active" electrode over the brain region) which may not always produce the desired brain current flow [26]. The need to normalize (wide) individual variations in response to tDCS is universally recognized (along with the desire to increase efficacy), and it is rational that normalizing brain electric field, should help reduce variability since brain electric field determines outcomes. Yet the use of computational models for individual optimization is rare and limited by accessibility to rapid modeling tools.

We note the value of individualization is evident in TMS studies when it is almost unheard of to apply the same intensity across subjects. It is no less important in tDCS, but as tDCS does not produce an overt physiological response such as TMS, computational models are valuable tool to individualize dose.

Example Results of Computational Analysis in Susceptible Populations

We conclude with some case studies to illustrate the application of computational models for informing clinical guidelines.

Case 1: Skull defects: There is interest in the application of tDCS during rehabilitation of patients with brain lesions or skull defects (i.e., with or without skull plates); for example subjects with traumatic brain injury (TBI) or patients undergoing neurosurgery. As some of the neurological sequelae are presumably consequences of disrupted cortical activity following the traumatic event, the use of tDCS to deliver current to both damaged and compensatory regions in such circumstances can be a useful tool to reactivate and restore activity in essential neural networks associated with cognitive or motor processing. In addition, because of the reported anti-seizure effects of tDCS [69], this technique might be useful for patients with refractory epilepsy who underwent surgery and have skull plates or decompressive craniectomy for trauma and cerebrovascular disease.

Despite rational incentives for investigation of tDCS in TBI or patients with other major neurological deficits and skull defects, one perceived limitation for the use of tDCS in these patients is the resulting modification of current flow by the skull defects and presence of surgical skull plates. Modeling studies can provide insight into how skull defects and skull plates would affect current flow through the brain and how to modify tDCS dose and/or electrode locations in such cases (Fig. 4.4, adapted from ref. [28]). For example, a skull defect (craniotomy) that is filled with

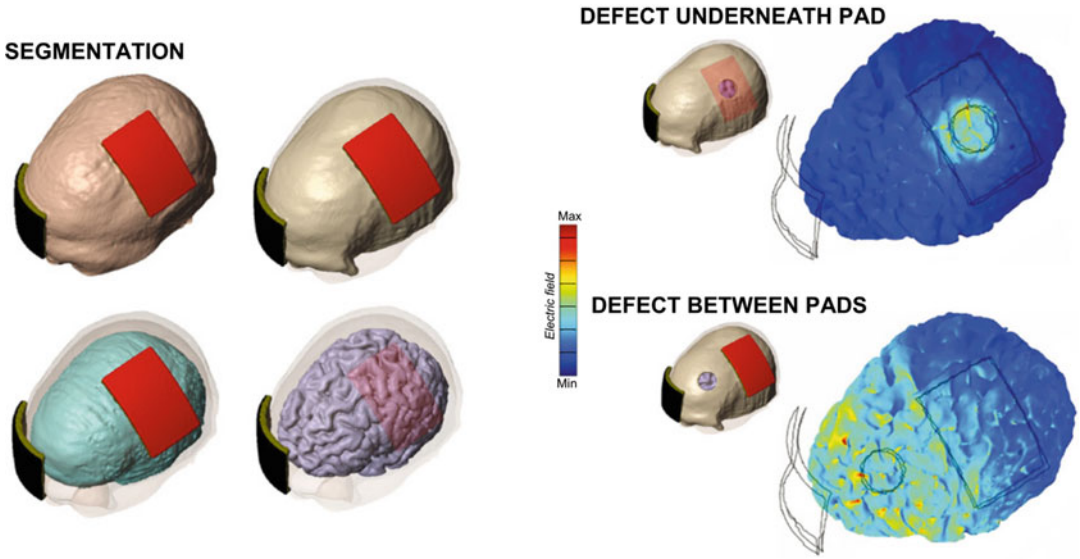

Fig. 4.4 Computational model of current flow in subjects with skull defects/plates. A defect in skull tissue which is the most resistive tissue in the head would hypothetically affect current flow in the underlying brain regions. Furthermore, the exact location of the defect (under/between the stimulation pads) in combination with the 'material' filling up the defect with the stimulation montage employed will influence induced current flow. Sample segmentation masks are shown on the *left*. A small defect under the anode pad (*top right*) leads to current flow in the cortex restricted to directly under the defect (avoiding the intermediate regions). A similar sized defect placed between the pads (*bottom right*) does not significantly alter current flow patterns in comparison with a healthy head with no defects (Adapted from ref. [28])

relatively highly conductive fluid or tissue represents a "shunt" pathway for current entering the brain but in a manner highly dependent on defect position relative to electrode montage. In such cases, the underlying cortex would then be exposed to a higher intensity of focused current flow. This in turn might be either beneficial in targeting the underlying brain region or hazardous if the increased current levels resulted in undesired neurophysiologic or pathological changes. Our modeling results confirm the notion that skull defects and skull plates can change the distribution of the current flow induced in cortical areas by tDCS. However, the details of current modulation depend entirely on the combination of electrode configuration and nature of the defect/plate, thus indicating the importance of individual analysis. Based on model predictions, application of tDCS without accounting for skull defects can lead to suboptimal and undesired brain current.

Case 2: Simulation of tDCS in subjects with idealized Deep Brain Stimulation (DBS) leads. Combination therapies incorporating tDCS are increasingly being investigated in drug-resistant instances of psychiatric disorders such as depression and schizophrenia [70, 71]. Subjects who have had DBS electrodes either as a comorbidity or due to an indication being investigated with tDCS or tACS do not necessarily have to be exclude from study. Computational models can the estimate the current flow artifact due to the presence of DBS implantation. At a minimum, safety can be inferred by comparing maximum current density or electric field in DBS subjects to known safe montages in healthy individuals. In Fig. 4.5, four montages were compared, once in a healthy-intact head and again in a head with a burr-hole defect resulting from the typical placement of subthalamic nucleus DBS. While a realistic DBS implantation would include insulation surrounding the lead and a protective cap in the skull opening, this model examined a worst case scenario in which only the burr hole from implantation is present. As seen in the cross-sectional current density images (dashed line), the fluid

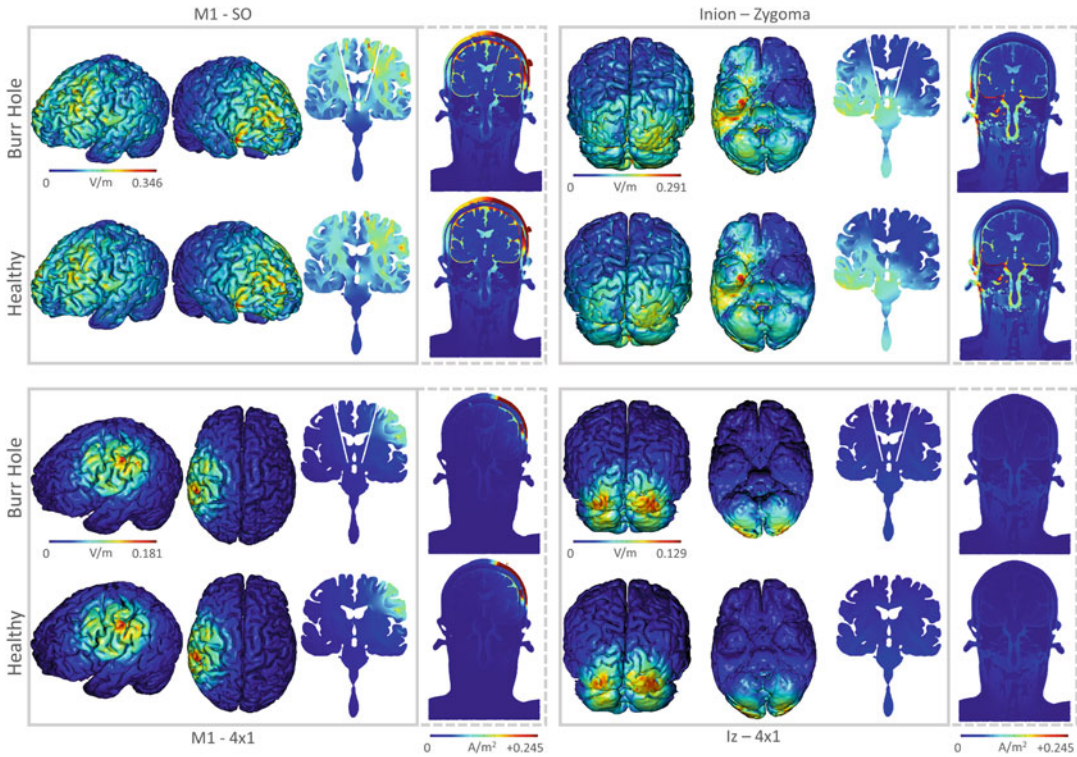

Fig. 4.5 Simulation of tDCS in subjects with idealized Deep Brain Stimulation (DBS) leads. Finite element models of tDCS with and without burr-hole defects typical in subthalamic nucleus deep brain stimulation. Common sponge (conventional) and HD-tDCS montages for motor and cerebellar stimulation are compared. Fluid-filled burr holes draw a greater amount of current density than what would normally exist with healthy tissue (*dashed images*). However, peak current density and electric field are minimally affected (less than twofold). HD configurations have lower deep brain electric field intensities in general in addition to being more confined. (Adapted from Truong, Bikson et al. in preparation)

filled implantation defect draws a greater proportion of current than intact healthy tissue. While current density and in turn electric field distribution are affected by the presence of the defect, peak electric field has less than a twofold change in intensity, which is within the variations seen between individuals and common tDCS protocols (1–2 mA) [9, 44]. Stimulation amplitude could be lowered to 1 mA out of an abundance of caution. The use of HD-tDCS electrodes in the 4x1 configuration (bottom row) can also be used to restrict both maximum intensity and spread of current, especially to deep brain regions.

Case 3: Pediatric populations: There is increasing interest in the use of neuromodulation in pediatric populations for a range of indications including rehabilitation, cognitive performance, and epilepsy treatment [72–75]. However, a rational protocol/guideline for the use of tDCS on children, has not been formally established. Previous modeling studies have shown that current flow behavior is dependent on *both* the tDCS dose (montage and current intensity) and the underlying brain anatomy. Because of anatomical differences (skull thickness, CSF volume, and gray/white matter volume) between a growing child and an adult it is expected that the resulting brain current intensity in a child would be different as compared to that in an adult. Evidently, it would not be prudent to adjust stimulation dose for children through an arbitrary rule of thumb (e.g., reduce electrode size and current intensity by the ratio of head diameter). Again, computational forward models provide direct insight into

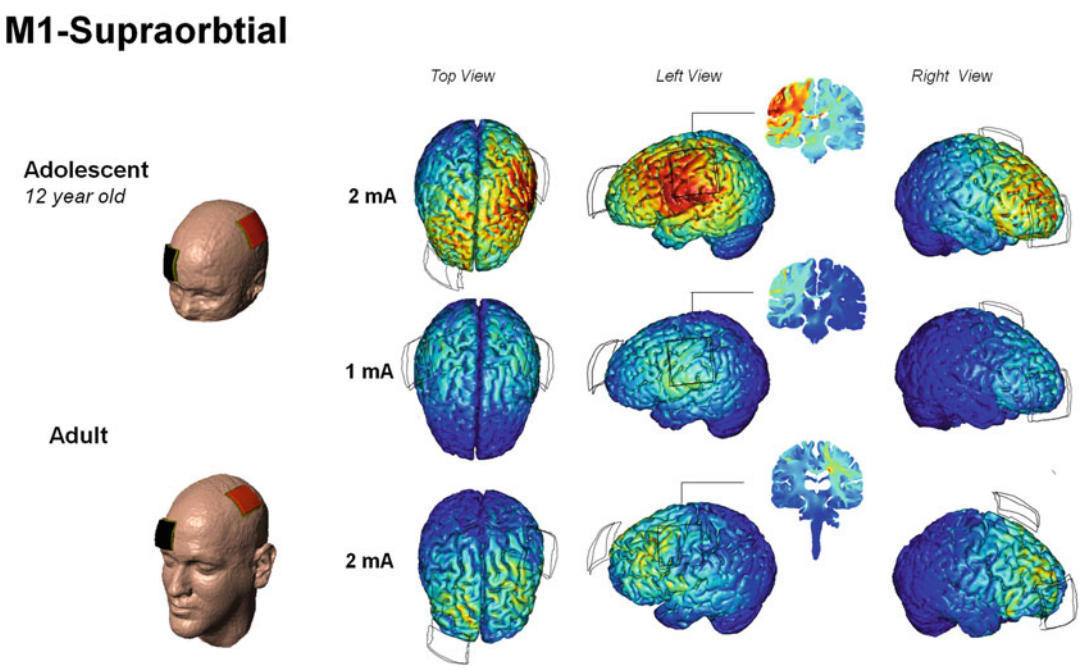

Fig. 4.6 Individualized head model of two adolescents as compared to an adult: Induced current flow for motor cortex tDCS at different intensities. 1 mA of stimulation in the adolescents is similar to 2 mA of stimulation in the adult

the relation between external tDCS dose and resulting brain current and thus can inform dose design in children. Figure 4.6 shows an example of a model of tDCS in a 12-year-old compared to that of a standard adult model. Both the peak and spatial distribution of current in the brain is altered compared to the typical adult case. In fact, for this particular case, the peak electric fields, at a given intensity, were nearly double in the 12-year-old as compared to the adult. Though questions remain about the impact of gross anatomical differences (e.g., as a function of age or gender) in altering generated brain current flow during neuromodulation, computational "forward" models provide direct insight into this question, and may ultimately be used to rationally adjust stimulation dose.

Case 4: The wide range of uses for tDCS makes it applicable to a diverse population that can include obese subjects. Montages that have been evaluated for pain, depression, or appetite suppression have been modeled in average adults, but unique challenges exist in the obese model (Fig. 4.7, adapted from ref. [76]). The additional subcutaneous fat present in the obese model warranted an additional layer of complexity beyond the commonly used 5 tissue model (skin, skull, CSF, gray matter, white matter). Including fat in the model of a super obese subject led to an increase in cortical electric field magnitude of approximately 60% compared to the model without fat (Fig. 4.7a.1–a.3). A shift was also seen in the spatial distribution of the cortical electric field, most noticeable on the orbitofrontal cortex.

To gain an intuition for how subcutaneous fat influences cortical electric field and current density, additional models examined a range of conductivity values from the conductivity of skull (0.010 S/m, Fig. 4.7b.1) to the conductivity of skin (0.465 S/m, Fig. 4.7b.8). Coincidentally, the conductivity commonly used for fat (0.025 S/m, Fig. 4.7b.4) was in the range that causes a peak increase in cortical electric field magnitude. It was postulated that more current was blocked by subcutaneous fat at an extremely low conductivity (Fig. 4.7b.1), while more current was

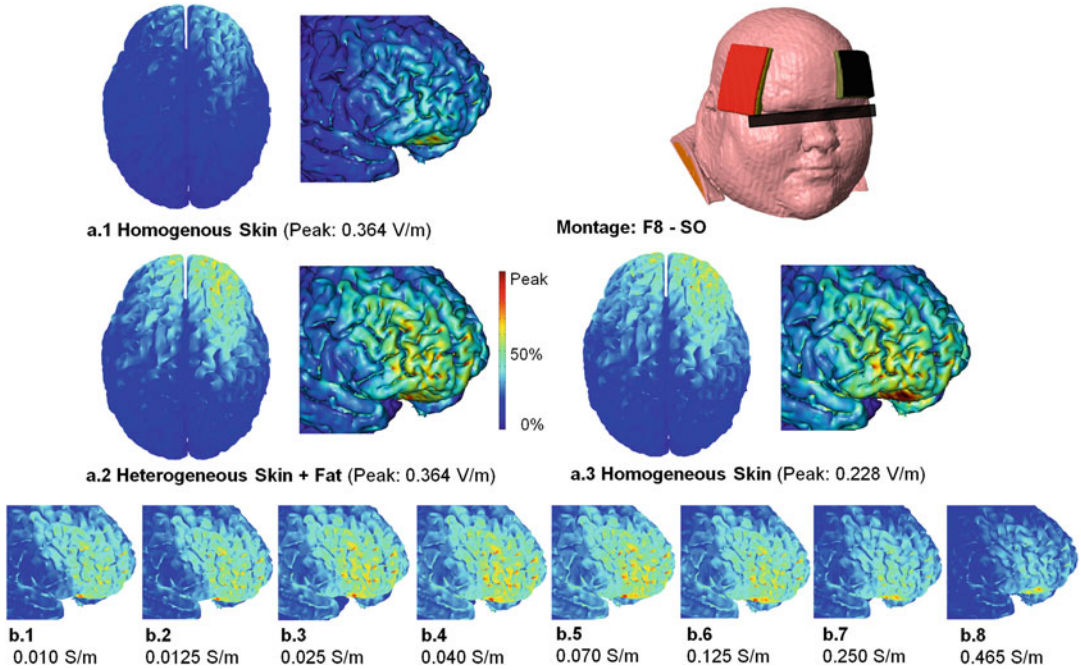

Fig. 4.7 Predicted cortical electric field during inferior prefrontal cortex stimulation via 5×7 pads. Two conditions, homogenous skin (*a.1*) and heterogeneous skin (*a.2*), are contrasted on the same scale (0.364 V/m per mA peak). The homogeneous skin condition is displayed (*a.3*) at a lowered scale (0.228 V/m per mA peak) to compare the spatial distribution to the heterogeneous condition (*a.2*). The effect due to a range of varying fat conductivities (*b.1–b.8*) is compared on a fixed scale (0.364 V/m per mA peak). The conductivity of fat (0.025 S/m) is within an optimum range of influence that causes an increase in peak cortical electric field when included (Adapted from ref. [76])

redirected at an extremely high conductivity. This, in effect, led to an "optimum" range of influence where the conductivity of fat is believed to reside.

Ultimately, the need to precisely parameterize models rests hand-in-hand with the intended use of the model. From an engineering perspective, the increased complexity of this model caused a noteworthy change within the subject modeled, but this change would not be clinically noteworthy if stimulation dose does not change from subject to subject. This clinical analysis requires an additional comparison between subjects and consideration of the wide variation already inherent in "typical" subjects [44]. What can be concluded, however, is that a comparison between models would require consistent parameterization of subcutaneous fat.

These cases demonstrate the potentially profound influence of lesions and skull defects on resulting current flow, as well as the need to customize tDCS montages to gross individual head dimensions. If tDCS continues to become a viable option for treatment in cases such as chronic stroke, the consideration of tDCS-induced current flow through the brain is of fundamental importance for the identification of candidates, optimization of electrotherapies for specific brain targets, and interpretation of patient-specific results. Thus, the ability and value of individualized tDCS therapy must be leveraged. Whereas, tDCS electrode montages are commonly designed using "gross" intuitive general rules (e.g., anode electrode positioned "over" the target region), the value of applying predictive modeling as one tool in the rational design of safe and effective electrotherapies is becoming increasingly recognized.

Electrode montage (i.e., the position and size of electrodes) determines the resulting brain current flow and, as a result, neurophysiological

effects. The ability to customize tDCS treatment through electrode montage provides clinical flexibility and the potential to individualize therapies [24, 26, 31]. However, while numerous reports have been published in recent years demonstrating the effects of tDCS upon task performance, there remain fundamental questions about the optimal design of electrode configurations with computational "forward" models playing a pivotal role.

Conclusion

While numerous published reports have demonstrated the beneficial effects of tDCS upon task performance, fundamental questions remain regarding the optimal electrode configuration on the scalp. Moreover, it is expected that individual anatomical differences in the extreme case manifest as skull defects and lesioned brain tissue which consequently will influence current flow and should therefore be considered (and perhaps leveraged) in the optimization of neuromodulation therapies. Heterogeneity in clinical responses may result from many sources, but the role of altered brain current flow due to both normal and pathological is tractable using computational "forward" models, which can then be leveraged to individualize therapy. Increasing emphasis on high-resolution (subject specific) modeling provides motivation for individual analysis, leading to optimized and customized therapy.

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Animal Studies in the Field of Transcranial Electric Stimulation

5

Doris Ling, Asif Rahman, Mark Jackson, and Marom Bikson

Abstract

Dozens of animal studies of transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) have provided insight into the cellular mechanism of stimulation. Biomarkers of tDCS/tACS responses at the neurophysiological, behavioral, and molecular levels provide a basis to design clinical interventions that engage specific targets. This chapter provides a broad introduction to methods and insights from animal models. Both tDCS and tACS are sub-threshold techniques, producing membrane polarization rather than firing. If the nervous system is engaged during tDCS/tACS, for example by cognitive behavioral therapy, then tDCS/tACS modulate this ongoing activity. Animal models have supported the basis for polarity-specific effects of tDCS ("anodal" excitation, "cathodal" inhibition) while also indicating limitations of simplistic dose strategies. tACS studies have focused on boosting of oscillations. Both techniques can modulate ongoing plasticity leading to lasting changes in brain function. As an adjunct therapy, tDCS/tACS may thus increase brain capacity for plasticity enhancing the effects of neuropsychiatric therapies, and compensating for disease-related decline.

Keywords

Translation • Preclinical • Rodent • Safety • Neuromodulation

Experimental Design of tDCS and tACS Animal Studies

There is a general perception that the rate of clinical trials on tDCS and tACS for a range of indications, including neuropsychiatric disorders, has outpaced research on the basic mechanisms of tDCS. Over the last few decades, the mechanisms by which tDCS and tACS work have been

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extensively tested in animal models and backed their application for treatment of neuropsychiatric disorders. Efforts to increase the effectiveness of tDCS/tACS interventions (e.g., changing stimulation dose) should be guided by ongoing and modern animal research.

The overall motivation for animal research of tDCS/tACS is similar to other translational medical research efforts: to allow rapid and safer application of stimulation protocols in research and clinical settings. Improving clinical efficacy and safety would require a thorough understanding of the underlying mechanisms being altered. To have meaningful relevance to clinical tDCS/tACS, animal studies must be designed with consideration for (1) correctly emulating the delivery of direct current (DC) or alternating current (AC) stimulation to the brain, and (2) measuring responses that can be used to draw clinically relevant inferences. Before reviewing the main insights drawn from animal studies, we outline the basis and pitfalls of translational animal research on tDCS/tACS and then highlight research on their application to psychiatric pathologies.

Like any model, direct current stimulation (DCS) and alternating current stimulation (ACS) of animals are intended to reproduce relevant features for human applications with the goal of (1) retrospectively providing a mechanistic explanation for findings in humans, and (2) prospectively progressing rational optimization of tDCS/tACS protocols. The tDCS/tACS parameter space is large, spanning dose selection (electrode montage, current intensity, duration, and, for ACS, frequency), the potential use of biomarkers to titrate and customize dose, subject selection, and pairing of tDCS/tACS with cognitive training. Comprehensively testing this parameter space in humans is impractical, thereby necessitating the use of animal models to guide tDCS/tACS development.

Classification of Animal Studies and Relevance to Clinical Protocols

The scope of this review includes animal studies testing the neurophysiological, behavioral, and molecular response of the brain to DCS and ACS, with a focus on macro-electrodes delivering sustained (seconds to minutes) rather than pulsed (milliseconds) waveforms. For the purpose of this review, studies referring to any type of direct electrical current to stimulate parts of the brain will be referred to as DCS or ACS. The term tDCS/tACS will be strictly reserved for referring to noninvasive DCS/ACS applications in human settings, and studies involving behaving animals. DCS/ACS animal studies can be broadly classified by method of stimulation (namely where the electrodes are placed) as (1) stimulation in animals using surface electrodes; (2) in vivo intracranial stimulation, with one electrode on the cortex; and (3) in vitro stimulation of tissues, such as brain slices. While these classifications underpin the decisions by animal experimentalists, understanding the rationale and limitations of animal models of DCS/ACS is important for any effort to leverage them in the understanding and design of tDCS/tACS treatment protocols.

1. Modern animal studies on DCS/ACS typically use transcranial stimulation with a skull screw which functions as the electrode, or skull-mounted electrolyte-filled cup and electrode [1–4]. DCS/ACS using surface electrodes are least invasive of the three outlined methodologies and can be subdivided into applications with electrodes that leave the scalp intact and those that do not. Electrodes that leave the scalp intact typically use adhesives as fixatives and require conductive solutions to interface the electrode with the skin. Subcutaneous electrodes are typically fixed with skull screws, but if the electrode penetrates completely through the skull, the stimulation method is no longer considered transcranial. The advantages of transcranial stimulation include preventing electrode electrochemical side products from reaching the brain which would confound any results. Rodents are typically used but cats are also sometimes used as well [5]. In rodent models, an “active” electrode is placed on the head and a “passive” return electrode is mounted on the body—this setup is typically used for unipolar stimulation which is used to provide a more uniform electric field throughout the brain. In a study on

anesthetized rabbits, four silver ball electrodes formed a single virtual electrode to stimulate the target brain region [6]. Alternatively, two cranial electrodes produce bipolar stimulation [7] that results in an electric field spectrum between the electrodes. Since the cranium is not penetrated, the effects of DCS are quantified through behavioral tests, noninvasive recordings (electroencephalogram, EEG), noninvasive electrical interrogation (e.g., transcranial magnetic stimulation, TMS; transcranial electrical stimulation, TES), or histology after sacrifice.

Stimulation across the skull in animals is the most relevant for informing tDCS/tACS clinical trials for neuropsychiatric disorders, as this class of studies offer the possibility to link neurophysiologic mechanisms with behavior [6]—though there are relatively few such studies at present and the relevance of animal behavior to clinical disorders remains debated (see below). Studies from this class are also the most relevant from the perspective of safety.

2. Classic DCS animal studies placed an electrode directly on the cortical surface [8, 9]. Cats, monkeys, and rats were typically used. When an electrode is placed inside the skull then potential interference from electrochemical changes at the electrode interface diffusing into the brain cannot be ruled out. While these electrochemical products can be polarity specific [10] and produce reversible changes, direct electrochemical diffusion from the electrode surface to the brain is not considered relevant for DCS. Steps to reduce interference from electrochemical by-products include using suitable electrodes (e.g., Ag/AgCl) and wrapping the electrodes in cotton to shield chemical changes [11]. Prolonged DCS through a poorly selected electrode material (e.g., steel) produces significant electrochemical accumulation on the metal, and would warrant careful scrutiny of results. For cortical electrodes, it is generally assumed that current flow through nearby cortex will be unidirectional. Passage of direct current through invasive electrodes is known to produce electrochemical lesions of the local tissue [5].This form of stimulation is relevant for informing the more fundamental aspects of DCS/ACS and excitability changes. For example the earliest notions about polarity-specific cortical excitability changes and the potential for lasting after effects when stimulation are sustained derives from this class of animal work. As mentioned above, studies from this class are less relevant from the perspective of safety than tDCS/tACS.
3. The use of brain slices to study the effects of weak DCS dates to work done in the 1980s [12–16], with comparable approaches used for ACS [17]. Brain slice models (usually rodent) allow probing of specific brain regions in detail using a range of quantitative electrophysiological, pharmacological, molecular, and imaging techniques. For in vitro DCS/ACS studies, the stimulation electrodes are typically placed in the bath at a distance from the tissue to shield electrochemical changes. In isolated tissue, the direction of current flow can also be precisely controlled. Techniques have been developed for stimulating in vitro monolayer cultures [18]. In a seminal series of papers, Chan and Nicholson used isolated turtle cerebellum to study DCS modulations of spiking patterns [19, 20]. Slice studies have provided the most quantitative and sophisticated insights into tDCS/tACS principles—leading to the development of hypothesis regarding mechanisms of actions regarding cell polarization, plasticity induction, and oscillation effects.

tDCS and tACS Dose

The dose of brain stimulation for tDCS and tACS has been defined by stimulation parameters that are controlled by the operator (Bikson et al. 2008; [21]), namely the electrode montage (shape, location, etc.) and the specifics of the waveform (duration, peak intensity in mA applied, and, for ACS, frequency). All the downstream effects of tDCS/tACS are a result of the current flow generated in the brain and are a direct function of dosage. Analogous to drug dosages, tDCS/tACS doses too small may lead to nonsignificant effects and doses too large have detrimental

consequences. Due to the convoluted structure of the head (that includes the skull, layers of meninges, and gyri surrounded with flowing cerebrospinal fluid), the electric field will vary considerably around different geometries and through different materials [22]. As a result, tDCS/tACS produce complex spatial current flow patterns across the brain, which results in a dose-specific electric field that varies significantly across brain regions. As a consequence, the current density at the electrodes does not homogeneously describe peak electric fields in the brain [23]. These electric field peaks represent centers of concentrated charge with weaker fields being generated in other parts of the brain. There are established methods to predict the electric field generated in the brain using computational models [22, 24]. Though methodological approaches vary, studies using realistic anatomy models have converged in their estimates of peak electrical fields generated during tDCS/tACS to 0.2–0.5 V/m (0.05–0.14 A/m2 current density) for a 1 mA peak tDCS/tACS dosage [22, 24, 25], though it has been proposed that tACS may produce significant larger fields [26]. The electric field scales linearly with current intensity such that 2 mA peak could produce intensities upwards of 0.4–1 V/m (0.1–0.28 A/m2 current density). There is no single electric field generated during tDCS/tACS but rather a range of electric field magnitudes are generated across the brain. This issue is further complicated by the fact that electric fields also vary as a function of head size, so applying the same dosage to a human and a mouse would not yield similar results. Therefore, the question is this: Given this complexity of current flow pattern (electric field distribution across brain structures), what are the best montages to be used in the treatment of neuropsychiatric disorders? This question is addressed further in the chapter of models.

The Quasi-Uniform Assumption

In creating an animal model, it is impractical to replicate the electric fields induced in each brain region during tDCS in all corresponding brain regions in a human. One solution is to only focus on the electric fields generated in the brain region of interest in the human, and then to locally apply the same fields on the corresponding brain region in an animal model. In doing so one implicitly adopts the assumption that fields are nearly uniform across small scales—this assumption has been termed the "quasi-uniform assumption" [27, 28] (Fig. 5.1). This approach is supported by the fact that electric fields generated are largely uniform across any specific cortical column (neuronal dendritic tree) of interest allowing a single electric field to describe a region of interest.

As previously explained, DCS experimental design falls into three categories (section "Classification of Animal Studies and Relevance to Clinical Protocols"). When using the quasi-uniform assumption to approximate the local electric fields in each of the experimental designs, oversimplifications in the assumption can result in substantial mismatches between calculated and actual electric field intensities. The limitations and methods to approach the issue are outlined below for each experimental design.

1. In the first case of transcranial stimulation of animals, the same modeling approaches that predict electric fields during clinical tDCS can be used to model and guide stimulation design [29]. In applying tDCS to animals it is important to consider how the position of the reference electrode influences current flow under the active electrode [30, 31]. As anatomically precise animal models are under development, concentric sphere models (simply scaled to size) can be used to determine electric field intensity generated in the animal brain [6]. In the absence of specific modeling of current flow in animals, and in cases where the electrode is placed directly on the skull, one can, to a first approximation, assume a maximum potential brain current density equal to the average electrode current density [32]. However, it is important to recognize that the direction of the electric fields generated across the brain, including in deep brain structures (particularly in higher animals with increasing convoluted cortex), may also vary. The electric field in a region of interest may also be measured with invasive electrodes [7], though

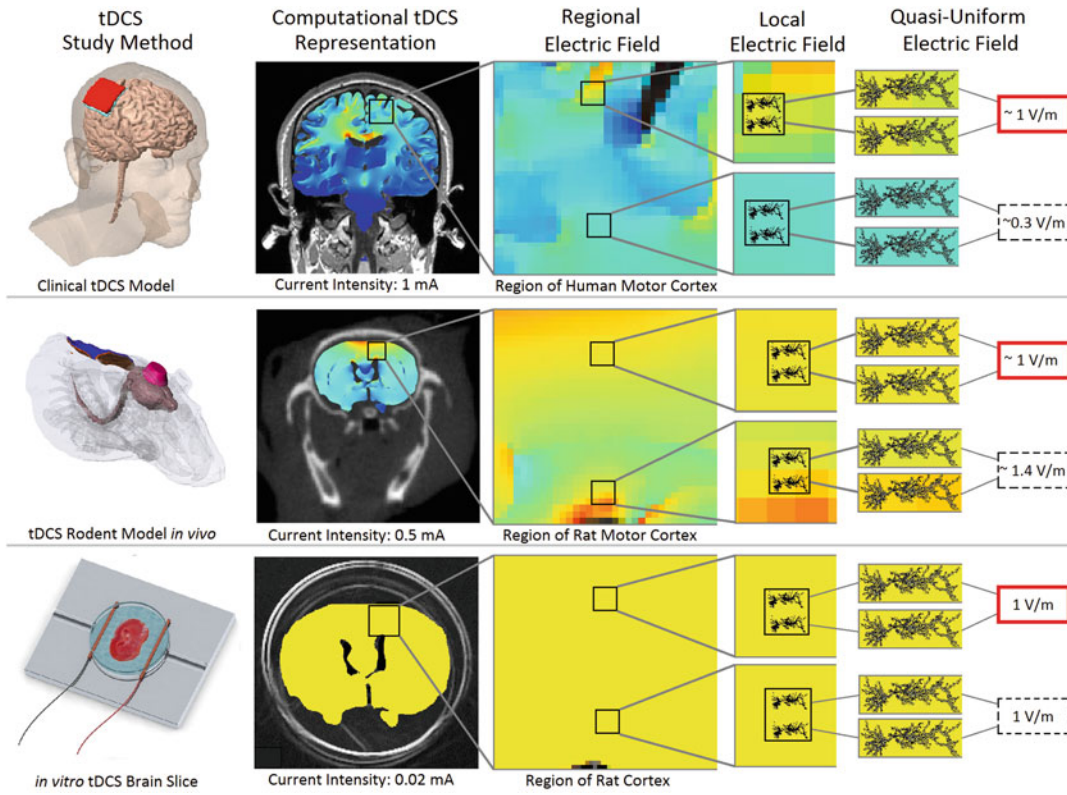

Fig. 5.1 The quasi-uniform assumption in animal models of tDCS. Current flow patterns predicted by FEM models are shown for human tDCS (*top row*), animal epicranial DCS (*middle row*), and brain slice DCS (*bottom row*). *Second column*: For human and epicranial stimulation, stimulation produces a globally nonuniform electric field, with higher electric field intensities generally in regions near the electrodes (indicated by hotter false *color map*); though local hotspots can be distributed for brain slice stimulation a uniform electric field is generated using large parallel wires. *Third column*: Consideration of regional electric field shows the electric field generation gradually over space. *Fourth column*: On the scale of single neuron, the electric field is largely ("quasi") uniform. *Fifth column*: The electric field is thus not uniform across the brain as a whole, but uniform across each neuron and indeed across local network of neurons. It is possible to match the electric field in a given region of human cortex, with electric field in a given region of animal brain, with an electric field generated in vitro. For illustration, at the current intensities used in each case (see values in *second column*) and the subregions selected in each animal model there is equivalence at 1 V/m. The equivalence, and more generally the local uniform nature of the fields, is the quasi-uniform assumption which implicitly informs every translational model of tDCS. Equivalence is not achieved by matching the applied current but by matching an electric field only in a specific region of interest

the insertion and presence of electrodes may itself distort current flow. It should also be noted that because the coupling constant also is much higher in humans than in other animals and will result in much larger polarizations in humans even when electric fields are matched—this discrepancy will be further discussed later.

2. In the second case, animal studies using a surface cortical electrode assume that the current density in the brain directly under the electrodes equals that *average* current density at the electrode. When scalp electrodes, such as sponges or cotton wrappers, are used, the total contact areas should be used in calculations. Depending on the electrode design, current density may be orders of magnitude higher at electrode edges than at the center of the electrode [24, 33, 34]. This is an issue aggravated for small electrodes where electric field near a monopole source can be very high leading to further potential complications [8]. As with unipolar stimulation, current spread throughout the brain (affecting both cortical and

subcortical structures) should be assumed when using return electrodes located away from the head [35].

3. In the third approach, including in vitro brain slice studies, the task is simplified by using long parallel wires placed in a bath. This setup generates a truly uniform electric field across the entire slice that can be readily calibrated to match tDCS levels [14, 36, 37]. The uniformity of the electric field across brain slices has been verified though exceptions have been reported. Inhomogeneities in the field may be due to the presence of stagnant conductive fluid around the brain slices that would alter current flow through the slice. Typically, the placement of the electrodes in the bath, away from the tissue of interest, protects the sample from electrochemical by-products. The simplicity and versatility of this technique make control of DC parameters in slice straightforward and allow for direct investigation of mechanisms not possible with other techniques.

Translation from Animal Studies to Clinical Applications: The Importance of Intensity

Many proposals for tDCS/tACS mechanisms fail to consider the much higher DCS/ACS intensities and/or durations used in some animal experiments. Recognizing that tDCS may produce weak outcomes, high intensities not reasonably used in humans are often intentionally applied to animal models in order to more reliably detect effects. Dosages are calculated by scaling down effect sizes based on the linear responses measured in animal models [17, 38]. In vitro studies also indicate a surprisingly linear response curve over low intensities [36, 39]. The in vitro studies that have explicitly explored the lower electric field limit of sensitivity to fields (see network effects; [37, 39, 40] report statistically significant responses at <0.2 V/m—fields within clinical tDCS/tACS ranges. Regardless, a cautious, rational approach reading dose–response should be taken.

Throughout this review, we emphasize caution when exploiting conclusions from studies using large DC/AC currents in animals that (far) exceed electric field magnitudes comparable to those generated during clinical tDCS/tACS—which is the overwhelming majority of them. While DCS and ACS can generate seizures, clinical tDCS/tACS intensities are orders of magnitude lower than those necessary to produce epiliform activity [41]. While these experiments are invaluable in suggesting tDCS/tACS mechanisms, just as with drugs, increasing dose beyond clinical levels can induce physiological changes not relevant clinically. For example, some animal studies have shown that application of DC can control neuronal process orientation and growth direction [42, 43], but both the duration and intensity of electric fields were often orders of magnitude greater than tDCS. Mechanisms such as electroporation and joule heating can be produced by some forms of electrical stimulation, but the waveforms required to produce these effects are not relevant for tDCS [22, 32, 44].

Safety Concerns

Any attempt to develop safety standards for tDCS/tACS requires assumptions about dose–response and variability in its effects. One approach uses the lowest documented current intensity to produce a measurable brain tissue response in an animal model for any stimulation duration. However, there may be a nonlinear minimum threshold for tissue damage or the dose–response curve may not be monotonic with very low intensities. However, animal studies are often for short term making long-term side effects of tDCS/tACS difficult to discern. They are also limited in time points for measurement—since the collection of tissue for analysis often requires terminal procedures we must assume that damage was irreversible and cannot exclude delayed damage responses.

Studies investigating the safety limits of prolonged DCS have shown that current densities above 15 A/m2 for durations longer than 10 min resulted in brain lesions in rats [44]. However, it

is unclear how this threshold for injury translates from animals to human brain tissue. In developing human safety guidelines it is prudent not to approach injury thresholds in clinical settings, especially given montage and individual differences. Consolidated animal DCS safety data scaled to humans using computational models indicate that current conventional clinical tDCS protocols are orders of magnitude below the threshold for tissue damage [32].

Relating Biomarkers from Animal Models to Humans

In considering the use of tDCS/tACS in clinical treatment, animal models of disease can be used, not simply to validate outcomes, but to characterize mechanisms and optimize stimulation protocols [4, 45]. To quantify tDCS/tACS efficacy, researchers have used noninvasive biomarkers of tDCS including spontaneous EEG [46–51] and TMS motor-evoked responses [15, 52], screening different dosage and time courses. These generic clinical measures of activity and excitability have rough animal analogs such as spontaneous firing rate, oscillations, and evoked responses—though these measures may not have the same range in animals and humans. More invasive measures of tDCS/tACS effects include protocols to measure gene expression and protein synthesis.

The primary human neurophysiology metric used to establish the acute and lasting effects of tDCS/tACS in humans is the transcranial magnetic stimulation (TMS) motor-evoked potential (MEP). Indeed, the establishment of modern tDCS can be traced to the discovery that tDCS can modulate TMS-MEP in a polarity- and montage-specific manner [15]. The development of other weak tES approaches, including tACS, followed. A common metric in animal trials is synaptic responses evoked by micro-electrical stimulation (e.g., field excitatory postsynaptic potentials, fEPSPs). These micro-recordings show how DCS/ACS effects evoked synaptic potentials in slice models and have served as the basis for the characterization of cellular mechanisms [6, 36, 38, 53]. Both TMS and microelectrode stimulation use suprathreshold stimulation of afferent pathways to assess how DCS/ACS modulates postsynaptic responses to the stimulation. These studies have given us insight into neural pathways and dose-specific modulation of excitability [6, 36, 38, 53] and emerging data suggests that there is a pathway dependence in humans as well [54]. For example, micro-electrical stimulation in brain slice models has shown that DCS outcomes vary depending on the specific fiber volley activated [5]. TMS is the preferred method for human use because it is noninvasive but the spatial resolution is much lower than with micro-electrode stimulation, which may account for some of the variability observed in clinical studies.

In addition to event-related potentials (ERPs) by electrical probes (TMS-MEP, TME-phosphenes, micro-stimulation), ERPs produced by environmental cues (e.g., light, SEP, VEP) can also be produced in human and animal models. Another direct neurophysiological marker found in animal DCS/ACS studies with human correlates is network oscillations which can be measured with EEG and field recordings. Despite differences in the etiology of oscillations between human and animal models (even when the frequency appears matched), mechanistic findings from animal studies on how DCS/ACS effects oscillations in a highly activity-dependent manner [39, 55] may help elucidate complex effects of tDCS/tACS in humans.

Neuronal Polarization

Any forms of electrical stimulation, including AC or DC, generate electric fields that lead to current flow across the brain [22, 56]. This current flow though the brain results in polarization of the neuron membranes which the current passes through. Finite-element models (FEM) have been used to incrementally approximate how neuron membrane potentials will react when exposed to such electric fields. Current flow into a specific membrane compartment will result in local membrane hyperpolarization, and flow out of another membrane compartment will result in

local membrane depolarization [36, 57]. It is fundamental to emphasize that the physics of electrical stimulation dictate that any neuron exposed to extracellular DCS/ACS will have some compartments that are depolarized and others that are hyperpolarized [19, 36]. The neuronal morphology relative to the DC/AC electric field determines the polarity of the neuronal compartments. Simplistically, during tDCS, for a typical cortical pyramidal cell, with a large apical dendrite pointed toward the cortical surface, proximity to a surface anode will result in somatic depolarization, and apical dendrite hyperpolarization [58]. For this same neuron, a surface cathode will result in somatic hyperpolarization and apical dendrite depolarization. For tACS the direction of current flow alternates and so the resulting membrane polarization also alternates—but at each instant, opposite poles of the cell are polarizing in opposite directions.

Though dendrites are polarized opposite to the soma, neuron excitability is conventionally assumed to most closely follow soma polarization. Since tDCS/tACS doses in humans are subthreshold—such that the level of polarization is insufficient to directly cause neuronal firing—polarizations in the somatic membrane potential are thought to influence excitability through modifications in the sensitivity to synaptic input [59].

The assumption that DC/AC electric fields induced somatic polarization are the leading driver of tDCS/tACS mechanisms (as opposed to dendrite polarization) is termed the "somatic doctrine" [38]. Though neuron activity is determined by the integration of activity in all neuronal compartments to varying degrees (dendrites, axon, presynaptic terminal, axon hillock), the somatic doctrine assumes that most functional outcomes can be directly correlated to the soma.

Polarity-Specific Effects for DCS and Implications for ACS

The concept that DCS produces polarity-specific effects is the most fundamental result from classic and ongoing animal studies, and underpins how tDCS protocols for neuropsychiatric disorders are rationalized. As early as 1870 Fritsch and Hitzig showed that application of a positive current (anode) to the cortex had stimulating effects, while a negative current (cathode) inhibits (a finding that itself contributed to early understanding that the cortex is electrically excitable; [60]—a finding that fits well with the somatic doctrine). Other studies [9, 61] helped establish that neural firing rate can be altered by DCS. In the early 1960s, animal studies [8, 62] confirmed polarity-specific changes in discharge rate and further showed excitability changes that are both cumulative with time and out-last stimulation. Early work testing tDCS for psychiatric disorders in fact derived from Bindman and colleagues. In 2000, when Nitsche and Paulus validated the polarity-specific effects of tDCS in humans using TMS, they were very much aware of these animal studies and their work established the convention of anode/cathode providing cortical excitation/inhibition. The earliest clinical trials with tDCS adopted strategies using the anode/cathode to enhance/inhibit function of underlying cortex [63], and this rationale continues to underpin most applications of tDCS to neuropsychiatric disorders (e.g., place anode electrode over left DLPFC to increase its function to treat depression; [64]). Though results from ongoing clinical trials designed based on the rationale anode/cathode excite/inhibit have been encouraging [36, 65], it is important to emphasize that more ongoing clinical neurophysiology and modeling studies suggest that changes in brain function with stimulation polarity are more complicated (e.g., drug-dependent increased cathode intensity from 1 to 2 mA can result in excitation; [66, 67]).

Quantifying Neuronal Polarization with Coupling Constants

In regard to quantifying how much polarization is produced by tDCS/tACS, the concept of the "coupling constant" is fundamental. In the 1980s, Chan and colleagues [19, 20] used turtle cerebellum recordings to model membrane polarization

under near-static electric fields. These monumental series of studies identified the basic morphological determinants for neuronal membrane polarization to applied DCS. However, considering the variety of neuronal morphologies within a brain and across species, one cannot assume that all neurons will polarize in the same manner. To address this, our group has quantified cell-specific polarization by weak DCS in hippocampus and cortex in rat brain slices [36, 58]. We assumed that for weak electric fields the membrane polarization produced by DCS/ACS is linear with electric field intensity along the primary neural axis. For uniform electric fields, the membrane potential polarization can thus be expressed as $Vtm = G \times E$ where Vtm is the polarization of the compartment of interest (volts), G is the "coupling constant" (meter), and E is the electric field (volts/meter) along the primary somatodendritic axis. The coupling constant is also referred to as the "coupling strength" or "polarization length."

Further analysis of coupling constants reveals that the maximal depolarization occurs when the electric fields are parallel with the somatodendritic axis, while electric fields orthogonal to the somatodendritic axis do not produce significant somatic polarization [19, 36]. The coupling strength is roughly related to the size of the cell and the dendritic asymmetry around the soma [58, 68] making pyramidal neurons relatively sensitive to polarization. For cortical pyramidal neurons, the typical polarity of somatic polarization is consistent with those predicted by the somatic doctrine (e.g., positive somatic depolarization for positive electric field). For rat hippocampus and cortical neurons the coupling constant for DCS was in the range of 0.1–0.3 mm [17, 36, 58]. In ferret cortical neurons the DCS coupling constant was approximately 0.25 mm [69]. Generally the maximal polarization is expected at dendritic tufts [36], but in animals should not exceed ~1 mV polarization per V/m electric field [19, 58, 59]. For ACS the coupling constant decreases with increasing stimulation frequency [17] as would be predicted by the RC behavior of the membrane (as evidence by step response experiments; [36]). In humans, assuming scaling of sensitivity with total neuronal length [70], somatic depolarization per V/m may be higher. Experimentally measuring the coupling constant of the soma and other membrane compartments in humans to tDCS remains a fundamental research question.

Synaptic Plasticity

There is a clinical need for lasting changes by tDCS/tACS, as it is impractical to stimulate continuously with electrodes on the head. The desire for lasting change means tDCS should influence plasticity during or after stimulation in the relevant pathway [4]. This section addresses the contribution of animal studies to understanding plasticity generated by weak DC and AC electric fields.

Animal studies in the 1960s established that weak DC current can produce lasting physical change in neural activity, which cannot be explained as persistent "reverberating circuit" of activation [71, 72]. Especially notable are animal studies by Bindman and colleagues [62] that showed that prolonged DCS can produce polarity-specific lasting cortical excitability changes. This study motivated their early work treating depressive patients with tDCS [11, 73]. Persistent polarity-specific excitability alterations were observed in a study using long stimulation protocols lasting up to 13 min [74, 75]. These multiminute protocols are frequently adopted in tDCS research. Lasting changes with AC stimulation have recently been demonstrated in animals when endogenous neural oscillations are present [55].

Long-lasting changes beyond the transient effects of DCS- and ACS-induced polarization would require synaptic changes. Moreover, both in humans and animal studies, changes in synaptically mediated evoked responses (see above) are considered reliable hallmarks of long-term plastic changes that could support lasting clinical effects.

Animal studies of tDCS/tACS allow us to formulate distinct theories on how stimulation can lead to lasting changes in function. Electric fields

generated by tDCS/tACS are subthreshold, in the sense that they are too weak to trigger action potential in quiescent neurons, resulting in only transient polarizations. These acute effects can lead to lasting changes in synaptic efficacy mediated through different paradigms such as the following:

1. Membrane polarization may trigger plastic synaptic changes in a manner independent of action potential generation—simply holding the membrane at an offset polarization initiates synaptic changes. However, in cortical brain slice models (with no background activity), weak polarization was not sufficient to induce plastic changes in synaptic efficacy [76].
2. Changes in action potential rate or timing, secondary to neuronal polarization, may affect synaptic plasticity. Classic animal studies indicated that weak DC stimulation is sufficient to induce short- and long-term plastic changes [8, 71]. However, these studies do not directly provide a causal link between altered neuronal activity during stimulation and prolonged after effects.
3. Incremental polarization of the membrane in combination with ongoing synaptic activity may induce synaptic plasticity. The theory is that the generation of plasticity requires synaptic coactivation during DC stimulation. It has been shown that in vitro synaptic potentiation under anodal stimulation only occurs with concurrent synaptic stimulation at specific frequencies [76]. In a rabbit study, DCS was combined with repeated somatosensory stimulation leading to polarity-specific lasting changes with cathodal stimulation [6]. If one assumes that DCS/ACS exerts a postsynaptic priming effect (polarization of soma) then coactivation of afferent synaptic input could be conceived as Hebbian reinforcement. This learning mechanism has been shown in brain slice models as well in vivo [77, 78]. Clinically this plasticity paradigm is broadly analogous to combining tDCS/tACS with a cognitive task or specific behavior that coactivates a targeted network or combining tDCS/tACS with TMS.
4. Incremental polarization of the membrane may boost ongoing endogenous synaptic plasticity similar to a model of associative learning [6]. Clinically this fourth paradigm is analogous to combining tDCS/tACS with training [79]. It has been shown in rat visual cortex slices that the same tetanic stimulation can induce LTD or LTP depending on the level of polarization of the postsynaptic neuron [80].
5. Meta-plasticity is defined as sustained polarization before, or potentially after, the generation of endogenous LTP that "primes" the brain to respond differently to potentiation. Evidence from brain slices [81] shows that priming with DCS modulates subsequent tetanus-induced LTP in a polarity-specific manner—though opposite to convention with soma hyperpolarization ("cathodal tDCS") enhancing plasticity.
6. Changes in network dynamics where the generation of LTD/LTP is explained through intervention with ongoing oscillations and may manifest as lasting changes in oscillation dynamics [55, 82]: Such modulation may reflect interference with the finely tuned excitatory-inhibitory synaptic balance during oscillations [39].

Aside from these possible synaptic plasticity effects there may be non-synaptic origins of lasting plastic changes following DCS/ACS. Though the synapse is typically considered the locus of plastic changes, "non-synaptic" changes have been noted after DC stimulation in peripheral axons [12]. In brain slice models, where background synaptic activity is absent, synaptic (orthodromic) and non-synaptic (axon, antidromic) can be precisely isolated allowing more precise isolation of synaptic and non-synaptic mechanisms. However, functional outcomes of non-synaptic changes in the CNS would still be expected to affect synaptic processing [83].

Network Effects

The consideration of how weak electric fields modulate active networks (e.g., oscillations) is a compelling area of ongoing research. Electrical recordings, of both intact brains and dissociated in vitro cultures, show that neuronal firing activity tends to synchronize and desynchronize

in phases. These rhythmic firing patterns, termed "oscillations," have been recorded in many species but are primarily studied in humans and rats [46]. Oscillations span a wide range of frequencies in multiple brain regions and are thought to play roles in sleep and memory encoding [84]. In healthy subjects, there is a high level of synchrony between the oscillations that occur in different brain regions. However, in patients with neurological disorders, whether due to cell death or network dysfunction, there is a loss or modification of this synchronous order. Currently, transcranial electrical stimulation is being investigated as a means to resuscitate endogenous oscillations with the ultimate goal of functional improvement.

Up until now, this review has discussed tDCS-induced cellular and synaptic modifications. Considering the oscillatory nature of transcranial alternating current stimulation (tACS), we will also briefly discuss the effects of tACS on oscillations in neural networks.

tDCS and Oscillations

Reports that DCS can alter spontaneous oscillations in animals span decades [85–87]. A significant number of studies on weak DC electric fields and network oscillations addressed epileptiform activity using pathological oscillation models in brain slice models. For example, DC electric fields influence the propagation rate of epileptiform activity [37, 88]. It has also been shown that DC fields up-regulate gamma oscillations in rat brain slices [39]. Interestingly, this increased activity led to a delayed compensatory ("homeostatic") regulation of the network such that the activity levels were normalized to baseline levels. This network adaptation was apparent when the DC field was turned off as the network was delayed in re-adjusting to the absence of the field. Network-level mechanisms may thus provide a substrate for activity-dependent homeostatic-like observations during tDCS [89].

tACS and Oscillations

During ACS, a specific frequency is applied typically using similar electrode montages as used in DCS. Most of the applied stimulation frequencies are within the human EEG frequency range [46, 90]. Repetitive weak ACS can entrain native activity by aligning the phase of these oscillations with that of the AC stimulation [48, 82, 91]. By definition, during prolonged DCS there is no basis for entrainment (there is no phase to the DC), giving ACS a unique theoretical advantage in this regard. In line with effects on the phase of endogenous activity, tACS can selectively modulate spike-timing-dependent plasticity in oscillating networks with specific resonant frequencies [92]. This presents a mechanism for tACS modulation of network activity to produce long-term effects in synaptic plasticity.

In a mouse brain slice model, weak ACS enhanced intrinsic oscillations but failed to induce a frequency shift of the ongoing oscillations for stimulation frequencies that were not matched to native oscillations [51]. These results suggest that the primary tACS mechanism may be to amplify, not override, endogenous network dynamics. In a ferret hippocampal slice model, tACS will form positive- and negative-feedback loops with endogenous oscillating mechanisms in modulating pharmacologically evoked slow-wave oscillations [69]. The distinct roles of the depolarizing and hyperpolarizing phases of tACS in oscillation entrainment have been studied in large-scale computation models [93]. These findings were then verified in anesthetized ferrets, supporting the future of dynamically tailoring stimulation frequency to the endogenous activity.

Applications to Clinical Pathologies

The noninvasive and inexpensive methods of tDCS/tACS have made it versatile and widely studied as a potential treatment for various diseases [94, 95]. tDCS/tACS is especially favorable as a psychiatric disorder treatment because

the effects can be directly assessed with behavioral tests. For these reasons, a majority of published findings are of tDCS effects in humans and relatively few are in animal models. Of the handful of animal studies, most involved highly invasive methodologies or sacrifices (e.g., tissue damage, brain slice, and protein-synthesis experiments). Nonetheless, some studies treating animal models of psychiatric disorders with tDCS are briefly outlined below.

Addiction

A handful of studies using tDCS as a treatment for addiction in humans have been conducted [96]. The studies primarily show that anodal tDCS of the inferior frontal gyrus can reduce cravings better than stimulation of the left dorsolateral prefrontal cortex [97]. Other studies show that tDCS can improve impulse control [98] and reduce risky behavior [99]. In a meta-analysis of addiction in humans, rTMS and tDCS were found to be equally effective at treating addiction [100].

Animal models of addiction primarily involved rats treated with transcranial magnetic stimulation (TMS) in the frontal cortex [101]. In a pilot study, applying 0.2 mA anodal tDCS to the frontal cortex for 20 min twice a day for 5 consecutive days was sufficient to reduce anxiety-like and depression-like behavior in nicotine-addicted mice [102].

Alzheimer's Disease

The main methods of noninvasive brain stimulation for Alzheimer's disease are TMS and anodal tDCS and preliminary findings suggest that both techniques reduced cognitive deficits in Alzheimer's patients [103–105]. Visual recognition memory was also improved after five daily sessions of anodal tDCS and effects persisted for at least 4 weeks after therapy (Boggio). In another Alzheimer's disease memory study, memory was found to improve in Alzheimer's patients receiving memory training regardless if they received tDCS or sham-tDCS [106]. Transcranial electromagnetic treatment was also found to reverse cognitive impairments in Alzheimer's disease transgenic mice. It was also shown that deep brain stimulation (DBS) of the hypothalamus and nucleus basalis of Meynert may improve cognitive function in Alzheimer's patients.

To replicate the cognitive symptoms of Alzheimer's disease, intraperitoneal injections of scopolamine were given to rats that subsequently received 0.1 mA of anodal tDCS twice a day, five times a week [107]. After 2 weeks of treatment, rats treated with tDCS had slightly increased cognitive function in comparison to the rats just treated with tacrine. After the 4 weeks of treatment, rats that receive tDCS therapy had motor behavior improvements and increased acetylcholine activity.

Chronic Stress

Though numerous studies have been shown in tDCS to have a therapeutic effect in animal models and in humans, the limits to gainful tDCS effects were only recently tested [108]. In this study, tDCS efficacy was measured in chronic stress mice models. After subjecting rats to chronic restraint-induced stress (CRS) for 11 weeks, rats were given 20-min anodal tDCS treatment sessions for 8 days. Behavioral tests were performed after the 11 weeks of CRS, immediately after and 24 h after tDCS treatment. Control rats were not subject to CRS but were randomly given either sham or tDCS treatment. tDCS was only able to decrease BDNF release in the spinal cord and brainstem of unstressed rats. Interestingly, CRS rats treated with tDCS had a weak reduction in pain sensitivity even though no change of BDNF levels was detected indicating that a different mechanism may be involved in the attenuation of pain sensitivity. The results from this study highlight that tDCS treatments alone may not be sufficient to produce long-term effects when chronic stress is present.

Prospects for Animal Research in tDCS/tACS Informing Ongoing Human Trials

A central challenge for tDCS/tACS studies is translating data collected from animal models of tDCS/tACS to inform the interpretation and design of human protocols. Historically, tDCS/tACS animal studies have informed human testing. The demonstration that prolonged (minutes) DCS/ACS protocols in animals can lead to short- and long-term plasticity encouraged the use of such protocols in humans [109]. The polarity dependence of DCS was first demonstrated in animal models. Animal models demonstrated that low-intensity DCS/ACS can modulate ongoing neuronal activity giving human technique credence of a cellular substrate [36]—countering the argument that weak fields, such as those applied in tDCS/tACS, are physiologically inert. In some cases, animal studies of DCS/ACS were conducted contemporaneously with human testing providing confirmatory evidence, for example, that AC can entrain oscillations [46, 92] of that tDCS plasticity is NMDA dependent [110].

On the other hand, there are scarce examples of modern animal tDCS/tACS studies influencing how human trials are conducted and analyzed. This reflects how tDCS/tACS protocols have remained largely unchanged with the majority of protocols applying 1–2 mA over 10–30 min using two large pad electrodes without any customization based on an individual's biomarkers. Developments in tDCS/tACS protocols were driven by clinical neurophysiology [65] rather than extrapolated from animal models. Often animal studies confirm findings in humans rather than suggesting novel improvements to the current protocols; a notable example being the identification of the role of BDNF polymorphism [76].

We believe development in animal tDCS/tACS studies combined with an increased emphasis on designing these experiments for clinical relevance would accelerate the development and application of tDCS/tACS in humans. This includes an increased emphasis of the plastic, rather than acute, effects of stimulation [40, 76]. Simultaneously, results from human trials also point to a need to critically address issues such as nonlinear dose–response, state dependency, and inter-subject variability. Animal experiments provide a degree of cellular resolution, state control, and rapid screening not available in human subjects to help detangle complex interactions [36].

We propose that meaningful translation to human applications would be the most accelerated by the exploration of data that *appears*, at first glance, to be conflicted between animals and humans. For example, the acute effects of DCS in animal are monotonic across a very wide intensity and brain-state range (e.g., anodal/cathodal almost always result in excitatory/inhibitory effects after accounting for orientation of neurons relative to field; [61, 81]). This is in direct contrast with clinical neurophysiology studies showing that many pharmacological, dose-dependent, and brain-state perpetrations can qualitatively change the direction of neuromodulation [39, 65]. As another example, ACS in animals can influence ongoing oscillations in a myriad of ways and is dependent on the nature of endogenous activity and stimulation frequency [46, 55, 90], while human testing with tACS and EEG usually explores only a basic single stimulation frequency [50]. Rather than speculating which protocols are ineffective, it would be useful to consider cellular effects from animals in comparison to network effects observed in human studies. The most impactful translational animal studies will be those that explain results from humans in previously unexpected ways and that can suggest nontrivial methods to optimize tDCS/tACS outcome in human trials.

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6 Cortical Inhibition and Excitation in Neuropsychiatric Disorders Using Transcranial Magnetic Stimulation

Natasha Radhu, Daniel M. Blumberger, and Zafiris J. Daskalakis

Abstract

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique used for the investigation of neurophysiological processes such as cortical inhibition, excitability, and plasticity. In the last 20 years, several studies have used TMS to study both cortical inhibition and excitation in psychiatric disorders. The purpose of this chapter is to focus on TMS studies which have enhanced our understanding of psychiatric illnesses such as schizophrenia (SCZ), obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and bipolar disorder (BD). Research to date suggests that SCZ, OCD, MDD, and BD are characterized by deficits in cortical inhibition and by abnormalities in cortical excitability. This chapter discusses current TMS research and highlights the application of innovative neurophysiological techniques to provide a clear platform from which diagnostic and therapeutic procedures can be developed. Changes in cortical excitability and inhibition provide evidence that can advance our understanding of the pathophysiology of psychiatric disorders.

Keywords

Transcranial magnetic stimulation (TMS) • Electromyography (EMG) • Electroencephalography (EEG) • Cortical inhibition • Cortical excitability • Plasticity • Connectivity • Motor evoked potential (MEP) • GABA • Psychiatric disorders

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Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive neurophysiological tool used to investigate the cortex in healthy and disease states [1]. Barker et al. first demonstrated that a single TMS pulse applied to the motor cortex

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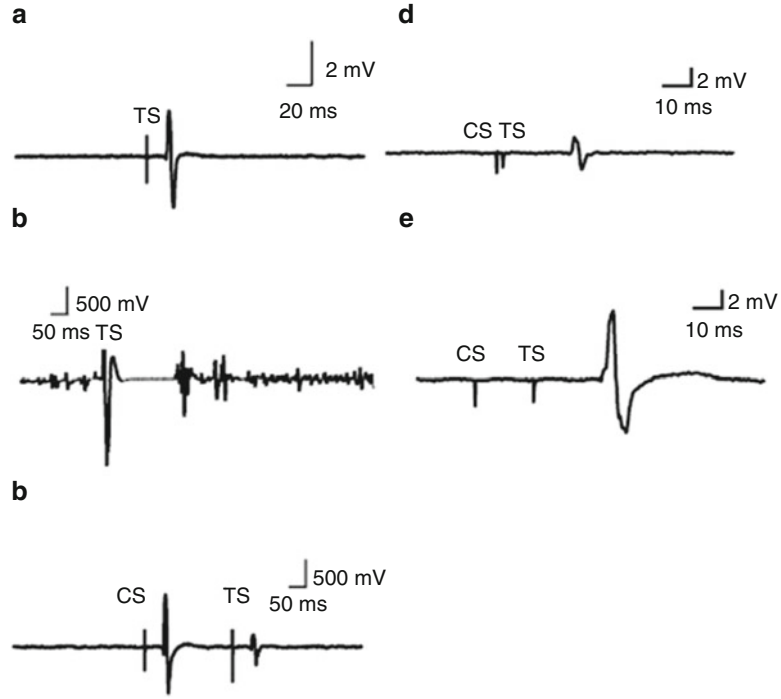

Fig. 6.1 Surface electromyography recordings from a right hand muscle. (**a**) A single test stimulus (TS) applied to the left motor cortex producing a motor evoked potential (MEP). (**b**) The cortical silent period (CSP) is induced following a 40% suprathreshold TS applied to the left motor cortex while the right hand muscle is tonically activated. The CSP starts at the onset of the MEP and ends with the return of motor activity. (**c**) Long-interval cortical inhibition (LICI) occurs when the CS precedes the TS by 100 ms and inhibits the MEP produced by the TS. (**d**) Short-interval cortical inhibition (SICI) occurs when a conditioning stimulus (CS) precedes the TS by 2 ms to and inhibits the MEP produced by the TS. (**e**) Intracortical facilitation (ICF) occurs when the CS precedes the TS by 20 ms, facilitating the MEP produced by the TS

could activate cortical tissues associated with the hand or leg muscles and this activation could elicit motor evoked potentials (MEPs), defined as the overall reaction of a peripheral muscle, captured through electromyography (EMG) recordings [1] (Fig. 6.1a). TMS is also a useful method to further understand the neurobiology of cognitive function, behavior, and emotional processing [2]. It involves the generation of a magnetic field through the use of an electromagnetic coil connected to a TMS device which induces an electrical current in the brain [3]. TMS is used as an investigational tool as it assesses a variety of cortical phenomena including cortical inhibition, excitation, and plasticity [4, 5].

Applications of TMS

TMS has been used for both therapeutic and diagnostic purposes [6]. The amplitude, area, latency, and duration of the TMS-induced MEP may be used to investigate the integrity of the corticospinal pathways and the activation threshold of the human motor cortex. Since this discovery, the combination of single and paired-pulse TMS with peripheral EMG recordings has allowed for examining various processes in the human motor cortex such as excitability, plasticity, cortico-cortical connectivity, as well as the interaction between excitatory and inhibitory

cortical processes. TMS activates cortical neurons transynaptically; therefore, the effects of TMS are highly dependent on cortical excitability. Several TMS measures provide insight into different neurotransmitter systems. The integration of EMG with TMS has offered a valuable tool for the assessment of pathological processes that underlie neurological and psychiatric disorders such as Parkinson's disease, Alzheimer's disease, schizophrenia (SCZ), obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and bipolar disorder (BD).

Importance of GABA

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain, critical for the modulation of cortical excitability and neuroplasticity [7, 8]. In the cortex, GABAergic interneurons have several important physiological functions, such as the downregulation of excessive cortical excitability (e.g., seizures) and neuroplastic generativity, as well as serving discriminative (e.g., top-down modulation) and cognitive processes (e.g., memory). Pyramidal cell activity is synchronized through a balance of inhibitory postsynaptic potentials (IPSPs) and EPSPs [9]. IPSPs are generated by GABAergic interneurons terminating on pyramidal cell [9]. Several lines of evidence suggest that pyramidal neuron firing is governed by GABA inhibitory interneurons (i.e., basket and chandelier cells). GABA interneurons are located throughout the uppermost layers of the cortex and form extensive synaptic networks of connectivity, though limited in number (i.e., GABA interneurons only represent 20–30 % of neurons in the cortex), one GABA interneuron typically connects extensively with several pyramidal neurons [10] forming neuronal networks that fire contemporaneously and their horizontal connections can extend up to 6 mm or more [11, 12]. It has been shown that certain forms of electrical or chemical stimulation can produce highly synchronous rhythmic IPSPs across multiple pyramidal neurons suggesting that synchronized IPSP waves propagate throughout cellular networks. If this synchronized activity is sufficiently large, then the amplitude of these signals will rise above the electrophysiological noise and result in observable oscillatory rhythms [13]. In this way, GABA-mediated synaptic inhibition plays a critical role in the production of neuronal synchronization in cortical circuits. Assessing GABAergic-mediated inhibition using TMS can provide information regarding the neurophysiological mechanisms underlying disease states.

Inhibitory TMS Paradigms

TMS is a safe method, used for both therapeutic and diagnostic purposes [6]. The combination of single- and paired-pulse TMS with EMG recordings permits altering the excitability of the motor cortex and observing the effect of this alteration on subsequent stimulation for investigational usage. In paired-pulse TMS, the first TMS pulse (conditioning stimulus (CS)) inhibits or facilitates the MEP response to the second TMS pulse (test stimulus (TS)) [6]. The nature and the strength of this modulatory effect depends on the intensity of the conditioning stimulus and the latency (i.e., interstimulus interval) at which it is delivered with respect to the test stimulus. The balance and interactions between cortical inhibitory and facilitatory circuits determine motor cortical excitability and output. In this section, several inhibitory TMS parameters are discussed, and evidence supporting their neurophysiological mechanisms is provided. The following measures are discussed: cortical silent period (CSP) [14], long-interval cortical inhibition (LICI) [15], short-interval cortical inhibition (SICI) [4], and transcallosal inhibition (TCI) [16].

Cortical Silent Period and Long-Interval Cortical Inhibition

CSP is a single-pulse TMS paradigm measured by stimulating the contralateral motor cortex of a moderately tonically active muscle (i.e., 20 % of

maximum contraction) with stimulus intensities ranging from 110 to 160 % of the resting motor threshold (RMT) resulting in the interruption of voluntary muscle contraction [14] (Fig. 6.1b). The duration of the CSP is typically measured from MEP onset to the return of any voluntary EMG activity, ending with a deflection in the EMG waveform, this can last up to 300 ms [17]. It has been shown that the first 50 ms represent spinal mechanisms of inhibition, while later inhibition is influenced by cortical networks.

LICI refers to the pairing of a suprathreshold CS followed by a suprathreshold TS at long interstimulus intervals (e.g., 50–100 ms), resulting in inhibition of the MEP produced by the TS in the contralateral muscle [15]. LICI is optimal when the CS precedes the TS by 100–150 ms [18] (Fig. 6.1c). It has been demonstrated that both CSP and LICI are mainly influenced by $GABA_B$ receptor-mediated inhibitory neurotransmission as evidenced by pharmacological studies [19, 20], the time course of the $GABA_B$ inhibitory postsynaptic potential [19, 21, 22] and the suprathreshold TMS pulse intensity used in these parameters [18]. For example, administration of baclofen ($GABA_B$ receptor agonist) has been shown to enhance LICI [20] and CSP [19]. Similarly, vigabatrin (GABA analog) has also been shown to increase LICI and CSP [23]. LICI and CSP are associated with high intensities of TMS producing longer periods of inhibition as $GABA_B$ receptor-mediated responses have higher activation thresholds and their inhibitory influence is longer [18]. Also, LICI is optimal when the CS precedes the TS by 100–150 ms [18] and CSP can last up to 300 ms [17], comparable to the time course of the $GABA_B$ receptor activation shown to typically peak around 150–200 ms post stimulus [21]. Furthermore, Farzan et al. found that a significant positive relationship between the suppression of MEP amplitudes in LICI and the duration of the cortical silent period (CSP) ($r=0.80$, $p<0.001$) [24]. Taken together, this evidence suggests that LICI and CSP are both related to $GABA_B$ receptor-mediated inhibitory neurotransmission.

Furthermore, LICI in both the motor cortex and DLPFC are related to $GABA_B$-mediated neurophysiological mechanisms. Previous data have demonstrated that LICI-induced suppression in the motor cortex and DLPFC are correlated ($r=0.71$, $p=0.03$) [25]. This study also demonstrated a strong relationship between EMG and EEG measures of LICI ($r=0.94$, $p<0.001$) in the motor cortex. In a follow-up study, the finding was replicated and extended as the correlation between EEG and EMG measures of LICI in the motor cortex ($r=0.85$, $p<0.001$) in 36 healthy subjects was found while also demonstrating a high test-retest reliability in the motor cortex (Cronbach's alpha = 0.93) and DLPFC (Cronbach's alpha = 0.97) [24]. Taken together, these above findings suggest that the cortical-evoked suppression induced by LICI is a valid and reliable method to assess $GABA_B$ inhibitory neurotransmission, and is mediated by similar mechanisms in the motor cortex and DLPFC.

Short-Interval Cortical Inhibition

SICI is a paired-pulse inhibitory paradigm that involves a subthreshold (below motor threshold) CS set at 80 % of the RMT that precedes a suprathreshold TS (above motor threshold), adjusted to produce an average MEP of 0.5–1.5 mV peak-to-peak amplitude in the contralateral muscle [4] (Fig. 6.1d). In this SICI paradigm conditioning stimuli are applied to the motor cortex before the TS at interstimulus intervals between 1 ms and 5 ms, resulting in inhibition of the MEP response by 50–90 % [4]. This parameter demonstrates a reduction of cortical excitability and reflects inhibitory effects mediated by $GABA_A$ receptors. Ziemann et al. demonstrated that SICI is increased by medications that facilitate $GABA_A$ inhibitory neurotransmission (e.g., lorazepam) in healthy individuals [26]. Wang and Buzsaki showed through computer simulations that the synaptic time constant for $GABA_A$ receptors approximately ranges from 10 to 25 ms [27]. This finding demonstrates that SICI is related to $GABA_A$ receptor-mediated inhibitory neurotransmission as evidenced by the similar time course of the $GABA_A$ inhibitory postsynaptic potential. SICI is associated with a low intensity CS, producing

shorter periods of inhibition. The $GABA_A$ receptor has a lower activation threshold and its inhibitory influence is brief [18].

Transcallosal Inhibition

The connectivity between motor cortical areas of each hemisphere can be investigated using a twin-coil paired-pulse technique known as TCI. This parameter involves applying a CS to the motor cortex of one hemisphere and is followed by a second stimulus (TS) applied to the other hemisphere. As a result, there is inhibition of the size of the MEP produced by the TS of the opposite motor cortex [16, 28]. This result is consistent with animal studies which show that stimulation of the motor cortex inhibits the contralateral motor cortex [29–31]. TCI can be observed at interstimulus intervals between 6 and 50 ms [16, 32] and at the shorter interstimulus intervals of 4–6 ms, a weak facilitatory effect is observed. Daskalakis et al. found that similar populations of inhibitory neurons may mediate LICI and TCI [33]. Therefore, TCI may be related to $GABA_B$ activity. This is consistent with the finding that lorazepam increased SICI but did not change TCI, suggesting that TCI is not related to $GABA_A$ activity [26].

Short Latency Afferent Inhibition

Short latency afferent inhibition (SAI) measures the effects of sensory stimulation on M1 excitability, assessed by applying a sensory stimulus at the wrist, followed by TMS of contralateral M1 [34]. Inhibition of the rest MEP occurs at interstimulus intervals between 20 and 600 ms [34].

Excitatory TMS Paradigms

TMS can also be used to examine cortical excitability, in this section, the following excitatory TMS paradigms will be discussed in the context of MEP amplitude, RMT, and intracortical facilitation (ICF).

MEP Amplitude

TMS uses electromagnetic induction to generate a strong fluctuating magnetic field, inducing intracranial currents [35]. Stimulation of the hand area of the motor cortex produces MEPS in the contralateral muscle and excitability can be measured with MEP amplitude using single-pulse TMS (Fig. 6.1a). MEP amplitude is measured as the average response to a series of pulses applied at a consistent TMS intensity. MEP amplitude can also be measured as the increasing MEP size produced with increasing TMS intensity, referred to as a MEP response curve [36].

Motor Threshold

Motor threshold is determined by first finding the motor "hot spot" by applying a single-pulse of TMS to the motor cortex while the coil is placed at the optimal position that generates the largest MEP from a target muscle. RMT is defined as the minimum stimulation intensity that produces a MEP > 50 μV in five of ten trials in a relaxed muscle [37]. The two muscles which are more easily accessible by TMS stimulation are the abductor pollicis brevis (APB) and the first dorsal interosseous (FDI) muscles. The RMT depends on largely on voltage-gated ion channels [38] and has been shown to represent membrane excitability in pyramidal neurons. For example, NMDA antagonists such as ketamine reduce motor threshold, the block of voltage-gated sodium channels increases motor threshold, and GABA has no influence on motor threshold. It has been also shown that drugs which block voltage-gated sodium channels, in particular anticonvulsants such as carbamazepine, lamotrigine, and losigamone, increase RMT [39].

Intracortical Facilitation

ICF is a paired-pulse paradigm that can be used to index excitatory activity in the motor cortex. In this paradigm, a CS is applied to the motor cortex before the TS at interstimulus intervals

between 7 and 20 ms which results in an enhanced MEP compared to that produced by the TS alone [4, 40] (Fig. 6.1e). It has been shown that ICF originates from excitatory postsynaptic potentials (EPSPs) transmitted by *N*-methyl-D-aspartate glutamate receptors [40]. Pharmacological studies have demonstrated a decrease of ICF by *N*-methyl-D-aspartate receptor antagonists such as dextromethorphan and memantine [41]. Benzodiazepines such as lorazepam ($GABA_A$ agonist) decreases ICF [26] and baclofen ($GABA_B$ agonist) decreases ICF [39]. However, research has demonstrated that ICF is not exclusively mediated by excitatory interneurons, but rather by a net balance between inhibition and excitability [42]. For a review of the pharmacological effects on inhibitory and excitatory TMS paradigms, please refer to Paulus et al. [38].

Short-Interval Intracortical Facilitation

Short-interval intracortical facilitation (SICF) represents a cortical facilitatory process whereby an initial suprathreshold stimulus suprathreshold and a second stimulus below threshold, applied at short intervals at three distinct peaks of interstimulus intervals (1.1–1.5, 2.3–2.9, and 4.1–4.4 ms) resulting in short-interval cortical facilitation.

Inhibitory Neurotransmission in Psychiatric Disorders

Several research studies have implicated GABAergic inhibitory deficits in the pathophysiology of neuropsychiatric disorders. Several lines of evidence suggest that cortical inhibition is impaired in SCZ, OCD, MDD and BD. With regard to TMS assessing psychiatric conditions, reduced motor cortex inhibition is a very robust finding across studies. For example, previous TMS studies have demonstrated motor cortex inhibitory deficits in cortical inhibition in patients with SCZ [43–51], OCD [52–54], MDD [55–58], and BD [59]. A recently published meta-analysis examined TMS parameters of cortical inhibition and facilitation in SCZ patients, MDD and OCD, hypothesizing an overall inhibitory deficit in severe psychopathology. This publication quantified all motor cortex inhibitory and excitatory paradigms with SCZ, OCD, and MDD. The analysis showed that inhibitory deficits were a ubiquitous finding across SCZ, OCD, and MDD and enhancement of excitability (ICF) was only found in OCD [60]. Specifically, they found significant effect sizes (Hedge's G) for decreased SICI, enhanced ICF and reduced CSP within the OCD population. For MDD, significant effect sizes (Hedge's G) were found for decreased CSP and SICI. Lastly, significant deficits in SICI were shown in SCZ. These findings are in line with previous literature that suggests motor inhibitory deficits among psychiatric disorders; however, this study suggests that each disease may have a distinct illness profile and response to treatment. Based on a systematic review by Bunse et al. [61], the authors found a ubiquitous inhibitory deficits in severe psychiatric illnesses as measured by TMS, however, no clear pattern of deficit in any individual psychiatric condition. The above findings demonstrate an overall general inhibitory deficit in severe psychiatric illnesses and the next section will discuss the specific neurophysiological impairments found in SCZ, OCD, MDD, and BD.

Inhibitory Impairments in Patients with Schizophrenia

Several lines of evidence suggest that abnormalities in cortical inhibition are an important neurophysiological mechanism in SCZ and these impairments have been shown to be related to GABAergic deficits. Benes et al. [62] first reported that patients with SCZ have morphologic changes in cortical GABA interneurons by demonstrating a decreased density of non-pyramidal cells (i.e., interneurons) in anterior cingulate layers II–VI and in prefrontal cortex layer II. More recent studies have also demonstrated deficits in cortical inhibition using TMS in patients with SCZ and have reported that clozapine is associated with potentiation of $GABA_B$ inhibitory neurotransmission when indexed by TMS [45, 47] . For example, Daskalakis et al. [47] reported that ten

clozapine-treated patients with SCZ had significantly longer CSPs compared with ten healthy participants and six unmedicated SCZ patients. A subsequent study by Liu et al. [45] with a large sample of 78 SCZ patients and 38 healthy controls confirmed that clozapine-treated SCZ patients demonstrated a longer CSP and reduced SICI compared with healthy control participants. However, patients treated with other antipsychotics and unmedicated patients demonstrated a significantly shorter CSP duration. These findings suggest that deficits in GABAergic inhibitory neurotransmission is involved in the pathophysiology of SCZ and that clozapine may potentiate $GABA_B$ receptor-mediated inhibitory neurotransmission. Additionally, across all SCZ patients in this study, CSP was inversely related to negative symptoms, while SICI was inversely associated with positive symptoms, highlighting the role of both $GABA_B$ and $GABA_A$ receptor-mediated inhibitory neurotransmission in SCZ. Using TMS, cortical disinhibition as reflected by reduced SICI has been detected in most of the studies examining this motor cortex parameter in SCZ, supporting the theory of deficient GABA in this disease. A very recent prospective-longitudinal study demonstrated that treatment with clozapine in SCZ patients is associated with an increase in CSP at 6 weeks after treatment [63] and from 6 weeks to 6 months there was no significant difference in CSP. These findings are consistent with neurochemical evidence demonstrating that there is a direct link between clozapine and the $GABA_B$ receptor [64]. These results suggest that clozapine increases $GABA_B$ receptor-mediated inhibition and may be involved in pathophysiology and treatment of SCZ. Since cortical inhibition aids suppression of neural noise by filtering irrelevant sensory information imperative for attention and cognitive performance, this deficient brain process may represent a key neurophysiological impairment found in this disease.

Cortical Excitability in OCD Patients

Several genetic studies have reported associations between OCD and dysfunctional GABAergic and glutamatergic genes [65–70]. Arnold and colleagues [71] found a positive association between variants in the 3′ untranslated region of the *GRIN2B* gene—the gene encoding the NR2 subunit of the *N*-methyl-D-aspartate (NMDA) glutamate receptor and OCD in 178 affected individuals from 130 families. Similarly, Whiteside et al., demonstrated increased levels of a combined measure of glutamate and glutamine relative to creatine were found in orbitofrontal white matter in patients with OCD [72]. Furthermore, Chakrabarty et al. showed significantly higher levels of glutamate in OCD [73]. Animal models confirm the role of corticolimbic glutamatergic hyperactivation in patients with OCD [74]. Zai et al., found a positive association between OCD and the $GABA_B$ receptor gene (GABR1) [65], implicating a relationship between dysfunctional $GABA_B$ and the pathophysiology of OCD. TMS studies with OCD patients have demonstrated decreased inhibition [52–54] and enhanced cortical excitability [52]. Richter et al. [52] found that patients with OCD have abnormalities in both $GABA_B$ and NMDA receptor-mediated neurotransmission. Deficits were found in inhibition and excessive intracortical facilitation of the motor cortex, a paradigm reflecting excessive NMDA-receptor-mediated excitatory neurotransmission, independent of medication status. Collectively these findings are consistent with genetic findings reporting GABA and NMDA-related genes involved in the pathophysiology of OCD [65–70]. However, motor cortex TMS studies are of limited interest as the pathophysiology of many psychiatric disorders are more closely associated with frontal brain abnormalities. Therefore, it is essential to evaluate the neurophysiology in brain regions that are more proximal to the underlying phenotype such as the DLPFC.

TMS and MDD Patients

Evidence suggests that MDD may be associated with abnormalities in cortical excitability, and more specifically deficits in cortical inhibition. For example, Fitzgerald et al. [58] assessed cortical excitability prior to a trial of repetitive TMS (rTMS) treatment in MDD patients. This study included 60 patients with treatment-resistant

depression (TRD), of which, 46 were medicated during the trial (antidepressants, mood stabilizers, and antipsychotics). The authors found a decreased SICI of the right motor cortex (1 ms interstimulus interval) and reported that an increased CSP in the left motor cortex predicted a poorer response to rTMS treatment. Bajbouj et al. [57] assessed 20 patients with MDD who had been washed off of medication for at least 4 weeks compared with 20 healthy participants. They found reduced SICI and CSP in patients with MDD, consistent with the hypothesis of deficient GABAergic tone in depression. Similarly, Lefacheur [56] demonstrated that MDD patients showed a reduced excitability of both excitatory (RMT, ICF) and inhibitory (CSP, SICI) processes in the left hemisphere when compared to healthy controls. More recently, Levinson et al. [55] examined cortical inhibition in 25 medicated individuals with treatment-resistant depression (TRD), 19 medicated euthymic participants, 16 unmedicated depressed patients and 25 healthy controls and found that all patients with MDD, regardless of symptom or medication state, demonstrated significant CSP deficits compared with healthy participants. Patients with TRD also demonstrated significant deficits in SICI compared with healthy participants. The findings above all held true after controlling for benzodiazepine use which has been shown to affect TMS parameters [55]. Since all MDD patients showed CSP abnormalities but only TRD subjects additionally demonstrated SICI reductions, the authors concluded that the depressed state may be overall associated with $GABA_B$ deficits, but severe symptomatology, as seen in TRD, may be associated with greater deficits in both $GABA_A$ and $GABA_B$ neurotransmission. Taken together, the above findings suggest that MDD is associated with deficits in GABAergic inhibitory neurotransmission and abnormalities in inhibitory functions of the motor cortex.

TMS in Patients with Bipolar Disorder

Limited neuroanatomical and neurophysiological evidence has demonstrated that BD patients have impaired cortical inhibitory neurotransmission [75]. Benes and Berretta found that the density of cortical GABA interneurons, which mediate cortical inhibition, is reduced in the anterior cingulate cortex among patients with BD [76] and also found a 30% decrease in cortical inhibitory GABAergic interneurons in BD, compared with a 16% decrease in patients with SCZ [76]. The data suggests a loss of GABAergic interneurons in both BD and SCZ. However, there is little in vivo neurophysiological evidence supporting such impairments in BD. Levinson et al. [59] used TMS to evaluate SICI, CSP, and IHI in 15 BD patients (13 medicated with a single mood stabilizer and two unmedicated) compared to 15 healthy control participants. They found that BD patients demonstrated significant deficits in SICI, CSP and IHI compared with healthy individuals. The authors concluded that GABAergic inhibitory neurotransmission is deficient in the motor cortex of patients with BD. Furthermore, the majority of patients were medicated and the evidence suggested that these inhibitory deficits were attenuated with treatment. Nevertheless, additional studies are needed with large unmedicated samples, and more severely ill patient populations.

Clinical Implications

TMS paradigms hold potential as biomarkers of psychiatric disorders and treatment response. Biomarker development will lead to strategies that prevent manifestation of the illness and increase our understanding of the underlying neurobiological mechanisms. However, further replication of findings is required. The use of TMS to establish molecular engagement of novel psychopharmacological and somatic treatments (i.e., electroconvulsive therapy, rTMS, magnetic seizure therapy, transcranial direct current stimulation (tDCS), or cognitive behavior therapy), particularly within the GABA and glutamate circuits, are other potential biomarker roles for these tests. Conceivably TMS measures of GABAergic and glutamatergic functioning could be used as biological markers of novel treatments that are aimed at enhancing inhibition or decreasing facilitation in the cortex.

Use of EEG

Electroencephalography (EEG) is a commonly used tool used for understanding the brain oscillations, whereby electrical activity of neurons is monitored by placing multiple electrodes along the scalp. EEG records event-related brain activity from the entire surface of the brain as electrical signals are primarily generated by coordinated output of neurons from the scalp's surface [77]. By contrast, when sensory stimuli are presented to subjects, evoked activity that is of greater electrical power is produced and recorded at the scalp surface when compared to resting EEG recordings. Such activity can be used to evaluate the neurophysiological mechanisms involved in the processing of emotional or cognitive stimuli. EEG records cortical oscillations from neural sources that span a range of frequencies: delta (0.5–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–80 Hz). At rest, EEG can be used clinically to diagnose tumors, seizures, encephalopathies, brain death and potentially as biological markers of neuropsychiatric illnesses [78–81] and is widely used due to high temporal resolution and low cost.

TMS Combined with EEG

Most of our current knowledge about the physiological properties has been derived from the motor cortex. A growing body of research is now exploring EEG concurrently with TMS, a valuable method for directly probing the oscillatory dynamics of regions throughout the brain. TMS has been combined with EEG to evaluate the effects of electromagnetic induction on cortical oscillations, a methodological combination that has generated important neurophysiological leads in both healthy and disease states [82, 83]. Many studies have demonstrated the tremendous potential for the recording of TMS-evoked potentials in both motor and nonmotor regions of the brain. TMS-EMG studies have shown to be invaluable in assessing the pathophysiology of neuropsychiatric disorders [55, 59, 84] and the effects of various medications on different neurotransmitter pathways in the cortex [26, 39, 41, 85–87]. However, combined TMS and EEG has the potential to extend such findings to frontal brain regions [25] and to provide evidence about important physiological mechanisms that are unique to individual brain regions [88].

Simultaneous EEG recording during TMS stimulation was previously unattainable because of the technological shortcomings of EEG amplifiers that would saturate for a long duration due to the large artifact produced by the magnetic stimulation. For example, application of a single-pulse of TMS would result in an artifact lasting for several seconds. Such long lasting artifact blocked the window of time during which neurophysiological processes such as cortical inhibition occur. Through advances in EEG amplifier technology, researchers have conducted series of studies to examine TMS paradigms in the motor cortex through simultaneous EEG and EMG recordings and in nonmotor regions of the cortex through EEG recordings.

Application of Combined TMS and EEG in Psychiatric Disorders

TMS-EEG allows for the investigation TMS-evoked potentials in motor and nonmotor brain regions. Additionally, the combination of TMS and EEG allows a more detailed assessment of the cortical inhibition and excitation balance of the cortex and also measures cortical connectivity by analyzing the spatiotemporal propagation of activity following TMS [89]. Daskalakis et al. and Fitzgerald et al. were the first to demonstrate that recording LICI (paired-pulse technique) through interleaved TMS-EEG was feasible [25, 90] in both the motor cortex and DLPFC in healthy subjects. In the motor cortex, EEG measures of LICI were represented by the reduction of cortical evoked activity in the electrode C3 that best represents evoked activity in the hand area of motor cortex closest to the optimal site of abductor pollicis brevis activation through TMS [91]. LICI was defined using the area under rectified unconditioned and conditioned waveforms for averaged EEG recordings between 50 and 150 ms post-test stimulus. This was an interval that was chosen as it represents the earliest artifact

free data (i.e., 50 ms after the TS) and reflects the duration of $GABA_B$ receptor-mediated inhibitory postsynaptic potentials (i.e., 250 ms after the CS) [92]. There was a significant inhibition in mean cortical evoked activity through LICI compared to the test stimulus alone in both the motor cortex and DLPFC (targeted through cortical co-registration methods [93]). Farzan et al. has demonstrated the validity, replicability, and test–retest reliability of LICI using the TMS-EEG method in both the motor cortex and DLPFC [24]. Similar research was also developed through experiments by Fitzgerald et al. who used equivalent methods and reported maximal inhibition from 50 to 250 ms in DLPFC, and between 50 and 175 ms in the parietal lobe and concluded that LICI may be recorded from several cortical regions with a time course similar to known $GABA_B$ receptor-mediated inhibition [94].

The combination of TMS with EEG allows for examining cortical inhibitory processes in neuropsychiatric disorders which are closely associated with impairments of cortical oscillatory activity in the frontal regions of the cortex. For example, impairments in gamma oscillations have been reported during cognitive performance in the prefrontal cortex in patients with SCZ [95, 96]. In this regard, we have demonstrated that patients with SCZ exhibit abnormal gamma oscillations during working memory performance [97]. Given these frontal gamma impairments, we conducted a TMS-EEG experiment to examine the integrity of LICI induced modulation of gamma oscillations in the DLPFC of patients with SCZ compared to healthy subject in whom, as described previously, LICI resulted in a significant inhibition of gamma oscillations following paired pulse stimulation of DLPFC [98]. Utilizing these EEG measures of LICI, which were shown to have high test-retest reliability [24], we have demonstrated that inhibition of gamma oscillations was selectively impaired in the DLPFC of patients with SCZ compared to both healthy subjects and patients with BD [99]. No deficits were observed in the EEG or EMG measures of LICI in the motor cortex or in modulation of any other frequency bands in the DLPFC. Patients with BD were similar to patients with SCZ in relation to severity of symptoms, illness duration, and history of psychosis, and about half of them were on antipsychotic medications. In addition, the extent of gamma inhibition did not correlate with the medication dosage, suggesting that the specificity of gamma inhibition deficits were to SCZ and the DLPFC is less likely to be part of a generalized deficit that is simply related to psychotropic medications and it may represent a candidate endophenotype for SCZ. In a more recent study, Radhu et al. [83] found significant deficits in LICI in patients with SCZ compared to healthy subjects but there were no significant LICI deficits in patients with OCD. LICI deficits in the DLPFC were also significantly greater in patients with SCZ compared to patients with OCD. The authors also showed no correlation with medication dosage. Finally, there were no significant LICI differences across all three groups in the motor cortex [83]. Combining these findings with evidence of impaired gamma modulation during cognitive performance in patients with SCZ, it may be hypothesized that the impairments of LICI in the DLPFC may explain the frontal cognitive deficits in this illness. Disturbances in chandelier cell functioning could impair the ability of cortical circuits to engage in high frequency synchronous oscillations [100], as a result, disrupted LICI may result from disordered synaptic wiring in key cognitive networks. Furthermore, Frantseva and colleagues demonstrated an increased TMS-induced cortical activation (in the gamma frequency range) that spread across the cortex as measured by TMS-EEG in SCZ, however, in healthy controls this activation faded away soon after stimulation [101]. Gamma oscillations represent an important neurophysiological process that may, in part, be responsible for optimal cognitive function and may explain why their functioning is largely localized to the DLPFC [98], shown to be dysfunctional in SCZ. To ascertain these findings further, future studies should examine the correlation between frontal inhibitory deficits, attentional processing and working memory performance in SCZ patients.

Clinical Applications of Brain Stimulation

Research has shown that pathological alternations of neuroplasticity are involved in neuropsychiatric diseases; brain stimulation techniques are able to induce a plastic reorganization of cortical circuits. The following neuromodulatory techniques will be reviewed: rTMS, theta burst stimulation (TBS) and tDCS. The research surrounding the applications of these therapeutic interventions in neuropsychiatric disorders will be discussed in this section. These treatment modalities have potential to last beyond the stimulation period and can also lead to a reduction in psychiatric symptoms.

Repetitive TMS

Previous research has demonstrated plasticity of the cortex and modifications in motor performance, memory, learning and behavior following the use of rTMS [102–107]. Conventionally, rTMS is administered through application of TMS pulses at a frequency of 0.5 Hz (interstimulus interval of 2 s) to 50 Hz (interstimulus interval of 20 ms). When TMS is given repetitively, it has been shown to have a neuromodulatory effect, for example, the repetitive administration of TMS pulses applied to a specific brain region results in summation of TMS induced alteration of cortical activity, thereby causing an effect which may outlast the stimulation period [108].

The proposed mechanism underlying the therapeutic effects of rTMS may be via the induction of increases or decreases in cortical excitability or inhibition [109]. Stimulus intensity, frequency and total number of pulses all contribute to these effects. For example, high frequency stimulation (>1 Hz) induces an increase in cortical excitability [108] and decreases SICI. Further, high frequency rTMS increases CSP, as only high frequency stimulation potentiates cortical inhibition [110, 111]. CSP lengthening may be used to guide treatment response [110, 111]. In contrast, low frequency rTMS (less than or equal to 1 Hz) reduces cortical excitability [112]. For a detailed review of the effects of rTMS on cortical excitability and inhibition, please refer to Fitzgerald et al. [109]. The application of active rTMS has been used as a therapeutic tool to improve and restore functional impairments in several neurological disorders, movement disorders as well as psychiatric disorders, with the most promising outcomes observed in the treatment of depression [113] and reducing excessive gamma oscillatory activity in SCZ [114]. It has been proposed that similar to pharmacological treatment the therapeutic efficacy of rTMS depends on the "dose" of treatment (i.e., frequency, number of pulses per session, and number of days of treatment) [115]. This technique has the ability of inducing long-lasting changes of neuronal activity in cortical tissues, but the mechanisms of these modifications and parameters used for treatment must be studied more extensively.

Theta Burst Stimulation

The use of TBS is a relatively new rTMS approach that has attracted a lot of interest due to its long lasting effect relative to the short administration period. TBS involves application of three bursts of 50 Hz rTMS repeated every 200 ms either continuously for a total of 40 s, or intermittently (every 8 s) for a total of 3 min. Continuous TBS (cTBS), and intermittent TBS (iTBS) are commonly used. cTBS involves either 300 or 600 pulses of uninterrupted TBS delivery, and has shown to reduce cortical excitability for up to 60 min. Using iTBS comprises of 2 s of TBS trains repeated every 10 s, with a total number of 600 pulses applied, and has shown to increase cortical excitability for at least 15 min. It has been shown that despite the relatively short duration of TBS administration (40 s in cTBS and ~3 min in iTBS) compared to the conventional rTMS (~25 min), the alteration of cortical excitability by TBS can last for about 70 min which is more than twice as long as the duration of the after effects reported in the conventional rTMS approaches [116, 117]. While 25 min of 1 Hz

rTMS may induce changes lasting for about 30 min, only 40 s of TBS may result in MEP modulation lasting for more than 60 min [118]. Previous TMS-EMG studies had shown that application of cTBS over the motor cortex results in suppression of MEPs at the periphery. Through combination of TMS-EMG with concurrent EEG recording, it has been demonstrated that the cortico-peripheral effect of cTBS involves a reduction in the cortico-muscular coherence within the cortical beta band oscillations measured thorough EEG C3 electrode in the primary motor cortex [119]. Nevertheless, due to its shorter duration of stimulation and lower intensity used, TBS may prove to be a more effective way of modifying brain activity and has been employed as a therapeutic tool, however, wider usage of TBS has yet to be implemented [120].

Transcranial Direct Current Stimulation

An additional noninvasive and nonconvulsive brain stimulation modality is tDCS, which changes cortical tissue "excitability" as a result of applying a weak (typically 1–2 mA) direct current via a pair of scalp electrodes overlying targeted cortical areas [121]. It serves as a potential treatment option in psychiatric disorders and is a novel treatment modality for depression [122], which may represent an alternative to pharmacological or psychological treatments. In contrast to other neurostimulation techniques, tDCS does not directly trigger action potentials in neuronal cells, but instead changes overall tissue excitability. There are two types of tDCS (anodal and cathodal stimulation), anodal tDCS involves placing the anode over the stimulation target and the cathode at the reference, shown to increase cortical excitability under the anode [89, 123]. Cathodal tDCS applies the opposite arrangement and has been shown to decrease cortical excitability under the cathode [89, 123]. These changes were not limited solely to the period of stimulation, but endured for minutes to hours afterward [123]. Recently, a meta-analysis of ten randomized controlled trials comparing active tDCS to sham tDCS, including 393 patients with major depressive episodes. They demonstrated that tDCS was superior to sham tDCS in the treatment of depressive episodes [124]. tDCS was used as monotherapy or as adjunctive treatment for depression in conjunction with medication and/or cognitive control training. The authors concluded that tDCS may represent an effective treatment option for patients with depressive episodes and further research is needed involving larger samples over longer periods of treatments. Furthermore, tDCS has demonstrated some efficacy in treatment-resistant major depression. Several open-label studies have suggested that left DLPFC cathodal and right DLPFC anodal tDCS may be an effective treatment configuration in more severely depressed patients [125–127]. Additionally, there has been very little research examining tDCS for enhancing cognitive performance in SCZ patients. Two recent trials In SCZ patients, showed that anodal tDCS applied to the left DLPFC significantly improved working memory performance [128, 129]. Limited studies have shown anxiety disorders; in a single case study, 2 mA 20 min tDCS (cathode—F3/anode—posterior neck) did not alter OCD symptoms, although depression and anxiety were improved [130]. More work needs to be done in OCD and anxiety disorders. Taken together, these abovementioned studies suggest that tDCS offers a generally acceptable tolerability and safety profile, low cost, ease of use, and portable, which may make it a useful alternative treatment approach in neuropsychiatric disorders.

Concluding Remarks

The results from the abovementioned studies are promising, demonstrating efficacy of various brain stimulation modalities such as rTMS, TBS, and tDCS in neuropsychiatric diseases. Changes in indices of excitability and inhibition may ultimately serve as a biomarker of treatment efficacy as these measures are reported to be altered in psychiatric disorders. The clinical use of TBS and tDCS is yet to emerge; further studies directly assessing the neural and behavioral effects of these techniques are required.

Discussion and Conclusions

TMS is an innovative technique that allows for the investigation of the cortical phenomena in both motor and nonmotor regions of the brain. Advances in cortical stimulation and cortical recording techniques over the past few decades have allowed for the systematic and noninvasive investigation of neurophysiological processes such as inhibition, excitation and plasticity. Among such advancements, concurrent TMS and EMG recordings have been instrumental in identifying and probing cortical processes that underlie the generation and modulation of MEPs.

There is significant potential for the future of this research to evaluate a variety of other neurophysiological processes in the cortex. Future studies may also permit the recording of plasticity in nonmotor brain regions. For example, 30 min of repeated stimulation of the median nerve applied simultaneously with TMS to the motor cortex results in long-term potentiation in the motor cortex through a paradigm known as PAS [131]. This cotemporaneous excitation of sensory afferents and motor interneurons translates into increased motor excitability. These and other plasticity measures have been previously shown to be impaired in SCZ [132, 133] and MDD [134]. Thus, combining TMS and EEG with PAS can be used to index plasticity in the DLPFC, and it can provide critical advantages when attempting to understand key brain mechanisms underlying learning and working memory. Future studies may also be used to examine potential regional pharmacological effects that may be of particular importance to illnesses whose pathophysiology may be more regionally specific.

Research to date suggests that disorders such as SCZ, MDD, OCD, and BD are characterized by specific deficits in cortical inhibition and abnormalities in cortical excitability. However, the findings are not entirely consistent. Factors that may play a role in the discrepant results include small sample sizes, differences in TMS parameters used, the use of heterogeneous populations, and presence of comorbid illness. Further, medications may affect outcomes of TMS measures and it is likely that different classes of psychotropic medications may do this in unique ways. As such, the inclusion of medicated individuals on various classes of psychotropic agents in these studies is a significant confounder of results. Addressing these issues systematically in future research would allow greater confidence in results and provide a more stable evidence base for elucidating biological markers and mechanisms involved in psychiatric illnesses. TMS-EEG offers a highly sensitive measurement of cortical activity from both the stimulated region and connected cortical areas. In particular, TMS-EEG enables the evaluation of TMS-evoked oscillations that may act as a marker for cortical excitation and inhibition, and provides valuable information from cortical areas not traditionally assessed using TMS. The ability to evaluate physiological response profiles of different oscillatory frequencies in response to TMS combined with EEG in the DLPFC may ultimately serve as a key technique for evaluating biological markers in psychiatric illnesses. Lastly, the efficacy of various brain stimulation modalities such as rTMS, TBS, and tDCS in neuropsychiatric diseases are promising. In conclusion, the use of TMS will continue to provide insight into the neurobiological underpinnings of psychiatric disorders.

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Neurocognitive Effects of tDCS in the Healthy Brain

7

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Abstract

This chapter provides an overview of the literature concerning the effects of tDCS on high-level cognitive functions in young healthy adults. tDCS has been found to modulate a multitude of components of cognition, but here we place a particular focus on studies that have examined working memory, attention, language, numerical cognition, general learning and memory. We additionally devote latter portions of the chapter to evaluating two other pertinent topics: the neurocognitive effects of tDCS in the healthy *older* brain and individual differences in the context of tDCS outcomes. Based on the studies reviewed, we conclude that tDCS holds substantial promise as a tool for exploring novel theoretical hypotheses, as well as for improving cognitive functions in both young and older healthy adults. However, the coherence of the evidence base and the translational potential of these findings is currently constrained by a number of factors, including pervasive inter-individual differences in response to tDCS, heterogeneity of tDCS protocols across studies and inadequate knowledge about the longevity of the effects.

Keywords

Transcranial direct current stimulation • Cognition • Working memory • Attention • Language • Memory • Cognitive enhancement • Numerical performance

Introduction

Across the multitude of studies that have examined the effects of transcranial direct current stimulation (tDCS) on human brain and behaviour, the population that has been assessed the most frequently is young healthy adults. Initially, the majority of studies with young healthy adults

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were designed as a precursor for patient studies. However, increasingly more studies have focussed solely on the effects of tDCS on the healthy brain. Typically, the main objectives of this research are to: (1) further our understanding of brain–behaviour relationships and generate functional hypotheses about constituent properties of the human brain; and (2) to appraise tDCS as a cognitive enhancer for neuro-typical individuals [1, 2], with the view to yielding potential applications for education, the workforce and the economy. In the present chapter, we review the literature concerning the effects of tDCS on high-level cognitive functions in young healthy adults, with a particular focus on working memory, attention, language, numerical cognition, and general learning and memory. We additionally devote latter portions of the chapter to evaluating two other pertinent topics: the neurocognitive effects of tDCS in the healthy *older* brain and individual differences in the context of tDCS outcomes.

Effects of tDCS on Working Memory

Working memory (WM) refers to the mental workspace that facilitates the temporary storage and online manipulation of goal relevant information, while ignoring non-relevant information [3]. WM is required for a wide range of cognitive abilities such as problem-solving, reasoning, language and learning, and is accordingly critically involved in many aspects of daily functioning. WM also appears to be particularly vulnerable to disruption, as evidenced by the several psychiatric and neurological conditions that are characterised by WM impairments. At the neural level, WM primarily relies on a frontoparietal network, chiefly comprised of the dorsolateral prefrontal cortex (DLPFC; [4]) and the posterior parietal cortex (PPC; [5]). The DLPFC is particularly critical for updating goal representations based on context [6–8], encoding task-relevant rules, associated responses, stimulus features and conflict [9]. The PPC, on the other hand, is primarily involved in the storage of perceptual attributes relating to spatial locations [10]. Consistent with this knowledge about the neural basis of WM, the vast majority of studies that have examined the effects of tDCS on working memory have targeted either the DLPFC or PPC. Some of the studies differ with regard to the paradigms they employed, but a variation of the n-back task has been used in the majority. The n-back task requires subjects to monitor a string of visual or auditory stimuli, and compare each new stimulus with a stimulus presented *n* trials previously. The load of the task is usually varied between 0- and 3-back, which is parametrically related to the cognitive demands. Performance on the n-back is typically evaluated via response time for stimulus detection and rates of correct and error responses. The methodological parameters for the tDCS studies reviewed in this section are summarised in Table 7.1.

Fregni and colleagues [11] were among the first to examine the effect of tDCS on working memory. They showed that after only 10 min of anodal tDCS over the left DLPFC, subjects produced significantly fewer errors and more correct responses on a 3-back WM task. On the other hand, neither cathodal tDCS over the same area, nor anodal tDCS over the primary motor cortex (M1), had any effect. Using a very similar task, Ohn and colleagues demonstrated that the beneficial effects of anodal tDCS on performance accuracy were stable for up to 30 min after the end of stimulation, an observation that has particular import for the translational potential of these findings.

At least, two other studies that investigated the effect of anodal tDCS over left DLPFC did not find changes in performance accuracy, but instead found that improvements were particular to response time parameters [12, 13]. The reasons for these disparate results are not clear. It is possible that different results in some cases may have been due to greater emphasis being placed on speed over accuracy when task instructions were being explained [14]. It is also possible that ceiling effects were present in the latter studies, since performance accuracy was relatively high at baseline. However, many other stimulation protocol differences may have also played a role. Some authors have suggested that longer

Table 7.1 The effects of tDCS on working memory ([39, 88] (BMC Neuroscience))

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Fregni et al. [11]	Crossover (active vs. sham)	15	F3/R SOA; R SOA/F3; M1/R SOA	1 mA (AoE: 35 cm^2) for 10 min, during verbal 3-back	A-tDCS over L DLPFC improved accuracy by ~9% (21.7 vs 19.8) and decreased number of errors by ~28% as compared to sham (4.7 vs 6.9). No impact after C-tDCS over L DLPFC or A-tDCS over M1. No impact on RT
Ohn et al. [15]	Crossover (active vs. sham	15	F3/R SOA; R SOA/F3	1 mA (AoE: 25 cm^2) for 30 min, during verbal 3-back	A-tDCS improved accuracy by 10% (at 20 min), 16% (at 30 min), 14% (at 30 min after) as compared to sham. No impact on error rates or RT
Ferrucci et al. [93]	Crossover (active vs. sham)	13	R MB/2 cm below the inion 2 cm below the inion/R MB	2 mA (21 cm^2), for 15 min prior to performance of the Sternberg task	Both A-tDCS and C-tDCS impaired a practice-dependent improvement in RT on the Sternberg task, that was apparent for sham tDCS
Mulquiney et al. [12]	Crossover (active vs. sham)	10	F3/R SOA	1 mA (AoE: 35 cm^2) for 10 min during 2-back	A-tDCS decreased RT in WM (2-back) for correct responses by ~2% compared to sham. No impact on accuracy. No impact on STM tasks
Teo et al. [13]	Crossover (active vs. sham)	12	F3/R SOA	1 or 2 mA (AoE: 35 cm^2) for 20 min during verbal 3-back	During the final 5 min of A-tDCS (2 mA) over L DLPFC RT improved significantly as compared to sham (~581 ms vs ~605.25 and ~629.49 ms). No impact on accuracy. No impact on STM after stimulation
Zaehle et al. [21]	Crossover (active vs. sham)	16	F3/R M; R M/F3	1 mA (AoE: 35 cm^2) for 15 min prior to performance of a verbal 2-back	A-tDCS improved RT as compared to C-tDCS and resulted in amplified oscillatory power in the theta and alpha bands under posterior electrode sites. C-tDCS had opposite effects on EEG measures. No impact on accuracy

(continued)

Table 7.1 (continued)

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Andrews et al. [16]	Crossover (active vs. sham)	10	F3/R SOA	1 mA (AoE: 35 cm^2) for 10 min, during task (verbal 2-back and 3-back) or offline	Online A-tDCS improved digit span forward by 5.5 % as compared to offline A-tDCS and sham. No information regarding online task outcome
Keeser et al. [46])	Crossover (active vs. sham)	10	F3/R SOA	2 mA (AoE: 35 cm^2) for 20 min, before numerical 3-back	A-tDCS had a positive impact on error rate, accuracy and RT. These behavioural improvements were accompanied by increased amplitude of two event-related components (P2 and P3) for the 2-back condition
Mylius et al. [19]	Parallel and crossover (active vs. sham)	24	F3/R SOA; R SOA/ F3; F4/L SOA; L SOA/F4;	2 mA (AoE: 35 cm^2) for 20 min during verbal 2-back	No significant differences in WM performance were observed between the active tDCS conditions and sham
Sandrini et al. [164]	Crossover (active vs. sham)	27	P3/P4; P4/P3	1.5 mA (AoE: 35 cm) for 13 min during verbal 1-back and 2-back	1-back: LA/RC (P3/P4) tDCS abolished practice-dependent improvement in RT as compared to sham (9 % vs. 0.65 %). 2-back: LC/RA (P4/P3) tDCS abolished practice-dependent improvement in RT (9.8 % vs. 0.45 %) as compared to sham. No impact on error rates
Boehringer et al. [27]	Crossover (active vs. sham)	40	R MB/2 cm below the inion	2 mA (AoE: 25 cm^2) for 25 min prior to performing a digit span task	C-tDCS, relative to sham, over the cerebellum was associated with an offline decline in performance on the digit span task, and blocked a practice dependent increase in digit span
Meiron et al. [20]	Parallel (active vs. sham)	41	F3/Cz; F4/Cz	2 mA (AoE: 16 cm^2), 15 min, during verbal n-back (four levels)	During online stimulation at highest WM loads males benefited from stim over L DLPFC as compared to sham, while females improved after stim over R DLPFC. No impact on RT. Online accuracy scores at the highest WM level was related to post-tDCS recall

Hoy et al. [165]	Crossover (active vs. sham)	18	F3/R SOA	1 and 2 mA (AoE: 35 cm^2) for 20 min prior to verbal n-back	Both 1 and 2 mA A-tDCS was associated with faster response times, compared to sham. These improvements were apparent immediately after stimulation and up to 40 min post-stimulation. Improvements in accuracy were also observed following 1 mA, but not 2 mA, suggesting a non-linear dose response to tDCS
Heimrath et al. [91]	Crossover (active vs. sham)	12	P8/P7; P7/P8	1 mA (35 cm^2) for 30 min prior to performing a visuospatial WM task	C-tDCS, relative to sham, improved visuo-spatial WM capacity, whereas A-tDCS, relative to sham, interfered with WM capacity when applied over the R parietal cortex. Polarity-specific modulations of electrophysiological correlates of WM were also observed
Gill et al. [18]	Parallel and crossover (active vs. sham)	23	F3/R SOA	2 mA (AoE: 25 cm^2) for 20 min during verbal 3-back or 1-back	A-tDCS when paired with performance of the verbal 3-back was associated with both faster and more accurate on the A-PASAT task, compared to sham tDCS, and compared with A-tDCS coupled with performance of the verbal 1-back
Nikolin et al. [39]	Crossover (active vs. sham)	16	4×1 ring arrays over F3; PT; and L MTL	2 mA (CD: ~.0032 mA/cm^2) for 5 min before and 15 min during the RAVLT	HD-tDCS over left DLPFC was associated with faster responding during a 3-back WM task. There was no effect on accuracy

N sample size, *R* right, *L* left, *AoE* area of electrode, *A* anode/anodal, *C* cathode/cathodal, *M1* primary motor cortex, *SOA* supraorbital area, *M* mastoid, *MB* musculus biccinator, *RT* response time, *A-PASAT* paced auditory serial addition task, *PT* planum temporale, *MTL* medial temporal lobe, *CD* current density, *RAVLT* Rey Auditory Verbal Learning Test

stimulation duration [15] and greater current density [13] might be associated with more pronounced WM improvements.

Andrews and colleagues also showed that anodal tDCS over left DLPFC applied concurrent to performance of an n-back task resulted in improved performance on a different type of WM paradigm (digit span) measured offline. They furthermore demonstrated that there was no improvement in digit span performance when tDCS was administered in the absence of any behavioural task [16]. Comparable findings were observed in a study by Martin and colleagues, wherein it was found that improvements on a WM cognitive training task were significantly better in subjects who received anodal tDCS during training as opposed to immediately before [17]. Gill and colleagues have recently corroborated and extended these findings by showing that the extent to which subjects showed tDCS-related improvements on a task that required working memory (Paced Auditory Addition Test) depended on whether they performed the 3-back or 1-back task while they received tDCS over the left DLPFC [18]. Collectively, these studies underscore how the effects of tDCS on WM are critically contingent on the cognitive demands that the subjects are enduring while they receive the stimulation. Furthermore, these studies highlight the potential for tDCS to enhance WM capacity in manner that generalises to tasks beyond those that the subject is engaged in while they receive the stimulation, and accordingly, also provide basis for suggesting that neuroplastic changes may be one of the mechanisms through which tDCS affects WM.

To the best of our knowledge only one published study has reported no improvement in WM with the anode over left DLPFC [19]. This study also observed no effect of WM with the anode over the right DLPFC. Meiron and colleagues have since suggested that gender might moderate the extent to which a subject will benefit from anodal tDCS over left, relative to right, DLPFC. That is, they found that males' WM performance benefited more from left DLPFC stimulation, whereas females benefited more from right DLPFC stimulation. Albeit, this gender-dependent dissociation was only apparent when task loads were high [20]. Consistent with several other studies, Zaehle and colleagues observed a tDCS-induced improvement in WM with the anode over the left DLPFC, and additionally found that when the cathode was placed over the same region it disturbed WM performance. Interestingly, they also identified that these behavioural effects were accompanied with amplification and attenuation, respectively, of oscillations in the theta and alpha electroencephalography (EEG) bands [21], thus offering a plausible neurophysiological substrate for the effects of tDCS on WM. In the context of WM tasks, activity in the theta band has been associated with memory encoding and retrieval [22]. Reductions in alpha band activity, on the other hand, are assumed to reflect a brain state, which is conducive to inhibiting non-task relevant information, and maintaining goal-directed focus [23].

Earlier in this section, we mentioned that the translational potential of tDCS findings is contingent on there being evidence of effects enduring beyond the stimulation period [15]. The 'real-world' application of these findings is also critically dependent on there being evidence of transfer to untrained tasks that should rely on the same neural networks targeted during the stimulation. Richmond and colleagues recently combined DLPFC tDCS with ten WM training sessions, which took place over the course of 2 weeks. Anodal tDCS combined with WM training enhanced WM in the verbal domain, relative to sham tDCS with WM training, and improvements were additionally observed in conceptually similar, but untrained, tasks [24]. This observation suggests that the tDCS combined with the WM training gave rise to changes in the neural network recruited during the trained task that conferred performance gains to untrained tasks that rely on the same neural network. This study is further notable for the fact that it was one of the first to examine the effect of multiple, as opposed to single, sessions of tDCS in the WM domain. Martin and colleagues [25] have also examined the impact of ten sessions of WM training combined with anodal versus sham DLPFC tDCS. Again, they showed that anodal, compared to sham, tDCS was associated with

better performance during the WM training task. Furthermore, a 4-week follow-up assessment revealed that the group that received anodal, but not sham, tDCS combined with the WM, exhibited greater gains on untrained tests of attention and WM (e.g. digit span), compared to a group that only received anodal tDCS. This observation suggests that repeated sessions of DLPFC tDCS in conjunction with WM training, as opposed to either WM training or DLPFC tDCS alone, may hold particular promise for fostering gains in WM performance.

Sandrini and colleagues explored the effect of parietal tDCS on WM. They applied bilateral tDCS over the PPC while subjects performed a 1-back or 2-back task. They observed an interesting double-dissociation between the tDCS montage and task, wherein performance on the 1-back task was impaired with left-anodal/right-cathodal and performance on the 2-back was impaired with left-cathodal/right-anodal. They concluded that this double dissociation might be due to differential engagement of each PPC in WM or changes in the interhemispheric balance of activity across this brain region. However, it is also possible that the differential effects might have been mediated by an impact on attentional, as opposed to memory, processes [26]. Heimrath and colleagues also investigated the effect of parietal tDCS on WM, however they focussed solely on the right PPC. They administered anodal, cathodal and sham tDCS over right PPC to each subject on 3 separate days, and found that tDCS affected visuospatial WM performance in a polarity-specific way. That is, anodal tDCS decreased WM capacity for stimuli attended in the left hemifield, whereas cathodal tDCS increased WM capacity for attended stimuli in the left hemifield. Of particular note, the increase in WM capacity with cathodal tDCS over right PPC was accompanied by a decrease in oscillatory power in the alpha band, which as mentioned above, is typically associated with gains in attentional control.

One tDCS study with young healthy adults has also examined the role of the cerebellum in WM [27]. In this study it was found that cathodal, relative to sham, tDCS over the cerebellum was associated with poorer performance on the digit span task, and additionally blocked a practice-dependent increase in digit span.

In sum, a respectable body of evidence has accumulated to suggest that tDCS applied over DLPFC, PPC, and cerebellum is capable of altering WM performance in young healthy adults. However, results are not entirely consistent, and discrepancies with regard to stimulation parameters and study designs are currently limiting the interpretation of results. Indeed, two recent meta-analyses [28, 29] have drawn the same conclusions, and have emphasised the need for future studies to systematically probe the impact of various stimulation parameters with the view to both elucidating the factors that mediate inconsistent findings, and optimising performance gains. However, as will be discussed below, even when stimulation protocols are identical, inter-individual differences in biological factors can also confound tDCS studies (section 'Neurocognitive Effects of tDCS in Healthy Older Adults').

Effects of tDCS on Attention

Attention is a complex construct that can be divided into at least three distinct subcomponents: spatial orienting, alerting, and executive control, each of which have specific neural correlates along frontoparietal networks [30]. Investigation of the potential of tDCS to modulate attentional processes is currently a relatively novel area of exploration. Table 7.2 summarises the methodological parameters for the studies that have been carried out in this area to date.

Stone and Tesche [31] reported that both anodal and cathodal tDCS over the left PPC was associated with a diminished ability to shift the focus of attention (i.e. spatial orienting) from stimuli that were subtending narrow visual angles to those subtending wide visual angles (local-to-global attention shift). The anodal tDCS effects lasted for at least 20 min post-stimulation, but the effects of anodal tDCS were particular to the switch from local to global stimuli. On the other hand, cathodal tDCS effects were only apparent

Table 7.2 The effects of tDCS on attention [39]

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Stone and Tesche [31]	Crossover (active vs. sham)	14	P3/R Forearm R; Forearm/P3	2 mA (AoE: 25 cm^2) for 20 min during an attentional switching task	Differential effects were observed for each active tDCS condition compared to sham. C-tDCS over P3 (left posterior parietal cortex) was associated with acute degradation of attentional switches, whereas A-tDCS over P3 was associated with persistent degradation of local-to-global attentional switching
Sparing et al. [166]	Parallel and crossover (active vs. sham)	20	P3/Cz; Cz/P3; P4/Cz; Cz/P4	1 mA (AoE: 25 cm^2) for 10 min before a visual detection task	Effects differed as a function of current polarity and stimulated hemisphere. A-tDCS over P3 or P4 biased visuospatial attention towards the contralateral hemispace, whereas C-tDCS biased visuospatial attention towards the ipsilateral hemispace
Bolognini et al. [33]	Parallel and crossover (active vs. sham)	20	P3/R DM; P4/R DM	2 mA (AoE: 35 cm^2) for 30 min during multisensory visual field exploration training	A-tDCS over the right, but not left, PPC increased the training-induced behavioural improvement in visual exploration, relative to sham tDCS
Coffman et al. [167]	Parallel (1 mA vs. 2 mA)	19	F10/L Bicep	1 mA or 2 mA (AoE: 11 cm^2) for 30 min during a visual detection task	Performance for the alerting component of the ANT was significantly better for subjects that received 2 mA compared to 1 mA tDCS
Gladwin et al. [87]	Crossover (active vs. sham)	14	F3/R SOA	1 mA (AoE: 35 cm^2), 10 min, during a modified Sternberg task	A-tDCS was associated with improved selective attention: faster RTs when distractor was present compared to non-distractor and sham conditions. No impact on accuracy
Nelson et al. [35]	Crossover (active vs. sham)	19	F3/F4; F4/F3	1 mA (AoE: 35 cm^2) for 10 min during a vigilance task	Both active, compared to sham, tDCS were conditions were associated with improvements in behavioural and cerebral hemodynamics of vigilance, with more pronounced improvements observed when the anode was placed over the left DLPFC
Roy et al. [34]	Crossover (active vs. sham)	24	F3/R SOA; P3/Cz P4/Cz	1.5 mA (AoE: 25 cm^2) for 20 min during a modified version of the ANT	A-tDCS over P4 was associated with improved attentional orienting, compared to sham and the other active tDCS conditions
Nikolin et al. [39]	Crossover (active vs. sham)	16	4 x 1 ring arrays over F3; PT; and L MTL	2 mA (CD: ~0.0032 mA/cm^2) for 5 min before and 15 min during the RAVLT	No effect of tDCS on sustained attention was observed for any of the HD-tDCS montages

DM deltoid muscle, *PPC* posterior parietal cortex, *ANT* attentional networks task

during stimulation, but effects were present for both the local to global, and global to local, attention shifts. Of note, there was no change from baseline in the active tDCS conditions in this study; the relative difference between active and sham tDCS was due primarily to increased performance in the sham condition relative to baseline. This study provided novel support for the role of the PPC in attentional orienting, and constituted the first successful modulation of attentional orienting using tDCS. An elegant study by Sparing and colleagues demonstrated that tDCS bidirectionally modulated visuospatial task performance in healthy subjects. More specifically, they showed that anodal tDCS over the PPC biased visuospatial attention towards the contralateral hemispace regardless of stimulation side, and the opposite effect was found with cathodal tDCS. This study accordingly provided novel causal support for the classic concept of interhemispheric rivalry, which was originally proposed by Kinsbourne 50 years ago [32]. Bolognini and colleagues were also interested in the effects of parietal tDCS on attentional orienting. They showed that anodal, compared to sham, tDCS over the right, but not left, PPC was associated with faster covert attentional orienting to contralateral targets during multisensory visual field exploration training [33]. The suggestion that the right PPC has a specialised role in attentional orienting has recently been further substantiated in another tDCS study by Roy and colleagues [34]. This tDCS-related effect on attentional orienting appears to be supramodal, as it was present irrespective of whether the stimuli were presented in the visual or auditory modality [33].

Nelson and colleagues [35] investigated the impact of tDCS on vigilance, which is closely related to the alerting component of attention. In this study subjects performed a simulated air traffic control task which required them to detect infrequent collision paths of aircrafts (targets), while not responding to the more frequent non-collision flight paths (non-targets), over the course of 40 min. tDCS was applied bilaterally over DLPFC, with the respective positions of the anode and the cathode flipped in two separate, counterbalanced, experimental sessions. In conjunction with the behavioural measure of vigilance, Nelson and colleagues also examined the effects of the stimulation on cerebral blood velocity as indexed by transcranial Doppler sonography, and cerebral oxygenation as indexed by near infrared spectroscopy [35]. Performance for the sham condition was characterised by a significant time-on-task vigilance decrement, as reflected by a lower target detection rate, slower response times, and a reduction in blood flow velocity, which are well-documented effect for vigilance tasks [36, 37]. In contrast, both active DLPFC tDCS conditions were associated with a relative improvement in target detection rate, reduced decrement in blood flow over time, and increased cerebral oxygenation. These findings are encouraging with regard to the potential use of tDCS to attenuate performance decrements stemming from requirements to sustain attention over prolonged periods of time. Coffman and colleagues have also provided support for the notion that the alerting component of attention can be modulated via tDCS. They showed that 2 mA, compared to 1 mA, of anodal tDCS over the right inferior frontal cortex was associated with improved performance on the attention networks task, which is designed to assess orienting attention, alerting attention, and executive control [38]. Notably, the effect was specific to the alerting component, and which lasted for more than an hour post-stimulation. Furthermore, alerting scores, following stimulation, for the group of subjects that received 2 mA, were significantly correlated with the proportion of hits on a target detection task. Nikolin and colleagues [39] have also examined the effects of tDCS on the alerting component of attention, as assessed by a continuous performance task (CPT). They targeted the left DLPFC with high-definition (HD) anodal tDCS. With HD-tDCS small electrodes are typically arranged in a 4×1 ring array, which putatively offers more focal stimulations compared to conventional montages involving only two electrodes. These authors did not observe any difference on attentional performance between sham and anodal tDCS applied over the left DLPFC, nor for tDCS applied over the planum temporale (PT) or left medial temporal lobe (MTL). While there was not necessarily a strong

theoretical basis for predicting an effect on sustained attention when the left MTL and PT were targeted, the lack of an effect following left DLPFC stimulation is at odds with other studies (e.g. [2, 35]). Many factors could have been at play here, but it is conceivable that the HD-tDCS array would have given rise to a distinct current flow that may have obviated critical attention-related regions in the frontal cortex that were modulated via the presumably more distributed current in the other studies.

It is readily apparent how tDCS-induced improvements in attention could have important implications for enhancing safety and performance efficiency across a myriad of real world domains. However, much more work is required to determine whether these effects are reliable, and whether they extend beyond the laboratory setting.

Effects of tDCS on Language

Language is a broad umbrella term that refers to the complex capacity to express and understand mental contents with highly structured streams of sounds, or manual gestures. To date, most studies that have investigated the effects of tDCS on language in healthy adults have focussed on the capacities for verbal fluency and picture naming, which rely on predominantly left lateralised, albeit distributed, frontal, temporal and parietal regions [40, 41]. The methodological parameters for the studies reviewed in this section are summarised in Table 7.3.

One of the first studies to examine the impact of left DLPFC tDCS on verbal fluency was carried out by Iyer and colleagues. They observed no effects with 1 mA of tDCS, but 2 mA of anodal tDCS was associated with a significant improvement in verbal fluency [42]. The effects of tDCS on many other capacities were also assessed, including attention, memory, reaction time and psychomotor speed, but performance on these measures did not differ across active and sham conditions. Further, cathodal tDCS showed no difference relative to sham for either level of stimulation intensity. Thus, this pioneering study by Iyer and colleagues pointed to a task-specific, polarity-specific and current intensity-specific enhancement of verbal fluency via tDCS over the left DLPFC.

Sparing and colleagues were interested in whether 2 mA of tDCS over Wernicke's area could modulate picture naming [43]. Subjects exhibited a significantly faster response times for picture naming for anodal tDCS over Wernicke's area. Again, these authors found no effect of cathodal tDCS over the same area, nor an effect of anodal tDCS over the homologous region in the right hemisphere. The authors did however find that the facilitatory effect was no longer evident when performance on the picture naming task was examined 5 and 10 min post-stimulation, suggesting that further work is required to determine whether enduring effects of this nature can be obtained. Fertonani and colleagues also explored the effect of tDCS on picture naming, however they chose left DLPFC as their target area [44]. They found that anodal tDCS over left DLPFC improved picture naming performance, and once again cathodal tDCS over the same region had no effect. Interestingly, as in the study by Sparing and colleagues [43], the facilitatory effect manifested as faster response times, while accuracy remained unchanged. Collectively, the results of the three studies discussed so far indicate that anodal tDCS is capable of improving language production when either Wernicke's area or DLPFC is targeted. This is consistent with the evidence that language production involves extensive activation of temporal and frontal regions [45], and that the application of tDCS over a discrete area of the cortex is associated with distributed neural network effects that are contingent on the anatomical and functional connectivity between the directly targeted cortical regions and the rest of the brain [46–49].

Grounded in the knowledge that language production could be modulated via tDCS to the left DLPFC [42, 44], Wirth and colleagues sought to investigate the electrophysiological mechanism underpinning these tDCS-induced changes [50]. They combined anodal tDCS over left DLPFC with EEG while subjects performed a picture naming and a semantic interference task.

Table 7.3 The effects of tDCS on language

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Iyer et al. [42]	Parallel (active vs. sham)	20	F3/R SOA; R SOA/F3	1 and 2 mA (AoE: 25 cm^2) for 20 min, during a verbal fluency task	2 mA, but not 1 mA, of A-tDCS over F3 was associated with improved verbal fluency relative to C-tDCS and sham. The effects of C-tDCS and sham did not differ from each other
Sparing et al. [43]	Crossover (active vs. sham)	15	CP5/Cz; Cz/CP5; CP6/Cz	2 mA (AoE: 35 cm^2) for 7 min during the performance of a picture naming task	A-tDCS over CP5 was associated with faster response times on the picture-naming task relative to C-tDCS and sham. The effects of C-tDCS and sham did not differ from each other
De Vries et al. [55]	Parallel (active vs. sham)	38	F5/R SOA; F6/L SOA	1 mA (AoE: 35 cm^2) for 20 min during artificial grammar learning	A-tDCS, compared to sham, was associated with an improved performance on a task involving the detection of syntatic violations that was performed 25 min post-stimulation
Wirth et al. [50]	Crossover (active vs. sham)	20	F3/R Shoulder	1.5 mA (AoE: 35 cm^2) for 37 min in total before and during a semantic interference task and picture naming	A-tDCS, compared to sham, was associated with an improvement in both behavioural and electrophysiological correlates of the task (as indexed by the semantic interference effect)
Fertonani et al. [44]	Crossover (active vs. sham)	12	F3/R Shoulder; R Shoulder/F3	2 mA (AoE: 35 cm^2) for 10 min prior to performance of a picture naming task	A-tDCS was associated with improved picture naming performance and faster response times, compared to C-tDCS and sham. The effects of C-tDCS and sham did not differ from each other
Holland et al. [53]	Crossover (active vs. sham)	10	FC5/R FPC	2 mA (AoE: 35 cm^2) 20 min during a picture naming task	A-tDCS, compared to sham, was associated with faster picture naming, and this behavioural effect correlated with a decrease in the BOLD signal in Broca's area
Vannorsdall et al. [58]	Crossover and parallel (active vs. sham)	20	F3/Cz; Cz/F3	1 mA (AoE: 27.04 cm^2) for 30 min during expressive language tasks that involved object naming and oral reading	A-tDCS, compared to sham, was associated with enhanced performance on a category-guided verbal fluency task. A net increase in the number of clustered words was also observed during A-tDCS, relative to a net decrease for C-tDCS (1.3 vs. −1.5 words)
Fiori et al. [54]	Parallel (active vs. sham)	30	F5/R FPC; R FPC/F5	2 mA (AoE: 35 cm^2) for 20 min during the articulation of tongue twisters	Performance during A-tDCS was associated with more accurate and faster articulation of the stimuli relative to baseline, whereas C-tDCS significantly reduced performance in terms of accuracy and RT relative to baseline. No significant differences were observed during the sham condition relative to baseline
Meinzer et al. [140]	Parallel (active vs. sham)	20	CP5/R SOA	1 mA (AoE: 35 cm^2) for 20 min during a word learning task. Protocol repeated over 5 days	A-tDCS, compared to sham, was associated with superior learning for both familiar and novel words. A-tDCS was also associated with a significantly steeper learning curve and more pronounced learning at the end of the training during a recall task. The beneficial A-tDCS effects were still apparent at a 1-week follow-up assessment

BOLD blood oxygen level dependent, *FPC* frontopolar cortex

In the latter task, semantic interference is defined as the difference in RT when subjects are required to respond to objects displayed in semantically homogeneous (e.g., grapes among cherries, pear, apple) versus heterogeneous (e.g., grapes among fly, cocktail, bed, car) contexts. At the behavioural level, Wirth and colleagues observed a reduction in semantic interference with anodal, compared to sham, tDCS, but no change in performance was found for picture naming. With regards to the EEG, it was found that the behavioural reduction in semantic interference correlated with an increase in the amplitude of event-related potentials over left, but not right, temporal electrode sites. These results were interpreted as reflecting a superior tuning of neural responses within language-related generators. A significant reduction of oscillatory activity in the delta band, believed to reflect neural disinhibition, was also observed during rest and picture naming after the stimulation had terminated. Wirth and colleagues accordingly contended that anodal tDCS over left DLPFC is capable of enhancing language-related neural processes both online and offline. They additionally suggested that the null effects for the picture naming task may be attributable to a variety of methodologically limitations, including protocol characteristics, stimulation duration, and tDCS inter-electrode distance (cf. [51]). However, some authors [52] have also highlighted the possibility that the null effect may have been due to a fundamental problem with their experimental design. Namely, the extensive and prolonged (30 min) activation of the language system in itself may have played a role. Hence, it not possible to tease apart whether the stimulation alone did not produce an effect on the picture naming task, or whether it was moreover the procedure that hindered a replication of the effect. Nonetheless, the EEG findings in this study are consistent with the notion that anodal tDCS induced an excitatory effect on frontally mediated neural processes and related language functions. The findings additionally highlight how meaningful changes in electrophysiological variables may be overlooked when researchers only investigate either the online or offline effects of tDCS on the EEG.

Holland and colleagues were also interested in the neurophysiological underpinnings of tDCS-induced changes in picture naming [53]. To this end, they acquired functional magnetic resonance imaging date during the application of anodal tDCS over Broca's area in the left inferior frontal cortex (IFC). The behavioural results revealed a significant reduction in picture naming response times with anodal, relative to sham, tDCS. The fMRI data indicated that anodal, compared to sham, tDCS significantly reduced the blood-oxygenation level-dependent (BOLD) signal in the left frontal cortex. There was also evidence of some regional specificity for this effect within the left frontal cortex; Broca's area, but not other regions, such as the precentral or anterior insular cortices, showed this tDCS-related modulation. The authors proposed that the reduction of the BOLD signal in Broca's area might be analogous to the facilitatory effects that are observed for picture naming when behavioural priming paradigms are employed [53]. Interestingly, another study, which also targeted Broca's area, has shown that anodal tDCS was associated with more accurate and faster articulation of tongue twisters, whereas cathodal stimulation disrupted performance [54]. Taken together, these two studies indicate that there may be some functional overlap between the regions and networks that support naming and speech repetition. It should be noted, however, that although both studies sought to target Broca's area, the precise location of the anode was different in each study (centred over FC5 versus F5 according to the international 10/20 EEG system). Thus, it is not possible to exclude the possibility that distinct regions or nodes of networks activated by the stimulation in each study, particularly given the absence of neurophysiological data in the latter study [54].

De Vries and colleagues carried out an interesting study where they explored the effects of anodal tDCS over the inferior gyrus (IFG) as applied during an artificial grammar learning paradigm. Anodal tDCS over the left IFG was associated with an improved performance on a subsequent grammatical decision task, as compared to sham tDCS, and anodal tDCS over right

IFG [55]. This tDCS-related improvement was particularly apparent for the detection of syntactic violations, a finding which may have future implications for facilitating recovery in some patients with post-stroke aphasia. Another study by Meinzer and colleagues showed that repeated sessions of anodal tDCS during a word learning task facilitated the recall of both novel and familiar words, relative to sham tDCS [56]. The beneficial effects of anodal tDCS were still apparent when the subjects were examined in a 1-week follow-up assessment. This latter finding indicates again that repeated sessions of tDCS might induce enduring effects in the stimulated network (cf. [57], which in turn highlights the potential for tDCS to modulate long-term plasticity in the context of intervention and language learning.

A study by Vannorsdall and colleagues [58] was motivated by the idea that the capacity for word retrieval during verbal fluency tasks relies on both automatic processes which are supported by temporal-parietal regions, and controlled processes which are supported by the left prefrontal region [59]. Vannorsdall and colleagues sought to determine whether left DLPFC tDCS can differentially modify controlled versus automatic processes involved in lexical retrieval on verbal fluency tasks, as assessed by 'clustering' and 'switching'. Clustering is assumed to reflect relatively automatic processing, whereas switching is thought to require a more controlled type of processing. Anodal, compared to sham, tDCS was associated with an increase in clustering, whereas cathodal tDCS was associated with decrease in clustering, as compared to sham. No effects were seen on switching for either current polarity. This study thus demonstrated that tDCS was capable of selectively altering automatic aspects of lexical retrieval in a polarity-dependent manner during a category-guided fluency task.

Despite their heterogeneities, the studies reviewed in this section collectively demonstrate that tDCS can modulate neural functioning in language networks, and associated behavioural indices in the healthy brain. These findings also hold promise for promoting functional recovery in patient groups that suffer from language impairments.

Effects of tDCS on Numerical Cognition

Numerical cognition is a key component of intellectual development, and is essential for everyday life. The importance of this capacity is particularly apparent in light of the evidence that dyscalulia, a deficit in comprehending arithmetic, can contribute to serious personal, social and economic problems [60, 61]. With regards to the functional neuroanatomy of numerical cognition, neuroimaging and transcranial magnetic stimulation (TMS) research has consistently highlighted the importance of the intraparietal sulcus (IPS), and surrounding parietal lobe structures [62–67]. As discussed below, a small but growing number of tDCS studies have also provided evidence to support the role of the parietal lobe, and the IPS, in this capacity (see Table 7.4).

Cohen Kadosh and colleagues conducted the first study to explore the effects of tDCS on numerical processing [57]. Over the course of 6 days, three groups of subjects trained on a number comparison task with novel number symbols while they received either sham tDCS, or one of two types of active tDCS. The active forms of tDCS both consisted of bilateral stimulation over the parietal lobes, but for one group the anode and cathode were placed over the right and left parietal lobes, respectively (RA/LC), whereas for the other group the respective locations of the anode and cathode were the other way around (RC/LA). Compared to the sham group, the RA-LC group showed significantly better and more consistent performance on a numerical Stroop task and numbers-to-space task. In contrast, the RC/LA group showed a relative impairment on these measures. The authors propose that the observed polarity-specific effect is consistent with the evidence that activity in the right parietal lobe correlates with mathematical proficiency [68, 69], as well as its particular involvement in automatic numerical processing [64] which would have been critical to performance on the numerical Stroop task. The authors additionally found that the tDCS-related improvement was still present when the subjects were examined at a 6-month post-training follow-up.

Table 7.4 The effects of tDCS on numerical cognition

Authors	Design	N	Anode/Cathode	Stimulation protocol	Results
Cohen Kadosh et al. [57]	Parallel (active vs. sham)	15	P4/P3; P3/P4	1 mA (AoE: 9 cm^2) for 20 min during learning of numerical symbols. Protocol was repeated over 6 days	Both forms of active, compared to sham, tDCS were associated with montage-specific changes in number learning and number mapping. The group that had the anode and cathode over P3 and P4, respectively, showed an improvement, whereas the group that had the anode and cathode the other way around showed deterioration
Iuculano and Cohen Kadosh [70]	Parallel (active vs. sham)	19	P3/P4; F3/F4	1 mA (AoE: 9 cm^2) for 20 min during learning of numerical symbols. Protocol was repeated over 6 days	Both forms of active, compared to sham, tDCS were associated with montage-specific changes in numerical processing. The parietal group showed improved numerical learning but compromised automaticity for the learned material, whereas the DLPFC group showed the opposite pattern of effects
Clemens et al. [72]	Crossover (active vs. sham)	10	P4/L SOA	2 mA (AoE: 35 cm^2) 20 min during the rehearsal of arithmetic fact	There was no difference between A-tDCS and sham for task performance, but fMRI measurements revealed a tDCS-related modulation of the neural correlates of multiplication
Kasahara et al. [73]	Crossover (active vs. sham)	16	P4/P3; P3/P4	2 mA (AoE: 35 cm^2) for 10 min during a mental calculation task	Bilateral tDCS with the anode over P3 and the cathode over P4 was associated with faster response times in subjects that showed left parietal lateralisation of activity on the mental calculation task, as indexed by fMRI
Hauser et al. [74]	Crossover (active vs. sham)	21	P3/R SOA; P4/L SOA; P3-P4/R SOA; L SOA/P3-P4	1 mA (AoE: 35 cm^2) for 25 min prior to performing subtraction and number comparison tasks	Left PPC A-tDCS, compared to sham, right PPC A-tDCS, bilateral A-tDCS and bilateral C-tDCS was associated with improved performance on a both the subtraction task and the number comparison task
Kasahara et al. [73]	Crossover (active vs. sham)	16	P4/P3; P3/P4	2 mA (AoE: 35 cm^2) for 10 min during a mental calculation task	Bilateral tDCS with the anode over P3 and the cathode over P4 was associated with faster response times solely in subjects that showed a lateralisation of brain activity on the mental calculation task
Artemenko et al. [168]	Crossover (active vs. sham)	16	P4/L SOA; P3/R SOA; L SOA/P4; R SOA/P3	1 mA (AoE: 25 cm^2) for 20 min during a mental calculation task	A-tDCS over P4 was associated with an improvement in place-value processing of the Arabic number system, compared to sham. No effects were observed for the other three active conditions

This prolonged enhancement provides reason to be optimistic that this combination of tDCS and training may have the capacity to bring about real-world improvements in numerical processing for young healthy adults, and potentially also mitigate the deficits that present in individuals with dyscalulia.

A cautionary note was, however, raised by some of the same authors in a subsequent study that employed a similar protocol [70]. In this study, all subjects were again trained on a number comparison task over the course of 6 days. However, subjects were this time divided into three subgroups wherein they concurrently received sham tDCS, RC/LA tDCS to the PPC and RC/LA tDCS to the DLPFC, respectively. The results revealed an interesting pattern of group differences. Namely, the group that received tDCS to the PPC showed improved numerical learning, but demonstrated compromised automaticity for the learned material, relative to the sham tDCS group. In contrast, the group that received tDCS to the DLPFC showed enhanced automaticity for the learned material, but their overall learning was compromised. This finding may indicate that cognitive enhancement of this nature may occur at the cost of other cognitive functions. A comparable call for caution emerged from the results of a study examining the effects of tDCS in subjects with high and low mathematics anxiety [71]. Here, it was found that bilateral DLPFC tDCS, compared to sham, was associated with faster response times for arithmetic decisions in subjects with high mathematics anxiety, but it impaired response times for subjects with low mathematics anxiety. Notably, both groups showed a small but significant impairment in executive control component of the ANT task. There is currently very few other reports of adverse effects in the literature, so much more research is warranted before strong inferences should be made about tDCS-related cognitive side-effects.

Clemens and colleagues were interested in whether a single session of anodal tDCS over the right angular gyrus (AG) would modulate the capacity to retrieve arithmetic facts, and/or the associated neurophysiological indices, as measured by fMRI [72]. The behavioural results indicated that tDCS did not modulate task performance significantly. The fMRI measures, on the other hand, revealed that bilateral AG activity was significantly higher for multiplication problems rehearsed during active tDCS, in comparison to multiplication problems rehearsed without tDCS, or during sham tDCS. Thus although this study did not find an effect on behaviour following a single session of tDCS, the fMRI findings nonetheless supports the potential for tDCS to produce effects in the neural substrates associated with the behaviour. This may suggest that multiple sessions, or stimulation of longer duration, would be necessary for the tDCS effects to manifest at the behavioural level.

Kasahara and colleagues carried out a study wherein they also acquired fMRI measures [73]. Here, one of the main questions of interest was whether individual differences in laterality of parietal activity during numerical processing would moderate the extent to which one would benefit from either LA/RC or LC/RA bilateral tDCS. They found that LA/RC bilateral tDCS was associated with an improvement on a mental calculation task solely in a subset of subjects that had previously shown a left hemispheric dominance for brain activity when performing that same task during at baseline. This finding is one of many that has highlighted the critical role of individual differences in brain state and structure in determining tDCS outcomes. See section 'Neurocognitive Effects of tDCS in Healthy Older Adults' for a review of this topic. In contrast to Cohen Kadosh and colleagues [57], Kasahara and colleagues did not observe any impairment in performance for either polarity of bilateral tDCS, for either subset of subjects.

Hauser and colleagues also reported that anodal tDCS over left IPS significantly enhanced performance on both a number comparison and a subtraction task, whereas neither bilateral anodal or bilateral cathodal tDCS, nor right IPS anodal tDCS, were associated with any changes in performance, relative to sham [74]. Most recently, Artemenko and colleagues carried out a study where they administered unilateral cathodal and anodal tDCS applied over both the left and right IPS, as well as sham tDCS, in five separate

experimental sessions. Their main outcome measure of interest was performance on an addition task. No effect of either cathodal or anodal tDCS applied over the left IPS was observed. There was also no effect for cathodal tDCS applied over the right IPS. There was however an association between anodal tDCS over the right PPC and performance on one specific component of the addition task, place-value processing.

For the most part, the tDCS studies reviewed in this section converge on the notion that the parietal lobes are critical neural substrates for numerical cognition. A number of inconsistent findings have been reported across studies, however. It is currently not possible to dissociate whether these discrepancies arise from methodological irregularities, individual differences within and across the study samples, or the reliability of tDCS for modulating the behavioural and neural indices of numerical cognition. Studies that have observed tDCS-related improvements with bilateral montages have invoked the notion that a reduction in interhemispheric competition might mediate the effect on numerical processing. However, there is also evidence to suggest that unilateral anodal tDCS may be sufficient to bring about improvements. It would be of interest for future work to directly compare the effect sizes that emerge with the bilateral and unilateral montages that have been found to be effective.

Effects of tDCS on Learning and Memory

An early definition of short-term memory (STM) stated that STM involves a conscious maintenance of stimuli over a short period of time (seconds), after which they are not present anymore [75]. STM is a crucial component of cognition and is thought to rely on distinct underlying neural systems from long-term memory (LTM), which is strongly associated with hippocampal processes. Baddeley [3, 76] postulated a model wherein STM consists of a 'verbal buffer' (phonological loop) and a 'visuospatial buffer' (maintenance of visual information). Initial neural representations are thought to be the repository of LTM representations. They are active during encoding as well as during STM or retrieval from LTM into STM [77]. LTM as opposed to STM involves the reactivation of past experiences that were not consciously available between the time of encoding and retrieval. It is defined as the mechanism by which acquired memories become stable and become resistant to interference [78–80]. Baddeley [81] described an 'episodic buffer', which draws on verbal and visuospatial STM buffers and LTM and introduced a 'central executive', which is thought to coordinate all subcomponents. A more recent model suggests that STM and LTM are not discrete, but that STM represents temporarily activated LTM components [82]. This view has been supported by several studies [83–86]. For example, Hannula and colleagues [80] demonstrated that the hippocampus is involved in memory processes even at very short time lags. In the following, we provide a synopsis of studies investigating the impact of tDCS on short- and long-term memory (for study parameters, see Table 7.5).

To date, only few studies investigated the impact of tDCS on STM. One study reported beneficial effects of tDCS over the left DLPFC when applied during a modified Sternberg task [87]. However, the authors observed significant improvements in reaction time only when additional distractor stimuli were presented during the delay period. Such a specific effect indicates that it might result from modulation of executive functions, such as inhibitory processes, which are known to involve frontal networks. No effects on accuracy were reported. Notably, Marshall et al. [88, 89] actually found detrimental effects on reaction times in a modified Sternberg task when applying bilateral tDCS with either two anodes or two cathodes over the DLPFC.

Studies that have targeted the parietal cortex additionally produced divergent effects on STM. Berryhill and colleagues [90] found that cathodal tDCS over the right parietal cortex applied during learning, impaired recognition, but not free recall in a visual STM task. Contrarily, Heimrath and colleagues [91] found an improvement in a spatial

Table 7.5 Effects of tDCS on general learning and memory

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
General learning and memory					
Kincses et al. [96]	Parallel (stimulation side) and crossover (active vs. sham)	22	F3/Cz; Cz/F3; V1/Cz; Cz/V1	1 mA (AoE: 35 cm^2) for 10 min, 5 min before and during probabilistic classification learning	A-tDCS over F3 improved learning compared to sham. No effect after C-tDCS or stim over V1
Marshall et al. [89]	Crossover (asleep and awake) and parallel (active vs. sham)	30 (males)	F3 and F4/R M and L M	0.26 mA/cm^2 (AoE: 5.3 cm^2), intermittent on/off for 15 s over 30 min, during slow-wave sleep. Declarative and procedural learning and mood were assessed	Bilateral A-tDCS during sleep enhanced word retention compared to sham. No impact when applied during wakefulness and no impact on procedural memory. After active but not sham tDCS positive affect decreased less and feelings of depression decreased
Vines et al. [100]; Flöel et al. [169]	Crossover (active vs. sham) Crossover (active vs. sham)	11 19	TP3/R SOA; R SMG (control)/L SOA CP5/R SOA; R SOA/ CP5	1.2 mA (AoE: 15 cm^2) for 20 min, offline, before pitch matching 1 mA (AoE: 35 cm^2) for 20 min, during the acquisition of novel object names	C-tDCS to L SMG affected short-term pitch memory performance (9 %) compared to R SMG and sham. A-tDCS was not associated with an improvement A-tDCS, compared to sham, was associated with better and faster associative learning
Elmer et al. [98]	Parallel (stimulation side) and crossover (active vs. sham)	20	F3/R M; R M/F3; F4/L M; L M/F4	1.5 mA (AoE: 28 cm^2) for 5 min, during verbal learning	C-tDCS to L DLPFC decreased number of words recalled after 25 min compared to sham (12 %). No effects on long-term retrieval and no effects of A-tDCS were found
Boggio et al. [103]	Parallel (active vs. sham)	30	T3/T4; T3/T4	2 mA (AoE: 35 cm^2) for 10 min, during encoding and retrieval (false memory)	Bilateral and unilateral tDCS reduced false memories (73 %) compared to sham. Bilateral tDCS decreased the number of false memories compared to unilateral stim (~1 vs. ~2 errors) and compared to sham (~1 vs. ~3.7 errors)

(continued)

Table 7.5 (continued)

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Kirov et al. [106]	Parallel (active vs. sham)	28	F3 and F4/R M and L M	Transcranial slow oscillation stimulation (tSOS, 0.75 Hz) for 30 min (5×5 min), 1 min ISI (density 0.517 mA/cm^2) during wakefulness either during or after learning	TSOS during wakefulness induced a local increase in endogenous EEG slow oscillations (0.4–1.2 Hz) and a widespread increase in EEG theta and beta activity. TSOS during learning improved verbal encoding, but not consolidation as assessed 7 h after learning
Chi et al. [104]	Parallel (active vs. sham)	36	Btw T7 and FT7/Btw T8 and FT8; Btw T8 and FT8/Btw T7 and FT7	2 mA (AoE: 35 cm^2) for 13 min, during visual memory task	LC/RA-tDCS resulted in improved visual memory (accuracy) by 110 % as compared to sham. No change after LA/RC-tDCS
Penolazzi et al. [107]	Crossover (active vs. sham)	12	Btw F3 and F4/Btw C3 and C4; Btw C3 and C4/Btw F3 and F4	1 mA (AoE: 35 cm^2) for 20 min, during encoding of pictures differing in affective arousal/valence	Double dissociation: bilateral RA/LC-tDCS improved recall of pleasant images compared to unpleasant/neutral images, while bilateral LA/RC-tDCS improved recall of unpleasant images compared to pleasant and neutral images
De Vries et al. [55]	Parallel (active vs. sham)	44 (and ten additional for control experiment)	Left Broca/R SOA; control exp: Cz/R SOA	1 mA (AoE: 35 cm^2) for 20 min during grammar learning	A-tDCS over Broca but not Cz was associated with improved classification. Acquisition was similar in groups
Marshall et al. [170]	Parallel (active vs. sham)	25 (non-REM), 16 (REM)	F3 and F4/R M and L M	Theta-tDCS at 5 Hz, 0.517 mA/cm^2 (AoE: 5.3 cm^2) for 5 min, 1 min ISI, during REM or non-REM sleep. Declarative and procedural learning and mood	Theta-tDCS during non-REM impaired consolidation of verbal memory compared to sham. No effect on consolidation in procedural memory. Stim during REM led to an increase of negative affect and did not affect consolidation
Javadi et al. [94]	Crossover (active vs. no stim)	13	F3/R SOA; R SOA/F3	1.5 mA (AoE: 12.25 cm^2 over target site, 30.25 cm^2 over nontarget site) for 1.6 s, during encoding or delay of a word memorisation task	A-tDCS during encoding improved accuracy and RT compared to late A-tDCS or no tDCS. C-tDCS during encoding impaired accuracy and RT compared to late C-tDCS or no tDCS. Stim during delay had no effect

Hammer et al. [99]	Crossover (active vs. sham)	36	F3/R SOA; R SOA/F4	1 mA (AoE: 35 cm^2) for 30 min, 10 min before and during errorful and errorless learning	C-tDCS impaired encoding and retrieval after errorful learning compared to errorless learning and sham. No impact of anodal stimulation
Bullard et al. [101]	Parallel (active vs. control)	34	F8/L arm	2 mA (AoE: 10.89 cm^2) or 0.1 mA (control) for 30 min, early/late during learning of threat stimuli	A-tDCS (2 mA) improved threat detection compared to control (0.1 mA). A-tDCS was more effective when applied during early learning
Clark et al. [1]	Parallel (active vs. sham)	96	Exp. 1–3: F10/L arm Exp. 4: P4/L arm	0.6 or 2 mA (AoE: 11 cm^2) for 30 min, control (0.1 mA), during learning of threat stimuli	Exp. 1–3: A-tDCS at 2 mA over R inferior PFC improved threat detection sign. more (26.6 %) as compared to control (0.1 mA, 14.2 %), while forgetting rate over 1 h was similar. Intermediate current strength (0.6 mA) was associated with an intermediate improvement (16.8 %) Exp. 4: A-tDCS at 2 mA over R PC improved accuracy sign. more (22.5 %) as compared to control (0.1 mA over F10)
Jacobson et al. [105]	Parallel (active vs. sham vs. no stim)	24	P3/P6; P6/P3 (control)	1 mA (AoE: 25 cm^2) for 10 min, during verbal encoding	LA/RC-tDCS improved accuracy, but not RT as compared to control stim. No effect after LC/RA-tDCS
Javadi and Walsh [95]	Crossover (active vs. sham)	32	A/C, F3/R SOA; R SOA/F3; C3/R SOA (control); R SOA/C3 (control)	1.5 mA (AoE: 1.23 cm^2) for 20 s A, for 30 s C during word encoding or recognition	During encoding A-tDCS over DLPFC improved accuracy, while C-tDCS impaired accuracy compared to sham. M1-tDCS had no impact. During recognition C-tDCS impaired recognition compared to sham, while A-tDCS showed a trend towards improvement

(continued)

Table 7.5 (continued)

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Jones et al. [102]	Crossover (active vs. sham)	20	P3/R cheek; P4/L cheek	1.5 mA (35 cm^2) for 15 min, during encoding or prior to retrieval during a verbal memory task	A-tDCS during encoding but not prior to retrieval improved learning and retrieval when applied over the left but not right PPC
Zwissler et al. [97]	Crossover (active vs. sham)	96	F3/R shoulder; R shoulder/F3	1 mA (AoE: 35 cm^2) for 15 min, before and during episodic learning	A-tDCS increased, whereas C-tDCS reduced the number of false alarms to lure pictures in the recognition task
Pergolizzi et al. [39]	Parallel (active vs. control) Crossover (active vs. sham)	52 (Exp 1); 72 (Exp 2) 16	Exp. 1: CP3/CP4; Exp. 2: Bilateral CP4/CP3; CP3/CP4 4×1 ring arrays over F3; PT; and L MTL	1.5 mA (AoE: 35 cm^2) for ~20 min before and during a false memory task 2 mA (CD: ~0.0032 mA/cm^2) for 5 min before and 15 min during the RAVLT	Converging results across the two exp. indicated that tDCS, compared to sham, was associated with significantly greater false recognition. Additionally, they found increased hits and false alarms with the right anode/left cathode montage HD-tDCS over left DLPFC was associated with faster responding during a 3-back WM task. There was no effect on accuracy
Pisoni et al. [109])	Parallel (active vs. control)	44	P3/P4; T3/T4	2 mA (AoE: 35 cm^2) for 15 min during recognition of a verbal learning paradigm	Bilateral tDCS was associated with an improvement in both accuracy and a d' sensitivity index in both the PPC and the TL groups but not reaction time, compared to sham. However, while the TL group showed enhanced performance for old item recognition, the PPC group was better at correctly recognising new ones
Short-term memory					
Marshall et al. [88]	Crossover (active vs. sham)	12	F3 and F4/R M and L M/R M and L M/F3 and F4	0.26 mA/cm^2 (AoE: 5.3 cm^2), intermittent on/off 15 s over 15 min, during visual STM task	Bilateral A-tDCS and C-tDCS both impaired RT as compared to placebo. No impact on accuracy

Ferrucci et al. [93]	Parallel crossover) (active vs. sham)	17	Cb/R arm; R arm/Cb; and in 5 subjects: Fp1-F3/Fp2-F4; Fp2-F4/FP1-F3	2 mA (AoE: 35 cm^2) for 15 min, before a numerical STM task	A-tDCS and C-tDCS impaired practice-dependent improvements in RT. In a subsample ($n=5$) additional C-tDCS over PFC improved RT. No effect on accuracy
Berryhill et al. [90]	Crossover (active vs. sham)	11	P4/L cheek; L cheek/P4	1.5 mA (AoE: 35 cm^2) for 10 min, during learning visual STM task	C-tDCS selectively impaired recognition but not free recall. A-tDCS had no effect
Heimrath et al. [91]	Crossover (active vs. sham)	12	A and C, Btw P8 and P10/Btw P7 and P9; Btw P7 and P9/Btw P8 and P10	1 mA (AoE: 35 cm^2) for 30 min, before visuospatial delayed matching-to-sample task (task combined with EEG)	While A-tDCS impaired capacity for contralateral stimuli, C-tDCS improved it. Both A-tDCS and C-tDCS affected capacity for ipsilateral stimuli compared to sham. tDCS altered ERPs (N2, P2, N3) and oscillatory power in the alpha band at posterior electrodes
Gladwin et al. [87]	Crossover (active vs. sham)	14	F3/R SOA	1 mA (AoE: 35 cm^2) for 10 min, during STM with distractors	A-tDCS improved RT when distractor was present compared to non-distractor and sham conditions. No impact on accuracy

See Nikolin et al. [39], also Flöel et al. [169]
Btw between, *Exp* experiment

delayed match-to-sample task when placing the cathode over the right parietal cortex. It should be noted, however, that in each study the anode was placed over the left cheek and the contralateral parietal cortex respectively, which likely resulted in different current flow. For Heimrath and colleagues, the improvement was observed for stimuli that were presented in the left visual hemi-field. On the other hand, STM decreased when the anode was placed over the right parietal cortex (with the cathode over the contralateral parietal cortex). Electrophysiological measures obtained simultaneously showed a decrease in alpha power after cathodal stimulation, which has previously been associated with inhibitory processes [92]. Ferrucci and colleagues [93] applied anodal and cathodal tDCS to the cerebellum and found an impairment of practice-dependent improvements in reaction times in a modified numerical Sternberg task, while accuracy was not affected. Generally, STM tasks tend to be afflicted with ceiling effects, as is often the case with simple cognitive tasks. This might be a reason why most studies show effects on reaction time, but not accuracy.

The enhancement of learning and long-term memory processes with tDCS has been investigated in a number of studies, mostly attempting to modulate the learning phase. Based on the knowledge of underlying neurobiological mechanisms of the respective domain tested, some studies targeted left prefrontal areas, some used bilateral stimulation approaches over frontal or parietal areas, and few targeted right prefrontal areas. Consequently, the use of different stimulation and testing paradigms makes it difficult to draw a comparison. Improvements in long-term memory have been reported when placing the anode over the DLPFC [94–97] or other prefrontal areas [55], while impairments were reported when the cathode was placed over the DLPFC [94, 95, 98, 99] or other prefrontal areas [100]. Notably, some studies found no detrimental effect when placing the cathode over frontal areas [96, 98] or found no improvement when placing the anode over left frontal areas [99, 100]. Few studies placed the anode over right prefrontal areas. Elmer and colleagues [94] found no effects in an episodic verbal memory task when either placing the anode or cathode over the right prefrontal region. Several studies investigated the learning of threat detection, which is thought to draw on right frontoparietal networks. They reported an improvement when placing the anode over the right prefrontal [1, 101] or right parietal region [1]. Bullard and colleagues [101] furthermore specifically investigated the timing of stimulation and found that tDCS applied at the beginning of the learning phase was more effective than when applied after the first hour of training. Jones and colleagues [102] placed the anode either over the left or right posterior parietal cortex and found a significant improvement in learning and retrieval only when stimulation was administered over the left but not right parietal area, and only during encoding but not prior to retrieval.

We previously discussed a study by Nikolin and colleagues [39] wherein they attempted to modulate sustained attention using HD-tDCS (see section ‘Effects of tDCS on Attention’). In the same study, they also assessed the effects of HD-tDCS over left DLPFC, PT and left MTL on declarative verbal learning and memory. HD-tDCS over the left DLPFC significantly improved the rate of declarative verbal learning. However, no effects on verbal learning, retention or retrieval were found tDCS applied over the PT and left MTL, with which the authors hoped to target the hippocampus. Thus, while the HD-tDCS montage employed in this study demonstrated promise for enhancing the rate of declarative verbal learning when applied over the left DLPFC, its capacity to modulate other regions involved in memory remains questionable. It is possible that the current flow generated by the HD-tDCS may not penetrate sufficiently deep to modulate structures such as the hippocampus.

Bilateral stimulation has been applied in numerous studies [89, 103–109]. Jacobson and colleagues [105] found improved verbal memory when administering bilateral tDCS with the anode over the left and the cathode over the right parietal cortex, during verbal encoding, but not

vice versa. One study found a tDCS-related double dissociation for the emotional valence of pictures that were to be memorised when applying bilateral tDCS over frontal areas [107]. Recall of pleasant images was facilitated when the anode was placed over the right hemisphere, while the opposite setup facilitated recall of unpleasant images. Similarly as the above-mentioned impact of tDCS on executive memory components, it is interesting to note that the modulation of valence might have been more prominent when considering the impact of tDCS on encoding.

Chi and colleagues [104] investigated the impact of bilateral tDCS over the anterior temporal lobe on visual memory. They found improvements when placing the anode over the right and cathode over the left anterior temporal cortex, but not vice versa.

A group of three studies applied intermittent bilateral stimulation using bilateral tDCS over the left and right DLPFC to investigate its impact on memory during sleep and wakefulness. All studies used two anodes over the DLPFC and placed the cathodes over the contralateral mastoids. In the first of these studies, intermittent stimulation was applied during slow-wave sleep and wakefulness [85]. The authors reported an increased retention of word pairs as well as increased slow oscillatory activity in comparison to sham stimulation when applying tDCS during sleep. However, declarative memory was not affected when stimulation was applied during wakefulness. In a second step, Kirov and colleagues [106] further explored electrophysiological parameters by administering bilateral slow oscillation stimulation (0.75 Hz) over bilateral DLPFC during wakefulness. As in the previous study, they found increased slow oscillatory activity and increases in theta and beta activity. This setup lead to improvements in memory consolidation during but not after learning. In the last study of this series, Marshall and colleagues [85] applied tDCS oscillating at theta frequency (5 Hz) during REM and non-REM sleep. The occurrence of theta during REM is known to be associated with memory consolidation. When applied during non-REM sleep they found a decrease in slow oscillatory activity and a decrease in memory consolidation when compared to sham stimulation, while tDCS during REM was associated with an increase in gamma-band activity but did not affect consolidation. Generally, the combination of stimulation with imaging methods can help us elucidate mechanisms that underlie different stimulation methods and their consequences on brain function and structure.

Boggio and colleagues [103] reported a significant reduction in false memories for active stimulation protocols, compared to sham. The active stimulation conditions involved placing the anode over the left ATL, while the cathode on the contralateral homologue area was either the same size or enlarged in order to mimic a unilateral stimulation. However, a recent study [108] used bilateral stimulation of the parietal lobes placing the anode and cathode on either side. They found an increased false recognition rate with either setup when compared to a sham group. Additionally, when placing the cathode over the left and the anode over the right parietal lobe, they found increased hits and false alarms.

Finally, Pisoni and colleagues [109] investigated the contribution of parietal and temporal cortices in declarative memory in a bilateral stimulation setup (anode over the left and cathode over the right cortex). They found that stimulation of either set of brain regions lead to improvements in a sensitivity index and accuracy, while reaction time was not affected. Interestingly, temporal stimulation showed an enhanced performance for the recognition of old items, while parietal stimulation was more effective for the recognition of new items.

As evident from the literature reviewed in this section, tDCS has successfully modulated many aspects of learning and memory. It is however important to note that many of the memory paradigms employed require components of executive functioning such as working memory, attention or inhibition, which are known to draw on frontal and frontoparietal networks. Advantageous results in the memory domain might therefore, at least partially, reflect indirect effects on executive functions.

Neurocognitive Effects of tDCS in Healthy Older Adults

Most of the studies investigating cognitive enhancement have been conducted in young healthy participants, and some have attempted to translate findings to older populations. However, in order to design optimal studies for the investigation of cognitive enhancement in older populations it is essential to explore the healthy older brain directly. In recent years the interest has hence turned to using tDCS in healthy older adults to: (1) improve cognitive functions; and (2) improve our understanding of the effects of brain stimulation in the older healthy brain in order to find better models for older patient populations. Table 7.6 contains the studies that have been conducted to date. Most of these studies investigate the memory domain and executive functions, which are the most likely to decline with advancing age.

Only a few tDCS studies have used the same paradigms and tDCS protocols for young and older subjects in order to shed light on differential processes related to ageing. Ross and colleagues applied anodal tDCS over the left or right anterior temporal lobe (ATL) during a verbal memory task and placed the cathode over the contralateral cheek. This area, particularly the right ATL, is important for associative memory such as person-specific knowledge and lesions in this area are known to impair person recognition and proper naming. In these studies, subjects looked at pictures of famous faces or landmarks and had to verbally recall the associated proper name. The inability to remember proper names is one of the most common complaints in older adults and various forms of associative memory appear to decline with healthy ageing. The arbitrary nature of the relationship between faces/landmarks and names makes this task particularly demanding. Ross and colleagues [110] found that brain stimulation during this task had differential effects on healthy older as compared to young adults. While stimulation over the right ATL significantly improved naming for faces in young adults, stimulation over the left ATL significantly improved naming for faces in older adults. Interestingly, both groups also improved numerically after stimulation of the contralateral ATL but differed in the dominance of the effect. The authors explained this difference with the HAROLD (Hemispheric Asymmetry Reduction in Older Adults) model [111]. This indicates that the employed tDCS protocol might be less beneficial to overcome inefficiencies, but more effective to directly support alternative networks, which are already involved in compensatory processes due to inefficient recruitment of specialised unilateral networks.

Boggio and colleagues [112] conducted a study on decision-making in older subjects, which had previously been carried out with young healthy subjects [113]. They compared bilateral tDCS (RC/LA or RA/LC) over the DLPFC to sham stimulation during a gambling task. In young subjects the RA/LC tDCS was associated with decreased risky behaviour, whereas both stimulation montages increased risky behaviour in older adults, albeit the effect size was greater for the RC/LA montage. Again, this finding supported the HAROLD model, which maintains that advancing age is associated with increased recruitment of bilateral networks for tasks that were formerly supported unilaterally. Notably, stimulation seemed to accentuate already increased risk behaviour in older adults.

Fertonani and colleagues [114] found an improvement of naming in older and young subjects when they applied anodal tDCS over the left DLPFC. However, a positive effect in the older groups was only observed when tDCS was applied during task execution, whereas both on- and offline (before task execution) stimulation lead to improvements in young subjects. The authors emphasised the importance of stimulation timing and suggested that differences might be due to a dysregulated Ca^{2+} homeostasis in the ageing brain, which affects long-term potentiation.

Berryhill and Jones [115] have demonstrated that factors such as levels of education may contribute to differential tDCS effects in older adults. They applied tDCS over the right or left DLPFC with the cathode over the contralateral cheek before a visual or verbal 2-back working memory

Table 7.6 The effects of tDCS in healthy older adults

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Boggio et al. [112]	Parallel (active vs. sham)	28	F3/F4; F4/F3	2 mA (AoE: 35 cm^2) total of 15 min delivered 5 min before, and during a 10 min gambling task	RC/LA was associated with choosing more high-risk prospects as compared with S and RA/LC
Ross et al. [110]	Crossover (active vs. sham)	14	T3/R cheek; T4/L cheek	1.5 mA (AoE: 35 cm^2) for 15 min during a verbal memory task	A-tDCS over the left ATL significantly improved naming for faces
Holland et al. [53]	Crossover (active vs. sham)	10	FC5/FPC	2 mA (AoE: 35 cm^2) for 20 min during a picture naming task	A-tDCS improved picture naming in the real group, which was correlated with a decreased BOLD signal in Broca's area
Flöel et al. [116]	Crossover (active vs. sham)	20	R TPC (close to T6)/L SOA	1 mA (AoE: 35 cm^2) for 20 min during object learning	No immediate effect of stimulation, but significantly better retention in real group after 1 week
Berryhill and Jones [115]	Crossover (active vs. sham)	25	F3/R cheek; F4/L cheek	1.5 mA (AoE: 35 cm^2) for 10 min during a working memory task	Subjects with higher education profited regardless of stimulation site or type of task, while subjects with lower education deteriorated
Meinzer et al. [48]	Parallel and crossover (active vs. sham)	40	L ventral IFG/R SOA	1 mA (AoE: 35 cm^2) for 20 min during a semantic word fluency task	A-tDCS improved performance levels of older subjects approaching performance levels of young subjects, which was correlated with a reduction of task-related hyperactivity in relevant neuronal networks
Harty et al. [117]	Crossover (active vs. sham)	24; 24; 24; 24	F4/Cz; F3/Cz; Cz/F4	1 mA (AoE: 35 cm^2) for 5×7.5 min during an error awareness task	A-tDCS over F4, but not C-tDCS over F4 or A-tDCS over F3, was associated with an increase in conscious detection of performance errors. This effect was recapitulated in a separate experiment

(continued)

Table 7.6 (continued)

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Fertonani et al. [114]	Crossover (active vs. sham)	40	F3/right shoulder	2 mA (AoE: 35 cm^2) for 4-5 min during a picture naming task or 10 min before the task (offline)	A-tDCS was associated with an improvement in older subjects was only observed when applied online, whereas both on- and offline A-tDCS lead to improvements in young subjects
Park et al. [119]	Parallel (active vs. sham)	40	F3/R arm; F4/L arm	10 sessions, 2 mA (AoE: 25 cm^2) for 30 min during cognitive training	Bifrontal A-tDCS was associated with an improvement in verbal working memory and short-term memory, which lasted over a period of one month and 7 days respectively
Manor et al. [118]	Crossover (active vs. sham)	37	F3/R SOA	2 mA (AoE: 35 cm^2) for 20 min during dual tasking (standing/ walking and arithmetic)	A-tDCS over F3 reduced the cost of dual task performance induced by performing a mental arithmetic task during standing and walking. Notably, single-task performance of standing, walking, and mental arithmetic was unaltered
Jones et al. [120]	Parallel (active vs. sham)	72	F4/L cheek; P4/L cheek; alternating F4 and P4/L cheek	10 sessions, 1.5 mA (AoE: 35 cm^2) for 10 min during verbal and visual working memory training	Significant differences between the real and sham groups emerged only after a no-contact follow-up period of one month in both the trained and untrained tasks. Effects were most pronounced in the most difficult task (spatial 2-back)

TPC temporo-parietal cortex

task. Subjects with higher education profited regardless of stimulation site or type of task, while subjects with lower education deteriorated. This result supports the HAROLD model only for subjects with higher education. The authors suggested that, participants in the high education group, unlike the low education group, might employ a particular WM strategy that enables better recruitment of DLPFC.

The inability to remember the location of objects is another common complaint amongst older adults. Flöel and colleagues [116] applied anodal over the right temporo-parietal cortex during the learning of positions of buildings on a street map in order to enhance non-verbal learning and memory. Immediately after 20 min of stimulation, learning in the sham and the real group was comparable, however, one week later recall was significantly better in the real group. This finding shows a single stimulation session possibly triggers physiological effects that could lead to a cascade of long-term plastic processes leading to cognitive improvements that are only visible later on. In this case retention rather than encoding was affected by stimulation, as indexed by a reduced rate of forgetting.

Meinzer and colleagues [48] assessed older adults using fMRI while concurrently applying tDCS over the left IFG during a semantic word fluency task. This approach gave valuable insight into online mechanisms showing that tDCS significantly improved performance levels of older subjects, such that their levels of performance approached that of young subjects. This improvement in performance was furthermore correlated with a reduction of task-related hyperactivity in relevant neuronal networks. A previous study using a similar combined tDCS/fMRI approach [53] had shown improvements in picture naming in a small group of older subjects who received anodal tDCS, and this behavioural effect was correlated with a decreased blood oxygen level-dependent (BOLD) signal in Broca's area.

In healthy older adults tDCS has also been applied to improve error awareness [117], a capacity which is compromised with older age, and also known to be deficient in several patient populations. In a cross-over study, Harty and colleagues found that anodal tDCS over right, but not left, DLPFC was associated with a significant increase in error awareness which could not be accounted for by changes in accuracy, slower response times, the neuromodulatory influence of the reference electrode, or expectancy effects due to greater somatic sensation. This result was recapitulated in a separate replication experiment. This study thus provided novel evidence to support the hypothesis that right lateralised DLPFC structures play a critical role in mediating awareness of cognitive functioning, which has been strongly suggested by an extensive literature on the phenomenon in clinical populations.

Manor and colleagues [118] demonstrated that anodal tDCS over the left DLPFC reduced the cost of dual task performance induced by performing a mental arithmetic task during standing and walking. Notably, single-task performance of standing, walking, or mental arithmetic was unaltered suggesting that tDCS enabled subjects to better maintain performance in the face of increased cognitive demand.

As can be seen from our synopsis so far, most studies applied one stimulation session only. However, several sessions might be more efficient and more likely to induce long-lasting benefits. To investigate this question, Park and colleagues [119] employed ten sessions of stimulation combined with a cognitive training. In the real stimulation group two anodes were placed over the left and right DLPFC and the cathodes over the contralateral arms. Subjects were stimulated with an intensity of 2 mA for 30 min during training and a range of cognitive functions were assessed at different time-points up to 1 month after the end of training. The authors reported significant improvements in the real group in verbal working memory and short-term memory in comparison with a sham group, which endured for 1 month and 7 days, respectively. Jones and colleagues [120] likewise applied ten sessions of tDCS and combined stimulation with working memory training. The anode was either placed over the right prefrontal, the parietal, or alternatingly over the prefrontal and parietal cortices, which are active during working memory tasks.

Besides direct training effects, the authors were specifically interested in near transfer effects on untrained tasks that assess working memory. Interestingly, and similar as in the study conducted by Flöel and colleagues [116], significant differences between the real and sham groups emerged only after a no-contact follow-up period of one month. Furthermore, effects were most pronounced in the most difficult task (spatial 2-back). The authors suggested that these findings could be either due to strengthened frontoparietal and/or frontostriatal connections.

The overall advantageous results of studies in older adults are promising and constitute an important advancement toward the development of tDCS as a tool to preserve or enhance cognitive functions in healthy older adults. Importantly, these results furthermore suggest that tDCS, and other non-invasive stimulation approaches (e.g. [121]), may have a different impact on the ageing brain. Numerous reasons may underpin the influence of age on tDCS effects. The natural aging process is associated with considerable changes in the structure and function of the brain at both macroscopic and microscopic levels. Aging additionally leads to an increase in the distance between the brain and the skull, as well as an increased proportion of cerebrospinal fluid (CSF; [122, 123]). This may be particularly significant as CSF has greater conductivity relative to cerebral matter, and may alter the current flow and decrease the current intensity at the cortical surface. The direct extrapolation of results from studies with young subjects is therefore inadequate, and further studies with older healthy subjects are needed in order to identify valid implications for older patient populations.

Inter-individual Differences in the Context of tDCS Outcomes

It is clear from the literature discussed thus far on the neurocognitive effects of tDCS in healthy adults that results from studies examining similar questions are not always consistent, and even a number of contradictory findings have emerged. It is widely acknowledged that the extensive heterogeneity of tDCS protocols significantly affects the reproducibility of results [124–126]. However, even when methodological parameters are held constant, inter-individual variability in response to tDCS can also confound results. As seen in the last section, the age of the subject is one factor that has been identified as a significant predictor of differential tDCS outcomes. In the following section, we provide an overview of studies that have provided insight on other factors that influence subjects' responsiveness to tDCS (see Table 7.7).

A growing number of studies are reporting that individual differences in baseline cognitive ability modulate tDCS outcomes in healthy adults [127–134]. Tseng and colleagues found that performance on a visual short-term memory task (VSTM) was enhanced with anodal tDCS to the right PPC only in subjects who had initially poor performance. It did not change performance for subjects with initially high performance [134]. Furthermore, concurrent EEG recordings revealed that the improvement in VSTM performance with tDCS was accompanied by increased amplitude of ERPs-associated attention deployment. On the other hand, those who did not improve already had relatively large amplitude ERPs, at baseline, before tDCS [134]. Employing a very similar VSTM paradigm, Hsu and colleagues also found that low, but not high, performers benefited from anodal tDCS [130]. This dissociation was also apparent in oscillatory activity in the alpha band. Namely, low performers showed decreased pre-stimulus alpha power in parieto-occipital regions for anodal, compared to sham, tDCS, whereas high performers, on average, showed no change in pre-stimulus alpha power. At least three other recent studies have also shown that lower levels of performance are associated with greater performance gains with anodal tDCS [128, 129, 135]. These patterns of behavioural and electrophysiological tDCS outcomes imply that individuals may be less likely to benefit from anodal tDCS if they are already exhibiting relatively high levels of performance.

However, at least three studies have provided evidence to suggest that the relationship between baseline performance and tDCS outcomes may

Table 7.7 Studies that have reported a correspondence between tDCS outcomes and inter-individual factors

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Tseng et al. [134]	Crossover (active vs. sham)	31	P4/L cheek	1.5 mA (AoE: 16 cm^2), 15 min, during a change visual short-term memory task	A-tDCS only improved performance in those participants with initially low performance
Jones and Berryhill [131]	Crossover (active vs. sham)	20	P4/L cheek; L cheek/P4	1.5 mA (AoE: 35 cm^2), 10 min during a change detection WM task	Both A-tDCS and C-tDCS improved performance in high-performing subjects, but impaired performance in low-performing subject HMMM (not always low performers that benefit)
Meiron and Lavidor [20]	Parallel (active vs. sham)	41	F3/Cz; F4/Cz	2 mA (AoE: 16 cm^2) for 15 min during a verbal n-back task	The extent to which subjects benefited from left or right DLPFC tDCS was gender-dependent: tDCS-related improvements in WM were observed in males following left DLPFC A-tDCS, whereas they were observed in females following right DLPFC
Plewnia et al. [141]	Crossover (active vs. sham)	46	F3/R SOA	1 mA (AoE: 35 cm^2) for 20 min during a Go/No-Go task	A-tDCS was associated with a deterioration in performance for subjects that were homozygous for the COMT MET/Met allele
Kasahara et al. [73]	Crossover (active vs. sham)	16	P4/P3; P3/P4	2 mA (AoE: 35 cm^2) for 10 min during a mental calculation task	Bilateral tDCS with the anode over P3 and the cathode over P4 was associated with faster response times in subjects that showed left parietal lateralisation of activity on the mental calculation task, as indexed by fMRI
Rosso et al. [138]	Crossover (active vs. sham)	24	R IFG/L SOA	1 mA (AoE: 35 cm^2) 15 min during a picture naming task	Baseline levels of functional connectivity between the right SMA and the Broca area homolog in the right hemisphere predicted a tDCS-related improvement in response times for the picture naming task
Hsu et al. [130]	Crossover (active vs. sham)	20	P4/L cheek	1.5 mA (AoE: 16 cm^2) 15 min, prior to performing a change detection task	Anodal stimulation affects the activity of pre-stimulus alpha frequency band but the effect may be more or less state dependent. Low-performers showed a decrement in alpha power after stimulation; High-performers already had a low pre-stimulus alpha band power to begin with and their activity was not strongly affected by external stimulation

(continued)

Table 7.7 (continued)

Authors	Design	*N*	Anode/cathode	Stimulation protocol	Results
Nieratschker et al. [142]	Parallel (active vs. sham)	41	R SOA/F3	1 mA (AoE: 35 cm^2) for 20 min during a Go/No-Go task	C-tDCS was associated with impaired response inhibition in subjects that were homozygous for the COMT Val/Met allele
Benwell et al. [127]	Crossover and parallel (active vs. sham)	38	P5/P6; P6/P5	1 or 2 mA (AoE: 16 cm^2) for 20 min during a line bisection task	A complex non-linear relationship between the effects of tDCS, baseline performance and tDCS intensity was observed
London and Slagter [133]	Crossover (active vs. active)	34	F3/R SOA; R SOA/F3	1 mA (AoE: 35 cm^2) for 20 min during a task tailored to assess the AB	A-tDCS decreased the AB in subjects that exhibited a large AB at baseline, but increased the AB in subjects with a small AB at baseline
Liang et al. [132]	Crossover (active vs. sham)	18	Fz/L cheek	1.5 mA (AoE: 16 cm^2) for 10 min prior to performing a stop signal task	Low, compared to high, performers on the stop signal RT task benefited more from A-tDCS as indexed by greater changes in MSE
Foroughi et al. [129]	Parallel (active vs. sham)	45	CP4/L upper arm	2 mA (AoE: 11 cm^2) for 30 min during a financial management task and a mental rotation task	Lower-performing individuals showed greater benefits of tDCS than higher-performing ones, thus suggesting that individual differences in baseline ability may modulate the behavioural effects of tDCS
Learmonth et al. [135]	Crossover (active vs. sham)	40	P3/R SOA; P4/L SOA	1 mA (AoE: 25 cm^2) for 15 min during a lateralised visual detection task	The effects of A-tDCS on target detection differed as a function of baseline performance as opposed to age (younger versus older adults): high performers benefited from A-tDCS to right PPC whereas low performers were impaired by A-tDCS to left PPC

IFG inferior frontal gyrus, *AB* attentional blink, *MSE* multiscale entropy

not be dichotomous or linear. First, London and Slagter [133] examined the effects of anodal and cathodal tDCS on the attentional blink (AB). They found that anodal tDCS decreased the AB in individuals that exhibited a large AB at baseline, but increased the AB in subjects with a small AB at baseline, and were able to rule out the possibility that this pattern of findings was due to regression to the mean. It is important to highlight that London and Slagter found no effect of either anodal or cathodal tDCS on the AB at the overall group level, further emphasising the need to take individual differences into account when evaluating the efficacy of tDCS. A study by Jones and Berryhill [131] also provided evidence to counter the notion that subjects with lower baseline performance are more likely to benefit. Here, they found that when the cognitive demands of a WM task were high, both anodal and cathodal tDCS over the right PPC improved change detection performance in high performing subjects, but impaired performance on low performing subjects. The authors suggested that low performing subjects may not have sufficiently engaged their right PPC to perform the task, which would preclude them from benefiting from the stimulation. However, the plausibility of this explanation is questionable given that low performers were negatively affected by the tDCS, relative to sham. Miniussi and colleagues have pointed out that due to the fact that the currents involved in tDCS are not sufficient to induce polarisation or depolarisation, it will only affect the firing of neurons that are already near threshold, meaning that neurons that are not engaged by a given task are unlikely to be modulated [136]. Benwell and colleagues identified an even more complex pattern of tDCS results that were influenced by individual differences [127]. Firstly, consistent with a previous report by Giglia and colleagues [137], at the overall group level they found a significant, albeit weak, association between bilateral LA/RC tDCS over the PPC and a rightward shift in point of subjective equality (PSE) on the landmark task. Crucially, however, a significant three-way interaction revealed that tDCS outcome depended on both tDCS-intensity and subjects' baseline level of discrimination sensitivity. Specifically, 1 mA of LA/RC tDCS led to a larger rightward shift in PSE for the subset of subjects with high, relative to low, discrimination sensitivity, whereas the reverse pattern was found for 2 mA of LA/RC tDCS: a larger rightward shift in PSE in the subset of subjects with low, compared to high, discrimination sensitivity. The results of these studies highlight how individual differences in cognitive performance and parameters of stimulation protocols interact to influence tDCS outcomes in a complex manner.

On a somewhat interrelated theme, studies have also reported on the impact of inter-individual differences in brain state and brain structure on tDCS outcomes [73]. For instance, Rosso and colleagues have shown that tDCS-related improvements in response times for a picture naming task varied as a function of baseline levels of functional connectivity between right SMA and the right hemisphere Broca homolog [138]. In a study previously mentioned in section 'Effects of tDCS on Learning and Memory', Marshall and colleagues have additionally shown that a tDCS-related improvement in declarative memory was only observed when tDCS was applied during sleep [89]. Of note, the tDCS was also found also to increase endogenous slow oscillations and spindle activity in the EEG directly after stimulation. This finding provided novel causal evidence for slow oscillations in memory formation, and also reconciles nicely with the body of literature that has highlighted sleep as a brain state that optimises the consolidation of declarative memories [139]. Further, while little tDCS research on this topic exists, a respectable amount of evidence suggests that neuroplasticity and responses to TMS vary as a function of individuals' circadian rhythms. For this reason, subjects participating in brain stimulation studies are frequently asked to provide subjective ratings of sleepiness, and efforts are made to carry out testing at similar times of day [34, 127, 140].

A number of studies have additionally highlighted the role of genetic polymorphisms in moderating susceptibility to tDCS. For instance, Plewnia and colleagues found that anodal tDCS

applied over the left DLPFC had a deleterious effect on performance of a Go/No-go task in subjects that were homozygous for the *COMT* Met-allele relative to Val-allele carriers [141]. A subsequent study involving the same first author has shown that cathodal tDCS over the left DLPFC impaired response inhibition in subjects that were homozygous for the *COMT* Val-allele, but had no effect on Met-allele carriers [142]. The COMT gene is known to be an important regulator of dopaminergic transmission, particularly in the prefrontal lobes. Interestingly, Lachman and colleagues have established that Val/Val homozygous individuals show the lowest levels of prefrontal dopamine, heterozygous individuals show intermediate levels, and Met/Met homozygous individuals show the highest. Further, it has been hypothesised that there is an optimal range of dopamine in the prefrontal cortex for cognitive performance, which can be characterised by an inverted-U-shaped relationship [143–145]. The results of these tDCS studies thus suggest that increasing neuronal excitability through anodal tDCS shifts dopaminergic activity in Met/Met homozygous subjects, who have characteristically high baseline dopaminergic activity, to the extreme right of the inverted-U curve, pushing them further beyond the level associated with optimal cognitive performance. On the other hand, cathodal tDCS shifts dopaminergic activity in Val/Val homozygous subjects, who have low baseline dopaminergic activity, to the far left of the inverted-U curve, pushing them further below the optimum for cognitive performance. These findings are compatible with a body of research, primarily based on the motor domain, which has described a non-linear relationship between GABA/glutamate concentrations and the effects of tDCS [146–148]. Accordingly, the characterisation of genetic information and neurotransmitter concentrations could prove advantageous for predicting how individuals will respond to tDCS.

As mentioned in section 'Effects of tDCS on Working Memory', Meiron and colleagues [20] have provided evidence to suggest that gender may also moderate the effects of tDCS. When they examined the effect of anodal tDCS over the DLPFC on WM performance, they found that males benefited more from left DLPFC stimulation, whereas females benefited more from right DLPFC stimulation. The authors interpreted these gender-dependent effects as reflecting a gender-differentiated lateralisation of regions recruited for WM. Gender-dependent effects of tDCS have also been documented in visual and motor domains [149, 150]. Many authors have implicated sex hormones as playing a role in driving different effects in males and females [151–154]. Inghilleri and colleagues have suggested that the cortical excitability of female subjects is only similar to males during the follicular phase of the menstrual cycle, when progesterone levels are relatively low and oestrogen levels are relatively high ([151]; see also [155]). Heeding this, some authors have recently begun to only administer tDCS to female subjects in the follicular phase of their menstrual cycle (e.g. [156]).

Many tDCS simulation studies have suggested that individual differences in a myriad of other anatomical and micro-architectural features influence current distribution, and hence the physiological and behavioural effects of tDCS. For instance, Opitz and colleagues have recently demonstrated that approximately 50 % of the variance in the electric field in human brain grey matter is explained by skull thickness, cerebrospinal fluid density, gyral depth and the distance between the targeted grey matter regions and the tDCS electrodes. Somewhat surprisingly, current density was not inversely related to skull thickness. Rather, the bigger proportion of highly conducting spongy bone in thicker skull areas gives rise to a more complex relationship between skull thickness and current density [157]. The impact of individual differences in subcutaneous fat [158], local tissue heterogeneities [159, 160], the orientation of neurons in particular neural regions [161] and gyral pattern [157, 162, 163] on tDCS current distribution have also been documented.

Importantly, Kim and colleagues recently modelled the current density induced by anodal tDCS over left DLPFC (cathode over right SOA), and found that the improvement in a WM task correlated with the simulated current density [146], suggesting that the work from simulations

has functional relevance. However, it should be noted that even when individual differences in current flow and density are accounted for, a number of the other factors discussed above may interact with each other resulting in a multifactorial influence on the induction of tDCS effects.

Conclusions

Research investigating the modulation of cognition using tDCS is one of the most rapidly growing fields in cognitive neuroscience today. As evident from the studies discussed in this chapter, tDCS holds considerable promise as a tool for exploring novel theoretical hypotheses, as well as for improving cognitive function in both young and older healthy adults. Substantial evidence has accumulated to support the idea that tDCS can affect working memory, attention, language, numerical cognition, learning and memory, and some of these effects are quite pronounced. Despite the respectable body evidence in support of tDCS-induced modulations in neural activity and behaviour across several cognitive domains and populations, there is also a substantial amount of inconsistent and even contradictory findings across studies. The heterogeneity of tDCS protocols utilised is a likely contributor to this variability [120–122], but burgeoning evidence suggests that inter-individual variability in response to tDCS may also have a significant impact on the nature, magnitude and direction of tDCS effects. Characterising the complex contribution of individual differences to the results of tDCS studies will be crucial for understanding and optimising the effect of tDCS in future studies. Efforts to incorporate physiological measures such as MRS, EEG, fMRI, and genetic profiling more routinely in tDCS studies will facilitate more informed interpretation of results. In addition, where possible, efforts should be made to recruit sufficiently large samples. Not only will this obviate the risk of underpowered studies, it will also enable subgroup analyses to be carried out which may elucidate the subject profiles that exhibit the optimal response to tDCS.

Furthermore, the vast majority of studies reviewed only reported short-term improvements in cognitive functioning following single sessions of tDCS, and rarely examined the extent to which the tDCS-induced effects generalised to related tasks that should rely on the same underlying neural processes. This currently constrains the translational potential of these findings, as cognitive enhancement regimes are only worthwhile if they can produce long-term changes in cognition, which in turn contribute positively to activities of daily living. Some studies have began to investigate the impact of multiple tDCS sessions, and have yielded promising results, but much more work along these lines is required before we will have a reasonable understanding of the optimal tDCS protocols for maximising long-term benefits, while also minimizing potential side-effects.

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Transcranial Direct Current Stimulation in Social and Emotion Research

8

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Abstract

Social and affective neurosciences are topics of increasing popularity and great urgency in contemporary brain research. Before the introduction of the noninvasive brain stimulation methods used presently, most of the research on social and emotional processes relied on behavioral methods, lesions, and/or correlational methods alone. The possibility to noninvasively and transiently interfere with the ongoing brain function using a site-specific technique as transcranial direct current stimulation (tDCS) allows us to understand brain–behavior relationships with another level of causality that cannot be achieved with imaging or behavioral methods alone. In this chapter, we will review how tDCS has been used in social and emotional neuroscience studies, with a focus on basic research.

Keywords

Emotion • Social • Neuroscience • Social interaction • Emotional regulation • tDCS • Decision-making • Prejudice

Introduction

Social and affective neurosciences are topics of increasing popularity and great urgency in contemporary brain research. The social and emotional aspects of cognition are inexorably linked, since the adaptive value of emotions is closely related to its social relevance and most social interactions seem to be related to some level of affective processing [1]. Social neuroscience is, therefore, an interdisciplinary field that combines methods and knowledge from cognitive and behavioral neuroscience, as well as social sciences, aiming to unveil how the human brain processes social information and how it can be modified by the complex social world that surround us [2]. Affective neuroscience is also an interdisciplinary field, combin-

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ing cognitive and behavioral neuroscience for the understanding of emotion processing [3, 4].

Before the introduction of the main noninvasive brain stimulation methods used presently, most of the research on social and emotional processes relied on behavioral methods, brain lesions, and electrophysiological studies, all of them considered as correlational methods. As discussed before in the present book, the possibility to noninvasively and transiently interfere with the ongoing brain function using a site-specific technique as transcranial direct current stimulation (tDCS) allows us to understand brain–behavior relationships with another level of causality that cannot be achieved with imaging or behavioral methods alone.

In this chapter, we will review how tDCS has been used in social and emotional neuroscience studies. With this purpose, this chapter is organized in two main sessions: emotion studies (including those that might involve some relevant social phenomena) and social cognition studies (gathering the ones that are not mostly focused on emotional processes). We will focus on basic research, as there are specific chapters in this book addressing tDCS effects on social and emotional processes related to neurological and psychiatric disorders.

tDCS on Emotion Studies

Emotions are present in our daily life, influencing the way we perceive the world and our behavior. According to Fridja [5], emotion is defined as a physiological, behavioral, and subjective response to a given situation. It is very important for decision-making, helping us to predict and rapidly react to internal or external demands [4].

Lippold and Redfearn [6], in one of the first studies investigating tDCS effects on emotion, reported that tDCS could affect participants' mood. In this study, tDCS was placed bilaterally over the frontal lobes with the reference placed on the leg. However, posterior attempts to replicate these results have failed so far [7, 8], probably due to participant selection: most of the participants recruited in the Lippold and Redfearn [6] study presented a history of psychiatric disorder. In addition, Lippold and Redfearn evaluated, mood subjectively, a procedure that could have biased the results. Furthermore, replication studies used only healthy subjects and double-blind designs.

Some studies have also tried to assess tDCS effects on healthy participants' mood [9–14], all of them stimulating the dorsolateral prefrontal cortex (DLPFC) but finding no significant results. Nonetheless, two studies were successful in modulating mood by stimulating the DLPFC of healthy volunteers [14, 15]. In these studies, participants were exposed to negative stimuli [15] or performed a task aimed at inducing frustration feelings [14]. In both studies, active tDCS significantly suppressed negative feelings in comparison to sham. In these cases, tDCS appeared to affect mood indirectly, preventing changes evoked by external stimuli, probably by controlling emotion regulation processes [16] or other interference mechanisms on emotion processing, rather than directly modulating mood.

What do these conflicting results tell us about tDCS effects on emotional processing? Some of them suggest that tDCS does not influence mood directly, as first proposed by Lippold and Redfearn [6]. Instead, it might have indirect effects on mood; probably by interfering with other cognitive processes involved in emotion processing, such as encoding and retrieval of emotional memory, detection of emotional prosody, detection of emotional facial expressions, emotion regulation, and fear conditioning.

Emotional Memory Encoding and Retrieval

A well-known phenomenon is that emotional events and stimulus are usually better remembered than neutral ones. Two important phases in memory consolidation are the encoding and retrieval: the former is the process involving the mechanisms related to the storage and creation of a memory and the latter is the process related to retrieval of already consolidated memories. At least two studies have assessed emotional memory encoding and retrieval after tDCS [13, 17]. Penolazzi et al. [17] stimulated fronto-temporal

areas bilaterally (left cathodal/right anodal and the opposite) during the encoding of emotional stimuli. They found that right cathodal and left anodal stimulation inhibited memory retrieval of pleasant stimuli, while the opposite montage inhibited retrieval of unpleasant stimuli. Using also a bilateral electrode montage, but this time over DLPFC, Morgan et al. [13] investigated whether stimulation of this area influenced memory retrieval of emotional stimuli; however, no significant effects were found.

These studies in tDCS and emotional memory addressed a promising topic, since they could help to clarify neural circuitries involved in emotional memory and could point to the possibility of using tDCS clinically, for example, in post-traumatic stress or depression. However, given their conflicting results, the limited number of investigations in the field and some limitations of the tDCS technique, it is not yet possible to circumscribe the role of DLPFC and fronto-temporal areas in emotional memory encoding and retrieval. The effects found by Penolazzi et al. [17] are intriguing, since anodal tDCS is typically related to facilitation or increased cortical activity and would most likely be associated with enhanced memory processing. In this case, a possible explanation could be that the anodal stimulation enhanced a competing neural population that disrupted the activity of emotional memory circuitry.

Emotional Prosody

Indeed, many cognitive and affective processes involve complex circuitries, recruiting various brain areas that may sometimes compete or share mutually inhibitory connections. This hypothesis may also explain the results found by Alexander et al. [18], who evaluated the effects of anodal and cathodal tDCS over the right inferior frontal gyrus (IFG) in emotional prosody stimuli presented on a dichotic listening paradigm. The authors have found that cathodal tDCS improved emotional prosody detection, probably inhibiting competing neural activations and acting as a noise filter. These results illustrate the complexity involved in using tDCS to address such intricate processes that rely on multiple interdependent neural populations.

Emotional Face Processing

Another relevant topic is how people process emotional faces, an ability that is on the core of our social skills. Most studies using tDCS to assess emotional face processing have focused on the role of temporal areas, DLPFC, and cerebellum in face processing [11, 19–21]. Boggio et al. [19] have applied bilateral tDCS with the anode over the left and cathode over right temporal cortex in subjects performing a go-no-go task with positive- and negative-valence emotional face expressions as stimuli. They found different effects according to gender when seeing sad faces, with a disrupted performance in men and an enhanced performance in women. The authors suggested that this effect was due to possible different networks subserving the perception of sad faces in women and men. These results also suggested the specialization of the temporal cortex role only on sad face processing, as no significant effects were found for positive facial expressions.

The role of temporal cortex on negative valence stimulus is not only restricted to faces, as another tDCS study has suggested by investigating biological bodily motion from point-light displays [22]. In this study, Vonck et al. [22] showed that anodal tDCS over right temporal lobe and contralateral supraorbital reference enhanced recognition of light points copying a biologically body motion in a negative emotional state, both in male and female participants. This study further suggests the role of the left temporal areas in negative emotion recognition not only from facial stimulus. An interesting point not addressed by the authors is a possible gender interaction effect, what could endorse the findings by Boggio et al. [19].

The role of other brain areas besides the temporal cortex in emotional face processing was also investigated. Ferrucci et al. [20] assessed the role of the cerebellum in emotional face recognition, finding that anodal and cathodal tDCS over the cerebellum could enhance the recognition of sad and angry faces [20], which high-

lights the role of the cerebellum in negative emotional face recognition. Also, anodal tDCS over the left DLPFC improved recognition of positive emotional faces, supporting the hemispherical specialization hypothesis for specific emotion processing, named the valence theory (see [23]). However, right DLPFC tDCS did not alter the recognition of negative emotional faces as expected [20], since this area has been believed to be involved in emotional face processing [24], at least for negative valence stimulus [23]. In fact, right DLPFC tDCS has only enhanced the recognition of fear faces in men [21].

In sum, these findings showed the role of the investigated areas in emotional face processing, suggesting specific circuitries for specific emotions. One question still unsolved is the role of lateralized prefrontal areas in emotional face and other emotional processing. The tDCS studies have suggested that DLPFC does not appear to have a general lateralized functioning for emotional valence, but a lateralized functioning linked to specific emotions, probably through the employment of cognitive resources in emotional processing.

Emotion Regulation

Emotion regulation is defined as the process by which one attempts to regulate his or her emotional experience and/or resulting behavior by cognitive control (for example, by attention deployment or reappraisal of emotional stimuli), aiming to achieve a more adaptive emotional response. The emotion regulation can be divided in two main techniques, those focusing to enhance (upregulation) or to diminish (downregulation) an emotional response. Almost all tDCS studies targeted the DLPFC, a critical brain area for executive functioning and emotional regulation [16]. Feeser et al. [25] investigated the role of right DLPFC in the emotional regulation of negative stimuli. The participants received anodal tDCS over the right DLPFC (reference on supraorbital contralateral area) while exposed to negative valence stimuli and were asked to upregulate or downregulate their emotions. Active tDCS altered skin conductance response (SCR) and arousal ratings of participants in comparison to sham tDCS, enhancing these responses in upregulation and decreasing in downregulation condition; findings that clarify the right DLPFC role in cognitive control and emotion regulation through reappraisal.

This assumption was supported by Pripfl and Lamm [26], in which anodal tDCS over the right DLPFC was related to higher levels of cognitive control during affective pictures appraisal, specifically of negative valence. This study also evaluated anodal stimulation over the left DLPFC, but without significant effects. These results are also in agreement with Rêgo et al. [15], in which right anodal DLPFC seemed to control the impact of negative valence stimulus on mood. However, in contrast to Pripfl and Lamm, Rêgo et al. [15] found the same effect in anodal stimulation of left DLPFC.

The effect anodal stimulation over left DLPFC on mood control was also observed in the study by Plewnia et al. [14]. Likewise, Peña-Gómez et al. [9] found decreased valence evaluation for negative valence pictures after tDCS of the left DLPFC. Moreover, previous studies found that anodal tDCS over the left DLPFC increased physical pain thresholds [27], and decreased unpleasantness and discomfort assessment during pain-related pictures observation [28, 29]. These contradictory results between those studies and Pripfl and Lamm could be due to adopted methods. Importantly, Pripfl and Lamm have used a high-definition tDCS. These devices are associated with a much higher focality than the standard tDCS procedures and this must be taken into account when analyzing these results [26].

tDCS might also have a substantial effect on peripheral physiological responses, suggesting an impact in autonomic processes. For instance, Brunoni et al. [30] showed that during anodal left/cathodal right DLPFC tDCS, participants presented increased heart rate variability and decreased salivary cortisol, especially during the visualization of negative valence pictures, supporting the role of right DLPFC on the top-down regulation of autonomic and neuroendocrine responses. Furthermore, as presented in a study conducted with patients with anxiety disorders by Heeren et al. [31], anodal tDCS over left

DLPFC combined with Attentional Bias Modification (ABM) strategy promoted shorter eye gaze fixations during the observation of visually threatening stimuli, suggesting a role of left DLPFC on the modulation of attentional control. Notwithstanding, we suggest that future tDCS studies should further investigate hemispheric and interhemispheric roles of DLPFC on emotion-related cognitive control, considering that the number of studies is still limited and that this could lead to new clinical applications in individuals with mood and anxiety disorders [32].

Social Pain

These studies illustrate the potential of neuromodulation techniques for the investigation of the neural mechanisms behind understanding other's emotions. In this same line, there are numerous works investigating pain perception and judgment of painful situations. More recently, Social Pain, which can be characterized as the experience of suffering due to personal losses or rejection and ostracism [33] has been studied using tDCS. Riva et al. [34] showed that anodal tDCS over the right ventrolateral prefrontal cortex (VLPFC) could reduce the discomfort and feelings of pain. More recently, the same group showed that, under the same protocol, participants who received active tDCS reported lower levels of aggressiveness after being ostracized in a *Cyberball task* [35]. Anodal tDCS stimulation over the right DLPFC also had a similar effect in aggressive behavior, leading to lower levels of self-reported aggressiveness in men [36]. Furthermore, when assessing the impact of DLPFC on the control of emotional suffering due to social pain, Kelley et al. [37] showed that when submitted to right DLPFC anodal tDCS, participants showed higher levels of rumination while being ostracized in the so-called *Cyberball* task (see [38] for review). Altogether, these studies provide causal evidence for the role of the DLPFC and VLPFC in emotional control processes and emotional reappraisal [16], highlighting the relevance of tDCS for the study of pain, empathy for pain (see [39] for a discussion of this issue), and social pain phenomena.

Fear Conditioning

Two studies have investigated the modulation of fear conditioning with tDCS, suggesting different roles for the left and right DLPFCs [40, 41]. In the study by Asthana et al. [40], cathodal tDCS over the left DLPFC (reference over the left mastoid) inhibited fear memory consolidation, while anodal stimulation did not show any significant effects. Mungee et al. [41] showed that anodal tDCS over the right DLPFC (reference over contralateral supraorbital area) led to enhanced fear memory consolidation. These results indicate different roles for left and right DLPFC, as suggested by the previous literature. However, it is important to remember that these different effects between Asthana et al. [40] and Mungee et al. [41] could be due to differences in the methods adopted (stimuli used or task demands could have directed participants to use distinct emotion regulation methods), or even in the reference electrode location, that could change current direction and effects.

In this topic, we have discussed some of the main tDCS studies in affective neuroscience. It is important to highlight some issues: first, tDCS is a suitable technique to modulate cortical areas, but its efficiency for modulating activity of subcortical areas appears to be only indirectly, probably through cortico-subcortical connections (e.g., [42–44]). Therefore, as affective processing is particularly dependent on many subcortical areas, many of these studies here presented aimed to indirectly interfere with emotional processes by top-down mechanisms or by targeting cortical areas that are known to indirectly modulate relevant subcortical structures. As we have mentioned before, the DLPFC is one of the main areas involved in top-down emotional regulation. Both left and right DLPFC appear to be involved in distinct aspects of emotion regulation by mechanisms that are not clear yet.

Social Neuroscience

As mentioned in the introduction section, it is not reasonable to disentangle the social from the affective aspects of the human experience.

Therefore, the separation between emotional and social aspects in the current text is strictly didactical and does not reflect the complexity of the interaction between these two constructs. With that being said, we will highlight some of the most successful investigations that have used tDCS in the elucidation of the neural correlates of prejudice and the neural processes behind social interaction and social decision-making, which have been intensively investigated in contemporary literature.

Implicit Prejudice

Although this is a controversial topic, it could be argued that the frequency of explicit demonstrations of prejudice (racial, social, and gender) might be declining in many cultures. Implicit prejudice—hidden biases that are not always explicit but may influence some behavioral responses—is a topic of great relevance in contemporary social neuroscience. It is important to note that there are substantial methodological challenges involved in investigating a behavioral bias of which subjects are frequently not aware of (see [45] for a review). The case of tDCS in implicit prejudice research is an example of how this technique may be elegantly integrated with classic behavioral paradigms in order to shed a new light on methodologically demanding research questions.

The implicit association test (IAT) is one of the most robust paradigms to investigate implicit prejudice. It allows for the investigation of interactions between different stimuli categories (e.g., faces of different ethnicities with words of different valences) in a fast forced-choice task that unveils biases that are frequently not explicitly accessible [46]. More recently, some groups started to investigate prejudice and its implicit associations using neuromodulation techniques as transcranial magnetic stimulation (TMS) and tDCS. These investigations have showed that the inhibition of the left DLPFC function was able to increase participant's gender bias [47] and religious bias [48] during IAT. These findings suggest that the left DLPFC may play a central role in inhibiting these stereotyped responses.

In this same line but using nonsocial stimuli, a recent tDCS work has also modulated the left DLPFC and found some interesting results. Gladwin et al. [49] found that tDCS of the left DLPFC did not affect the implicit bias processes in the association of insect images and insect names when using an IAT. Taken together with the works of Cattaneo et al. [47] and Crescentini et al. [48], these results could be interpreted as suggesting that there is a left DLPFC specialization for the processing of social (in contrast to nonsocial) bias.

Social Decision-Making

Social decision-making may be defined as the process by which a person chooses between alternatives in the context of social interaction [50]. So far, most studies combining social decision-making and neuroscience have focused on neuroimaging methods, but some new relevant studies have used noninvasive brain stimulation techniques and found exciting results. We will start by presenting studies that have investigated the role of the perception of fairness and social norm compliance in social decision-making.

A seminal investigation of this issue was conducted by Knoch et al. [51] using TMS during the ultimatum game (UG). The UG is a resource-sharing task used to investigate reaction to unfairness, where a player (the responder) have to respond to money sharing proposals from another player (the proposer) that might range from very fair to very unfair. If the responder accepts the offer, both players gain the amount, whereas if the responder rejects the offer both players get nothing. Knoch et al. [51] inhibited the right DLPFC activity during the UG and found that participants playing as responders had increased acceptance rates of unfair proposals, suggesting that the right DLPFC may mediate unfairness evaluation. These exciting results were later replicated by the same group using cathodal tDCS [52], a finding that supports tDCS as a suitable tool for social neuroscience research and that tDCS and TMS results may be compatible in many cases.

A few other works have also paired tDCS with modified versions of the UG with exciting results, in contrast to the standard task that just assesses the

effect of unfairness from the point of view of the responder. Recent experiments have started to investigate the effects of unfairness when the responder has to decide for himself ("myself condition") or on behalf of a third-party [53] and found that inequity aversion may be observed on both "myself" and "third-party" conditions. Civai et al. [53] have also found that the medial prefrontal cortex (MPFC) is particularly active in the myself condition.

In a subsequent study, Civai, Miniussi, and Rumiati [54] have used tDCS in order to better understand the causal role of MPFC in inequity evaluation. They found that cathodal tDCS over left MPFC (midpoint between Fpz and Fp1) led to diminished rejection of unfair proposals in the "myself" but not on the "third-party" condition, supporting the hypothesis derived from previous fMRI studies suggesting that the MPFC is particularly engaged in the judgment of fairness in more egocentric conditions. This adds new relevant information on the fact that there is a distinct and complex neural circuitry to deal with egocentric vs. allocentric conditions.

A more recent study introduced the variable punishment in the UG. Ruff, Ugazio, and Fehr [55] have used a task developed by Spitzer et al. [56] in which two players should divide an initial endowment. One player was a proposer and should suggest a division rate to a second player, the receiver. Two different conditions are available: a control and a punishment one. In the control condition, the receiver could only accept the proposal passively, similar to a dictator game, while in the punish condition the receiver could spend money to punish the proposer. The authors found, in this neuroimaging study, that the punishment condition led the proposers to comply with the social norms and share the endowment more fairly and that this behavioral adaptation was related to an enhanced activation of right DLPFC, left VLPFC, and bilateral orbitofrontal cortex. Ruff et al. [55] modulated the right DLPFC with anodal and cathodal stimulation to investigate the role of the right DLPFC on norm compliance. They found that, in the punishment condition, the anodal stimulation (compared to sham) led the proposer to transfer more money after punishment, enhancing norm compliance. Contrary to that, the cathodal stimulation turned the proposers more self-interested and less oriented by social norms of fairness, diminishing the quantity transferred to the receivers. In the control condition (where the receiver could only accept passively), the stimulation acted in the opposite way. These results help to support the role of the right DLPFC in a network linked to norm compliance, but as highlighted by Sanfey et al. [57], the fact the punishment and the control conditions were oppositely affected by tDCS suggest that this network may be more complex than previously expected.

As social norm compliance may be affected in many clinical conditions, studies showing a significant modulation of these processes by tDCS highlight its potential as a social cognition rehabilitation tool for clinical populations. Social interaction is another field of research in social neuroscience where tDCS might have a promising clinical relevance too. Below are some basic research examples that not only support this clinical potential, but also seem to have helped to overcome some methodological challenges in investigating higher-order cognitive processes such as this one.

Perspective Taking

Perspective taking is a critical skill for effective social interaction and closely related to empathy and consequently to the development and maintenance of positive social connections (for a review see [58]). As Conson et al. [21] demonstrated, although promoting faster negative emotion recognition in males, right anodal/left cathodal tDCS over DLPFC decreased participants' ability to assume the perspective of others during a visual perspective taking task. Another relevant study has investigated the neuromodulation of temporo-parietal junction (TPJ) in participant's performance on three social cognition tasks: on a motor imitation task, a spatial perspective-taking task, and a self-referential task [59]. Although some neuroimaging studies have suggested the involvement of the TPJ in abilities related to the execution of these tasks, TPJ tDCS effects were not the same for all tasks. This study has showed that

anodal TPJ tDCS improved the control of self-other discrimination related to the imitation and perspective-taking tasks, while did not have any effect on mental attribution ability, as evaluated by the self-referential task [59]. This study has helped to clarify the involvement of TPJ in empathy and its role in self-other discrimination.

Hogeveen et al. [60] have expanded these findings by testing the effects of anodal tDCS over the right TPJ or right inferior frontal cortex (IFC) on imitative control functions. Interestingly, anodal tDCS of the right IFC improved the ability to inhibit imitation in a task when it was required but, at the same time, increased the imitation behaviors during a social interaction task (which is related to better social interaction). Thus, it seems that IFC is somehow involved in imitation, but in a way that is dependent on the task performed. In addition to that, anodal tDCS over TPJ was associated with increased ability to inhibit imitation but had no effect on the imitation during the social interaction task. These findings suggest a direct role of the IFC in imitative behavior and an indirect one of the TPJ in a way that is dependent on the social demands.

Conclusions

We have presented an overview of some of the most relevant investigations of social and affective neuroscience involving tDCS. We would like to argue that two things are clear after this review. First, that tDCS is indeed a valuable tool for contemporary social and affective neuroscience research, bringing important new insight into classical research questions and complementing the current knowledge of the field with another level of causality in bridging brain and behavior. Second, that the technique is still not used as much as would be appropriate given its potential. In fact, if we consider the works that have been presented here, we may argue that tDCS is indeed a technique that has brought a number of new insights into technically challenging questions of classical psychological science. Assessing causality and not being time limited in the same way as other brain investigation techniques (e.g., event related potentials and fMRI) may be highlighted as some of its major strengths. Given that, we hope to see more tDCS in social and affective neuroscience research in the future.

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Multimodal Association of tDCS with Electroencephalography

9

Nadia Bolognini and Carlo Miniussi

Abstract

In the last decade, in the field of neuromodulation, we have observed an increase in the popularity of approaches that combine transcranial electrical stimulation (tES) with additional methods to establish, in vivo, the neurophysiological consequences of a given experimental or therapeutic manipulation. We are at the beginning of the development of multimodal approaches, and several methods are available that can be combined with tES to study brain functions. This chapter aims to introduce the reader to some basic principles of this multimodal approach. We begin with a brief definition of multimodal association and a description of the advantages of such an approach. Afterwards, we provide a more specific description of how we can combine tES with electroencephalography (EEG). We show that EEG is a feasible and reliable way to track electrophysiological changes induced by tES, deepening our understanding of the mechanisms of action of this tool and revealing the key role of several stimulation features. In neuropsychiatric diseases, a combined tES-EEG approach may allow the prediction of clinical responses to tES, the discrimination of responders from non-responders, improvement in the efficacy of tES, and the tracking of tES-induced neuroplastic changes associated with recovery.

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Introduction: A Brief Picture of the Present State of Research

In recent years, there has been an exponential rise in the number of studies that employ non-invasive brain stimulation as a means of gaining understanding of the neural substrates that underlie normal (see Chap. 8) and pathological behaviour (see Chap. 2) and as an adjuvant tool for treating brain dysfunction associated with neuropsychiatric disorders (Chaps. 13–21).

As clearly explained in the previous chapters of this book, non-invasive brain stimulation includes several methods that can be divided into two main categories: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). The latter includes different modalities, namely, transcranial direct current (tDCS), alternating current (tACS) and random noise (tRNS) stimulation. All of these methods involve the application of weak electrical currents to the scalp using at least two electrodes [1]. These currents induce changes in the electrical activity of neurons, which in turn modifies the neurons' synaptic efficiency. Although these changes are insufficient to induce action potentials, they introduce variation in the response thresholds of the stimulated neurons [2]. Typically, through this variation, anodal tDCS and tRNS increase neuronal excitability and cathodal tDCS decreases excitability, whereas tACS modifies neuronal excitability through the entrainment of the desired neuronal firing frequency [3]. All of these aspects of tES are well described in the other chapters of this book, where the reader can see that, thanks to important developments that have been made in recent years, many technical difficulties that were originally faced during the development of tES in human research have been solved, the methodological foundations have been laid [1], and now we are beginning to clarify the mechanisms of action of tES.

On these solid foundations, we are now expanding and refining the experimental and clinical use of tES, and fostering an integrated use of this technique with neuroimaging is one of these future goals. This chapter aims to introduce the reader to some basic principles of the multimodal approach. We begin with a brief definition of "multimodal association" and then move on to a description of the advantages of such an approach. Afterwards, we provide a more specific description of how we can combine tES with electroencephalography (EEG). In this respect, we list the basic technical elements that allow the best integration of tES, and in particular tDCS, with EEG. Finally, we show how this approach can be used for diagnostic or prognostic purposes in neuropsychiatry.

Principles of Multimodal Association

Over the last decade, we have observed an increase in the popularity of approaches that combine more than one method to establish, in vivo, the consequences of a given experimental manipulation, due to the increased accuracy of multiple imaging techniques [4]. The possibility of altering brain functions with tES, while simultaneously assessing those functions with neuroimaging, is essential to understand whether and how tES affects sensory-motor, cognitive, and affective functions. In general, every method

used to track changes in brain activity has its pro and cons. For example, EEG has an excellent temporal resolution but has limitations in the spatial component; functional magnetic resonance imaging (fMRI) has the opposite features: good spatial resolution and low temporal resolution. Moreover, electrophysiological and haemodynamic/metabolic signals reflect distinct aspects of the underlying neural activity. From a methodological perspective, the combination of complementary approaches within the same experimental setting, and therefore within the same time frame, should boost the amount of information that we can obtain beyond what is achievable with each method independently. Therefore, the ideal situation is to combine non-invasive brain stimulation with the collection of both behavioural indexes of changes and more than one measure of brain activity (e.g. fMRI, EEG, and magnetic resonance spectroscopy) to overcome the intrinsic limits in spatial and temporal resolution of each recording technique; this will offer a more complete framework for understanding the effects of tES in vivo [5] by tracking changes at different levels of analysis (behavioural and neural).

The main challenge of the multimodal association approach is a technical one, given that the limits of combining different devices are mostly due to technical problems. This challenge implies clear understanding of the functional principles of the combined methods and of the distinct (due to the different measures), but linked, neural effects that are being measured (e.g. electrophysiological vs. haemodynamic). Moreover, we must be aware of, if and how, the recorded signal is being altered by such combinations. For example, tES involves the use of currents that not only change the function of neurons but also the capability of the EEG amplifier and electrodes to record the signal. Similarly, tES current flow produces a magnetic field, and MRI recording is sensitive to local magnetic fields [6]. It follows that we need to identify a reliable method to record data during concurrent stimulation and registration without affecting signal quality to obtain a biological signal that accurately reflects the measured process, rather than a technical artefact.

Advantages of Combining tES with Other Methods

We are at the beginning of the development of such multimodal approaches, but we have at our disposal several methods that can be combined with tES to study brain functions. The simplest and best-known one is the use of TMS to track cortical excitability shifts induced by tES, as traditionally conducted in studies in the tES literature, such as in the seminal studies by Priori and colleagues [7] and by Nitsche and Paulus [8] at the turn of this century (see Chap. 7). Another approach involves the recording of the metabolic changes that are brought about by tES by means of fMRI or positron emission tomography (PET). PET and fMRI offer a clear picture of the whole brain's activity with uniform sensitivity and high spatial resolution, as elegantly presented by Stagg and colleagues (Chap. 10).

One supplemental, method that can be used to obtain images of human brain functioning is EEG. EEG allows measuring the electrical activity of populations of neurons, which comprises the brain's activity, while a subject is in a given state (e.g. open or closed eyes; at rest or performing a perceptual or behavioural task). Neural activity generates electrical currents that pass through the skull and give rise to small potential fluctuations/differences, which can be recorded by means of electrodes fixed to the scalp. EEG has a relatively poor spatial sensitivity; nonetheless, it offers some important advantages if combined with tES, given that both are based on the same electrophysiological basis. EEG is based on the theory of volume conduction, which describes the flow of ionic currents that are generated by nerves and cells in the extracellular space. tES uses the same principles to change neuronal states, although the current is applied to the scalp to reach the neurons. In other

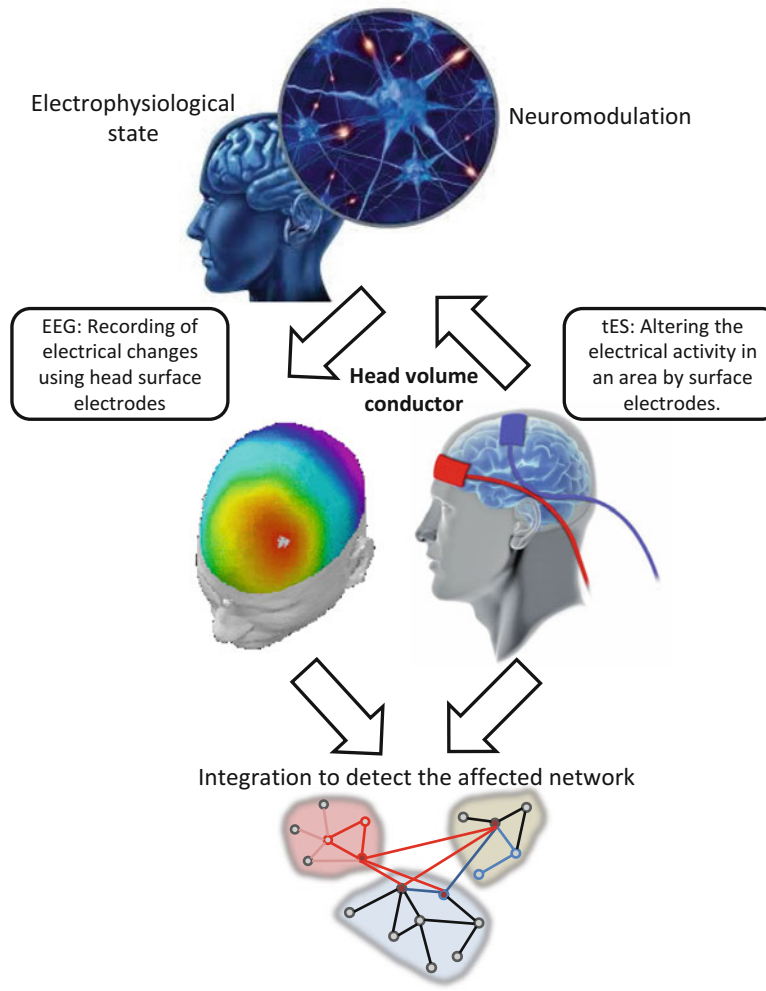

Fig. 9.1 The currents that are recorded by electroencephalography (EEG) result from transmembrane currents in neurons; these currents can be specifically modified by transcranial electrical stimulation (tES). Stimulating a cortical area is likely to affect the underlying region in addition to other areas of the system, and this pattern of activation may be responsible for the final tES-induced behavioural effect. By combining tES and EEG, it becomes possible to acquire simultaneous measurements of the activity of the entire brain, providing a broad picture of cortical responses and a focal picture of which network has been affected

words, the advantage of recording the EEG during tES lies in the fact that the measured signal is directly coupled to neuronal electrical activity and therefore reflects the electrical state of neurons (Fig. 9.1). Currents recorded with EEG result from transmembrane currents in neurons, which are the currents that can be specifically modified by tES. In brief, tES can change membrane permeability and, consequently, ionic current flows [9–11], while EEG measures the voltage fluctuations that result from ionic current flows [12]. Consequently, the recording of EEG during tES provides an assessment of the effects of tES on neural processing in the stimulated brain region. Crucially, the local activation caused by tES spreads trans-synaptically to distal connected areas. Such activity propagation can be reliable traced by simultaneous EEG recording, which therefore reflects rapid causal interactions among multiple groups of neurons or, at least, areas. Hence, EEG offers the potential to simultaneously identify local and distal neural responses to tES, enabling elucidation of the stages of processing over time and across circuits [13, 14]. This property is relevant because although tES modifies neuronal activity in a circumscribed area under the stimulating electrode [15, 16], changes in cortical excitability do not remain confined to the stimulated area, but spread to interconnected regions [17]. In tES research, one of the main goals of multimodal neuroimaging is the evaluation of such network

changes. Indeed, according to the process of emergence, the behavioural output of a complex system, such as our brain, arises via specific interactions between minor entities; consequently, the final tES effect cannot be merely ascribed to the response of simpler subunits that compose the stimulated area. Therefore, evaluating the effects at the level of network activity is fundamental for interpreting and predicting the final behavioural outcome of tES; in this sense, the EEG system is a valuable tool.

The objective of the next section is to describe the essential technical steps to create an optimal combination of tES with EEG recording.

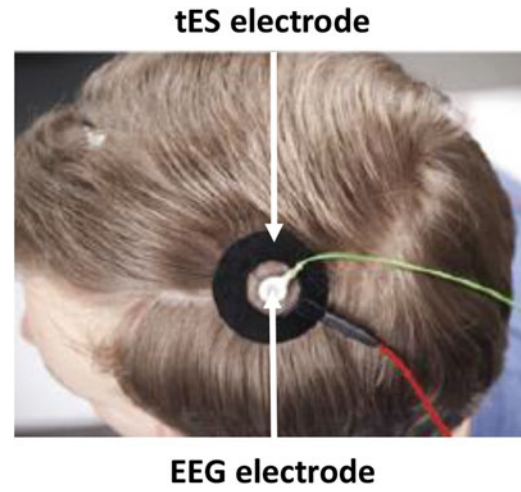

Fig. 9.2 Depiction of an experimental set up that utilises two concentric electrodes: a central electrode to record the EEG signal and a ring electrode to deliver tES. From Sehm et al. [33]

tES–EEG Technical Aspects

There are two main methodological approaches to combining tES and EEG that depend on the temporal relationship between tES delivery and EEG recording: the "offline" method, which evaluates the short-term and long-term aftereffects that follow tES delivery; and the "online method," which evaluates the immediate changes that occur during tES [18]. Only the online method can be defined as a true multimodal approach (e.g. [19–26]), although the offline method can also provide important information.

When designing an experiment, it is crucial to specify whether an online or an offline method is going to be adopted because these two approaches require completely different technical procedures and provide different information about the mechanisms of action of tES.

Pragmatically, the first technical problem to face is how to position the tES electrodes without interfering with the EEG electrodes. An ideal solution would be to have dedicated pre-cabled caps in which the stimulating electrodes are mixed with the recording electrodes [24, 27–29]; unfortunately, this is not always realisable because dedicated systems are required. The simplest solution is to locate the so-called "active" (or target) electrode under the cap, making sure that EEG electrodes are not over or close to it. Here, a net-shaped elastic mesh tissue bandage can be used to fix the tES electrode; this will avoid interference with the EEG electrodes. Nevertheless, this arrangement is not ideal because it does not provide easy access to the tES electrode if any problem occurs, and electrodes can drift from their original location. An additional issue is the production of bridging between electrodes. Therefore, some researchers have placed plastic foil on the top of tES electrodes with the aim of preventing unwanted bridging or contact with the EEG cap [19, 30]. An alternative solution is to deactivate the EEG electrodes that are positioned over the active tES electrode [31]. A final option is to create a dedicated tES-EEG cap by making some specific gaps (cuts) on the cap between EEG electrodes. This approach would enable direct access to the active tES electrode [21]. In addition, tES electrodes can be shaped in a more rounded form so that they can be fitted between EEG electrodes [32] or even as rings so that the EEG electrode can be located in the centre of the tES electrodes [33], as shown in Fig. 9.2. It should be noted that reducing the electrode's surface area increases current density; accordingly, the current intensity should be adapted. With respect to the return (reference) electrode, it can be located "out" of the recording space (e.g. shoulder, cheek, part of the forehead, but it should be considered that locations like

supraorbital or similar can affect the prefrontal cortex, see for instance [2], and other Chapters). If it is necessary to locate it on the head, one of the procedures described above for the active electrode should be adopted.

While in sequential recording (offline method), we face only the challenge of positioning the tES and EEG electrodes over the scalp to avoid reciprocal interference, the co-registering of the online method involves additional problems. As stated before, EEG is used to record electrical activity over the scalp, whereas tES involves the application of electrical current over the same scalp, but at a different order of magnitude (i.e. bigger). Therefore, the co-registering can be technically challenging because the tES-induced charges in the electrodes, amplifiers and skin can saturate the recording amplifier for few seconds before recovery of the EEG signal. In general, the new generation of amplifiers offers a large operational range for the registration of electrophysiological signals; this range is obtained by adjusting the amplifier sensitivity, which allows the co-registration without many problems, apart from a few seconds of saturation (~2 s) when the tES current is switched on and off or when an intensity variation is introduced. In some cases, the artefact appears only in the EEG channels close to the tES electrodes [20]. In this respect, although we can use, with some precautions, the "standard" tES electrodes placed in saline-soaked sponges during EEG recording, tES could also be delivered through sintered AgCl electrodes [28, 34], i.e. the same electrodes used to record EEG. The advantage of AgCl-sintered ring electrodes, for recording EEG, is that they are less sensible to polarisation effects and therefore have optimum long-term stability and low-frequency noise [35].

Generally speaking, in the standard approach a physiological saline solution is applied to wet the sponge, taking care that the solution does not soak too much the hair (causing dripping) while ensuring that the sponges remain consistently wet. If caution is not used, the physiological solution can leak from the sponges; if this is the case, the features of the contact area will be modified, and they might even cause bridging between the tES and EEG electrodes or between EEG electrodes. To improve scalp contact and avoid unwanted bridging between electrodes, it is possible to apply an electro-conductive gel under the surface of the electrode (without a sponge) to make the contact area, and therefore the current distribution, uniform (see [36] for suggestions on electrode setting and to avoid unwanted skin sensations). In some cases, there is also the possibility to use conductive EEG "adhesive" and a relatively dry paste (i.e. Ten20®; Weaver and Company; Colorado USA), which holds the electrodes in place and prevents bridging due to leaking of the gel [23, 25].

A final important point is related to the noise that can be introduced by the tES device during EEG recording. Indeed, the stimulating device is composed of an electronic circuit that can be the source of unwanted external noise. This noise can be minimised or eliminated by using a stimulator with adequate isolation. It is possible to test and quantify these problems by performing experiments with a phantom head, as done by Veniero et al. [37]. In this way, one can easily identify an unwanted artefact, such as instrumental frequency injection. "Phantom" data can also be used to define the spectral characteristics and the spatial distribution of tES-related, non-physiological artefacts; eventually the tES data retrieved from the phantom can be compared with the sham data.

Filtering the data with a 0.5–70-Hz band pass filter can effectively remove artefacts related to tES [20]. Moreover, independent component analysis can be used for the detection and removal of artefacts related to ongoing electrical stimulation [28, 38].

While all the above-mentioned considerations are equally relevant for all tES modalities, tACS or tRNS involve an important additional challenge because they act by inducing an oscillation that contaminates the entire recorded signal. In this case, it has been suggested that it might be possible to clean the signal from tACS-induced artefacts with dedicated algorithms for data analysis [39]. Nevertheless, further developments in this direction are still needed.

In the next section, we will focus on the tDCS-EEG combination because the bulk of work regarding the multimodal association approach involves tDCS. A description of the combination

of other tES techniques with EEG, with online and offline designs, can be found in the following works: tACS [6, 40–47], pulsed/oscillatory stimulation [48–50], and tRNS [31].

tDCS–EEG in Studying Cortical Excitability, Connectivity and Plasticity

As discussed above, the basic mechanisms underlying the direct neuromodulatory effects of tES are well established due to several studies of animal models [51, 52] and human subjects [53]. Nevertheless, several studies have also highlighted the complexity of the technique and the non-linearity of the induced effects [54–56], as well as the large intra-subject variability [57–59]. Overall, our understanding of tES-induced online and offline effects on neural activity remains fragmented. Given these premises, the importance of electrophysiological studies aimed at clarifying the consequences of neuromodulation by tDCS becomes evident. EEG-based investigations are even more important if we consider that tDCS-induced effects are sensitive to the specific state of the stimulated area [6, 60–63].

Another issue is related to the spatial and temporal resolution of tDCS, which are considered to be very low; however, recently, this picture has been shown to not always be true. Many lines of evidence, including those that combine tDCS and EEG, indicate that the final effect, on both behaviour and neural activity, can be very focal [64]. The specificity of the effects of tDCS effects results from the fact that this form of brain stimulation principally affects neurons that are close to the discharge threshold, which means that the final effect emerges from a change in the activity of a specific, circumscribed neural network, which is related to the subject's state or to a given cognitive process [65, 66].

Since the beginning of this century, EEG has been used to track the products of cortical excitability shifts brought about by tES (e.g. [67]) and to predict the spatio-temporal dynamics of functional connectivity (e.g. [17]). The online and offline methods described, above as well as the issue of how the combined tDCS-EEG approach can be utilised in interactive and rhythmic (i.e. using repetitive TMS; [68]) manners, have been extensively discussed elsewhere [18, 69]. In the following section, after we report a gross description of the main studies in this field, we will briefly describe only the more recent advances (for an overview of the seminal works, see the review paper by Miniussi and coworkers [18]).

The majority of the studies have recorded EEG activity in the resting state, such as by analysing neural oscillations associated with tDCS by frequency changes [20, 22, 24, 26, 28, 30, 70–74] or by recording the effects of tDCS on functional connectivity [17]. In some instances, TMS was also incorporated to probe changes in excitability or connectivity before and after tDCS [23, 72].

Many studies have recorded EEG activity to evaluate how tDCS modulates the activity of different sensory areas, including visual [20, 67, 75], auditory [76] and somatosensory [33, 77–80] areas. Others studies have analysed event-related potentials (ERPs) or changes in signal frequency in an active state, that is, during the execution of a task, in different contexts, including mismatch negativity [63], inhibitory control [21, 81], working memory [82–85], motor imagery [86], finger tapping [87], and language [88, 89]. It is very difficult to compare and reconcile the results from all of these studies given their heterogeneity with respect to the stimulation parameters (e.g. density and duration), electrode montage (i.e. bipolar vs. unipolar), studied population, targeted areas, and the task performed by the subjects. Collectively, the main message offered is that the tDCS-EEG combination can be used to effectively evaluate changes in cortical excitability, connectivity and plasticity. Such changes depend on several factors, a finding that again stresses the existence of a "non-linear" brain response to tDCS, which reflects the variability of behavioural outcomes [58, 59].

In particular, investigations of cortical rhythms have shown that tDCS directly modulates rhythmic cortical synchronisation during and after its delivery. The majority of these studies found an increase in almost all bands (delta, theta, alpha,

and beta), which appeared to be more prevalent and reliable after anodal tDCS compared to other stimulation modes (i.e. cathodal). Neuronal networks are very sensitive to electric field modulation [90], and the efficacy of tDCS might depend on the intrinsic network structure [91]. In this context, it is has also been suggested that network effects may be related to the concepts of noise and stochastic resonance [66], where a weak stimulation (such as the neuromodulation itself) that is added to the system's fluctuations enhances (or reduces) the biological signal, in turn potentiating the response of the network itself.

An interesting result regarding the interaction between brain activity and stimulation was recently reported by Accornero et al. [20]. The authors evaluated changes in EEG frequency as a marker of excitability changes induced by different electrode montages, bipolar and unipolar, that targeted the prefrontal cortex. The bipolar montage involved positioning of both electrodes over prefrontal areas (cathodal right and anodal left, or vice versa), whereas in the unipolar montage, one electrode was positioned over the prefrontal cortex, while the other was positioned on the opposite wrist. The first finding was that anodal tDCS induced changes in the mean frequency of the EEG; these changes occurred very rapidly (after 1 min of stimulation) and remained substantial and consistent throughout the whole stimulation period (15 min). The second, and most interesting, finding was related to the interaction between the electrode montage and the stimulated cortex, as indexed by changes in the EEG mean frequency that were constrained to the cortical area that was stimulated. As illustrated in Fig. 9.3, anodal tDCS to the left prefrontal area, cathodal tDCS to the right prefrontal area, or both together (bipolar stimulation), increased the EEG mean frequency; in contrast, when the montage was "reversed", meaning cathodal tDCS to the left prefrontal area or anodal tDCS to the right prefrontal area, but not both together, the EEG mean frequency was decreased. The changes induced by unipolar anodal and cathodal tDCS were similar in terms of absolute size (anodal tDCS increased cortical excitability, whereas cathodal tDCS decreased it) but were specific for the stimulated site, showing that the primary aspect that determined the decrease or increase in the mean frequency was related to the role played by the circuitry of the frontal cortex that was stimulated [20]. This evidence shows how prefrontal areas act "as a whole" to modulate the brain activity recorded by EEG, highlighting that the main factor that determines whether the mean frequency will decrease or increase is not only the stimulation, but the combination of stimulation type with the stimulated network. This type of result is relevant when we want to test the efficacy of a montage for pathologies such as depression, because an imbalance in the activity of the prefrontal cortices is considered to be of key importance in this type of application [92, 93]. This evidence may also be important as a potential explanation for the frequent finding, in both cognitive and perceptual studies, of the failure of some electrode montages (e.g. cathodal) to effectively modify (e.g. inhibit) prefrontal activity.

Therefore, considering that EEG frequency correlates with many psychological features also relevant for clinical symptoms, such as mental arousal level [94] and mood and performance in various tasks [95, 96], it becomes obvious that a priori knowledge of which tDCS montage and methodology is most effective in inducing changes in EEG frequency could guide the optimal therapeutic use of tDCS.

The impact of the intensity of the electrical current was illustrated in a work by Hoy and coworkers [82]. At least in healthy subjects, anodal tDCS at 1 mA was shown to induce greater effects in cognitive enhancement than an intensity of 2 mA; accordingly, increased theta event-related synchronisation and alpha event-related desynchronisation were detected with EEG co-registration mainly following the 1 mA stimulation as compared to sham [82]. Additionally, several other works have shown that tDCS modulates the amplitude and latency of only some ERP components in a very specific way (see Reinhart and Woodman for a commentary), although not to the same extent in every condition (e.g. [63]), nor in every single

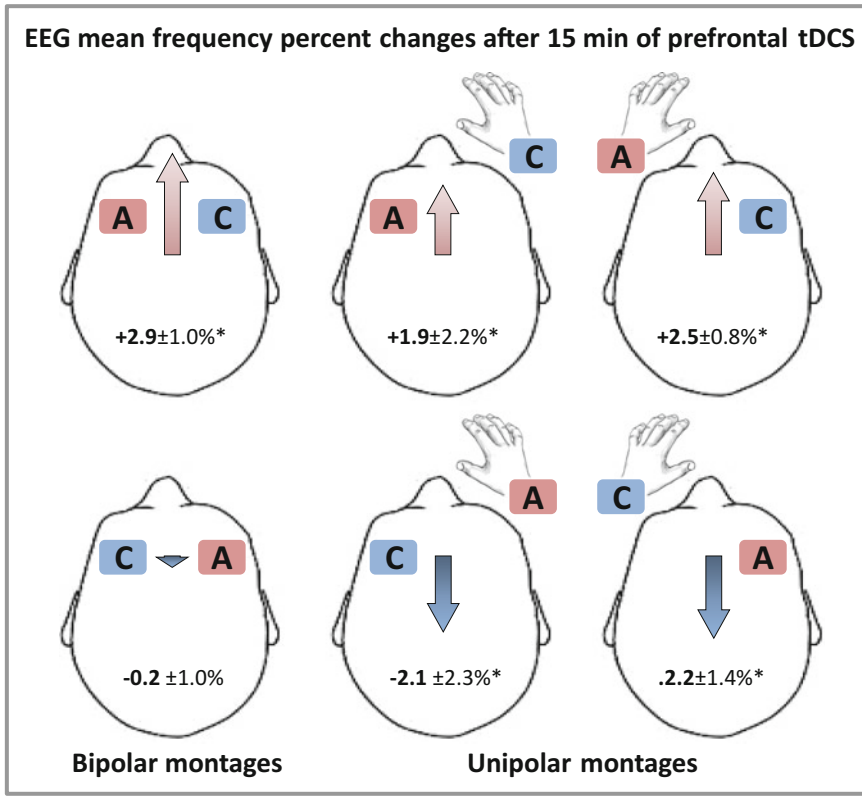

Fig. 9.3 Percentage change in the EEG mean frequency recorded after 15 min of stimulation compared with that recorded at baseline (5 min before tES). Values are the mean ± standard deviation. The *vertical arrow* height indicates the magnitude of the intensity of the effect. *A* anodal, *C* cathodal. Adapted from Accornero et al. [20]

individual (e.g. [84]). Overall, the key point from these studies is that the final tDCS effect depends on the state of the neural system at the time of the stimulation.

Impey and Knott [63] found that tDCS induces a modulation of the mismatch negativity elicited by an auditory sensory discrimination task, and the observed effect was condition-specific and not spatially constrained to the stimulated area. They found changes, elicited by tDCS, in the mismatch negativity component, which originates from the prefrontal cortex, although the stimulating electrode was located over the temporal cortex. Of interest, the modulation was present only when the deviant changes were difficult to detect and was absent in easy conditions. This last result suggests that the effects of tDCS are sensitive to task difficulty (e.g. [13, 60]).

Along the same line, a study by Tseng and colleagues [84] showed that the outcome of tDCS is not always uniform; rather, it depends on individual differences in performance level. In a visual short-term memory task, in low performers, who did not originally show elevated waveforms amplitudes in the EEG components, which reflect improvement in attentional deployment and memory access (i.e. the N2pc and contralateral delay activity or sustained parietal contralateral negativity), anodal tDCS over the posterior parietal cortex was able to improve their performance and the related EEG components, whereas high performers did not benefit from concurrent anodal tDCS, as demonstrated by the lack of behavioural improvement; accordingly, they showed equally large waveforms in the above-mentioned EEG components, both before and after tDCS.

The take-home message from these few examples is that tDCS can change cortical excitability and that such changes can be reliably detected with EEG. Importantly, the effects of tDCS are not mapped as a unidirectional, linear change solely on the stimulation features, such as polarity, intensity, and electrode montage; in the same, behavioural changes by tDCS are not always linear and systematic in every experimental condition. All these changes depend on the stimulation parameters, as well as the brain state during the tDCS delivery [97–99]. As discussed in the previous sections, applying an electrical field to a non-linear dynamic system, such as the brain, seems to have many non-trivial effects that preclude a simple extrapolation onto behaviour. For this reason, the use of the combination of EEG and tDCS offers additional insight into the level of action of tDCS, as EEG can contribute to the identification and understanding of the physiological conditions associated with non-linear tES induced-effects; which may be, in some instances, even unforeseeable, when based only on behavioural outcomes. The concurrent adoption of EEG will enable more reliable clearer predictions of what we should expect after the application of tDCS in a given task. This knowledge becomes even more important if tES is used with therapeutic purposes because of the inherent difficulty in predicting clinical outcomes and thus of determining the individual patient's response to tES. In the following section, an overview of the clinical feasibility of simultaneous tDCS and EEG recording in neurological and psychiatric diseases is provided.

Multimodal Imaging as a Diagnostic/Prognostic Tool in Neuropsychiatric Disorders

Behavioural studies have revealed many potential therapeutic applications of tDCS, in particular as a rehabilitation tool for a wide variety of diseases that involve changes in cortical excitability (e.g. [2, 100–104]; see also Chaps. 13–21). Deepening our understanding of the neuroplastic effects of tDCS is essential to improve clinical outcomes of rehabilitation. From this perspective, the combined use of tES and EEG in clinical practice should allow the identification of prognostic factors as well as predictors of the clinical response to stimulation. This knowledge has the obvious implication of increasing the success rate of tES-based rehabilitation programmes by making them individually tailored. This is the clinical challenge of the combination of tES and EEG; nevertheless, to date, few studies have been performed on patients following these lines, even though multiple opportunities can be foreseen.

Beginning with the simplest application, Faria et al. [28] polarised the brain of epileptic patients with tDCS to induce functional changes and recorded online EEG activity to observe changes in epileptogenic activity. Abnormal increases in the excitability of the cerebral cortex are fundamental characteristics of epilepsy. Interictal epileptiform activity on EEG reflects this indirectly. Thanks to its neuromodulatory features, tDCS may have the ability to modulate the excitation-inhibition balance, which may make it useful for treating human epilepsy as well as other diseases whose pathophysiology depends on an alteration of the balance between excitatory and inhibitory inputs in the cortex [105, 106]. In epilepsy, EEG recording can be used to track online whether cathodal tDCS can potentially reduce ictal events, allowing continuous monitoring of interictal activity, as biomarker, during the stimulation period [28]. In patients with refractory epilepsy, repeated sessions of tDCS, with the cathode positioned over the area of epileptogenic activity, were shown to induce a significant reduction in interictal epileptiform EEG discharges.

Roizenblatt et al. [107] used EEG to evaluate whether tDCS-induced pain changes in fibromyalgia are associated with changes in sleep structure by comparing changes in EEG sleep parameters induced by anodal tDCS of the primary motor cortex (M1) or of the dorsolateral prefrontal cortex (DLPFC), with the return electrode over the contralateral supraorbital area. Anodal tDCS was shown to affect sleep depending on the site of stimulation: whereas M1 stimulation increased sleep efficiency, decreased arousal, and

increased delta activity in non-REM sleep, DLPFC stimulation decreased sleep efficiency, increased REM and sleep latency, increased alpha activity, and decreased delta activity in non-REM sleep. Importantly, the decrease in REM latency and the increase in sleep efficiency that were brought about tDCS over M1 were associated with an improvement in fibromyalgia. These findings are relevant to understanding the possible mechanisms at the basis of tDCS-induced pain relief in fibromyalgia and suggest that the effects likely depend on sleep modulation that is specific to the modulation of M1 activity [107].

EEG can also be used to predict clinical responses to tDCS. Vanneste and coworkers [108] explored whether the functional state of the brain at baseline could be used to discriminate between responders and non-responders to a tDCS-based treatment of tinnitus. Towards this aim, they evaluated if the activity and connectivity pattern of responders to bi-frontal tDCS differed from that of non-responders. Prior to tDCS application, the baseline EEG activity of the responders showed increased functional connectivity in the gamma band, which was not detected in non-responders [108].

Another important aspect, as suggested by the study of Notturno et al. [87], is that tDCS can change the strength of synaptic connections between motor areas [17], which may favour motor recovery. Indeed, the induction of local modulation of membrane polarisation as well as long-lasting synaptic modifications by tDCS over M1 could result in changes in both local band power and in the functional architecture of the motor network. Therefore, the optimal use of tDCS in post-stroke motor rehabilitation may be based on direct evaluation of functional connectivity changes, as indexed by EEG recording during or after tDCS [14].

It has also been suggested that knowledge of the changes in cortical oscillations induced by tES is relevant for treating specific pathologies that are associated with alterations of oscillatory brain activity in specific frequency bands [76], especially when specific tES effects can be regarded as causal determinants of the pathological symptoms. In this framework, the evaluation of electrophysiological activity may represent the most important step for developing ad hoc therapeutic tES protocols [109].

Another interesting development is the use of tDCS in combination with EEG-based brain–machine interface systems (BCIs). BCIs are used to record, decode, and translate measurable neurophysiological signals that are associated with the user's intention or state to drive external devices. For instance, EEG-based BCIs can be used to permit action through brain signals that are acquired and decoded by means of EEG oscillations or event-related brain potentials [110]. A recent study [25] evaluated, in healthy subjects, the feasibility of combining EEG-based BCIs with tDCS by investigating the influence of simultaneous tDCS on EEG recordings across different frequency bands. Participants were instructed to self-regulate EEG-recorded motor-related oscillations (i.e. desynchronisation of the my rhythms that are associated with motor imagery), which were translated into online cursor movements on a computer screen. During the BCI session, sham or active tDCS was delivered: the active tDCS electrode was placed immediately anterior (1 cm) to the EEG electrode used for online BCI control (C4), and the reference electrode was placed over the left supraorbital region. The application of tDCS was associated with a significant signal increase across the lower frequency bands (delta and theta) in the proximity of the stimulation electrode as well as at larger distances (>8 cm). Similarly, an offline method was used to evaluate the increase of mu rhythm in stroke patients [111]. Mu rhythm of the affected hemisphere increased significantly after anodal tDCS over the primary motor cortex, whereas it did not change after sham tDCS [111]. This evidence provides the first demonstration that the delivery of tDCS in close proximity to an EEG channel for learned self-regulation of brain oscillatory activity is feasible and safe. The potential to modulate, with tDCS, the activity of cortical brain areas that are functionally related to BMI control is important for improving the therapeutic applicability and practicality of BMI use and opens up new opportunities for the investigation of the association between learned

self-regulation of brain activity, including oscillatory activity, and tDCS-induced behavioural changes.

In brief, these few examples illustrate how the combination of EEG and tES can be used in clinical settings, to identify both patients who could potentially respond to a rehabilitation protocol based on neuromodulation and which tES protocol would be suited for a given patient (predictive role); on the other hand, combing EEG and tES may allow the evaluation of cortical activity changes that form the basis of a clinical improvement (assessment role), enriching our understanding of the mechanisms of action of neuromodulation in neuropsychiatric diseases.

Conclusions and Final Remarks

Research must certainly move ahead to improve the development of multimodal association approaches. There is still much work to do to determine the optimal implementation of tES with simultaneous EEG recoding. First of all, it is necessary to develop and share theoretical models and standardised procedures of application and analysis; the present knowledge provides inspiration for important progress in this field. As reported in this overview, at least in healthy subjects, many behavioural effects brought about by tES have been substantiated by electrophysiological data, and we are learning that changes in some tES parameters are fundamental for improving the efficacy of the stimulation and for modelling behavioural effects. All of these aspects need to be further explored, in patients with psychiatric or neurological diseases as well, because we cannot take for granted that a protocol that has been found to be effective in healthy subjects could be simply and directly transferred to a clinical setting. In particular, because of the idea that the effects of tES are strongly dependent on the system state, application of the parameters that have been developed in healthy populations might not induce the same response in a system that has a completely different homeostasis due to pathological alterations of brain functioning.

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tDCS and Magnetic Resonance Imaging

10

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Abstract

Transcranial direct current stimulation (tDCS) is an increasingly promising potential therapeutic intervention in the treatment of a range of psychiatric and neurological conditions. However, before its full potential can be utilised more must be understood about its effects on the underlying brain tissue, both in regions local to the site of stimulation and those more anatomically distant. Magnetic resonance imaging approaches have the potential to study the modulation of brain activity by tDCS, and here we review the functional MRI and MR spectroscopy studies involving tDCS. We review the basis of the most commonly used approaches for both fMRI acquired at rest and during a task performance. We then go on to summarise the studies that have been performed to date in healthy controls and in patients with a range of psychiatric conditions, before discussing what conclusions can be drawn. It is to be hoped that this will prove a useful summary both for clinicians who wish to understand more about the neurophysiological basis of tDCS and for researchers who wish to perform their own tDCS/MR experiments.

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Introduction

Transcranial direct current stimulation (tDCS) is a promising tool for neuroscience applications and a potential adjunct therapy for a range of neurological and psychiatric disorders. However, before we can fully utilise the potential of tDCS more needs to be understood about the neural mechanisms underpinning stimulation. In the past, the effects of tDCS have been studied primarily through experiments utilising transcranial magnetic stimulation (TMS), sometimes in combination with pharmacological agents [1] which have added greatly to our understanding of the local physiological effects of stimulation.

In recent years, however, there has been an increasing interest in using advanced neuroimaging techniques to study the effects of tDCS, both in healthy controls and clinical populations. Once the technical difficulties are overcome (see below), the combination of tDCS with magnetic resonance (MR) is a powerful tool that allows study not only of the brain regions directly stimulated by tDCS, but unlike most TMS approaches, we can also understand how tDCS modulates activity in the rest of the brain.

It is worth noting, particularly in a book highlighting the use of tDCS in psychiatric disorders, that the effects of tDCS are likely dependent on the site of stimulation; the duration of stimulation; and the electrode configuration used, to a greater or lesser extent. The vast majority of studies investigating the mechanistic underpinnings of tDCS have studied the "conventional" electrode placement as first described by Nitsche and Paulus [2] (Fig. 10.1a), with one electrode over the primary motor cortex (M1) and one over the contralateral supraorbital ridge. We therefore concentrate here on studies using this montage, though we have highlighted important studies using different electrode placements where we believe that these will be of importance in the context of the potential treatment of psychiatric disorders. However, it is important to note that while some of the findings from studies involving an M1 montage will be applicable to other sites, it cannot be assumed and further studies are warranted with any electrode montage of interest.

Combining tDCS and MRI

tDCS can be combined with MRI either in a sequential or concurrent approach. In sequential acquisition, the stimulation is delivered outside of the scanner with the participant placed in the scanner before and immediately following the stimulation period. Alternatively, stimulation can be delivered within the bore of the scanner (concurrent acquisition) either at the same time as collecting MR data or during rest (Fig. 10.1b).

Both approaches have been used successfully, with concurrent acquisition more favourable in most cases due to logistical and timing issues associated with removing and replacing the participant before subsequent MR data can be collected. Concurrent acquisition also has the advantage that pre- and post-stimulation data can be controlled for reproducibility (in terms of placement for spectroscopy voxels or high-resolution fMRI slices). While there are obvious advantages to concurrent stimulation, integration of tDCS to MRI requires multiple extra considerations including MR specific kit, additional setup criteria and potential adverse effects on MR acquisitions. The following should be seen only as a summary of the most significant risks of the approach, and given the inherent risks of the technique, tDCS should only be used in the scanner environment by trained individuals.

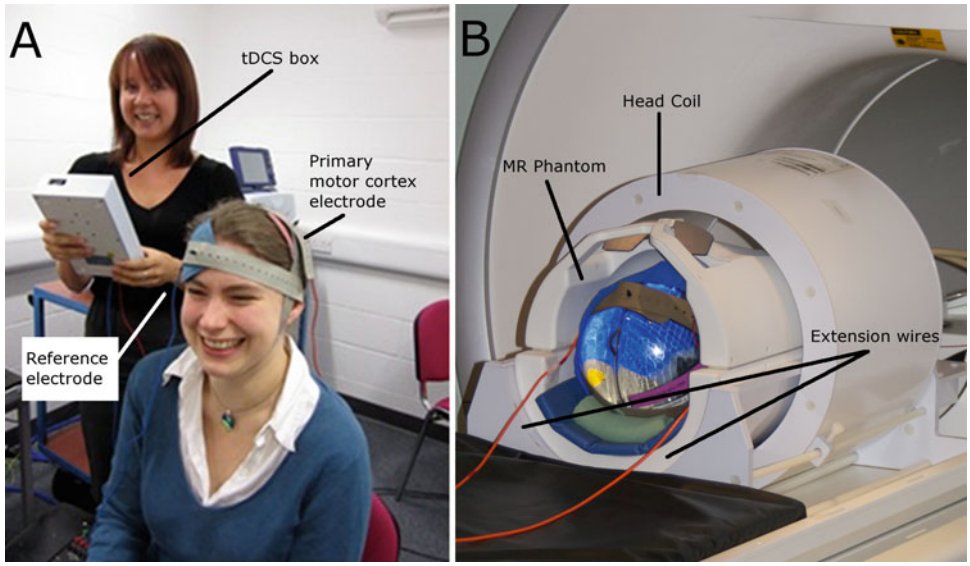

Fig. 10.1 (**a**) Overview of the "conventional" tDCS electrode configuration most studied in the literature—one electrode over the left primary motor cortex and one over the right supraorbital ridge. (**b**) Example set-up of tDCS in the MR environment, showing careful placement of extension leads and the stimulator kept out of the magnetic field

Concurrent tDCS/MRI requires a specialist kit that is MR compatible and rigorously tested. The electrodes used in this case should be fitted with high-ohmic resistors to prevent induction of eddy currents within the stimulating leads. Additional care should be taken to keep the leads away from the participant to prevent RF burns and run parallel to the bore without loops to prevent eddy currents. The tDCS stimulator must be kept in the control room and monitored closely by a researcher for the duration of the stimulation.

In addition, and in contrast to tDCS outside of the scanner, electrodes must be carefully prepared with high conductance electrical paste (such as that used for EEG) as saline-soaked sponges will dry out over time, making their use unsuitable for MRI scans that ordinarily last around 60–90 min. Dry sponges result in poor conductance of the electrical current, which can be uncomfortable or even painful for the participant and may result in skin burning in severe cases. For more details on the use of tDCS in the MR environment, see [3].

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a versatile and non-invasive tool that can be used to inform our understanding of how tDCS can modulate activity within the brain. The majority of the studies discussed here rely on the quantification of the blood oxygen level dependent (BOLD) contrast, the most widely used fMRI technique, although other fMRI techniques are available, of which arterial spin labelling (ASL) (see later) is perhaps the most relevant in the context of psychiatric disease.

BOLD Functional MRI

The BOLD signal relies on relative changes of deoxygenated haemoglobin (DeoxyHb) and oxygenated haemoglobin (OxyHb) caused by local changes in brain activity, and is therefore an indirect

measure of neuronal activity. The BOLD signal is reliant on the magnetic properties of these two compounds. DeoxyHb contains an iron molecule making it paramagnetic; meaning it has a significant interaction with the applied magnetic field during MRI. By contrast, OxyHb is diamagnetic, so has little effect on the magnetic field. Therefore, if the ratio of OxyHb:DeoxyHb changes within a localised region of tissue as a result of local neuronal activity, then this can be detected using BOLD fMRI. However, the precise relationship between changes in neuronal activity and a detectable change in the BOLD signal is complex and not yet fully understood [4].

Resting-State fMRI

Functional MRI acquired while the subject is lying in the scanner at rest, and commonly following the instruction "not to think of anything in particular" is an increasingly used method of studying the brain. Without a super-imposed task to perform, the ongoing physiological fluctuations in the BOLD signal associated with quiet wakefulness can be recorded. In any given brain region the BOLD signal will vary across time as a function of ongoing neural activity. By studying the relationship of the BOLD signal from one brain region to that of others, regions where the time course of fluctuations are highly correlated can be identified, and these regions are said to be "functionally connected". Studies of functional connectivity can be made using a wide array of statistical methods including those utilising graph theory and independent component analysis (ICA) approaches (for more detail see, for example [5]).

"Resting-state networks" (RSNs) are robust distributed networks that show coordinated and highly reproducible fluctuations in activity between spatially distinct but anatomically closely connected areas while subjects lie at rest [6–8]. RSNs are identified using an ICA approach and are being widely investigated due to observed differences during different cognitive and clinical states. RSNs are thought to reflect intrinsic functional architecture in the brain, and separable networks can be identified within resting fMRI data which closely reflect brain regions that are active during task performance (Fig. 10.2) [9, 10]. While the physiological underpinnings of changes in RSN connectivity are not understood and are still very much the focus of investigation and open to often complex interpretation [11], it is clear that RSNs are highly sensitive to changes in connectivity in a wide range of diseases [12–14], and that resting state fMRI is a potentially powerful approach for the study of a wide range of clinical conditions as it removes the confound of task performance [15].

tDCS Has Significant, but Somewhat Unclear, Effects on Resting Functional Connectivity

The absence of any confound of task performance, and the relative ease with which resting-state fMRI experiments can be performed has meant the publication of a relatively large number of studies utilising the combination of tDCS and rs-fMRI in recent years. tDCS has been demonstrated in a number of studies to modulate resting functional connectivity between a number of brain regions, although to date no clear consensus across the literature has emerged as to the specific pattern of stimulation-induced changes [16–22] (see Table 10.1 for full details). This lack of agreement between studies as to the effects of tDCS most likely reflects differences in MR acquisition and stimulation parameters, as well as the likely sensitivities of different analysis approaches, but makes interpretation of the literature as it stands somewhat problematic.

tDCS as a Potential Tool to Understand the Basis of Resting Functional Connectivity

Recently, attempts have been made to understand the basis of the RSNs using magnetic resonance spectroscopy (see later), which allows the quantification of specific neurochemicals, particularly glutamate and GABA, within a region of interest. Two studies have now demonstrated a relationship between GABA levels in M1 and the degree of functional connectivity within the motor RSN [22, 26], such that higher levels of inhibition are

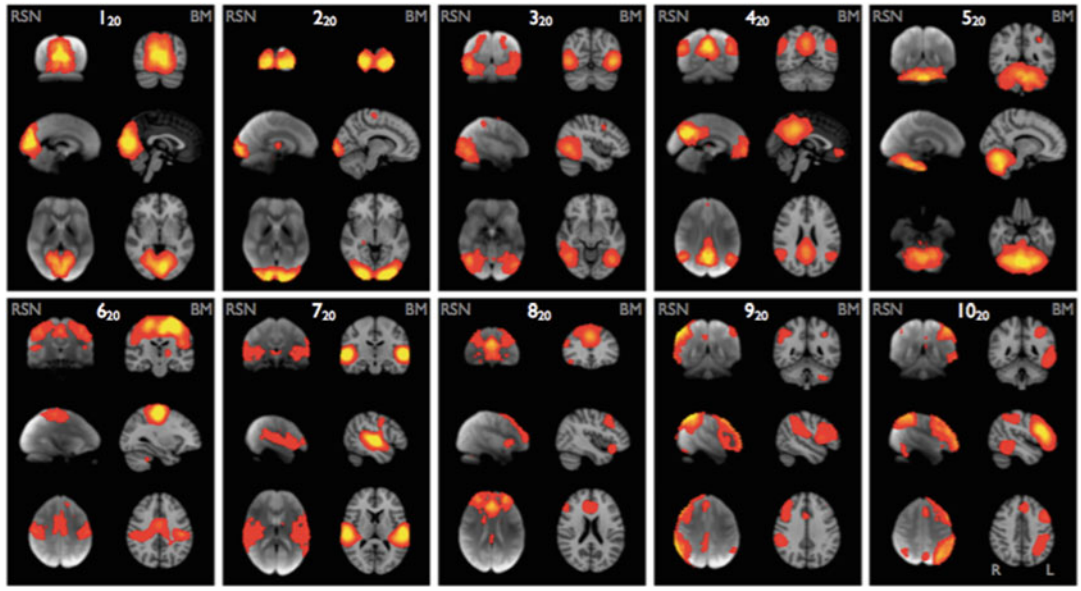

Fig. 10.2 Correspondence of resting-state networks and task activation networks. RSNs are shown on the *left* of each panel, on the *right* is the corresponding task activation network from the BrainMap Activation database. A close correspondence across all functional domains can be seen. From [10]

related to lower connectivity within the network (see Fig. 10.3). However, although anodal tDCS applied to M1 has been shown to modulate both GABA levels [22, 38, 39] and RSN strength [21, 22], the degree to which GABA and RSN strength are modulated by tDCS does not seem to be related in the same individual [22]. In addition, another group has demonstrated a similar relationship between GABA and RSN strength in the default mode network [40], and others have suggested relationships between local glutamatergic concentration and connectivity [40, 41]. These findings, if replicated, may begin to shed light on the physiological basis the RSNs, and the ability of tDCS to modulate both GABAergic and glutamatergic activity may play an important part in answering this potentially very important question. However, it is important to note that the finding that tDCS modulates resting connectivity has only been established to any great extent in healthy subjects, and how these findings may translate to clinical populations is not yet clear (Table 10.2).

Task-Based fMRI

Task-based fMRI is a versatile tool that can be used to inform our understanding of how tDCS can modulate activity within the brain while a task is being performed. Task-based fMRI is reliant on BOLD signal changes resulting from changing neural activity in task-based areas of the brain, and can result in whole-brain data with a high spatial and reasonably high temporal resolution. The ability to combine concurrent tDCS stimulation and fMRI imaging has allowed studies to characterise the effects of stimulation on various cortical regions; however the motor cortex is one of the most widely studied.

Studies in Healthy Controls

Behaviourally, anodal tDCS applied to M1 concurrently with a motor task has been shown to improve performance in a variety of domains, including motor speed and dexterity [55, 56], and motor learning and adaptation [55, 57, 58]. By contrast, cathodal tDCS has been shown to have little or no effect on learning [55, 58] or simple

Table 10.1 Summary of all studies combining tDCS and resting-state fMRI

Reference	Number of Subjects	fMRI Contrast	Healthy Subjects/Clinical Population	Electrode Montage	Electrode Size	Type of Stimulation	Length/ Intensity of Stimulation	Analysis Method	Summary of Main Findings
Polanía et al.[16, 18])	13	BOLD	Healthy	Left M1/Right FPC	35cm2 for both electrodes	Bipolar (real/ sham, within subject)	10mins, 1mA	Graph Theory	· tDCS induced neuroplastic alterations correlate with changes in functional connectivity. · Voxel-based graph theoretical analysis is a powerful approach to track for functional alterations.
Polanía et al.[17, 23]))	14	BOLD	Healthy	Left M1/Right SOR	35cm2 for both electrodes	Anodal/ Cathodal/ Sham	10mins, 1mA	Graph Theory	In dorsolateral BA4 region, cathodal tDCS boosted local connections, while anodal tDCS enhanced long distance functional communication within M1. The more efficient the functional architecture of M1 was at baseline, the more efficient the tDCS-induced functional modulations were.
Sehm et al.[20, 24]))	12	BOLD	Healthy	Unilateral: Right M1/Left SOR Bilateral: anode over right M1, cathode over left M1	35cm2 for both electrodes	Unilateral/ Bilateral/ Sham	20mins, 1mA	ECM – graph-based method	· Bilateral tDCS modulated changes in primary and secondary motor and prefrontal regions · Unilateral tDCS affected prefrontal, parietal and cerebellar areas (no direct effect under stimulating electrode)

Sehm et al.[19]))	12	BOLD	Healthy	Unilateral: Anode over left M1, cathode over right SOR	35cm2 for both electrodes	Unilateral (anodal)/ Bilateral/ Sham	20mins, 1mA	Seed-based functional connectivity analysis	· Bilateral tDCS results in decreased interhemispheric functional connectivity during stimulation and an increase in intracortical functional connectivity within left M1 after termination of stimulation.
				Bilateral: Anode over left M1, cathode over right SOR					· Unilateral stimulation resulted in similar effects during stimulation but no changes were observed after termination of tDCS.
									· Conclusion that different tDCS montages affect the modulation of inter- and interhemispheric connectivity
Amadi et al. [25]	11	BOLD	Healthy	Left M1/Right SOR	35cm2 for both electrodes	Anodal/ Cathodal/ Sham	10mins, 1mA	Seed-based and ICA	· Cathodal tDCS increased in inter-hemispheric coherence of resting fMRI signal between the left and right SMA, and between the left and right hand areas of M1. A similar trend was documented for the premotor cortex.
									· Increased functional connectivity following cathodal stimulation was apparent within ICA-generated motor and default mode networks
Stagg et al.[26, 27]))	10	BOLD	Healthy	Left M1/Right SOR	35cm2 for both electrodes	Anodal	10mins, 1mA	ICA	Anodal tDCS increases resting motor network connectivity.
Bachtiar et al.[22, 28]))	12	BOLD	Healthy	Left M1/Right SOR	35cm2 for both electrodes	Anodal/Sham	20mins, 1mA	ICA	Anodal tDCS reduced GABA concentration and increased functional connectivity in the stimulated cortex, however these changes are not correlated.

(continued)

Table 10.1 (continued)

Reference	Number of Subjects	fMRI Contrast	Healthy Subjects/Clinical Population	Electrode Montage	Electrode Size	Type of Stimulation	Length/ Intensity of Stimulation	Analysis Method	Summary of Main Findings
Pereira et al.[29])	16	Not specified	Parkinson's Disease Patients	Configuration 1: anode: left DLPFC, cathode: right SOR	35cm2 for both electrodes	Anodal	20mins, 2mA	ICA	Functional connectivity was significantly more enhanced by tDCS to DLPFC than TPC.
				Configuration 2: anode: left TPC, cathode: right SOR					
Minami et al. [30]	9 patients, 10 controls	BOLD	9 subjects with tinnitus, 10 healthy controls	Anode: Right primary auditory cortex (pSTG)	Not specified	Not specified	10mins, 1mA	Seed-based analysis	Functional connectivity between left and right auditory cortex is significantly weaker in tinnitus patients than controls. tDCS over auditory cortex modulated auditory-based functional connectivity differently in control and tinnitus patients. More research required into how auditory functional connectivity is modulated in patients with tinnitus
				Cathode: left primary auditory cortex (pSTG)					
Meinzer et al.[31])	36 (18 MCI patients, 18 matched controls)	BOLD	Patients: MCI due to Alzheimer's Disease	Anode: left ventral IFG, Cathode: right SOR	Not specified	Anodal/Sham	20mins, 1mA	ECM	Anodal stimulation led to widespread connectivity changes in patients compared to controls, including a reversal of an abnormal pattern in several regions including medial frontal and lateral fronto-temporal cortices, bilateral sensorimotor regions and right cerebellum.
			Controls: Healthy age matched, no MCI						No major group differences or stimulation-induced differences to the default mode network, in which disruptions have previously been reported in MCI.

Meinzer et al.[32])	40 (20 elderly and 20 young)	BOLD	Healthy: elderly and young	Stimulating electrode: left ventral IFG	Stimulating: 35cm2	Anodal/Sham	20mins, 1mA	ECM	Anodal tDCS induced a more "youth-like" connectivity pattern in older adults suggesting that a single session of anodal tDCS can temporarily reverse non-beneficial effects of ageing on cognition and connectivity.
				Reference electrode: right SOR	Reference: 100cm2				
Park et al. [33]	39	BOLD	Healthy	Anode: left DLPFC, Cathode: right SOR	25cm2 for both electrodes	Anodal/Sham	20mins, 1mA	Parametric random-effects analysis	Anodal tDCS of the left DLPFC increased interhemispheric connectivity at rest, which is hypothesized to be associated with tDCS effects on cognitive functions
Clemens et al. [34]	11	BOLD	Healthy	Anode: right angular gyrus, Cathode: left SOR	35cm2 for both electrodes	Bipolar	20mins, 2mA	Probabilistic ICA	Bipolar tDCS results in large-scale changes of activity within several RSNs, as well as local changes under the stimulating electrode.
									Increased ICA-generated functional connectivity in cerebellum, medial occipital, sensorimotor, right fronto-parietal and superior frontal gyrus.
									Decreased functional connectivity in right putamen and lateral occipital areas
Peña-Gómez et al. [35]	10	BOLD	Healthy	Experiment 1: anode: left DLPFC, cathode: right SOR	35cm2 for both electrodes	Anodal/Sham for both configurations	20mins, 2mA	ICA	After active stimulation, functional network connectivity revealed increased synchrony with the anti-correlated (AN) network components and reduced synchrony with DMN components.
				Experiment 2: anode: right DLPFC, cathode: left SOR					

(continued)

Table 10.1 (continued)

Reference	Number of Subjects	fMRI Contrast	Healthy Subjects/Clinical Population	Electrode Montage	Electrode Size	Type of Stimulation	Length/ Intensity of Stimulation	Analysis Method	Summary of Main Findings
Keeser et al. [36]	13	BOLD	Healthy	Anode: left DLPFC, Cathode: right SOR	35cm2 for both electrodes	Anodal/Sham	20mins, 2mA	ICA	After real tDCS compared to sham tDCS, significant changes of regional brain connectivity were found for the DMN and fronto-parietal networks close to the stimulation site and in connected brain regions.
									Prefrontal tDCS modulated resting state functional connectivity in distinct functional networks of the human brain
Meinzer et al.[37])	20	BOLD	Healthy	Stimulating electrode over BA44/45 (Broca's Area)	Stimulating: 35cm2	Anodal/Sham	Approx. 17 minutes, 1mA	ECM	Under anodal tDCS, resting state fMRI revealed increased connectivity of the left IFG and additional major hubs overlapping with the language network.
				Reference electrode: right SOR	Reference: 100cm2				
Alon et al. (2011)	4	BOLD	Healthy	Anode: right M1, Cathode: left SOR	31.5cm2 for both electrodes	Anodal/Sham	12 min 48 s (split into two blocks), 2mA	Seed-based analysis	Anodal tDCS reduced connectivity measures in the right and left regions of interest. Suggestion that non-invasive brain stimulation during fMRI may down regulate the motor cortex's resting-state network connectivity.

BA Broadman's area, *DLPFC* dorsolateral prefrontal cortex, *ECM* eigenvector centrality mapping, *FPC* fronto parietal cortex, *ICA* independent component analysis, *IFG* inferior frontal gyrus, *MCI* mild cognitive impairment, *pSTG* posterior superior temporal gyrus, *RSN* resting state network, *SOR* supraorbital ridge, *SMA* supplementary motor area, *TPC* tempo-parietal cortex

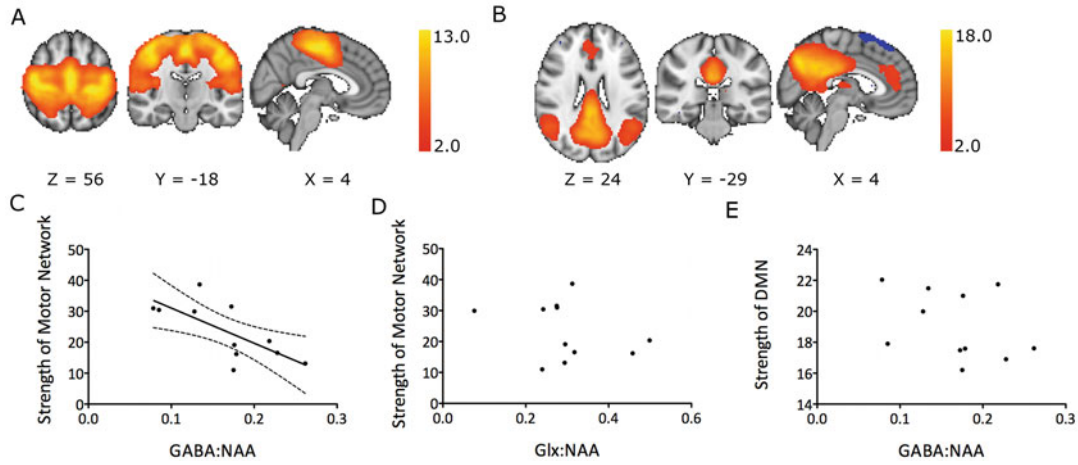

Fig. 10.3 The neurochemical basis of RSN strength. (**a**) Group mean motor RSN. (**b**) Group mean default mode RSN, which served here as a control network to assess the specificity of any relationships seen. (**c**–**e**) A significant relationship was demonstrated between M1-GABA and functional connectivity within the motor RSN ($r = -0.71$, $p = 0.01$; **c**) but not between M1-Glx and motor network functional connectivity (**d**) nor between M1-GABA and functional connectivity within the DMN (**e**). Figure reproduced with permission from [23]

reaction time [55]. Task-based fMRI has been utilised in a number of studies to understand not only the activity changes underlying these behavioural effects within the stimulated cortex, but also more anatomically distant neural changes.

Baudewig and colleagues initially confirmed the feasibility of combining functional MRI and tDCS [59]. In this study, the BOLD signal was recorded in a group of six subjects before and after 5 min of tDCS. The authors reported small stimulation-induced changes in activation in the supplementary motor area (SMA), an effect still noticeable 15 min after the end of stimulation.

Since this work, a number of imaging studies in healthy controls have investigated the effects of tDCS on motor-related activity [42, 45, 46, 52, 53]. Of these, one investigated the effects of a conventional electrode montage (left M1 and the right supraorbital ridge) and a stimulation period of 10 min, on the performance of a simple motor task [42]. Participants completed a simple visually cued serial reaction time task for 15 min before and immediately after tDCS (anodal, cathodal or sham). The results indicated an expected increase in activation after anodal stimulation compared to sham in the stimulated M1, ipsilateral dorsal premotor cortex (dPMC) and SMA. After cathodal stimulation, an increase in BOLD signal was observed under the stimulating electrode (left M1). Additionally, an increase in task-related activation was observed in the contralateral (right) M1, dPMC and SMA (Fig. 10.4).

Arterial Spin Labelling

As discussed in some detail above, BOLD fMRI is the most common method of assessing neural activity changes during or following tDCS. However, while BOLD has a relatively high signal-to-noise, meaning that data can be acquired over relatively short timescales, making it highly suitable for clinical use, the physiological underpinnings of the BOLD effect are complex and currently relatively poorly understood. This may be of particular importance in clinical populations, where changes in blood supply or neurovascular coupling may be expected.

An alternative approach is that of ASL. ASL is a relatively novel fMRI technique that is able to quantify changes in tissue perfusion directly in the brain. It has a much lower signal to noise ratio than BOLD fMRI, which initially limited its use in clinical populations, but with the advent of

Table 10.2 Summary table of all tDCS studies combining tDCS with task fMRI

Reference	Number of Subjects	fMRI Contrast	Healthy Subjects/Clinical Population	Electrode Montage	Electrode Size	Type of Stimulation	Length/Intensity of Stimulation	Task	Summary of Main Findings
Stagg et al.[38, 42])	15	BOLD	Healthy	Left M1/Right SOR	35cm2 for both electrodes	Anodal/ Cathodal/ Sham	10 minutes, 1mA	Visually cued serial reaction time task before and after tDCS	· Anodal tDCS led to short-lived activation increases in M1 and SMA within stimulated hemisphere.
									· Cathodal tDCS led to increase in activation in contralateral M1 and dorsal PMd, as well and increased functional connectivity between these areas and the stimulated left M1.
Stagg et al. [43]	11	BOLD	Stroke Patients (at least 6 months post stroke)	Anodal: anode on ipsilesional M1, cathode on contralesional SOR.	35cm2 for both electrodes	Anodal/ Cathodal/ Sham	10 minutes, 1mA	Visually cued motor task with simple response time and choice response time conditions	· Significant behavioural improvements produced by anodal stimulation to ipsilesional hemisphere are associated with a functionally relevant increase in activity within ipsilesional M1 in patients following stroke.
				Cathodal: anode on contralesional M1, anode on ipsilesional SOR.					· Anodal stimulation to ipsilesional hemisphere led to 5-10% improvement in reaction time, with an associated increase in movement-related cortical activity in stimulated M1 and functionally interconnected areas.
									· Cathodal stimulation to contralesional hemisphere let to functional improvement when compared to sham stimulation.
Lindenberg et al. [44]	20	BOLD	Chronic Stroke	Anode: ipsilesional M1	16.3cm2 for both electrodes	Bilateral	5 sessions of bi-hemispheric stimulation (30mins, 1.5mA) or sham stimulation with simultaneous physical/ occupational therapy	Alternating flexion and extension of elbow/wrist	· Stronger activation of intact ipsilesional motor regions found post-intervention in real stimulation group, not change in the control group.
				Cathode: contralesional M1					

Lindenberg et al.[45])	17	BOLD	Healthy, older participants	Unilateral anode: left M1, cathode: right SOR	Unilateral: Anode: 35cm2, Cathode: 100cm2	Unilateral/ Bilateral/ Sham	30mins, 1mA	Motor choice reaction task (and overt semantic word retrieval task - reported in [46, 47])	Both anodal and dual tDCS can potentially be used to counteract age-related impairment of interhemispheric interactions.
				Bilateral: anode: left M1, cathode, right M0	Bilateral: 35cm2 for both electrodes				Differential effects of bihemispheric compared to uni-hemispheric stimulation may not merely be mediated by an "add on" effect of anodal and cathodal stimulation, but rather due to complex bihemispheric network modulations.
Meinzer et al.[46, 47])	18	BOLD	Healthy, older participants	Unilateral anode: left M1, cathode: right SOR	Unilateral: Anode: 35cm2, Cathode: 100cm2	Unilateral/ Bilateral/ Sham	20mins, 1mA	Overt semantic word retrieval task (and motor choice reaction task - reported in [45]	M1 stimulation can improve word-retrieval in healthy older individuals, confirming language-motor interaction extend beyond action-specific material as previously shown.
				Bilateral: anode: left M1, cathode, right M1	Bilateral: 35cm2 for both electrodes				Provide a rationale to explore the effectiveness of M1 stimulation as an alternative and clinically feasible adjunct therapy approach in post-stroke aphasia.

(continued)

Table 10.2 (continued)

Reference	Number of Subjects	fMRI Contrast	Healthy Subjects/Clinical Population	Electrode Montage	Electrode Size	Type of Stimulation	Length/Intensity of Stimulation	Task	Summary of Main Findings
Meinzer et al.[32])	40 (20 elderly and 20 young)	BOLD	Healthy: elderly and young	Stimulating electrode: left ventral IFG	Stimulating: 35cm2	Anodal/ Sham	20mins, 1mA	Overt semantic word retrieval task	During sham stimulation, task-related fMRI demonstrated enhanced bilateral prefrontal ability in older adults was associated with reduced performance.
				Reference electrode: right SOR	Reference: 100cm2				Anodal tDCS significantly improved performance of older adults up to the level of younger controls and significantly reduced task-related hyperactivity in prefrontal cortices, anterior cingulate gyrus and precuneus.
									Suggestion that a single session of anodal tDCS can temporarily reverse non-beneficial effects of ageing on cognition and brain activity. These findings may translate to novel treatments to ameliorate cognitive decline in normal ageing.
Ulm et al. [48]	1	BOLD	Chronic aphasia (4.7 years post stroke)	Anode: based on location of peak activity in baseline scan - ~75% upwards from F7 to F3 (target: left inferior frontal gyrus)	Anode: 35cm2	Anodal/ Sham	20mins, 1mA	Picture naming task	Feasible to target an individualised stimulation site in post stroke aphasia during simultaneous fMRI to assess the underlying neural signatures of tDCS-action in post stroke aphasia.

Holland et al. [49]	10	BOLD	Aphasic stroke patients	Anode: left IFC, Cathode: right frontopolar cortex	35cm2 for both electrodes	Anodal/ Sham	20mins, 2mA	Overt picture naming task	Anodal tDCS had significant behavioural and regionally specific neural facilitation effects. Faster naming responses correlated with decreased BOLD signal in Broca's area. Could indicate that Broca's area could be a suitable candidate target site for tDCS in neurorehabilitation of anomic patients, whose brain damage spares this region.
Meinzer et al.[31])	36 (18 MCI patients, 18 matched controls)	BOLD	Patients: MCI due to Alzheimer's Disease Controls: Healthy age matched, no MCI	Anode: left ventral IFG, Cathode: right SOR	Not specified	Anodal/ Sham	20mins, 1mA	Overt semantic word-retrieval task	Anodal stimulation led to improved performance on the overt word retrieval task was accompanied by reduced hyperactivity in bilateral prefrontal cortex.
Alekseichuk et al. [50]	17	BOLD	Healthy	Anode over Oz and Cathode over Cz according to EEG system	25cm2 for both electrodes	Anodal/ Sham	10mins, 1mA	Visual stimuli: "wedges" and "rings" shown directly before and after stimulation	Anodal tDCS induced a small but significant increase in BOLD response evoked by a visual stimulus, with no after effects. This study also used tACS (10Hz) which resulted in no online, but a widespread offline effect of BOLD activity.

(continued)

Table 10.2 (continued)

Reference	Number of Subjects	fMRI Contrast	Healthy Subjects/Clinical Population	Electrode Montage	Electrode Size	Type of Stimulation	Length/Intensity of Stimulation	Task	Summary of Main Findings
Spiegel et al. [51]	5	BOLD	Amblyopic patients	Stimulating electrode over Oz and reference electrode over Cz according to EEG system	Stimulating electrode: 43.2cm2, Reference electrode: 109.25cm2	Anodal/ Sham	15mins, 2mA	2-alternative force choice design (orientation discrimination: horizontal/ vertical)	Anodal tDCS transiently improved contrast sensitivity in a subset of adults with amblyopia and equated the cortical response to inputs from the amblyopic and fellow eyes.
									Suggest that anodal tDCS may be of use in the treatment of amblyopia alone or in combination with other interventions.
Pereira et al.[29])	16	BOLD	Parkinson's Disease Patients	Configuration 1: anode: left DLPFC, cathode: right SOR	35cm2 for both electrodes	Anodal	20mins, 2mA	Verbal fluency paradigm	tDCS to DLPFC increased performance on the phonemic fluency task, after adjusting for baseline phonemic performance
				Configuration 2: anode: left TPC, cathode: right SOR					tDCS to specific brain regions may be able to enhance phonemic fluency in PD.
Meinzer et al.[37])	20	BOLD	Healthy	Stimulating electrode over BA44/45 (Broca's Area)	Stimulating: 35cm2	Anodal/ Sham	Approx. 17 minutes, 1mA	Semantic word generation task	Anodal tDCS improved word retrieval and was paralleled by selectively reduced task-related activation in the left ventral IFG, an area specifically implicated in semantic retrieval processes.
				Reference electrode: right SOR	Reference: 100cm2				
Alon et al. (2011)	4	BOLD	Healthy	Anode: right M1, Cathode: left SOR	31.5cm2 for both electrodes	Anodal/ Sham	12 min 48 s (split into two blocks), 2mA	Self-paced bilateral finger-thumb opposition task	Anodal tDCS reduced connectivity measures in the right and left regions of interest. Suggestion that non-invasive brain stimulation during fMRI may down regulate the motor cortex's resting-state network connectivity.

Kwon et al.[52])	12	BOLD	Healthy	Anode: left M1, Cathode: right SOR	35cm2 for both electrodes	Anodal/ Sham	2mins, 1mA	Grasp-release hand movements at metronome-guided frequency of 1Hz	Significant differences in voxel count and peak intensity were observed between real tDCS and sham tDCS.
									Anodal tDCS application during the motor task enhanced cortical activation on the underlying targeted motor cortex, seeming that tDCS induced more cortical activity and modulated brain function when concurrently applied with a motor task.
Antal et al.[53])	20	BOLD	Healthy	Anode: left M1, Cathode: right SOR	35cm2 for both electrodes	Anodal/ Cathodal	Alternate blocks of 20s, 1mA and no stimulation	Finger tapping	Neither anodal nor cathodal tDCS induced a detectable BOLD change. However in comparison to a voluntary finger tapping task without stimulation, anodal tDCS during finger tapping resulted in a decrease in the BOLD response in the SMA.
									Cathodal stimulation did not result in a significant change in the BOLD response in the SMA, but a trend could be seen.
Jang et al. [54]	14	BOLD	Healthy	Anode: left M1, Cathode: right SOR	35cm2 for both electrodes	Anodal/ Sham	20mins, 1mA	Grasp-release hand movements at metronome-guided frequency of 1Hz	Anodal tDCS increased cortical excitability of underlying motor cortex in the human brain.

BA Broadman's area, *DLPFC* dorsolateral prefrontal cortex, *FPC* fronto parietal cortex, *ICA* independent component analysis, *IFG* inferior frontal gyrus, *M1* primary motor cortex, *MCI* mild cognitive impairment, *pSTG* posterior superior temporal gyrus, *SOR* supraorbital ridge, *SMA* supplementary motor area, *tACS* transcranial alternating current stimulation, *TPC* tempo-parietal cortex

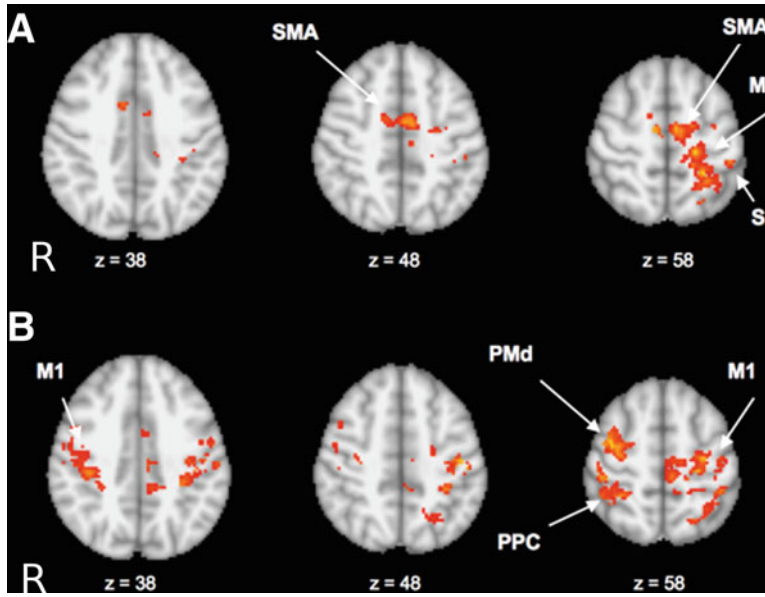

Fig. 10.4 (**a**) An increase in task-related BOLD signal was observed after anodal stimulation to the left M1 compared with sham stimulation in the left M1, left primary somatosensory cortex (S1), left posterior parietal cortex (PPC) and supplementary motor area (SMA). (**b**) An increase in BOLD signal was observed after cathodal stimulation to the left M1 compared with sham in the left M1, right M1, right PPC and right dorsal premotor cortex (PMd). Figure adapted with permission from [35]

ultra-high field imaging it has become more widely used. ASL has two significant advantages over the BOLD signal: (1) It is primarily sensitive to low-frequency signals and is therefore the ideal modality to detect blood flow changes induced by the minutes-long tDCS protocols commonly used and (2) the physiological basis of the contrast is inherently simpler to understand than BOLD, a factor particularly important in clinical populations where many factors may change.

Zheng and colleagues performed the first tDCS/ASL study, and showed non-polarity-specific effects, with an increase in perfusion in the stimulated M1 after short periods of both anodal and cathodal tDCS [60]. A subsequent ASL study during concurrent tDCS to the left dorsolateral prefrontal cortex (DLPFC) found a polarity-specific effect of tDCS, with an increase in perfusion during and after anodal tDCS and a decrease in perfusion during and after cathodal tDCS [61], a finding in line with animal models [62]. This study also went on to analyse the tDCS-induced changes in perfusion across the whole brain and demonstrated significantly increased perfusion during anodal tDCS in those areas anatomically connected to the DLPFC [61]. Interestingly, the same increased perfusion effects were not seen in the period immediately following stimulation, despite increased cortical excitability continuing post-stimulation in similar studies over the motor cortex. It is not clear why this should be case, but as discussed above, the effects of tDCS are likely highly dependent on the site of stimulation and electrode placement, and it is also possible that further excitability changes post-stimulation are maintained by factors that do not in themselves induce an increase in cortical perfusion in the resting brain.

Magnetic Resonance Spectroscopy

Understanding how transcranial direct current stimulation (tDCS) affects neuronal activity is of vital importance to discovering the mechanisms by which tDCS alters behaviour. As well as studying BOLD and ASL signals, we can also use

magnetic resonance (MR) techniques to investigate the effects of tDCS at a deeper level; by examining how tDCS affects the neurochemicals which go on to cause these activity changes. We can achieve this by using magnetic resonance spectroscopy (MRS), a technique that enables us to detect and quantify concentrations of different metabolites within a volume of tissue.

MRS was first performed in the human brain in 1985 [63], and since then has been primarily used to investigate metabolic changes in pathological states. MRS relies on many of the same principles as magnetic resonance imaging (MRI); it measures signals produced by the behaviour of certain diamagnetic molecules within a magnetic field. While MRI focuses on the variations in signal across space, MRS examines signals produced from only one volume of tissue. A number of atomic nuclei have diamagnetic properties, including ^{1}H, ^{31}P and ^{13}C MRS, of which ^{1}H MRS is used most widely. The ability of MRS to discriminate between different molecules relies on the fact that the structure of the molecules within which these atoms are bound, and the environment surrounding these molecules, influence the behaviour of the atoms within the magnetic field. MRS focuses on very small differences in the signals produced by the atoms contained within different metabolites in a volume of interest (VOI).

The spectra produced by specific metabolites can be determined by performing spectroscopy on a specifically designed object or "phantom" that contains that metabolite alone. The characteristic peaks and frequencies of many neurochemicals are therefore known, meaning that these metabolites can be identified from sample spectra. The signal amplitudes of the peaks in a spectrum are directly proportional to the corresponding compound's concentration within the target volume of tissue (see Fig. 10.5 for an example spectrum).

Signals in MRS are typically summed across a large volume in comparison with other forms of MR imaging (e.g. around 3 cm × 3 cm × 3 cm in ^{1}H MRS compared with 3 mm × 3 mm × 3 mm in MRI); this creates an increase in the signal produced by given metabolites relative to the background noise. However even summing across a large area, only metabolites present in millimolar concentrations are detectable. Fortunately, many neurochemicals involved in neurotransmission and metabolism are present in concentrations above this threshold, but others (for example dopamine) are not, making their detection and quantification impossible with current MRS methods.

^{1}H-MRS

Hydrogen atoms form a part of many of the molecules within the brain and body. The molecule with by far the highest concentration is water, but many of the brain's endogenous neurochemicals, controlling metabolism and neural firing, also contain hydrogen at concentrations high enough to allow detection by ^{1}H MRS. The neurotransmitters glutamate and GABA (gamma-aminobutyric acid) are of most relevance and interest to research investigating the neurochemical effects of tDCS. Both of these neurotransmitters are involved in mechanisms that selectively alter synaptic strength, for example long-term potentiation-like (LTP-like) processes within the neocortex [66–70]. These LTP-like process are thought to be the main mechanism controlling learning in the brain, and improvements in learning across many tasks, particularly in the motor domain, have been demonstrated with anodal tDCS (see [1] for a review). It has therefore been proposed that modulation of GABA and glutamate levels may be at least in part the mechanism by which anodal tDCS improves learning of a task performed concurrently; an argument strengthened by studies showing that drugs acting on glutamatergic and GABAergic receptors can alter these behavioural aftereffects [71, 72].

MRS is a technique which requires a large number of options to be pre-specified: volumes of interest must be decided in advance, as must scanner sequences, that determine which molecule signals can be resolved. Traditionally MRS only allowed spectra to be obtained of one volume of interest at a time, but recent software developments for ultra-high-field 7 T MR scanners have demonstrated robust spectra from two or more

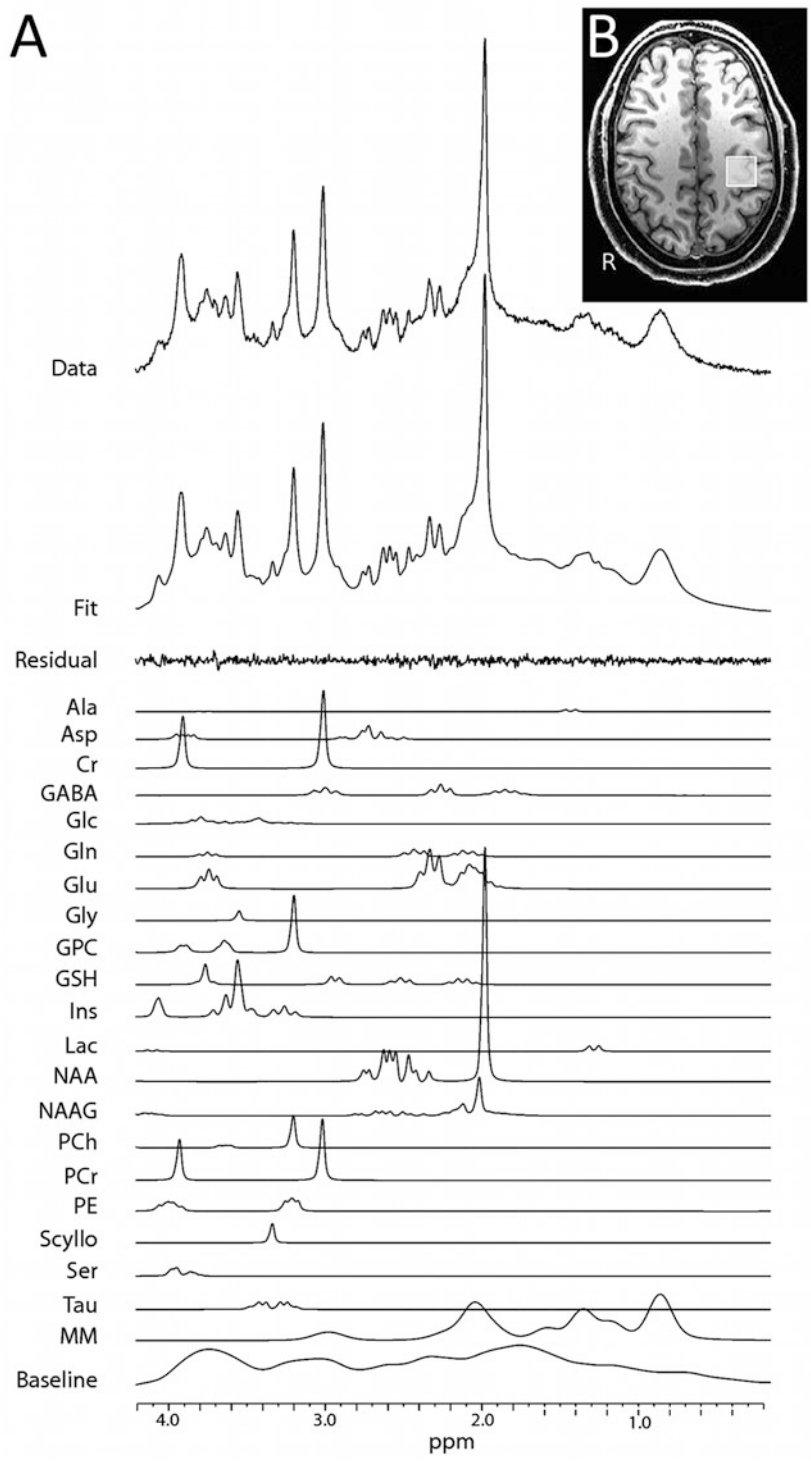

Fig. 10.5 (**a**) An example of a spectrum produced by ^{1}H MRS at 3 T using the SPECIAL sequence from a 2×2×2 cm M1 voxel. The original MRS data is shown in the *top row*. The *next row* is the full model fit produced from LCModel [68]. The high quality of the fit is demonstrated by the small residual signal remaining after fitting; shown by the row labeled "residual". Individual fits for all neurochemicals are also demonstrated—each neurochemical has multiple fitted peaks that reflect the individual protons within the molecule. Quantification of metabolites within a sample can be achieved by linear combination of these individual metabolite spectra. (**b**) Location of the left primary motor cortex (M1) voxel. Figure reproduced with permission from [52]

voxels simultaneously (e.g. [73]). This technique has been used to record from both stimulated M1, and the contralateral M1 concurrently, increasing the amount of information which can be gained about the effects of tDCS outside of the target cortex. However tDCS has been shown to induce an electric field which is dispersed across a large area [50], some of which may lie outside the examined volume. Often a control region is tested to ensure that changes observed in one volume are not in fact global changes. However, MRS still cannot tell us the whole story about the brain changes occurring in areas beyond the VOI.

So far, MRS research on tDCS has taught us about isolated effects of certain stimulation types on certain neurochemicals within small volumes of cortex. To be able to draw global conclusions on the effect of tDCS on neurochemistry across the whole brain, or to be able to judge whether the effects of tDCS vary depending on stimulation area, many more studies are needed. MRS only provides information on volumes and metabolites which we have specified a priori, and so we must be careful to guide our choices based on the knowledge we already have.

Neurochemicals of Interest

A number of neurochemicals can be measured using ^{1}H-MRS, of which the following are of most interest for tDCS-MRS studies.

Glutamate

Glutamate is the main excitatory neurotransmitter in the brain, and is essential for the development of normal synaptic connections and learning. Glutamate is stored in synaptic vesicles before being released into the synaptic cleft. Once released at the synapse, glutamate can contact either post-synaptic ionotropic receptors (NMDA, AMPA or kainate), or metabotropic receptors linked to G-proteins. A critical mechanism of LTP is to increase the number of these post-synaptic receptors. This form of neuroplastic change is invisible to MRS; however the process is dependent on glutamate release. This glutamate release may result in an overall increase in glutamate concentration within the volume, a change which may be detected by MRS, though the relationship between receptor density changes and the MRS glutamate signal is not yet clear.

After binding and unbinding with post-synaptic receptors, most glutamate is taken up by neighbouring astrocytes and metabolised into glutamine. The resonances produced by glutamate and glutamine are difficult to separate, except at very high field strengths, due to the similarities in their molecular structures. Due to this, a composite Glx signal, made up of contributions from both glutamate and glutamine, is often reported. An additional challenge to the interpretation of these MRS signals is their summation across a large volume of tissue. It is therefore not possible to discriminate between levels of neurotransmitter within different pools, or to gain information about where in the cell molecules are located. Furthermore, while glutamate has a highly important role in neurotransmission, the significant majority of glutamate in the brain is involved in metabolism and not neurotransmission, making changes in this resonance somewhat difficult to link with changes in behaviour. For more details see [75].

GABA

GABA is the main inhibitory neurotransmitter within the brain, but it also has a role as a metabolite. It is metabolised from glutamate by the enzyme glutamic acid decarboxylase (GAD). ^{1}H MRS has demonstrated a correlation between measures of GABA and glutamate [65], which is expected given their close relationship. GABA is found in three distinct pools within the brain: as a metabolite within the cytoplasm of GABAergic interneurons; within synaptic vesicles; and extracellularly both in the synaptic cleft and in the surrounding intercellular fluid. Attempts have been made to correlate MRS measures of GABA with paired-pulse transcranial magnetic stimulation (ppTMS) measurements of GABA receptor activity. Neither GABAA nor GABAB receptor activity, or a combination of the two was able to describe the MRS GABA signal. One ppTMS measure, 1 ms SICI, which has been proposed to

reflect the activity at extra-synaptic GABAA receptors [65], has however been shown to correlate with MRS GABA levels. Additionally, MRS measured GABA levels have been shown to be closely related to CSF-GABA level [76], suggesting that in the resting state MRS-assessed GABA probably most closely reflects extra-synaptic GABA tone. However, as extracellular GABA is derived from intracellular pools, it is still not clear what aspects of GABAergic processing a change in the GABA signal, as a result of neuromodulation, may represent. For more details see [77].

N-Acetylaspartate Acid and Creatine

Other molecules which commonly produce peaks in ^{1}H MRS spectra are *N*-Acetylaspartic acid (NAA) and creatine. NAA is one of the most concentrated molecules in the brain and is thought of as a marker for neuronal health, with reduced levels being indicative of disease [78, 79], brain injury [80–82] or psychiatric disorders [83]. Within healthy brains however, it is thought of as being present at a stable concentration, and so is often used as a reference chemical within MRS, where concentration of other molecules in the tissue volume are given as a ratio of NAA [84]. Total creatine, a measure made up of signal contributions from both creatine and phosphocreatine (Cr + PCr), can also be used for this purpose. Creatine and phosphocreatine are vitally important molecules for energy storage and transmission within cells.

^{31}P-MRS

Phosphorus MR spectroscopy (^{31}P MRS) can be performed in much the same way as ^{1}H MRS, but is tuned to the range of resonant frequencies of phosphorus atoms. Many molecules, which the body and brain depend on for energy transport and release, contain phosphorus. High-energy phosphates within the energy transportation molecules ATP and phosphocreatine create large peaks; and lower amplitude peaks are created by sugars, lipids and inorganic phosphates, which are all present at lower concentrations within the brain. By measuring the concentrations of ATP, inorganic phosphate and phosphocreatine simultaneously, the energy metabolism of the volume can be estimated. However, despite this potential utility, ^{31}P MRS is less widely used than ^{1}H MRS as it requires specialised hardware to record the resonance frequencies. Additionally ^{31}P MRS only has approximately 7 % of the sensitivity of proton MRS, meaning it requires long acquisition times and has only a low spatial resolution.

Combining tDCS with MRS

The majority of studies investigating the effects of tDCS on ^{1}H MRS-measured neurochemistry have focused on anodal and cathodal tDCS applied to M1. Work by our group and others [22, 38, 39, 85] has demonstrated that anodal tDCS over M1 caused a decrease in MRS measured GABA levels in the stimulated area of cortex (Fig. 10.6a).

The above studies indicate that a decrease in MRS measured GABA may be a reliable effect of anodal M1 tDCS. It has been proposed that this GABA decrease may be responsible for the accelerated learning effects seen when tDCS is performed in conjunction with motor training (see above), an idea which is supported by multiple lines of evidence. Normal motor training, without stimulation, causes a decrease in GABA: MRS-measured GABA has been demonstrated to decrease in the primary sensorimotor cortex after training the contralateral hand on an isometric motor sequence learning task [86]. The decrease in GABA seen with tDCS correlates with the degree of motor learning: inter-individual responsiveness in MRS measured M1 GABA levels to ipsilateral, anodal tDCS correlated with individual's degree of motor learning on a serial reaction time task (performed without stimulation), and the amount of fMRI signal change [39] (Fig. 10.6b). Baseline levels of GABA in patients are correlated with the behavioural gains induced by stimulation: higher initial GABA levels within the ipsilesional M1 of stroke patients predicted greater percentage improvement on a reaction time task [87]. Finally, GABA decrease after

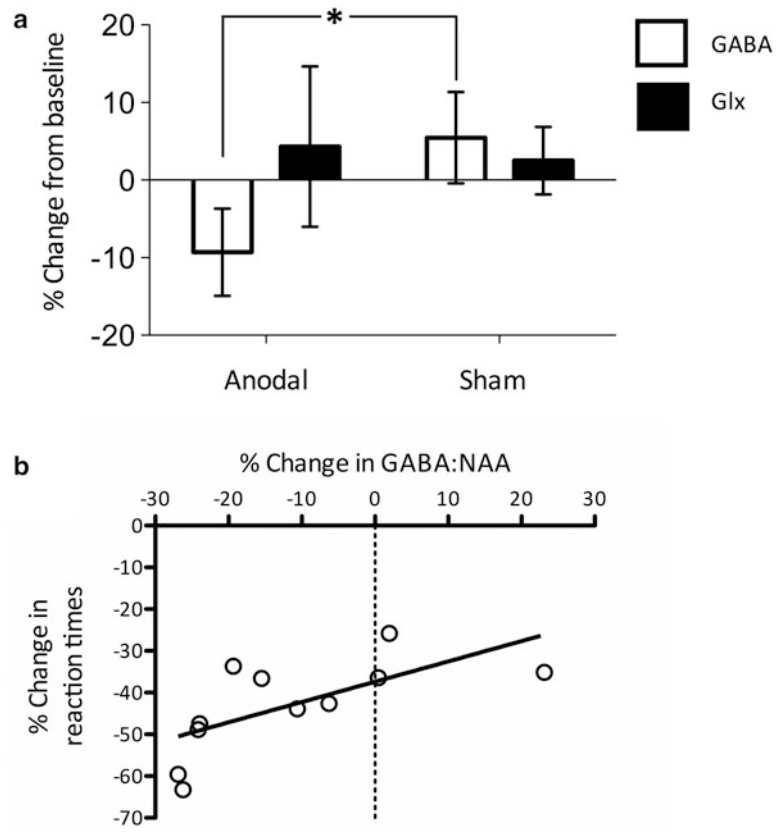

Fig. 10.6 (**a**) A decrease in MRS-assessed GABA concentration in the left M1 is observed after anodal tDCS applied to this region. No significant decrease is seen after sham stimulation. Figure adapted from [24] with permission. (**b**) The degree of anodal tDCS-induced decrease in GABA on one day correlates with the decrease in reaction times in an explicit sequence learning task (a marker of motor learning) performed on a separate day, such that subjects who have a greater decrease in GABA due to anodal tDCS are also those who learn most. Figure adapted from [25] with permission

training on a motor adaptation task with tDCS has been shown to correlate with improvements on the task: anodal tDCS-induced changes in ipsilateral M1 MRS-GABA levels correlated with model-based motor adaptation learning [85]. Taken together, this indicates that the decrease in GABA as measured may be responsible for the behavioural effects of tDCS.

Decreases in MRS-measured GABA levels after tDCS on M1 have been reliably demonstrated [22, 38, 39], but changes in levels of other metabolites have also been reported. For example, in a study by Rango and colleagues [88] a decrease in myoinositol concentration was the only change detected after 30 min of anodal tDCS over M1. However, the scanner sequence used in this study meant that the GABA signal was not examined, and this change in myoinositol has not been replicated [38].

The MRS-measured effects of tDCS in the parietal cortex have also been observed. Two studies from the same group found an increase in Glx beneath the anodal electrode, while finding no change in the same region of the contralateral cortex [41, 89]. One of these studies also demonstrated an increase in NAA beneath the anodal electrode [89]. These studies show markedly different findings than those examining tDCS over M1 where Glx increases in the anodally stimulated cortex have not been demonstrated. This raises an interesting question about whether the location of brain stimulation alters its effects on neurochemistry, or whether this is a facet of the different MRS approaches used in these studies, but it is not possible to draw global conclusions as neither of these parietal cortex studies examined GABA changes.

A final example of the use of MRS to study the effects of tDCS has been to observe changes

associated with tDCS on the chronic pain condition fibromyalgia. It has been shown that tDCS over M1 in fibromyalgia causes changes in diverse brain regions, not necessarily close to the stimulation area, for example a decrease in Glx was demonstrated in the anterior cingulate cortex, which is part of the pain matrix [90]. The group who experienced anodal tDCS also reported a decrease in pain ratings, and so these widespread effects may be modulated indirectly by changes in pain rather than purely due to stimulation in distant areas. However, this finding does raise interesting questions about whether the effects of tDCS are as focal as assumed when choosing an MRS volume of interest.

Conclusions and Future Directions

tDCS is showing increasing promise as a therapeutic tool in the treatment of psychiatric disorders, but for that promise to be realised more must be understood of the underlying effects on the brain, both in health and disease. However, while studies are beginning to increase our understanding of both the local and distant effects of tDCS, the combination of tDCS and MRI is within, at the moment, from the so-called infinite parameter space.

tDCS is a technique with a high number of degrees of freedom: there are several different stimulation types; multiple different electrode placement montages; varying stimulation intensities and lengths; and important differences in its behavioural effects depending on whether stimulation is performed concurrently or prior to the task. The number of neuroimaging approaches utilised and the significant question over which results from studies in healthy controls can be translated into clinical populations mean that there is currently little consensus over the likely neural correlates underlying the promising behavioural effects of tDCS seen in a range of psychiatric disorders.

However, neuroimaging offers great potential to allow the study of the neural effects of tDCS, once the technical difficulties of combining tDCS and MR have been overcome. It is to be expected that as stimulation parameters with clear clinical significance are developed, neuroimaging will play a vital role in refining our stimulation approaches in clinical populations.

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Target Engagement with Transcranial Current Stimulation

11

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Abstract

Transcranial electric stimulation (tES) applies a weak electric current to the scalp, which causes an electric field that changes brain activity and behavior. Despite the rapidly growing number of studies that report successful modulation of behavior in both healthy participants and patients, little is known about how tES modulates brain activity. In this chapter, we discuss what we know and what we do not know about the targeting of brain networks with tES. We provide an in-depth review of studies that use computational models, *in vitro* and *in vivo* animal models, and human participants to elucidate the mechanism of action of tES. The main emerging

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themes are (1) that the stimulation interacts with endogenous network dynamics, (2) functional connectivity represents an attractive and underexplored target for tES, and (3) that low-frequency cortical oscillations during sleep and anesthesia have become the flagship network target to elucidate the mechanisms of tES.

Keywords

Transcranial current stimulation • tACS • tDCS • Noninvasive brain stimulation • Cortical oscillations • Sleep oscillations • Functional connectivity • Electric fields • Entrainment • Plasticity

It has been known for a long time that electricity interacts with both the central and peripheral nervous systems. Today, electric brain stimulation is used both as a research tool for the study of brain function and as a clinical tool for the treatment of neurological and psychiatric disorders. In this chapter, we will focus on one form of noninvasive brain stimulation, transcranial electric stimulation (tES, also referred to as transcranial current stimulation, tCS), which has recently attracted broad attention due to a large number of promising results.

TES applies a weak electric current to the scalp. We will focus on two main types of tES: transcranial direct current stimulation (tDCS) which applies a constant current and transcranial alternating current stimulation (tACS) which uses a sine-wave stimulation waveform. The aim of tES is to modulate brain function; the *target* of tES is the electrical activity in brain circuits. Most tES studies, however, only use behavioral outcomes and do not measure the changes in brain activity caused by stimulation. Therefore, the questions of how and by what mechanism tES engages network-level targets in the brain have remained mostly unanswered.

Here, we will review the research that is aimed at uncovering the mechanisms by which tES modulates neuronal network dynamics and behavior. As we will see, the mechanisms of action by which the application of weak electric fields modulates neuronal activity have been studied with a range of different methods. In vitro studies using live slices of hippocampus and neocortex have contributed to a mechanistic understanding of the effect of weak electric fields on neuronal activity at the cellular and microcircuit levels. *In vivo* studies in animals have enabled the characterization of the effects of tES on intact brains with invasive recording methods. Noninvasive electrophysiology and imaging studies have contributed insights into how stimulation interacts with endogenous network activity in humans. In addition to these experimental approaches, computational modeling studies have provided important insights into targeting of specific networks and their endogenous dynamics. The combination of these methods has proven to be very useful to understand how a weak electric field can change brain function.

In this chapter, we will provide an overview of the potential mechanisms of tES that have been uncovered using these diverse methodological approaches. First, we will review animal studies. This is followed by a discussion of computational modeling studies, which provide mechanistic insights on the effects of tES at a cellular and network level. Next, we will focus on human studies that measured changes in brain activity by tES. Then, we turn our attention to the future and delineate what we believe are the rising new areas of tES research that deserve particular attention by the field. First, we propose that functional connectivity, which measures how different brain areas interact, is one of the most promising new targets for tES. Second, we look at one promising network target where the different methodological approaches discussed here have come together in a synergistic way: low frequency oscillations during sleep and anesthesia. Together, this chapter aims to equip the reader with a comprehensive understanding of how tES engages network targets and of what the future of tES may look like.

Mechanistic Insights from Animal Studies

Although tES is a noninvasive stimulation modality with an outstanding safety track record for the use in humans, studies in animal models are of high importance. Animal studies play a crucial role in understanding the mechanisms by which tES modulates brain activity. First, animal experiments allow for the use of invasive electrophysiology such as the insertion of recording microelectrodes into the brain. Such recordings overcome the technical difficulties of simultaneously stimulating and recording electric activity since action potential signals occur in a different frequency band (typically 300–5000 Hz) than the stimulation artifacts, which exhibit a spectral peak at the stimulation frequency (typically below 100 Hz). Therefore, the stimulation artifact can be removed by high-pass filtering for the study of neuronal firing. Second, reduced *in vitro* preparations such as the slice preparation offer the opportunity to study the effects of weak electric fields under controlled experimental conditions.

Effect of Electric Fields on Individual Neurons

One of the first observations of the effect of electric fields on neurons goes back many decades when Terzuolo and Bullock [1] applied a 1 mV/mm field to spontaneously active cardiac ganglion neurons of a lobster. The spontaneous firing rate of the cells was increased by the electric field. Similar modulation of neuronal firing rates by constant electric fields was also reported for other species [2, 3]. In 1988, Chan and colleagues [4] demonstrated that an applied electric field depolarizes the membrane voltage even when action potentials were blocked with the sodium-channel blocker tetrodotoxin. This demonstrated that the membrane depolarization caused by electric fields was a passive event, i.e. no opening or closing of ion channels was required. Rather, the ions within neurons change position in the presence of an external electric field. As the charge carriers redistribute within the cell to compensate for the applied field, the intracellular potential changes. The two distal poles of the structure aligned with electric field exhibit a depolarization and a hyperpolarization, respectively. This process is called *polarization* and depends on the overall length of the neuron as measured along the direction of the applied electric field (Fig. 11.1). Therefore, the orientation and size of the cell play a role in the response to the application of electric fields.

In addition, the change in the membrane voltage also depends on both the amplitude and frequency of the applied field. To demonstrate that the change in membrane voltage is dependent on the strength of the electric field, fields ranging from −40 to +60 mV/mm were applied along the somato-dendritic axis of CA1 cells and the change in membrane voltage at somata recorded in acute hippocampal slices [5]. The resulting polarization linearly depended on the strength of the applied electric field. This work was then extended to sine-wave (AC) electric fields in CA3 pyramidal cells [6]. The change in membrane potentials resulting from AC electric fields were less than those of DC fields of the same strength. The relationship between the field strength and the membrane depolarization was still linear but the slope, which quantifies the change in membrane voltage for every V/m of electric field, was decreased with increased frequency. Frequencies ranging from 5 to 100 Hz were applied and the change in the slope exponentially decays with the frequency of the applied electric field. This frequency dependence is caused by the low-pass filtering property of the passive cell membrane.

Interactions of Network Oscillations and Electric Fields

The change in membrane voltage of a single neuron by tES electric fields is too small to evoke action potentials in a cell at its resting potential in absence of synaptic input. Therefore, the effects of tDCS and tACS depend on the interaction of the applied stimulation and the endogenous network dynamics [7].

In particular, slice experiments have provided important insights on the interactions between the ongoing network activity and the applied

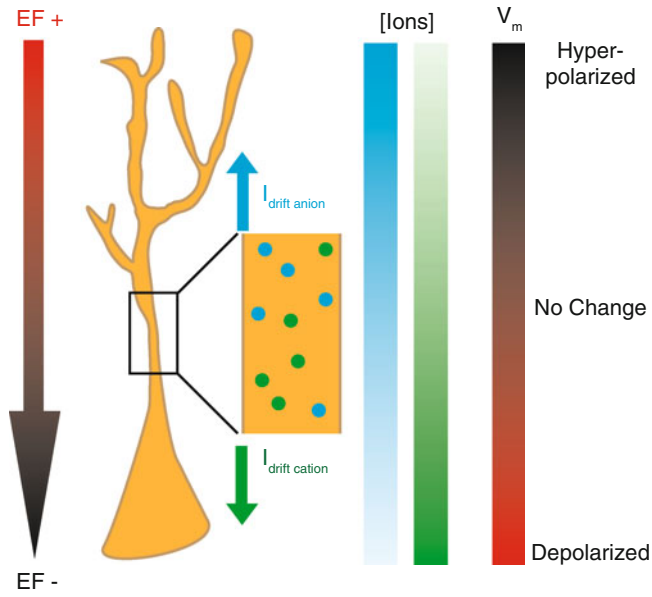

Fig. 11.1 Schematic illustration of how an electric field changes the membrane voltage of a neuron. The electric field (EF) is indicated with the arrow to the left of the neuron. When an electric field is applied (parallel to the somato-dendritic axis of a neuron), cations and anions move in opposite direction to cancel out the electric potential gradient imposed by the field within the neuron. The membrane voltage is defined as the difference between the electric potentials inside and outside the cell. Therefore, the gradient in the extracellular potential leads to a net depolarization of one end of the neuron (cell body) and a hyperpolarization of the other end of the neuron (distal apical dendrites)

electric fields. Few slice preparations exhibit spontaneous network oscillations, presumably because of (1) the relative lack of synaptic inputs due to the deafferentation inherent to this preparation and (2) impaired neuromodulatory tone in tissue slices in comparison to the intact brain. However, oscillations may occur spontaneously in the slice preparation in more in vivo-like ionic conditions [10] and in response to pharmacological activation [11]. More recently, optogenetic stimulation has uncovered in vivo-like activity patterns in the slice preparation [12]. Therefore, these experimental strategies can be combined with the application of external electric fields for the study of the mechanisms of tES. For example, pharmacological activation of hippocampal slices caused the emergence of gamma oscillations that were susceptible to weak DC electric fields [13]. Interestingly, the effect of the DC field was asymmetric with regards to the polarity. Hyperpolarizing fields were more effective at suppressing this network oscillation than depolarizing fields which were more effective at enhancing the same activity pattern. In case of AC fields, for sufficiently low stimulation frequency, the amplitude of the gamma oscillation was periodically modulated, reminiscent of the theta-nested gamma oscillation [14]. The most complex effect occurred if the stimulation frequency was similar to the frequency of the endogenous oscillation. In this case, three simultaneous frequencies were observed. The endogenous oscillation was reduced (but still present) while oscillations half a harmonic above and below the endogenous frequency appeared. Thus, the effects of AC stimulation can be highly nonlinear since in linear systems the observed output exhibits the same frequency as the input signal. In other words, neuronal networks may act as an energy transfer filter whereby energy in one frequency may be shifted into different frequency bands.

The interaction of electric field stimulation and endogenous oscillation appears to not only depend on the frequencies of both but their relative amplitudes. In a study of low frequency (1 Hz) oscillations evoked by optogenetic stimulation, it was observed that electric fields of a mismatched frequency would enhance the power of the endogenous

oscillation often without increasing power at the frequency of the electric field [15]. This occurred when the optogenetic drive and therefore the "endogenous" oscillations were strong and the electric field was relatively weak. However, the power of the oscillations at the stimulation frequency was enhanced when the magnitude of the endogenous oscillation was reduced (lower light intensity for optogenetic stimulation) or the strength of the electric field was increased. Taken together, the response of neural networks depends both on the frequency and the power (relative to the endogenous oscillation) of the electric field used for stimulation. Furthermore, these results demonstrate that the response of cortical networks to tES may be nonlinear in nature.

So far, we have focused on the response to stationary stimulation waveforms; however, endogenous neural activity is not stationary. To this end, endogenous activity may be better manipulated with feedback control algorithms than with static pre-programmed stimulation waveforms. One such example is the modulation of seizure-like, epileptiform electric events in slices. The application of DC fields can suppress epileptiform activity in hippocampal slices, which exhibit spontaneous seizure-like activity, however the network quickly adapted to the stimulation and epileptiform activity returned [16]. In a follow-up study, nonstationary electric stimulation was applied to suppress seizure-like activity [17]. The authors were able to suppress seizure activity for 16 min using a negative feedback stimulation paradigm on a hippocampal slice which exhibited seizure events every 40 s. Critically, spontaneous activity still occurred while epileptiform activity was suppressed. Thus, in the case of suppression of epileptiform activity with tES, these studies show that adaptive feedback stimulation may have greater effect on network dynamics than constant stimulation. Indeed, there is also evidence that feedback stimulation has uses outside of suppression of aberrant activity. In spontaneously oscillating slices of ferret visual cortex, positive feedback stimulation with electric field was shown to decrease the length of time between cortical up states and increase the strength of the endogenous oscillation [18]. Conversely, the application of negative feedback stimulation to the slices reduced strength of the endogenous oscillation. Interestingly, this effect was accomplished with stimulation amplitudes similar to the amplitude of endogenous electric fields recorded in vivo (1 mV/mm).

Outlasting Effects of Electric Fields

One of the most exciting aspects of tES is that the effects of stimulation can outlast the stimulation as demonstrated by sustained modulation of motor-evoked potentials after completion of stimulation [19]. This "outlasting effect" of tDCS has been studied in animal models and slice preparations. Most in vitro studies have reported no outlasting effects of weak electric fields, however the stimulation duration in these studies was typically short. With a longer stimulation duration, outlasting effects were observed more than 10 min after the end of 10 min DC stimulation with higher field amplitudes (i.e. 10 mV/mm and higher) than what can be expected to occur with tES in humans [20]. In vivo, tDCS over somatosensory cortex applied to rabbits modulated eye blink conditioning; however, an outlasting effect of tDCS only occurred for cathodal stimulation [21]. The underlying mechanism was probed by paired pulse experiments which revealed that spike-time-dependent long-term depression (LTD) was activated by tDCS. Moreover, the resulting LTD was suppressed by pharmacological blockade of adenosine receptors by a local injection. Similarly, evoked potentials were enhanced by application of electric fields in vivo in anesthetized rats, with effects that outlasted the stimulation for hours [22]. Both long-term potentiation (LTP) and paired-pulse facilitation (PPF) were increased after DC field application in hippocampal slices [23]. Intriguingly, LTP (but not PPF) was also enhanced in hippocampal slices of rats which had received anodal tDCS 24 h earlier. Application of an NMDA antagonist prevented LTP induction but not paired pulse facilitation. In slices of mouse motor cortex, the application of DC field enhanced synaptic strength when paired with a low-frequency electric stimulation of afferent pathways [24]. Importantly, this observed form of LTP depended on NMDA receptors and

brain-derived neurotrophic factor (BDNF). Today's limited evidence therefore suggests that tDCS activates multiple, diverse plasticity mechanisms, both pre- and postsynaptic, depending on the brain region, polarity (anodal vs cathodal) of stimulation, and other poorly understood factors. In addition, enhancement of oscillation following tACS has also been attributed to plasticity [8], however direct experimental evidence for such a mechanism is lacking.

Interaction of Cellular and Network Mechanisms

The main target of tES is cortical networks due to their positions closest to the stimulation electrodes. The circuits in neocortex are composed of different cell types that exhibit distinct morphology and electrophysiological properties. Importantly, not all cell types respond equally to weak electric fields. This was demonstrated by the combination of patch recordings of the somatic membrane voltage with careful reconstruction of cell morphology [25]. Layer 5 (L5) pyramidal cells were shown to have the largest change in membrane voltage in response to externally applied electric fields due to their morphology and orientation within cortex. These cells exhibit an elongated somato-dendritic axis that spans from L5 to L1. In addition, the somato-dendritic axis is approximately perpendicular to the surface of the brain meaning that the cells are properly aligned to receive energy from an external electric field orthogonal to the skull. Note that the folding of cortex introduces additional complexity, which for the purpose of this section we do not further discuss. Because L5 pyramidal neurons are the likely primary targets of tES, we can expect that their response to stimulation plays a critical role in the modulation of cortical network dynamics. Therefore, considering the intrinsic dynamics of this cell type will provide clues with regards to the network-level effects of stimulation. The response of L5 pyramidal cells to subthreshold changes in membrane voltages, particularly in the prefrontal cortex, has been well studied by current-clamp whole-cell patch clamp experiments; these cells respond best to subthreshold perturbations in the theta frequency (4–8 Hz) band [26, 27]. This suggests that electric fields of a given strength will cause the largest subthreshold oscillations in the theta band and that AC field stimulation preferentially modulates low-frequency oscillation in the cortex. However, direct experimental evidence confirming this link between single cell excitability, cell morphology, and network level effects has not yet been reported.

Computational Models

Despite the extensive investigation of cognitive and clinical applications of tES, the exact mechanisms of tES in modulating neuronal activity in humans have remained only partially understood. In the above section, we have discussed key findings on mechanisms of tES from animal experiments. Here, we provide an up-to-date review of computational models of tES, focusing on recent advances in modeling techniques and their applications.

Forward Models

Computational forward models determine the current flow in biological tissue and can predict the resulting electric field during tES. The current density distribution in the head depends on a number of dose parameters, including electrode number, position, size, shape, and electric current amplitude and waveform. Different electrode *montages*, positioning of the stimulation electrodes, result in distinct current flow through the brain. Although such flexibility allows for customization and optimization of tES paradigms, it also renders the optimal choice for engaging a specific brain circuit more difficult to identify. Perhaps most importantly, forward models allow us to relate the amount of current applied to the scalp to the magnitude and the direction of the resulting electric field in the targeted brain areas [28]. By calculating current density distributions, forward models provide accurate and detailed description of current flow patterns, thus greatly facilitating the rational design and optimization of tES parameters.

Computational forward models of tES have evolved from the simple concentric sphere models

assuming simplified geometries to low-resolution anatomy-based models to high-resolution, anatomically accurate models based on individual structural magnetic resonance imaging (MRI) scan. Lacking regional anatomical differences, the concentric sphere models were successfully used to determine the main effects of different electrode montages [28]. Such simplified models are particularly beneficial for initial evaluation of the effects of different electrode configurations. For example, a finite-element concentric sphere human head model for simulating a range of different electrode configurations showed that concentric ring electrode causes electric field distributions with higher spatial focality than more commonly used electrode types and montages [29]. In contrast, low-resolution anatomy-based models incorporate both anatomical structure and individual patient-specific features, but the anatomical accuracy is limited because cortical folding, ventricles, and tissue anisotropy are usually not taken into account. Consequently, such models are not able to capture local nonuniformities in electrical field distribution [30]. Despite these limitations, low-resolution models have offered valuable insights in informing tES montage design and how pathological changes of brain and skull anatomy affects current density distribution. A number of low-resolution models developed by Wagner et al. (2004, 2006 and [31]) serve this purpose. In one tDCS study [31], the comparison of several electrode montages commonly used in clinical application showed that smaller electrodes led to greater current shunting through the scalp. In the same study, the analysis of current density distribution between healthy and stroke head models under tDCS demonstrated that lesions substantially altered spatial targeting, which may interfere with the treatment outcome. Lastly, high-resolution anatomically accurate models based on MRI scans have become a promising tool in assisting the design of customized and individualized tES protocols as they allow for accurate representation of current density distribution in the brain (for a comprehensive review, see [32]). These high-resolution models advance our understanding of tES effects and may eventually lead to improved stimulation for optimized and customized therapy. Below we review a few examples to illustrate the merit and utility of high-resolution models in the design and analysis of tES. It is important to note that most of these modeling results are awaiting physiological proof.

The actual pattern of current flow produced by tES is greatly shaped by anatomy and tissue properties [28]. To achieve similar treatment outcome despite patient-to-patient variability in head and brain anatomy, it is important to know the sensitivity of electrical field distributions to normal anatomy variation for a given electrode montage. High-resolution models provide an ideal tool to analyze the underlying basis for individual variation during tES. For example, a detailed analysis of the influence of cerebrospinal fluid (CSF) showed that electric fields may be clustered at distinct gyri/sulci sites due to details of CSF flow [33]. Together with other high-resolution models [34–36], this study suggested that individual variability in dosing of tES could arise primarily due to gyri-specific dispersion of current flow more than differential skull dispersion as previously thought.

High-resolution models have contributed significantly to the design and validation of new tDCS montages. The conventional tDCS applies weak direct currents to the scalp via sponge-based rectangular pads. High-definition tDCS (HD-tDCS) uses arrays of small scalp electrodes for stimulation [27]. A high-resolution MRI-based finite element model of the human head demonstrated that the 4×1 ring electrode configuration [four "return" (cathode) disk electrodes arranged in a circular fashion around an "active" (anode) center electrode] resulted in significant improvement of spatial focality [33]. To what extent such increased spatial focality improves treatment outcomes remains an open question.

Furthermore, high-resolution models allow for safety and efficiency analysis of tES application in populations at increased risk of negative side-effects. For example, there is a growing interest in applying tES in children for the treatment of disorders such as autism and epilepsy. However, due to anatomical differences, the same stimulation dose that is safe for adults may be hazardous to children. In order to establish the comparable safety and tolerability dose in children,

cortical electric field maps at different stimulation intensities and electrode configurations were determined using a high-resolution MRI-derived finite element model of a typically developing, anatomically normal 12-year-old child [37]. Simulation results indicated that, for a given stimulus intensity, the maximal electric fields in the adolescent brain were twice as high as in the adult brain for conventional tDCS and nearly four times as high for a 4×1 high-definition tDCS electrode configuration. Thus, special caution needs to be taken when applying tES to the pediatric population. Another vulnerable population is patients with traumatic brain injury or decompressive craniectomy, who often have skull defects or surgically implanted plates. To safely apply tES in these patients, safety guidelines need to be established. In order to evaluate the impact of skull defect on current density distribution under tDCS, a MRI-derived finite element head model with several conceptualized skull injuries including two types of skull defects and two types of skull plates was developed [38]. Interestingly, simulation results indicated that skull defect provided a preferential pathway for current flow to concentrate in the brain. Under such conditions, the underlying cortex would be exposed to a higher intensity of focused current flow, raising important clinical and safety considerations. Together, these studies show that computational forward models are an essential tool for safe (and optimal) targeting of the brain structure of interests.

Computational Neural Models

Different from computational forward models, computational neural models of tES focus on the effects of electrical stimulation on neuronal excitability and network dynamics. Neural models of tES are desirable since they provide a solid computational framework to readily explore the neural mechanisms underlying tES-induced behavioral/treatment outcome and the effects of stimulation parameters such as frequency and amplitude in the case of tACS. Although there exist a number of cellular and network models of electrical stimulation [39–47], few are dedicated to the study of tES. Below, we focus on three neuronal network models that specifically investigate the effects of tES on cortical activity [45–47].

During neural activity, the superimposition of electrical currents from a large population of neurons that have similar spatial orientation gives rise to a potential in the extracellular medium. This electric field is the source of the electroencephalogram (EEG) recorded from the scalp [48, 49]. Scalp EEG activity shows oscillations in a variety of frequency bands which reflect the synchronous activity of thousands or millions of cortical neurons [50] and are associated with different behavioral states (e.g. waking and sleep [51]). Abnormal or disrupted cortical oscillations are a hallmark of a number of neurological and psychiatric disorders including schizophrenia and depression [52]. The mechanisms by which externally applied fields modulate the activity of cortical neurons remain unclear. The three computational studies [45–47] aim to elucidate how cortical dynamics are modulated by tES.

The computational study by Molaee-Ardekani and colleagues [47] analyzed in detail how cortical neuronal assemblies are affected by the electrical field induced by tDCS and how local field potentials (LFPs) respond to the applied electrical field. The authors constructed a macroscopic computational model (neural mass model) of the cerebral cortex including subpopulations of pyramidal cells and inhibitory interneurons connected with realistic models of synapses. Model parameters were adjusted to reproduce evoked potentials (EPs) recorded from the somatosensory cortex of the rabbit in response to air-puffs applied to the whiskers. The application of tDCS was modeled as a perturbation on the mean membrane potentials of pyramidal cells and/or interneurons. Simulation results demonstrated (1) that a feedforward inhibition mechanism must be included in the model to accurately replicate the actual EP and (2) that electric fields had to modulate interneurons to replicate the experimental findings.

EEG signals usually contain oscillations in multiple frequency bands that can be analyzed by power spectrum. To capture the origin of tDCS-induced alterations in the EEG power spectrum, Dutta and Nitsche [46] developed a thalamocortical neural mass model that contained four

subpopulations of cortical cells (excitatory pyramidal cells, excitatory interneurons, slow inhibitory interneurons, and fast inhibitory interneurons) and two subpopulations of thalamic neurons (excitatory thalamo-cortical cells and inhibitory reticular thalamic neurons). This thalamo-cortical network model was used to simulate the subject-specific EEG power spectrum changes during and following tDCS by varying synaptic parameters. Model simulation showed that anodal tDCS enhanced activity and excitability of the excitatory pyramidal neurons at a population level in a nonspecific manner and led to mu-rhythm (9–11 Hz) desynchronization. The model further showed that the tDCS effects on mu-rhythm desynchronization depended on the stimulation polarity, consistent with experimental observations [53].

Recent human studies have demonstrated that sine-wave stimulation waveforms (tACS) induce frequency-specific effects on brain dynamics measured by EEG [54–56], suggesting that tACS may present a more targeted stimulation paradigm for the enhancement of cortical oscillations than tDCS. However, it remains unknown how periodic, weak global electric fields alter the spatiotemporal dynamics of large-scale cortical networks. To address this question, Ali and colleagues [45] developed a large-scale two-dimensional cortical network consisting of 160,000 (400×400) pyramidal cells and 40,000 (200×200) interneurons modeled by Izhikevich neural dynamics [57, 58]. Simulations revealed distinct roles of the depolarizing and hyperpolarizing phases of tACS in oscillation entrainment, which entailed moving the network activity toward and away from a strong nonlinearity provided by the local excitatory coupling of pyramidal cells. Interestingly, the model demonstrated that recovery of synaptic depression played an important role in the entrainment of network activity by tACS and that sparse global stimulation was more effective than spatially localized stimulation. The simulations further revealed that entrainment by tACS was mediated by "Arnold tongue" dynamics so that stimulation frequency matched with the endogenous frequency was most effective in entraining the oscillating network. These findings provide a detailed mechanistic understanding of tACS at the level of large-scale network dynamics and give support for tACS as a more targeted stimulation paradigm for the treatment of neuropsychiatric illnesses with impaired cortical oscillations.

Future Directions

Together, computational models of tES play a critical role in visualizing the electrical field distribution, understanding the mechanistic action of tES on neuronal network dynamics, and optimizing stimulation parameters to guide the design of the next generation of tES. While anatomically accurate high-resolution MRI-based forward models guide the rational design and optimization of tES electrode montages, neuronal models constrained by neurophysiological measurements provide a mechanistic understanding of the effects of tES on cellular and network dynamics and thereby provide guidance for the rational design of the stimulation waveform. As most existing neural models of tES are either neural mass models or simplified spiking models that lack accurate ion channel dynamics, it is desirable to construct biophysically realistic neuronal models of tES. We anticipate that such models will further illustrate at both the cellular and network levels how the stimulation dynamics interact with the intrinsic neuronal dynamics to give rise to the state-dependent effects of tES. Furthermore, there is an increasing demand for the incorporation of neural models into computational forward models of electric current flow to thoroughly explore how tES-induced electric fields modulate cellular excitability and network dynamics as a function of time and space.

Effects of Weak Electric Fields on the Human Brain

Even before observations of interactions between electricity and brain activity, electrical currents have been used for treating various disorders such as headache and epilepsy. Initial treatments involved using live electric rays and electric catfishes [59]. Efforts by a number of pioneers

including Walsh, Galvani, Volta, and Aldini lead to the establishment of the field of bioelectricity and subsequently the development of *electrotherapy* [60]. Interest in electrically polarizing brain regions using transcranial weak current stimulation for treating symptoms of psychiatric disorders increased in the 1960s and 1970s with a number of studies showing positive outcomes [61–64]. However, development of drugs which appeared to be more effective in treating psychiatric disorders led to waning interest in transcranial stimulation.

During this period, the predominant understanding of how stimulation produces such effects was based on evoked potentials observed in animal studies. When a positive polarization is applied across the cortex, there is an increase in evoked response amplitude and conversely, there is decrease in evoked potential amplitude when a negative polarization is applied [65, 66]. In essence, stimulation was thought to affect the excitability of neurons. In humans, one of the first studies to look at excitability change after transcranial direct current stimulation (tDCS) was performed by Priori et al. [67]. Weak DC current (< 0.5 mA) was applied over motor cortex and excitability was tested using single pulse transcranial magnetic stimulation (TMS) to trigger an evoked response. The resulting motor-evoked potential (MEP) amplitudes served as a physiological measure of change in excitability. Anodal and cathodal stimulation indeed modulated the MEP amplitude, however factors such as the temporal order of the stimulation paradigm appeared to matter. A clearer result emerged from a more comprehensive study by Nitsche and Paulus [19] where they showed that anodal stimulation led to an increase in MEP amplitude and conversely cathodal stimulation led to a decrease in MEP amplitude. Interestingly, the change in amplitude lasted for a few minutes after completion of tDCS and returned to baseline after 5 min. Also, the size and duration of the after-effect depended on the stimulation duration and current intensity.

Neurophysiology of tDCS in Humans

Increasing interest in tDCS has led to an exploration of possible modalities that can provide more insight into neurophysiological effects. Consequently, tDCS has been used in conjunction with other neurophysiological approaches. Electroencephalography (EEG), the earliest approach for measuring brain activity in humans, was also one of the earliest modalities used in studying the effect of current stimulation [68].

Analogous to the approach of using MEPs for evaluating excitability change in motor cortex, Antal et al. [69] used visual-evoked potentials (VEPs) to study excitability change caused by tDCS. They found that the amplitude of N70 component of the VEP in EEG was increased by anodal stimulation and conversely, decreased by cathodal stimulation over visual cortex. In another study [70], tDCS was found to affect the P100 component (anodal tDCS caused decrease in amplitude while cathodal tDCS caused increase in amplitude) of the VEP and the duration of the after-effect of tDCS depended on the duration of stimulation. Of note, as so often in this literature, the choice of return electrode was different. This may explain the different findings across studies. In both studies, stimulation did not affect the latency of the VEP. Similarly, the effects of tDCS on somatosensory-evoked potentials (SEPs) have been studied. A 9-min application of cathodal tDCS to somatosensory cortex decreased the N20 component of the SEP for up to an hour after stimulation while there was no significant change with anodal tDCS [71]. In another study, tDCS applied over motor association areas produced changes in SEP amplitudes as well as MEP amplitudes. Interestingly, the effects were inversely related. Anodal stimulation decreased amplitudes of MEPs while amplitudes of SEP components increased compared to cathodal stimulation [72]. Other studies have evaluated pain perception using laser-evoked potentials (LEPs) after tDCS and found that only cathodal stimulation produced a change in the amplitudes of N2 and P2 components of LEPs [73, 74]. The effects of tDCS on auditory-evoked potentials (AEPs) have also been evaluated and significant effects of stimulation polarity and stimulation locations (temporal vs temporo-parietal) have been found [75].

Apart from evoked potentials, EEG oscillations have also been investigated for elucidating the effect of tDCS. In a study accompanying the

previously mentioned study by Antal et al., cathodal tDCS was found to decrease power in the beta band (15.625–31.25 Hz) as well as the gamma band (31.25–62.5 Hz) related to VEPs [76]. A study by Ardolino et al. [77] evaluated the changes in spontaneous EEG activity following application of cathodal tDCS over motor cortex and found increases in power in the delta and theta bands. In another study, the effect of tDCS on mu event-related desynchronization (ERD) caused by imagined hand movements was studied [53]. The change in power of mu rhythms was used as a measure of ERD. Anodal tDCS increased mu ERD while cathodal tDCS decreased mu ERD. The changes were attributed to the change in excitability caused by tDCS. There have also been studies which evaluated tDCS-induced changes in EEG activity patterns observed during sleep. These are covered in detail in the last section of this chapter.

The use of tDCS and EEG can be divided into two approaches—the *offline* approach, where EEG is collected after tDCS treatment, and the *online* approach, where EEG is collected concurrently with tDCS application. The former approach allows evaluation of the after-effects of stimulation while the latter approach allows study of the effect of stimulation on ongoing dynamics. Most of the studies described above fall under the offline category. A few of the studies have attempted to concurrently record EEG signals when stimulating with tDCS and have found noise to be the limiting factor. In a study assessing the efficacy of tDCS as a treatment for epilepsy, tDCS produced high-frequency artifacts that contaminated the EEG [78]. These artifacts were removed using an independent component analysis (ICA) algorithm. In another study [79], tDCS electrodes were placed between EEG electrodes and a band-pass filter between 0.5 and 70 Hz was found sufficient to remove the artifacts produced by tDCS.

Magnetoencephalography (MEG), which records brain activity by measuring magnetic fields produced by neuronal activity, is a similar modality that has been used with tDCS. MEG (at least partially) overcomes the main limitation of using tDCS concurrently with EEG, namely the limited source localization capability due to volume conduction. Soekadar et al. [80] applied tDCS over motor cortical areas of healthy volunteers performing a button-press task and assessed task-related changes in alpha and beta frequency bands from concurrently recorded MEG. Using a mathematical approach that provided spatially selective noise reduction and source localization, they were able to successfully isolate the stimulation current as a source. By separating this identified source from other sources that corresponded to brain oscillations, they were able to remove the stimulation artifacts.

Functional magnetic resonance imaging (fMRI) which relies on blood oxygenation level dependent (BOLD) signal to detect changes in activity in different brain regions is another commonly used approach to measure neurophysiological changes associated with tDCS. Compared to EEG and MEG, fMRI provides higher spatial resolution in terms of identifying the anatomical regions affected by stimulation. However, the temporal resolution is poorer than EEG/MEG as the changes in BOLD signals are observed a few seconds after neuronal activation. In one of the earliest studies, cathodal tDCS over motor cortex was shown to produce decreased activation [81]. As in the case with early tDCS-EEG studies, this study used an offline approach, i.e., there was no stimulation during fMRI data acquisition. This was due to the potential safety hazard caused by magnetic fields from the MRI scanner inducing currents in the stimulation electrodes. Once this concern was resolved by the addition of current limiting resistors, it became possible to perform concurrent fMRI-tDCS studies [82]. Overall, such studies have helped to elucidate the spatial distribution of the effects of tDCS in terms of motor and visual functions as well as functional connectivity between different regions. The latter topic is covered in detail in the Functional Connectivity section.

Mechanisms of tDCS in Humans

A common observation in most neurophysiological studies discussed above is that tDCS produces a change in excitability of the region being stimulated. Alterations in membrane potential changes

are thought to be the main mechanism underlying the change in excitability in both anodal and cathodal stimulations. Blocking sodium and calcium channels using pharmacological agents led to decrease or complete abolition of the effects of anodal tDCS in humans. While there was no change in the effects of cathodal tDCS, this still supported the hypothesized hyperpolarization effect of cathodal tDCS [83]. The outlasting effects of stimulation have been attributed to synaptic plasticity such as LTP that depends on NMDA receptors. Indeed, an NMDA antagonist suppressed the outlasting effects of tDCS [84]. The effect of cathodal tDCS is likely also the result of synaptic plasticity since it is also abolished by blockade of NMDA receptor blockade [83]. Synaptic long-term depression [85] is thus a strong candidate mechanism. Further supporting the idea that synaptic plasticity underlies the outlasting effects is the observation that individuals with brain-derived neurotrophic factor (BDNF) Val66Met polymorphism showed lower effect of tDCS-induced change in MEP compared to individuals without the polymorphism [24].

Moreover, studies involving magnetic resonance spectroscopy have shown that tDCS polarity affects local accumulation of neurotransmitters. Stagg et al. [86] showed that anodal tDCS reduced concentrations of GABA while cathodal tDCS reduces concentration of glutamate (with a correlated decrease in GABA concentrations as well). Given the fact that increased firing rates have been shown to decrease GAD-67 activity and decreased firing rate is correlated with decreased glutamate/glutamine cycling, the idea that anodal tDCS increases and cathodal tDCS decreases excitability (and consequently firing rate) is therefore further supported by these spectroscopy results. In another study by Clark et al. [87], application of anodal tDCS over parietal cortex led to an increase in glutamate and glutamine levels. The effect was local as only the region in the ipsilateral hemisphere showed an increase compared to the same region in the contralateral hemisphere. The relation between reduction in extracellular GABA concentration and motor learning suggests that modulation of GABA levels is another possible mechanism which explains the observed effects of tDCS. This idea has received further support in a recent study [88] which showed that the effect of anodal tDCS over primary motor cortex produced a local decrease in the GABA concentrations and the tDCS-induced concentration change predicted motor learning performance.

Neurophysiology of tACS in Humans

The renewed interest of the scientific community in tDCS has led to the recent development of novel tES paradigms. One particular approach, transcranial alternating current stimulation (tACS) has garnered considerable interest and is now the topic of a large and rapidly growing number of scientific studies [89–91]. Transcranial alternating current stimulation is a type of noninvasive electrical brain stimulation where oscillating, (typically) sinusoidal currents are applied to the scalp and underlying brain tissue of an individual. Many different frequencies have been used throughout the literature, but it is most common to apply currents in the frequency range of observed periodic phenomena in the brain such as local field potentials and EEG oscillations. This follows from the assumption that mimicking the structure of endogenous electrical brain activity is the best way to interact with and influence the sources of such activity. Various studies have combined neurophysiological measurements with tACS in attempts to show that oscillatory noninvasive brain stimulation indeed influences the activity of the human brain. Most of these studies have found outlasting effects of tACS when examining EEG before and after stimulation, providing the first evidence that approximately matching the stimulation frequency to the frequency of prominent endogenous oscillatory brain activity yields effects on EEG activity at that frequency. A smaller number of studies have also measured the effects of tACS during its administration.

One of the first studies to record EEG and apply tACS found no effect of tACS on EEG activity or motor-evoked potentials [92], but several subsequent studies found outlasting effects of theta-frequency tACS on EEG theta power [93], alpha-frequency tACS on EEG alpha power

[8, 56, 94], and gamma-frequency tACS on EEG gamma coherence [95, 96] and alpha power [95]. The first evidence for outlasting effects of tACS on EEG was found by Zaehle and colleagues [56]. In this study, participants performed a vigilance monitoring task for the stimulation portion of a single 16 min session (3 min of EEG recording, 10 min of stimulation, 3 min of EEG recording). During the task, participants were required to fixate on a crosshair on a computer monitor and press a button whenever the crosshair rotated 45°. At the beginning of the session, the authors determined the peak individual alpha frequency (IAF) from the single-channel EEG data by calculating the spectral peak in the alpha band during a 1 min closed-eyes recording. Either sham tACS or approximately 1 mA (peak-to-peak) tACS at the IAF was applied under the assumption that matching the stimulation frequency would best enhance endogenous alpha power. The tACS amplitude was titrated just below the thresholds of visual phosphene induction or skin sensation. They compared the average amplitude spectrum of 1 s windows between the baseline and the post-stimulation epochs for both stimulation conditions and found a significant increase in alpha power relative to baseline in the IAF-tACS condition and not for the sham stimulation condition. Specifically, this increase was found to be in the neighborhood of the IAF across participants (IAF ± 2 Hz). Neuling et al. then investigated if the effects of tACS were also dependent on the brain state of participant [94]. They utilized the well-known alpha power difference between the eyes-open and eyes-closed to test the hypothesis that the state of endogenous alpha oscillations would in part determine the EEG response to alpha-frequency tACS. The authors recorded 5 min of whole-head EEG activity, then applied the sham or verum IAF-tACS during an auditory oddball task, and finally recorded EEG for 30 min after the task. The protocol for the other experimental group was exactly the same except participants had their eyes closed for the entirety of the experiment. In this study, tACS enhanced the alpha power for the entire 30 min post-tACS recording window. This effect was specific to the eyes-open (low endogenous alpha power) experiment, and no such power enhancement occurred during the eyes-closed (high endogenous alpha power) experiment. They also found that IAF-tACS enhanced coherence between P3 and P4 alpha activity for the eyes-closed condition, but not the eyes-open condition. These electrophysiological changes did not result in a change in oddball task performance as measured by reaction time and sensitivity. While the authors argue that the effects seen in these studies result from the entrainment of endogenous alpha oscillators to the tACS frequency, Vossen et al. found similar alpha power enhancements in the absence of evidence for entrainment [8]. The authors conducted a 4-session within-participant study with three active tACS conditions and one sham tACS condition. During each session, participants performed a basic visual detection task for 22–30 min with a 2 min EEG recording before and after. During the task, the authors administered tACS at the individual alpha frequency (determined in the first session and used for all subsequent sessions) with individually adjusted intensity (1.35–2 mA peak-to-peak). Each tACS protocol consisted of intermittent bursts of tACS, two of which were 80 cycles on followed by 80 cycles off and the other 30 cycles on followed by 30 cycles off. The difference between the two 80 cycle on/off conditions was whether or not the tACS phase was continuous throughout the experiment relative to the phase of a virtual sine wave at the tACS frequency for the full duration of the task. This was termed the "long continuous condition". The "long discontinuous condition" shifted the start of each tACS burst such that the phase difference between the virtual sine wave and the administered tACS changed by a randomly selected 0, 90, 180, or 270°. For the 30 cycle burst condition the onset phase was not disrupted (short continuous). The comparison of the pre-stimulation and post-stimulation EEGs showed significant alpha power enhancement for both the long conditions and long discontinuous conditions relative to sham stimulation, but no significant difference between the two conditions. For the uncontaminated EEG epochs during the stimulation protocols, they assessed the degree of phase locking present after each burst of stimulation in terms of inter-trial phase coherence (ITPC) in the alpha band. They hypothesized that entrainment

"echoes", or brief periods of phase consistency in the alpha oscillation across trials, would likely be present if each tACS burst entrained the endogenous alpha oscillation to its phase. However, they found no difference in ITPC between the stimulation conditions or the sham condition (essentially measuring spontaneous phase consistency in the alpha oscillation). These results have been interpreted in favor of a spike-timing dependent plasticity framework to explain outlasting elevation of alpha power after tACS.

While studies that observe the after-effects of tACS have elucidated a robust set of neurophysiological changes attributable to oscillatory noninvasive brain stimulation, they can merely speculate about the changes that occur during stimulation to achieve the observed results. This is why studies that performed tACS while acquiring neurophysiological data such as EEG [97] and MEG [98] are of particular interest. Helfrich et al. [97] devised an artifact removal method that allowed them to measure EEG during a visual oddball task accompanied by the administration of 10 Hz tACS. In this study, participants performed a standard color-mismatch visual oddball paradigm where the presentation of each stimulus was aligned to one of four phase bins of the tACS waveform. The authors recorded 59-channel whole-head EEG while administering the 1 mA peak-to-peak current. To remove the artifact potential from the EEG, which is approximately, but not exactly, a sine wave at 10 Hz due to fluctuations in scalp impedance and various other sources of nonstationarity, the authors first constructed artifact templates from moving neighborhoods of recording epochs by a moving average approach. These artifact templates were then subtracted from their respective artifact-contaminated EEG segments to yield semi-cleaned EEG data. The remaining tACS artifacts were captured by decomposing each EEG time-series into its principal component subspace via principal component analysis (PCA). Components that were clearly artifactual in nature were removed and the time-series reconstructed from the remaining components in this final step. The authors assessed the validity of this approach by contaminating artifact-free data with similar artifacts found when they applied tACS (somewhat nonstationary 10 Hz sine waves 2–4 orders of magnitude greater than typical EEG potentials). The study of the preprocessed EEG showed an enhancement of mainly occipital alpha power during tACS application, and the enhancement was strongest at the stimulation frequency. The phase-locking value (PLV) between the tACS waveform and alpha-band frequencies of the EEG was significantly greater during tACS application than that during sham stimulation, and this PLV enhancement was constrained to occipital brain regions. Interestingly, the authors found a phasic modulation of oddball target detection accuracy as a function of the tACS phase during target presentation. Given that the phase of the alpha oscillation is known to influence the perception of visual stimuli [99–101], combined with the observed enhancement in endogenous alpha power, this study provides compelling evidence that 10 Hz tACS over occipital brain regions may entrain disparate endogenous alpha oscillations to a similar phase, resulting in an increase in occipital alpha synchronization. While this approach is a promising direction for the study of the neurophysiology of tACS, it has yet to be replicated in the literature.

More recently, a study by Neuling et al. [98] detailed a different approach to study the "online" effects during stimulation based on MEG. The authors applied IAF-tACS at weak (50 μA peak-to-peak) and strong (between 100 μApp and 1.5 mApp) current levels while acquiring 306-channel MEG. Participants performed several tasks well-established to induce alpha modulations and each participant completed three blocks consisting of sham stimulation, weak tACS, or strong tACS. The authors found substantial contamination of the sensor-level signals by tACS-induced magnetic artifacts, but were able to recover meaningful event responses by using linearly constrained minimum variance (LCMV) beamforming to project the measured magnetic fields into a grid of dipolar sources within the Montreal Neurological Institute (MNI) coordinate system. The source signals determined with this method showed alpha activations/suppressions and auditory/visual average event responses that were surprisingly similar to those obtained during sham stimulation. Importantly, these effects are all within-condition

and localized to the same regions as seen during sham tACS, whether or not that happened to be near or away from the stimulation electrodes. Furthermore, the presence of similar enhancements *and* reductions of alpha power during all three tACS conditions strongly supports the idea that measured source activity is physiological in nature during all three conditions.

Mechanism of tACS in Humans

The interest in tACS as a tool for manipulating cortical dynamics as well as a therapeutic option for treating CNS disorders with aberrant cortical and thalamo-cortical oscillations is relatively recent compared to tDCS. Correspondingly, the mechanisms by which tACS produces change are also less certain.

The primary targets for tACS in humans are oscillations observed in EEG and different studies have shown that tACS indeed alters the strength of oscillations [8, 56, 94, 97]. Given the periodic nature of stimulation as well as the stimulation target, concepts from dynamical systems are generally borrowed to explain the mechanism of action of tACS. The different cortical oscillations are considered to be generated by self-sustained oscillators with phase as a free parameter [102]. Depending on the level of abstraction, neurons or networks of neurons or individual brain regions are treated as these oscillators. One leading hypothesis is that the brain region targeted by tACS is composed of many oscillators and tACS produces a realignment of the phase of the oscillators to the phase of stimulation waveform. This is defined as entrainment [9]. Once the oscillators are aligned, it is assumed that oscillations continue even after the removal of stimulation until entropy of the system pulls them back to the initial state. An alternate hypothesis is that tACS preferentially strengthens synapses between neurons by spike-timing dependent plasticity (STDP) and this facilitates the effects of stimulation to be present after the removal of stimulation.

Studies involving tACS and EEG in humans have attempted to elucidate which of the above-mentioned mechanisms might be prevalent. The study by Helfrich et al., where healthy volunteers were stimulated with 10 Hz tACS during a visual oddball task, found an increase in phase-locking value between stimulation waveform and EEG waveform (after stimulation artifact removal) during stimulation [97]. This was postulated as evidence for entrainment as the results satisfied the key requirements for entrainment as proposed by Thut et al. [9]. In another study, tACS applied at the individual alpha frequency produced an enhancement in alpha power when the participants had their eyes open compared to the condition where they had their eyes closed [94]. This result provides additional support to the entrainment hypothesis. In the eyes-closed condition, the phases of the oscillators within the region targeted by tACS can be considered to be aligned to each other resulting in a strong endogenous alpha oscillation. In the eyes-open condition, however, the phases of the oscillators are not aligned with each other and tACS is able to cause synchronization of the phases of the oscillators resulting in stronger alpha oscillations. However, in the study where tACS was applied in an intermittent manner, scrambling the phase of stimulation current between consecutive trials did not produce effects different from the stimulation where the phase of the stimulation current was maintained to be continuous across all trials [8]. The authors argue that the results imply entrainment is not the underlying mechanism as the enhancement produced by stimulation with scrambled inter-trial phases should have been lesser than that produced by stimulation with continuous phase. Also, enhancement was stronger when stimulation frequency was close to the individual alpha frequency. If the entrainment hypothesis were true, the enhancement should have been higher at the stimulation frequency and not the individual alpha frequency. Additionally, as mentioned before, the absence of difference in inter-trial phase coherence between sham and stimulation conditions suggested that the outlasting effects of stimulation was not caused by entrainment. The authors propose a simplified STDP model to account for the effects of stimulation. Although plasticity is a plausible mechanism underlying the outlasting effects of tACS, there have been no studies in humans that explicitly show that this is indeed the case.

Thus, there is no clear consensus as to the mechanism underlying tACS. While the ideas of entrainment and plasticity seem mutually exclusive, this is not necessarily true. A realignment of phase may lead to strengthening of synaptic connections between the neurons because of STDP. Conversely, strengthening of synapses may lead to increased phase locking and consequently entrainment. Future studies trying to answer this question will be well served to include this consideration when designing the study as well as when trying to interpret the results.

Probing Functional Connectivity with tES

In this section, we will discuss a promising new target for tES, namely the dynamic interaction of neuronal networks within the brain. We will first introduce functional connectivity that quantifies such interactions and then discuss how tES could be used to modulate functional connectivity. The brain can be viewed of as a complex, high-dimensional network that dynamically changes over time. This network consists of billions of neurons with links, or connections, existing between individual neural cells, populations of neurons as well as different regions within the brain [103]. The network connectivity is not random, thus suggesting that specific connections are crucial for the processing and integration of new information [104, 105]. This idea is reinforced by the ability of the brain to form new connections during development as well as in response to input from the environment or induced trauma, a process known as neuroplasticity [106]. In this process, connections which are infrequently utilized are eliminated while those frequently used for information transfer are strengthened, essentially "pruning" synaptic connections in an activity-dependent process [107, 108].

We can think of the functional connectivity in the brain on three distinct levels as described by Polania et al. [106]: connectivity between individual cells (micro-scale level), connectivity between neuronal populations (meso-scale level), and connectivity between brain regions (large-scale level). Analysis on these different scales has allowed researchers to address a wide range of questions about the fundamental dynamics of the brain in physiological and pathological states.

The identification of network connectivity on the micro-scale level has received considerable attention from the computational community. Numerous methods have developed for the analysis of network connectivity on this level, an interest that in particular has been driven by the development of the multielectrode array (MEA) platform [109, 110]. Whether used in vitro or implanted in vivo the MEA allows for the recording of putative single-cell neuronal activity, often in the form of neuron spike trains, thus permitting individual cell-to-cell connectivity analysis. The techniques used to analyze these data can be characteristically divided into three classes. On one end of the spectrum, nonparametric methods assume no underlying model of the cell dynamics or of the interactions between cells. Cross-correlation and transfer entropy are two popular nonparametric approaches (see [111, 112] for a review and comparison of these methods). On the other end of the spectrum, parametric methods exist, which assume an underlying model for the cell dynamics as well as a model for the interaction between individual cells. For example, in [113] the authors considered the network connectivity problem in the state space framework whereby network connectivity was estimated using nonlinear Kalman filtering and a generic spiking neuron model. In between these two opposite ends of the spectrum, semiparametric methods exist as a mixture of both nonparametric and parametric approaches. For example, a semiparametric method may make no assumption about the cell dynamics, but it may assume an underlying model for the cell-to-cell interactions. In particular, the Cox connectivity method as explored in [114, 115] assumes that the interactions between neurons are modeled by a proportional hazard function.

The application of micro-scale connectivity analysis is limited in its scale and by the invasive nature of the recording technique it relies on. More applicable in the context of studying the human brain is analysis of connectivity on the meso- and large-scale levels. On this level, EEG and fMRI

have been used to determine functional connectivity at a larger spatial scale. Both methods allow for the noninvasive collection of signals related to neuronal activity; importantly, both offer specific spatial and temporal limitations in regards to their implementation [106]. EEG, which records electrophysiological neural activity through electrodes placed on the scalp, offers a high temporal resolution although its spatial resolution is poor. On the other hand fMRI, a neuroimaging technique capable of capturing hemodynamic activity which has been correlated with neural activity [116, 117], offers a much poorer temporal resolution but an improved spatial resolution. Regardless of their limitations, these techniques have been used to great effect in whole-brain functional connectivity analysis. Here the use of methods such as seed-based connectivity, independent component analysis, and graph theory has played a prominent role. In particular, the use of graph theory as a way of quantifying functional connectivity has gained increasing popularity [118, 119]. Mathematically, a graph consists of nodes which are linked by edges or connections. In the case of EEG the nodes are represented by the electrodes on the scalp and in the case of fMRI the nodes are represented by the blood-oxygen-level dependence, or BOLD. The connections within the network are then detected by linear or nonlinear correlations between the individual nodes. Specifically, these techniques have been used together to identify the resting-state functional connectivity of networks (see [120–122] for several reviews on the method).

Noninvasive brain stimulation techniques such as TMS and tDCS have been shown to significantly affect network functional connectivity. A large body of literature has examined the role of TMS in altering network connectivity (see [123] and the references within). Application of tDCS to the prefrontal cortex resulted in a significant change in the resting state functional connectivity [124]. Anodal tDCS improved [125] cognitive performance, paralleled by an increase in connectivity of the left inferior frontal gyrus, an area believed to be responsible for language functions. Application of tDCS to the left primary motor cortex was shown to alter the functional connectivity of cortico-striatal and thalamo-cortical circuits [126]. A promising direction in the field of noninvasive brain stimulation for therapeutic purposes is the use of tACS, as discussed in detail in the above section. There are only few studies that targeted functional connectivity with tACS. In-phase tACS of two fronto-parietal sites versus anti-phase tACS improved working memory [127], in agreement with previous EEG work. In a recent work by Helfrich et al. [95], the authors showed that tACS could be used to modulate interhemispheric brain connectivity.

While brain stimulation has been used with great success for the treatment of psychiatric and neurological disorders [128], the exact underlying mechanisms behind the success or failure of the stimulation for treatment remain mostly unclear [129]. Recent research has suggested that the pathology driving a range of neuropsychiatric diseases is network-based [116]. Abnormality in network connectivity has been implicated in particular for patients suffering from stroke [130–132], depression, and schizophrenia [133–135]. Given the potential effects of noninvasive brain stimulation on connectivity, and the prevailing belief that several neuropsychiatric diseases are driven by network abnormalities, it seems natural to address the question of therapeutic intervention not only from a brain stimulation framework but also from a network connectivity framework. In a paper by Fox et al. [128], the authors were able to map relationships between successful and unsuccessful stimulation sites across the treatment of 14 different neurological and psychiatric diseases. Their analysis revealed that sites where invasive deep brain stimulation (DBS) was effective for treatment were functionally connected to sites where TMS or tDCS were implemented effectively. These findings strongly suggest the importance of brain functional connectivity in stimulation procedure. While the integration of connectivity analysis and brain stimulation for therapeutic purposes is still in its very early stages, the initial results are encouraging [116].

The future role of functional connectivity in combination with brain stimulation is promising and thought-provoking at the same time. We must ask ourselves to what extent these functional connectivity mappings of the brain can use to guide our treatment of the various neuropsychiatric

diseases. In considering this, several future areas of inquiry come to mind. As mentioned earlier, tACS has been identified as a promising therapeutic treatment for disorders characterized by rhythmic cortical disturbance due to its frequency-specific modulation [95], and has been recently utilized for tremor suppression in Parkinson's patients [136]. As we think about the relationship between pathological brain states and abnormal network connectivity, this begs the question of whether or not functional connectivity can be modulated on a frequency basis using tACS. Understanding how network connectivity may or may not change as a function of tACS frequency may help guide our frequency-specific stimulation in treating these disorders.

Application of tES to Sleep Oscillations

A complete understanding of the effects of tES on human brain activity and behavior will require linking the findings of the microscopic domains (cellular recordings, computational models) to the discoveries from the macroscopic domains (human studies with EEG, MEG, and fMRI). Sleep is a promising frontier in terms of bringing these different levels of analysis together. More specifically, the slow oscillation (< 1 Hz) represents a strong candidate for such an undertaking for several reasons. First, we have an advanced understanding of the cellular and synaptic mechanisms underlying slow oscillations (SO). Second, weak electrical fields with frequencies mimicking the frequency of cortical SO have been applied in brain slices in vitro, in rats in vivo, and humans, and also studied in computational models. Third, SO can be artificially induced in vivo with anesthetic agents. We will discuss these three points in more detail.

Mechanisms of Slow Oscillations

In order to understand the effects of DC, oscillatory DC (rhythmic stimulation with a DC offset), or AC stimulation, we need to understand the mechanisms underlying different endogenous brain rhythms. SO are prevalent during slow-wave sleep and can be observed under anesthesia in vivo and in vitro, when the medium mimics in vivo conditions of the cerebrospinal fluid [10]. Mechanistically, SO have been very well studied and have been suggested to be generated and sustained in the neocortex [137–139] although thalamic circuits may also contribute [140]. This allows for investigating these rhythms in cortical slices [10]. The SO represents a low-frequency oscillation (~1 Hz) in the membrane potential of cortical neurons [141, 142] with the neurons alternating between so-called UP and DOWN states [139, 143]. The UP state is associated with the depolarized, i.e. active, phase of cortical neurons and most cortical neurons fire action potentials during this state [144]. During the DOWN state, neurons are silent and do not fire action potentials. These DOWN states can last for several hundreds of milliseconds and represent the prolonged hyperpolarizing phases of cortical neurons [144]. The synchronization of the slow oscillation of many neurons leads to the characteristic slow waves (< 4 Hz) seen in depth and surface EEG [142, 143, 145]. Of note, the prolonged silent or hyperpolarized phase, synchronized across many neurons, is unique to the slow oscillation during natural sleep and anesthesia [146, 147].

Internal dynamics need to be taken into account to understand which aspects of the slow oscillation can be modulated by weak electrical fields [148]. Specifically, for SO, the transition to the DOWN state is associated with activity-dependent reduction in synaptic strength that is maximal at the end of the UP state [148–151]. Thus, modulating the termination of UP states that are intrinsically determined may be difficult. In contrast, the transition from DOWN to UP state is driven by slight depolarizations that shorten the down-state [148]. This idea of differential susceptibility of different phases of the SO cycle has been supported by an in vitro study of ferret slices [18] and a computational model [152].

Modulating the Slow Oscillation with Weak Electric Fields

Modulation of SO using AC, DC, and oscillatory DC waveforms has gained significant interest in the last decade for the following reasons. First, SO has been implicated in coordinating other sleep rhythms (e.g. sleep spindles), providing a restorative function and promoting memory consolidation [155]. Thus, applying electrical stimulation to further boost SO will help to prove their causal role in the proposed processes [153]. Second, SO induces very pronounced endogenous electric fields and is therefore ideally suited to study the importance of those extracellular fields in entraining physiological neocortical network activity [18]. Thus, manipulation of SO with weak electrical stimulation has been probed in slices, in vivo in rats and ferrets, in humans, and in computational models.

Frohlich and McCormick [18] used the in vitro neocortical SO from acute slices of ferret visual cortex to demonstrate that externally applied weak electrical fields (physiological amplitudes that are found in vivo) and endogenous electric fields can directly modulate neuronal dynamics. Recorded oscillations are therefore not only a mere epiphenomenon of the underlying neuronal activity but rather actively modulate neuronal activity. The application of constant depolarizing currents (corresponding to anodal tDCS in humans) accelerated the slow oscillation frequency by shortening the duration of the down states (with no concurrent modulation of the up-state duration). Frohlich and McCormick [18] further highlighted the importance of ongoing network activity for weak electrical fields to have an effect. They applied sine-wave electrical fields that approximately matched the frequency of the spontaneous network oscillation and found that the SO became more periodic and entrained to the applied field. Importantly, weak external electrical fields preferentially enhanced the slow oscillation when their frequency was matching the intrinsic frequency. Along this line, Schmidt et al. [15] used an optogenetic approach to further confirm that weak alternating electric fields only enhanced endogenous oscillations when the stimulation frequencies were matched to the endogenous oscillations. In addition, ongoing network activity is necessary to amplify the effect of weak electrical fields by bringing the membrane voltage of neurons close to the threshold [18]. These important *in vitro* results hint at the fact that the amplification of network-wide weak perturbations by synaptic interaction may be an important aspect of the mechanism of tES.

Frohlich and McCormick [18] provided further support for this hypothesis with a computational network model showing that neuronal activity modulations by weak electric fields can be explained by small but simultaneous somatic depolarization of all neurons in the network. In a multi-scale computational model, Reato et al. [152] demonstrated that that intrinsic network dynamics of slow oscillatory activity can rectify mixed polarizations leading to an unidirectional increase of firing rates in case a monophasic alternating current is used (ON/OFF periods with ramp-up ramp down properties). Due to the cortical folding of the cortex, the applied electric fields show bi-directional polarities throughout the cortex, thus some regions might receive anodal stimulation while others experience cathodal stimulation. Thus, applying a constant DC would lead to both an increase and decrease of firing rates. In contrast when using monophasic alternating DC, the computational model predicts that entrainment occurs regardless of polarity (this applies for monophasic stimulation) via a modulation of the duration of the endogenous up- and down-state. Specifically, UP states will align with the ON phase of the anodal stimulation and the down-states with the ON phases of the cathodal stimulation and therefore only a rectified increase but no decrease in firing rate will be obtained [152]. However, this model only holds true if the OFF period of the alternating current field has a current strength of 0. Collectively, the findings from *in vitro* and computational studies emphasize that if and how tES affects neuronal activity depends on the intrinsic network activity (and on the applied field parameters).

To fully understand how tES affects SO in humans, we need a comprehensive physiological understanding of tES-induced effects on neuronal activity in the intact brain. This issue has been investigated by applying tES at frequencies of

cortical SO to multiple cortical regions in anesthetized and behaving rats [154], and anesthetized ferrets [45]. Ozen et al. [154] placed the stimulation electrodes on the surface of the skull or on the dura. Extra- and intracellular recordings showed an entrainment (phase-locking) of neurons to the externally applied sinusoidal electrical field. This effect was more pronounced if the network already exhibited intrinsic SO (anesthesia), further emphasizing that effectiveness of tES rests upon the internal network dynamics. Considering that rodents have lissencephalic brains and the human cortex exhibits pronounced folding which leads to uncontrolled and mixed field orientations, it is difficult to directly interpolate *in vivo* findings in rodents to humans. The ferret represents a model species with a gyrencephalic brain that helps overcome this limitation. Applying tACS at different slow oscillatory frequencies (0.5–3.5 Hz), Ali et al. [45] showed that multi-unit activity in anesthetized ferrets is entrained to the specific applied frequency. Whether this effect is restricted to a stimulated network that already exhibits intrinsic slow oscillatory activity remains unknown because only anesthetized ferrets were investigated.

SO have been proposed to play a key role in sleep-dependent memory consolidation [155]. Marshall et al. [153] were the first to demonstrate causality in this memory process by applying monophasic, slow-oscillatory tDCS (0.75 Hz, also compare [152]) during the first half hour of NREM sleep in healthy sleeping subjects. They found a significant increase in declarative memory along with increased slow-oscillatory and slow spindle activity (8–12 Hz) in stimulation-free EEG intervals (1 min intervals without stimulation in alternation with five 5 min stimulation periods). As mentioned in previous parts of this book chapter, the pronounced stimulation artifacts in the EEG prevent an accurate analysis of the EEG during tES application. Along this line, Reato et al. [152] predicted with their computational model (approximating the stimulation settings from [153]) that the rectified increase in firing rate leads to a faster downscaling of synaptic strength. Convincing evidence exists that SO are involved in downscaling synaptic connections to ensure the synaptic homeostasis of the brain [156] with high firing rates favoring synaptic depression [157, 158]. In addition, this downscaling process might lead to an increased synaptic signal-to-noise ratio that could explain the beneficial effect of sleep on memory consolidation [156, 159, 160]. Assuming that stimulation accelerates synaptic downscaling by increasing the firing rate, the rate of downscaling should be decelerated after the stimulation has stopped [152]. Their assumption was confirmed in the human dataset recorded by Marshall et al. [153]. Marshall et al. were further able to replicate the behavioral and EEG findings in rats [161, 162]. In addition, some studies were able to replicate, at least partially, the findings from Marshall et al. [155] in humans [163–166]. However, other groups found contradicting results on EEG and memory consolidation when applying monophasic slow-oscillatory tDCS [167, 168]. One of the differences between the studies was the waveform of the used tDCS pulse, e.g. Marshall et al. [155] were using ramp-up, ramp-down shaped pulses, and Sahlem et al. [167] were applying square-waves. Whether and how the tDCS pulse shape is critical for the effectiveness of oscillatory tDCS needs to be further investigated with the interdisciplinary toolkit discussed in the previous sections of this chapter. In addition, whether pure tACS (non-monophasic) in the slow-oscillatory frequency range has a similar effect on human brain network activity has so far not been studied and remains to be determined.

Anesthesia as a Tool to Study Slow Oscillations

Certain anesthetic agents (e.g. ketamine-xylazine, urethane, propofol) allow for the induction of SO that resemble the SO of natural sleep [169]. The main features of the slow oscillation (high amplitude waves generated by an alteration of UP and DOWN states) found during sleep can be mimicked by anesthesia [146, 147, 170]. Thus, anesthesia is used to model SO. In contrast to humans, it is very difficult to predict and schedule natural sleep, and more specifically slow wave sleep, in

rodents or ferrets for studying tES effect on SO. Thus, anesthesia was used to approximate slow wave sleep *in vivo* [45, 154] for testing the effects of tES on slow brain rhythms. Both studies, discussed in more details above, demonstrated enhancement of oscillatory activity in response to approximately frequency-matched stimulation. Thus, anesthesia can indeed serve as a model system to understand the neurophysiological effects of tES. Furthermore, the depth of sleep-like states and therefore the level of synchronization of SO can more easily be modulated by different anesthetic doses. Consequently, the role of the internal network state in the effectiveness of tES to enhance SO can more specifically be investigated. Nevertheless, future studies should further investigate effects of tES on SO in naturally sleeping animals because some features of the SO differ between anesthesia and natural slow-wave sleep, e.g. the rhythmicity and synchrony across the cortex [146, 147, 170].

Outlook

In this book chapter, we have attempted to pull together results from a vast set of different neuroscience methods to delineate how tES engages network targets in the brain. We have first introduced basic results on changes in excitability of individual neurons, followed by a discussion of modulation of network dynamics *in vitro* and *in vivo*. We then considered computational models as a complementary strategy to investigate the spatial targeting (forward models) and the targeting of neuronal dynamics (neural models). Next, we reviewed studies in humans that used noninvasive monitoring of brain activity (EEG, MEG, and fMRI) to demonstrate targeting of brain network dynamics by tES. In particular, we focused on the underlying dynamic principles that guide the interaction between tES and endogenous network dynamics. We then provide two unique perspectives that we believe will be central to furthering our understanding of targeting brain networks with tES. First, we look at functional connectivity and discuss how such analysis strategies that focus on dynamic interaction between activities at different locations within the brain will be vital for understanding global effects of brain stimulation. Second, we consider low-frequency rhythms during sleep and anesthesia as a case study for how the different methods discussed in earlier sections of the chapter can come together not only for understanding the mechanisms of tES and but also for the design of effective tES strategies to modulate memory consolidation. We hope that this review provides an integrated overview of today's research on how tES targets network dynamics and inspires a new area of rational design of brain stimulation to target physiological and pathological network states.

Given the noninvasive and low-cost nature of tES combined with the promising behavioral results, it is imperative to understand the underlying mechanisms of tES. The various levels of investigation described in this chapter, from microscopic to macroscopic and from in silico to in vivo domains, are essential to arrive at a holistic understanding of the mechanisms of tES. Once this is achieved, rational design of tES paradigms to target specific network dynamics will become the norm. Ultimately, this will help to usher in a new area of neuroscience in which tES serves as a broadly used, effective research tool for probing and understanding functional networks of the human brain as well as a transformative therapeutic tool for treating disorders of brain networks.

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Cerebellar and Spinal tDCS

12

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Abstract

In the last 5–7 years, cerebellar and spinal DC stimulation received growing attention by experimental and clinical neuroscientists. Although the clinical efficacy of cerebellar and spinal tDCS awaits confirmation in large, clinical, randomized controlled studies, there are now several important key points underlying their mechanisms of action that should be discussed. Briefly, delivering DC currents for few minutes over the cerebellum or spinal cord can induce persistent, polarity-dependent excitability changes persisting several minutes after the current offset. Cerebellar DC stimulation can elicit neurophysiological and behavioral changes both in the motor functions and in cognitive-behavioral domain. Spinal cord DC stimulation elicits neurophysiological and behavioral changes related to spinal cord functions, but, interestingly, also changes in the brain functions that may arise from the activation of tonic afferent systems to the brain. Future studies should endeavor to assess whether experimental data translate into benefits in real life, lengthen behavioral benefits, investigate how changing stimulation variables influences tDCS-induced effects, determine possible interactions with other treatments, and improve patients' selection.

Keywords

Cerebellar tDCS • Transcutaneous spinal DC • tsDCS • Cerebellum • Spinal cord

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Cerebellar Transcranial Direct Current Stimulation: Technique's Overview and Clinical Applications

The cerebellum has been considered for a long time to play a role in motor function (in the control of balance and intentional voluntary movement). However, neuroimaging [1], clinical/lesional [2], and neuromodulation [3] studies have shown that the cerebellum also plays a key role in many motor, cognitive, and emotional processes. In addition, studies have also shown that the cerebellum is implicated in many psychiatric disorders including attention-deficit hyperactivity disorder, autism spectrum disorders, schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders [4].

The cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways allow the cerebellum to affect information processing in cortical areas responsible for cognitive and emotional processes [4]. These intricate connections between the cerebellum and other structures can explain why cerebellar damage can lead to various psychiatric disorders.

A recent possible way of gathering insights into the functional role of the human cerebellum in psychiatric and neurological disorders may be provided by transcranial direct current stimulation (tDCS) [5].

The need for a noninvasive tool to influence cerebellar function in normal and pathological conditions led researchers to develop cerebellar tDCS [3]. Cerebellar tDCS depends on the principle that weak direct currents delivered at around 2 mA for minutes over the cerebellum through surface electrodes induce prolonged changes in cerebellar function [6]. Usually, the stimulating electrode is placed over one or two cerebellar hemispheres and the other (return electrode) over the buccinator muscle, over the scalp or the right shoulders [6].

Though current evidence leaves open possible (transynaptic or antidromic) changes in other brain or brainstem structures, the physiological effects elicited by cerebellar tDCS arise mainly from functional changes in the cerebellum itself. Cerebellar tDCS could interfere with membrane polarization in Purkinje cells and in other neurons, fibers (mossy fibers and climbing fibers), and glial cells. DC stimulation applied to the cerebellar cortex in the decerebrated cat influences Purkinje and granular cell activity in a polarity-specific manner; while anodal DC flowing in the dendrite–axonal direction increases tonic neuronal activity, cathodal DC decreases it [7].

Cerebellar tDCS modulates several cerebellar skills in humans including motor control, learning, and emotional processing [3]. Several studies suggest that tDCS may be a valuable tool for the treatment of neuropsychiatric conditions such as depression, schizophrenia, addiction, and chronic pain [8, 9]. Research has also demonstrated cognitive improvement in some patients undergoing tDCS [10].

For instance, tDCS treatments for depression have used bifrontal montages with anodal (excitatory) stimulation targeting the left dorsolateral prefrontal cortex (DLPFC) [11]. There is limited research examining the effects of alternative electrode montages.

The first study aimed to examine the feasibility, tolerability, safety, and efficacy of two alternative electrode montages were conducted by Ho and colleagues [12]. They studied two different montages, fronto-occipital (F-O) and fronto-cerebellar (F-C), to target respectively midline brain structures and the cerebellum in 14 depressed participants. For F-O montage, the anode electrode was placed over the left supra orbital area and the cathode over the occipital area, for F-C montage the anode electrode was placed over the cerebellum and the cathode over the occipital area. The intensity of stimulation was set at 2 mA and delivered for 20 min/die for 3 consecutive weeks. Mood and neuropsychological functions (memory and frontal lobe functions) were assessed at baseline and after 4 weeks of tDCS. Using a computational modeling based on one healthy participant, they demonstrated that the novel montages resulted in greater activation in the anterior cingulated cortices and cerebellum than the bifrontal montage. They also showed that after 4 weeks of tDCS, overall mood improvement was observed under the F-O and F-C conditions and no significant

neuropsychological changes were found. Results of this open-label pilot study found both montages safe and feasible. The small sample size and the absence of a sham control group are major limitations of the study.

Successively, Minichino and colleagues [13] aimed to improve sleep quality of 25 euthymic outpatients with a diagnosis of bipolar disorder (BD) type I or II through the administration of prefronto-cerebellar tDCS. They placed the cathode electrode over the right cerebellar cortex and anode over the left dorsolateral prefrontal cortex (DLPFC); the intensity of stimulation was set at 2 mA and delivered for 20 min/die for 3 consecutive weeks. The sleep quality was assessed at baseline and after the tDCS treatment using Pittsburgh Sleep Quality Index (PSQI). They demonstrated that PSQI total score and all PSQI subdomains significantly improved after treatment.

Furthermore, Minichino and colleagues [14] using the same previous protocols [13] studied the effects of tDCS applied to cerebellar and prefrontal cortices on neuropsychological functioning of 25 euthymic patients with BD. All participants were assessed through the Rey Complex Figure Test delay and copy and the Neurological Examination Scale at baseline and after therapy with tDCS. The results of the present research suggest that concomitant prefrontal-excitatory and cerebellar-inhibitory tDCS might have a positive effect on visuospatial memory and executive functioning in euthymic BD patients, quantified through neuropsychological and neurological measures. The small sample size and the absence of a sham control group are major limitations of these two studies.

More recently, Bation and colleagues [15] in an open-label pilot study assessed the efficacy and the safety of orbitofrontal cortex (OFC) cathodal tDCS coupled with cerebellum anodal-tDCS in eight patients with treatment-resistant obsessive–compulsive disorder (OCD). Cathode electrode was placed over the left OFC and the anode over the right cerebellum for 10 sessions (twice a day) of 2 mA. Patients were assessed four times, once before tDCS and three times after: immediately after the ten sessions of tDCS, 1 and 3 months later. The effect of tDCS on the severity of obsessive and compulsive symptoms was assessed using the Yale–Brown Obsessive and Compulsive Scale score (Y-BOCS) and a self-reporting OCD Visual Analog Scale (OCD-VAS) given to the participant. The effect of tDCS on the severity of depressive symptoms was assessed using the Montgomery and Asberg Depression Rating Scale (MADRS).

They reported a significant 26.4 % decrease of Y-BOCS score, and the beneficial effect lasted during the 3-month follow-up. No effect of tDCS was observed on depressive symptoms. This open-label pilot study demonstrates for the first time the clinical interest of orbitofrontal and cerebellar tDCS in combination with SSRI in patients with treatment-resistant OCD. These promising results should be confirmed in large placebo-controlled trials.

The few cerebellar tDCS studies in psychiatric patients we reviewed here taken together, despite their heterogeneities, show that cerebellar tDCS is safe, feasible, and might improve psychiatric symptoms. Cerebellar tDCS probably could influence psychiatric symptoms through highly complex mechanisms, it could induce neuroplasticity throughout a distributed cortico-subcortical network. Premised that the clinical efficacy of cerebellar tDCS in patients with psychiatric disorders remains to be ultimately established by large, controlled clinical studies, future research work should systematically assess the clinical patient features predicting the optimal response: type and site of stimulation, time since the pathology occurred, age, gender, concurrent drug treatments, and comorbidities can all influence the tDCS effect.

Future research directions should include studies to clarify whether cerebellar tDCS could be combined with behavioral therapy, and whether these noninvasive techniques could be used to stimulate multiple brain sites. A study in a larger homogeneous population is needed to further investigate the possible therapeutic benefit of cerebellar tDCS.

Transcutaneous Spinal Direct Current Stimulation: Technique's Overview

As for the cerebellum, a new and fascinating target for noninvasive current stimulation has emerged in the recent years. Spinal cord is a critical, yet less understood, final pathway for motor control, but also acts a "highway" for modifying brain and brainstem function. Transcutaneous spinal direct current stimulation (tsDCS) is a noninvasive technique for modulating spinal cord activity in animals and humans [16–20]. DC stimulation intensity ranges from 1.5 to 2.5 mA, with effects lasting for minutes to hours [21]. After the first reports [19], this technique has come into increasingly widespread use, especially for modulating conduction along lemniscal pathways and nociceptive spinal system [22–24]. The device is the same used for transcranial direct current stimulation, but no conclusive remark has been reached so far regarding the position of electrodes over the spinal cord, ultimately influencing current density and distribution in biological tissues [25]. This remains a critical issue, together with inter-individual variability due to genetic polymorphisms, thus modifying neurophysiological and psychophysical response in an unpredictable way [26].

For lumbar spinal cord stimulation, the active electrode is commonly placed over the spinous process of the tenth thoracic vertebra and the reference above the right shoulder [19, 20], while for cervical modulation the active electrode is positioned on the seventh cervical vertebra and the reference either on the right shoulder [27] or on the anterior neck [28]. By analogy with the tDCS, placing the return electrode over the shoulder is the preferred montage, as it reduces interference between anodal and cathodal effects.

Mechanisms of Action

Putative Mechanisms of Action at a Spinal Level

Recent modeling studies have proved that, despite some inter-individual differences due to age and anatomical variability, the electrical field induced by tsDCS is longitudinally directed along all the vertebral column, especially when the return electrode is placed over the right arm or over Cz [25], confirming that both ventral (motor) and dorsal (sensitive) spinal tracts undergo identical electric field strength. Different from transcranial direct current stimulation (tDCS), anodal tsDCS has probably an overall inhibitory effect on spinal cord activity [19, 20, 28, 29]. Particularly, while anodal polarization could act directly on corticospinal descending pathways, without changes in postsynaptic motor neuronal excitability, the cathodal one seems to interfere with interneuronal networks [17, 27, 30]. By analogy with the effects of direct currents on peripheral nerves, it has been hypostasized that anodal tsDCS leads to a hyperpolarizing "anodal block" [31]. Conversely, there is an extensive debate whether cathodal tsDCS has or not polarity-specific effects on segmental activity [28]. Overall, as suggested for tDCS [32], rather than be simply specular, anodal and cathodal tsDCS may have quite similar effects on different targets. That widens the field of therapeutic applications, raising at the same time the possibility of a combined use of transcranial and spinal polarization in a number of clinical conditions, as proved in chronic stroke [33]. From a practical point of view, the same DC device could be used to simultaneously stimulate the cerebellum spinal cord and cerebral cortex, thus enhancing the tDCS after-effects.

Putative Mechanisms of Action at a Supra-Spinal Level

Many studies have proved possible supra-spinal mechanisms of action of spinal direct current stimulation, both in animal [34] and human models [30, 35], possibly synchronizing the activity among different cortical areas and inducing neuroplasticity [36]. That is not surprising also considering the literature about invasive current stimulation (SCS), suggesting a possible modulation of glutamatergic cortical interneurons in patients with neuropathic pain [37]. Moreover, it is known that alternating currents epidurally delivered to the posterior columns of the spinal

cord are able to modify sensory processing at thalamic relays and cortical levels [38]. Recently, studies from our laboratories have explored two main no-spinal targets, the (a) GABA(a) cortical interneurons, mediating the so-called short intracortical inhibition (SICI) [30], and the (b) interhemispheric processing [35]. Other groups did not confirm data about GABA(a); nonetheless, they studied a different anatomical region, with different recording montage and stimulation intensity [39].

Perspective on Clinical Studies

Different from cerebellar tDCS, only few studies have been published to date about the application of tsDCS in human disorders and little is known about its spinal and long-range (supra-spinal) effects both in health and disease. Although elusive, the possibility to interfere with cognitive processes by using spinal polarization is intriguing. First studies showed that tsDCS modulates somatosensory potentials evoked by stimulation of posterior tibial nerve, the post-activation H-reflex dynamics [23, 24] and the flexion reflex in the human lower limb [40]. In this view, Truini and colleagues [29] have proved that anodal spinal polarization leads to a significant decrease of the amplitudes of laser-evoked potentials (LEPs) derived from lower limb, thus modulating both the sensory-discriminative and affective-emotional dimension of pain. More recently, tsDCS has been successfully used both for interfering with maladaptive phenomena taking place in spinal cord injured patients [22] and improving symptoms in patients with restless legs syndrome [41]. Mechanisms of action of tsDCS have only partly been elucidated, but likely rely both on local (spinal) and supra-spinal effects. The later aspect is particularly attracting; in spinal cord injury (SCI) tsDCS may interfere with the maladaptive reorganization of cortical sensorimotor maps, thus improving motor output and preventing central pain sensitization [36]. That implies that tsDCS could be useful also as an early rehabilitation strategy in patients with acute brain lesions, such as stroke, when other NIBS tools are not indicated due to safety concerns.

Theoretically, spinal DC may be also used to improve the effects of tDCS in a number of neuropsychiatric disorders likely characterized by impaired interhemispheric balance, ranging from schizophrenia and obsessive–compulsive disorder [42, 43] to major depression [44].

Putative ways to nonspinal targets are to date only speculative, but evidence in animals showed that supra-spinal effects of invasive spinal polarization could be induced by the modulation of indirect spinal projections to noradrenergic locus coeruleus (LC) neurons, which has widespread projections to the neocortical brain [45–47]. Alternatively, a critical role in brain plasticity after a SCI seems to be played by a reorganization of the serotonergic ascending pathways [48–51]; serotonergic system interferes also with bottom-up and top-down modulation of motor responses, especially through parallel and partially overlapping projections arising from the median and dorsal raphe nuclei [52–54]. As the serotonergic projections seem to participate in the regulation of different functional systems (motor, somatosensory, limbic), tsDCS may ultimately modulate this connectivity.

tsDCS could be of particular interest as a noninvasive, safe promising therapeutic tool in managing a number of human diseases. This technique could be useful also as a rehabilitation strategy in patients with brain lesions or even in the treatment of neurological disorders characterized by abnormal interhemispheric processing. In addition, the possibility to modulate supraspinal and intracortical processing of motor inputs makes tsDCS a useful approach, complementary to either SCS or noninvasive brain stimulation techniques, to modify spinal drive through nonspinal mechanisms.

Why Should Psychiatrists Be Interested in Cerebellar/Spinal DC Stimulation?

Despite the uncertainties, cerebellar and spinal tDCS for its simplicity, low cost, and possibility of online use has a great potential in the field of restorative psychiatry symptoms. This potential must however be developed through strictly

controlled and methodologically sound experimental and clinical research work [55].

Delivering DC currents for few minutes over the cerebellum or spinal cord can induce persistent, polarity-dependent excitability changes persisting several minutes after the current offset. Cerebellar DC stimulation can elicit neurophysiological and behavioral changes both in the motor functions and in cognitive-behavioral domain. Spinal cord DC stimulation elicits neurophysiological and behavioral changes related to spinal cord functions, but, interestingly, also changes in the brain functions that may arise from the activation of tonic afferent systems to the brain.

Future studies should endeavor to assess whether experimental data translate into benefits in real life, lengthen behavioral benefits, investigate how changing stimulation variables influences tDCS-induced effects, determine possible interactions with other treatments and improve patients' selection.

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Part II

Applications of tDCS in Neuropsychiatric Disorders

Mood Disorders

13

André Brunoni and Colleen Loo

Abstract

Major depressive disorder (MDD) is an incapacitating condition associated with significant personal, social, and economic impairment. Nearly 30 % of patients present drug refractoriness, reinforcing the need to develop novel therapeutic strategies for MDD. TDCS might be an alternative for these patients considering its tolerability, portability and ease of use. In this chapter, we reviewed putative tDCS antidepressant mechanisms as well as clinical evidence based on open and controlled studies and meta-analyses. Present evidence indicates that tDCS may be an effective treatment strategy for MDD. Finally, there are no studies specifically examining the efficacy of tDCS in bipolar depression and mania, which are urgently needed in order to address tDCS effectiveness for bipolar disorder.

Keywords

Major depressive disorder • Bipolar disorder • Depression • Transcranial direct current stimulation • Noninvasive brain stimulation • Clinical trial • Meta-analysis • Systematic review

Major Depressive Disorder

Introduction

Major depressive disorder (MDD) is an incapacitating condition associated with significant personal, social, and economic impairment. Patients with MDD present a "double burden," characterized by a lower quality of life associated with a higher prevalence of medical comorbidities [1]. The main symptoms of MDD include persistent low mood, anhedonia (i.e., diminished pleasure

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in previous significant activities), impairment in sleep, psychomotor retardation, weight changes, and negative thoughts that range from pessimism to guilt and suicidal ideation. Moreover, although only the most severe spectrum of depression is associated with suicide, its chronic, incapacitating symptoms make depression one of the most incapacitating conditions worldwide—in fact, MDD is projected to be the second most disabling condition by 2020 [2].

In addition, depression is a chronic, recurrent disorder, as nearly 80 % of patients relapse after the treatment of an episode [3]. Finally, about one-third of patients have treatment-resistant depression (TRD)—i.e., the failure to achieve adequate response of symptoms after adequate antidepressant treatment trials [4, 5]. In fact, the high prevalence of failure to respond to antidepressants is an important concern when managing major depression. In this context, the National Institute of Mental Health-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial confirmed that cumulative response and remission rates after two antidepressant treatments are 63 % and 56 %, respectively [6, 7]. After three failed treatments, response and remission rates decay to 16 and 13 % [6]. After four trials of treatment, including antidepressant medications and cognitive behavioral therapy, nearly 30 % of patients fail to achieve remission, i.e., have ongoing depressive symptoms despite appropriate psychological and pharmacological treatment [6]. These data reinforce the need to develop novel therapeutic strategies for MDD in order to offer alternatives to patients who fail to respond to antidepressants or who have intolerance or contraindication to these drugs.

The dorsolateral prefrontal cortex (DLPFC) is as an important site of dysfunction in depression mainly due to left hypo-function and right hyperfunction [8]. Neuroimaging studies also show structural alterations in fronto-cingulo-striatal (FCS) circuits—for instance, a recent meta-analysis found volumetric reductions in these circuits in depressed vs. healthy volunteers [9]. Current treatment approaches provide further support for abnormalities in discrete neural networks in MDD. For instance, volumetric analysis of MDD patients taking sertraline revealed an increment in gray matter volume over the left DLPFC [10], while high-frequency rTMS increased fractional anisotropy in the left middle frontal gyrus [11].

The imbalance between cortical and subcortical brain activities might also be involved in MDD pathophysiology. Response to fluoxetine was associated with a marked reduction in local cerebral blood flow as well as changes in downstream limbic and cortical sites as measured with positron emission tomography [8]. The effects of chronic deep brain stimulation for patients with refractory depression have also been investigated—for instance, the DBS protocol targeting the subgenual cingulate region, which is known to be metabolically overactive in treatment-resistant depression, showed clinically relevant outcomes [12].

Other brain areas, such as the amygdala and the hippocampus, have a lower volume in depressed patients when compared to controls [13, 14]. In addition, functional studies suggest a high level of activity in the ventro-medial prefrontal cortex (vmPFC) and a low level of activity in the DLPFC. In addition, patients with major depression have lower excitability in the left motor cortex [15], in the left hemisphere [16] and a higher brain activity in the right cortex [17]. These findings suggest a “differential activity” in certain brain areas in patients with MDD, which may explain some symptoms of depression: for instance, psychomotor retardation and executive function impairment (related to the DLPFC), feelings of guilt and hopelessness (related to hippocampus and amygdala dysfunction), anhedonia (related to nucleus accumbens) and negative emotional judgment (related to left-right imbalance) [18–20]. In fact, two major pathways can be determined here: the cognitive-executive pathway, in which a hypoactive DLPFC fails to regulate areas related to executive functioning and the affective-somatic pathway, in which a hyperactive vmPFC modulates erratically areas related to feelings of negative affect and self-awareness [21]. The rationale in using different brain stimulation therapies, including tDCS, is based on their mechanisms of inhibiting or enhancing activity of these pathways.

Technical Aspects of Using tDCS in Major Depression

Based on the rationale that the left DLPFC is a key brain area involved in MDD pathophysiology and that its stimulation is associated with depression improvement [22], the main target for anodal tDCS has been the left (hypoactive) DLPFC (F3 on the 10–20 EEG system)—in fact, virtually all tDCS studies in MDD placed the anode over this region (see the section "Clinical Evidence"). The cathode position varies among studies—most of them used the cathode over the right supraorbital area that is considered neutral in terms of the influence of cathodal stimulation effects on the treatment. Other studies have chosen to place the cathode over the right DLPFC [23, 24] or lateral frontal area [25] according to the theory of prefrontal asymmetry that this brain area is hyperactive in MDD and therefore applying the inhibitory effects of cathodal stimulation over this area would help to improve depressive symptoms. Alternative tDCS montages have also been tested [26], aiming to stimulate other deeper, key brain areas in MDD, such as the anterior cingulate cortex, nucleus accumbens, and basal ganglia (fronto-extracephalic, fronto-occipital, and bitemporal montages), and the cerebellum (fronto-cerebellar montage) [27, 28].

The "dose" of tDCS might also influence its efficacy. In fact, there is no standard definition of how to measure the "dose" of tDCS delivered in a clinical study: factors that determine the amount of current injected are the size and position of electrodes, the electric current intensity, the duration of the tDCS session and the total number of sessions. Therefore, the tDCS "dose" can be expressed in terms of current intensity (usually 1–2 mA), current density (intensity divided by the square area of the electrodes, usually from 0.28 to 0.8 A/m^2) and charge density delivered per session (intensity multiplied by session duration, usually from 336 to 1440 C/m^2). In a recent individual patient data meta-analysis, tDCS dose was associated with greater depression improvement across six randomized clinical trials [29]. The interval between sessions (e.g., every other day, once daily, twice daily) might also influence the clinical effects. For instance, daily tDCS (compared to every other day) led to greater increases in cortical excitability over a 5-day period [30].

Finally, tDCS effects in depression seem to be influenced by other concomitant interventions. Regarding pharmacotherapy, tDCS had greater antidepressant effects when started simultaneously with sertraline [24], and showed lower antidepressant effects in patients on concurrent benzodiazepine medication [24, 31]. TDCS combined simultaneously with cognitive control training presented superior efficacy in one randomized clinical trial [32] but not in other [33].

Mechanisms of Action

Although the antidepressant mechanisms of action are still elusive, it is supposed that tDCS acts by increasing cortical excitability and neuroplasticity of the DLPFC, hypoactive in depression, and, by restoring this brain area to normal activity, tDCS ameliorates depressive symptoms. For example, tDCS has been shown to improve affective and cognitive processing in depressed patients [34–36]—since the DLPFC is involved in such processing in depression, these findings suggest that tDCS modulates DLPFC activity. There is also evidence that tDCS increases neuroplasticity. For example, depressed patients receiving frontal tDCS showed increased neuroplasticity, tested over the adjacent motor cortical area (which also received some stimulation, given the diffuse nature of tDCS) [37];. Nonetheless, neuroimaging or quantitative EEG studies are still needed to identify regional changes in functional activation, which correlate with the antidepressant effects of tDCS.

One study found that the serotonin transporter genetic polymorphism (SLC6A4), which codifies the pre-synaptic serotonin reuptake transporter (SERT), predicts antidepressant tDCS efficacy, with long/long homozygotes displaying a larger improvement comparing active vs. sham tDCS, but not short-allele carriers [38]. In fact, antidepressant effects of tDCS seem to involve the serotonergic system, as shown in the pharmacological

study of Nitsche et al. [39], which found that the excitability-enhancing effects of anodal tDCS were boosted with citalopram whereas the excitability-decreasing cathodal effects were reversed—leading to, in fact, excitability-enhancing effects. This proof of concept was subsequently demonstrated in the SELECT clinical trial, which showed the antidepressant effects of tDCS were enhanced by sertraline [24]. Nitsche and colleagues suggested that citalopram administration might activate serotonin-sensitive potassium channels that decrease outward potassium current, therefore extending calcium influx into the synaptic cleft [40]. The net result would be, ultimately, increased LTP after anodal tDCS and conversion of inhibition into facilitation for cathodal tDCS. Sertraline is also involved in cortical/amygdala regulation. Acute and chronic stress, which may form the pathophysiological basis of at least some forms of depression [41], are associated with cortical hypoactivity and subcortical hyperactivity [42]—i.e., a "bottom-up" pattern that is more prone to occur in *s*-carriers, as such patients have increased amygdala response to anxiogenic stimuli [43]. Possibly, such modulation is implicated in tDCS antidepressant effects, which would be impaired in individuals with an overactive amygdala (such as *s*-carriers).

Dopamine might also be involved in the antidepressant mechanisms of tDCS, considering that the use of dopamine agonists and antagonists modify tDCS-induced cortical excitability [44, 45]. Moreover, it was shown that genetic polymorphisms of catechol-*o*-methyltransferase (COMT, an enzyme that degrades cathecolamines such as dopamine) influence tDCS effects on executive functions and response inhibition in healthy volunteers [46, 47]. However, COMT polymorphisms have not been evaluated in depressed patients receiving tDCS.

Conversely, there is no evidence to date that tDCS induces any specific changes in peripheral biomarkers that have been associated to MDD pathophysiology. For instance, decreased heart rate variability (HRV) is observed in depression, which reflects autonomic dysfunction (decreased vagal tone) [48], although HRV levels do not change after tDCS treatment [49]. Moreover, decreased brain-derived neurotrophic factor (BDNF) levels have been found in depression, suggesting that depression is associated with decreased neuroplasticity (the "neurotrophin hypothesis of depression"), and BDNF levels increase after treatment with pharmacotherapy [50], but not after tDCS—this was also observed for non-BDNF neurotrophins [51, 52]. Finally, the "inflammatory hypothesis of depression" postulates that MDD incorporates an increased production of pro-inflammatory cytokines, which leads to an over-activation of the hypothalamic-pituitary-adrenal axis as well as monoaminergic disturbances and inflammatory cytokines. Nonetheless, tDCS does not specifically decrease cytokine levels after treatment [53]. One possibility for these negative findings is that the effects of tDCS are restricted to the brain, exerting no or minimal influence on peripheral activity. Nonetheless, to date there is no peripheral biomarker associated with tDCS efficacy in MDD.

Clinical Evidence

It should be acknowledged that the investigation on the effects of tDCS as an antidepressant therapy dates from the 1960s. However, the lack of methodological rigor on some parameters such as the target area, current strength, electrode size, reference electrode position, number of sessions, and duration of each session might explain some contradictory findings between the studies. For instance, Arfai et al. [54] did not find significant effects on depression in a randomized, double-blinded, sham controlled study where tDCS ($i = 0.25$ mA) was applied on frontal cortex with the reference on the thigh; on the other hand, Redfearn et al. [55], in an open pilot study, found a reduction of depressive symptoms after tDCS ($i = 0.02$–0.25 mA) over frontal areas with the reference electrode on the knee (for extended reviews see [56–58). This scenario only began to change in the last 15 years with new tDCS protocols in which the parameters of stimulation were better defined and further developed. Also, the emergence of other techniques of brain stimulation, such as TMS, allowed a better understanding of

Table 13.1 Summary of open-label tDCS trials in major depression

Author	Sample (*n*)	Anode	Cathode	Intensity (A/m^2)	Number of sessions	Depression improvement (%)
Rigonatti et al. [59]	42	F3	RSO	0.57	10 (1×/day)	36.20
Ferrucci et al. [60]	14	F3	F4	0.57	10 (2×/day)	32.1
Ferrucci et al. [61]	32	F3	F4	0.57	10 (2×/day)	27.70
Brunoni et al. [62]	31	F3	F4	0.57	10 (2×/day)	45.2
Martin et al. [27]	11	F3	R arm	0.57	20 (1×/day)	42.80
Dell'Osso et al. [63]	23	F3	F4	0.57	10 (2×/day)	31.30
Brunoni et al. [31]	82	F3	F4	0.57	10 (2×/day)	18
Ho et al. [28]	14	F3	Occ/Cer	0.57	20 (1×/day)	44/16

RSO right supraorbital area, *F4* right dorsolateral prefrontal cortex, *R arm* right arm, *Occ/cer* occipital/cerebellar

the effects of tDCS effects on cortical excitability. In the past decade, some open-label and randomized, double-blinded, sham-controlled clinical trials on the effects of tDCS on depression have been conducted, as we discuss below.

Open-Label Studies

Rigonatti et al. [59] compared the clinical effects of active prefrontal tDCS vs. a 6-week treatment protocol with 20 mg/day fluoxetine, finding that the effects of both therapies were similar. Ferrucci and colleagues [60] used tDCS in 14 patients with severe depression using 2 mA per day, twice a day for 5 consecutive days, demonstrating an improvement of about 30 % on depressive symptoms. In another study, Ferrucci et al. [61] evaluated 32 patients, finding that tDCS improvement was greater in severe depression (50 %) than those in mild/moderate depression (10 %). Brunoni et al. [62] used anodal tDCS over the left DLPFC in 31 patients (14 with bipolar and 17 with unipolar depression). Depressive symptoms in both study groups improved immediately after the fifth session. The beneficial effect persisted after 1 week and 1 month. Another recent open study [63] demonstrated the efficacy of tDCS in 23 patients with refractory depression, with a mean reduction in symptoms of 25 %. Martin et al. [27] performed tDCS sessions consecutively for 20 days, with 2 mA for 20 min, in 11 patients with depression. In this open study, which placed the cathode on the right deltoid muscle, there was also a significant reduction in symptoms of about 44 %.

Brunoni et al. [64] in a open-label study of 82 patients with unipolar and bipolar depression, found that 5 days of twice-daily tDCS significantly improved depression symptoms. This study also showed that the effects of tDCS are enhanced when associated with antidepressants and decreased with benzodiazepines. Finally, a pilot study tested two novel tDCS montages, recruiting seven patients to receive fronto-occipital (F-O) and seven patients to receive fronto-cerebellar (F-C) tDCS. All patients received 20 sessions of tDCS (2 mA, 20 min per session). Patients receiving F-O tDCS presented a significant reduction of 44 % of depressive symptoms; whereas patients receiving F-C tDCS had a nonsignificant reduction of symptoms. The study suggested that F-O montage is a promising antidepressant treatment [28] (Table 13.1).

Randomized, Sham-Controlled Trials

Fregni et al. [65], in the first modern, sham-controlled, randomized clinical trial, found a significant decrease in the Hamilton Depression Rating Scale and Beck Depression Inventory after 5 days of active stimulation with 1 mA for 20 min once daily in ten patients, with a mean reduction in depression scores of 60–70 % for active tDCS group relative to baseline. Similar results were demonstrated in a further study in antidepressant-free patients with recurrent major depressive episodes after 5 days of active tDCS stimulation [66] with 18 patients. Boggio et al. [67] recruited 40 patients with moderate to severe

depression, evaluating depression improvement immediately after 10 consecutive weekdays of stimulation and 30 days later. Only prefrontal tDCS reduced depressive symptoms significantly, with effects sustained at 30-day follow-up.

After these positive results, three other studies reported negative findings. Loo et al. [68] recruited 40 patients to receive active vs. sham tDCS and did not find significant differences between these groups. However, treatment was provided for only five treatment sessions, 3 days per week (same parameters as the initial Fregni et al. [65] study). This study also did not exclude patients with personality disorders. Palm et al. [69] recruited 22 patients with depression and randomized them to receive 1 mA stimulation, 2 mA stimulation or sham tDCS in a crossover design. Active and placebo tDCS was applied for 2 weeks, but no differences in depression improvement were found. Finally, Blumberger et al. [23] did not find significant differences between active vs. sham tDCS in a tertiary sample of 24 highly refractory patients. All these studies acknowledged methodological limitations (notably small sample sizes) that could have undermined the efficacy of tDCS.

In fact, the two largest tDCS trials observed that tDCS was an effective treatment for depression. Loo et al. [25] randomized 64 patients to receive active or sham tDCS (2 mA, 15 sessions over 3 weeks), followed by a 3-week open-label active treatment phase. Mood and neuropsychological effects were assessed. There was significantly greater improvement in mood after active than sham treatment. Attention and working memory improved after a single session of active but not sham tDCS. There was no decline in neuropsychological functioning after 3–6 weeks of active stimulation. Brunoni et al. [24] enrolled 120 antidepressant-free patients with moderate and severe depression who were randomized in four arms (2×2 design): sham tDCS and placebo pill, sham tDCS and sertraline, active tDCS and placebo pill, and active tDCS and sertraline (the study name was Sertraline vs. Electric Current Therapy to Treat Depression Clinical Trial—SELECT-TDCS; its design is described in [70]). The tDCS parameters were 2 mA per 30 min/day, for 2 weeks and two extra tDCS sessions every other week until week 6 (study endpoint); the dose of sertraline was fixed (50 mg/day). The main findings were that: (1) combined tDCS/sertraline was significantly more effective than the other treatment groups in reducing depressive symptoms; (2) tDCS and sertraline efficacy did not differ; (3) active tDCS as a monotherapy was also more effective than the placebo group. Of note, it was also found that (1) there was no decline in cognitive improvement after tDCS or sertraline treatment; (2) there were five cases of hypomanic/manic episodes in the combined treatment group vs. one case in tDCS-only, one case in sertraline-only and no cases in the placebo arm (although this difference was not statistically significant); (3) use of benzodiazepines and treatment-resistant depression were both predictors of lower response; and (4) treatment was well tolerated with mild adverse effects, which were of similar frequency in both arms, except for skin redness that was more prevalent in the active group. Biological markers were also evaluated.

In 2014, two randomized, sham-controlled trials evaluated the efficacy of tDCS combined with cognitive control therapy (CCT), an intervention that aims to increase prefrontal cortical activity through working memory tasks (in both cases, an adapted version of the Paced Serial Addition Task, PASAT). Segrave et al. [32] enrolled 27 patients to receive tDCS and CCT, sham tDCS and CCT, and sham CCT and tDCS (2 mA, five sessions). All treatments led to a reduction in depression severity after five tDCS sessions, but only the combined tDCS/CCT treatment resulted in sustained antidepressant response at week 4. The study suggested that CCT enhances antidepressant outcomes of tDCS. In contrast, Brunoni et al. [33] randomized 37 participants to receive sham tDCS and CCT or active tDCS and CCT (2 mA, ten sessions) and found similar antidepressant improvement in both groups. However, further analysis showed that in older patients, those with greater improvement in CCT task performance also had greater antidepressant improvement with active tDCS.

The last RCT published hitherto was a phase-II trial in which 24 escitalopram-resistant depressed patients were randomized to receive

Table 13.2 Summary of controlled tDCS trials in major depression

Author	Sample (*n*)	Anode	Cathode	Intensity (A/m^2)	Number of sessions	Results
Fregni et al.2006 [65]	10	F3	RSO	0.28	5 (every other day)	Positive
Fregni et al.2006 [66]	18	F3	RSO	0.28	5 (every other day)	Positive
Boggio et al. 2008 [67]	40	F3	F4	0.28	10 (1×/day)	Positive
Loo et al.2010 [68]	40	F3	RSO	0.28	5 (every other day)	Negative
Palm et al. 2011 [69]	22	F3	RSO	0.28/0.57	10 (1×/day)	Negative
Blumberger et al. 2012 [23]	24	F3	F4	0.57	15 (1×/day)	Negative
Loo et al.2012 [25]	64	F3	RSO	0.57	15 (1×/day)	Positive
Brunoni et al.2013 [24]	120	F3	F4	0.8	10 (1×/day)	Positive
Segrave et al. 2014 (Segrave cct)	27	F3	RSO	0.57	5 (1×/day)	Mixed
Brunoni et al. 2014 [33]	37	F3	F4	0.8	10 (1×/day)	Mixed
Bennabi et al. 2015 [71]	23	F3	RSO	0.57	10 (2×/day)	Negative

RSO right supraorbital area, *F4* right dorsolateral prefrontal cortex, *R arm* right arm, *Occ/cer* occipital/cerebellar

two daily sessions of tDCS for 5 days (2 mA, ten sessions over 1 week) (Table 13.2). In this study, tDCS did not induce clinically relevant antidepressant effects in active and sham stimulation groups [71].

Follow-Up Studies

Two studies evaluated the efficacy of tDCS in the maintenance phase of the depressive episode. One of them [70] recruited 42 patients who were tDCS responders from the SELECT-TDCS trial and performed tDCS sessions every other week for 3 months and then every month for 3 additional months (tDCS sessions were interrupted earlier in case of relapse, characterizing failure treatment). In this follow-up study, treatment-resistant depression was significantly associated with an increased relapse rate (over 80 % in 6 months). On the other hand, >80 % non-refractory patients sustained clinical response for at least 6 months. In this trial, the overall relapse rate in 6 months was around 50 %, with most relapses occurring in the first 3 months. The other study [72] also followed responders previously treated in a randomized clinical trial ($n=26$) and performed weekly tDCS sessions for 3 months, followed by tDCS sessions every other week in the remaining 3 months. Similarly, a relapse rate around 50 % in 6 months was observed. However, most relapses occurred after the 3 initial months, when tDCS sessions were further spaced. Therefore, although the evidence is very preliminary, these trials suggest that intensive continuation treatment during early follow-up might be recommended to sustain clinical improvement.

Meta-Analyses

The first two published meta-analyses for tDCS in depression showed disparate results—interestingly, these meta-analyses evaluated the same randomized clinical trials, although using different outcome measures—i.e., Kalu et al. [73] employed continuous outcomes (depression improvement), finding positive results, and Berlim et al. [74] dichotomous measures (response and remission) for estimating the effect size of the intervention, finding nonsignificant results regarding tDCS efficacy. In an updated meta-analysis including data from SELECT-TDCS, not included in the previous meta-analyses, active vs. sham tDCS was more effective using both continuous and categorical outcomes, with the effect being small to moderate [75].

Finally, one individual patient data meta-analysis was recently performed in order to further assess efficacy and to identify predictors of response. Data were extracted on an individual patient basis and pooled from six randomized sham-controlled trials, enrolling 289 patients. Active tDCS was significantly superior to sham for response (34 % vs. 19 %, respectively; OR = 2.44, 95 % CI = 1.38–4.32, NNT = 7),

remission (23.1 % vs. 12.7 %, respectively; OR = 2.38, 95 % CI = 1.22–4.64, NNT = 9) and depression improvement (B coefficient = 0.35, 95 % CI = 0.12–0.57). Treatment-resistant depression and higher tDCS "doses" were, respectively, negatively and positively associated with tDCS efficacy. In this study, the effect size of tDCS treatment was comparable to those reported for repetitive transcranial magnetic stimulation and antidepressant drug treatment in primary care [29].

Bipolar Disorder

The use of tDCS in bipolar depression has not been as yet sufficiently investigated, with only one open-label study comparing the efficacy of tDCS in unipolar vs. bipolar depressed patients and showing efficacy in both conditions [62]. Another open study evaluated a sample of unipolar and bipolar patients for 3 months, but did not report results separately for the unipolar and bipolar groups [63]. Finally, Pereira-Junior et al. reported on pilot results from a double-blinded study in progress, in which five patients with bipolar depression received active tDCS. Response and remission rates were, respectively, 40% and 20 % [76]. Regarding efficacy in mania, the evidence is limited to one single case report showing improvement of manic symptoms after five sessions of tDCS that was applied with the anode over the right and the cathode over the left DLPFC [77].

There are four stand-alone case reports in literature [78–81] and some reports in randomized clinical trials of mania or hypomania induction after tDCS treatment. Some of these occurred in patients with unipolar depression, i.e., with no prior history of mania or hypomania. Most of these episodes resolved spontaneously, with tDCS withheld for a few days, or with small dose adjustments/introduction of a new pharmacotherapy, although one of them was a full-blown episode of mania with psychotic features [81].

It is difficult to estimate the precise frequency of this adverse effect or, even, if it is directly caused by tDCS or if the case reports represent events that occurred coincidently with the repeated tDCS sessions. It is also unclear if having a diagnosis of bipolar disorder places a patient at higher risk of a manic switch with tDCS, as has been suggested for other brain stimulation therapies. Therefore, the same recommendations of care for depressed patients are also valid when using tDCS as an antidepressant treatment—i.e., careful observation of the patients' clinical outcomes while on a clinical treatment. Further, patients should be carefully assessed for history of bipolar disorder and history of switching into mania with past antidepressant treatments, as these factors may indicate a higher risk of manic switch with tDCS. In these patients, concurrent treatment with mood stabilizer medications during the tDCS treatment course should be considered.

Discussion

The response rate of tDCS ranged from 20 to 40 %, with open-label trials showing discretely better results than the active arms of sham-controlled trials. Such improvement is in the same range of antidepressant drug treatment [82] and, in fact, two studies that directly compared tDCS vs. fluoxetine [59] and sertraline [24] found similar improvement rates in the pharmacological and non-pharmacological arms. This could suggest that tDCS might be a *substitute* for pharmacotherapy when its use is hindered, for instance, due to medical conditions [83]. The advantages of substituting tDCS for medicines is that tDCS does not cause systemic effects, has no serious adverse effects, and the problem of pharmacological interactions is avoided. One the other hand, the necessity of daily tDCS sessions requires patients to be in daily attendance, which may be difficult for outpatients. In this context, the development of portable, remotely supervised "home-use" tDCS devices could help in this issue, as the number of visits to the clinical center would be dramatically reduced [84].

Moreover, other reviewed studies evaluated the role of tDCS as an *augmentation* strategy for pharmacotherapy, showing that the combined

therapy of tDCS with antidepressant drugs, particularly SSRIs, was associated with superior improvement. On the other hand, tDCS combined with CCT showed mixed results; therefore, this association should be evaluated further in future trials.

Another critical and unclear point is the optimal treatment protocol during the maintenance phase. Only two follow-up studies were carried out hitherto [70, 72] with relatively poor results, with a relapse rate of around 50 % in 6 months. We propose that the same strategies under research for rTMS could be employed here, namely more frequent stimulation sessions and use of antidepressant drugs during the maintenance phase. Preliminary data in a few patients suggests that repeated course of tDCS in those who relapse may be safe and effective but this needs further evaluation [85].

Finally, though results to date are promising, it should be underscored that not all clinical trials yielded positive results and one meta-analysis failed to show superiority from active tDCS to sham treatment. Some reasons for these mixed findings include relatively small sample sizes, disparate treatment modalities (including number of sessions, cathode positioning, duration and intensity of the sessions) and different depression characteristics (regarding refractoriness, severity, mean age, unipolar vs. bipolar depression, and concomitant use of pharmacotherapy). In our individual patient data meta-analysis we found that tDCS efficacy in treatment-resistant depression is lower. Nonetheless, further randomized clinical trials are necessary and, in fact, several trials are currently being performed worldwide. Although we cannot presently conclude that tDCS is *definitively* effective in depression, in the next few years a definite answer regarding tDCS clinical efficacy is expected.

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Schizophrenia

14

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Abstract

This chapter proposes an overview of current evidence and future directions for using tDCS in schizophrenia. To date, the effects of tDCS have been investigated in three main outcomes: (1) to alleviate auditory verbal hallucinations using a frontotemporal tDCS montage (the anode placed over the left dorsolateral prefrontal cortex coupled with the cathode placed over the left temporoparietal junction); (2) to alleviate negative symptoms using a frontal montage (the anode placed over the left dorsolateral prefrontal cortex coupled with the cathode placed over the right dorsolateral prefrontal cortex, the right supraorbital region or extra-cephalically); and (3) to enhance cognitive functions, using different tDCS montages. Promising results have been reported for these three outcomes. tDCS can decrease the severity of symptoms such as auditory verbal hallucinations and negative symptoms by about 30 % and enhance a wide range of cognitive functions (e.g., working memory, self-monitoring, facial emotion recognition). However, most studies to date are case-reports and open labeled studies with small samples. Thus, large randomized controlled studies are needed to confirm the usefulness of tDCS in schizophrenia.

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Keywords
Schizophrenia • Auditory verbal hallucinations • Negative symptoms • Cognition • tDCS

Introduction

Schizophrenia is a frequent and debilitating psychiatric condition occurring in about 1 % of the general population. The clinical expression of schizophrenia is heterogeneous, and symptoms are usually classified into five main dimensions: positive (e.g., hallucinations, delusions), negative (e.g., flat expression, avolition), depression, disorganization, and grandiosity/excitement. Symptoms of schizophrenia are usually alleviated by psychopharmacological medications. However, up to 30 % of treated patients still report disabling symptoms such as auditory verbal hallucinations, negative symptoms, and cognitive deficits [1, 2]. These treatment-resistant symptoms are associated with a higher risk of relapse and worse prognosis, justifying the need for developing novel alternative approaches.

Over the last decade, various nonpharmacological approaches such as noninvasive brain stimulation (NIBS) techniques have been developed in order to alleviate treatment-resistant symptoms in patients with schizophrenia. NIBS techniques are safe tools to modulate brain activity and connectivity in living humans. These approaches were based on neuroimaging studies that have highlighted some brain correlates of schizophrenia symptoms: auditory verbal hallucinations were associated with hyperactivity in the left temporoparietal region [3] and frontotemporal dysconnectivity [4]; negative symptoms and cognitive deficits were associated with structural and functional abnormalities in the prefrontal cortices [5]. According to their neuromodulatory effects, NIBS techniques were thus proposed to reduce treatment-resistant symptoms in patients with schizophrenia by targeting the brain regions that showed abnormal activities. One of the NIBS techniques recently used in these patients is transcranial direct current stimulation (tDCS).

The first studies investigating the use of tDCS to improve symptoms of schizophrenia have been published in 2011. Since then, a rapid increase in the number of published articles in the field was observed (Fig. 14.1)—in fact, 20 studies investigating the clinical interest of tDCS in schizophrenia were indicated as "ongoing" on clinicaltrials.gov database in September 2015 (ten in North America, four in Europe, two in Middle East, one in Australia, one in South America, one in Africa, and one in East Asia) suggesting the international growing interest of tDCS for schizophrenia.

Two tDCS montages for schizophrenia have been mostly used. The first one, a frontotemporal electrode montage, is proposed to reduce treatment-resistant auditory verbal hallucinations. In this montage, the anode (presumably excitatory) was placed over the left prefrontal cortex and the cathode (presumably inhibitory) was placed over the left temporoparietal junction [6, 7]. The second one is proposed to reduce treatment-resistant negative symptoms and to improve cognitive functions by targeting the left prefrontal region. In this montage, the anode was placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right supraorbital region, the right DLPFC or extra-cephalically [8, 9].

The aim of this chapter was to investigate whether tDCS can alleviate symptoms and improve cognitive functions in patients with schizophrenia. Hence, we reviewed studies investigating the clinical effects of tDCS on auditory verbal hallucinations, negative symptoms and other symptoms of schizophrenia. We also reviewed studies focusing on the effects of tDCS on cognitive functions in patients with schizophrenia. After a description of current evidence regarding the interest of using tDCS in patients with schizophrenia and the brain correlates of clinical and cognitive improvements, we also discussed the safety of this approach and how tDCS parameters can be optimized to improve efficacy.

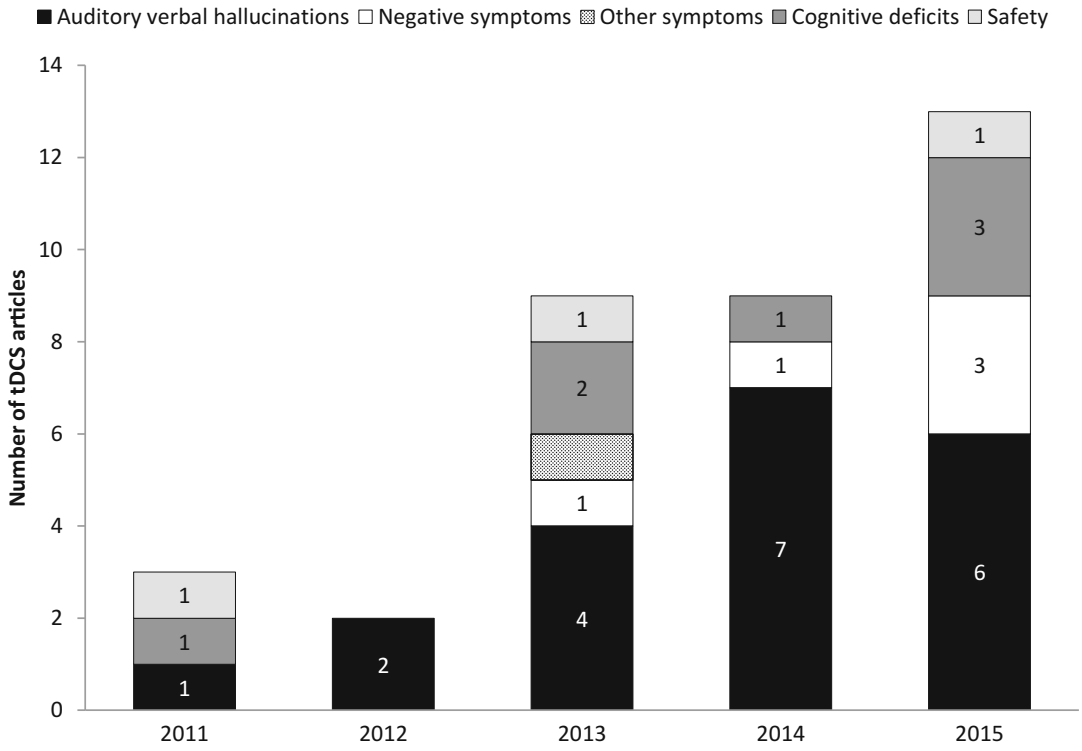

Fig. 14.1 Number of published articles per year examining the effects of transcranial direct current stimulation (tDCS) in patients with schizophrenia. Articles investigating the effects on auditory verbal hallucinations, negative symptoms, other symptoms, cognitive deficits, and safety have been listed (*Source*: PubMed/Medline)

Effects of Frontotemporal tDCS on Auditory Verbal Hallucinations

Twenty-one studies investigated whether tDCS targeting the frontotemporal network can improve the symptoms of treatment-resistant auditory verbal hallucinations in patients with schizophrenia (see Table 14.1). Among them, three randomized sham-controlled studies have reported a significant effect of active tDCS on auditory verbal hallucinations as compared to sham [6, 26, 27]. In the first one [6], 30 patients with schizophrenia received ten sessions of 20 min of either active (2 mA) or sham tDCS delivered twice daily on 5 consecutive days. Electrodes were placed on the scalp based on the 10/20 international EEG system, with the center of the anode placed between F3 and FP1 (assuming to correspond to the left prefrontal cortex) and the center of the cathode placed between T3 and P3 (assuming to correspond to the left temporoparietal junction). Auditory verbal hallucinations were assessed using the Auditory Hallucination Rating Scale (AHRS). Patients receiving active tDCS reported a significant 31 % decrease of their treatment-resistant auditory verbal hallucinations whereas patients receiving sham tDCS reported a nonsignificant 8 % decrease [6]. Remarkably, the effect of tDCS on auditory verbal hallucinations was still significant at 1 and 3-month follow-up [6].

Similar results were reported using the same tDCS protocol in two randomized controlled studies published in 2015 [26, 27]. It is important to stress that samples enrolled in these studies partially overlapped with the study sample of Brunelin et al. [6]. In the first study, Mondino et al. [26] reported a significant 46 % reduction in the frequency of auditory verbal hallucinations assessed by the first item of the AHRS after 10 sessions of

active tDCS, whereas a nonsignificant 10% decrease was reported in the sham group. In the second one, a significant 28% decrease in auditory verbal hallucinations measured by the AHRS was reported after the ten sessions of active tDCS, whereas a nonsignificant 10% decrease was reported in patients receiving sham tDCS [27].

Using the same electrodes montage, promising effects of tDCS for reducing auditory verbal hallucinations were also reported in 4 open labeled studies including 23 [25], 21 [17], 16 [28], and 6 [18] patients with schizophrenia. All studies included patients with schizophrenia receiving ten sessions of 20 min of active 2 mA tDCS delivered twice daily on 5 consecutive days. In the first one, Shivakumar et al. [25] recruited 23 patients and assessed their auditory verbal hallucinations using the "auditory hallucination" subscale of the Psychotic Symptom Rating Scale (PSYRATS). Patients showed a nearly 30% significant decrease of their treatment-resistant auditory verbal hallucinations after tDCS. Bose et al. [17] recruited 21 patients and assessed the auditory verbal hallucinations, also using the "auditory hallucination" subscale of the PSYRATS. After tDCS, patients showed a significant decrease (32.7%) in auditory verbal hallucinations. Brunelin et al. [28] recruited 16 patients and assessed their auditory verbal hallucinations using the AHRS. After tDCS, patients showed a significant 20% decrease in auditory hallucinations. In Ferrucci et al. [18], six patients were included and assessed using the Cardiff Anomalous Perceptions Scale (CAPS). After tDCS, patients showed a 33% decrease in frequency and a 40% decrease in distress of auditory verbal hallucinations.

Thirteen case-reports also investigated the effects of frontotemporal tDCS on auditory verbal hallucinations in patients with schizophrenia. Of note, three of them observed a complete remission of auditory verbal hallucinations after tDCS [11, 12, 19]. Indeed, Rakesh et al. [11] and Shivakumar et al. [12] assessing auditory verbal hallucinations with AHRS, reported that ten sessions of 20 min of active 2 mA tDCS delivered twice daily on 5 consecutive days allowed complete remission of auditory verbal hallucinations. Shivakumar et al. [19], assessing auditory verbal hallucinations with the "auditory hallucinations" subscale of the PSYRATS, reported a complete remission of auditory verbal hallucinations for at least 3 months after ten sessions of tDCS delivered twice daily for 20 min at 2 mA. Two case studies also highlighted the efficacy and safety of maintenance tDCS sessions for 1 and 3 years [14, 19]. Shivakumar et al. [19] reported a complete remission of auditory verbal hallucinations assessed with the PSYRATS "auditory hallucinations" subscale during 1 year after ten sessions of tDCS delivered twice daily for 20 min at 2 mA. In fact, the patient presented three relapses within 1 year, which were successfully managed with only two sessions of tDCS (in 1 day). Andrade [14] reported a decrease in auditory verbal hallucinations assessed with clinical scales during 3 years of tDCS delivered domiciliary once then twice daily, for 20 then 30 min at 1–3 mA intensity. Within 2 months, the patient self reported a 90% improvement.

Finally, a randomized sham controlled study failed to replicate the beneficial clinical effect of tDCS on auditory verbal hallucinations assessed by a single item on the Positive and Negative Syndrome Scale (PANSS) measuring hallucinations severity [20]. In this study, 15 sessions of tDCS (2 mA, 20 min) were delivered once a day during 3 consecutive weeks using either a left frontotemporal montage (with the anode over F3 and the cathode over the T3-P3) in 11 patients with schizophrenia or an original bilateral montage with four electrodes (two anodes over F3 and F4 and two cathodes over T3-P3 and T4-P4) in 13 patients with schizophrenia. In a recent case-report study, Bose et al. [24] reported that 18 sessions of left frontotemporal tDCS (with the anode placed midway between F3 and FP1 and the cathode over the T3-P3) had no effect on auditory verbal hallucinations as assessed by the "auditory hallucination" subscale of the PSYRATS. However, when switching the electrode montage to the right side of the brain with the anode placed over the right DLPFC (between F4 and FP2) coupled with the cathode over the right temporoparietal junction (between T4 and

Table 14.1 Summary of studies investigating the effects of frontotemporal tDCS on auditory verbal hallucinations in patients with schizophrenia

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Homan et al. 2011 [10]	Case	1	44	M	FP2/T3P3	10 (1/day)	1	15	1. Decrease in HCS score (−60 %) 2. Decrease in PANSS score (−20 %) 3. Decrease in PSYRATS score (−16 %) 4. Decrease of rCBF in Wernicke's area (BA22), left Heschl's gyrus (BA41/42), and Broca's area (BA44/45) Sustained effect on symptoms at 6-month follow-up
Brunelin et al. 2012a [7]	RCT	30 15A 15S	37.7	22M/8F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (−31 %) Sustained effect at 1 and 3-month follow-up 2. Decrease in PANSS score (−13 %)
Brunelin et al. 2012 [6]	Case	2	37.5	M	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (patient 1: −77 %; patient 2: −48 %) 2. Decrease in PANSS score (patient 1: −20 %; patient 2: −49 %) Sustained effects at 3-month follow-up
Rakesh et al. 2013 [11]	Case	1	24	M	F3FP1/T3P3	10 (2/day)	2	20	1. Complete cessation of AH measured by AHRS 2. Improvement in measured by an increase in IRS from 1 to 5
Shivakumar et al. 2013 [12]	Case	1	28	F	F3FP1/T3P3	10 (2/day)	2	20	1. Complete cessation of AH measured by AHRS 2. Improvement in insight measured by an increase in IRS from 0 to 5
Shiozawa et al. 2013 [13]	Case	1	31	M	F3/Oz F3/T3P3	10 (1/day) 10 (1/day)	2	20	1. Decrease in AHRS score (−20 %) 2. Decrease in visual hallucinations measured by LSHS score (−20 %) 3. Decrease in general (−29 %), positive (−38 %) and negative symptoms (−27 %) assessed by PANSS
Andrade 2013 [14]	Case	1	24	F	F3/T3P3	1–2/day at home during 3 years	1–3	20–30	1. Decrease in AH and general symptoms measured by clinical ratings
Nawani et al. 2014 [15]	Case	1	31	M	F3/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (−30 %) 2. Increased changes in amplitudes of N100 induced by tetanic blocks. These changes were reported only for the frontal electrodes

(continued)

Table 14.1 (continued)

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Nawani et al. 2014 [16]	Case	5	33.2	2M/3F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (−30 %) 2. Modulation of N100 amplitude in the auditory cortex during "talk" and "listen" conditions: before tDCS, no differences between N100 amplitudes in talk and listen conditions After tDCS, smaller N100 amplitude during "talk" as compared to "listen"
Bose et al. 2014 [17]	Open	21	33.1	9M/12F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in PSYRATS AHS scores (−32.7 %) 2. Improvement in insight measured by an increase in SAI scores from 7.8 ± 4.4 to 12.2 ± 4.2 Correlation between the both
Ferrucci et al. 2014 [18]	Open	6	41–66	ND	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in frequency (−33 %) and distress (−40 %) of AH measured by the CAPS. The effects lasted up to 1 month 2. Decrease in PANSS negative symptoms scores (−24 %)
Shivakumar et al. 2014 [19]	Case	1	42	F	F3FP1/T3P3	10 (2/day)	2	20	1. Complete cessation of AH measured by the AHS of PSYRATS during 1 year. 2 sessions at relapse allow maintenance of beneficial effect
Fitzgerald et al. 2014 [20]	RCT	11 13	39.3	15M/9F	F3/T3P3 F3 + F4/ T3P3 + T4P4	15 (1/day)	2	20	1. No significant decrease in PANSS AH score (unilateral: −17 %; bilateral: −14 %) compared to sham (−7 %; −3 %). No effects in total PANSS scores, PANSS positive symptoms and PANSS negative symptoms 2. No effect on SANS
Narayanaswamy et al. 2014 [21]	Case	1	22	F	F3FP1/T3P3	10 (2/day)	2	20	After the ten sessions of tDCS: 1. No changes in AHRS scores 2. No changes in SANS scores During the subsequent 2 weeks: 1. No changes in AHRS scores 2. Decrease in SANS scores (−30 %) At 6-month follow-up: 1. Decrease in AHRS scores (−37 %) 2. Decrease in SANS scores (−60 %)

Shenoy et al. 2015 [22]	Case	1	25	F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHS of PSYRATS (−25 % immediately after the ten sessions and −95 % 4 months after tDCS sessions) 2. Safety and tolerability during pregnancy assessed using sonography
Praharaj et al. 2015 [23]	Case	1	49	M	F3/T3P3	5 (1/day)	2	20	1. More than 90 % decrease in frequency and duration of AH after the 1st session 2. Decrease in PSYRATS AHS score 3. No effect on PSYRATS delusion score 4. Subjective report of reduction in distress associated with AH Symptoms return to baseline 6 days after the last tDCS session
Bose et al. 2015 [24]	Case	1	37	F	F3FP1/T3P3 F4FP2/T4P4	18 (1/day) 20 (1/day)	2	20	After 18 sessions of F3FP1/T3P3 tDCS: 1. No effects on AHS of PSYRATS 2. No effects on "attentional salience" item of the AHRS After 20 sessions of F4FP2/T4P4 tDCS: 1. Decrease in AHS of PSYRATS (−31.4 %) 2. Decrease in "attentional salience" item of the AHRS (from 6 to 4)
Shivakumar et al. 2015 [25]	Open	23	33.4	10M/13F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in PSYRATS AHS after tDCS. Greater decrease in the COMT val/val group ($n=11$) than in the met group (val/met or met/met; $n=12$)
Mondino et al. 2015 [26]	RCT	28 15A 13S	Active: 36.5 Sham: 39.2	9F/6M 7F/6M	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in "frequency" item of the AHRS (−46 %) 2. Improvement in internal source monitoring performances (decrease of externalization bias) Correlation between both

(continued)

Table 14.1 (continued)

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Mondino et al. 2015b [27]	RCT	23 11A 12S	Active: 36.7 Sham: 37.3	8M/3F 7M/5F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS scores (−28 %) 2. Decrease in PANSS negative score (−17 %). No effects on PANSS positive symptoms and general psychopathology 3. Effects on rs-FC of the left TPJ measured by fMRI: decreased rs-FC of the left TPJ with the left anterior insula and the right inferior frontal gyrus. Increased rs-FC of the left TPJ with the left angular gyrus, the left dorsolateral prefrontal cortex and the precuneus Correlation between the reduction of AHRS scores and the reduction of the rs-FC between the left TPJ and the left anterior insula
Brunelin et al. 2015 [28]	Open	16	41	6M/10F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS scores (−20 %) Greater decrease in nonsmokers (−46 %) than in smokers (−6 %)

tDCS electrodes placement was described according to 10/20 EEG system: F3: Left dorsolateral prefrontal cortex; F4: Right dorsolateral prefrontal cortex; FP2: Right supraorbital region; FP1: Left supraorbital region; Oz: Occipital region; T3P3: Left temporoparietal junction; T4P4: Right temporoparietal junction; T3: Left temporal region; T4: Right temporal region

A active, AH auditory hallucinations, *AHRS* auditory hallucination rating scale, *AHS* auditory hallucinations subscale, *BA* Brodmann's area, *CAPS* Cardiff anomalous perceptions scale, *F* female, *fMRI* functional magnetic resonance imaging, *HCS* hallucination change score, *I* intensity, *IRS* insight rating scale, LSHS, Launay–Slade hallucination scale, *M* male, *n* number of subjects, *PANSS* positive and negative syndrome scale, *PSYRATS* psychotic symptom rating scale, *rCBF* regional cerebral blood flow, *RCT* randomized controlled trial, *rs-FC* resting-state functional connectivity, *S* sham, SAI schedule for assessment of insight, *SANS* scale for the assessment of negative symptoms, *tDCS* transcranial direct current stimulation, *TPJ* temporoparietal junction

P4), 20 sessions of tDCS induced a 31.4 % reduction of auditory verbal hallucinations.

In sum, among the studies investigating the effects of frontotemporal tDCS on auditory verbal hallucinations, the intensity of stimulation varied from 1 to 3 mA for a 15- to 30-min duration. The size of the electrodes was mostly 35 cm^2 (7 × 5 cm), but some studies used 25 cm^2 electrodes (5 × 5 cm; [14, 23]). tDCS regimen consisted in 5–20 sessions of tDCS delivered either once or twice daily. Auditory verbal hallucinations were assessed using various standardized multidimensional scales such as the PSYRATS or the AHRS, but also using single item assessments such as the "auditory hallucinations" item of the PANSS [20] or the "frequency" item of the AHRS [26]. These assessments and outcomes may not have the same sensitivity to capture changes in auditory verbal hallucinations. Further studies are needed to confirm promising effects observed on auditory verbal hallucinations following frontotemporal tDCS in patients with schizophrenia.

Effects of Frontotemporal tDCS on Other Symptoms

Remarkably, among studies reporting a reduction of auditory verbal hallucinations in patients with schizophrenia following tDCS, some also observed a decrease in general symptoms of schizophrenia [6, 7, 10, 14], positive symptoms [13], negative symptoms [13, 18, 21, 27], and insight into the illness [11, 12, 17]. In addition, Shiozawa et al. [13] investigated the effect of ten sessions of tDCS with the anode over F3 and the cathode over the occipital region (Oz) followed by ten sessions with the anode over F3 and the cathode over the temporoparietal cortex (T3-P3) on visual and auditory verbal hallucinations in a patient with schizophrenia. They reported that ten sessions of each electrode montage lead to a reduction of hallucinations in both visual and auditory modalities.

Predictive Markers of Response to Frontotemporal tDCS on Auditory Verbal Hallucinations

Two open labeled studies investigated potential predictive markers of response to tDCS [25, 28]. Shivakumar et al. [25] investigated the effects of frontotemporal tDCS in 23 patients with treatment-resistant auditory verbal hallucinations divided into two groups depending on their COMT Val158Met polymorphism. A significant reduction of auditory verbal hallucinations was observed in both groups. However, patients with the val/val COMT polymorphism ($n = 11$) showed a greater reduction in auditory verbal hallucinations than met-allele carriers (val/met or met/met polymorphism; $n = 12$). The COMT Val158Met polymorphism may thus modulate response to tDCS. An excessive dopamine transmission has been implicated in the clinical expression of positive symptoms. The Val variant catabolizes frontal dopamine at up to four times the rate of its methionine counterpart, suggesting that lower extracellular dopamine rates in the frontal region predicts beneficial clinical outcome in patients with AVH.

Brunelin et al. [28] reported a mean 20 % decrease of auditory verbal hallucinations following 10 sessions of frontotemporal tDCS in 16 patients with treatment-resistant auditory verbal hallucinations. In this sample, patients with a comorbid tobacco use disorder showed a nonsignificant 6 % reduction in auditory verbal hallucinations, whereas nonsmokers displayed a significant 46 % reduction in auditory verbal hallucinations. Thus, smoking may prevent the effect of repeated sessions of frontotemporal tDCS in patients with treatment-resistant auditory verbal hallucinations. It has been hypothesized that interactions between antipsychotic medication and nicotine may influence dopamine transmission and in turn modulate tDCS effects on neural plasticity.

Furthermore, one case study suggested that some clinical characteristics such as attentional salience of auditory verbal hallucinations could

influence site-specific response to tDCS. Namely, Bose et al. [24] described the case of a patient with high attentional salience auditory verbal hallucinations that failed to respond to left-sided frontotemporal tDCS but that decreased after right-sided frontotemporal tDCS.

Brain Correlates of the Effects of Frontotemporal tDCS on Auditory Verbal Hallucinations

Several studies used fMRI and EEG to investigate how tDCS modulates the brain when reducing auditory verbal hallucinations in patients with schizophrenia.

In a first single case study, Homan et al. [10], reported that tDCS decreased the regional cerebral blood flow in Wernicke's area (BA22), left Heschl's gyrus (BA41/42), and Broca's area (BA44/45), as well as auditory verbal hallucinations. This work supports the hypothesis that tDCS applied over the left temporoparietal junction reduces auditory hallucinations by normalizing brain activity, specifically by suppressing the hyperactivity observed in the language-related network during auditory verbal hallucinations [3].

In a randomized sham controlled study including 23 patients with schizophrenia, Mondino et al. [27] reported that active tDCS decreased resting state functional connectivity of the left temporoparietal junction with the left anterior insula and the right inferior frontal gyrus and increased resting state functional connectivity of the left temporoparietal junction with the left angular gyrus, the left dorsolateral prefrontal cortex and the precuneus as compared to sham tDCS. These changes in functional connectivity were accompanied by a reduction of auditory verbal hallucinations. Moreover, there was a correlation between the reduction of auditory verbal hallucinations and the reduction of the resting state functional connectivity between the left temporoparietal junction and the left anterior insula. These results also suggest that the reduction of auditory verbal hallucinations induced by tDCS was associated with a modulation of the brain activity within an auditory verbal hallucinations -related brain network, including brain areas involved in inner speech production and monitoring.

Using EEG, Nawani et al. [16] investigated the effects of ten sessions of left frontotemporal tDCS on auditory verbal hallucinations and on the amplitude of the auditory evoked potential N100 in five patients with schizophrenia. The N100 amplitude was measured when patients were listening to speech stimuli and when they were asked to produce speech. The authors reported that patients with schizophrenia showed no difference at baseline between N100 amplitudes generated in talk and listen conditions. This absence of N100 modulation during talking as compared to listening is suggested to reflect abnormalities in the corollary discharge. After tDCS, the amplitude of N100 was significantly smaller during talking than listening. Thus, tDCS seems to restore the N100 amplitude modulation when reducing auditory verbal hallucinations.

In a case study, Nawani et al. [15] tested whether the same protocol of left frontotemporal tDCS had an effect on cortical plasticity measured by EEG. Namely, they measured the N100 amplitude evoked by an auditory oddball task before and after a tetanic block before and after tDCS. The authors reported that ten sessions of frontotemporal tDCS reduced auditory hallucinations and increased the modulation of the N100 amplitude induced by the tetanic block. This effect was measured in the frontal region only. Since a change in N100 amplitude after tetanic block is considered as an indicator of neuroplasticity, these results suggested that tDCS modulates cortical neuroplasticity in patients with schizophrenia.

Effects of Frontal tDCS on Negative Symptoms and Other Symptoms of Schizophrenia

Five studies investigated the clinical effect of tDCS on treatment-resistant negative symptoms of schizophrenia (see Table 14.2). In these studies, the targeted brain region was the DLPFC, mainly its left part. This brain region was targeted with tDCS by placing the anode over the left DLPFC (F3) and the cathode either over the supra orbital region (FP2), the right DLPFC (F4) or the right

Table 14.2 Summary of studies investigating the effects of frontal tDCS on negative symptoms and other symptoms in patients with schizophrenia

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (n/day)	*I* (mA)	Duration (min)	Outcomes and main results
Palm et al. 2013 [8]	Case	1	19	M	F3/FP2	10 (1/day)	2	20	1. Decrease in PANSS total scores (−29 %), negative (−25 %) and positive (−37 %) subscores 2. Decrease in SANS scores (−28 %) 3. Decrease in depression assessed by CDSS (−82 %) Effects on FC measured using fMRI: reduced FC in the subgenual cortex, the anterior cingulate, the medial frontal gyrus, the and superior frontal gyrus 4. Increase in TMT performances 5. Decrease in the number of errors at the SOPT
Palm et al. 2014 [9]	RCT	20	ND	ND	F3/FP2	10 (1/day)	2	20	1. Decrease in SANS scores 2. Decrease in PANSS total scores 3. Effects on FC measured using fMRI: Deactivated cluster in the nucleus accumbens, subgenual cortex and striatum
Kurimori et al. 2015 [29]	Open	9	40.3	3F/6M	F3/Right deltoid	10 (1/day)	2	20	1. Decrease in PANSS negative symptoms scores (−24 %). Decrease in total PANSS scores (−8 %). No change in PANSS positive and general symptoms
Gomes et al. 2015 [30]	RCT	15 7A 8S	A: 43.3 S:34.2	5M/2F 6M/2F	F3/F4	10 (1/day)	2	10	1. Decrease in PANSS negative symptoms scores (−20 %) in the active group (versus −0.5 % in the sham group). Decrease in general and total PANSS scores (−15 % and −12 %) in the active group (0 % in the sham group). No effect on PANSS positive symptoms scores 2. No effect on depression assessed by CDSS 3. No effect on global functioning assessed by GAF
Shiozawa et al. 2013 [31]	Case	1	65	F	F3/F4	10 (1/day)	2	20	1. Decrease of catatonic symptoms assessed by BFS scores until complete remission (4 months after tDCS sessions)

tDCS electrodes placement was described according to 10/20 EEG system: F3: Left dorsolateral prefrontal cortex; F4: Right dorsolateral prefrontal cortex; FP2: Right supraorbital region

A active, *BFS* Bush–Francis scale, *CDSS* Calgary depression scale, *F* female, *FC* functional connectivity, *fMRI* functional magnetic resonance imaging, *GAF* global assessment of functioning, *I* intensity, *M* male, *n* number of subjects, *PANSS* positive and negative syndrome scale, *RCT* randomized controlled trial, *rs-FC* resting-state functional connectivity, *S* sham, *SANS* scale for the assessment of negative symptoms, *SOPT* self ordered pointing task, *tDCS* transcranial direct current stimulation, *TMT* trail making test

deltoid. In the first study, Palm et al. [8] reported that 10 sessions of tDCS delivered once a day with the anode placed over the left DLPFC (F3) and the cathode electrode placed over the right supra orbital region (FP2) reduced treatment-resistant negative and positive symptoms in a patient with schizophrenia. In a further randomized sham controlled trial with 20 patients with negative symptoms, Palm et al. [9] reported that ten daily sessions of active tDCS as compared to sham tDCS decreased negative symptoms as measured by the Scale for the Assessment of Negative Symptoms (SANS) and general symptoms as assessed by the PANSS. These beneficial clinical effects were maintained at the 2-week follow-up assessment.

These beneficial effects of tDCS on negative symptoms were also reported more recently in an open-label study including nine patients with schizophrenia [29] and in a randomized sham-controlled study including 15 patients with schizophrenia [30]. In the first study, patients received ten daily sessions of tDCS with the anode placed over the left DLPFC (F3) and the cathode placed over the right deltoid muscle [29]. After tDCS, patients showed a significant 24 % reduction in negative symptoms assessed by the PANSS negative subscale as compared to baseline. In the second study, patients received ten daily sessions of either active or tDCS with the anode placed over the left DLPFC (F3) and the cathode placed over the right DLPFC (F4) [30]. After tDCS, patients receiving active tDCS showed a significant 20 % reduction in negative symptoms as measured by the PANSS negative subscale whereas patients receiving sham tDCS showed no significant difference. Patients receiving active tDCS also reported a significant 15 % reduction in PANSS general symptoms as compared to patients receiving sham tDCS.

Brain Correlates of the Effects of Frontal tDCS on Negative Symptoms

Only one case study and one randomized controlled study investigated how tDCS modulates the brain when reducing negative symptoms in patients with schizophrenia. In the case study, Palm et al. [8] used fMRI to measure the effects of ten sessions of tDCS with the anode placed over the left DLPFC and the cathode placed over the right supraorbital region (FP2) on resting-state functional connectivity. Following tDCS, the patient showed a reduction in positive and negative symptoms and a reduced functional connectivity in the anterior part of the default mode network including the subgenual cortex, the anterior cingulate, the medial frontal gyrus and superior frontal gyrus. In a larger sample including 20 patients with schizophrenia, the same group of authors reported that the clinical improvement in negative symptoms observed after patients received tDCS was accompanied by a significant reduced functional connectivity within the nucleus accumbens, the subgenual cortex and the striatum [9].

Effects of Frontal tDCS on Other Symptoms

In a case study, Shiozawa et al. [31] reported a reduction in severity of catatonic symptoms in a patient suffering from treatment- and electroconvulsive therapy-resistant catatonic schizophrenia following ten sessions of tDCS delivered once a day with the anode over F3 and the cathode over F4. After 1 month, the remission of symptoms was complete and lasted for at least 4 months.

Effects of TDCS on Cognitive Functions

Cognitive deficits are a key feature in patients with schizophrenia. Several studies explored whether tDCS could improve cognitive functions in patients with schizophrenia (Table 14.3).

In the first study, Vercammen et al. [32] reported that a single session of active tDCS had a facilitating effect on probabilistic association learning measured by the weather prediction test in patients who displayed the best learning abilities before stimulation. In this study the anode was placed over the left DLPFC (F3) and the cathode over the right supraorbital region (FP2).

Table 14.3 Summary of studies investigating the effects of tDCS on cognitive functions in patients with schizophrenia

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Vercammen et al. 2011 [32]	Cross-over	20	37.6	10F/10M	F3/FP2	1	2	20	1. No effects on probabilistic learning assessed by the WPT in the whole sample. Significant improvement of performances in participants showing adequate performances at baseline
Ribolsi et al. 2013 [33]	Cross-over	15	34.3	4F/11M	P3/Right shoulder P4/Left shoulder	1	1	10	1. Anodal stimulation applied over P4 partially corrected the lack of leftward bias described using a line bisection task
Hoy et al. 2014 [34]	Cross-over	18	42.2	6F/12M	F3/FP2	1	0; 1 and 2	20	After stimulation at 2 mA intensity: 1. Increase in working memory performances assessed by the n-back task until 40 min after tDCS session After stimulation at 1 mA intensity: 1. No effect of 1 mA stimulation on working memory
Rassovsky et al. 2015 [35]	RCT	Anode 12 Cathode 12 12S	45.8 47.8 41.6	2F/10M 6F/6M 4F/8M	FP1/FP2	1	2	20	1. Anodal tDCS increases the identification of facial expressions assessed by the FEIT 2. No effect on social cognition assessed by the MSCEIT 3. No effect on social perception assessed by the PONS 4. No effect on theory of mind assessed by the ASIT 5. No effect on cognitive functions assessed by the MCCB composite score
Smith et al. 2015 [36]	RCT	30 14A 16S	A: 46.7 S: 44.8	14M/3F 10M/6F	F3/FP2	5 (1/day)	2	20	1. Increase in the MCCB composite score, the MCCB working memory score and in attention-vigilance domain scores in the active group as compared to sham 2. No effect on PANSS scores 3. No effect on smoking assessed by self report of cigarettes smoked and breathalyzer CO levels 4. No effect on cigarette dependence assessed with the cigarette dependence scale 4. No effect on craving assessed by the QSU

(continued)

Table 14.3 (continued)

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Schretlen et al. 2015 [37]	Cross-over no sham	5 patients 6 first degree relatives	50	6F/5M	F3/F4 F4/F3	1	1.5	30	1. No effect on motor speed assessed by the GPT and the FTT 2. No effect on processing speed assessed by the PCT 3. Increase in novel design production with no changes in world fluency productivity assessed by the CIFA 4. No effect on WMS-III spatial span and WAIS-III digit span forward (assessing attention) 5. Increase in overall backward span test performance (assessing working memory) during anodal versus cathodal tDCS
Hoy et al. 2015 [38]	Cross over	18	42.2	6F/12M	F3/FP2	1	0, 1 and 2 mA	20	After stimulation at 2 mA intensity: 1. Increase in working memory performance measured by the 2-back task at 20 and 40 min post-stimulation 2. Increase in gamma event-related synchronization measured by EEG at 40 min post-stimulation After stimulation at 1 mA intensity: 1. No effect on working memory 2. No effect on gamma event-related synchronization

tDCS electrodes placement was described according to 10/20 EEG system: F3: Left dorsolateral prefrontal cortex; F4: Right dorsolateral prefrontal cortex; FP2: Right supraorbital region; FP1: Left supraorbital region; P3: Left parietal region; P4: Right parietal region

A active, ASIT, awareness of social inference test, *CIFA* calibrated ideational fluency assessment, *CO* carbon monoxide, *EEG* electroencephalography, *F* female, *FEIT* facial emotion identification test, *FTT* finger tapping test, *GPT* grooved pegboard test, *I* intensity, *M* male, *MCCB* MATRICS consensus cognitive battery, *MSCEIT* Mayer–Salovey–Caruso emotional intelligence test; *n* number of subjects, *PANSS* positive and negative syndrome scale, *PCT* perceptual comparison test, *PONS* profile of nonverbal sensitivity, *QSU* questionnaire of smoking urges, *RCT* randomized controlled trial, *S* sham, *tDCS* transcranial direct current stimulation, *WAIS III* Wechsler adult intelligence scale, 3rd ed, *WMS-III* Wechsler memory scale, 3rd ed, *WPT* weather prediction test

In another study, Hoy et al. [34] observed beneficial effects of the same electrode montage on working memory performances measured using the n-back task. These beneficial effects lasted up to 40 min after the end of the stimulation period and were associated with an increase in frontal gamma event related synchronization [38]. Ribolsi et al. [33] reported a reduction of visuospatial attention deficit in patients with schizophrenia after a single session of tDCS where the anode electrode was placed over the right parietal (P4) and cathode over the left shoulder.

Several studies investigated the effects of anodal tDCS applied over the left DLPFC on cognitive functioning of patients with schizophrenia using a standardized battery of cognitive tests. In one of them, Rassovsky et al. [35] tested the effect of a single session of either anodal or cathodal tDCS applied over FP1 or FP2 (with the reference electrode placed over the upper right arm) on social cognition and cognitive functions in 36 patients with schizophrenia. Social cognition was measured using the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) that assesses four components of emotional processing, the Facial Emotion Identification Test (FEIT) that assesses the identification of facial emotion, the Profile of Nonverbal Sensitivity that assesses social perception, and the Awareness of Social Inference Test that assesses theory of mind. Cognitive functions were assessed using the MATRICS Consensus Cognitive Battery (MCCB) composite score. Following anodal tDCS, patients showed a significant improvement in the FEIT only, indicating that a single session of anodal tDCS over the prefrontal cortex might enhance identification of facial emotion in patients with schizophrenia.

In another study, Schretlen et al. [37] compared the effects of two 30-min sessions of tDCS, applied either with the anode over the left and cathode over the right DLPFC or with the reverse montage, on working memory and on a brief battery of cognitive measures in five outpatients with schizophrenia and six first-degree relatives of patients with schizophrenia. No differences were reported between tDCS conditions on motor speed assessed by the Grooved Pegboard Test and the Finger Tapping Test and on processing speed assessed by the Perceptual Comparison Test. No effects of tDCS condition were observed on attention assessed by the Wechsler Adult Intelligence Scale, 3rd Ed. Digit Span and Wechsler Memory Scale, 3rd Ed. Spatial Span. Working memory performances assessed by backward digit and spatial span were shown to be improved during anodal stimulation of the left DLPFC relative to cathodal stimulation. In addition, patients showed an increase in novel design production without alteration of overall productivity at the calibrated ideational fluency assessment during anodal versus cathodal tDCS.

Finally, only few studies investigated the effects of repeated sessions of tDCS on cognition in patients with schizophrenia. For instance, in a randomized double-blind, sham-controlled study, Smith et al. [36] investigated the effects of five sessions of either active or sham tDCS on cognition assessed by the MCCB composite score, psychiatric symptoms assessed by the PANSS, and smoking and cigarette craving in 37 patients with schizophrenia or schizoaffective disorder who were current smokers. tDCS was delivered with the anode placed over F3 and the cathode electrode placed over the right supra orbital region (FP2). Patients receiving active tDCS, as compared to sham, showed a significant improvement in the MCCB composite score, in the MCCB working memory score and in attention-vigilance domain scores. However, no significant effects were observed on clinical symptoms assessed by the PANSS, hallucinations, cigarette craving, and cigarettes smoked.

In a double-blind sham controlled study, Mondino et al. [26] tested the effects of ten sessions of left frontotemporal tDCS on source monitoring performance and treatment-resistant auditory verbal hallucinations in 28 patients with schizophrenia. Source monitoring was defined as the ability to discriminate between internally generated words and externally produced words. After ten sessions of active tDCS, patients performed better at recognizing internally generated words as compared to sham tDCS. In addition, there was a negative correlation between the reduction in the frequency of treatment-resistant

auditory verbal hallucinations and the increased recognition of internally generated words.

Safety of Using tDCS for Treating Schizophrenia

The reviewed articles investigated the impact of at least one tDCS session on more than 300 patients with schizophrenia. The duration of the tDCS session lasted from 10 to 30 min, with the intensity of stimulation ranging from 1 to 3 mA. Among expected adverse events following a session of tDCS [39], patients with schizophrenia more commonly reported tingling or itching sensations under the electrodes as well as sleepiness. No study reported any serious adverse event. In addition, ten sessions of tDCS delivered once or twice daily were well tolerated by specific populations such as patients with childhood-onset schizophrenia (mean age 15 years old; range 10–17) [40], female patients during pregnancy [22], and patients with comorbid skin condition [41]. Importantly, these studies did not observe any worsening of symptoms. An important improvement for patients with severe handicaps would be to have the possibility of tDCS to be delivered at home. Indeed, this was suggested for one patient with schizophrenia [14]. However, to allow this practice, the national authorities should establish recommendations ([42], also discussed in Chap. 26 of this book).

Optimizing tDCS Efficacy on Symptoms of Schizophrenia

Optimizing tDCS Parameters

The use of tDCS in schizophrenia is just at its beginning. There are still numerous unanswered questions including optimal stimulation parameters such as intensity, duration, and the number of sessions. Concerning stimulation intensity, tDCS has been mostly delivered at 1, 1.5, and 2 mA. Some studies comparing 1–2 mA stimulation suggested that 2 mA is the cut off for an optimal efficiency in reducing clinical symptoms and improving cognitive functions in schizophrenia [14, 34]. In that line, an interesting case study reported the safety of a 3 mA stimulation [14]. Concerning the duration of a session, most studies used sessions of a 20-min duration each. However, few studies reported beneficial effects of different session durations. For instance, Homan et al. [10] reported reduced auditory verbal hallucinations following ten sessions of tDCS delivered once daily at 1 mA during 15 min in a patient with schizophrenia. In another single case study, Andrade [14] enhanced tDCS duration from 20 to 30 min without adverse effects. In a randomized controlled study, Gomes et al. [30] reported the effects of ten sessions of tDCS delivered once daily at 2 mA during 10 min on negative symptoms and general symptomatology in 15 patients with schizophrenia. Concerning the number of sessions to deliver, patients with schizophrenia showed improvement after ten sessions delivered once or twice per day. One study, delivering 15 sessions of tDCS once per day, did not show any significant effect on auditory hallucinations [20]. In one case study, delivering five sessions of tDCS once per day induced a substantial reduction of auditory hallucinations that lasted at least 6 days [23]. To sum up, even if there is still much to learn about the tDCS optimal parameters, gathered evidence suggests that ten sessions of tDCS of 20-min duration and at a 2 mA intensity delivered once or twice per day produce a positive outcome such as reducing symptoms and improving cognition in patients with schizophrenia.

Other Modalities of Transcranial Electric Stimulation in Schizophrenia

Other forms of transcranial electric stimulation besides tDCS, such as high frequency oscillatory unidirectional *transcranial random noise stimulation* (tRNS) [43], have been tested in schizophrenia. To date, two studies investigated the effects of unidirectional tRNS with high frequencies ranging from 100 to 640 Hz, in patients

with schizophrenia. Palm et al. [44] reported an improvement in negative symptoms after 20 sessions of tRNS with the anode applied over the left DLPFC cortex and the cathode over the right supraorbital cortex. Haesebaert et al. [45], using the left frontotemporal montage during ten sessions of tRNS, observed a reduced severity of auditory hallucinations and an improved insight into the illness. Moreover, one study investigated the effects of transcranial slow oscillatory direct stimulation applied at a frequency of 0.75 Hz during phase 2 of sleep in 14 patients with schizophrenia [46]. In this study, slow oscillatory tDCS was applied at an intensity of 0.3 mA through two spherical 8 mm diameter electrodes placed bilaterally over F3 and F4 and at the mastoids. Stimulation was delivered for five blocks of 5 min separated by 1-min intervals free of stimulation. The authors reported that patients displayed greater performances to retain verbal information following active as compared to sham stimulation. A significant elevated mood was also observed in the morning after stimulation as compared to the morning after sham stimulation.

Combining tDCS with Other Approaches

tDCS studies most often include patients with schizophrenia suffering from treatment-resistant symptoms, and thus, treated with several medication classes including typical, atypical antipsychotics and selective serotonin reuptake inhibitors. These treatments should be taken into account when studying the impact of tDCS sessions. Indeed, in studies involving healthy subjects, dopaminergic, serotonergic, and GABAergic agents/drugs have been shown to have an impact on motor cortex excitability after tDCS sessions [47, 48]. For example, tDCS aftereffects in healthy subjects are considerably reduced with sulpiride [48]. With this in mind, it seems important that the studies investigating the effect of tDCS in patients with schizophrenia should determine the optimal association between pharmacology and the tDCS protocol. For example, a major depression study showed that bifrontal tDCS efficacy was reduced with concomitant use of benzodiazepine drugs [49]. Such interactions might also occur in patients with schizophrenia. Future work is therefore needed to study the association between tDCS effects, medication, and even nicotine intake [28] with tDCS efficacy in schizophrenia.

Another interesting approach, with the aim to improve tDCS effects on symptoms, could involve combination with neurocognitive strategies such as cognitive remediation therapy [50, 51]. For example, tDCS has been shown to improve working memory [52], therefore it could work with cognitive training as to enhance both cognitive and clinical efficacy. Further studies are needed to determine the optimal associations with the aim of improving clinical outcomes.

Conclusion

In this chapter, we reviewed and discussed studies investigating the usefulness of tDCS to reduce symptoms and improve cognitive functions of patients with schizophrenia. To date, two electrode montages seem to stand out: one frontotemporal montage with the anode placed over the left prefrontal cortex and the cathode placed over the left temporoparietal junction, which may reduce auditory verbal hallucinations; and one frontal montage with the anode placed over the left DLPFC and the cathode placed over the right DLPFC or the right supraorbital region which may also have beneficial clinical outcomes, mainly on negative symptoms. However, as the use of tDCS is quite recent and since most studies reviewed here were case-reports and open labeled studies with small samples, further randomized controlled trials with large samples are needed to confirm the efficacy of tDCS in schizophrenia. Moreover, further investigations have to be conducted to determine biological correlates and the optimal stimulation parameters to use to better impact on the symptoms of schizophrenia.

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OCD, Anxiety Disorders, and PTSD

15

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Abstract

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), obsessive-compulsive and related disorders, anxiety disorders, and trauma-related disorders are now categorized as separate psychiatric conditions. However, they share common clinical features for which similar treatment strategies are applied. Due to a high prevalence of these disorders and their high rate of treatment resistance, the investigation of new interventions to include in their treatment algorithms is paramount. In OCD, neuroimaging findings of cortical-striatal-thalamic-cortical circuit hyperactivity and the evidence of clinical effectiveness of low-frequency TMS suggest that the application of cathodal tDCS to the pre-supplementary motor area (pre-SMA) and the orbitofrontal cortex (OFC) could induce positive results, as pointed out by some preliminary results. In healthy subjects and in one patient with GAD, tDCS to the dorsolateral prefrontal cortex (DLPFC) has shown promising results in modulating attention to threat and symptoms of anxiety, respectively. In PTSD, the combination of a computerized working memory training with tDCS over DLPFC was reported to revert some cognitive,

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emotional and neurophysiological abnormalities; moreover, based upon fear extinction models, the combination of exposure therapy and tDCS might also be applied in this disorder. Ultimately, despite the intriguing rationale and some encouraging results, tDCS for OCD, GAD, and PTSD must be considered still in its infancy.

Keywords

Anxiety • Obsessive-compulsive disorder • OCD • General anxiety disorder • GAD • Post-traumatic stress disorder • PTSD • Transcranial direct current stimulation • tDCS

Introduction

Obsessive-compulsive and related disorders, anxiety disorders and trauma-related disorders are considered three different groups of psychiatric conditions, and are described in three different chapters of the last edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1]. However, these disorders share some important clinical features, including increased perception of thread, worry, harm avoidance, and neurovegetative hyperarousal. These similarities probably account for the shared response to treatments such as selective serotonin re-uptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT). Taken together, they have a 12-month period prevalence of approximately 14 % and a lifetime prevalence of approximately 21 % in the general population, with very high costs for the community [2]. Moreover, these disorders can display high rates of partial or no response to first and second line treatments [3] and can lead to high levels of personal suffering, social dysfunction and family burden, which are comparable to those found in schizophrenia [4].

Therefore, the search for a better understanding of their etiology and for new treatment strategies is paramount. In this chapter we focus on the rationale of using tDCS for the treatment of obsessive-compulsive disorder (OCD), anxiety disorders, and post-traumatic stress disorder (PTSD), and we review the available clinical data and published scientific literature.

OCD

It has been proposed that OCD results from aberrant functioning of cortico-striato-thalamo-cortical circuitry including the medial prefrontal cortex (i.e., supplementary motor area-SMA and anterior cingulate cortex-ACC), the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and basal ganglia [5, 6]. This model inspired the neurosurgical approaches to OCD, which turned out to be effective treatments, as evidenced by the FDA humanitarian use approval for high frequency deep brain stimulation (DBS) in treatment-resistant cases [7]. However, the need for noninvasive alternatives for patients who do not respond to standard treatments (e.g., serotonin reuptake inhibitors or CBT) remains.

While rTMS has shown promise when applied to the pre-SMA and to the OFC [8], tDCS has been less investigated for the treatment of OCD. Therefore, questions about which area(s) should be targeted by tDCS and which parameters should be used still need to be addressed.

DLPFC is a crucial area for the cognitive and emotional control as well as the most frequently targeted region in psychiatric applications of noninvasive brain stimulation (NIBS) techniques. However, in the very first clinical application of tDCS in OCD, cathodal tDCS resulted ineffective when applied to this cortical area [9].

Based upon the neuroimaging evidence of hyperactivity in the orbitofrontal cortex (OFC) of OCD patients, other studies targeted this region using cathodal inhibitory tDCS. In a case report, ten tDCS sessions (2 mA, 20 min) were delivered

twice a day with a 2-h interval, with the cathode (35 cm^2) placed over the left OFC and the anode (100 cm^2) placed over the contralateral occipital region. No adverse event was reported. At the end of the tDCS treatment no variation of symptoms severity was observed. One month after the completion of tDCS sessions, it was observed a 26 % reduction in severity of obsessive and compulsive symptoms measured using the Yale-Brown Obsessive Compulsive Scale scores [10]. These findings are consistent with a previous study reporting a similar reduction in obsessive and compulsive symptoms after low-frequency rTMS was applied to the left OFC [11].

Subsequently, the same group of researchers combined cathodal stimulation of the left OFC with anodal stimulation of the right cerebellum, using two active electrodes of 35 cm^2, to decrease OCD symptoms in patients with treatment-resistant OCD. In an open-label pilot study, eight patients with treatment-resistant OCD received ten sessions (twice a day) of 2 mA tDCS applied with this new montage. OCD (Y-BOCS and OCD-VAS) as well as depressive (MADRS) symptoms were measured before tDCS, immediately after the end of treatment, 1 and 3 months after the tenth tDCS session. The study reported a significant 26.4 % (±15.8) decrease of Y-BOCS score ($p = 0.002$). The beneficial effect lasted during the 3 month follow-up. No effect of tDCS was observed on depressive symptoms. At end point, five out of eight patients had a decrease of ≥25 %; and three out of eight patients had a decrease of ≥35 % in Y-BOCS score. The treatment was well tolerated [12].

Another suitable area of tDCS application in OCD is the pre-SMA, which has been found to be hyperactive in OCD patients during performance of cognitive tasks related to attentional aspects of action control [13, 14]. In fact, the evidence deriving from the clinical efficacy of inhibitory rTMS on this area [15] and from neurophysiological measures of altered motor cortex excitability in OCD [16], that normalized after 1-Hz rTMS to the pre-SMA [17], suggest that the premotor/motor system is abnormally hyperactive in OCD, and that there is a pathophysiological link between such hyperexcitability and OCD symptoms.

However, there is conflicting evidence about whether cathodal or anodal tDCS should be applied on pre-SMA to relieve OCD symptoms. While one study reported the successful treatment of two OCD patients using anodal tDCS over the left pre-SMA with the reference electrode placed on the contralateral SO region [18], another case study reported OCD symptoms worsening using anodal tDCS and improvement using cathodal tDCS over the bilateral pre-SMA with extracephalic reference electrode [19]. This last montage resulted effective also in a double blind, randomized, controlled, partial crossover trial, which showed anti-obsessional effects of cathodal and not anodal monocephalic tDCS over bilateral pre-SMA [D'Urso, under review in Depression and Anxiety]

A computational study has been conducted to simulate the path of the electric current through the brain during cathodal tDCS, aiming to optimize the use of tDCS in OCD and to help designing future trials [20]. This study found that the application of the active electrode (cathode) over the pre-SMA, with the reference electrode (anode) positioned in an extracephalic location (i.e., the subject's right deltoid), resulted in a distribution of the electrical field from the medial prefrontal cortex to the striatum, therefore reaching the cortical and subcortical brain areas which are crucially involved in the pathophysiology of OCD. Based on this model and on the promising results about the efficacy of cathodal tDCS to pre-SMA in treatment-resistant OCD, a large randomized controlled trial testing the clinical and neurobiological effects of tDCS in OCD is underway.

Therefore, as with rTMS, the most promising brain areas for tDCS application in OCD seem to be pre-SMA and OFC.

tDCS in Anxiety Disorders

Anxious patients typically show negative biases in perception and memory, and such biases in emotional processing are believed to play a fundamental role in the maintenance of anxiety disorders. Coherently, the cognitive neuropsychological model of antidepressants action assumes

that in anxiety disorders such treatments work by reversing negative cognitive biases [21]. Following the administration of anxiolytic and antidepressant treatment, early changes in emotional processing have been observed in healthy subjects and clinical groups; specifically, the cognitive changes might be predictive of later therapeutic response in patients [22].

In addition, attentional control is highlighted in models of trait anxiety [23] and DLPFC activity has been negatively correlated with trait anxiety in neuroimaging studies examining attentional control over emotional and nonemotional stimuli [24]. This suggests that modulating DLPFC activity has the potential to causally modify attentional control, which has particular relevance to trait anxiety. In fact, in a study by Heeren et al., tDCS to the DLPFC led to reduced vigilance to threatening stimuli in healthy subjects [25]. In this study the attentional bias (faster reaction times) to fearful faces was present in the sham tDCS group, whereas in the active tDCS group it was reversed, likewise with antidepressant and anxiolytic treatment [26]. Specifically, the bipolar-balanced montage (anode on the left DLPFC and cathode on the right DLPFC) significantly abolished the normal pattern of fear vigilance observed in the sham condition and suggests that intervening bilaterally, to change activity in both left and right DLPFC, may be critical for the observed anxiolytic-like effects.

The above results in healthy volunteers reveal an anxiolytic-like effect of DLPFC tDCS on a cognitive biomarker relevant to clinical anxiety and indicate a potential neurocognitive mechanism (reduced fear vigilance) that may partially mediate the clinical efficacy of prefrontal tDCS in anxiety disorders [27].

One more evidence that subjects with anxiety disorders show an attentional bias for threat is that Attention Bias Modification (ABM) procedures have been found to reduce this bias; results indicate that combining ABM and anodal tDCS over the left DLPFC reduces the total duration that participants' gaze remains fixated on threat, as assessed using eye-tracking measurement. As the tendency to maintain attention to threat is known to play an important role in the maintenance of anxiety, these findings suggest that anodal tDCS over the left DLPFC may be considered as a promising tool to reduce the maintenance of gaze to threat [25].

The next logical step is to assess whether an enduring therapeutic effect can be found and if early neurocognitive changes in patients can predict response to treatment of anxiety.

In a case report on the effect of tDCS in GAD Shiozawa et al. [28] performed 15 consecutive daily tDCS sessions in 3 weeks (except for weekends). The cathode was positioned over the right dorsolateral prefrontal cortex (DLPFC), and the anode was placed extracephalically over the contralateral deltoid. In each daily session a direct current of 2.0 mA for 30 min was administered. Anxiety symptoms substantially improved during the 15-day treatment course. After 1 month of treatment, the patient was asymptomatic and reported significant clinical improvement. The use of cathodal stimulation over the right DLPFC was chosen based on recent neuroimaging and brain stimulation studies. In an open-label trial with ten patients, Bystritsky et al. [29] used an anxiety task during functional neuroimaging to identify the cortical brain area to be stimulated with low-frequency rTMS. In all patients, the right prefrontal cortex was consistently activated and, after low-frequency rTMS over the right DLPFC over 6 weeks, all participants improved. Interestingly, low-frequency rTMS over the right DLPFC was also associated with improvement in anxiety symptoms in treatment-resistant depression [30] and in panic disorder with depression [31, 32]. In the tDCS case study, cathodal stimulation over the right DLPFC might have diminished neuronal activity in this area, secondarily modulating other cortical and subcortical structures involved in GAD pathophysiology such as the medial prefrontal cortex, the amygdala, and the insula [33]. It is also possible that the left DLPFC was secondarily modulated by the decrease in activity of the right DLPFC.

tDCS in PTSD

Brain regions involved in the anxiety network including the amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC), and the insular cortex somewhat overlap with the network involved in the acquisition of fear and its extinction, particularly relevant to PTSD [34]. PTSD patients seem to have deficits in extinction learning and/or recall [35], impairments that seem to be acquired after having developed PTSD [36]. It has been suggested that the deficit in recall extinction could explain the maintenance of PTSD symptoms and/or relapse following treatment [37]. In terms of neural correlates, this impaired ability for extinction memory has been linked with less activation in the vmPFC and the hippocampus and higher activation in the amygdala and the dACC [35].

If we understand the circuit and its maladaptive plastic changes, we can formulate and test hypotheses about the therapeutic efficacy of selective manipulation of these brain regions and networks. This can be achieved by using neuromodulation techniques in an attempt to reestablish homeostatic balance and healthy patterns of information processing.

More specifically, if we can find ways of enhancing fear extinction memory in the laboratory within samples of healthy participants and replicate them in clinical population, we could consider these tools as potential adjuncts to augment the memory trace formed during exposure therapy, which could ultimately lead to a decrease in symptoms severity and a lesser likelihood of relapse. The combination of tDCS and exposure therapy, as already shown for the combination of tDCS and CBT in depression [38], might have a synergistic effect in producing a clinical result in PTSD. The principle of the two interventions is the same: promoting the memory trace being formed during exposure therapy so that it becomes stronger. Because PTSD is well known for the deficit in recall extinction, enhancing extinction could benefit patients suffering from this disorder as well as from those anxiety disorders which share this cognitive feature. Clearly, this idea taps into the neural mechanisms of fear extinction that are relevant to some but certainly not all features and symptoms of PTSD.

Evidence for modulation of fear learning and extinction using tDCS remains scarce. In one study cathodal stimulation of the left DLPFC led to an inhibitory effect on fear memory consolidation compared to anodal and sham stimulations, as indicated by decreased skin conductance response to the conditioning stimulus presentation during extinction training at day 2. Thence this study suggests that left DLPFC cathodal stimulation interferes with processes of fear memory consolidation [39]. Furthermore, tDCS has been used in combination with a computerized working memory training in four patients suffering from both PTSD and poor working memory. This combined treatment led to the improvement of the cognitive and emotional disturbances as well as to the change of the neurophysiological measures which are usually found altered in PTSD, such as the P3a component of event related potentials (ERP) in response to novelty stimuli and the alpha peak frequency [40].

Nonetheless, we need a better understanding of how different tDCS parameters impact the PTSD circuitry to be able to design hypothesis-driven trials and confirm both safety and clinical efficacy.

Conclusion

Despite an intriguing rationale and some encouraging preliminary results, the application of tDCS in OCD, anxiety disorders, and PTSD is still in its infancy, and many mechanistic as well as clinical questions remain to be answered.

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Neurodegenerative Cognitive Disorders

16

Tarek K. Rajji

Abstract

Neurodegenerative cognitive disorders have a huge impact on our societies, especially as the general population continues to grow older. These disorders include various dementias including Alzheimer's dementia as the most common one. To date no effective treatments have been identified. Transcranial Direct Current Stimulation (tDCS) has been tested for its effects in patients with neurodegenerative disorders, especially patients with Alzheimer's dementia. In general, studies show a positive effect on cognition with good tolerability. However, studies to date are limited by small sample sizes, large variability in parameters of stimulation, and lack of long-term interventions and assessments. Future studies need to address these limitations. Further, future research could focus on combining tDCS with other cognitive enhancing interventions, more personalization of stimulation using modeling approaches, and aiming at preventing cognitive decline and cognitive manifestation of neurodegenerative disorders.

Keywords

Alzheimer's dementia • Cognition • Lewy body dementia • Neurodegeneration • Parkinson's disease • Prevention • tDCS

Neurodegenerative cognitive disorders, also referred to as dementias, affect more than 46 million people worldwide [1]. By 2050, this number is estimated to be more than 131 million. The current costs associated with dementia are estimated to be US $818 billion. To date, there are no interventions to prevent, cure, or even slow down these disorders. Alzheimer's dementia (AD) is the most common form of dementia. Other forms of dementia include vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease dementia, and others.

Transcranial Direct Current Stimulation (tDCS) is a noninvasive brain stimulation method

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that can be safely administered to conscious outpatients (i.e., it does not require general anesthesia or surgical implantation of a device). It utilizes low intensity electrical current either to increase cortical excitability with an anodal electrode or to suppress cortical excitability with a cathodal electrode [2]. Given its ease of use, portability, and high potential of scalability, several studies have tested the effect of tDCS in patients with dementia. Most studies have focused on patients with AD.

Alzheimer's Dementia

In Ferruci et al. [3], ten participants with AD (mean age: 75.2, SD: 7.3) received three 15-min tDCS sessions in a random order and 1 week apart: anodal tDCS, cathodal tDCS, and sham tDCS. Two stimulators were used. For each stimulator, one electrode was placed over the temporoparietal area (left or right) and the other over the right deltoid muscle. Current was 1.5 mA. Cognition was assessed before and 30 min after each session. Anodal tDCS improved word recognition and discrimination (by 17 %) while cathodal tDCS impaired both.

In Boggio et al. [4], ten participants with AD aged 70–92 years received two 30-min sessions of unilateral anodal tDCS—one session to the left DLPFC, another to the left temporal cortex—and a third session of sham tDCS. Reference electrode was placed over the right supraorbital area. Current was 2 mA. Cognition was assessed during stimulation. Anodal tDCS at both sites improved performance on a visual recognition memory task by 18 % for the DLPFC and 14 % for the temporal cortex [4].

The above two studies were followed by others that assessed the impact of a course of tDCS on cognition. In Boggio et al. [5], 15 participants with mild to moderate AD (mean age: 78.9, SD: 8.2) received daily for 5 consecutive days 30-min sessions of bilateral anodal or sham tDCS in a random order. Anodes were placed over the temporal lobes. Reference electrode was placed over the right deltoid muscle. Current was 2 mA. Cognition was assessed before the first tDCS session, at the end of treatment on day 5, 1 week later, and then 4 weeks later. Anodal tDCS not only resulted in improvements in visual recognition memory, but also these improvements persisted for 4 weeks following the course of tDCS. The percent change from baseline was about 11 %. tDCS was well tolerated by all participants.

In Khedr et al. [6], 34 participants with mild to moderate AD (mean age: 69.7, SD: 4.8) were randomized to receive anodal tDCS, cathodal tDCS, or sham tDCS. tDCS was applied to the left DLPFC for 25 min daily for 10 days. The reference electrode was placed over the contralateral supraorbital region. Current was 2 mA. Follow up assessments were conducted immediately, 1 and 2 months following tDCS course. Other than for a couple of participants experiencing transient itching, headache, and dizziness, tDCS was well tolerated. Both anodal and cathodal tDCS resulted in improvement on Mini-Mental State Examination (MMSE) [7] compared with sham tDCS. The two forms of active tDCS did not differ. Improvement on MMSE was by about four points with an initial improvement immediately following tDCS, an additional improvement 1 month later, and persistence of this improvement one additional month later.

Thus, studies that assessed the impact of a course of tDCS on cognition not only demonstrated a positive effect but also persistence of these effects several weeks following the end of the intervention. A parallel line of research is to investigate whether these pro-cognitive effects of tDCS can optimize performance in response to other cognitive enhancing interventions, or whether they can be augmented through these other interventions.

In Cotelli et al. [8], 36 participants with mild to moderate AD (mean age ~77) were randomized to receive anodal tDCS combined with memory training, sham tDCS combined with memory training, or anodal tDCS combined with motor training. tDCS was applied to left DLPFC for 25 min, 5 days a week for 2 weeks. The reference electrode was placed on the right deltoid muscle. Current was 2 mA. tDCS was initiated at

the beginning of each training session which also occurred 5 days a week for 2 weeks. Memory training consisted of training on face-name association task. Assessments were conducted at baseline, after the 2 weeks of tDCS course, and then 3 and 6 months from the start of the tDCS course. Both groups who received memory training experienced improvement in face-name association talk compared with the group who received motor training. The improvement persisted at 3 month follow-up. However, there was no significant generalization to other cognitive tasks beyond what the participants trained on. More importantly, groups who received anodal or sham tDCS, combined with memory training, did not differ in performance. These findings are in contrast with a single case report published on the combination of tDCS with cognitive training. In Penolazzi et al. [9], one patient with mild AD, age 60, received one course of anodal tDCS, daily for 20 min for 10 days, over the left DLPFC. Reference electrode was placed over the right supraorbital area. Current was 2 mA. Each tDCS was followed by 45 min of cognitive training. Two months later, the patient received the same course of cognitive training but with sham tDCS. Following the first course, the patient experienced improvement in global cognitive function and it persisted for 1 month. There was no such improvement following the second course.

Patients with AD not only experience cognitive dysfunction, but also significant behavioral and psychological symptoms. One study focused on the effects of tDCS on apathy. In Suemoto et al. [10], 40 participants with moderate with AD (mean age: 80.5, SD: 7.5) were randomized to receive anodal or sham tDCS delivered to the left DLPFC for 20 min, every other day for six sessions over 2 weeks. Reference electrode was placed over the right orbit. Current was 2 mA. Assessments were conducted at baseline, 1 week into the tDCS course, at the end of the 2-week course, and then 1 week after completing the course. The primary outcome measure was the score on the Apathy Scale [11]. tDCS was well tolerated with minor side effects, mainly scalp burning sensation and tingling. The two groups did not differ on Apathy Scale at any of the time points of assessments, nor did they differ on other secondary measure, including cognitive, mood, and caregiver burden measures.

Given the preliminary yet positive evidence supporting a pro-cognitive effect of tDCS in patients with AD, it is logical to assess its effects in pre-AD stages of the illness for potentially more impact on the course of illness. In Meinzer et al. [12], 18 participants with mild cognitive impairment (MCI) due to AD (11 amnestic MCI and seven multiple domain MCI) (mean age: 67.4, SD: 7.3) received, in a cross-over design, one session of anodal or sham tDCS to the left inferior frontal gyrus for 20 min. The sessions were separated by 1 week. The reference electrode was placed over the right supraorbital region. Current was 1 mA. Participants received tDCS while performing a semantic word-retrieval task and undergoing fMRI. tDCS was well tolerated. During sham tDCS, participants performed worse than healthy control participants. In contrast, during anodal tDCS, their performance normalized to become comparable to that of the healthy control participants. This normalization was accompanied by normalization of task-related and resting-state brain activity as measured with fMRI.

Notwithstanding that those studies to date need to be replicated in larger samples, the mechanism underlying any pro-cognitive effect of tDCS in patients with AD is largely unknown. In one study, repetitive tDCS with ten 20-min sessions delivered daily over 2 weeks to the frontal cortices of rats models of AD has been shown to reduce spatial learning and memory deficits that these rats experience. It also resulted in histological changes suggestive a protective effect of tDCS against Aβ induced neurotoxicity [13].

Lewy Bodies Dementia and Parkinson's Disease

Lewy body dementia accounts for 3–15 % of all dementias [14, 15]. It is typically characterized by fluctuating cognitive impairments, visual hallucinations, and Parkinsonian motor symptoms. It is also considered an umbrella that includes

dementia of Lewy bodies and Parkinson's disease dementia. The diagnosis of dementia with Lewy bodies is made when the motor symptoms develop within 1 year of the onset of cognitive deficits. In contrast, a Parkinson's disease dementia diagnosis is made when the motor symptoms had been present for more than 1 year prior to the cognitive deficits [16]. Cholinesterase inhibitors are recommended for the treatment of Lewy body dementia, though their clinical impact is modest [17, 18].

In contrast to patients with AD, patients with Lewy body disease experience significant impairments in attention, executive function, and visuospatial abilities early on during the illness. These impairments may even precede deficits in learning and memory [19–21].

tDCS has been tested for its effects on Lewy body dementia associated cognitive deficits. It has also been tested for its effects on cognitive impairment associated with Parkinson's disease per se, i.e., without a full manifestation of dementia.

In Boggio et al. [22], 18 participants with Parkinson's disease (mean age: 61.1) received one session of anodal tDCS delivered to the left DLPFC for 20 min. Reference electrode was placed over the right orbit. They also underwent a session of M1 stimulation and sham tDCS to the left DLPFC. Current was 1 mA in one set of experiments and 2 mA in another set. Before and during the last 5 min of each tDCS session, participants were administered a working memory task. All experiments were well tolerated. tDCS at 1 mA did result in any working memory change, In contrast, at 2 mA, left DLPFC stimulation resulted in more correct responses than M1 or sham tDCS. No change in speed of response was found.

In Pereira et al. [23], 16 participants with Parkinson's disease (mean age: 61.5, SD: 9.9) were randomized to receive one session of anodal tDCS to the left DLPFC or left temporoparietal cortex in a counterbalanced order, for 20 min. Reference electrode was placed over the right supraorbital area. Current was 2 mA. Anodal tDCS to the DLPFC resulted in improved phonemic but not semantic fluency. It also resulted in enhanced functional connectivity and task-related deactivation as measured with fMRI.

In Doruk et al. [24], 18 participants with Parkinson's disease (mean age: 61, SD: 8) were randomized to receive anodal tDCS delivered to the left or right DLPFC, or sham tDCS for 20 min, daily, 5 days a week, for 2 weeks. Reference electrode was placed over the contralateral supraorbital region. Current was 2 mA. Assessments were conducted at baseline, at the end of tDCS course, and 1 month following baseline. Overall, tDCS was well tolerated with reports of tingling, sleepiness, mild headache, neck pain, skin redness, and trouble concentrating. Anodal tDCS, irrespective of laterality, resulted in improved performance on Trail Making Test B, an executive function test, at the end of the tDCS course and that persisted at 1 month of follow-up. Sham tDCS resulted in improvement at the end of tDCS course, but the improvement did not persist. No significant effects were observed on other cognitive functions.

In Elder et al. [25], 13 participants with Lewy body dementia (mean age: 64.8, SD: 7.7), including eight with Parkinson's disease dementia and five with dementia with Lewy bodies, received a single session of anodal tDCS delivered to the left DLPFC for 20 min. Reference electrode was placed over the right deltoid muscle. Current was 2.8 mA. Before and 10 min after the stimulation, attentional and visuospatial cognitive tasks that have been shown to detect Lewy body dementia specific deficits were administered. Participants experienced improvements on some of the attentional but on none of the visuospatial tasks following tDCS. tDCS was well tolerated (Table 16.1).

Conclusions and Future Directions

Overall the current literature suggests that tDCS is potentially a useful nonsurgical neurostimulation modality to improve cognition in patients with neurodegenerative disorders. The literature is limited by the generally small samples studies.

Table 16.1 Publication on tDCS and cognition in neurodegenerative disorders

Authors (year)	Disease	*N*	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Results
Ferruci et al. (2008) [3]	Alzheimer's dementia	10	75.2 (7.3)	1.5	1	Anodal, cathodal, or sham over left or right temporoparietal Reference over right deltoid	Anodal stimulation at both sites improved word recognition and discrimination. Cathodal stimulation impaired both
Boggio et al. (2009) [4]	Alzheimer's dementia	10	70–92	2	1	Anodal or sham over left dorsolateral prefrontal cortex or left temporal cortex Reference over right deltoid	Anodal stimulation at both sites improved visual recognition memory
Boggio et al. (2012) [5]	Alzheimer's dementia	15	78.9 (8.2)	2	5 consecutive	Anodal over bilateral temporal cortices Reference over right deltoid	Compared to sham stimulation, active stimulation improved visual recognition memory and these improvements persisted for 4 weeks
Khedr et al. (2014) [6]	Alzheimer's dementia	34	69.7 (4.8)	2	10 consecutive	Anodal, cathodal, or sham over left dorsolateral prefrontal cortex Reference over supraorbital region	Anodal and cathodal stimulation improved performance on Mini-Mental State Examination immediately and the improvement persisted at 1 and 2 months
Cotelli et al. (2014) [8]	Alzheimer's dementia	36	~77	2	10 (5 days a week for 2 weeks)	Anodal, or sham over left dorsolateral prefrontal cortex Both combined with memory or motor training Reference over right deltoid	Memory training improved face-name association and the improvement persisted at 3 months. Anodal tDCS did not affect performance
Penolazzi et al. (2015) [9]	Alzheimer's dementia	1	60	2	10 consecutive	Anodal over left dorsolateral prefrontal cortex Each tDCS session was followed by cognitive training Two months later, cognitive training without tDCS Reference over right supraorbital region	tDCS combined with cognitive training improved global cognitive function that it persisted for one month. No improvement without tDCS

(continued)

Table 16.1 (continued)

Authors (year)	Disease	*N*	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Results
Suemoto et al. (2014) [10]	Alzheimer's dementia—focus on apathy	40	80.5 (7.5)	2	6 every other day	Anodal over left dorsolateral prefrontal cortex Reference over right supraorbital region	tDCS had no impact on apathy
Meinzer et al. (2015) [12]	Mild cognitive impairment	18	67.4 (7.3)	1	1 during a semantic word-retrieval task and functional MRI	Anodal or sham over left inferior frontal gyrus Reference over right supraorbital region	Anodal stimulation normalized performance, and task-related and resting-state brain activity compared to healthy participants
Boggio et al. (2006) [22]	Parkinson's disease	18	61.1	2	1 or 2	Anodal over left dorsolateral prefrontal cortex or left motor cortex Reference over right orbital region	2 mA anodal stimulation improved working memory
Pereira et al. (2013) [23]	Parkinson's disease	16	61.5 (9.9)	2	1	Anodal over left dorsolateral prefrontal cortex or left temporoparietal cortex. Reference over right orbital region	Stimulation improved phonemic but not semantic fluency
Doruk et al. (2014) [24]	Parkinson's disease	18	61 (8)	2	10 (5 days a week for 2 weeks)	Anodal or sham over left or right dorsolateral prefrontal cortex or left motor cortex Reference over contralateral supraorbital region	Both anodal stimulation improved executive function and it persisted for 1 month
Elder et al. (2015) [25]	Lew body dementia	13 (including eight with Parkinson's disease dementia)	64.8 (7.7)	2.8	1	Anodal over left dorsolateral prefrontal cortex Reference over right deltoid	Stimulation improved attention

Hence, confirmatory and adequately powered studies are urgently needed.

The literature suggests that if tDCS is to be effective with a persistent impact, it needs to be delivered repetitively, similar to most other interventions for brain disorders. Studies assessing different durations of courses of tDCS along with different frequencies per week will help characterize the dosing of tDCS. This is especially critical for patients with neurodegenerative disorders who may either need to commute to a center where tDCS is to be delivered or may depend on caregivers and their availabilities to administer it.

Electrodes placement and current intensity are two other variables that need further studying in various disorders. The current literature supports the use of anodal tDCS in general and 2 mA currents. Further personalization could be supported by modeling studies. Modeling studies predict the flow of current during tDCS [26] and help minimize the impact of morphological variation on tDCS effects. Again, this is highly salient to patients with neurodegenerative disorders who are likely to have experienced cortical shrinkage and tissue loss and using individualized tDCS dosing based on patient's specific morphological characteristics may be necessary in future trials [27].

Combining tDCS with other interventions will add also another level of complexity to be systematically investigated. tDCS interferes with neuroplasticity mechanisms [28, 29] as do other interventions such as cognitive training [30]. Timing of tDCS in relationship with another intervention will need to consider the potential interference of one intervention with another at the level of neuroplasticity mechanisms.

Finally, there are other neurodegenerative disorders that tDCS would still need to be tested for, e.g., frontotemporal dementia. It also needs to be further tested in pre-dementia stages such as mild cognitive impairment as well as in populations that are at high risk of developing dementia to assess whether it will have any cognitive preventative impact, e.g., patients with depression [31], schizophrenia [32], or others.

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Impulsivity and Substance-Use Disorders

17

Sara Labbe and Shirley Fecteau

Abstract

Substance-use disorders (SUD) have devastating consequences since the relapses are recurrent even after years of abstinence. The compulsive and repetitive drug intake is associated with neurobiological adaptations in the dopaminergic reward pathway and abnormality in the activity of frontal areas. In past years, there has been growing interest for applying transcranial direct current stimulation (tDCS) to the dorsolateral prefrontal cortex (DLPFC) as a tool for modulating safely and noninvasively the reward pathway in patients with SUD. Enthusiastic results have shown that a single tDCS session can reduce symptoms of SUD such as craving, a major factor contributing to relapse. The actual state of literature is encouraging since repeated tDCS sessions led to neuroplasticity and induce long-term effects such as reducing drug intake. Although several questions still remain to be addressed, there is growing evidence that tDCS has the potential to be used as a clinical tool in the treatment of substance and non-substance abuse. This chapter gives an overview of the recent use of tDCS in SUD studies. We also point out hypotheses that could explain the neural mechanisms underlying the beneficial effects of tDCS in these subjects. We suggest that tDCS applied to frontal areas modulates the reward pathway through direct top-down processes and indirectly by improving cognitive processes such as impulsivity.

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Introduction

Substance-use disorders (SUD) are defined as "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems" (American Psychiatric Association, 2013). SUD is a major problem of public health, especially because of its recurrence. The current approaches to maintain abstinence, reduce withdrawal symptoms, and prevent relapses mainly consist of pharmacological treatments and psychotherapy. Despite these treatments, SUD remains one of the most important chronic disorders in our society. The development of new therapies to treat SUD is thus much needed. Application of noninvasive brain stimulation such as transcranial direct current stimulation (tDCS) in patients with SUD has brought encouraging results in reducing substance use and craving. In this chapter, we first review the neural substrates of substance use and craving; two important outcomes in studies on SUD. We then discuss the rationale for targeting the dorsolateral prefrontal cortex (DLPFC) with tDCS in patients with SUD. This is followed by a review of the effects of tDCS in tobacco, cannabis, alcohol, and stimulant-use disorders. We then conclude by discussing two hypotheses that may explain the effects of tDCS in patients with SUD. Indeed, the exact mechanisms underlying the beneficial effects of tDCS remain unclear and two neurocognitive hypotheses, which are not mutually exclusive, have been proposed. The ultimate aim of this chapter is to contribute to the discussion on the potential hypotheses that may underlie beneficial effects of tDCS in SUD in order to promote development of future tDCS protocols for these clinical populations.

Neural Substrates of Substance-Use Disorders

The use of substances as well as pleasant food or even some behaviors (e.g., gambling) can be perceived as rewards that increase dopamine secretion in subcortical structures. The increase of dopamine in the nucleus accumbens core (NAc) (ventral striatum) through the ventral tegmental area (VTA) is the starting point of the mesolimbic dopaminergic circuit, also called the reward pathway. These sublimbic structures have connections with limbic structures, among these, the hippocampus. The reward pathway also involves mesocortical connections with frontal areas, such as the medial prefrontal cortex, the orbitofrontal cortex (OFC), and the DLPFC. These cortical structures are associated with higher cognitive and motivational functions responsible for driving the actions through top-down processes [1, 2]. For example, the mesocortical pathway enables the organism to remember the pleasant aspects of stimuli and repeat complex behaviors that lead to these rewarding stimuli. The reward pathway had a role in the evolution to satisfy basic needs such as eating, drinking, and reproduction. However, when stimulated by chemical substances or by repeated reward-related behaviors (e.g., gambling), the reward pathway may become maladaptive and associated with substance and non-substance related disorders (e.g., pathological gambling) [3–5].

Neural Substrates of Craving

Craving is a DSM 5 criterion of SUD and is characterized as "an intense desire or urge for the drug that may occur at any time but is more likely

when in an environment where the drug previously was obtained or used" [62]. Craving contributes to relapse, which may occur even after several years of substance abstinence [6–8]. Thus, reducing and resisting craving seem to be a key goal to prevent relapse and maintain abstinence.

In SUD studies, craving can be measured by standardized questionnaires in which subjects are asked to rate their levels of craving on a visual-analog scale (VAS). Most of SUD studies used cue-reactivity paradigms in which craving level is assessed before and after presentation of stimuli depicting substance intake, manipulation of the substance itself, and/or by asking subjects to recall previous experiences of substance intake [9]. An interesting aspect of cue-reactivity paradigms is that resisting craving can also be assessed [10]. Neuroimaging studies have extensively used this paradigm to study the neural activation underlying craving and craving resistance. It has been reported that resisting craving elicits activity in the dorsal medial prefrontal cortex whereas craving itself has been extensively associated with activity in the DLPFC [11–14]. Further, positive correlation between the level of self-reported craving and activation in the DLPFC have been reported in Positron Emission Tomography (PET) [11–13] and functional Magnetic Resonance Imaging (fMRI) studies [14–16]. Moreover, the activation in the DLPFC is of similar extent in both patients with SUD and non-substance-use disorders (e.g., pathological gambling) as demonstrated by a recent fMRI study using a cue-reactivity paradigm inducing cocaine craving or gambling urge [17].

The Use of tDCS Applied to DLPFC in SUD

Most tDCS studies in patients with SUD applied the electrodes bilaterally (e.g., one electrode to each hemisphere) or unilaterally to the right or left DLPFC. In the latter case, one electrode is positioned to one hemisphere and the other one to the contralateral orbit. The DLPFC has been the region of interest to apply tDCS in SUD for three main reasons. First, the DLPFC can be noninvasively targeted with surface electrodes that tDCS devices use. Second, as mentioned previously, this region is involved in the reward pathway through the mesocortical tract and its activity has been associated with craving. Thus, the activity of prefrontal areas could affect the dopamine secretion in limbic structures through top-down processes [18]. Finally, the DLPFC is involved in cognitive functions that are known to be impaired in patients with SUD. As it will be discussed below, tDCS applied to the DLPFC might promote some cognitive processes such as cognitive impulsivity or decision making which in turn contribute to prevent relapse. This is further discussed in the conclusion of this chapter.

Tobacco-Use Disorder (TUD)

The *World Health Organization* estimates that tobacco use causes six millions of deaths per year, worldwide. Tobacco intake results in the binding of nicotine on nicotinic cholinergic receptors (nAChRs) which target dopamine secretion in the reward pathway. Neuroimaging studies demonstrated that the activity of prefrontal areas, including the DLPFC, increases following cue-reactivity paradigms [11, 14, 19–22].

A pioneering study in TUD [23] investigated the effects of tDCS using a sham-controlled, crossover design. The authors exposed patients who smoked an average of 18 cigarettes a day to a cue-reactivity paradigm involving smoking videos and cigarettes manipulation. Craving levels were measured using a 5-item VAS before and after 20 min of tDCS at 2 mA and sham. Subjects received three conditions in a random order: (1) anodal to the right DLPFC coupled with cathodal to the left DLPFC, (2) reverse electrode montage, and (3) sham tDCS. Interestingly, both active conditions similarly decreased craving (reduction of 20 %) when comparing levels between pre- and post-tDCS whereas there was no significant change for the sham condition. The same team then applied five daily repeated tDCS sessions in

patients with TUD using the same stimulation parameters (20-min sessions at 2 mA) in a two-arm, sham-controlled parallel design [24]. Patients received either (1) active stimulation with the anode and cathode to the left and right DLPFC, respectively or (2) sham tDCS. After each session, the active tDCS group reported reduced cue-induced craving levels as compared to the sham tDCS group. The decrease in craving was cumulative following each of the consecutive sessions (except the last, fifth session). Furthermore, most patients in the active group (11 out of 13) but not in the sham group showed a decrease of 30% of cigarette smoked. Later, Fecteau et al. [25] investigated the effects of repeated tDCS sessions in patients with TUD who wished to quit smoking. The authors applied 5-day tDCS regimen (30-min sessions at 2 mA) in a sham-controlled, crossover design targeting both DLPFC (right anodal/left cathodal). The number of cigarettes smoked, cue-induced craving, and decision-making process were measured with the Ultimatum Game and the Risk Task. When patients received active as compared to sham tDCS, they smoked a lesser number of cigarettes. This decrease was still significant 4 days following the end of the last (fifth) tDCS session. Also, when comparing craving scores on the subscale of *Desire to Smoke* (*Questionnaire of Smoking Urges*) before and after the end of the fifth session, craving was reduced when patients received active as compared to sham tDCS. There was however no significant changes on the other subscales (*Anticipation of Positive Outcome, Intention to Smoke and Relief from Negative Affect*). Also, when patients received active as compared to sham condition, they rejected more often offers of cigarettes but not offers of money at the *Ultimatum game*. Finally, there was no difference between active and sham conditions at the *Risk Task*. This indicates that active tDCS modulates the decision-making process related to cigarettes (e.g., *Ultimatum game*) but did not modulate the risk taking of the tobacco users.

The effects of tDCS applied to the frontal-parietal-temporal (FPT) association area (20 min at 1 mA) on cigarette consumption were also studied using a sham-controlled, parallel design [26]. Two electrodes montage were used: (1) two cathodes to the FPT of each hemisphere and two anodes over the occipital cortex of each hemisphere, and (2) the anode and the cathode to the left and right FPT, respectively. Subjects who received cathodal tDCS over both FPTs reduced their daily cigarette consumption, whereas those who received other tDCS conditions reported no change.

Finally, in a sham-controlled, parallel design, Xu et al. [27] investigated whether anodal tDCS (20 min at 2 mA) to the left DLPFC modulates craving, negative affect, and attentional processing in abstinent tobacco smokers. Subjects were asked to remain abstinent of cigarette consumption since overnight. They were exposed to a cue-reactivity paradigm including videotapes, images depicting cigarettes, and cigarette manipulation. There was a significant reduction in the *urge to smoke* score following active tDCS as compared to before tDCS. However, this was not significantly different from the sham session. However, the total score of the *Profile of Mood States* questionnaire were significantly different between active as compared to sham tDCS. This implies a decrease in the score of subscales of anxiety, depressive mood and confusion. Finally, there was no significant effect of active tDCS as compared to sham on a computerized attentional task. This task however involved digits instead of smoking-related stimuli.

Among the tDCS studies on SUD, the most investigated population remain subjects with TUD. These results provide insights that tDCS applied to the DLPFC can modulate tobacco craving and consumption. The next steps would be to include longer follow-up in order to target the optimal tDCS parameters (e.g., electrode montage, intensity, number of sessions) and to identify the most susceptible patients to respond to tDCS treatment (e.g., light as compared to heavy smokers).

Cannabis-Use Disorders

Cannabinoids is the most widely illicit drug used in the United States (American Psychiatric Association, 2013). The cannabinoid molecule

bind to the cannabinoid receptors CB1 and CB2 located in VTA and into the shell of the NA; both regions involved in the reward pathway. To date, there is only one study that investigated the effects of tDCS on cannabis use disorder [28]. Using a sham-controlled, parallel design, the authors studied the effects of tDCS (15 min at 2 mA) to the DLPFC on craving and risk taking in 25 chronic cannabis users. The subjects were however asked to remain sober for 24 h before the session. Subjects received either 1—left anodal/right cathodal, 2—left cathodal/right anodal or 3—sham tDCS session. The Risk task was assed following tDCS session. The right anodal/left cathodal tDCS montage decrease the self-reported craving. Further, on the *Risk Task*, subjects in both active tDCS groups showed an increase in risk taking as compared to the sham group.

Alcohol-Use Disorders (AUD)

AUD is a common disorder with a prevalence of 29 % in the USA and is widely associated with the presence of comorbidity. The active molecule of alcohol is ethanol which is a nonselective agent. One of the non-specific effects of ethanol is to increase the dopamine secretion in mesolimbic area, leading to the pleasurable effect. As with other SUD, activity in prefrontal cortex has been associated with presentation to cue-reactivity paradigm. Specifically, it has been reported that exposure to alcohol-related cues increases activity in the DLPFC in subjects with AUD but not in healthy subjects [29].

In a sham-controlled, crossover design, Boggio et al. [30] investigated the effects of tDCS (20 min at 2 mA) applied to DLPFC on alcohol craving in patients with AUD. The subjects were involved in a rehabilitation program and were abstinent for 41 days at the time of testing. The conditions consisted of one single tDCS session with (1) the anode to the right and cathode to the left DLPFC; (2) the opposite montage; and (3) sham tDCS. Craving was measured using a cue-reactivity paradigm with videos of alcoholic drinks before and after tDCS. Following both active tDCS conditions, the cue-reactivity paradigm failed to induce craving. There was no significant difference between the two active conditions. In contrast, there was an increase of craving following the paradigm for the sham tDCS condition.

In a larger phase II clinical trials study, Klauss et al. [31] investigated whether repeated tDCS sessions to the DLPFC could reduce alcohol consumption in patients with AUD. In a sham-controlled, parallel design, subjects received two daily sessions for 5 consecutive days with the anode and cathode applied to the right anodal and left DlPFC, respectively. Subjects received either active (2 mA) or sham tDCS. Each daily session lasted 13 min and was separated by 20 min. There was significantly more sober subjects 6 months after the end of active condition (8/16 subjects) as compared to sham condition (2/17). There was however no significant decrease in craving between group as measure by the *Obsessive Compulsive Drinking Scale* (OCDS).

In a recent study [32], the effect of tDCS on the negative perception of alcohol-related cues was investigated in patients with AUD. The authors proposed that tDCS modulates the negative affect associated with alcohol, which may, in turn, contributes to reduce alcohol craving. The authors conducted a sham-controlled, parallel study in which subjects received 10 min of tDCS (1 mA). The electrodes were positioned either (1) to the DLPFC or (2) to the right inferior frontal gyrus (IFG). To assess how alcohol is perceived (e.g., as positive or negative), subjects performed the *Implicit Association Task* (IAT) before and after tDCS sessions. The IAT consists of classifying alcohol-related words as positive or negative. Subjects who received the active tDCS condition reported a decrease in craving. However, their negative and positive perception of alcohol-related words was not modulated as compared to the sham group. Thus, the authors concluded that the reduction in craving induced by tDCS may not be explained by an increase of the negative perception for alcohol.

In summary, the study of Boggio et al. and den Uyl et al. [30, 32] showed that tDCS could decrease alcohol craving. Furthermore, in a study with a larger sample size, Klauss et al. [31] demonstrated

that repeated tDCS sessions led to higher rate of sobriety without decreasing the self-reported craving. These results raised the hypothesis that repeated sessions increased the craving resistance and reduce alcohol consumption. Futures studies should include large sample size and repeated sessions to investigate this hypothesis.

Stimulant-Use Disorders

Stimulants substance such as cocaine or methamphetamines are highly addictive and powerful drugs as they directly stimulate the mesocorticolimbic reward pathway. As others drugs, relapses are often preceded by exposure to drug-related cues leading to craving [33]. It has been reported that subjects with stimulant use disorders as compared to healthy subjects do not show the same frontal brain activation when watching videotapes of cocaine use. According to fMRI and PET studies, an increased activity in the frontal areas such as the DLPFC, orbitofrontal and the anterior cortex cingulate (ACC) has been reported during a cue-reactivity paradigm in these subjects [13, 15, 34–39]. This activity is also related to the intensity of the self-reported craving [37].

In a sham-controlled, parallel design, Conti et al. [40] studied the effect of bilateral tDCS for 20 min at 2 mA on the activity of the ACC during exposure to crack-related images. Recent crack-cocaine abstinent (≤31 days) subjects received either (1) tDCS applied to the DLPFC (right anodal/left cathodal) or (2) sham tDCS. Using the low-resolution brain electromagnetic tomography (LORETA), they found that the sham tDCS group showed the predicted increase of activity during the cue-reactivity paradigm whereas the active group showed a decrease in activity of this region. This indicates that tDCS could decrease the activity related to exposure to cue-reactivity paradigm. The same team then applied repeated sessions of tDCS to the DLPFC [41]. They studied the effect on the event-related potentials in the ACC following cue-reactivity paradigm. In this study, recent abstinent crack-cocaine users were randomly assigned to receive five daily consecutive sessions of active (right anodal/left cathodal, for 20 min at 2 mA) or sham tDCS. There was however a high dropout rate: only nine subjects completed the entire protocol (three in sham group and six in active group). That could explain the non-significant effect between the active and the sham group on the event-related potentials in ACC. They however reported that five out of six subjects in the active group were sober until the 3-month follow-up whereas only one subject remained abstinent in the sham group.

On a larger clinical trial including 36 recent abstinent crack-cocaine users, Batista et al. [42] administrated five daily anodal tDCS sessions to the right DLPFC (cathodal to the left DLPFC). The subjects were separated in two groups: (1) active (20 min at 2 mA) and (2) sham tDCS. The active tDCS group led to significant decrease in the self-reported craving. This study did not include a cue-reactivity paradigm. The authors also reported an increase in the overall perception of quality of life in the active group, as measured by the World Health Organization questionnaire. In contrast, the score for perception of quality of life decrease in the sham group.

Another team investigated the effects of tDCS on risky behavior on recent abstinent cocaine users and healthy subjects using the *Balloon Analog Risk Task* (BART) [43]. This computerized task consists to pump virtual balloon where each pump give an amount of money. However, if the balloon reaches his individual explosion point, the subject loses all the accumulated money. In a sham-controlled, crossover design, the subjects received three tDCS sessions to the DLPFC: (1) left cathodal/ right anodal, (2) left anodal/right cathodal, and (3) sham tDCS. Before applying tDCS, Gorini et al. [43] measured the impulsivity in cocaine and healthy users using an impulsivity scale (BISS-11). As expected, the cocaine users presented higher impulsivity score as compared to healthy subjects. The right anodal tDCS condition decreased the risk taking in the BART for the cocaine users and the healthy subjects. Conversely, the left anodal condition led to an increase in risk-taking but only for the cocaine user group.

In a sham-control crossover study, Shahbabaie et al. [44] investigated the effect of a single tDCS

session on methamphetamine craving in meth-abstinent patients. This team administrated a cue-reactivity paradigm before, during, and after 20 min of tDCS at 2 mA. The montage consists to uni-hemispheric stimulation with the anode placed to the right DLPFC and the cathode to the contralateral supraorbital area. The authors administrated a computerized cue-induced craving assessment task in which subjects were ask to rate their level of craving in a VAS scale following each drug-related or neutral images. There was a significant decrease in craving during active tDCS as compared to sham tDCS but this effect was no longer significant for the measure following the tDCS session.

The results of tDCS studies applied on subjects with stimulant-use disorders provide promising preliminary results on craving. However, dropout is a major problem in this population, especially when the protocols involved repeated tDCS sessions. All of the studies discussed above recruited abstinent patients involved in rehabilitation programs instead of current stimulant users. For these reasons, the effects of repeated tDCS sessions on cocaine consumption have been little studied.

Discussion and Conclusion

In this review, we reported that the current state of knowledge pointed toward beneficial effects of the application of tDCS to the DLPFC in patients with SUD. In most of these studies, the main outcome was the self-reported craving following a cue-reactivity paradigm. Promising results showed that craving is reduced following a single tDCS session. A summary of the effects of tDCS on craving in patients with SUD is presented at Table 17.1.

Several studies revealed encouraging results following daily repeated sessions which could in return reduce substance intake. However, it remains unknown how tDCS modulates neuronal functionality considering SUD symptoms are reduced. Two hypotheses, not mutually exclusive, could explain the underlying mechanisms of tDCS in SUD.

The first one postulates that tDCS applied to DLPFC directly affects the neural substrates associated with craving. Indeed, a change in the activity of the DLPFC may in turn modify the dopamine secretion in the sub-limbic structures through mesocortical connections. Thus, the reduction in craving frequently reported in the studies discussed above could be explained by a direct effect of tDCS on the dopaminergic pathway.

A second hypothesis suggests an indirect effect of tDCS on craving by improving cognitive functions. Studies have extensively shown that patients with SUD as compared to healthy subjects differ in their decision-making process and impulsivity [35, 45–49]. Indeed, subjects with SUD exhibited more risk taking decisions than healthy subjects. The implication of the frontal cortex in these functions is now well established. For instance, it has been reported that activity of the DLPFC decreases in patients with SUD performing decision-making and impulsivity tasks [50, 51]. High level of impulsivity also contributes to not resisting craving, to relapse and is a predictor of developing SUD [49, 52]. It has also been reported that patients with SUD showed abnormalities in their frontal cortical activity which could explain a lack of self-control and an increase in the salience of the substance [1]. The combination of impulsivity with a reinforcing reward pathway could thus guide patients with SUD toward maladaptive behaviors in presence of the substance, despite their wish to quit using it.

Moreover, it has been demonstrated that tDCS applied to the DLPFC modulates cognitive functions in healthy subjects. Specifically, tDCS applied to prefrontal areas increases the response inhibition in healthy subjects [53–55] and decreases risk-taking [56, 57]. Thus, tDCS applied to the DLPFC in patients with SUD could improve their cognitive functions by decreasing risk taking behavior and impulsivity (e.g., increases response inhibition) and contribute to resist craving and maintain abstinence. Indeed, neuropsychological studies showed that a recovery of these cognitive functions is associated with abstinence [58, 59]. These cognitive improvements are also associated with neural recovery such as increase in thalamic metabolism [60].

Table 17.1 Description of transcranial direct current stimulation studies on craving in substance-use disorders

Author, year	Design (*n*)	tDCS parameters	Targeted regions (anode position)	Methods to evaluate craving	Main results
Tobacco-use disorder					
Fregni et al. 2008, [23]	Sham-controlled crossover (24)	1 session/condition, 2 mA, 20 min	L DLPFC (bilateral) R DLPFC (bilateral).	Cue-provoked craving, VAS	Decreased cigarette craving in both active tDCS conditions and sham
Boggio et al. 2009 [24]	Sham-controlled parallel (27)	5 daily consecutive sessions, 2 mA, 10 min	L DLPFC (bilateral)	Cue-provoked craving, VAS	Decreased cigarette craving in active group
Xu et al. 2013 [27]	Sham-controlled crossover (24)	1 session/condition, 2 mA, 20 min	L DLPFC with cathode over right supraorbital	Urge to Smoke Scale (UTS)	No difference between active and sham sessions
Fecteau et al. 2014 [25]	Sham-controlled crossover (12)	5 daily consecutive sessions, 2 mA, 30 min	R DLPFC (bilateral)	Cue-provoked craving, Questionnaire of Smoking Urges	Decreased craving in the *desire to smoke* subscale following the last (fifth) active tDCS session. No effect on other subscales
Cannabis-use disorders					
Boggio et al. 2010 [28]	Sham-controlled parallel (25)	1 session, 2 mA, 10 min	L DLPFC (bilateral) R DLPFC (bilateral)	VAS	Decreased cannabis craving for the R DLPFC group only
Alcohol-use disorder					
Boggio et al. 2008 [30]	Sham-controlled crossover (13)	1 session, 2 mA, 20 min	L DLPFC (bilateral) R DLPFC (bilateral)	Cue-provoked craving, Alcohol Urge Questionnaire (AUQ)	Decreased alcohol craving on both active tDCS condition and sham session
Klauss et al. 2014 [31]	Sham-controlled parallel (35)	2 daily sessions for 5 consecutive days, 2 mA, 13 min	R DLPFC (bilateral)	Obsessive Compulsive Drinking Scale (OCDS)	No difference between active and sham group on craving
Den Uyl et al. 2015 [32]	Sham-controlled parallel (48)	1 session, 1 mA, 10 min	R inferior frontal gyrus, cathode over left supraorbital L DLPFC, cathode over right supraorbital	Alcohol Approach and Avoidance Questionnaire (AAAQ)	Decreased alcohol craving after the DLPFC stimulation group only
Stimulant-use disorders					
Gorini et al. 2014 [43]	Craving not assessed				
Shahbabaie et al. 2014 [44]	Sham-controlled crossover (30)	1 session/condition, 2 mA, 20 min	R DLPFC and cathode over L supraorbital	Cue-induced craving task (CICT), VAS	Decreased stimulant craving in active as compared to sham session
Conti et al. 2014a [40]	Craving not assessed				
Conti et al. 2014b [41]	Sham-controlled parallel (9)	5 daily consecutive session, 2 mA, 20 min	R DLPFC (bilateral)	Crack-related cue, Brief Cocaine Craving questionnaire	No changes in craving for both groups
Batista et al. 2015 [42]	Sham-controlled parallel (36)	5 daily consecutive session, 2 mA, 20 min	R DLPFC (bilateral)	Items from the Obsessive Compulsive Drinking Scale	Decreased stimulant craving in active as compared to sham group

N sample size, *R* right, *L* left, *mA* milliampere, *min* minutes, *VAS* Visual Analog Scale, *DLPFC* dorsolateral prefrontal cortex

Several challenges still remain for future tDCS studies in patients with SUD. Among these, the optimal stimulation parameters still need to be established. Studies in SUD mostly deliver tDCS bilaterally (one electrode to each DLPFC) instead of unilaterally (e.g., cathode over contralateral supraorbital). However, both positive and negative results were obtained with either the anode or cathode applied to the right hemisphere. Future work is required to determine whether the effect of anodal is more effective in one hemisphere than the other. Also, future tDCS studies should screen participants according to their history of consumption. For example, older participants with SUD suggest a longer history of consumption as compared to younger participants. Indeed, the neurobiological adaptation of the dopaminergic pathway may not be the same for a participant with recent SUD as compared to years of substance abuse. In order to avoid confounding variables, the presence of comorbid disorders altering neuronal functioning (e.g., depression) should also be taken into consideration. Finally, although substance craving seems to share a common neurophysiological basis, this feeling is complex and can be expressed differently between subjects. Thus, futures studies should assess craving using different subscales. For example, the *Standardized Questionnaire of Smoking Urges* distinguishes between the *intention to smoke* and *the desire to smoke* which are two separate components of craving [61].

Finally, as described previously, the frontal areas such as the DLPFC and the OFC contribute to the maladaptive behaviors related to substance intake through the mesocortical pathway. Most studies on tDCS in SUD are presently focused on craving intensity assessed with VAS. However, since tDCS modulates the activity of these frontal and prefrontal regions, the resistance of craving including the patient self-control in the presence of the substance as compared to the craving itself should also be studied.

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Epilepsy

18

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Abstract

Treatment of drug-resistant epilepsy has seen major advancements in the recent years with the availability of several neurostimulation techniques, among which noninvasive tDCS has emerged as a viable option. Cathodal tDCS has the capacity to induce reductions in cortical excitability in humans resembling classical forms of long-term depression. The tDCS antiepileptic potential has been tested in three controlled clinical trials thus far, outcomes of which are mixed with respect to seizure suppression. In general, more profound suppression of epileptiform EEG activity, rather than suppression of clinical seizures has been observed after cathodal tDCS. As a result, preclinical in vivo and in vitro tDCS studies aimed at obtaining mechanic insights into tDCS effects are on the rise as means to improve clinical tDCS protocols for focal and patient-specific stimulation, and also as studies that will identify tDCS–pharmacotherapy combination therapies.

Keywords

Epilepsy • Seizures • Cortical excitability • NMDA receptor • GABA-A receptor • Long-term depression • In vivo • In vitro

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Introduction

Introduction: Neuromodulation in Epilepsy

The rise of interest in neuromodulation is particularly relevant in epilepsy, where seizures are resistant to pharmacotherapy in approximately 1/3 of all instances, a statistic that has not changed despite the introduction of >20 new antiepileptic drugs in the late twentieth and early twenty-first

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century [1, 2]. Accordingly, neurostimulation protocols are emerging as potentially valuable tools for seizure control.

Stimulating the nervous system with electricity to treat neuropsychiatric symptoms that include epilepsy is not new. In the first century AD, the Roman physician Scribonius Largus documented treating headaches by applying electric torpedo fish to the head, and another Roman physician, Pedanius Dioscorides, in 76 AD applied the torpedo fish to a patient with epilepsy [1]. As brain stimulation in general, neuromodulation for epilepsy has advanced considerably in recent years. Neurostimulation protocols can be coarsely divided into either invasive or noninvasive. Among the invasive options are vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS). Noninvasive protocols include trigeminal nerve stimulation (TNS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS).

tDCS in Epilepsy

Applied to the mammalian cerebral cortex, tDCS induces both acute and sustained change in cortical excitability. After a short exposure time to one session, typically 20–30 min, cathodal tDCS leads to a reduction in cortical excitability, while anodal tDCS predictably increases cortical excitability. Beyond the neocortex, experimental in vitro DC stimulation (DCS) indicates a potential for similar modulation of excitability in the hippocampus [3–5]. In epilepsy, the capacity of cathodal tDCS to reduce cortical excitability has prompted research into this technique's antiepileptic potential [6, 7].

The relatively low intracranial currents associated with tDCS likely account for its favorable safety profile. In contrast to other noninvasive neurostimulation techniques like TMS, seizures have not been associated with tDCS in humans, even in the vulnerable population with epilepsy. The remaining side-effects are largely limited to skin irritation at the electrode sites [8, 9].

Clinical Studies

In humans with epilepsy, clinical tDCS data are limited. In a review of published clinical data in epilepsy through 2015, San Juan and colleagues [7] identified data from 65 individual patients where five were participants in a randomized sham-controlled double-blind crossover study, 55 were divided between two randomized sham-controlled studies (both double-blinded with respect to EEG interpretation), and the remaining five were described in case reports.

tDCS clinical trial results, while inconclusive, are overall encouraging. In a randomized sham controlled study of adults ($N = 19$; average age 24 years) with medically refractory epilepsy secondary to MRI-positive malformations of cortical development, 1mA cathodal tDCS was delivered in a single session for 20 min using surface sponge electrodes (35 cm^2) arranged with the cathode over the seizure focus and the anode over the region with either normal EEG, or the least frequent epileptiform abnormalities in case of multifocal epilepsy. In the sham control condition, the stimulator was turned off after 5 s to generate the similar initial itching sensation without any current for the remainder of the stimulation period. Clinical seizures were monitored by diary and electrographic abnormalities were measured by 20-min EEGs obtained at baseline, as well as immediately after, 15 days, and 30 days after stimulation. EEG readers were blinded to the treatment condition. The results indicate that cathodal tDCS was safe and well-tolerated in this population. The frequency of interictal epileptiform discharges was reduced by 64 % immediately after tDCS. A favorable trend towards seizure reduction (44 % in treatment group vs. 11 % in control group) was detected, but significant differences in clinical seizure frequency between treatment and control groups were not identified. Notably, the electrographic response and the trend toward seizure reduction lasted as long as one month in some patients [10].

In a study of pediatric patients with refractory focal epilepsy ($N = 36$), children (6–15 years old) received a single treatment session of sham tDCS

or verum cathodal 1 mA tDCS for 20 min. Cathodal tDCS in this study was also administered via a 35 cm^2 sponge electrode placed over the epileptogenic focus as cathode, centered on the electrode with the international 10–20 EEG electrode placement system location where interictal spikes of sharp waves were greatest in amplitude, and the reference anode was placed on the contralateral shoulder. While the treatment group received the current for 20 min, in sham stimulation, the current was discontinued just after 30 s in a blinded setting. Epileptiform discharges (spikes and sharp waves) per 30 min of EEG recording at baseline, over time after treatment: 15 min, 24 h, 48 h, and 4 weeks were compared. EEG readers in this study as well were blinded of the treatment condition. The results indicate that tDCS was well tolerated and corresponded to significant 50 % decrease in the EEG spike frequency at 24 h and 58 % at 48 h after active stimulation. Moreover, a statistically significant, but small decrease of 5 % in the clinical seizure frequency was observed in the verum tDCS group with no difference in sham treated group [8]. However, in another study on five pediatric patients with focal, refractory continuous spikes and waves during slow sleep, cathodal tDCS (1 mA, 20 min) applied over a seizure focus failed to suppress continuous focal spikes in sleep [11]. Here the active cathodal tDCS was administered via a 25 cm^2 sponge electrodes placed on the area of peak negativity, and the anode was placed on the opposite end of the spike dipole, corresponding to the area of peak positivity the discharge. Stimulation in this instance was during wakefulness, and spike-wave index measures were in sleep. There were no adverse events reported during the study or follow-up.

In addition to seizure suppression, tDCS may have a role in mitigating behavioral symptoms that are commonly comorbid with epilepsy. In a recent pilot study of 37 adults with temporal lobe epilepsy, Liu and colleagues explored the tDCS effects on depression and memory dysfunction in these patients [12]. Two milliamps, 20 min tDCS was delivered for 5 days with anode over the left dorsolateral prefrontal cortex and cathode over the right supraorbital area. While the active treatment group received current for 20 min, the current during sham control stimulation was ramped up only for 30 s and thereafter ramped down. The 5-day tDCS course corresponded to a modest improvement in depressive symptoms immediately after active treatment. Notably, investigators did not find an increase in interictal discharge frequency thus indicating tDCS safety for applications other than seizure suppression in patients with epilepsy.

Data from the three clinical studies that include cephalic placement of the anode electrode also support the relative safety of anodal tDCS in the population with epilepsy. A natural concern for anodal tDCS is the potential for seizure exacerbation by mechanisms that enhance cortical excitability in the healthy population. Such cortical activation may be even more relevant in the population that is defined by a vulnerability to seizure. Yet, neither seizure exacerbation nor increase in epileptiform EEG activity was found in conditions where the anode electrode was over quiescent cortex, or the positive side of the spike dipole, or the dorsolateral prefrontal cortex [10–12].

Preclinical Studies

The mixed outcomes of human tDCS trials in epilepsy underscore the need for preclinical studies that may inform future clinical tDCS study design. Notably, as the term “transcranial” is not relevant for in vitro brain stimulation, “DCS” rather than “tDCS” is often used to describe the stimulation condition in preclinical studies.

Preclinical DCS research can provide insight is the mechanism by which DCS may produce a sustained antiepileptic effect. This was recently addressed by Chang and colleagues who studied the cathodal DCS effect on acute chemoconvulsant in isolated mouse thalamocingulate brain slices, an in vitro model of frontal lobe epilepsy. In their experiment, brain slices were stimulated by two parallel Ag/Ag-Cl electrodes connected to an isolated stimulator were placed external to the slice in a recording chamber to generate a uniform electric field (4 mV/mm). Spontaneous

excitatory postsynaptic currents (EPSCs) were recorded, as were epileptic EPSCs induced by bath application of either the potassium channel blocker 4-aminopyridine or the $GABA_A$ receptor antagonist bicuculline. Consistent with past studies, cathodal DCS suppressed evoked synaptic transmission and spontaneous EPSCs, a finding that the authors attributed to real-time neuronal membrane hyperpolarization. However, the antiepileptic effect persisted in this model, and was shown to be dependent on activation of the n-methyl-D-aspartate (NMDA) type glutamate receptor, thus behaving in ways like the well-described phenomenon of NMDA-dependent long-term depression (LTD) of excitatory synaptic strength [13]. The value of such data is in identification of a molecular pathway by which DCS may suppress seizures. This not only satisfies a scientific curiosity, but offers an opportunity to test whether pharmacotherapy that facilitates a component of this pathway may also facilitate the antiepileptic efficacy of tDCS, which, as above, is incomplete in clinical practice. However, systematic in vitro studies that investigate the molecular substrate of the DCS antiepileptic effect are rare. More commonly, in vitro DCS data provide insight into the electrophysiologic basis of seizure suppression by tDCS. For instance, early in vitro studies in a low-calcium hippocampal slice model identified that epileptiform discharges may be suppressed by field strengths in the 1–5 mV/mm range and that such suppression is polarity dependent [14, 15].

Among the more specialized applications that can be tested in animal epilepsy models is the capacity for cathodal tDCS, applied as a pretreatment to prophylaxis against seizures. This was first tested by Liebetanz and colleagues in a modified cortical ramp-stimulation focal seizure model in rats. In these experiments, tDCS was delivered with unilateral epicranial conductive electrodes to rat sensorimotor cortex, and threshold for localized seizure activity was determined by trains of pulsatile stimulation (50 Hz; 2 ms; 2 mA) delivered through the same epicranial contact. One group of animals received cathodal tDCS (100 μA) for 30 and 60 min, or anodal tDCS for 60 min. In another group the current intensity was doubled (200 μA) and stimulation durations were halved in all three condition. The main finding of the work was that cathodal tDCS caused an elevation of localized seizure threshold lasting for ≥2 h. In contrast, anodal tDCS had no significant effect on seizure threshold, confirming in vivo a polarity-dependent anticonvulsant tDCS effect, and absence of seizure exacerbation by anodal stimulation, as suggested also by clinical tDCS trials [16].

In complement to the preclinical study of tDCS in focal seizures [16], the antiepileptic potential of cathodal tDCS was also demonstrated in a rat amygdala-kindling temporal lobe epilepsy model. Here, Kamida and colleagues demonstrated that cathodal tDCS reduced clinical seizure severity and EEG after discharge duration, while elevating the afterdischarge threshold in amygdala-kindled rats, and these effects lasted at least 1 day after the last tDCS session (30-min daily treatment at 200 μA for 1 week). This treatment regimen also corresponded to improved cognitive performance on the Morris water maze [17]. The same group also investigated the effects of cathodal tDCS on convulsions in a rat pup lithium-pilocarpine status epilepticus model. In this study, rats were treated for 2 weeks with 200 μA cathodal tDCS delivered for 30 min per session using epicranial electrodes. Monitored over 2 weeks post stimulation, the authors found a significant 21 % reduction in the frequency of convulsions between sham and cathodal tDCS treated rats suggesting an antiepileptic effect. Among other findings, long-term treatment with cathodal tDCS also had neuroprotective effects on the rat hippocampus and led to improvements in performance of the water maze spatial memory task [18].

The above data indicate an intriguing prospect for tDCS as a means to interfere with epileptogenesis, rather than just seizures. The search for an effective and safe antiepilepotgenic treatment is an active field in experimental epilepsy. The unmet need for such treatment is underscored by complete absence of clinical antiepileptogenic interventions: for instance, none of the approximately 40 drugs that are prescribed to treat seizures are antiepileptogenic. Thus further studies

of tDCS in its capacity to prevent the onset of epilepsy after an epileptogenic brain injury such as trauma, stroke or status epilepticus may yield valuable product.

In contrast to in vivo experiments that tested a delayed antiepileptic tDCS effect, in a recent study by Dhamne and colleagues, cathodal tDCS was tested in the acute seizure setting that approximates status epilepticus to assess an immediate anticonvulsant effect. In this experiment, investigators modeled the realistic scenario that seizures will have already started by the time tDCS is deployed in the clinical arena. Moreover, a patient with status epilepticus will be likely to have received an anticonvulsant before the start of tDCS. Cathodal tDCS in this experiment was delivered via a scalp electrode for 20 min at either 1 mA, 0.1 mA or, in the control condition, 0 mA. And to simulate a likely clinical combination, tDCS was also tested in combination with lorazepam, a first-line anticonvulsant benzodiazepine that is routinely administered to human patients with epilepsy. The results identify electrographic seizure suppression within minutes of 1 mA cathodal stimulation. Moreover, a combination of tDCS and a sub-effective lorazepam dose suppressed seizures better than either intervention, suggesting that cathodal tDCS may act synergistically with lorazepam [19]. Of translational relevance for future clinical application, these data indicate an important direction for neuromodulation research toward systematic testing of combination drug-device therapy in epilepsy

Conclusion

Given that the rate of drug-resistant epilepsy has not changed much in recent years, tDCS offers a plausible noninvasive and nonpharmacologic option to improve seizure control in patients with intractable seizures. Although tDCS antiepileptic effects have yet to be substantiated in large clinical trials, the benign tDCS side-effect profile suggests a favorable risk–benefit ratio and high likelihood of near-future implementation in clinical epilepsy. The inconsistent findings with respect to seizure suppression in the few controlled trials underscore the need for improved protocols for focal and patient-specific stimulation to enable superior targeting of the seizure focus [20–22]. Additionally, clinical tests of tDCS antiepileptic capacity have been limited to trials of single stimulation sessions. This is in contrast to other fields where tDCS is delivered daily in multiple sessions to produce a sustained neuromodulatory effect [12, 23–25], and preclinical studies that test multiple tDCS exposures [17, 18]. Thus, future trials may incorporate a multi-session stimulation strategy. Last, novel neuroprotective and antiepileptogenic tDCS applications are suggested by preclinical research, and also may lead to disease-modifying treatment strategies in future clinical embodiments of this technology.

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Pain Syndromes

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Abstract

The twentieth century was characterized by great discoveries in medical sciences, which enhanced our knowledge of mechanisms of disease and allowed for the development of pharmacological therapies to treat a large number of pathologies. During the same period, striking advances were accomplished in the pain field, particularly after the introduction of the concept of pain as a complex phenomenon rather than a simple sensation or a mere symptom. Moreover, at least part of the brain mechanisms related to such a complex experience has been revealed over the last decades with the advance of the neuroimaging field. Nonetheless, adequate pain control, especially in chronic pain patients, is still considered a challenge for clinicians worldwide. In this context, tDCS emerges as a promising mode to provide noninvasive modulation of dysfunctional neural networks present in chronic pain. Indeed, the results of several studies suggest that tDCS can produce long-lasting pain relief in different chronic pain syndromes, including migraine, fibromyalgia, and neuropathic pain. Nevertheless, it is still necessary to establish the most suitable protocols for each chronic pain disorder. Moreover, it is imperative to reveal the neuromechanisms related to tDCS-induced analgesia.

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Introduction

Pain is a phenomenon that has been identified and explored since the beginning of time, in distinct cultures and civilizations. Pain is a disabling symptom common to several pathologies and it is considered the primary reason that leads individuals to seek medical care [1]. Nevertheless, its concepts and definitions have been modified considerably throughout the centuries and especially during the second half of the twentieth century, when it evolved from a notion of a purely sensory event to a model of a complex and multifaceted experience. Indeed, since the outstanding work of Melzack and Casey (1968), it has been accepted that pain is not restricted to a sensory-discriminative dimension, which is unquestionably important to the full characterization of a given noxious stimulus (e.g., nature, location, intensity, and duration). Instead, pain is considerably more complex than that, since it includes not only nociception but also encompasses motivational-affective properties, intrinsically connected to the reticular formation and limbic system, and a cognitive-evaluative dimension, processed by higher order cortical areas, and that exerts control over the other two dimensions (e.g., sensory-discriminative and cognitive evaluative) [2]. Such concept led clinicians and researchers that take part in the field to define pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," a concept that goes beyond nociception [3].

Pain is classically differentiated into two basic categories: acute or chronic. Although overly simplistic, this classification can be extremely useful in the clinical setting, since acute and chronic pain has distinct clinical presentations. Furthermore, chronic pain is usually incapacitating and associated with greater psychological and social impairment to the sufferers [4–7]. The adequate management of chronic pain is still considered a challenge for clinicians worldwide and its prevalence as well as the impact it produces in healthcare systems have been hugely studied and debated in the last years [8]. Therefore, other than distinguishing acute and chronic pain based only on arbitrarily chronological markers (classically 3 or 6 months) it is important to understand the pathophysiological events underlying both conditions.

In fact, the struggle to treat chronic pain derives mostly from the difficulty to understand its complex mechanisms, which leads researchers in the field to focus their attention towards the biological mechanisms related to this. In fact, the intricate machinery that triggers and maintains chronic pain has been partially unveiled. It has been established that a maladaptive plasticity affecting both the peripheral and the central nervous systems and associated with central and peripheral sensitization plays a major role [9].

Another essential aspect that must always be considered is that chronic pain does not represent a single nosological entity, since it comprises a variety of conditions of somatic, neuropathic, or even psychological origins, each one with particular characteristics [10]. For instance, it has been reported that different symptom profiles (e.g., pain quality and its spatial properties) can distinguish patients with neuropathic pains (e.g., postherpetic neuralgia painful diabetic, painful idiopathic sensory polyneuropathy, peripheral neuropathy) from those subjects with nociceptive pain (e.g., non-neuropathic low back pain and osteoarthritis) [11, 12]. Such findings very likely reflect the presence of specific events, concurring to the mechanisms of each particular chronic pain syndrome. For instance, a reduction in the intracortical inhibition has been shown in patients

with peripheral neuropathic pain, but not in osteoarthritis patients, which might suggest the presence of specific mechanisms related to neuropathic and nociceptive pain [13]. Moreover, a huge variability occurs in the course of chronic, especially neuropathic, pain among the individuals affected. This variability depends on the body region affected and is believed to be the result of interactions between etiological and environmental factors as well as genetic polymorphisms. In the future, the precise identification of dysfunctional mechanisms, representative of each chronic pain syndrome, will permit the development of more individualized treatments, which will probably result in a significant improvement of efficacy and decrease of side effects [14].

Due to the enormous challenge of treating chronic pains with the pharmacological therapies and surgical interventions currently available, clinicians and researchers have devoted to develop and enhance clinical strategies to provide relief for chronic pain patients, especially those suffering from refractory conditions. In this context, despite the long history in the use of electrical brain stimulation to provide pain relief [15], the use of neuromodulatory techniques to this purpose has only received considerable attention in the last three decades, especially after the studies of Tsubokawa et al. in the early 1990s [16, 17] that successfully applied motor cortex stimulation (MCS) to treat chronic neuropathic pain syndromes. As a matter of fact, the choice of the motor cortex as a target for pain treatment occurred after the unexpected discovery that thalamic hyperactivity could be decreased by MCS, while sensory cortical stimulation failed to produce comparable results [16–18]. In reality, a possible connection between the motor cortex and pain had emerged years before with the report of successful facial pain relief after cortical removals of both postcentral (sensory) and precentral (motor) cortex facial representations, in two patients [19], while cortical removals limited to the postcentral gyrus did not result in lasting pain relief for central pain sufferers [20]. In the following years after Tsubokawa work, clinical studies investigated the efficacy of MCS as well as noninvasive neuromodulatory techniques, to treat chronic pain disorders [21–25]. Furthermore, the ability of those methods to modulate the activity of faulty neural networks was also demonstrated [26].

Among the noninvasive neuromodulatory therapies applied for pain control, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are the most investigated. One of the main advantages of adopting protocols restricted to noninvasive methods of neuromodulation is the lower incidence of side effects. Although rare cases of TMS-related seizures have been documented [27, 28], typically only minor and transient side effects, such as tingling, transient headaches, skin irritation, itching, burning sensation, and nausea, occur with noninvasive procedures [29, 30] as long as the safety criteria are followed [31, 32].

With respect to tDCS, it is considered an effective method to modulate brain activity. Moreover, it permits a reliable sham condition and its technical operation is relatively simple [24, 25, 33, 34]. All these features make this procedure particularly suitable for pain studies. Not surprisingly, since its reintroduction in neurophysiological and clinical research, during the late 1990s and early 2000s [35, 36], several studies have reported that it is an effective method to treat distinct chronic pain syndromes, including fibromyalgia [25, 37–40], pain due to traumatic spinal cord injury [24, 41–43], chronic pelvic pain [44], refractory orofacial pain [45], postherpetic neuralgia [46], painful diabetic polyneuropathy [47], chronic neuropathic pain following burn injury [48], neurogenic pain [49], trigeminal neuralgia [50], low back pain [51], migraine [52–54], and chronic temporomandibular disorders (TMD) [55]. However, the effectiveness of tDCS for pain control is still a matter o debate in the literature. Although the results of a recent meta-analysis suggest that tDCS provides a significant reduction of pain levels [56], according to the results of another study, there is insufficient evidence that this method is effective to treat chronic pain in all patients [29]. Nevertheless, it is important to emphasize the elevated heterogeneity of the samples evaluated

in those studies, which included subjects affected by chronic pains associated with a great variety of diseases (e.g., fibromyalgia, spinal cord syndrome, multiple sclerosis, and migraine), the majority presenting completely unrelated pathophysiological mechanisms, which in turn may have impacted the findings.

Another important aspect that must be considered when interpreting the results of these clinical trials is the presence of adequate subject blinding during active and sham stimulation. As a matter of fact, it has been reported that incomplete blinding may exaggerate the clinical outcome by 25 % [57]. This aspect is especially prominent with TMS, since auditory clues along with the sensation of stimulation occur with active but not sham stimulation [58, 59]. Thus, some novel TMS strategies have been elaborated to address this concern [60]. Regarding tDCS, the feasibility of conducting double-blind sham-controlled clinical trials has been reported at current intensities of 1 mA in tDCS-naive participants [61, 62]. However, it has been reported that similar to TMS, active tDCS stimulation could be distinguished from sham at a current intensity of 1.5 mA [30], and both subject and operator blinding would be compromised at intensities of 2 mA since active and sham stimulations could be markedly differentiated [63].

One crucial feature, specifically related to tDCS, is the type of montage chosen. *M1-SO* is the montage classically adopted for pain studies. In this setup, the anode (positive pole) is placed over the region corresponding to primary motor cortex (M1) and the cathode (negative pole) over the contralateral supra-orbital (SO) area [64, 65]. Nevertheless, along the recent years other montages have been successfully built and tested, including *DLPFC*, that used both electrodes (anode and cathode) positioned over the dorsolateral prefrontal cortex (DLPFC) and *Cz-Oz*, with the anode over the vertex and the cathode over the occipital cortex. *M1-SO*, *DLPFC*, *and Cz-Oz* have been referred as conventional montages, since they use the same large electrodes (5 × 7 cm) positioned in different locations [53, 54, 66], and some of those methods have been compared. It has been reported that fewer subjects can distinguish sham, anodal, and cathodal stimulation when Cz-Oz is the montage applied. On the other hand, more subjects would recognize the type of stimulation when M1-SO is applied [67]. However, future studies must confirm such findings.

More recently, high-definition-tDCS (HD-tDCS) montages, using smaller, ring electrodes, have been developed, with the goal of increasing the focality of the electrical current. HD-tDCS montages include *HD-tDCS 4 × 1*, with the anode centered on the EEG 10–20 location C3, surrounded by four cathodes, over Cz, F3, T7, and P3 and HOPE *HD-tDCS 2 × 2*, with two anodes and two cathodes positioned across the face/head region of M1. In the case of 2 × 2 HD-tDCS, it was especially tailored based on MCS parameters [55, 64, 68–70]. On chronic temporomandibular disorder (TMD) patients, five daily sessions with this montage provided significant improvements on clinical pain and motor measurements compared to the placebo group, with pain relief above 50 % at 4-week follow-up, and increase in pain-free mouth opening at 1-week follow-up. There was also decrease in pain area, intensity, and their sum measures contralateral to the M1 stimulation, not the ipsilateral side, during the treatment week. In addition, no changes in emotional values were shown between active and placebo TMD groups.

Interestingly, recent studies, using computational models, have demonstrated that the strength of the regional current flow generated by tDCS differs significantly among distinct conventional and HD-tDCS montages [68] (Figs. 19.1 and 19.2) and even changes in the intracortical functional connectivity generated by conventional tDCS depend on the montage chosen [71]. Therefore, it is possible to postulate that each tDCS montage could be utilized to target specific dysfunctional areas in chronic pain patients, or extrapolating this concept, different montages could be chosen to treat distinct pain disorders. Further, HD-tDCS montages should be preferable when increased focality is a goal. Another important feature that should be considered is the possible reduction of undesirable

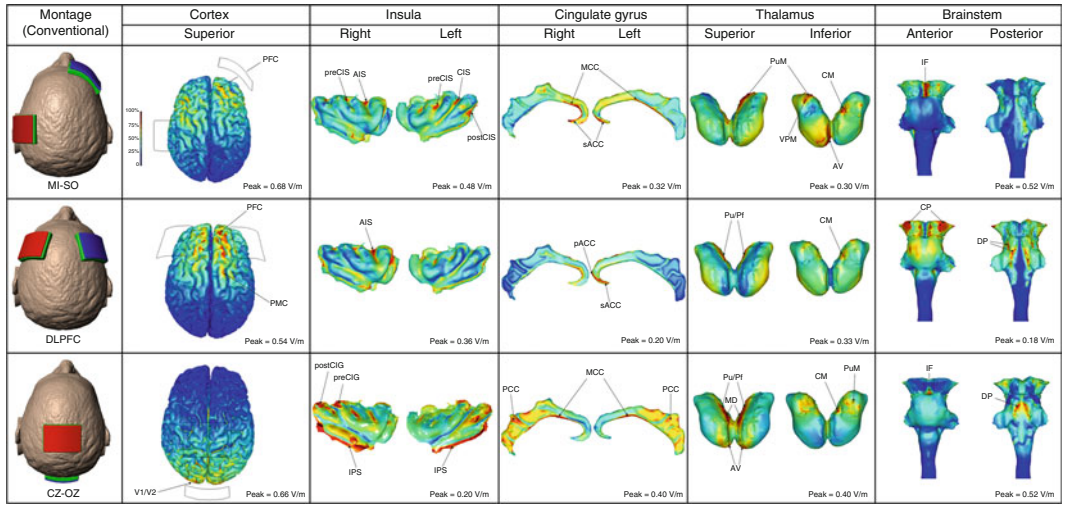

Fig. 19.1 Electrical current distribution through cortical and subcortical brain structures in three distinct conventional tDCS montages [68]

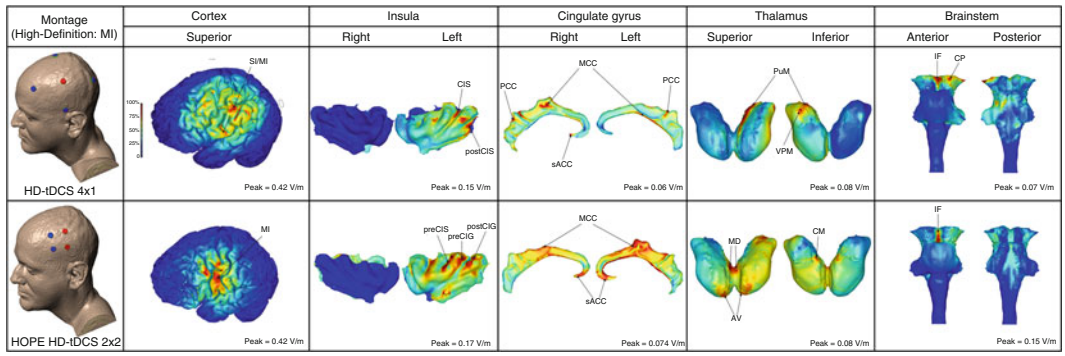

Fig. 19.2 Electrical current flow delivered through the brain in two HD-tDCS montages [68]

effects with more focused stimulation techniques, though the safety profile is considered very good particularly in the case of tDCS [29].

Despite the vast number of studies investigating the clinical effects of tDCS and the mounting evidence suggesting its analgesic effects, many of its mechanism aspects remain practically unexplored and it is still not possible to fully comprehend how it modulate the brain activity. Nevertheless, some of the underpinnings related to tDCS mechanisms have been elucidated by recent studies. Past studies reported the occurrence of immediate as well as long-lasting changes in the cortical excitability [31, 36, 72]. In addition, studies with computational models, which can predict the patterns of the current distribution throughout the central nervous system (CNS), have indicated that not only outer brain areas but also deeper and even more remote brain regions, such as insula, cingulate, thalamus, and brainstem, can be reached by tDCS [52, 68]. Considering that the presence of neuroplasticity, occurring at the structural [73–80], functional [81–86], and even molecular level [87–91], has been consistently reported in patients with a variety of chronic pain conditions, it is possible to speculate that acting at cortical and subcortical structures tDCS could contribute to revert the

ingrained neuroplastic changes developed by chronic pain patients. Remarkably, the effects of anodal and cathodal tDCS on cortical excitability can be suppressed by the *N*-methyl-D-aspartate (NMDA) receptor antagonist dextromethorphan (DMO) [92]. Such results support the hypothesis that synaptic plasticity can be driven by tDCS and that the analgesic effects of this neuromodulatory technique can be related to neuroplasticity changes involving brain areas related to pain and pain-related neural networks, which are dysfunctional in chronic pain patients.

Supporting this hypothesis, tDCS-induced changes in the levels of Glx, a combined marker of glutamine and glutamate, and *N*-acetylaspartate (NAA) that provides information regarding neuronal integrity, have been recently demonstrated in anterior cingulate cortex [93]. Such findings confirm the results of a previous study that had reported changes in the levels of Glx with tDCS. However, in that case, the changes were detected in the parietal area beneath the anode [94]. Another interesting result is the trend of increase in the levels of GABA, a major inhibitory neurotransmitter, in the anterior insula, produced by tDCS [93].

Furthermore, changes in the mu-opioid neurotransmission induced by M1 tDCS have been documented in both healthy subjects [46] and in a case report of chronic pain patient [95]. Interestingly, the activation of the endogenous mu-opioid system occurred with both active and sham stimulation. However, the pattern of regional opioidergic activation permitted the differentiation between sham and active tDCS (Fig. 19.3). While changes in the mu-opioid

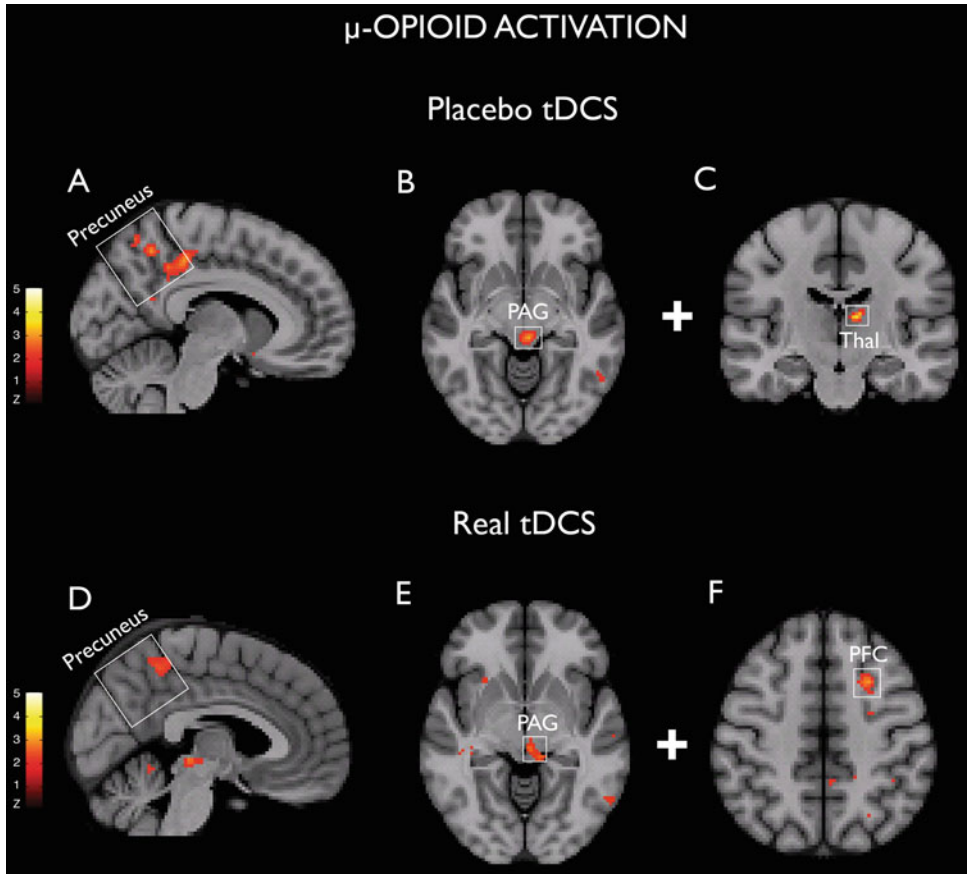

Fig. 19.3 μ-Opioid receptor (MOR) activation induced by placebo (**a**–**c**) and active (**d** and **e**) tDCS. (**a** and **d**) Precuneus MOR activation in the sagittal plane. (**b** and **e**) PAG MOR activation in the axial plane. (**c**) Left thalamus (Thal) MOR activation in the coronal plane. (**f**) Left prefrontal cortex (PFC) MOR activation in the axial plane [95]

receptor availability in the periaqueductal grey matter (PAG) and precuneus occurred during both sham and active stimulation, changes in the thalamus were specific for sham tDCS, corroborating the thalamic mu-opioid activation reported in previous placebo studies [96, 97]. On the other hand, changes in the prefrontal cortex (PFC) were only observed during active tDCS. Those findings possibly indicate that a placebo effect contributes to the beneficial effects obtained with tDCS, when applied to produce analgesia. Supporting this hypothesis, changes in the levels of NAA were found in the posterior insula after M1 tDCS [93]. Although still very preliminary, these findings also suggest that mutual as well as specific mechanisms can be associated with placebo and active tDCS [95]. Nevertheless, there are several aspects related to the neuromechanisms elicited by tDCS that still must be answered. At the current stage, it is important to establish a complete characterization of the clinical effects as well as the putative mechanisms associated with tDCS in each chronic pain syndrome. The following sections discuss the main findings of studies investigating the effects and mechanisms of tDCS in some major chronic pain syndromes (e.g., migraine, fibromyalgia) and also in neuropathic pains.

Effects and Putative Mechanisms of tDCS in Different Chronic Pain Syndromes

Fibromyalgia

Fibromyalgia is a condition that affects 2–8 % of the general population [98–100]. This syndrome was originally defined by the presence of tenderness and chronic spontaneous widespread pain [101]. Since women have much more tender points than men, fibromyalgia was almost exclusively found in women, when using that characterization [102]. Nonetheless, recent diagnostic criteria do not require counting the number of tender points. Instead, it is entirely based on patient's symptoms [103]. With this diagnostic criteria, the female:male ratio is 2:1 [100]. Multiple symptoms occur in fibromyalgia, including widespread pain, cognitive and physical fatigue, mood disturbance, pain catastrophizing, autonomic dysfunction, and sleep and memory disturbances [102]. History of regional musculoskeletal pain, irritable bowel syndrome, headache, and TMD, among other conditions, is also usually observed in fibromyalgia patients [104].

Fibromyalgia has been referred as a centralized pain state, implying CNS origin of or amplification of pain [102]. In fact, there is mounting evidence, deriving mainly from neuroimaging studies, that confirms the occurrence of functional changes in the CNS activity of fibromyalgia patients. Those changes involve not only the cerebral blood flow [105] but also regional changes in the γ-aminobutyric acid (GABA) concentrations [106], dopaminergic [107] and opioidergic systems [87], as well as altered brain connectivity [84, 86, 108]. Linking those findings with the lack of effectiveness of drugs commonly applied to treat peripheral pains and higher effectiveness of centrally acting drugs in the treatment of fibromyalgia patients [102], it is very likely that neuromodulatory methods can provide some degree of pain relief for individuals affected by this syndrome.

As a matter of fact, one of the pioneer studies exploring the possible use of tDCS for pain treatment was performed in fibromyalgia patients [25]. In that study, positive results that lasted for 3 weeks after the end of the treatment period were obtained with five sessions (2 mA/20 min of stimulation) of M1-SO tDCS but not with DLPFC tDCS or sham. The outcomes of that proof of concept research were also important to confirm the safety of the procedure, especially when applied in chronic pain patients, since only few and mild adverse effects, with a frequency similar in the verum and sham groups, were found. Furthermore, the absence of antidepressant effects could suggest that DLPFC-tDCS might not be the most suitable montage in fibromyalgia patients. Nonetheless a subsequent study demonstrated significant improvements of pain and quality of life with both M1-SO and DLPFC montages, when applying protocols consisting of

ten sessions (2 mA/20 min) of stimulation [40]. Interestingly, M1-SO montage resulted in long-lasting outcomes, as assessed at 30 and 60 days after the end of the period of stimulation, stressing the importance of the treatment duration to the long-term effects of tDCS, at least in fibromyalgia patients. The analgesic and long-term effects of tDCS in samples that included fibromyalgia patients have been confirmed in other studies, even when applying lower currents [109], unusual montages (e.g., cathodal-SO) [38], or the combination of tDCS and rehabilitation programs [37]. More recently, significant pain decreases have been reported with only a single session of anodal or cathodal 4×1 HD-tDCS, when compared to sham [39]. These findings endorse the use of HD-tDCS montages in future fibromyalgia trials. As previously discussed, HD-tDCS techniques enhance the current focality, which remains practically restricted to M1. Considering that the most pronounced analgesic effects are achieved with M1 stimulation, it is reasonable to advocate that HD-tDCS montages specifically targeting M1 should be preferred to treat chronic pain syndromes, including fibromyalgia. In fact, the question whether the use of a somatotopically oriented stimulation through smaller electrodes optimizes the analgesic effects induced by tDCS has been proposed since the first study of tDCS in chronic pain [24]. However, the clinical relevance of increasing focality must be confirmed, since modeling studies have proved that conventional montages are able to modulate several deeper structures related to pain. Although also affected by the electrical current, those areas are not reached at the same intensity with HD-tDCS montages [52, 68].

Despite the increasing number of studies investigating the clinical aspects of tDCS in fibromyalgia, the specific mechanisms by which tDCS modulates pain pathways in this disorder have not been explored in depth. The results of one of the few studies in the topic suggest that M1-SO tDCS could possibly act by altering the levels of GABA, glutamate, and glutamine (Glx) and NAA in pain-related brain areas, such as the anterior cingulate, the anterior insula, and the thalamus (Fig. 19.4). In addition, the

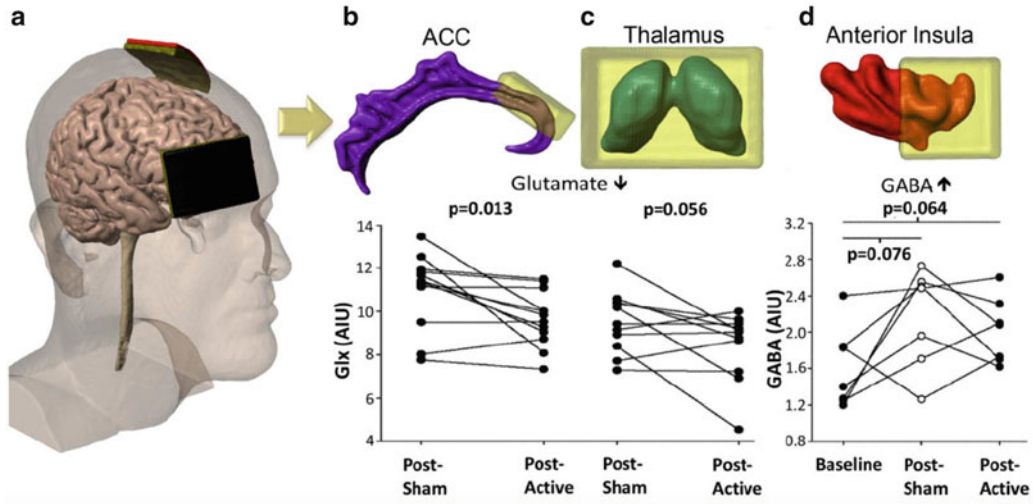

Fig. 19.4 tDCS and 1H-MRS protocol. *Top left image* (**a**): M1-SO tDCS montage. This is followed on the *right* by the segmentation of the regions of interest (ROIs): cingulate cortex (**b**), thalamus (**c**), and anterior insula (**d**). *Bottom images*: Longitudinal changes in glutamate + glutamine (Glx) as well as GABA following five daily active tDCS in patients with fibromyalgia (FM). *Left bottom graph*: Individual data points show Glx concentrations in ACC in patients with FM, in whom post-sham and post-active tDCS samples were obtained. Glx decreases in ACC ($p = 0.013$) following active tDCS treatment. *Center bottom graph*: Same for thalamus ($p = 0.056$). *Right bottom graph*: Individual data points show a trend on increasing GABA concentrations (AIU) in the anterior insula ($p = 0.064$) following active tDCS treatment [93]

baseline levels of Glx in the anterior cingulate can predict the clinical responses to tDCS [93]. Interestingly, significant increases in the levels of NAA in the posterior insula were found after sham tDCS, which suggests the presence of a placebo effect underlying the tDCS-induced analgesia. Nevertheless, more studies are needed to confirm those findings and to expand the current understanding regarding the mechanisms by which tDCS acts in fibromyalgia.

Migraine Headache

Migraine is characterized by recurrent attacks of unilateral pulsating headache, associated with nausea and/or photophobia and phonophobia [110]. Its lifetime prevalence is around 14 % [111]. Two subtypes are encountered: migraine without aura and migraine with aura. Migraine without aura is characterized by headache with some specific aspects and symptoms associated. Migraine with aura is characterized by the presence of transient focal neurological symptoms (e.g., visual or sensory symptoms) that precede or accompany the headache [110]. In some patients migraine evolves from an episodic form to a chronic condition, referred as chronic migraine (CM). CM is defined as a headache that occurs on 15 or more days per month for more than 3 months, and that features the aspects of migraine headache on at least 8 days per month [110]. Besides, medication overuse has been considered the main cause of symptoms suggestive of chronic migraine [110]. As in other painful syndromes, the progression from an episodic to a chronic form is marked not simply by an increase in the number of episodes, but also by the occurrence of other phenomena, such as allodynia (pain due to a stimulus that usually does not provoke pain) as well as hyperalgesia (increased response to a normally painful stimulus). In fact, allodynia affects a large proportion of migraine sufferers [112–115] and is more common in migraine than in other primary headaches [116].

Along with the largely documented neural and neurovascular mechanisms, it has been proposed that central sensitization, which may lead to cutaneous allodynia, plays a role in the migraine pathophysiology [117, 118]. Interestingly, our group has recently demonstrated the presence of altered mu-opioid receptor functioning in the periaqueductal grey and red nucleus associated with ictal trigeminal allodynia, developed during a thermal challenge, in migraine patients [91]. Furthermore, neuroimaging studies have confirmed the presence of neuroplastic changes associated with migraine headache [74, 75, 77, 82, 83, 90]. When analyzed together, these findings corroborate the development of research protocols to investigate the use of noninvasive neuromodulatory tools, such as tDCS, to modulate the activity of pain-related structures and perhaps reverse faulty mechanisms that constitute the basis of the migraine pathophysiology.

Regarding the clinical use of tDCS in migraine patients, there are still few studies in the literature and they differ with respect to the montage chosen as well as the patient selection. The most used montages are M1-SO [52] and Cz-Oz [53, 54, 66]. Positive effects, such as pain reduction, decrease in the duration of attacks and in the number of migraine-related days posttreatment were reported in a study that applied Cz-Oz tDCS [53]. On the other hand, the frequency of migraine attacks was not affected, which might be explained by the relatively low intensity (1 mA), duration (15 min), and frequency of the stimulation applied (three sessions per week during 3 weeks). Increasing those parameters might have produced stronger effects in that study but it might have also impacted the sham arm of the study and the placebo condition, which was considered optimal, based on the side effects reported. Nonetheless, another limitation of that preliminary study that must be considered when interpreting the results is the heterogeneity of the experimental group analyzed, consisting of patients diagnosed with migraine with aura and without aura and chronic migraine. Interestingly, persistent analgesic effects induced by tDCS were found in a sample consisting only of patients diagnosed with episodic migraine without aura [54]. In that study, each subject received preventive treatment with anodal tDCS applied to the visual cortex (1 mA/15 min) twice a day, during

8 weeks. Active stimulation reduced the frequency and duration of the migraine attacks as well as migraine days and the acute medication intake for a period of 4.8 weeks [54]. The same study showed that tDCS is able to induce a transient increase in the habituation in migraineurs, which could be one of the mechanisms underlying tDCS-induced analgesia in migraine patients.

In another tDCS study, significant decreases in the pain intensity, length of episodes, and clinical impression have been reported in chronic migraine patients treated with M1-SO tDCS [52]. Unexpectedly, only long-term effects (4 months after the period of treatment) were detected in that study, while immediate effects could not be demonstrated. Such findings could also be related to the protocol chosen, consisting of every other day stimulation, instead of daily sessions. Nevertheless, the most important contribution of that study was the detection of peaks of current flow in deeper pain-related structures (e.g., cingulate, thalamus, insula, and brainstem), demonstrated through a finite element model analysis, which has been confirmed afterwards [68].

tDCS can also provide insights into the pathophysiology of migraine headache, as demonstrated by a study that reveled, through a combination of tDCS and TMS, different patterns of changes in the cortical excitability induced by tDCS [119]. Anodal tDCS stimulation produced an increase in the visual cortex excitability in both healthy subjects and migraine patients, with larger variations observed in the group of migraine patients with migraine with aura. Conversely, cathodal tDCS (Cz-Oz) resulted in a decrease in the cortical excitability of healthy volunteers, but did not alter the cortical excitability in migraine patients, suggesting the presence of deficient inhibitory process in the cortex of migraine patients and indicating that a more prominent inhibitory dysfunction occurs in migraine with aura, when compared to migraine without aura [119]. In a following study that also combined TMS and tDCS, cathodal tDCS, but not anodal tDCS, restored the abnormal facilitatory response to hf-rTMS in migraine patients [120]. The presence of interictal visual cortical hyperexcitability has also been found in another study applying a similar methodology [121]. The same study reported significant reductions in duration and number of migraine attacks as well as painkiller intake when cathodal visual cortex stimulation was applied as a prophylactic therapy. Nevertheless, such effects were not higher than in a group of migraine patients that received sham stimulation [121]. Intriguingly, the beneficial effects obtained in the active group were not correlated to changes in cortical excitability, indicating that the analgesic effects induced by tDCS in migraineurs may occur independently of cortical excitability normalization.

Although still scarce, the data currently available suggest that tDCS can be a useful tool to treat migraine headache. However, it is still necessary to define the specific montage that offers more beneficial effects as well as the ideal parameters (e.g., current intensity, duration and frequency) that should be used in migraine patients. To accomplish those objectives, furthers studies, with larger sample sizes and individualizing different forms of migraine headache, will be necessary.

Neuropathic Pains

The IASP taxonomy (Merskey et al. 1994), revised in 2012 (http://www.iasp-pain.org/Taxonomy#Neuropathicpain), defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system." However, neuropathic pain is considered an umbrella term that encompasses distinct disorders, such as trigeminal and postherpetic neuralgias, painful diabetic polyneuropathy, painful nerve lesions, radiculopathies, and postamputation pain. Moreover, several CNS disorders (e.g., spinal cord injury, multiple sclerosis, and stroke) can be associated with neuropathic pain [122, 123]. The prevalence of neuropathic pain on the general population ranges from 2 to 3% [124, 125] but this number can be even higher. It has been estimated that the prevalence of pain with neuropathic characteristics can be around 6.9–10% [126]. Neuropathic pain is considered challenging to manage [127]. Furthermore, it often produces significant negative impact on quality of life [128]. The mechanisms that trigger and

maintain neuropathic pain symptoms have not been totally unveiled. Nonetheless, peripheral as well as central mediation, which involves complex physiological events, is certainly important [9, 129, 130]. Considering the satisfactory results produced by MCS in neuropathic pain patients [17, 23, 131], it is reasonable to consider the use of tDCS to reduce the negative impact provoked by such disorders on the patients affected, or even as a predictive method for invasive therapies.

In fact, the first study investigating the efficacy and safety of tDCS in chronic pain was performed in patients with refractory neuropathic central pain due to traumatic spinal cord injury. The results indicated the presence of significant positive results on pain, without significant effects on anxiety and depression associated with five consecutive sessions of M1-SO tDCS but not with sham [24]. Remarkably, the magnitude of the results obtained in that study was impressively high, with a mean pain response of 58 %. Besides, the lack of changes in cognitive and motor performed associated with tDCS verified in that study corroborated the safety of the procedure and supported the development of further tDCS studies in chronic pain patients. A recent study confirmed the safety and efficacy of anodal M1 stimulation in patients with neuropathic pain associated with spinal cord injury. Strikingly, a significant association was found between the decrease of pain intensity and increase in the peak theta–alpha frequency at the site of stimulation, with only a single session of tDCS [132].

A further study, evaluating patients with painful diabetic polyneuropathy, showed significant higher analgesic effects of M1-SO tDCS, when compared to DLPFC tDCS and sham, indicating that M1-SO tDCS might be an optimal montage for neuropathic pain studies [47]. In other studies, M1-SO tDCS produced more significant and in some cases longer lasting results in neuropathic pain patients when combined with another therapy, such as transcutaneous electrical nerve stimulation [49] or visual illusion [41]. Nonetheless, in both examples tDCS alone also granted beneficial effects to the patients evaluated.

Little is known regarding the mechanisms of M1-SO tDCS in chronic neuropathic pain syndromes. In a previous study, our group demonstrated for the first time significant changes in the availability of mu-opioid receptor in pain-related structures (insula, cingulate, nucleus accumbens, and thalamus) during a single session of M1-SO tDCS in a postherpetic neuralgia patient [46]. Such findings are very similar to those obtained with MCS in refractory neuropathic pain patients [133, 134] and strongly suggest the contribution of the mu-opioidergic system to the tDCS-driven analgesia in neuropathic pain patients.

It is important to emphasize that negative results have also been reported with tDCS in neuropathic pain conditions. For example, in one study, five sessions of anodal M1 tDCS stimulation failed to produce analgesia in patients with neuropathic pain due to spinal cord injury, contrasting the findings of previous studies. Noteworthy, the duration of the injury in the patients of that study was longer than in other studies, suggesting that the pain decreases related to tDCS also depend on the pain duration [43]. Negative results of M1-SO tDCS in neuropathic pain have been documented in other studies. Nonetheless, those results should be interpreted cautiously, since in those cases the protocol consisted of single sessions of stimulation [42, 48], which in some cases could not be enough to produce significant analgesia and especially in refractory neuropathic pain patients.

Concluding Remarks

The current scientific literature indicates that tDCS is a safe and well-tolerated procedure that can be effectively used as a prophylactic or even acute therapy in different chronic pain syndromes. Nevertheless, there are still many questions that must be answered before it can be clinically applied in a large scale. Future studies should not only focus on establishing the ideal montages and protocols for each pain syndrome, but also on determining to what extension a placebo effect contributes to its analgesic effects and more important the pain-related neural mechanisms that can be targeted and potentially modulated by tDCS.

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Stroke

20

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Abstract

Stroke is the leading cause of long-term disability due to various impairments such as motor weakness, visuospatial neglect, aphasia, dysphagia, cognitive decline, spasticity, depression, and central pain. Although functional improvement from these impairments is important to reduce the burdens of stroke survivors, the effects of conventional rehabilitation approaches are still modest and the novel therapeutic approaches are being needed. TDCS could be applied as an adjuvant therapy for rehabilitation in stroke patients as it can potentially facilitate motor, cognitive, and language recovery after stroke, by providing the methods to modulate brain activity or plasticity in a specific region at the network level. Therefore, TDCS is currently under active investigation in the stroke rehabilitation field. In this chapter, the clinical application of TDCS in the field of stroke rehabilitation is discussed.

Keywords

Stroke • Rehabilitation • Neuromodulation • Transcranial direct current stimulation • Impairment • Plasticity

Stroke is defined as a "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than that of vascular origin" by the "World Health Organization" [1].

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Stroke is one of the leading causes of long-term severe disabilities worldwide [2], and about 50 % of stroke survivors have some kinds of long-term disabilities [3]. The absolute number of stroke survivors is increasing worldwide and the increase in global burdens of stroke is expected [4]. Impairments after stroke include motor weakness, coordination and balance problems, apraxia, spasticity, sensory loss, hemispatial neglect, aphasia, dysarthria, aphasia, central pain, shoulder pain, depression, cognitive problems, and behavioral

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problems depending on the affected area of the brain. Although many treatment strategies including conventional rehabilitative approach have been applied to reduce these disabilities, their effects are still limited and the novel therapeutic approach is being needed [5].

TDCS provides the methods to modulate brain activity or plasticity in a specific region at the network level [6]. TDCS is under active investigation in the stroke rehabilitation field. Modern theory states that functional recovery after stroke is a re-learning process with a partially disrupted neural network [7]. This re-learning process can be enhanced by inhibiting competing maladaptive cortical areas or facilitating local cortical activities during rehabilitation practice using TDCS. Recent bench-to-bedside research has demonstrated promising results on stroke recovery by using either brain stimulation alone or in combination with conventional rehabilitation. TDCS could be applied as an adjuvant therapy for rehabilitation in stroke patients as it can potentially facilitate motor, cognitive, and language recovery after brain injury. Theoretically, it is more beneficial to apply TDCS earlier than later because this period is an active period of brain reorganization or plasticity [8, 9]. The changes of brain network after stroke can be monitored using neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET).

Up to now, among noninvasive brain stimulation (NIBS) techniques, only application of the repetitive transcranial magnetic stimulation (rTMS) device for treatment of drug-resistant depression has been granted US Food and Drug Administration approval [10, 11]. Applications of TDCS for stroke patients are currently off-label. Large-scale phase III clinical trials and meta-analysis in the field of TDCS application in stroke are required to achieve a high level of evidence.

Currently, according to proof-of-concept studies, the beneficial effect of TDCS in the clinical setting is still modest. Optimal stimulation protocols in terms of optimal clinical samples, delivery timing, duration, and stimulation parameters are still unclear [12].

In this chapter, the clinical application of TDCS in the field of stroke rehabilitation is discussed, as well as post-stroke impairment syndromes such as motor weakness, visuospatial neglect, aphasia, dysphagia, cognitive decline, spasticity, post-stroke depression, and post-stroke central pain.

Motor Recovery

Acute stroke therapies such as tissue plasminogen activator (tPA) and mechanical thrombolysis that promote brain reperfusion within an optimal time period are presently available. Yet, half of stroke patients still suffer from residual motor weakness [13]. Also, these therapies are effective only when delivered in a very short period of time of a few hours after stroke onset.

To promote motor recovery after stroke, exercises featuring task-oriented high-intensity repetitive training are being clinically applied [5]. Constraint-induced movement therapy (CIMT), robotic training, neuromuscular electrical stimulation, training with virtual reality, and body weight-supported treadmill training are a few examples.

Small placebo-controlled trials have investigated the clinical effects of TDCS for motor recovery as an adjuvant modality to these behavioral therapies. These studies revealed a change in cortical motor excitability or improvement of motor function after TDCS.

One possible strategy to enhance motor recovery after stroke is to simply increase the cortical excitability of affected motor cortex. Another possible strategy is mainly based on the theory of inter-hemispheric competition or rivalry [14–16]. In the inter-hemispheric rivalry theory, the activities of motor cortexes are counterbalanced by trans-callosal inhibitory projections. However, trans-callosal inter-hemispheric inhibitory influences from the unaffected motor cortex to the affected motor cortex are relatively increased compared to the opposite direction (from the affected to unaffected motor cortex) after stroke, leading to over-inhibition of the affected motor cortex and impeding motor recovery of the

paretic side [16, 17]. Therefore, restoration of the excitability of affected hemisphere can be expected by inhibiting the motor cortical activity of the unaffected hemisphere [16].

Therefore, trans-cranial induction of either facilitation of the affected motor cortex (M1) using anodal TDCS or inhibition of unaffected M1 using cathodal TDCS can enhance motor recovery of the paretic limb (Fig. 20.1).

Single or multiple sessions of either facilitatory anodal TDCS applied to affected M1 [16, 18] or inhibitory cathodal TDCS to unaffected M1 [19, 20] have shown to enhance paretic upper limb recovery beyond the stimulation period.

If repeated sessions of stimulation are applied, longer lasting after effect can be expected [21]. Reis et al. [22] showed that multiple sessions of anodal TDCS enhance long-term retention and consolidation of acquired motor skills as compared to sham stimulation in healthy participants.

Although first positive results for enhancement of motor function came out from anodal TDCS protocols, anodal protocol over affected M1 is reported to produce less beneficial effects than cathodal TDCS protocol over unaffected M1 according to recent studies [23, 24]. Kim et al. [23] tested whether multiple sessions of TDCS in combination with occupational therapy could induce greater motor recovery in the paretic upper limb than sham stimulation plus occupational therapy in subacute stroke patients. The authors recruited 18 patients with hand paresis and randomly assigned them to one of the three 10-day sessions of intervention: anodal TDCS over the affected motor cortex, cathodal TDCS over the unaffected motor cortex, or sham stimulation. Only cathodal TDCS led to a greater recovery of paretic hand assessed with the Fugl-Meyer assessment score than the sham stimulation at 6-month follow-up, whereas anodal TDCS just showed trends toward greater improvement.

Bi-hemispheric TDCS, combining anodal TDCS over the affected hemisphere plus cathodal TDCS over the unaffected hemisphere, has been applied in healthy subjects [25, 26] and stroke patients [27, 28]. Kang and Paik [25] compared unilateral versus bilateral TDCS when performing a motor learning task in 11 healthy subjects and found no significant difference in induced implicit motor sequence learning between two interventions, although both interventions were more effective than sham TDCS. Therefore, it is still not clear whether bi-hemispheric TDCS is more effective on motor recovery than unilateral TDCS.

TDCS can be combined with other therapies. One study tested whether combining somatosensory stimulation and TDCS induces larger or longer lasting after effects than somatosensory stimulation or TDCS alone [29]. The study combined peripheral nerve stimulation to the affected hand with anodal TDCS on the ipsi-lesional M1, and combined stimulation resulted in a greater improvement in the number of correct key presses relative to either stimulation alone or sham stimulation. This improvement was maintained until 6 days after the end of the interventions. However, combining TDCS during robot-assisted bilateral arm training in subacute stroke patients showed no differences in motor improvement between TDCS and sham stimulation [30].

Recently, Triccas et al. reported the results of a meta-analysis for multiple sessions of TDCS on upper extremity function after stroke [31]. Eight randomized controlled trials were included for analysis (Table 20.1). Real TDCS combined with rehabilitative therapy showed a small, nonsignificant effect on upper extremity functional recovery after stroke. This result was consistent with a recently published Cochrane review, which reported no beneficial effect of TDCS for improvement of activity of daily living and only moderate positive effect on upper limb motor recovery [32]. Clinical trials using TDCS for upper limb impairment in stroke patients were heterogeneous in terms of chronicity of stroke, mode of TDCS delivery, and combined intervention, and their sample sizes were relatively small.

TDCS for motor recovery after stroke mainly focused on upper limb impairments. This may be due to deep midline location of leg motor area close to the medial longitudinal fissure and unclear pathophysiological reorganization of leg motor areas after stroke [33]. Clinical trials using TDCS to improve the gait functions have not been reported, although several small pilot

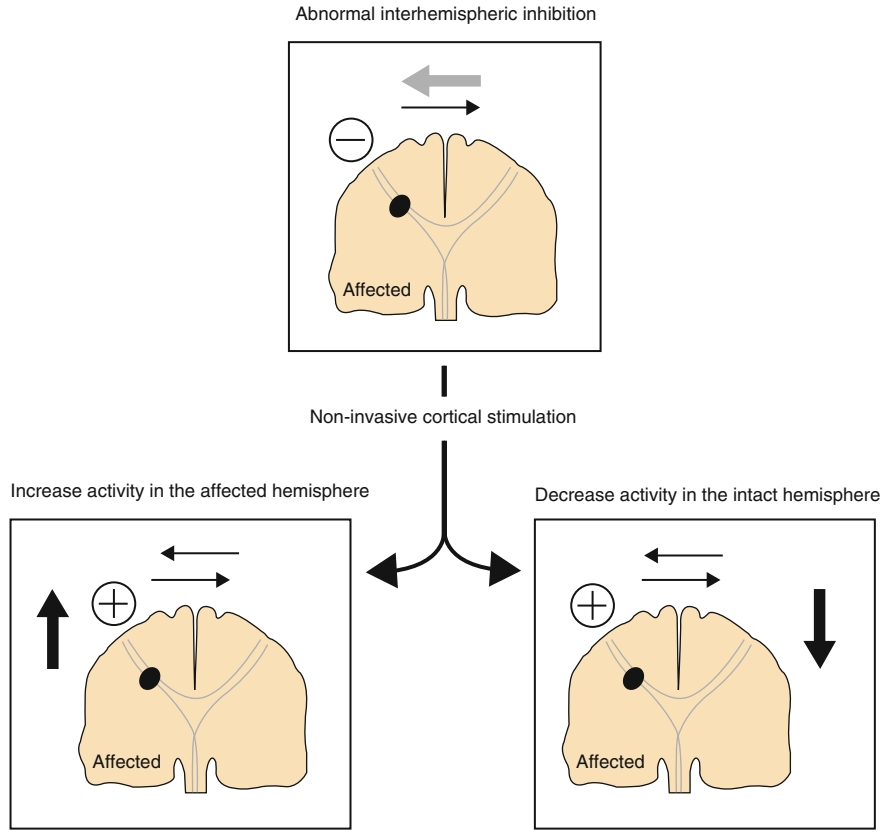

Fig. 20.1 Strategy to improve motor function after stroke. After stroke, trans-callosal inter-hemispheric inhibitory projection from the unaffected motor cortex to affected motor cortex is elevated compared to inhibitory tone from affected to unaffected motor cortex after stroke. Therefore, either facilitation of affected motor cortex using anodal TDCS or inhibition of motor cortex of the unaffected hemisphere using cathodal TDCS could be a strategy to improve motor function of paretic upper limb (figure modified from Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet neurology 2006;5:708–12.)

studies using rTMS for gait improvement in chronic or subacute stroke patients reported positive results [34, 35].

The recent absence of positive results of a multicenter phase III clinical trial on cortical epidural stimulation to enhance motor improvement after stroke suggested important caveats in applying TDCS to stroke patients for motor recovery [41]. A previous phase II feasibility trial with epidural stimulation guided by functional MRI for the optimal stimulation site in patients with chronic stroke was successful [42]. However, in phase III trial, a limited number of patients (less than 20% of participants) showed a motor-evoked response, which may be one of the main factors that led to unexpected failure. Post hoc subgroup analysis showed a significant improvement in patients with evoked motor response, in whom corticospinal integrity was supposed to be preserved. When we consider that functional recovery after stroke is an essentially motor relearning process with a partially disrupted neural circuit [7], the corticospinal integrity has to be at least sufficient to allow motor recovery to occur. Therefore, integrity of corticospinal descending pathways should be checked using TMS or tractography before applying TDCS.

Improvement of motor function after TDCS is still modest and more studies are needed to assess its long-term benefits on a larger number of patients [43]. Further fine establishment of stimulation protocols to maximize the beneficial

Table 20.1 Characteristics of TDCS studies included in the meta-analysis (reprinted with permission from Triccas et al. Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis. Clinical Neurophysiology 2015) [31]

	Objective	Design	Groups	*N*	Mean age (years)	Mean time since stroke	TDCS stimulation intensity/duration/ hemisphere	Training period (weeks)	Outcomes according to the ICF (I = impairment, A = activity, P = participation)
Kim et al. [23]	TDCS and OT on UL motor recovery	Single-blinded RCT	Anodal and OT	6	55.3	34.0 days	(1) 2 mA (2) 20 min (3) TDCS during rehabilitation (4) Anodal: ipsi-lesional cathodal: contra-lesional	10 sessions over 2 weeks and 30 min OT	FMA[a] (I) MBI[a] (A)
Lindenberg et al. [27]	TDCS and PT and OT on UL motor recovery	Double-blinded RCT	Cathodal and OT	5	53.6	19.4 days	(1) 1.5 mA (2) 30 min (3) TDCS during rehabilitation (4) Anodal: ipsi-lesional cathodal: contra-lesional	Daily sessions of 60 min OT and PT	FMA (I) fMRI[a] (I) WMFT[a] (A)
			Sham and OT	7	62.9	22.9 days			
			Bi-hemispheric and OT	10	61.7	30.5 months			
Bolognini et al. [36]	TDCS and CIMT on UL motor recovery	Double-blinded RCT	Sham and OT	10	55.8	40.3 months	(2) 2 mA (2) 40 min (3) TDCS during rehabilitation (4) Anodal: ipsi-lesional cathodal: contra-lesional	14 daily sessions of 4-h CIMT[a]	FMA (I) JTT[a] (I), HG[a] (I), Resting Motor Threshold and trans-colossal inhibition (I), MAL[a] (A), BI (A)
			Bi-hemispheric and CIMT	7	42.6	44.4 months			
Hesse et al. [30]	TDCS and RT on UL motor recovery	Double-blinded RCT	Sham and CIMT	7	50.9	26.0 months	(2) 2 mA (2) 20 min (3) TDCS during rehabilitation (4) Anodal: ipsi-lesional, cathode: contra-lesional	30 sessions over 6 weeks involving 20-min RT	FMA (I) MRC[a] (I) MAS[a] (I) BI[a] (A) BBT[a] (I)
			Anodal and RT	32	63.9	3.4 weeks			
Nair et al. [37]	Cathodal/sham TDCS and OT on UL motor recovery	Double-blinded RCT	Cathodal and RT	32	65.4	3.8 weeks	(1) 30 min (2) 1 mA (3) TDCS during rehabilitation (4) Cathodal: contra-lesional	5 daily sessions of 1-h OT	ROM[a] (I) FMA[a] (I) fMRI (I)
			Sham and RT	32	65.6	3.8 weeks			
			Cathodal and OT	7	61.0	33 months			
Khedr et al. [38]	Anodal/cathodal/sham TDCS and rehabilitation UL motor recovery	Double-blinded RCT	Sham and OT	7	56.0	28 months	(1) 25 min (2) 2 mA (3) TDCS before rehabilitation	6 daily sessions of 1-h rehabilitation (passive movement and range of motion exercises)	National Institute of Health Stroke Scale (I) Orgogozo MCA scale (I) MRC (I) Resting and Active Motor Threshold
			Anodal and therapy	14	58.1	13.8 days			
Lee et al. [39]	Cathodal TDCS and virtual reality program on UL impairments	Double-blinded pilot RCT	Sham and PT	45	49.3	4.9 months	(1) 20 min (2) 2 mA (3) TDCS during OT and virtual reality (4) Cathode over contra-lesional M1	5 sessions per week for 3 weeks of 30 min each session of virtual reality	MAS (I), Manual Muscle Test (I) Manual Function Test (I). FMA (I). BBT (I). Korean MBI (A)
			Cathodal and OT	21	60.3	17.4 days			

(continued)

Table 20.1 (continued)

	Objective	Design	Groups	*N*	Mean age (years)	Mean time since stroke	TDCS stimulation intensity/duration/ hemisphere	Training period (weeks)	Outcomes according to the ICF (I=impairment, A=activity, P=participation)
Viana et al. [40]	Anodal TDCS and virtual reality on UL impairments	Double-blinded RCT	Anodal TDCS and virtual reality	10	56.0	31.9 months	(2) 13 min (2) 2 mA (3) ?before/during and after rehabilitation (4) Anode over ipsi-lesional M1	3 sessions per week for 5 weeks of 1 h each session	FMA (I), WMFT (I), MAS (I) Dynamometry (I), Stroke Specific Quality of Life Scale (P)
			Sham TDCS and virtual reality	10	55.0	35.0 months			

[a]*BI* Barthel index, *BBT* box and block test, *CIMT* constraint-induced movement therapy, *fMRI* functional magnetic resonance imaging, *FMA* Fugl-Meyer assessment, *HG* hand grip, *MAS* modified Ashworth scale, *MAL* motor activity log, *MBI* modified Barthel index, *MEP* motor-evoked potential, *MRC* Medical Research Council Strength, *ROM* range of motion, *MT* motor threshold, *OT* occupational therapy, *PT* physiotherapy, *WMFT* Wolf motor function test

effect of TDCS, in terms of parameters revealing better effect and maintenance, optimal candidate, and time selection for intervention and individualized stimulation target localization depending on the pattern of reorganization, should be pursued [44].

TDCS seems to be a safe and promising intervention for motor recovery after stroke and may be potentially used as an adjuvant therapy when appropriately combined with conventional or other new rehabilitation therapies. It is unlikely that TDCS alone makes the brain form appropriate connections required for recovery. TDCS may strengthen existing connections or help the brain to form new connections. Therefore, TDCS techniques should always be accompanied by behavioral training.

Visuospatial Neglect

Neglect is defined as an impaired or lost ability to respond to various sensory stimuli presented from the contra-lesional side in a patient with cortical damages [45]. Visuospatial neglect in the first months after a stroke is common, and is estimated to occur in about 82 % of right cerebral hemisphere strokes and 65 % of left cerebral hemisphere strokes [46]. Neglect is related with poor functional recovery [47].

Various rehabilitation therapies for neglect have been investigated such as visual scanning, optokinetic stimulation, neck muscle vibration, caloric- or galvanic-vestibular stimulation, and prism adaptation [48]. However, these preexisting treatment tools have shown limited effect.

Recently, TDCS has emerged as a possible treatment tool for neglect. The current rationale for application of TDCS for visual spatial neglect after stroke is also based on the theory of interhemispheric rivalry. Usually a right hemispheric lesion after stroke causes the attention vector generated by the right hemisphere to be weaker and results in reduced inhibition on the left hemisphere [49]. This disinhibition of left hemisphere supposedly leads to increase in the excitability of the intact left hemisphere and rightward deviation of the visual field [49]. Therefore, the current purpose of TDCS for neglect is to reduce the hyperexcitability of intact left hemisphere and/or to increase the excitability of injured right hemisphere, which are expected to rebalance the rightward deviation.

In one study using TDCS for post-stroke neglect, only one session of anodal TDCS over the affected posterior parietal cortex with 2 mA demonstrated improvement in the percent deviation score of the line bisection test and the omissions of cancellation test [50]. In another study, the effect of anodal TDCS over the affected posterior parietal cortex and cathodal TDCS over the unaffected posterior parietal cortex was investigated in ten post-stroke neglect patients [51]. Both anodal and cathodal TDCS showed some improvements in the clinical test, compared to sham TDCS.

Based on these two small studies, the expected increase of cortical activity on the affected hemisphere induced by anodal TDCS or decrease of cortical activity on the unaffected hemisphere induced by cathodal TDCS seems to improve the neglect symptom after stroke. However, randomized controlled parallel design studies with adequate sample size have not been reported yet, convincing that evidence for TDCS on post-stroke neglect is currently lacking.

Aphasia

Aphasia is defined as an acquired loss or impairment of the language after brain damage [52]. About 24–30 % of patients show various types of aphasia after stroke and the pattern of recovery varies among patients [53, 54]. Aphasia causes substantial disability in daily life and is an important prognostic factor for general functional outcome in stroke patients [55].

Speech language therapy is usually the primary therapeutic modality in aphasia rehabilitation following stroke [56]. Although many speech language therapeutic approaches are being applied for clinical practice, current evidence is lacking to draw any conclusion regarding the effectiveness of a specific speech language therapy approach [57].

The recent development of neuroimaging allows the investigation of brain connectivity in language and neuroplastic changes during aphasia recovery. Recovery from aphasia is a process of reorganization and neuroplasticity in the complex language network, and initial severity and recovery potential depend on the extent of damage to the bi-hemispheric functional network [58, 59]. TDCS can modulate the excitability of cortical regions that are connected with specific language networks involved in aphasia, and can enhance the reorganization process leading to better recovery [60]. Promising results from some studies using TDCS have been reported in post-stroke aphasia patients.

Currently, TDCS for aphasia therapy has been based on the pattern of reorganization. One strategy is to recruit peri-lesional area by increasing the excitability using anodal TDCS. Another strategy is to recruit right unaffected homologous cortical area using anodal TDCS (when they are beneficial and subserve some language function), or inhibit right homologous cortical area using cathodal TDCS, when they are deleterious and exerting increased inhibitory influence on left cortical area, impeding functional recovery of peri-lesional reorganization [61, 62].

Restoration of the original activation pattern within the preserved language network seems to be the most effective strategy toward good aphasia recovery and a satisfactory recovery can be expected if peri-lesional areas are activated. In a sham-controlled crossover study, five sessions of anodal TDCS over the left hemisphere that was activated during picture-naming task on an fMRI demonstrated more improvement than sham TDCS [63]. Fridriksson et al. got similar results in a double-blind, sham-controlled study, showing reduced reaction time during naming task after anodal TDCS [64]. However, Polanowska et al. recruited early-phase Broca's aphasia patients and delivered 15 consecutive sessions of anodal TDCS or sham TDCS on Broca's area, followed by 45 min of speech language therapy. The authors did not show beneficial effect of anodal TDCS over sham TDCS [65]. Monti et al. also failed to demonstrate the positive effect of anodal TDCS over the left frontotemporal area on post-stroke aphasia. In their study, cathodal TDCS over lesioned hemisphere rather than anodal TDCS showed positive results [65].

Anodal TDCS can be applied to the healthy hemisphere when recruitment or disinhibition of homotopic language areas in the non-dominant hemisphere seems to be beneficial. Vines et al. pursued this approach and showed that combining anodal TDCS with melodic intonation therapy further induced recovery from post-stroke aphasia [66].

Previous reports have documented increased activation in right frontal areas during the performance of various language tasks in non-fluent aphasia, and this increased activation might be the consequence of a loss of active interhemispheric inhibition from homologous regions in the lesioned hemisphere [67].

Along with this line, the effect of inhibitory cathodal TDCS over the right hemisphere on post-stroke aphasia has been studied. Kang et al. investigated whether inhibitory cathodal TDCS over the contra-lesional right Broca's homologue area could enhance picture naming in aphasia after stroke [65]. Ten right-handed patients received an intervention of cathodal TDCS (2 mA for 20 min) and of sham TDCS (2 mA for 1 min) for 5 consecutive days in a crossover design combined with simultaneous conventional speech therapy. Picture-naming performance was improved after cathodal TDCS, but no significant changes were found after sham TDCS. The authors further investigated the factors associated with better responses to TDCS combined with speech therapy in 37 post-stroke aphasia patients [68]. Ten sessions of speech therapy for 30 min over 2–3 weeks were applied and cathodal TDCS over the Broca's homologous area in unaffected hemisphere with 1 mA for 20 min was combined during speech therapy. After this intervention, significant improvement in aphasia quotient was observed and patients with less severe (over 10 % in the aphasia quotient) and fluent type of aphasia showed greater improvement.

A recent Cochrane meta-analysis reviewed six studies using TDCS for enhancing recovery from aphasia in stroke patients [69]. They concluded that currently there is no evidence of the

effectiveness of either anodal or cathodal TDCS when correct picture naming was used as an outcome, although it appears that cathodal TDCS over the non-lesioned hemisphere might be a more promising approach.

Dysphagia

Dysphagia is a common impairment after stroke. Reported incidences are widely discrepant, ranging from 19 to 81 % depending on the definition, time, and assessment tool [70]. Post-stroke dysphagia has been known to increase the risk of aspiration pneumonia and mortality [71]. Current management for post-stroke dysphagia includes diet and fluid modifications, compensatory maneuvers, position changes, and rehabilitation exercises [65].

Reorganization of the swallowing motor cortex after stroke is associated with recovery from dysphagia [72]. TDCS is expected to play a role to enhance the swallowing motor cortex reorganization after stroke. Swallowing is a neuromuscular process dually innervated by both hemispheres. It has been proposed that activation of contra-lesional hemispheric projections may be beneficial for dysphagia recovery after stroke [65]. However, it is still controversial whether the stimulation of lesional vs. the contra-lesional hemisphere is more beneficial [65].

In one small pilot study, anodal TDCS over the sensorimotor cortex in the unaffected hemisphere representing the swallowing muscles was applied to 14 patients with subacute unilateral cortical infarction, over the course of 5 consecutive days associated with concurrent standardized swallowing therapy [65]. This intervention showed a transient improvement in swallowing function. Jafferson et al. showed that anodal TDCS increased the excitability of pharyngeal motor cortex in an intensity-dependent manner, with little influence on trans-callosal spread [73].

Yang et al. also investigated the effects of TDCS combined with conventional swallowing therapy on dysphagia after stroke [74]. Sixteen patients received anodal (1 mA for 20 min) or sham TDCS over the pharyngeal motor cortex in the affected hemisphere during 30 min of conventional swallowing training for 10 days. Greater improvement after anodal TDCS was observed compared to the sham group at 3 months post-intervention, after controlling for age, initial stroke severity, lesion size, baseline dysphagia score, and time from stroke onset. Shigematsu et al. also showed similar results in post-stroke dysphagia patients [75].

Pisegna et al. recently published a meta-analysis result of NIBS (four rTMS and three TDCS studies) for post-stroke dysphagia [65]. In this meta-analysis, NIBS showed a significant moderate pooled effect size and studies stimulating the unlesioned hemisphere showed a better effect size compared to those stimulating the lesioned hemisphere.

Cognitive Decline

Cognitive decline after stroke is common and gives a substantial burden to patient's caregivers and society [76]. Therefore, effective rehabilitative intervention to improve cognitive function such as attention and memory is crucial.

Recently, in the field of cognitive rehabilitation after stroke, TDCS has been investigated as a new therapeutic tool to improve attention and working memory. Kang et al. [77] demonstrated that anodal TDCS over the left dorsolateral prefrontal cortex (DLPFC) improves attention in stroke patients. This suggests that TDCS could potentially be used during concurrent rehabilitative training to improve attention. Another randomized crossover trial showed that cathodal TDCS over unaffected primary motor area could improve the selective attention measured by the Stroop interference test in chronic stroke patients [65]. For memory improvement, a small sample-sized single-blind randomized crossover trial showed that anodal TDCS over DLPFC improved accuracy in a two-back working memory task in stroke patients [65].

These small pilot studies using TDCS for cognitive decline after stroke showed promising results, but further studies with larger sample size are required.

Spasticity

Spasticity is defined as "a velocity-dependent increase in tonic stretch reflexes or muscle tone with exaggerated tendon jerks as one of components of the upper motor neuron syndrome" [78]. Spasticity occurs during the recovery stage after stroke and the prevalence at 12 months after stroke reaches about 38 % [79]. Post-stroke spasticity is associated with poor motor recovery, activity limitations, pain, and contractures [65]. Non-pharmacological interventions including stretching, splint, and heat or cold modalities can be applied as a first-line therapy, but the effect may be temporary and may not be effective in some cases. Pharmacological intervention with oral medications can be used for general spasticity but side effects or possible harmful effects for neuroplasticity should also be considered [80]. Therefore, TDCS has a room for therapeutic application for post-stroke spasticity by modulating the cortical activity and hence decreasing the muscle tone.

Only two TDCS studies for post-stroke spasticity have been reported. Wu et al. conducted a sham-controlled randomized trial with 90 stroke patients with spasticity [65]. Patients received cathodal ($n=45$) or sham stimulation ($n=45$) over the affected primary sensory motor cortex, 20 min per day, 5 days per week, for 4 weeks along with conventional physical therapy. Significantly more patients in the cathodal TDCS group showed a clinically important difference after treatment. In a randomized, double-blinded, crossover study of Ochi et al.[81], 18 chronic stroke patients with moderate-to-severe arm impairments were allocated to either anodal TDCS over the affected hemisphere or cathodal TDCS over the unaffected hemisphere along with the robot-assisted arm training. Both interventions showed significant improvements in spasticity measured by modified Ashworth scale.

Post-stroke Depression

Post-stroke depression (PSD) is common and prevalence varies from 15 to 30 % according to the population characteristics and time from stroke onset [65]. PSD is a strong predictor for poor functional recovery [65]. PSD is usually responsive to pharmacologic treatments with serotonin reuptake inhibitors such as citalopram [82] but there are some cases that are refractory to medications.

TDCS can be a potential useful modality to treat this refractory PSD, considering the positive effect in previous major depression studies [83], lower side effect profile [83], and more immediate effect than a serotonin reuptake inhibitor [84]. However, randomized clinical trials using TDCS for PSD have not been reported yet. Only one case report demonstrated the improvement of PSD after anodal TDCS over the left DLPFC (2 mA for 30 min for 10 days) [85]. Further pilot studies for PSD are needed.

Central Post-stroke Pain

Central post-stroke pain (CPSP) is a chronic neuropathic pain, persisting more than 3 months, after stroke [86]. CPSP can develop immediately or years after stroke onset and the prevalence at 6 months and 1 year after stroke is 2.7–25 % [87, 88]. Pharmacological intervention using tricyclic antidepressants, pregabalin, or opioid analgesics can be approached, but its effect is usually limited and lack in clinical evidence [89].

One hypothesis for development of CPSP is a disorder of brain network reorganization after stroke [90]. Therefore, TDCS, applied to modulate the brain network, can be a potential application for CPSP refractory to pharmacological treatments. Although high-frequency rTMS over the primary motor cortex showed a short-term benefit on pain after single-session application [91] and guidelines published by European Federation of Neurological Societies commented a transient reduction in pain after rTMS in central neuropathic pain (Level B recommendation) [92], evidence of effectiveness of TDCS on CPSP is still lacking. A recent Cochrane review demonstrated that TDCS over the primary motor cortex could not reduce the pain in various neuropathic conditions including CPSP [91].

Conclusions

TDCS can enhance the recovery from various impairments after stroke in combination with preexisting conventional rehabilitation approaches, through the modulation of brain activity and connectivity. Portability, safety, and easy applicability enable the TDCS to be applied more widely than other brain stimulation techniques in the stroke rehabilitation. To maximize the beneficial effect of TDCS, more researches to establish optimal stimulation protocols in terms of parameters according to the different impairments and reorganization patterns after stroke are required.

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Transcranial Direct Current Stimulation in Disorders of Consciousness

21

Thibaut Aurore, Di Perri Carol, and Laureys Steven

Abstract

Transcranial direct current stimulation (tDCS), a noninvasive cortical stimulation modulating cortical excitability, has been previously reported to transiently improve working memory and attention by stimulating the left dorsolateral prefrontal cortex (DLPF) in patients with stroke as well as Parkinson's and Alzheimer's disease. As regards disorders of consciousness (DOC), we have recently shown that a single session of tDCS over the left DLPFC can improve sign of consciousness in about 43 % of patients in minimally conscious state (MCS). The transient clinical improvement observed in patients in MCS following tDCS seem to require residual grey matter and metabolic activity in the stimulated area and in structures known to be involved in awareness and arousal, such as the precuneus and the thalamus. These findings suggest that tDCS might be a feasible treatment to promote recovery of new signs of consciousness in patients with DOC. Nevertheless, it also suggests that some patients may be more suited to benefit from tDCS than others. Apart from clinical treatment, tDCS combined with transcranial magnetic stimulation has been shown to induce different responses in terms of connectivity and excitability in MCS as compared with unresponsive patients.

Although tDCS on patients with DOC has not been yet fully investigated, the so far reported studies have revealed promising results as regards improvement of signs of consciousness.

We here provide an overview of the tDCS studies on patients with DOC.

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Transcranial direct current stimulation • Coma • Vegetative state/unresponsive wakefulness syndrome • Minimally conscious state • Disorders of consciousness • Traumatic brain injury • Neuromodulation • Rehabilitation

Introduction

Definition of Disorders of Consciousness (DOC)

Various definitions of consciousness have been so far proposed by scientists, neuroscientists, or philosophers. Nevertheless, a universally accepted definition has not been yet agreed. As such, it is widely accepted that consciousness is a multicomponent term involving a series of cognitive processes such as attention and memory [1, 2]. At the bedside, mainly for scientific purposes and didactical reasons, consciousness has been oversimplified into two main components: arousal and awareness. Arousal (also referred to as vigilance or wakefulness) is necessary to experience awareness and has been considered as the level of consciousness. Anatomically it is related to structures in the brainstem, and it is clinically evidenced by opening of the eyes [3]. Awareness refers to the ability to live experiences of any kind and has been felt to represent the content of consciousness [4]. Awareness itself has been subclassified into internal awareness (i.e., awareness of self) and external awareness (i.e., awareness of the environment). At present there is no singular marker of awareness, but its presence can be clinically deduced from a range of behaviors and motor outputs (e.g., responses to command, visual pursuit) which indicate that an individual can perceive self and surroundings [5]. From the anatomic point of view, internal awareness is related to midline frontoparietal regions such as the mesioprefrontal cortex (MPFC)/anterior cingulate cortex (ACC) and precuneus/posterior cingulate cortex (PCC). External awareness seems to depend on lateral frontoparietal regions [6, 7]. Functional connectivity within these networks and between these networks and the thalamus has shown to be important for consciousness sustainment [8].

Patients in coma are neither awake nor aware [9]. This condition is self-limited and usually cannot last longer than 4 weeks, after which patients either evolve to brain death (i.e., permanent loss of brainstem functions) or recover consciousness or evolve to a vegetative state, recently termed also unresponsive wakefulness syndrome (VS/UWS) [10]. Patients in VS/UWS are awake but they are unaware of themselves and their surroundings, hence exhibit only reflex behaviors [11]. When patients regain minimal and fluctuating signs of awareness, not encompassing the ability to communicate consistently, they are considered in minimally conscious state (MCS) [12]. Based on their capacity to follow commands, MCS patients have been further classified in MCS– and MCS+ [13]. Patients who recover a level of consciousness sufficient for functional communication and/or object use are referred to as emerging from minimally conscious state (EMCS). The boundaries between these different states of consciousness are not always sharp but often are progressive transitions. The gradual transition from coma to recovery is illustrated in Fig. 21.1.

Current Treatment and Limitations in Patients with Disorders of Consciousness (DOC)

Clinical management of patients in VS/UWS and MCS is particularly challenging as this population is susceptible to misdiagnosis [15, 16] and lacks effective treatment options [17].

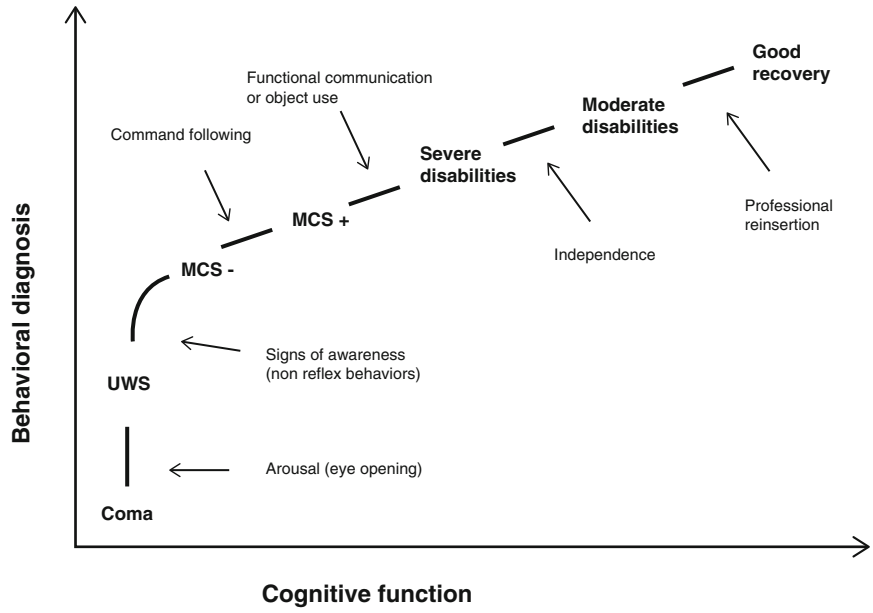

Fig. 21.1 Different clinical entities encountered on the gradual recovery from coma, illustrated as a function of cognitive and motor capacity. Restoration of spontaneous or elicited eye-opening, in the absence of voluntary motor activity, marks the transition from coma to unresponsive wakefulness syndrome (UWS). The passage from the UWS to the minimally conscious state minus (MCS−) is marked by reproducible evidence of "voluntary behavior." Simple command following characterizes the MCS plus (MCS+). Emergence from MCS is signalled by the return of functional communication or object use. Adapted from ref. [14]

The gold standard for the diagnosis of this population is the clinical evaluation through use of standardized and sensitive clinical scales such as the Coma Recovery Scale-Revised (CRS-R) [18]. Through behavioral assessment we can evaluate motor responsiveness and we only indirectly deduce the consciousness level. But the lack of motor responsiveness does not necessarily implies the lack of consciousness, as patients can suffer from different disabilities impairing their responsiveness, such as paralysis, aphasia, and fluctuation in arousal level [15, 19].

Advances in neurophysiology and neuroimaging techniques witnessed in the last decade can now offer the possibility to overcome the limits of the clinical assessment in the detection of possible retained consciousness in unresponsive patients.

A proper diagnosis in this patients' population is imperative, especially if one considers that a misdiagnosis may contribute to premature withdrawal of life-sustaining care and lead to inappropriate medical management such as neglect of pain treatment [17]. Indeed, an accurate diagnosis would have a strong impact on the quality of life and rehabilitation of the patient. For example, failure to detect sign of consciousness may limit access to specialized neuro-rehabilitation centers and, therefore, somehow decrease patients' possibilities to recover.

While several studies have focused on improving the diagnosis of these patients, to date only a few studies have investigated treatment options in order to improve their rehabilitation and their quality of life. At present, there are no evidence-based guidelines regarding the treatment of patients with DOC [17]. Until recently, the medical community has viewed patients in VS/UWS and MCS with great pessimism regarding both prognosis and effective treatments. Unfortunately, this pessimism results in the negligence of patients, especially in the chronic stage, in terms of health care as no improvement is expected. Nevertheless, in the past 10 years a number of

studies have reported that some patients in MCS could improve even several years after the insult [19, 20] and several treatments can enhance signs of consciousness [21–23].

So far, there are no universally accepted drug options to treat these patients. As regards pharmacological agents, some studies have shown that amantadine [22], apomorphine [25], intrathecal baclofen [26], and zolpidem [27] can sometimes improve behavioral signs of consciousness in patients with DOC (see Table 21.1). However, only amantadine has been shown to increase signs of consciousness in a large cohort of acute and subacute patients with DOC in a placebo-controlled trial [22]. One of the most common adverse effects of this drug is the occurrence of epileptic seizures, which can be extremely frequent in this population and can significantly affect their cognitive state [28]. Moreover, the mechanisms underlying the recovery of behavioral signs of consciousness observed in some patients with DOC following the administration of these drugs are still poorly understood.

Zolpidem, a selective beta agonist, has shown to be impressively efficient, inducing the recovery of communication or functional use of objects in patients in MCS (i.e., emergence from MCS). Nevertheless, an extremely low percentage of patients benefit from this drug and so far its mechanism of action and the reason why only a few subject respond to it needs still to be elucidated [23, 28, 29].

As regards neurophysiological treatment, deep brain stimulation (stimulation of the intralaminar

Table 21.1 Main studies using amantadine, apomorphin, baclofen, or zolpidem treatment in patients with disorders of consciousness

Authors	Drug	Design	*N* (etiology)	Time since injury	Results
Giacino et al. [22]	Amantadine (antiviral and an anti-parkinsonian; NMDA antagonist and indirect dopamine agonist)	Prospective, multicentric, randomized, double-blind, placebo-controlled	184 (TBI)	1–3 months	Amantadine group: faster recovery; decrease of DRS scores and increase of behavioral bench markers on the CRS-R
Fridman et al. [25]	Apomorphine (dopamine agonist used in Parkinson disease)	Prospective case series	8 (TBI)	1–4 months	Functional recovery with decrease of the CNC, DRS and increase of GOS scores
Whyte and Myers [24]	Zolpidem (nonbenzodiazepine GABA agonist hypnotic used to treat insomnia)	Mutlicentric, double-blind, randomized study	15 (8 TBI)	3 months to 23 years	1 responder (UWS to MCS+); increase in CRS-R score, visual pursuit, response to command
Thonnard et al. [27]	Zolpidem	Open label study	60 (31 TBI)	2 months to 26 years	12 patients showed improvement in CRS-R scores. Change of diagnosis in 1 patient (from MCS+ to EMCS)
Sara et al. [26]	Baclofen (GABA agonist used to decrease spasticity)	Case report	5 (2 TBI)	6–10 months	Clinical improvement in all patients after 2 weeks (increase in CRS-R scores)

DRS disability rating scale, *CRS-R* Coma Recovery Scale, *CNC* Coma/Near-Coma Scale, *GOS* Glasgow Coma Scale, *NMDA N*-methyl-D-aspartate, *GABA* γ-aminobutyric acid, *TBI* traumatic brain injury, *UWS* unresponsive wakefulness syndrome, *MCS* minimally conscious state, *EMCS* emergence from MCS

nuclei of the thalamus) [23] has shown to improve signs of consciousness in patients in MCS. However, this technique is invasive and did not induce such a clinical improvement to progress into a different clinical diagnostic entity [30].

Transcranial direct current stimulation (tDCS) is a form of cortical stimulation which has shown to improve recovery in several disabling neurological pathologies, such as Parkinson's, Alzheimer disease, stroke, and traumatic brain injury [31]. tDCS is noninvasive, safe, inexpensive, easy to carry out device and, importantly, it does not induce seizure or severe side effects as observed with Amantadine or deep brain stimulation.

tDCS in Disorders of Consciousness (DOC)

Pilot Studies

Several studies have shown that a single anodal stimulation of a damaged cortical area in post stroke or TBI patients can improve the function of the stimulated area. An anodal session of tDCS over the motor cortex (M1) can enhance motor function [32, 33]. Likewise the stimulation of the prefrontal cortex has shown positive effects on memory [34, 35, 36] and attention [37]. Given the abovementioned encouraging results showing enhancement of motor and cognitive functions following tDCS, we decided to test its efficacy on behavioral recovery in patients suffering from DOC [37, 38].

In a first pilot study, we aimed to test the effect of prefrontal tDCS on patients with DOC, both VS/UWS and MCS, acute-subacute (<3 months) and chronic, and with traumatic and nontraumatic etiologies. We assessed the effect of a single session of anodal tDCS of the left DLPF cortex on consciousness, as evaluated by means of the Coma Recovery Scale-Revise [18], known to be, to date, the most sensitive scale for behavioral assessment in patients with DOC. Fifty-five patients with DOC were recruited to receive both anodal and sham tDCS in a crossover study design: 25 in VS/UWS (age: 42 ± 17 years; nine women; interval since insult: 24 ± 48 months; 6 posttraumatic) and 30 in MCS (age: 43 ± 19 years; seven women; interval since insult: 43 ± 63 months; 19 posttraumatic). During tDCS, the current was increased to 2 mA from the onset of stimulation and applied for 20 min. Treatment effect was assessed by means of standardized CRS-R [18].

At the individual level, tDCS responders were defined as those patients who presented a sign of consciousness (i.e., command following; visual pursuit; recognition, manipulation, localization, or functional use of objects; orientation to pain; intentional or functional communication; after tDCS that was not present before anodal nor before or after sham tDCS sessions).

At group level, a treatment effect was observed in the MCS ($p = 0.003$) but not in the VS/UWS ($p = 0.952$) patients' group (Fig. 21.2).

At individual level, 13/30 (43%) patients in MCS showed a tDCS-related improvement (i.e., showed a clinical sign of consciousness never observed before). Two acute (<3 months) patients in VS/UWS out of 25 (8%) showed a tDCS response (i.e., showed command following and visual pursuit present after the anodal stimulation not present at baseline or pre- or post-sham tDCS). In addition, no tDCS related side effects were observed.

These results have shown that a single session of left DLPF tDCS may transiently improve CRS-R scores in patients in MCS in the absence of side effects, suggesting a residual capacity for neural plasticity and temporary recovery of (minimal) signs of consciousness in some patients in MCS. These findings appear of critical importance especially if one considers there are limited evidence-based pharmacological or nonpharmacological treatment options for severely brain-damaged patients with DOC, and particularly in the chronic setting [16, 40]. Indeed, in this study, out of the 13 patients in MCS who showed a tDCS response, five were included >12 months (115 ± 101 months) after the acute insult. This suggests that chronic MCS patients, even years after the brain injury, have still the ability to improve and recover some new signs of consciousness. On the other hand, no improvements were observed in

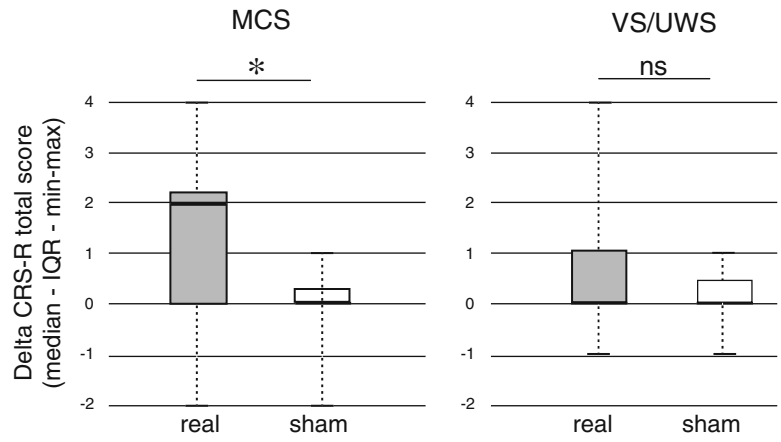

Fig. 21.2 Median (*black line*) of Coma Recovery Scale-Revised (CRS-R) total scores delta (i.e., CRS-R post tDCS minus CRS-R pre tDCS) and interquartile range for patients (IQR, *boxes*) in minimally conscious state (MCS) and unresponsive wakefulness syndrome/vegetative state (VS/UWS), with minimal and maximal values. In *grey*, the results for the real tDCS and in with the sham tDCS. An *asterisk* denotes statistical significance at $p < 0.05$ and NS stands for nonsignificant. From ref. [38]

patients in VS/UWS, in line with previous studies showing capacity for neural plasticity in patients in MCS rather than VS/UWS [41].

The main limit of this study is the short term beneficial effect of the tDCS. Indeed, behavioral improvements were observed for not longer than 2 h from the stimulation. As in daily clinical practice longer effects are required, studies using repeated tDCS sessions are warranted to elucidate whether this technique might be a feasible treatment in clinical practice.

In another study five repeated tDCS sessions (one daily) were performed on patients with DOC [39]. Ten patients with DOC were included (age range: 19–62; three women, duration since insult: 6 m to 10 years; five post-traumatic). All patients received sham tDCS for 20 min per day, 5 days per week, for 1 week, and real tDCS for 20 min per day, 5 days per week, for 2 weeks. An anodal electrode was placed over the left primary sensorimotor cortex (2 MCS − 3 VS/UWS) or the left DLPF cortex (1 MCS − 4 VS/UWS), with cathodal stimulation over the right eyebrow. Improvements were assessed with the CRS-R.

All patients in MCS showed clinical improvement immediately after tDCS session. Only one patient in MCS received tDCS over the left DLPF cortex, as well as four patients in VS/UWS. The MCS patient who received tDCS over the left DLPF cortex showed a behavioral improvement (i.e., recovery of localization to pain). One patient who received the primary sensorimotor stimulation and was in an MCS for 1 year before treatment (postoperative infarct) emerged from MCS at 12-month follow-up. No effects on patients in VS/UWS were observed.

Taken together, the above described studies suggest that tDCS, on both left DLPF (MCS, n = 31) and primary sensorimotor cortex stimulation (MCS, n = 4), might be a promising tool in the rehabilitation of patients in MCS. Nevertheless, future studies are warranted to investigate the long-term effect of the repeated tDCS session, as they required by clinical practice.

In this context it is worth to stress that tDCS seems to be a safe device. Indeed, in a total of 65 patients (both MCS and VS/UWS) included in the two studies no severe side effects were observed, even considering that many of these patients had severe brain injuries with widespread lesion possibly involving the stimulated areas. Moreover, although it is well know that brain injured patients are more vulnerable to epileptic seizure, and some of them were even under an epileptic

treatment due to previous seizures, no seizures as side effects were observed. With the limits of a small population, the abovementioned findings suggest that tDCS can be safely used in the treatment of patients with severe brain injury and DOC.

Neuronal Correlates of tDCS in DOC

The mechanisms of action of tDCS remain only partly understood and several clinical trials have shown that the proportion of tDCS responders may vary from 40 to 80 % [41–44]. Concerning patients with DOC, we recently reported that left DLPF tDCS could improve signs of consciousness in 43 % of patients in MCS [38]. If these findings suggest the potential interest of tDCS as a treatment for DOC, they also highlight the lack of a clinical improvement following tDCS in more than half of the patient population. The natural step was, therefore, to define the structural and functional brain features of those patients that are likely to respond to tDCS [45].

Using multimodal neuroimaging analyses, including fludeoxyglucose positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI), the previously described subgroup of tDCS responders [38] has been characterized. Out of the 21 patients in MCS that were included in the analyses, eight were tDCS responder (four posttraumatic, four nontraumatic, four men) and 13 were nonresponder (eight posttraumatic, five nontraumatic, ten men).

A common pattern of metabolic preservation (as detected by FDG-PET) and grey matter preservation (as detected by MRI), was observed in tDCS responders as compared with nonresponders, whilst no specific behavioral patterns of improvement among the patients who showed clinical improvement following left DLPF cortex tDCS could be detected. The transient improvement of signs of consciousness following tDCS seemed to require grey matter integrity and/or residual metabolic activity in three brain regions: (a) the presumed stimulated area (i.e., left DLPF cortex), (b) long distance cortical areas such as the precuneus, and (c) subcortical brain areas known to be involved conscious processes (i.e., thalamus) see Fig. 21.3.

tDCS as a Diagnostic Tool

It has been recently shown that tDCS could also be used as a diagnostic tool to differentiate MCS from VS/UWS patients [47]. In a recent study, cortical connectivity and excitability were assessed by means of dual-site TMS approach [48]. More specifically the authors recorded resting motor threshold, motor evoked potential amplitude and latency, central conduction time, intracortical facilitation and short-interval inhibition, as well as interregional interactions between left primary motor cortex (M1) and right dorsal premotor cortex (PMd) and pre-supplementary motor area (SMA). After the first testing, tDCS (real or sham) was applied over the orbitofrontal cortex (anode between Fp1 and Fp2 and cathode over Cz, according to the 10–20 international system). TMS was performed 60 min after tDCS, as well as 60 min later.

Behaviorally, no patients showed any CRS-R scoring changes after tDCS. The results showed an increase in MEP amplitude, an intracortical facilitation, and a premotor–motor inhibition reduction in MCS. Concerning VS/UWS patients, tDCS had no effects on three patients out of seven, whereas it induced a reduction of premotor–motor inhibition and a partial increase of M1 excitability in the remaining four. Here, a correlation between CRS-R total score and premotor–motor connectivity and M1 excitability modulation was also observed.

The authors suggested that the four patients who were diagnosed as being in VS/UWS but showed an increase in cortical connectivity and excitability had actually covert consciousness not detected by the clinical exam, as previously reported in the literature [49–51].

This study shows that tDCS can detect residual connectivity in clinically VS/UWS patients, who may sub sequentially recover behavioral signs of consciousness, suggesting an added prognostic value.

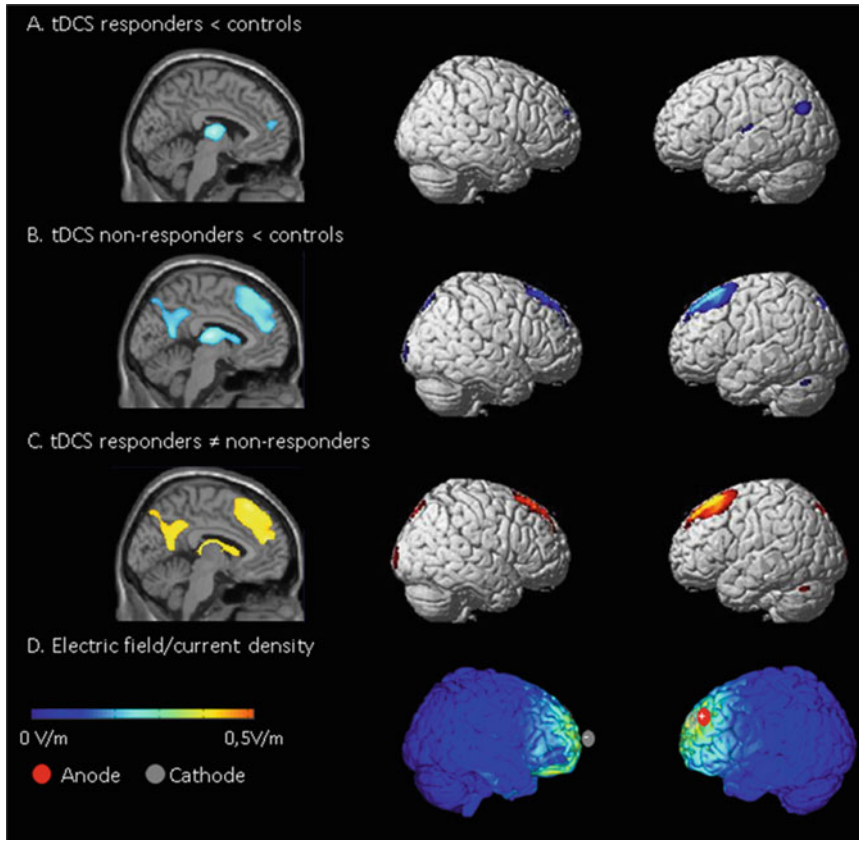

Fig. 21.3 Positron emission tomography (PET): Brain areas showing hypometabolism (in *blue*), as compared to controls, in patients in a minimally conscious state (FEW corrected): (**a**) eight tDCS-responders and (**b**) 13 nonresponders. (**c**) Regions with less hypometabolism in responders as compared to nonresponders (in *red*). (**d**) Theoretical tDCS induced electric fields. Note that behavioral responsiveness to short duration left dorsolateral prefrontal cortex (DLPFC) tDCS correlates with less impaired metabolism in the areas presumed to be stimulated by tDCS (left DLPFC and mesiofrontal cortices) but also of distant cortical (precuneus) and subcortical (thalamus) regions. From [46]

Long-Term Effects

tDCS long-term effects are required in order to be used in a daily clinical practice. In this context, several sessions of tDCS may be required in order to achieve the desired effect. A study of repeated tDCS over the primary motor cortex in healthy volunteers highlighted a consolidation mechanism which lasted up to 3 months after five tDCS sessions [52]. Unfortunately, not enough comparable multiple-day stimulation studies have been carried out to assess whether repeated tDCS sessions could be efficient at improving motor or cognitive skills in healthy volunteers. Nevertheless, in neurological patients with motor or cognitive deficits, tDCS has shown positive effects that last several weeks or even months when the stimulation is repeated for 5 or 10 consecutive days. Based on the abovesaid, we believe that repeated stimulation might be required to induce reliable improvements that could warrant its implementation in clinical daily practice.

Our next challenge is, therefore, to test the effects of repeated stimulation sessions on DOC

patients carried out 5 days consecutively and to evaluate the benefits, in terms of CRS-R, a week from the end of the stimulations. This would elucidate whether tDCS could be used as a therapeutic tool on a daily basis in clinical practice, in rehabilitation centers, nursing homes or even at the patient's home. Moreover, it would demonstrate whether an increased number of stimulations could also enhance the beneficial effect (as measured by effect size) and increase the number of patients who respond to the treatment.

Conclusions and Future Directions

In this chapter we describe the potential therapeutic effects of tDCS on patients with DOC. We show that almost half of the patients in MCS had behavioral improvement after a single stimulation. We also identify that the transient increase of signs of consciousness in patients with DOC upon tDCS requires residual metabolic activity and grey matter preservation in cortical and subcortical brain areas important for consciousness recovery (i.e., left DLPF cortex, precuneus, and thalamus) [46]. Moreover, tDCS, coupled with TMS, has also shown to be able to differentiate MCS from VS/UWS patients. Most importantly, tDCS has shown to be a handy and safe and feasible device, also when applied on patients with DOC.

Even though these first findings seem encouraging, further studies are required in order to investigate the long-term effect of tDCS in this population of patients. A first step would be to perform repeated stimulation sessions in addition to the previously described protocol (i.e., left DLPF tDCS). Furthermore, assessing the tDCS long-term effects would elucidate the duration of its effects and whether it might be a feasible device in the daily clinical practice.

Different areas of stimulations should also be tested according to patients' cortical damage. Indeed, we have recently shown that DOC patients need a partial preservation of the stimulated area to respond to tDCS. Consequentially, a stimulation of a (partially) preserved area would be more effective than stimulating a damaged brain region.

Neuroimaging acquisition before and after a tDCS session should be carried out in order to target the proper area to stimulate. This might give the opportunity (a) to investigate the effect of tDCS on patients' cortical activity and excitability, (b) to reveal the differences between responders and nonresponders, and (c) to better identify the patients who could benefit from left DLPF tDCS or M1 tDCS or any other areas. The final aim is to develop a patient's tailored stimulation to give him/her the best chance to recover a certain degree of autonomy.

It should be kept on mind that although patients with DOC are, by definition, not able to communicate, they may perceive pain and retain emotional behavior [53]. Therefore, we strongly recommend to use solely parameters that have been already tested in healthy subjects or patients with neurological dysfunction (able to give a feedback), without any severe side effects being reported.

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Part III

The Clinical Use of tDCS

Safety and Tolerability

22

André Brunoni, Colleen Loo, and Michael Nitsche

Abstract

TDCS most common adverse effects are burning, tingling, itching, headache, and discomfort on the site of stimulation. These adverse effects occur in up to one-third of patients and are generally mild, short-lived, and well-tolerated. Skin redness is a common adverse effect that occurs in most patients, although skin burning is rare and often associated with repeated tDCS sessions and poor humidification of sponges. Severe adverse effects, including seizures, cardiac arrest, permanent disability and damage, have not been reported in tDCS adult trials thus so far. Regarding safety, studies indicate that the doses used clinically are much lower than necessary to induce lesions and are not associated with damage. Nonetheless, the statement that tDCS is "safe" should be tempered down considering that its adverse effects are often under-reported in most studies and the risk of induction of adverse effects in special populations (e.g., hypomanic switch in depressed patients, or seizures in patients with epilepsy) has not been sufficiently investigated yet.

Keywords

Adverse effect • Safety • Itching • Tingling • Headache • Erythema • Discomfort • Transcranial direct current stimulation • Seizure • Skin

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Introduction

Transcranial direct current stimulation has been applied increasingly in recent years to alter brain function in healthy humans and patients suffering from neurological and psychiatric diseases. Although in many papers the presence or absence of side effects is mentioned, and suggest a favorable profile, systematic data aggregation of safety data and studies primarily aimed to explore safety of the technique are rare. Correspondingly, it is important to distinguish between tolerability and safety in a strict sense. The former describes the presence of uncomfortable and unintended effects, which do not however induce structural or functional damage (e.g., tingling, and itching sensation under the electrodes), whereas the latter refers to damaging effects per se. Similarly, according to the Food and Drug Administration (FDA), an adverse effect—defined as any undesirable experience associated with the use of a medical product in a patient—can be divided into common and serious, the latter referring o patient outcome of death, life-threatening condition, hospitalization, disability or permanent damage, congenital anomaly, need of an intervention to prevent permanent impairment or damage, or other serious, important medical events (notably seizures or convulsions). In this chapter we discuss the main issues regarding safety and tolerability of tDCS.

Tolerability

Common Adverse Effects

Poreisz et al. [1] collected data from 567 tDCS sessions delivered over different cortical areas from previous studies of their group. They observed that a mild tingling sensation (70.6 %) was the most common side effect, followed by fatigue (35.3 %), itching (30.4 %), and, less frequently, headache (11.8 %), nausea (2.9 %), and insomnia (0.8 %). All side effects were mild, short-lived, and well-tolerated, and for most symptoms the rate was not different between active and sham stimulation. Brunoni et al., in a systematic review and meta-analysis, collected data from all tDCS clinical studies performed from 1998 to August 2010 [2]. Of 209 studies (172 articles, encompassing almost 4000 subjects), 56 % monitored adverse effects and, of those, 63 % reported at least one adverse effect. According to the retrieved studies, similar rates in the active vs. sham arms of the most commonly reported adverse effects were observed, namely headache, itching, burning sensation, discomfort, and tingling (Table 22.1).

Table 22.1 Adverse effects of transcranial direct current stimulation

Sensation	Active group	Sham group
Itching	46 (39.3 %)	27 (32.9 %)
Tingling	26 (22.2 %)	15 (18.3 %)
Headache	17 (14.8 %)	13 (16.2 %)
Burning sensation	10 (8.7 %)	8 (10 %)
Discomfort	12 (10.4 %)	11 (13.4 %)
Total	117 studies	82 studies

Rate of adverse effects in clinical transcranial direct current stimulation studies. Adapted from Brunoni et al., International Journal of Neuropsychopharmacology, 2011 [2]

This systematic review also showed, however, that only eight studies systematically addressed the frequency and intensity of adverse effects. In other words, almost all studies failed to systematically report the frequency and intensity of adverse effects. Although this could indicate that these effects might be benign and well tolerated, this also indicates that the prevalence of tDCS-related adverse effects is probably underestimated in literature. Therefore, the authors recommended that all tDCS clinical studies should provide estimates of the frequency and intensity of adverse effects observed.

After this study, Kessler et al. [3] evaluated side effects in 131 subjects undergoing 277 tDCS sessions, finding that sensory side effects are common, of low severity, more common in the active compared to sham tDCS and included tingling (76 %), itching (68 %), burning sensation (54 %), and pain (25 %). In this context, Russo et al. [4] assessed adverse effects and the level of comfort experienced by 149 subjects that received a total of 195 tDCS sessions in a

Table 22.2 Summary of studies evaluating common adverse effects

Author	Study design	*N*	Main adverse effects	Comments
Poreisz et al. [1]	Individual patient data	567	Tingling (71 %), fatigue (35 %), itching (30 %), headache (12 %)	Most rates were similar in active vs. sham tDCS
Brunoni et al. [2]	Meta analysis	3836	Itching (39 %), tingling (22 %), headache (15 %), burning sensation (9 %), discomfort (10 %)	Rates were nonstatistically higher in active tDCS (vs. sham)
Kessler et al. [3]	Individual patient data	277	Tingling (76 %), itching (68 %), burning (54 %), pain (25 %)	Rates were higher in active tDCS. (vs sham)
Fertonani et al. [5]	Individual patient data	693	Itchiness, pain, burning sensation, heat, pinching, iron taste, fatigue, discomfort	Frequency not described, adverse effects' intensity was associated with higher current and larger electrodes

double-blind fashion. The authors reported no serious adverse effects, overall low rate of common adverse effects and also that levels of comfort increased over time, which were discretely higher (i.e., more comfortable) for sham stimulation. Finally, Fertonani et al. [5] analyzed data from 531 subjects—693 different sessions—receiving tES (mostly tDCS, but also other forms of stimulation). Similarly to other studies, they observed that the most common effects were itchiness, pain, burning sensation, fatigue, and discomfort, which were mild, well-tolerated, and short-lived (Table 22.2).

Skin Reddening

Another common and underreported side effect is tDCS-induced erythema, i.e., the reddening of the skin that occurs after tDCS. The intensity of this adverse effect varies in patients; most of them experience only mild redness whereas a few others might have more intense skin reddening. Erythema is due to direct effects of the current on the skin, but may also arise from the physical pressure of the electrode pad, which must be strapped firmly against the skin to ensure good contact. Although not particularly uncomfortable for almost all patients, skin reddening may be a threat to adequate blinding if it occurs more frequently or persistently in the active arm, although redness is also observed after sham due to electrode pressure over the skin. The mechanisms involved in erythema induced by the current are only partially understood, but this phenomenon seems to be caused by increased blood flow in the dermal vessels that occurs as a direct result of the current application, and also probably due to the release of multiple neuropeptides by primary afferent nerves following noxious and non-noxious stimulation, with secondary release of vasoactive substances, histamine and prostaglandins [6]. In a study investigating this issue, Guarienti et al. [7] evaluated the effects of 2 mA, 30-min anodal/cathodal tDCS on skin reddening. They observed that the erythema was more prominent over the anode than the cathode, although it was mild in both conditions. The erythema was also short-lived, lasting less than 18–24 min. Moreover, erythema was less intense in subjects with darker skin color and was not influenced by gender, age, and smoking habits. Finally, the authors observed that erythema intensity was decreased by previous application of topic ketoprofen.

Parameters Associated with Adverse Effects

Several factors influence the perception and intensity of adverse effects. One factor is current intensity - higher intensities are usually associated with more adverse effects. In a systematic investigation of the threshold for perception of stimulation, Ambrus et al. [8] observed that at 0.4 mA half of subjectsreported the presence of sensation, whereas at 1 mA all subjects were able to perceive the stimulation. In addition, composition of electrolyte solution seems to play a role:

electrolyte solutions with lower NaCl concentrations (15 mM) seem to be more comfortable during tDCS than solutions with higher NaCl concentrations (220 mM) [9]. Dundas et al. [10] recommended the use of solutions with relatively low NaCl concentration, in the range 15–140 mM (i.e., of similar or lesser strength as "normal saline" (154 mM), as tDCS at these concentrations is more likely to be perceived as comfortable, requires low voltage, and still allows good conduction of current. A means to enhance tolerability might be also to apply topical anesthetics to alleviate local adverse effects associated with tDCS [9, 11].

The size of the electrodes may influence discomfort. Turi et al. [12] compared different subject groups that received tDCS with 25 or 35 cm^2-sized electrodes. When current density (averaged across the electrode surface) was kept constant, larger electrodes were associated with greater cutaneous discomfort. However, when current intensity was kept constant, there was no difference. This suggests that higher current intensity is related to more cutaneous discomfort, even when electrode size is increased to compensate. Fertonani et al. [5] in a post hoc analysis of more than 600 tES sessions suggested that both current intensity and electrode size affected discomfort. Ambrus et al. [13] observed that in contrast electrode shape does not matter in terms of perception—if both have the same surface area, standard rectangle and circular electrodes induce similar skin sensations.

Acceptability in Clinical Trials

Acceptability is a term used in controlled clinical trials to evaluate the number of dropouts that occur in the experimental treatment compared to the control intervention. Acceptability is low if dropouts occur significantly more frequently in the experimental treatment, since this suggests that the excess dropouts happened due to intolerable adverse effects. It is important to assess if a new treatment is not only effective but also well-tolerated by the patients, otherwise the intervention would only be applied to a restricted number of individuals.

Meta-analyses of tDCS randomized clinical trials that investigated this issue by collecting data from randomized, sham-controlled tDCS trials for depression found that the dropout rate of patients in the active vs. sham arms of tDCS is similar [14, 15]. These results suggest that continuous, daily application of tDCS for several days is an acceptable and tolerable procedure at least for depression studies. In fact, studies evaluating acceptability of tDCS for other neurologic and psychiatric conditions did not report a higher rate of dropouts following active stimulation [16].

Safety

Serious Adverse Effects

No serious adverse effects, according to the FDA literature, regarding tDCS have been reported in any tDCS clinical study performed from 2000 onwards, including induction of seizure, stroke, cardiac arrest, and other life-threatening events. Moreover, safety studies revealed that tDCS does not change heart rate variability at rest [17], does not increase the serum levels of neuron-specific enolase, a brain enzyme associated with neuronal death [18], and does not qualitatively alter electroencephalographic activity [19].

TDCS safety was also explored in animal studies (see Chap. 5 and Chap. 13 in this book). One important study was performed by Liebetanz et al. [20] that explored the safety limits of tDCS stimulation in rats by using increasingly larger current intensities and thereafter performing histological evaluations. The authors found that the threshold necessary to induce brain lesions in rats was 52,400 C/m^2, two orders of magnitude larger than the charge density applied in humans. Although these results cannot be directly transferred to human studies, they corroborate clinical studies showing that the technique is safe when used according to standardized parameters. Stimulation over holes or fissures of the cranial bone, which can result in an increase of current density, should however be avoided [21].

Skin Lesions

Palm et al. [22] reported five cases of skin lesions in a tDCS study on depressed patients. After 5 days of 2 mA stimulation using tap water-soaked sponges, patients presented lesions showing extensive redness and brown crusty lesions under the cathode. Lesions seemed also to be associated with high skin impedance. Frank et al. [23] reported three cases of skin lesions under the anode in patients with tinnitus. The current dose was 1.5 mA and tap water-soaked sponges were used. Rodriguez et al. [24] reported four cases of skin burn under the cathode. In these cases, saline-soaked sponges were used and the impedance was adequate. Finally, Wang et al. [25] reported a skin lesion under the cathode after a single tDCS session, using a 2 mA current and sponges soaked in 46 mM NaCl.

To conclude, skin damage caused by tDCS has been occasionally reported. It is unclear whether this adverse effect is more common under the anode or the cathode or which factors increase its risk, although it seems that tap water-soaked sponges and high impedance were more frequently associated with it—in fact, a higher impedance is observed in tap water (vs. saline) soaked sponges [26]. To avoid this side effect, Loo et al. [27] suggested some precautions such as screening patients for skin diseases and checking the skin site where the electrode is placed for lesions before each session. The authors also advised to avoid abrasion of the skin and to ask patients to report during stimulation whether tDCS induced pain; the latter may serve as a potential early indicator of risk of skin damage. This approach may not be foolproof though, Palm and colleagues noting that cutaneous sensation was not related to the development of skin lesions [26].

Safety in Neuropsychiatric Samples

Many tDCS studies were performed so far in healthy participants and not in neuropsychiatric samples, although this number is rapidly changing given the increasing number of ongoing clinical trials. In patients with clinical conditions, not only the physiologic mechanisms of tDCS should be considered, but also whether tDCS can cause specific side effects when used in a disorder. For instance, in patients with depression, some cases of hypomania/mania have been reported after tDCS treatment, although it is difficult to infer whether tDCS *caused* these symptoms or they occurred as part of the natural history of the disease [28–30] (see Chap. 5 and Chap. 13 in this book).

Anodal (excitability increasing) tDCS was never associated with seizures in healthy subjects, although this event could was reported recently in a patient [31], a 4-year old male with history of prematurity, left dominant spastic paresis and infantile spasms. He had been seizure-free for 2 years on antiepileptic medication. Anodal tDCS (1.2 mA, 20 min) was performed over the right paracentral region. Four hours after the third session of stimulation, the patient developed a partial onset seizure characterized by speech arrest, confusion, leftward eye gaze deviation, left arm clonic movements, and secondary generalization, which required administration of intravenous midazolam. The patient's lateralized semiology suggested that the seizure onset was from the frontocentral region, corresponding to the region of anodal stimulation.

Therefore, though the occurrence of seizures or other serious adverse effects is rare, extra caution may be warranted in neuropsychiatric patients and further studies assessing the safety of tDCS in patients with neuropsychiatric disorders are warranted. Nonetheless, the frequency of adverse effects in these populations is still rare.

Functional Impairment

Functional safety encompasses the induction of cognitive, behavioral, or other disturbances (particularly permanent function reductions), which are not intended by the application of tDCS. Put simply, this occurs because different brain networks interact with each other, and the enhancement of the activity of one region can

occur at the expense of a decrease in activity of another one. In one study with healthy subjects, it was shown that tDCS over the posterior parietal cortex enhanced numerical learning whereas automaticity for learned materials decreased. Vice-versa, tDCS over the dorsolateral prefrontal cortex impaired the learning process and improved automaticity [32]. Another study in depressed subjects found that a single session of bilateral tDCS over the dorsolateral prefrontal cortex impaired implicit learning acquisition compared to sham [33].

Contraindications

There are few, relative contra-indications for tDCS. As the electrodes are placed over the skin, they should not be placed directly above areas of impaired skin (including areas with chronic skin diseases) to avoid skin damage and skin burn. TDCS should also not be applied directly over areas with implanted metallic plates, to avoid heating or preferential conduction over this area. For patients with a history of previous neurosurgical procedures, neurologic malformations or brain neoplasias, it is proposed that the tDCS stimulation approach can be modeled for that individual patient—using high-definition, computational forward models based on that patient's head anatomy, reconstructed from MRI scans—to inform on the brain area that will receive most of the electrical current [34]—however, this approach has not been empirically validated. Likewise, the use of tDCS in special populations such as children and pregnant women should be carefully considered, with recommendations that lower current intensities are used in the young [35]. Finally, there is no data to support the use of tDCS beyond the standard parameters tested so far in research settings, i.e., tDCS sessions given: (a) more than twice daily; (b) more than 40 min per session or (c) using current densities above 0.125 A/m^2 [9, 11]. In such cases, the protocol should be tested first under controlled settings.

Conclusion

Within the standard parameters of use outlined above, the evidence indicates that tDCS is a well-tolerated technique, with few, mild side effects. Although tDCS is considered to be "safe," as the (battery-driven) tDCS device is limited to delivering a low-dose current which has effects on cortical excitability (though not to the extent of directly inducing action potentials), and no major or serious adverse effects for tDCS have been reported, such findings do not imply that tDCS is "universally safe" and should therefore be used without limits or controls. . First, there are no data regarding tDCS use beyond the limits commonly used in experimental setting regarding current intensity, session duration and interval between sessions. Second, it is possible that tDCS enhances activity in one brain area at the expense of decreasing activity in another brain area—for instance, in our clinical trial in which tDCS presented antidepressant effects, we also found that it prevented implicit-learning acquisition during a probabilistic classification learning task, possibly by decreasing activity in brain areas responsible for implicit memory learning [33]. In this context, it is possible that "wrong" stimulation parameters for several days may have unwanted consequences leading to maladaptive plasticity. Finally, tDCS is a relatively novel technique and longer-term follow-up studies are still warranted for fully addressing the clinical safety of tDCS.

Taken together, currently applied tDCS protocols seem to be safe, and well tolerated. This assumption does, however, not necessarily apply for any tDCS protocol, outside parameters and clinical populations tested. Thus, general statements like that "tDCS is safe" independent from protocol specifications should be avoided. Moreover, this assumption is only valid if common exclusion criteria for tDCS/noninvasive brain stimulation (metal in the head, pacemaker, no stimulation over fissures, or cranial holes, causing locally enhanced current density) are respected. Special consideration should also be given when

determining safety and tolerability in children, where parameters safely used in adults may have a different safety and tolerability profile.

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Home-Based tDCS: Design, Feasibility and Safety Considerations

23

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Abstract

Transcranial direct current stimulation (tDCS) utilises straightforward technology but nonetheless has the potential to be used as a treatment for a wide range of neurological and psychiatric conditions. Though modern tDCS devices are relatively recent developments, promising results from a growing number of studies and subsequent interest among clinicians and the broader public are such that manufacturers have begun marketing tDCS devices for home use. This chapter outlines the features of tDCS that position it well for such an application while also discussing the importance of a more measured approach to treatment provision and oversight. tDCS is a safe, well-tolerated procedure when administered correctly and used within established parameters but practical and safety considerations should be taken into account when delegating tDCS administration to patients. The current state of research using home-based tDCS devices is also reviewed and further, although yet to be tested, applications are noted. Whether as a stand-alone or adjunct treatment, devices that enable tDCS to be self-administered in a patient's own environment may constitute a treatment option that is more accessible, cost effective and convenient compared to clinic- or hospital-based brain stimulation treatments.

Keywords

Transcranial direct current stimulation • Device • Noninvasive • Brain stimulation • Self-administered treatment • Remote supervision • Neuromodulation • Efficacy • Safety • Feasibility

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Introduction

Over recent years, there has been a marked increase in the number of tDCS devices being marketed for home use (e.g. the Brain Stimulator; foc.us; Soterix mini-CT). Indeed, there are many features of tDCS technology and operation that lend itself to being more readily adaptable for home use compared to other non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS). However, despite its recognised potential, tDCS has as yet not been approved for any therapeutic applications and current research continues to investigate questions regarding optimal therapeutic parameters and whether there should be limits to its use. Promotion of its wider use, therefore, specifically in the context of home use, should be tempered by an awareness that tDCS is still not yet a fully realised treatment.

Nonetheless, given the burgeoning popular and commercial interest in neuromodulation techniques, a discussion on guidelines for the home use of tDCS is timely. This chapter presents factors that should be taken into account when adapting tDCS for home use particularly with regard to device design, operator training, patient safety and monitoring. While there is growing interest in testing home-based tDCS in clinical trials [1–4], recommendations here are put forward with the view that tDCS will ultimately be more widely available as a treatment option under routine clinical care and supervision.

tDCS Suitability for Home Use

tDCS is typically administered via battery-powered devices that range in dimension from the size of a hand to no greater than a small shoebox and weigh no more than 2 kg. Due to their portability, tDCS devices (including their attendant equipment—electrodes, cables and headbands) have the most potential of all brain stimulation techniques for distribution and use outside clinical centres (see Fig. 23.1 foe examples). In addition, although operation of tDCS devices is not particularly complicated, operation could be further simplified to as easy as pressing a start button as newer machines could allow all stimulation parameters (i.e., current intensity, duration and number of sessions) to be pre-programmed. This would allow clinicians to ensure that the stimulation applied is kept within standard protocols that are known to be safe and prevents patients from using the device beyond their prescribed course.

When adhering to standard stimulation parameters—typically no more than 2.5 mA and 30 min duration—repeated sessions of tDCS are known to have a benign side effects profile and are well tolerated [5–7] (also see Chap. 22 of this book that discusses safety aspects of tDCS). The most commonly reported side effects are mild to moderate tingling, itching and/or a burning but not painful sensation at the electrode sites [8] that do not normally last beyond the stimulation period. Headache, light-headedness or fatigue may occasionally be reported during or after a session but are also usually mild to moderate, transient and rarely require medication. Provided that patients follow standard operation, are made aware of common side effects, and reporting procedures and instructions for seeking help are in place should an adverse event arise, tDCS administered at home should be as safe and well tolerated as tDCS administered in research/clinical centres.

Costs of tDCS operation and equipment also compare favourably to other brain stimulation techniques. As tDCS as envisaged for home use can be self-administered, there are no costs associated with clinic staff or facilities nor costs of travelling to and from a treatment centre, which usually involves attending every weekday for at least 2 weeks. Home-based tDCS would also afford greater accessibility for patients living in remote areas or patients who are less mobile or home bound, thereby encouraging better treatment adherence. Moreover, with the cost of a home-based tDCS device and consumables not exceeding a few hundred dollars, its affordability will make it a viable option for a greater number of people as a treatment that can be purchased outright and used as needed under a clinician's supervision.

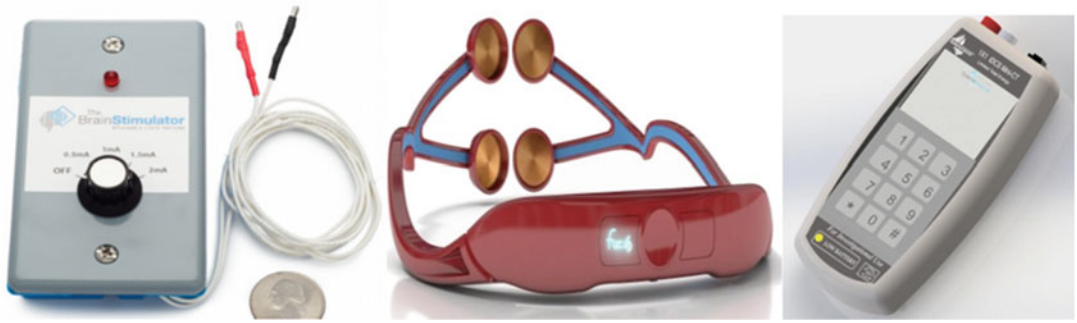

Fig. 23.1 Examples of tDCS devices developed for self-administration either autonomously or under clinical supervision

Device and Equipment Design

Until recently, tDCS devices have been primarily designed for clinician-administered stimulation within the context of a medical or research setting. However, the rapidly growing interest in home use necessitates devices that lend themselves to self-administration and take into consideration practical design issues as well as additional safety features.

All devices should meet regulatory requirements for commercial medical devices as a compromise in quality standards could lead to reduced overall safety and unanticipated side effects. Maintenance of these standards should also provide assurance that findings from clinical studies may be applicable to at-home use. Device safety features should include measures to restrict use within prescribed limits; that is, manual alterations of the intended stimulation parameters should be prevented by, for instance, locking devices to specific stimulation parameters (e.g. current intensity, duration, number of sessions) with devices programmed to deliver a stimulation session only when a single-use code is entered.

In terms of design, devices should feature large, clearly labelled buttons and cable slots for easy operation, and be accompanied by plainly written but comprehensive directions for use. The device interface should include an easily readable screen to monitor device performance with helpful readouts such as the stimulation time remaining, current intensity and impedance in real time. A dynamic impedance readout in particular will allow the user to be continuously aware of their "dose" quality and if in case of any irregularities, discontinue stimulation or make adjustments according to prescribed guidelines. For safety, it would be necessary to have a clear abort feature so that the stimulation can be safely terminated at any point by the user. As an additional safety feature, devices could also be designed to either be paused or automatically power down if abnormalities in impedance are detected. To preserve battery charge, devices should automatically shut off after a specific period of inactivity.

Headset design and electrode placement is an equally important consideration for at-home administration. Electrode placement is one of the critical determinants in achieving behavioral results [9]. If incorrectly positioned, unanticipated negative side effects may occur, including the reversing of polarity that could lead to unintentional disturbance of certain functions [10]. Headsets need to be uniform for standardised placement and adjustable for individual differences in head size and shape. Clear labels and markers on the headset can help guide correct placement.

Also important for headset design is the electrode montage to be used. Some montages would be more readily self-administered than others such as a bifrontal montage in which the user can directly see the electrode positioning in a mirror and make adjustments as needed. A montage in which electrodes need to be placed on the occipital area would be more difficult to directly check, though not impossible with, for example, the use

of a second mirror to enable a rear view. However, the electrode placement process for any montage could be facilitated by having a headset specifically designed for the montage to be used where electrodes can be fastened onto the headset at particular sites possibly standardised according to the 10–20 EEG system. Training users to identify key anatomical landmarks such as the nasion and inion as additional reference points should also assist in the relative positioning of the headset and electrodes.

Regarding electrode preparation, it would be important to have a standardised procedure for moistening the electrode sponges with saline as the recommended conducting solution. Electrode sponges that are too dry could lead to poor conductance or skin discomfort at the electrode sites while excessive moisture could lead to the current being shunted away from the intended target or unintentional weakening of the current intensity by being diffused over a wider area. To facilitate adequate moisture, sponges could be provided pre-moistened with saline and in sealed plastic until opened for use, or at the very least, the saline could be premeasured via syringe. Sponges could also be designed to indicate (e.g. by change of colour), when optimal saturation has been reached.

tDCS has a growing do-it-yourself community with many instructions for the design and use of devices already available on the Internet. These devices can be purchased directly without a prescription, training, or supervision. The potential safety concerns are apparent and their unsupervised use is not advisable given that there is an absence of safety standards with regard to prevention of device malfunction, governance to prevent overuse, and sanitary practices [11]. Some devices on the market may meet minimal manufacturing standards and/or include safety features (e.g. meters to prevent overuse) but little is known concerning their design and safety apart from information provided by the companies. Any claims for benefit are made independent of any governing oversight as there is no regulation of these devices or any certification process. The United States Federal Drug Agency does not approve or regulate the devices and it also does not verify any stated therapeutic use. For the two companies currently marketing tDCS devices directly to consumers for self-administration (i.e. the Brain Stimulator and foc.us), only one (a foc.us device) has been included in a clinical study. In this study, 24 college students were administered one session of active (1.5 mA) or sham stimulation for 20 min [12]. The active condition was well-tolerated overall but associated with significantly more uncomfortable sensations at the electrode sites (e.g. burning, tingling) than sham. Other than this initial study, the safety and tolerability of the use of these devices, and especially any clinical benefit, remains largely unknown.

Patient Selection and Contraindications

tDCS is now being trialled to treat a number of psychiatric and neurological conditions including depression [5, 13], stroke recovery [14, 15], neuropathic pain [16, 17] and auditory hallucinations in schizophrenia [18, 19] although very few studies have done so using home-based tDCS. While patient and condition specific criteria such as symptom profile, severity and comorbid conditions will determine the suitability of home-based tDCS, there are a number of common criteria that should be considered when assessing patient suitability.

The most practical consideration is the likelihood of the patient adhering to the prescribed course and capacity to self-administer or receive tDCS from a carer as failure to meet basic treatment requirements would result in suboptimal, if not ineffectual, treatment at best. Of greater concern, while there are few absolute contraindications that would preclude a patient from receiving tDCS, there should be particular note of conditions that could interfere with the normal current flow or affect the conductance. The presence of metal or implanted medical devices in the head are widely accepted as absolute contraindications as their conductivity can affect current concentrations and shunt the current away from the intended target. History of serious brain injury or neurological surgery would be considered more on a case-by-case basis depending on the location and

extent of anatomical changes as the size of skull defects could influence the distribution of peak cortical fields [20]. Other conditions such as history of headache or migraine, stroke or seizure would not necessarily be considered as absolute contraindications but may be application specific as such conditions may themselves be the target for treatment in some clinical trials of tDCS.

Special attention should also be given to any existing skin disorder and the condition of the scalp particularly at the intended electrode sites as skin burns can result from multiple tDCS sessions applied to the same scalp area if skin integrity is compromised [21, 22]. tDCS should not be applied if there are skin breakages, lesions, cuts, rashes, acne, pitting or excessive sensitivity and dryness at the electrode sites as the current may become focalised around the damaged area and potentially result in skin burns. Even using a lower current intensity to that originally intended would not be advisable as there is no guarantee that this will prevent further damage. However, as there is some degree of latitude with tDCS to slightly adjust electrode positioning without drastically changing the resultant stimulated cortical area, the electrodes could be moved if appropriate to avoid directly stimulating the affected skin.

There are no medications that are contraindicated for use with tDCS although effects of certain medications should be considered when assessing the likelihood of tDCS benefitting a patient. Benzodiazepines have been associated with a worse outcome in depressed patients receiving tDCS [23] although the exact mechanism by which they modulate tDCS effects have not been fully elucidated and could depend on a combination of factors such as their effect on GABA receptors and downstream modulation of remote cortical and subcortical areas [24]. Carbamazepine and flunarizine have been found to selectively eliminate the excitatory effects of anodal tDCS while dextromethorphane prevented induction of prolonged effects of tDCS irrespective of polarity [25]. These results suggest that any medications that affect neuroplasticity via actions on sodium and calcium channels as well as NMDA receptors, could modulate tDCS effects. However, whether or not concurrent use of such medications is permitted would depend on the intended use of tDCS as selectively eliminating or potentiating effects of anodal or cathodal tDCS could have specific beneficial applications.

Training and Credentialing

In clinical trials of tDCS, operators require training sessions with experienced staff before reaching competency in tDCS administration with most training usually focused on ensuring correct electrode placement and scalp contact. While tDCS devices developed for home-use have been designed to make electrode placement as simple and reliable a process as possible via headbands or caps to fasten the electrodes, it is nonetheless recommended that patients at least attend an initial training and credentialing session before being approved to take home a tDCS device. The purpose of such a visit would not only be to ensure that a patient can competently operate a tDCS device and safely administer tDCS but also to give the patient a working knowledge of tDCS principles and safety as well as giving an opportunity for the overseeing clinician to address aspects of the tDCS procedure and technique that may be specific to the patient.

Patients should first be given a demonstration of how the tDCS device is set up and operated, familiarising them with the device features and interface as well as use and maintenance of the associated equipment (i.e. headband, cable leads, electrodes, sponge sleeves and conducting solution). This would also include checking the equipment for wear that could affect stimulation quality such as oxidation and residue forming on the leads and tears or scratches on the electrodes.

Demonstration of the actual tDCS procedure should cover routine preparation for tDCS such as checking the scalp sites for any skin irritation or breakage, gently swabbing the skin with alcohol swabs to remove surface oils or dirt, and preparing the sponge electrodes in the conducting solution (usually saline). Correct electrode and headband placement should then be shown with particular attention on ensuring consistent positioning of the electrodes as well as maintaining firm and even

contact between the entire sponge electrode surface area and the scalp. As tDCS devices are designed to automatically run pre-programmed parameters once started, the only routine procedures for patients to follow during tDCS would be to periodically add saline to the sponge electrodes to avoid drying and maintain conductance, wipe dry any excess saline dripping from the sponge electrodes, and check the stimulation contact quality (if available via the device readout).

To formalise the training process and ensure consistent standards, a credentialing process may then be conducted to assess the patient's demonstrated competence against specific criteria, which may include items outlined below.

Skin and electrode preparation

- Parting hair to expose stimulation area and gently swabbing the skin with alcohol swabs.
- Checking skin for irritation and breakage.
- Checking equipment for wear and tear.
- Preparing sponge electrodes with the appropriate amount of conducting solution.
- Attaching the sponge electrodes onto the headband.
- Placing and securing the band on the head with the electrodes in the correct position and orientation.
- Adjusting band placement and tightness as needed.

Machine preparation

- Connecting the cable leads to the tDCS device.
- Connecting the leads to the electrodes.
- Understanding the electrode contact quality readout (if available) and adjusting the electrode and headband set-up accordingly.
- Entering the activation code to initiate stimulation.

During tDCS

- Monitoring contact quality.
- Adding appropriate amount of saline at designated intervals.
- Drying excess saline from scalp and face.

After stimulation

- Removing the headband and electrodes.
- Rinsing and cleaning electrodes.

Following satisfactory completion of training and credentialing, patients may also be supplied with a treatment diary to record the day/time of their treatment sessions and any side effects experienced. The diary should also include a procedural checklist that patients must follow and check off in sequence as they self-administer tDCS. Clinicians may also want to consider having the patient undergo their first tDCS session at the initial training/credentialing visit so that the patient is familiarised with the typical sensations of tDCS (e.g. tingling, itching) and issues relating to side effects can be immediately addressed.

Ongoing Monitoring and Oversight

Ideally, patients should continue to be under the supervision of a clinician during a course of home-based tDCS. This oversight is important for technical and safety reasons. For patients inexperienced with tDCS, even when credentialed to take a device home, there will be an ongoing learning process to streamline the placement of the tDCS headset and electrodes. Oversight and coaching via real-time monitoring can greatly assist in this learning process especially during the first few home-based tDCS sessions while ensuring the device continues to be operated correctly in the patient's home environment.

Periodic monitoring by a clinician during the tDCS course is also important to check for adverse or unintended effects of the stimulation and other possible changes in the patient's status where continued stimulation may not be advisable. Further, as stimulation may also be administered concurrently with other treatments, the monitoring process should include checking for potential unexpected interactions (e.g. with a medication) [13].

In addition to the safety issues, monitoring is recommended to determine the efficacy of stimulation. However, it may be difficult for an

individual to objectively evaluate whether their stimulation is leading to the intended effect. For example, change in mood or cognitive functioning may be difficult to determine without objective measures administered prior to starting a course and then repeated following course completion.

Patient Safety

The primary safety considerations with home-use tDCS relate to ensuring the safe administration of tDCS in the patient's home environment and their health and welfare during the treatment course. When approved to use a tDCS device at home, patients should be given a list of standard safety precautions to minimise any risk of harming themselves or damaging the tDCS device. Such a list may include the following:

- When administering tDCS, the rubber electrodes must always be covered by the sponges and never directly in contact with the scalp as this could lead to skin burns. Typical tDCS side effects such as tingling or itching should never be painful. If you feel any pain concentrated in one area, immediately abort stimulation. Remove the headband and check the skin for any redness or discolouration. Notify your treating team before proceeding any further.
- tDCS will automatically stop if the contact quality between the sponge electrodes and scalp drops to a critical level. The current intensity will quickly drop to zero and you may feel some transient light-headedness or even see a phosphene flash. These symptoms are not unusual but you must contact your treating team so that they can investigate the cause of the poor contact quality.
- Over repeated use or after rough handling of the rubber electrodes while inserting into or taking out of the sponge sleeves, the rubber electrodes may start to scratch or tear. This can lead to poor contact quality with tDCS not being able to start. At the start of each session, check the rubber electrodes for any tears and notify the treating team if any are present before proceeding any further. When inserting or removing the electrodes, always hold between the fingers and not the fingernails.
- Avoid spilling any liquids on the tDCS device. Do not use the device if it has been exposed to any liquids or is wet. Notify the treating team if this occurs.
- Ensure that the tDCS device is kept on a flat, secure surface during tDCS and avoid any sudden head movements as this could lead to pulling on the cables and causing the tDCS device to fall onto the floor.
- Do not administer tDCS over skin that is irritated or damaged including any cuts, scars, scratches or pimples as this could lead to the current becoming concentrated in one area and causing skin burns. You must notify the treating team if any of these are present at the electrode sites.

As part of the patient's treatment diary, a structured questionnaire checking for typical side effects that may arise during or after tDCS should be included with patients instructed to record the presence/absence of each side effect as well as the severity and duration. Any side effect that is rated as severe or atypical of tDCS, regardless of whether the patient feels it is related to the tDCS treatment, should be reported and assessed by the treating team before any further tDCS sessions are administered.

tDCS is a low risk procedure and is not expected to cause serious adverse events. However, guidelines that help patients to identify and document adverse events may be useful in managing any potential risks. An adverse event may be defined as any untoward medical occurrence that is temporally associated with the use of tDCS regardless of whether or not it results in the patient's hospitalisation. Any worsening of a pre-existing condition may also be considered an adverse event. Occurrence of any adverse event should be reported by the patient to the treating team and assessed before any further sessions are conducted. As patients will be receiving tDCS as a treatment for an existing psychiatric, neurological or other health condition, clear instructions should be communicated

to patients, their families and/or carers in case of an emergency. While the exact safety plan may be specific to the patient's condition, information regarding an emergency contact number and contact details for the nearest clinic or hospital should be provided in the event that the patient may not be able to obtain immediate help from their treating doctor.

Home-Based tDCS Studies

No study to date has investigated the relative efficacy of tDCS administered in a clinical setting compared to home use. Notably however, there are now a few initial studies of home-based tDCS that can potentially inform on the viability of differing approaches to how tDCS should be provided and supervised. One option is to simply provide participants with devices and directions for self-administration without ongoing training procedures or monitoring in real-time of any adverse events. One trial has reported results with this approach, using a 2-week crossover design (1.0 mA or sham) for the treatment of trigeminal neuralgia [3]. While results ($n = 17$) were promising in terms of clinical benefit (pain reduction), and no adverse events were reported, there was a high dropout rate ($n = 7$), due in part to difficulties with device use.

A second option is to study continued tDCS use after a treatment period in a clinic setting to either sustain or increase an initial clinical response. This option has less potential for safety concerns given that it would almost always be an individualized approach working directly with a clinician and repeated sessions for continuous therapy have been found to be safe [7], although on the other hand such an approach could increase dropout rates. As an example of this approach, one case study has reported spanning at least 100 sessions for the treatment of hallucinations in schizophrenia. The patient experienced initial improvement in a clinic, with doses ranging between 1 and 3 mA and was continued with once or twice daily sessions nearing 3 years to sustain benefit. No adverse events were reported [1]. For this approach, the tolerability would be established and the participant would have extensive experience with the procedures for stimulation. At-home use to extend clinical benefit may also be appropriate for managing transient symptoms as they occur. Future applications may include situational uses such as promoting wakefulness [26], managing an emerging mood state [27], or enhancing an aspect of performance (e.g. to increase or sustain attentional vigilance) [26, 27].

A third and most structured approach to the study of tDCS home use is to apply structured training procedures and real-time supervision. Standards and guidelines have been proposed by a working group of diverse clinical investigators interested in studying tDCS administered by patients or their carers [2]. Central to these recommendations is specially designed equipment that both carefully regulates and records use. Extensive training procedures and safety checks at each step overseen by a study technician can guide safe application to ensure the safest and most tolerable use. A protocol following these guidelines has been developed for at-home use of tDCS in a currently ongoing study of multiple sclerosis (MS) patients [28]. After a period of training, all stimulation sessions are provided under real-time supervision using a telemedicine platform. The device used is a pre-programmed device (Soterix Mini-CT) dependent on a code to "unlock" delivery of only one stimulation (or sham) session at a time. A study technician only provides the unlock code once a series of safety and tolerability checks have been met, including correct headset placement. With this protocol, targeting 10 sessions over 2 weeks, 20 participants have completed a total of 192 sessions without any adverse event or discontinuation of any session. There has been high tolerability and compliance, suggesting that the best model for providing home-based tDCS may be one that incorporates comprehensive training and ongoing supervision of patients during the treatment course.

Further Approaches Using Home-Based tDCS

Whilst there is growing evidence that tDCS as a stand-alone treatment is efficacious for some conditions such as depression [29], home-based tDCS has further potential as an adjunct treatment. For example, the past decade has seen a dissemination of psychological therapies via computer or Internet-based programs with a growing number of studies indicating that such therapies delivered in this way can be an efficacious treatment for depression [30–32]. Along with these developments, researchers have also begun investigating ways to further enhance the antidepressant effects of brain stimulation techniques such as tDCS and TMS by combining them with either a psychological therapy such as cognitive behaviour therapy or a cognitive training task [33–35]. The rationale is that by administering a cognitive activity that engages the same brain regions targeted by transcranial stimulation, synergistic antidepressant effects may result. Home-based tDCS has the potential to facilitate these developments by enabling completely decentralised treatment delivery with patients self-administering tDCS while carrying out a cognitive intervention via computer. Although there is promising preliminary evidence for such a treatment combination, the first randomised, controlled trial to investigate its feasibility and efficacy has yet to be conducted.

A recent case series of six patients has also investigated whether TMS could be a viable substitute for maintenance electroconvulsive therapy (ECT) especially for patients who are unable or unwilling to continue ECT or who do not experience a sustained benefit [36]. Self-report scores indicated all patients, following response to a course of ECT, maintained or improved their clinical state up to at least 6 months with maintenance TMS although two patients had relapsed by 9 months. To date, no trial has directly compared the relative efficacy of TMS and tDCS, nor have there been further trials of maintenance TMS following an ECT course. However, if found to be comparable, tDCS, as a maintenance treatment, can offer the added advantage of a more affordable, easily accessible alternative to TMS due to it being more amenable for home use. Moreover, having a home-based device may afford a clinician greater agility in adjusting their patient's tDCS "dose" (specifically, the frequency of tDCS sessions) in response to any symptom fluctuations as treatment would not depend on the patient's ability to travel to a treatment centre nor on the availability of clinic staff.

In summary, among brain stimulation techniques currently available, tDCS is the best positioned to be made available as a home-based, self-administered treatment option. Provided that tDCS devices intended for home-use can be designed to ensure reliable and consistent delivery of stimulation in a less controlled, non-clinical environment, tDCS has the potential to be an easily accessible and affordable treatment for a broad range of patients who may be limited from accessing other clinic-based treatments due to distance, cost or time constraints. Given these prospects and the burgeoning interest from consumers, the first randomised, controlled trials of take-home tDCS are greatly anticipated.

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Ethical Aspects of tDCS Use in Neuropsychiatry and the Risk of Misuse

24

Rachel P. Wurzman and Roy H. Hamilton

Abstract

There is growing enthusiasm about the potential of tDCS to be of value to clinical treatment and cognitive enhancement in neuropsychiatry. Yet despite its promise, the use of tDCS in clinical and nonclinical contexts faces several scientific and ethical challenges, which must be considered to protect against unanticipated or even adverse effects on individuals and groups in society. Scientific challenges include the lack of precise understanding of tDCS mechanisms, the present unreliability of predictions for the magnitude and nature of an individual's response to stimulation, the need for tDCS research to better capture dynamic effects in highly heterogeneous populations in whom comorbid diagnoses and the concurrent use of (multiple) medications may interact independently and interactively to affect tDCS response. Ethical challenges include issues of safety, character, justice, and autonomy. These considerations prompt a need to anticipate the trajectories of current and potential future use of tDCS both within and outside of clinical contexts, as there are likely to be evolving social and cultural consequences of tDCS use within neuropsychiatry. Likewise, neuroethical consequences from nonclinically oriented tDCS use are likely to have an impact on the way tDCS is used—and sought out—in clinical contexts. The accessibility of tDCS and its likelihood for broad use outside of medical contexts make it especially important to consider the promises, potential perils, and likely trajectories of tDCS use in multiple contexts from the outset. In this chapter, we reflect upon the way that the present degree of scientific understanding of tDCS motivates, justifies, and sometimes cautions against tDCS use.

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Introduction: Is tDCS Hope or Hype?

There is growing enthusiasm about the potential of transcranial direct current stimulation (tDCS) to be of value for clinical and cognitive enhancement purposes. With headlines like "Got a problem—put your electric thinking cap on" or "Trying a 9-volt shortcut to expertise," hundreds of enthusiastic print media articles have been published in the last few years [1–3]. The majority of media attention to tDCS has been optimistic and has praised the putative benefits of the technology [2]. However, while the tone of such coverage speaks in part to the considerable therapeutic potential of tDCS for disorders of cognition and mood, it also highlights the need to distinguish hope from hype. More than that, the science of tDCS and its potential applications present practical and ethical obstacles that warrant serious contemplation.

In many ways, practical and ethical considerations for tDCS mirror those of other forms of brain stimulation or neural interventions more broadly, but there are a few key features about tDCS that set it apart. Compared with other forms of noninvasive brain stimulation such as transcranial magnetic stimulation (TMS), tDCS is cheap, accessible, and portable. These factors multiply the contexts and applications for tDCS, some of which could present ethical, legal, and social problems if tDCS use were to become more widespread. At the same time, its very high level of accessibility also limits the range of potential actions that can be taken to prevent potentially problematic developments. Its low cost and relative technological simplicity make tDCS applicable to a broader set of contexts than other forms of invasive or even noninvasive brain stimulation, as it doesn't require surgery and can be easily self-administered. Consequently, tDCS is highly amenable to direct-to-consumer product development and marketing, as well as to increased use in so-called para-clinical contexts for enhancing cognitive and behavioral abilities, such as in the workplace, on the battlefield, or as a cosmetic enhancement in daily life. This potential for broad use both inside and outside of medical contexts calls for special consideration of the promises, potential perils, and implications for tDCS in the field of neuropsychiatry—both in how it is practiced as well as how it is perceived.

This chapter starts by exploring the promise of tDCS, first as a tool in cognitive neuroscience research, then as a clinical intervention, and finally as a technology to enhance normal cognition. Next, the scientific and ethical perils of tDCS are discussed in terms of the current state of the science, and how that informs the ways we think about the ethical challenges that tDCS poses with respect to safety, justice, character, and autonomy. For example, how can and should (or should not) knowledge learned in controlled research contexts be translated for potential safe and effective tDCS administration to complex real-world patients with multiple diagnoses, often on multiple medications? If cognitive self-enhancement becomes a social norm, what effects will that have on social structures, personal development, perhaps even clinical norms for what is considered normal versus pathological? Finally, we consider the ways in which tDCS presents specific advantages as well as challenges to neuropsychiatry and its role in society.

The field and scope of tDCS use (and other noninvasive brain stimulation and cognitive enhancement interventions) may already be developing at a rate that exceeds the pace of our scientific understanding [4]. One needs only to look at the recent and upcoming products released by the companies Thync (*Thync*, *Los Gatos*, *CA*) and Halo neuroscience (*Halo Neuroscience*, *San Fransisco*, *CA*)—not to mention their marketing

approaches—to glimpse the future role that tDCS could come to play in daily life. We may not be able to predict the rate at which the potential pitfalls may develop, but we can be sure that if tDCS continues to develop along its present trajectory, ethical, legal, and social issues will eventually arise. It is therefore important to consider these issues now, so that we can take proactive steps to mitigate against potentially unintended and undesirable consequences.

The Promise of tDCS

tDCS as a Cognitive Neuroscience Tool

Noninvasive brain stimulation (NIBS) methods are highly useful to cognitive neuroscience, in that they are used to modulate activity in brain regions or networks with varying degrees of anatomical selectivity and functional specificity. In general, NIBS add significant inferential strength to the ability of cognitive neuroscience to decipher causal brain region-function and network-function relationships. Following stimulation, subsequent changes in cortical activity, measured directly or indirectly by probing sensorimotor or cognitive behavioral functions, afford improved understanding of how brain activity in one region contributes to cognition and behavior. In recent years, tDCS has seen increasing use in the cognitive neuroscience community, with the number of publications published per year increasing over fivefold since 2010 [2]. TDCS has been applied to a variety of cognitive domains, including but not limited to skill learning, memory, executive functions, creativity, language, spatial processing, and social cognition [5]. This section provides a brief partial review of studies in which tDCS has been shown to manipulate cognition in informative ways, some of which have possible clinical applications.

With respect to learning and memory, acquisition and retention of new procedural skills has been experimentally enhanced using tDCS. One study found that, compared to sham stimulation, increased motor cortex excitability and enhanced learning of motor movements resulted when simple repetitive practice was paired with anodal tDCS [6]. Similarly, tDCS delivered over 5 days paired with training on a complex motor task resulted in increased improvement between daily stimulation sessions and persistent superior skill retention 3 months after stimulation [7]. The implications of this are that repeated administration of tDCS may have "off-line" effects that consolidate skill acquisition, effectively enhancing the long-term effects of rehearsal on performance. Declarative verbal memory has also been investigated using tDCS. For example, stimulation applied to the left dorsolateral prefrontal cortex had the effect of increasing the rate of verbal learning [8]. Consistent with this, another study found that tDCS delivered to the same site but with the opposite polarity had an inhibitory effect on verbal learning [9].

Various executive functions such as cognitive and behavioral impulse control and working memory have also been investigated with tDCS. One study found that orbitofrontal cortex stimulation with tDCS enhanced decision making and improved cognitive impulse control, without any concurrent effects on attention, mood, or motor impulse control [10]. In another study, tDCS improved response inhibition, which refers to the ability to inhibit an action once initiated [11]. For working memory (WM) and related functions, tDCS-induced improvements of performance on some tasks appear to depend in part on the level of cognitive demand of the tasks. For example, one group found that stimulation over the right cerebellum or left DLPFC increased accuracy and decreased response times for an arithmetic task that was more difficult and attentionally demanding, but not for an easier arithmetic task [12, 13]. Similarly, Gill and colleagues (2015) found that stimulation effects were readily observed when a more cognitively demanding working memory task was used during stimulation, but not when the task was less challenging [14]. Importantly, these effects also required that domain-specific cognitive behaviors be engaged during stimulation; stimulation-induced improvements were absent when tDCS was not paired with a relevant behavioral task [14, 15]. In other work, cathodal tDCS was used to enhance aspects of cognitive flexibility, presumably by inhibiting certain frontal lobe functions. This research,

which found that subjects could come up with more uncommon uses for everyday objects with inhibitory stimulation of the left, but not right, prefrontal cortex, suggests that creativity could be enhanced by stimulation that increases the influence of unfiltered bottom-up information [16].

It may be possible to significantly enhance the ability to learn new languages using tDCS. For example, anodal tDCS over language regions of cortex enhanced new vocabulary learning in healthy young adults [17]. Even without a reference object to associate with a novel "nonword," tDCS facilitated the acquisition of the phonological form of the nonwords into long-term memory, beyond the stimulation session [18]. Reading skills may also be enhanced using tDCS. Compared with sham stimulation, subjects receiving real tDCS subjects exhibited significantly better nonword reading efficiency. Curiously, this seemed only to apply consistently to below-average readers in the cohort; subjects who were more efficient readers to begin with saw much more variable changes in reading performance during real tDCS [19].

TDCS has been used to manipulate and enhance aspects of visuospatial processing. For example, we showed [20] that anodal tDCS over the right posterior parietal cortex could be used to selectively enhance detection of left-sided allocentric targets, which is to say that stimulated subjects were better able to detect the left side of visual targets independent of where the targets were in the subjects' visual fields. Interestingly, tDCS has also been used to manipulate how spatial and temporal processing contribute to higher order mental representations, such as the perception of cause and effect. In a study by Woods and colleagues [21], subjects were asked to make judgments about the causal relationship between two virtual objects (i.e., did one object cause the other to move by striking it), while the spatial and temporal features of the objects' motions were manipulated. Consistent with the role of the parietal cortex in spatial processing, the authors found that parietal tDCS selectively influenced how sensitive subjects were to spatial manipulation as it related to their perception of causality. On the other hand, frontal cortex stimulation influenced both spatial and temporal judgments with respect to causality, consistent with the overarching role of the frontal cortex in cause-and-effect reasoning [22].

Brain stimulation has also been used to alter social cognition and behaviors, including those that affect moral decision making that balances self-interest with social values. For example, individuals will often reject an offer that they perceive as highly unfair, although accepting the offer would still be to their benefit, as reciprocal punishment for the perceived unfairness (a concept know as "altruistic punishment"). Noninvasive inhibitory stimulation of the right DLPFC makes people less likely to reject marginally beneficial but unfair offers, even when consciously recognized as highly unfair, suggesting that direct current stimulation might also be used to calibrate the impact of economic self-interest on people's enforcement of social norms [23, 24]. In research on lie detection, tDCS has been demonstrated to alter individuals' deception skills in fairly specific ways, such as influencing someone's deceptive abilities when trying to conceal one's guilt or in situations such as card games. Early studies found that the act of lying increases cortical excitability on both sides of the brain [25]. People became better liars in a simulated interrogation task when cathodal tDCS was used to inhibit the anterior prefrontal cortex. Not only did stimulation make people better at concealing guilty knowledge, decreasing the kinds of signals that a polygraph detects when someone is lying, it also decreased their feelings of guilt over deceiving the experimenter [26]. On the other hand, anodal excitation of the dorsolateral prefrontal cortex made people worse at pretending not to have knowledge about something true, like whether a particular card is in their hand; interestingly, this effect did not extend to subject's behavior when bluffing or telling the truth [27].

One of the advantages of NIBS compared to classical methods in cognitive neuroscience and cognitive neurology like lesion studies is that these technologies can be used both to interfere with and enhance cognitive functions, at least temporarily. For example, the aforementioned studies on executive function and creativity illustrate how inverting the polarity of stimulation over brain regions responsible for cognitive control can either result

in favoring of cognitive abilities that require heavy filtering of extraneous information, such as sustained attention and working memory, or in favoring cognitive abilities that benefit from unfiltered intrusion of extraneous information, such as divergent thinking and creativity [10–16]. While enhancing aspects of cognition using such manipulation is a powerful tool for making inferences about brain function, it also opens the door to considering whether technologies like tDCS could be used to facilitate cognitive processes in patients with neurologic or psychiatric disorders of cognition, as well as in cognitively healthy individuals. For example, the ability of tDCS to manipulate perception of cause and effect could have implications for understanding and treatment of psychiatric disorders such as schizophrenia and obsessive compulsive disorder (OCD), where abnormal causal perceptions can contribute to symptoms [28, 29]. Moreover, the enhancement of allocentric spatial processing found by Medina and colleagues (2013) could have important implications for the treatment of spatial neglect in stroke patients [22], and studies related to executive function could lead to applications in a wide range of neurologic and psychiatric disorders [10–15]. Further research will be required so that group-level results from cognitive neuroscience studies, which are principally designed to reveal brain function, can be translated to clinical applications in which the goal is to alter specific functions in single individuals.

tDCS as a Clinical Intervention

With respect to clinical contexts, a growing body of literature suggests that tDCS is a potentially effective therapy for a wide variety of neuropsychiatric syndromes and symptoms, as well as other neurologic conditions affecting cognition [30, 31]. Depression and chronic pain in particular are two areas in which a substantial number of clinical trials support the utility of tDCS to alleviate symptoms [32, 33]. For depression, tDCS to the prefrontal cortex has shown promise as a treatment and medication adjunct to improve therapeutic outcomes [34–41]. With respect to tDCS as a treatment for pain, clinical trials for tDCS have been performed for chronic lower back pain [42, 43], chronic pain in the elderly [44], chronic temporomandibular disorders [45, 46], chronic pain in irritable bowel syndrome [47], neuropathic pain [48] such as in fibromyalgia [49, 50], or multiple sclerosis [51], and chronic pain associated with CNS damage from spinal cord injury [52] or stroke [53]. Although the results of clinical trials have in some cases been mixed [54], the potential utility of tDCS for clinical pain applications has been demonstrated in studies that show tDCS can affect aspects of nociception, pain thresholds, and affective (i.e., emotional) components of pain processing in healthy individuals [55–59]. Other neuropsychiatric conditions in which tDCS has been investigated include attention deficit hyperactivity disorder (ADHD) [60], schizophrenia [61–65], Alzheimer's disease [66] and mild cognitive impairment (MCI) [67], tinnitus [68], obsessive-compulsive disorder (OCD) [69], and generalized anxiety disorder [70]. TDCS is also being considered for PTSD, based on observed effects in fear extinction [71] and attentional bias for threat in anxiety [72, 73].

Other clinical applications for tDCS include disorders characterized by problematic behaviors related to abnormal executive function, including addictions and risk-taking behaviors [74, 75]. Studies have shown that tDCS may be useful for decreasing cigarette cravings and smoking behavior [76–80]. Interestingly, study of risk-taking behavior in smokers versus non-smokers found that tDCS was associated with personality-dependent effects [75], which emphasizes that existing cognitive patterns influence the specific nature of tDCS effects. Cravings and substance abuse in alcoholism [81–84] and drug addiction to methamphetamine [85] and crack cocaine [86–88] were also responsive to tDCS. Preliminary clinical studies of tDCS applied to DLPFC to intervene in obesity and disordered eating behavior have seen positive results. These have mostly examined acute tDCS effects on subjective reports of food craving, and attentional bias for food as probed with eye tracking following a single session of stimulation [89–93]. One 8-day, randomized, sham-controlled, crossover study found that anodal DLPFC stimulation decreased specific and nonspecific subjective

appetite and was associated with a decrease in calorie consumption at a standardized multi-choice test buffet by 14%, with a specific reductions in consumed carbohydrates [94].

Substantial promise has been found for tDCS in post-stroke neurorehabilitation. Following stroke, tDCS has been shown to assist in upper motor limb recovery from paresis [95, 96]. Similarly, anodal tDCS to the posterior parietal cortex mitigated unilateral visuospatial neglect [97] in one study, and in another study the response to prism-adaptation therapy was improved when therapy was paired with tDCS [98]. Anodal tDCS to the right premotor cortex also mitigated one patient's anosognosia for hemiplegia during stimulation [99], and in another case study, cognitive neglect therapy paired with biparietal tDCS, but not sham stimulation, enhanced the patient's response to therapeutic cognitive training [100]. Additionally, multiple studies have shown that when tDCS is paired with speech and language therapy, naming ability can be improved in stroke patients with aphasia [101–110]. Another neurorehabilitation application may be to post-stroke attentional decline, as anodal tDCS to the left DLPFC also improved attention in stroke patients, resulting in increased accuracy on a cognitive task of executive function [111]. Finally, tDCS is also being explored as enhancement to learning and memory in normal aging and in states of cognitive impairment [112–115].

Not coincidentally, tDCS has been explored clinically in many areas where the underlying impaired cognitive constructs have been shown in cognitive neuroscience research to be manipulable using stimulation. For example, cognitive neuroscience studies showing effective tDCS modulation on decision-making, including risk-taking, reward-seeking, impulsivity, and fairness consideration are considered as promising for addictive disorders, in which the hallmarks of clinical symptomatology are compromises in such decision-making capacities [116].

There are many practical reasons to favor tDCS in clinical settings. In addition to being small and portable, tDCS is inexpensive compared to other neuromodulation technologies like TMS. As currently used tDCS protocols are also safe, tDCS is an ideal form of neuromodulation to pair with existing therapies, and could potentially be self-administered by patients who may benefit from repeated stimulation on a regular basis.

tDCS to Enhance Normal Cognition

In addition to clinical applications and cognitive neuroscience studies designed to elucidate brain function (described above), there has been growing interest in explicitly enhancing normal cognition. In particular, tDCS joins a variety of neuroscience tools applied to so-called neuroergonomic purposes, referring to applications intended to aid human operators in the performance of their work duties [20]. Academic investigations for this purpose include—and in many cases expand upon—cognitive neuroscience studies of effects on isolated cognitive abilities, by examining tDCS effects on the performance of more complex tasks. Frequently, these experiments involve more naturalistic paradigms with clear applications to specific occupational functions, and assess improvements in the cognitive functions of implicit memory (e.g., procedural and motor learning; probabilistic learning), explicit learning and memory (e.g., declarative memory encoding with retrieval), working memory, attention, and perception [117]. For example, tasks in which tDCS has shown accelerated learning, enhanced performance, and/or prolonged training effects include threat detection in virtual-reality simulated urban warfare scenes [118–120], simulated air traffic controller games [121], a complex multi-task game "Space Fortress" [122], and an image analysis task in which target objects must be identified from synthetic aperture radar images of terrain with buildings and vehicles [123]. Not surprisingly, much of this research has been funded by the US Department of Defense [124].

On the other end of the spectrum from defense and security organizations, a community of individual "do-it-yourself" (DIY) tDCS users are also actively pursuing cognitive self-improvement [125]. The practices of this community were recently described in detail by Wexler [126]. The DIY community refers collectively to tDCS use outside of professional or academic settings, and can be subdivided

into those who seek to enhance their cognition and those who intend to alleviate clinical symptoms of neuropsychiatric disorders [126].

A burgeoning wearables market is also emerging, producing tDCS products controlled by companion apps for cognition and athletic performance enhancement, in both healthy individuals and clinical populations. Two of these companies supply direct-to-consumer devices for recreational and lifestyle indications (Thync and Foc.us), and another has a stimulator intended for healthy and "impaired" populations in a well-funded development pipeline (Halo Neuroscience; http://halo-neuro.com/#science) [124]. These companies are at the forefront of trends that could potentially to lead to widespread, if not ubiquitous, use of neuromodulatory technologies in daily life.

However, at present the effects of tDCS are far from established. Despite growing excitement about the possibility of using tDCS for enhancement of otherwise normal cognition, caution is warranted before extrapolating observations and lessons learned in cognitive neuroscience and clinical contexts to cognitive enhancement in healthy individuals due to fundamental differences in the theoretical, practical, and ethical issues related to each (as will be discussed in the next section).

The Perils of tDCS

Despite its promise, the use of tDCS in cognitive neuroscience, clinical research, and para-clinical applications faces several scientific and ethical challenges, which must be considered to protect against unanticipated or even adverse effects on the bio-psycho-social health of individuals and communities. It is especially important to accurately assess the state of the science, and reflect upon the way that the present degree of scientific understanding of tDCS motivates, justifies, and sometimes cautions against tDCS use.

Scientific Challenges

Scientific challenges stem from the fact that there is much that we do not yet understand about the underlying neural mechanisms of tDCS. Our incomplete understanding of tDCS mechanisms is underscored by data that indicates that the effects of stimulation on brain function are neither monotonic nor invariant. The initial dogma based on studies in motor cortex, which attributed enhancement or diminishment of cortical excitability to anodal or cathodal stimulation, respectively, often conflicts with experimental results. On the contrary, dose-response relationships are still poorly understood. For example, one study found that 1 mA cathodal stimulation diminished motor cortex excitability, but 2 mA cathodal stimulation enhanced it [127]. Similarly, doubling the time of stimulation can reverse the behavioral and cortical excitability effects [128, 129]. Moreover, the "anodal-facilitation versus cathodal-disruption" schema is a clear oversimplification; particularly beyond motor cortex, anodal and cathodal stimulation does not have equal and opposite effects on behavior. In cognitive studies, anodal and cathodal stimulation is sometimes found to have the same net facilitative effect on behavior, or only one stimulation polarity over the target will be found to influence a given behavior [11].

More broadly, we know that stimulation parameters matter a lot, but we are limited in our knowledge of what difference they actually make. For example, finite element models of tDCS-induced electrical current flow tell us that the size and location of the "reference" electrode strongly influences the effects of stimulation [130, 131]. Small changes in electrode position and individual head shapes can also greatly modify current flow patterns [132, 133]. However, the results of these models vary considerably based on model assumptions [134]. In other words, the best tools we have for understanding what stimulation is doing are themselves quite limited.

Other unknown variables when considering the perils of broader applications of tDCS to enhance cognition are the interactions that brain stimulation may have with comorbid diagnoses and the concurrent use of medications. The interaction of brain stimulation with agents that act on different neurotransmitters is of special concern in neuropsychiatry, since many (or perhaps most) people who suffer from these problems are taking

one or more such medications. Some drugs have been found to have profound, complex and varied influences on tDCS-induced neuromodulation [135–137]. In one very large clinical study of tDCS and depression, an additional naturalistic study systematically evaluated how tDCS responses were affected by concurrent treatment with psychiatric medications, including benzodiazepines, serotonin-noradrenergic reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), first- and second-generation antipsychotics, and mood stabilizers, and found that medication-stimulation interactions are significant considerations [138]. Specifically, they confirmed that antidepressants generally increased tDCS effects, but found that taking benzodiazepines actually worsened outcomes. They also found that tDCS did not interact with non-benzodiazepine anticonvulsants and antipsychotics, which are frequently used as mood stabilizers in patients with depression. Considering that there have been reports of hypomanic switches after tDCS in depression patients [139, 140], including an episode of manic psychosis in a stimulated patient taking sertraline [36], these findings warrant further investigation in order to develop safety guidelines for treating mood disorders with tDCS [141].

In sum, we have an incomplete understanding of how stimulation parameters and other dose variables act on the brain or interact with medications. This lack of precise mechanistic understanding limits our ability to predict the effects of tDCS in individuals. It is essential that clinicians and self-applicators of tDCS temper their enthusiasm with an understanding of these limitations. There are ethical and pragmatic obligations to resolve these uncertainties and to seek a more detailed mechanistic understanding of tDCS.

Ethical Challenges

The potential for tDCS use to become widespread raises a number of social and existential risks that must be carefully weighed against its benefits. By their nature, the effects of tDCS on cognition and affect blur the distinctions between treatment and enhancement. Moreover, its accessibility makes its use especially difficult to confine within the bounds of clinical medicine. Thus, ethical issues raised by tDCS cannot be viewed solely through a clinical ethics lens. Like pharmacological treatments that also have the potential to be used for enhancement purposes, the use of tDCS has not and will not remain in the medical realm. However, there is much still unknown about cognitive enhancement [4], both in terms of the science and in terms of its broader effects in ethical, legal, and social spheres. As discussed below, the ethical issues surrounding tDCS can be broadly categorized into concerns regarding *safety*, *justice*, *character*, and *autonomy*. The latter three concerns deal with potential trajectories of tDCS technology development and use patterns that are, at present, still speculative. However, it is important to consider the ethical implications of possibilities so that the negative consequences can be anticipated, and if possible, avoided.

Safety

In most traditional ways of thinking about safety, tDCS is of low concern; all current evidence indicates that tDCS delivery by currently applied protocols is very safe. While there are some recognized minor risks associated with tDCS such as mild headache and a mild itching or burning sensation under the electrodes [142], the risk of obvious physical injury from tDCS is extremely low. The most severe recognized potential medical risks associated with tDCS are burns to the skin and complications resulting from electrical equipment failures [143–145], but these are very rare and more likely to result from DIY systems than commercially manufactured stimulators.

The main potential concern with safety is that tDCS may alter cognition in unintended ways [146, 147]. Evidence suggests that stimulation at different sites may benefit some cognitive abilities but impair others [148]. Additionally, inhibiting or exciting the same region of brain can elicit different types of benefits. For example, anodal stimulation to the

lateral prefrontal cortex not only improved working memory, but also related fronto-executive functions that require a high degree of cognitive control, such as selective attention and set-switching. However, some aspects of cognitive flexibility and divergent thinking could be more consistent with a loosening of cognitive control, resulting in less "top-down" regulatory filtering of low-level information. Accordingly, cathodal stimulation to lateral prefrontal cortex has been shown to enhance cognitive flexibility in tool use [16]. Viewed together, these studies raise theoretical concerns that stimulation delivered with the intent of enhancing attention or working memory could have detrimental tradeoffs for cognition associated with creativity.

These kinds of tDCS-induced mental tradeoffs have been demonstrated for other aspects of cognition [148]. For instance, Iulcano and Kadosh (2013) recently explored how tDCS affected two dissociable aspects of learning that were relevant to mastery of a novel mathematical task: skill acquisition rate, and skill automaticity whereby tasks are performed quickly, effortlessly, and without conscious intention. Using tDCS to brain regions associated with learning (posterior parietal cortex; PPC) or automaticity (DLPFC) the investigators demonstrated a double dissociation wherein tDCS to the PPC enhanced learning rate but impaired automaticity while tDCS of the DLPFC enhanced automaticity at the expense of learning rate [148].

The nature of stimulation benefits may be specific to certain traits or states. For example, tDCS improved arithmetic decision making efficiency in healthy subjects who had high levels of pre-existing math anxiety, but it slowed reaction times in healthy subjects who had low-math anxiety, whose arithmetic efficiency was already unimpaired [149]. In several studies, state-dependent tDCS effects were linked to one's starting level of ability, with factors that lead to better performance at baseline associated with less improvement, and potentially impairment [114, 150, 151]. In a related fashion, the effects of tDCS on learning and memory task may depend on the stage of training [152].

In some cases where tDCS is associated with worse outcomes, stimulation does not directly cause cognitive degradation, but rather may block typical improvement by factors such as practice. One group discovered this while looking at the effects of tDCS on repeated IQ testing, employed as a means to simultaneously assess multiple domains for cognition. The study found that practice-related improvements for subtests of fluid intelligence (e.g., perceptual reasoning) were specifically attenuated when right, left, *or* bilateral anodal tDCS was delivered before retesting [153]. While in retrospect these results are consistent with expected effects of frontal anodal tDCS on cognitive flexibility, the authors initially hypothesized that tDCS would improve IQ test performance because previous studies had found that other types of task performance were improved by such stimulation. Such evidence highlights that tDCS is not a panacea, and further suggests that perhaps we should consider a more nuanced notion than "cognitive enhancement" for framing tDCS applications.

One of the challenges in understanding the risks, benefits, and trade-offs of using tDCS to enhance cognition is that, while many in the DIY stimulation community and elsewhere look toward the cognitive neuroscience community to inform how stimulation for enhancement could be pursued, the fundamental approach taken by most cognitive neuroscience studies does not adequately address the "cognitive safety" of enhancement with tDCS in at least two ways. First, the scientific methodology used in most cognitive neuroscience studies of tDCS only test one or a very limited number of cognitive functions in order to test specific hypotheses about the relationships between the brain areas stimulated and those specific mental operations. They do not test to make sure there are no deleterious effects on every other intellectual function. Second, cognitive neuroscience studies generally do not test for the durations that one might consider relevant if one was trying to make long-term changes in cognition. We simply do not know what the effects of increased frequencies and durations of stimulation are for individuals with healthy cognition. While this is not terribly relevant for basic

cognitive neuroscience studies, it is extremely relevant for cognitive enhancement studies, due to the increased likelihood of repeated and potentially prolonged stimulation sessions in the latter. Similarly patient studies do not wholly inform what the likely effects of neural enhancement with brain stimulation are because the brains in which therapeutic stimulation is being applied have already been altered by disease. Thus, safety considerations for tDCS underscore that the science has yet to support the technical application of tDCS for unmitigated cognitive enhancement.

Justice

Distributive justice refers to the equitable distribution of benefits. The development of "cosmetic" tDCS as a boutique service for cognitive remediation or enhancement could exacerbate social disparities by introducing a new type of "cognitive" privilege for those who can afford to exogenously treat or augment their own intellect [154]. Moreover, if boutiqued cognitive enhancement becomes a norm that is taken for granted, expectations regarding a "normal" range of cognitive abilities could become distorted to the point where unaugmented cognition is perceived as pathological. This could result in (further) medicalization of systemic disadvantage, which may introduce further obstacles to the remediation of social inequality, since access to education, medical care, and nutrition are already inequitable. Thus, explicit "cognitive health" disparities might further entrench systems of privilege and socioeconomic inequality. In many ways, this problem is not new or unique to enhancement with NIBS, but is symptomatic of the already vast separation in privilege between the haves and the have-nots.

On the other hand, compared with other technologies (including pharmaceutical agents) with utility as treatments or enhancements, justice may arguably constitute less of an issue for tDCS than other neurotechnologies, because it is relatively inexpensive and easy to create and employ with only modest technical training [155]. Noninvasive brain stimulation in healthcare is currently inequitable; if tDCS could confer comparable benefits while requiring less medical or technological infrastructure, it could increase justice in medically oriented neurostimulation [156].

Character

Issues of character relate to our essential humanity and how we find meaning in life. Ethical issues of character with brain simulation are those that impact our experience of personhood [157]. With its potential to alter our experience of behavior and cognition, brain stimulation raises two key questions. The first question is about identity and the integral core constellation of mental and behavioral characteristics that define us. It asks, "To what extent *can* and *should* we have the ability to change the core of who and what we are?" In part, the answers depend on the degree to which the core traits that distinguish us are considered to be stable, consistent, and integrated, and whether tDCS can disintegrate or change this subjective "core." The second question is about Self and the potential long-term consequences of self-enhancement on character building, as well as other more general aspects of psychosocial development, both within individuals and as a society. What sort of experiences are necessary for wisdom and maturity and virtue, and what are the consequences of avoiding them? These questions have already been deeply explored for neural interventions, in particular invasive deep brain stimulation (DBS) [158–162]. However, the scope of access to tDCS adds an additional dimension to such ethical consideration, as the potential effects on character development or change shifts from being an issue that affects select patients and their loved ones to something that could extend more directly to everyone.

Aspects of life experience that are not necessarily subjectively positive are integral to shaping a person's bearing, demeanor, and personality. It is a widely accepted social norm that adversity breeds character. If cognitive and emotional challenges can all be eased by exogenously stimulating the brain, how does that affect the resilience

and moral quality of a society in which this life of convenience is available? On the other hand, how much suffering is enough, and who gets to decide? After all, we do not consider it a moral failing if a person treats pain associated with childbirth or medical procedures. At what point, if any, does relief from difficult experiences diminish us? The consequence of tDCS on individual development ultimately affects society and culture in ways that are evolving and reciprocal, because social dynamics among individuals and groups influence, and are influenced by, the ambient culture. Thus, the adoption of widespread self-enhancement will bring questions about whether there should be limits to alter our fundamental nature to the forefront in formulating social and policy responses to growing use of tDCS.

Despite potential concerns, the effects of widespread tDCS use on character may not necessarily be negative. For instance, ongoing research is exploring the role of the brain in sports and fatigue (http://www.neuroelectrics.com/use-case/), and seeks to leverage this understanding to develop stimulation that could remove neural obstacles to maximum physical athletic performance. One could argue that removing obstacles to maximum performance *given maximum effort* is a categorically different type of enhancement than enhancement that makes something require *less* effort. In such a context, tDCS could be viewed as an *enabling* tool that could *enhance character*, rather than to act as a *substitute* for qualities that character would ordinarily supply to ensure success, such as commitment, patience, perseverance, and self-transcendence. This distinction is potentially relevant not only to athletics, but also to treatment in neuropsychiatry, wherein stimulation could potentially enable rather than rather than substitute for self-driven efforts to cultivate positive character traits. For example, enhancement of executive function in someone with ADHD to improve impulse control and the ability to sustain attention might *enable* such individuals to practice acts of high character, such as finishing what one has started or keeping commitments. The cardinal distinction applying to both situations is that high sustained effort is still required, and that absent the intervention, there are limits to the degree that such effort could affect performance. Assuming that the same amount of effort is exerted with or without tDCS, what is the true nature of the effect, if any, on the character of the athlete or individual with ADHD? These are all largely philosophical and psychological questions whose answers hinge on arguments about the relative influence afforded to *situational context* versus *personality* when assessing of character. Although this subject is beyond the scope this chapter, it is worth noting that a meaningful discussion of the impact of tDCS on character may require further consideration of a broader conceptual framework to address the daunting philosophical challenge of relating concepts such as identity and self to behavior and neurobiological functions.

Autonomy

Autonomy can be thought of as the right to one's own life, to make choices based on reasons and motivations that are not the product of manipulating or distorting external forces. In the context of tDCS, autonomy can be considered in terms of two types of freedom: (1) the freedom *not* to be stimulated, and (2) the freedom *to be* stimulated.

The freedom *from* stimulation can be threatened by hard or soft coercion. In hard coercion, the individual is forced into an activity for the perceived "good of society". Neuropsychological hard coercion is far from unheard of. Examples include psychopharmacologic agents given to soldiers to maintain battlefield performance and chemical castration to diminish the libido of imprisoned sex offenders [163, 164]. It is not all that hard to imagine cognitive enhancement with brain stimulation potentially following a similar course with similar vulnerable populations. With soft coercion, the individual feels societal pressure to keep up with norms and mores. As we know from many examples in professional sports, in high-stakes competitive environments, individuals turn readily to performance enhancers to give themselves a competitive edge. With respect to mental performance, we can see examples of

soft coercion currently in individuals who take pharmacologic cognitive agents in hopes of optimizing their performance at school or work. With respect to neuropsychology, the hazard of soft coercion again highlights that tDCS could potentially blur the distinctions between pathologically poor brain function and brain function that is normal but suboptimal for the tasks one desires to accomplish.

The freedom *to* be stimulated is unlikely to be overtly threatened given the accessibility of tDCS components. In this, lessons can be learned from other examples of cognitive self-enhancement, and cosmetic applications of medical technologies, including neuropharmacology. While it is important to remember that individuals are free to do as they see fit with respect to their own bodies and minds, inevitably, autonomy must necessarily be balanced with other ethical imperatives that arise from pragmatic or moral justifications, such as the need to consider the health of the community. Just as soft coercion can be used to encourage stimulation, social pressures can be exerted to influence the actions of those who would elect to use tDCS for medical or enhancement purposes. Given the complexity of the issues surrounding the use of tDCS for medical or enhancement, monolithic laws are unlikely to be helpful—or effective.

Ethical Considerations Pertaining to Neuropsychiatry

It may be taken for granted that the principle ethical considerations for tDCS with respect to the practice of neuropsychiatry boil down to whether tDCS is an acceptable way to treat patients. To this end, it is important to keep in mind that the distinction between normal and pathological is indiscrete and often culturally determined. Importantly, individuals whose thoughts and behaviors may objectively deviate from typical behavioral norms do not always do so in a way that leads to suffering; the moral imperative to medically treat dysfunction depends on the qualitative impact it has on an individual's life rather than the mere presence of abnormality [165]. Indeed, neurodiversity is increasingly being recognized as an intrinsic and valuable part of the spectrum of human experience that confers value and vigor to our overall ability to cognitively adapt to social and environmental changes [166]. Medicalizing neurodiversity pressures individuals and professionals (to some extent) into enforcing conformity to sociocultural norms of what is considered a "valuable" life. Neuropsychiatry as a field should consider tDCS alongside other dilemmas involving neurodiversity that drive the overall societal disposition towards psychiatry. These are not necessarily different issues than those pertaining to medicating neuropsychiatric disorders, but the fact that one doesn't necessarily need a prescription to self-administer tDCS (in some form) could shape perspectives on whether neuropsychiatric therapeutic applications of tDCS are perceived as legitimate, relative to other contexts in which tDCS could be used for enhancement or recreation.

Neuropsychiatry as a field should also be aware of the ways that widespread and even non-medical use of tDCS could influence perceptions of normality versus pathology. It can, at times, be difficult to distinguish between true "diseases" of the mind and more mundane dissatisfaction with mental states. Psychological aspects of individuals that are considered to be symptoms can often be conceptualized as traits that vary along a continuous spectrum of expression, for example, from inattentiveness to an attention deficit, or from sadness or emotional exhaustion to depression. This slippery slope of spectrum is especially problematic considering the capacity of tDCS to alter intellectual performance or mood. While most neuroscientists would argue that we are still far from being able to reliably alter mental states on an individualized basis using tDCS, the marketing for products like Thync and subjective experiences reported by DIY users indicate that at least the *perception* that tDCS can be used to induce targeted changes to mood (for example) exists presently. Having the power to so easily remedy dissatisfaction with one's mental states using tDCS—or even just believing that one has that power—has the potential to further obscure boundaries between what is considered normal, sub-clinical, or pathological.

Clinical fields that purport to distinguish between normal and pathological mental functioning face special obstacles when clinical values conflict with sociocultural norms, such as individuality or self-reliance. This has implications for clinical uses of tDCS. It is already difficult to determine when it is ethical to use technology to intervene in one's mental functioning. Widespread use of neural enhancement technologies like tDCS could further pathologize aspects of cognitive performance that would otherwise be considered along a spectrum of normalcy. This distortion could have the effect of decreasing individual autonomy by exerting positive pressure on clinical professionals to treat patients using neurostimulation or on individuals to "treat" themselves. As with pharmacological self-enhancement, some individuals might seek neuropsychiatric treatment for the purpose of procuring access to such technology as opposed to alleviating the suffering caused by illness. Thus neuropsychiatrists run the theoretical risk of becoming dispensers of cognitive commodities in tDCS as well as neuropharmacology. On the other hand, if there is general cultural pushback to increasing use of NIBS for self-enhancement, the application of tDCS in neuropsychiatric contexts, even where therapeutically beneficial, could come to be seen as problematic. Consider, for example, the stigma that popular culture has placed on electroconvulsive therapy (ECT), a highly effective treatment for refractory and life-threatening cases of depression, and how that stigma has had a sustained negative influence on its acceptance and use as a therapy. If tDCS becomes similarly stigmatized, this could raise obstacles to the development effective treatments for a variety of neurologic and neuropsychiatric conditions.

Several points raised in this chapter also have ethical implications for clinician-patient encounters. Because tDCS is not yet approved for specific clinical indications, we will here consider concerns that apply primarily to users of DIY or direct-to-consumer products. As public use of these technologies becomes more widespread, patients may sometimes confide to their neurologists or psychiatrists that they are experimenting with tDCS for self-treatment. In this situation, it is important that patients understand the safety consequences tDCS, including possible unintentional alteration of cognition or emotions. It will also be important for patients to recognize the current limits of the scientific literature, which cannot reliably predict what effects tDCS will have in the context of polypharmacy or other concurrent treatments. Conversations about the state of tDCS science and what is and is not known about tDCS might help patients to make better-informed decisions for themselves. However, insofar as there is currently no compelling evidence of serious medical risk posed by tDCS, some patients may be inclined to disregard the advice of their clinician and continue to self-administer tDCS in ways that, at least theoretically, seem potentially deleterious. This raises ethical issues of how best to engage with the patients regarding the risk of tDCS misuse in the absence of clear evidence for or against long-term harms. The issue of clinical misuse or overuse is similarly likely to arise in the event that tDCS is approved for specific indications such as depression or pain. While there is no clear one-size-fits-all strategy for navigating this topic with patients, it is an issue that neurologists and psychiatrists should be aware and ask about in their patients, especially as awareness of the therapeutic potential of tDCS becomes much more widespread in the public sphere.

Conclusion

In sum, there are pragmatic considerations specific to the practice of neuropsychiatry that bear weight in assessing both the utility and risks of employing tDCS as therapy. As it is presently understood, the mechanism of tDCS effects may be of particular utility for disorders in which dysfunction coincident and overlapping neural circuits leads to a range of psychiatric and cognitive symptoms. Targeting those common neural substrates with tDCS may lead to a variety of salutary effects in patients with complex disorders of mood, affect, and cognition. However, stimulation of overlapping neural circuits may also give

rise to cognitive tradeoffs that should prompt caution, particularly when the intent is to use tDCS to enhance normal cognition as opposed to treat disease. It is important to consider what is known versus what is not known about tDCS when designing clinical and cognitive research studies, and even more so when developing public policy and communicating with potential tDCS users (both consumers and patients). Clinicians and neuroscientists alike have an ethical responsibility to ensure that the lay public can access accurate information about what is and is not known about the mechanisms, effects, and safety of tDCS. In some cases, this may mean tempering unbridled enthusiasm for tDCS expressed in media coverage. The benefits and risks of tDCS clearly vary according to the context of administration, both with respect to the research, clinical, and cosmetic purposes for stimulation, as well as the states and traits of individual recipients.

All these considerations prompt a need to anticipate the trajectories of current and potential future use of tDCS both within and outside of clinical contexts, as there are likely to be dynamic broader social and cultural consequences of tDCS use within neuropsychiatry. Likewise, neuroethical consequences from nonclinically oriented tDCS use are also likely to have an impact on the way tDCS is used and sought out by patients. Thus, the use of tDCS in neuropsychiatry may have profound impacts not only on the social-cultural milieu, but also on the perceptions and practices of neuropsychiatry as a field.

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Regulatory Aspects

25

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Abstract

The increased research on transcranial direct current stimulation (tDCS) around the world reflects its potential as a therapeutic tool for many neuropsychiatric disorders. The simple technology and positive results on safety and efficacy have led to its increased use in research and clinical practice. However, there is no current regulation of tDCS by the Food and Drug Administration (FDA) in the USA for clinical use. Most of tDCS studies are considered of minimal risk, requiring only the Internal Review Board (IRB) approval to conduct a research study. Uses other than research include off-label and compassionate treatments. Special considerations on patient selection and the application of tDCS must be taken into account to optimize the technique and guarantee a safe practice. Further knowledge of tDCS experience in other countries and their combined efforts can help to promote the appropriate and safe use of this technique.

Keywords

tDCS • Medical device • Regulatory • FDA • IRB • Off-label • Compassionate treatment • Nonsignificant risk device

Abbreviations

CE	Conformité Européene
CES	Cranial electrotherapy stimulation
FDA	Food and Drug Administration
HD-tDCS	High definition-transcranial direct current stimulation
IDE	Investigational device exemption
IRB	Institutional Review Board
NIBS	Noninvasive brain stimulation
NSR	Nonsignificant risk
PMA	Premarket approval
SR	Significant risk
tDCS	Transcranial direct current stimulation

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Introduction

The field of noninvasive brain stimulation (NIBS) has undergone considerable advances in the last decade. The increased research on transcranial direct current stimulation (tDCS) around the world reflects its potential as a therapeutic tool through the modulation of cortical excitability, and its safety and efficacy have motivated scientists to increase its use in several conditions such as stroke [1–4], chronic pain [5, 6] cognitive impairment [7–9], and neuropsychiatric disorders [10–13].

Compared to other NIBS techniques, the relatively ease of use, portability, and low cost of tDCS makes it an attractive technique that can be easily accessed and used without any supervision, including nonmedical reasons. Therefore, it is important to have regulatory guidelines regarding the use of tDCS in both research and clinical practice. Currently, there is no international consensus with well-defined regulations for the use and distribution of tDCS [14]. In this chapter, we provide an overview of the regulatory process, the current status of tDCS in the USA and other countries, tDCS devices, special considerations on patient selection, and the practical aspects involving the use of tDCS.

FDA Regulation of Medical Devices

The federal agency responsible for regulating medical devices in the USA is the Food and Drug Administration (FDA). This agency has defined a medical device as an "*instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article, including a component part, or accessory which is*:

- *Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,*
- *Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*
- *Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.*" [15].

Before receiving the permission by the FDA to be legally marketed, the medical device submission enters in a review process for premarket and postmarket approvals. In the first case, the FDA classifies the medical devices according to the risk they pose to the consumers. Class I Medical Devices include devices such as elastic bandages or examination gloves for which general controls provide sufficient evidence of safety and efficacy. Class II Medical Devices include devices posing moderate risk to the patients, such as infusion pumps for the treatment of pain. Finally, for Class III Medical Devices, there is insufficient information to assure their safety or efficacy. Examples that fall in this last category are heart replacement valves or deep brain stimulating electrodes [16, 17].

Additionally, this classification determines the regulatory requirements that the manufacturer must follow. A device classified as Class I is exempt from the premarket notification. In the case of moderate and high-risk devices, the clearance is carried out through a premarket approval (PMA) or Product Development Protocol Processes [16]. The PMA process is usually longer and consists of conducting clinical studies to provide evidence of safety and efficacy of the medical device; most Class III and novel devices pass through this process in order to receive the FDA approval.

Furthermore, the premarket submission of a 510 (k) notification must be done to demonstrate that the device is substantially equivalent to a device that is already in the market. This notification includes information regarding the design and characteristics of the device and its components, as well as the clinical or nonclinical studies that were done to support the performance of

the device. This is required to assess the quality of the new device and thus, be able to compare to the current available devices. Most Class I and II devices are exempt from this submission before their sale; they do however undergo further control requirements [18]. This 510 (k) notification is also required for already marketed devices when there have been changes in their technology or a new indication for their use is foreseen.

Once the FDA approves the medical device for marketing, the manufacturer must follow other postmarket requirements: labeling and advertising, manufacturing, postmarketing surveillance, device tracking, and adverse event reporting [16].

Currently, there is no regulation of tDCS devices for therapeutic uses. The FDA regulates Cranial Electrotherapy Stimulation (CES) devices, but does not consider tDCS as a CES due to the use of direct current stimulation and the difference in electrode placement [19]. However, considering the FDA framework on medical devices as above discussed, tDCS could be contemplated and regulated as such, considering its intended use for the treatment of different medical conditions and its effects on brain function.

tDCS in Research

All clinical evaluations of investigational devices are under the Investigational Device Exemption (IDE) regulation [20, 21]. This exemption allows the new device to be used in clinical trials to provide information regarding its safety and effectiveness. Moreover, it distinguishes between significant and nonsignificant risk devices studies and, based upon this, the process for the study approval may vary. Clinical studies using devices classified as significant risk (SR) require both the FDA and the Institutional Review Board (IRB) approval before the initiation of the study, and in order to obtain the FDA approval, the investigator must submit the IDE application. Specific information including details about the sponsor, report of prior investigations and the investigational plan is required to apply. Furthermore, the sponsor must demonstrate that the potential risks to which the subjects may be exposed are reasonable in relation to the anticipated benefits and generation of scientific knowledge.

For studies involving nonsignificant risk (NSR) devices, only the IRB approval is required, and the sponsors' submission of the IDE is made directly to the IRB. The sponsors should also provide the study proposal and an explanation of why the device study should be considered as a NSR. If the IRB agrees, the study can begin without submission of an IDE application to the FDA. However, if the IRB determines it is a SR device, the sponsor has to report this decision to the FDA within a week (CFR Part 812.150(b)) [22, 23].

Finally, the approval of the proposed research by the IRB is based on the same criteria involving any FDA-regulated product; where the decision takes into account the risks and benefits of the investigational device and the contribution to science [24].

In the case of tDCS, these devices have been considered of NSR by the IRBs, so an IDE submission to the FDA is not required. Furthermore, its use has also been considered of minimal risk by some IRBs, which allows tDCS studies to be approved through an expedited review procedure [14, 22]. However, this is not indicative of its approval or the clearance by the FDA for the use of tDCS in scenarios other than research.

To date, the only companies having an IDE for tDCS devices by the FDA are Soterix Medical Inc. (tDCS and HD-tDCS) and NeuroConn [14]. The regulation of these devices has been subject to the FDA Quality System guidelines.

tDCS in Clinical Practice

Besides research, health care professionals in the USA can prescribe tDCS as an off-label treatment. This term refers to the use of a therapy that has proved to be safe within established parameters, for a purpose that has not been approved by the FDA. Considering that it is performed under the physician´s professional and ethical judgment, the FDA has developed Clinical Practical

Guidelines intended to help them make decisions regarding individual patient care [25]. Off-label uses of tDCS include motor recovery in stroke, improvement of balance and gait in cerebral palsy, and pain improvement in fibromyalgia.

Since the FDA has no legal authority to regulate clinical practice, unsupervised application of tDCS needs to be carefully reviewed for ethical and safety considerations. Off-label treatment should be applied according to the conventional protocols, with the approved devices and by trained personnel to guarantee safety and efficacy of the tDCS.

It is also important to consider that there is insufficient information regarding the long-term effects of stimulation, so this practice should be conducted with caution.

Furthermore, people who are not eligible to participate in a clinical trial may be able to get tDCS outside of a clinical trial through a "compassionate treatment." According to the FDA it can be considered as an option in patients with serious or life-threatening conditions that do not respond to currently approved treatments [26]. To date, this option has been accepted in most countries, considering the course of neuropsychiatric diseases and the limited treatment options [14].

The application of tDCS in either scenario must be ruled by ethical and legal considerations. Every medical research involving participation of human beings should be preceded by careful assessment of the benefit–risk ratio, an equitable selection of subjects and the obtainment of informed consent [27]. Especially for the latter, it is important to use simple and clear language to describe the tDCS procedure, as well as its potential benefits and adverse events.

TDCS Devices

The stimulation devices must meet safety requirements to be suitable for medical or scientific use. Generally, the use of battery driven devices is preferred because it prevents the delivery of dangerous high voltages and/or currents to the patient in case of technical problems. The device must be designed to indicate and allow adjustment of the parameters by the operator, specifically the output current, voltage, and duration of the stimulation. Furthermore, the protection of the patient must be enhanced through the presence of a gradual increase or decrease ("ramp-up" and "ramp-down" phase) of the desired current over a defined time interval (e.g., 30 s) at the beginning and the end of the stimulation, respectively. Moreover, the devices should have an accessible stop button to abort the stimulation in case of any adverse events.

Finally, it is recommended that an impedance monitoring system is included in these tDCS devices. The optimization of the technique might rely as well in the quality of the electrode preparation and the voltage demands to maintain the direct current magnitude [28, 29].

FDA-approved iontophoresis devices have been used by clinicians and researchers for tDCS in the off-label program. Iontophoresis devices use direct current stimulation (approximately $\leq$4 mA) to introduce ions of soluble salts or other drugs through the skin. These devices lack of many of the controlled elements mentioned previously, so its use as off-label treatment should be done with caution. In addition, they manage different doses and they were not designed to deliver current to the brain, and thus, they would not be ideal for performing tDCS [29].

Commercial devices claiming to have the same technology used for tDCS are already being sold to the public in the USA and other countries. Devices such as *foc.us* [30, 31] promoting the improvement of cognitive performance have raised concerns among health care professionals and researchers. In the first place, the company declares that as their product is not considered a medical device, no FDA regulation is required. In addition, these types of devices are usually designed with fixed stimulation parameters whose safety and/or efficacy have not been proved yet.

Indeed, a recent study in healthy volunteers assessed the effect of online and off-line foc.us tDCS applied over the prefrontal cortex on working memory. The authors showed that active stimulation (constant current of 1.5 mA during

20 min with a linear fade-in/fade-out of 15 s) with foc.us, compared to sham, significantly decreased the ability to monitor and update information in the working memory [31].

This device exemplifies that commercial devices may be sold without proper validation, that may result in inadequate use of the technique. In the case of foc.us, it has been presented as an alternative to "Conformité Européene" (CE) marked tDCS devices that have shown positive results on the working memory in healthy subjects [9, 32].

Furthermore, the media has encouraged programs such as Do-It-Yourself (DIY), where step-by-step tutorials on how to build a tDCS device and its application are widely available for untrained individual users [33]. Enthusiastic benefits of these devices are promoted without taking into account the population, parameters of stimulation, and medical background of the users. This reflects the need of regulation on devices that are being advertised in the media as potential tDCS devices carrying the risk of negative neuroplastic effects and misuse.

Considerations on Patient Selection

A careful patient selection is the core for an adequate tDCS intervention, and they evolve as daily publications define and refine the specific parameters of stimulation that maximize the benefits of the tDCS therapy and reduce the adverse events. However, the patient population, the medical illness, and the interaction between concomitant treatments are factors that must be taken into account before the application of tDCS.

tDCS Candidates

The identification of subjects who are appropriate candidates either for a study or an off-label program must be conducted carefully. Although specific inclusion criteria may vary according the specific study, certain considerations must be assessed in each patient to guarantee the safety and efficacy of tDCS:

- History of neurological and psychiatric conditions
- History of traumatic brain injury with loss of consciousness
- History of brain surgery or tumor
- History of seizures
- Presence of metallic plates in the head
- History of alcohol or substance abuse
- Use of psychopharmacological drugs
- Children
- Pregnancy

Ideally, tDCS should be adjusted in a patient-specific manner to select the best tDCS approach, reaching adequately the targeted region and avoiding safety concerns. As an example, skull defects or stroke related lesions might need modification of tDCS dose montages [28].

General exclusion criteria include the presence of unstable medical conditions (i.e., heart disease), intracranial metallic implantation or other conditions that may increase the risk of the stimulation [28].

In addition to the appropriate patient selection, it is important to assess and report adverse events/safety during and after tDCS. The following items are included in the proposed questionnaire by Brunoni et al. to survey tDCS adverse effects: headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, acute mood changes and others. The subject should enter a value from 1 to 4 (1, absent; 2, mild; 3, moderate; 4, severe) to each item and, if present, assess if it is related to the tDCS [28, 34] (Also see Chap. 23 of this book for a discussion regarding safety).

tDCS in Pediatrics

There are limited reports of the use of tDCS in the pediatric population, mainly due to safety concerns that rise when adult studies with tDCS are extrapolated to children. To date, the optimal dose of tDCS for safety and efficacy in the pediatric population has not been well established. Studies reporting the use of tDCS in children have considered the following stimulation

parameters: duration of stimulation up to 20 min, current intensities from 1 to 2 mA, and bilateral (anodal and cathodal) or cathodal montages [26, 35, 36] in conditions such as refractory epilepsy, schizophrenia, and autism. Serious adverse events have not been reported yet, and the most common adverse events are tingling and itching at the electrode site [26]. Although published data suggest that the use of tDCS in children is well tolerated, special considerations have to be taken into account.

Previous modeling studies have shown that the potential variability in the tDCS efficacy between these populations may result from differences in brain size, neuroplasticity, development, and age-dependent anatomical features (i.e., skull thickness, and white and gray matter volumes) [37–40]. For example, the scalp brain distance increases with age due to increases in extra-axial CSF space and skull thickness. Considering that the bone conductivity is low and that the skull thickness in children is decreased compared to an adult, the transmission of the current would be higher. Furthermore, the decreased amount of extra axial CSF would provide less shunting of the current and more focal stimulation [37, 40, 41].

In the case of the white and gray matter proportion, is important to consider that after reaching the maximum brain volume by age 5, the gray matter volume decreases approximately 1.1 % per year and there is an estimated increase of 1.5 % in the white matter volume until 18 years of age [39, 42–44]. The differences in this proportion, reflecting maturation in the brain structure, influence the depth of the current penetration being higher in a pediatric patient.

Another important anatomical feature dependent on age and sex is the head circumference [37]. Approximately, the 98 % of the total head circumference growth occurs before age 18 years. After the greatest gains in head growth during the first year of life, the head circumference increases as a lower pace until adulthood. At the age 8 years, the mean head circumference for boys is 52 cm and for girls 51 cm. Once they reach the age 18 years the mean head circumferences are 56 and 55 cm for boys and girls, respectively [45]. This anatomical factor, as well as the size of the conventional tDCS electrodes, affect the focality of the stimulation. As the conventional tDCS protocol uses 5 cm by 5–7 cm sponges wrapped rubber electrodes, their use in a small head circumference would end up covering the majority of the scalp, thus losing focality [37].

Based on the empirical experience with tDCS in children and the considerations mentioned previously, tDCS given within the standard parameters is well tolerated. However, due to the limited safety studies and the lack of information about the neurophysiological effects with different parameters of stimulation, caution is warranted for pediatric populations. In fact, the benefits of tDCS must be clear before designing clinical trials, especially in children with very young age (≤7 years), taking into account the phases of brain development, tDCS potential of neuroplastic changes, and the risk of inducing maladaptive plasticity in these patients.

tDCS in Pregnancy

To our knowledge, few studies have been performed on tDCS in pregnant patients. In healthy subjects, a recent study showed that tDCS does not induce any significant changes in the autonomic function, ventilation rate or core body temperature [46–48]. These results, in addition to the localized nature of tDCS [49] and the low risk of seizures, suggest that tDCS is unlikely to cause any significant risk to the fetus. To date, a case report showed successful application of tDCS in a pregnant woman with schizophrenia, with no adverse events reported on the fetus [50]. Furthermore, a pilot study using tDCS for the treatment of major depression during pregnancy [51] provided a basis for the development of future larger multicenter studies including this population.

Although further studies are required to have solid evidence of the safety profile of tDCS in pregnancy, a conservative therapeutic approach for future clinical trials and also potential off-label use appears to be justified in the case where a clear benefit for the patient is present.

Considerations on Application of tDCS

As clinical practice and research on tDCS advances, several practical aspects such as the setting and the person who should apply this technique turns relevant. For tDCS research studies, the IRBs usually do not require the principal investigator to be a licensed physician but an expert in the tDCS technique, its principles, neurophysiological changes and the potential side effects. Besides this, safety must be guaranteed defining a protocol for emergency response within the study protocols in case the subject has any unexpected adverse effect.

Even though there is no consensus regarding the training and the accreditation requirements for performing tDCS, it is important that the principal investigator guarantees proper training including basic knowledge of brain physiology, mechanisms of tDCS, potential risks, and the different protocols. Trained professionals may include MDs, technicians, psychologists, physiotherapists, and engineers, as in other techniques such as transcranial magnetic stimulation [52]. In our Neuromodulation Center at Spaulding Rehabilitation Hospital in Boston, the program includes twenty hours of theoretical and training sessions given by experts in the field, followed by the corresponding assessments and certification.

In the clinical practice, a licensed physician is responsible for prescribing tDCS as an off-label or compassionate treatment. During these sessions, the trained personnel must have full access to emergency and life-support equipment to manage any potential acute complication of the treatment.

TDCS Experience in Other Countries

For other countries leading tDCS research such as Brazil and Germany the regulations regarding the use of tDCS in research and the clinical practice depends on the local/governmental regulations. In addition, we include the example of South Korea where the experience with tDCS has been limited.

In Brazil, the regulatory considerations for tDCS are very similar to the USA. Clinical trials using tDCS require the approval by the local ethics committee (Comitê de Ética em Pesquisa, CEP). As the IRBs in the USA, the CEP bases the final decision on the statement of ethical principles from the World Medical Association-Declaration of Helsinki [24]. In addition, the National Ethics Committee (CONEP) may also be involved in the statutory regulation of basic and clinical tDCS research especially in the situation of international multicenter trials. Further regulatory assessment is the responsibility of the National Health Surveillance Agency (ANVISA), that is in charge of the supervision and administration of medical devices such as tDCS. Currently, the only device that has been registered by the ANVISA for the use of tDCS is provided by the company "NEUROCONN GMBH." Although the tDCS device has not been approved for clinical use, the off label and compassionate tDCS use are considered in specific situations [14].

In the case of Germany, clinical trials which may be initiated by the producer of the device require the approval of the local ethics committee and the Federal Institute for pharmaceutical and medical products (BfARM), which is the corresponding federal entity. In the case of nonclinical trials, the local ethics committee is free to assess the risk-benefit ratio of the study and its decision is sufficient to approve or not the study [14]. Besides research, off label and compassionate tDCS are provided in the context.

Finally, South Korea regulation on tDCS has shown to be very strict. To date, no tDCS device has been approved by the Korean Ministry of Food and Drug Safety (MFDS). TDCS has been considered to have a class II risk profile and thus, its approval requires preexistent evidence either from research studies performed in South Korea or abroad.

The application and regulation for the device approval are variable, some study protocols require approval just from the local IRB and others from the MFDS. In either case, this process is repeated for every single trial and the tDCS devices should be destroyed after the study [14]. Further uses of tDCS have not been reported.

Conclusion

We provide an overview of the regulatory aspects and special considerations for the use of tDCS in the USA. In the case of other countries leading tDCS research, the requirements for its use vary according to their local/federal laws. We consider that the involvement of the international community is crucial for the establishment of consistent tDCS regulatory aspects and the development of guidelines for its use in research and clinical practice. The active participation of the scientific community in this process of tDCS will be helpful to mitigate the potential risks of misuse and the uncertainty of long-term effects on the brain, which are not fully known.

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Clinical Research and Methodological Aspects for tDCS Research

26

Adam J. Woods and Donel M. Martin

Abstract

Although transcranial direct current stimulation (tDCS) is seemingly simple and easy to apply, specific aspects of sound application and design must be taken into consideration to obtain reliable results in clinical and research settings. This chapter provides an overview of methodological, design, and application techniques important for technically sound application of tDCS. Topics covered in this chapter include: clinical/research trial design; patient/participant screening practices; electrode selection, preparation, and placement; montage selection; assessment for adverse events/safety, and functional effects monitoring. This chapter is intended: (1) to provide information for education of researchers and clinicians new to tDCS, (2) to provide a description of methodological details important for experienced tDCS researchers and clinicians attempting to replicate clinical and research outcomes, and (3) to highlight methodological details important for consideration in clinical and research applications of tDCS.

Keywords

Transcranial direct current stimulation • Methodology • Design • Application • Reproducibility • Technical guide • Safety • Patient and participant screening • Electrodes preparation • Montage selection

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Introduction

Transcranial direct current stimulation (tDCS) was reintroduced as a method for noninvasive brain stimulation (NIBS) in humans approximately 15 years ago, in 1998–2000 [1, 2]. Since its reintroduction to the scientific and clinical community, the application of tDCS across a variety of healthy, psychiatric, and neurological populations has increased exponentially. However, like many nascent fields, methods used to apply tDCS have varied over the past 15 years. This variation, together with a lack of standardized reporting methods for the field, has likely played a role in issues of reproducibility for certain effects previously demonstrated with tDCS [3]. Specifically, variability in tDCS application methodology, design, stimulation parameters, and other factors have undermined the ability to reproducibly apply tDCS within and between patients and healthy subjects. For example, inconsistent placement of electrodes alters the location and intensity of stimulation to various brain regions [4]. In contrast, different levels of stimulation intensity (e.g., 1 vs. 2 mA) result in partially nonlinear changes in hypopolarzing versus hyperpolarizing resting membrane potentials under anode versus cathode electrodes, respectively [5]. Furthermore, certain medications can alter excitability effects of tDCS on resting membrane potentials (e.g., serotonin selective reuptake inhibitors, SSRIs; [6]) relative to effects previously shown in healthy adults not taking these medications. These are only a few examples of methodological and design factors that significantly alter the potential outcomes of clinical or research applications of tDCS. Unfortunately, studies often do not provide the level of methodological detail required to guide clinicians/researchers new to the field of tDCS or experienced researchers attempting to replicate study effects. These details are of critical importance for not only reproducing effects from a given study and consistent clinical outcomes, but also for education of a new generation of tDCS researchers and clinicians.

In this chapter, we provide guidance on methodological and design aspects of tDCS, covering basic methodological issues, effective approaches, and reproducible methods for the application of tDCS in both clinical and research settings. These materials are intended to provide easily implemented and reproducible methods for both new and experienced tDCS researchers and clinicians.

Clinical/Research Trial Designs

Protocol Intensity/Duration/Repetition

When designing an experimental or intervention protocol it is important to choose tDCS parameters (i.e., stimulation intensity, duration and repetition) based on the outcome being investigated (i.e., neurophysiological, cognitive, or behavioral), as well as the clinical population being studied. This is because findings with the use of particular parameters for one outcome may not directly correspond with another similar or different outcome, or in a different subject population. Neurophysiological responses (e.g., MEP amplitudes) to tDCS and other noninvasive brain stimulation techniques, for example, have been shown to have little or no correspondence to motor learning capacity [7]. As such, stimulus parameters chosen based on findings of effects on MEP amplitudes measured in the motor cortex in healthy participants may not produce equivalent effects on alternative outcomes (e.g., cognitive or behavioral) when assessed following stimulation of the same or different brain regions. This principle also can apply to the administration of stimulus parameters found effective for healthy subjects to clinical populations. Whilst 1 mA stimulation intensity delivered over the left dorsolateral prefrontal cortex for 10 min improved working memory performance in healthy participants [8], 2 mA stimulation intensity for 20 min was necessary to produce similar effects in patients with schizophrenia [9].

Similarly, this principle may equally apply when choosing the interval for repeated tDCS administrations, for example, in intervention protocols. This appears to be the case, as both the stimulus polarity and interval between sessions can interact to cause different effects on out-

comes. In healthy subjects, differently spaced intervals (i.e., 0 min to 24 h) between consecutively applied tDCS given with the cathode electrode over the motor cortex has been shown to directly affect both the magnitude and duration of post stimulation neurophysiological effects [10]. Similar differential behavioral effects due to both the polarity and duration of the spaced interval on cognitive outcomes have been found, with improvement in working memory performance following two sessions of tDCS with the cathode electrode over the left prefrontal cortex, although not when the anode electrode was placed over the same region, given 10 min apart [11]. The latter finding additionally highlights the potential role of metaplastic effects within the stimulated region on outcomes (i.e., when tDCS is administered again during the after effects of a previous tDCS administration).

Taken together these collective findings suggest that if no prior reference study exists when designing an experimental or intervention protocol, titration of tDCS parameters in relation to stimulus intensity, duration, and repetition should be considered. This can be achieved, for example, through a clinical pilot. Such piloting can also be invaluable for informing future studies.

Methodological Aspects of Online and Offline Protocols

A potentially important methodological consideration when designing an intervention or study using tDCS is the timing of tDCS administration in relation to task execution. That is, when tasks are given, it is important to determine whether these are performed during the application of tDCS (i.e., "online"), or following tDCS administration (i.e., "offline"). This consideration is based on evidence indicating that both the physiological and behavioral effects of tDCS are different during and after stimulation. For example, functional neuroimaging has shown that while an increase in regional blood activity occurs during stimulation, activity is reduced immediately following stimulation [12]. Different behavioral outcomes have also been demonstrated with "online" compared to "offline" protocols. While improved motor learning was found to occur with "online" stimulation, decreased learning was found when the same task was performed "offline" [13]. Similarly, better performance on a cognitive training task was found with "online" compared to "offline" tDCS, with greater maintenance of learning found the following day [14]. When evaluating outcomes in interventions involving repeated tDCS administrations these effects should also be considered, as "offline" effects or "aftereffects" immediately following tDCS administration may affect task performance and/or other measurements, for example, cognitive or neurobiological changes following a course of tDCS for depression. While these aftereffects have primarily been shown in the context of research studies [1, 15, 16], their impact should be carefully considered in multi-session treatment studies.

A further methodological consideration is the relative effect of task related activity within stimulated regions, as this has also been shown to affect outcomes. For example, different effects on post stimulation cortical excitability have been found depending on whether subjects were sitting passively at rest during tDCS, paying attention to a cognitive task, or actively engaging the stimulated region with performance of a motor task [17]. Further, the relative level of task-related activity has also been found to be relevant. Whilst performance of a slow motor task during anodal stimulation of the motor cortex significantly improved learning and increased cortical excitability, poorer learning and decreased cortical excitability was found when subjects performed a fast motor task [18]. Relative activity levels during tDCS have further been shown to affect whether neuroplastic changes occur following stimulation, with ongoing background activity shown to be necessary to induce long term potentiation in an in vitro animal model [19].

As such, both the timing of task execution and the relative state of stimulated regions in relation to tDCS administration together are potentially important considerations when assessing outcomes for a particular study or intervention. Correspondingly, attempts should be made to

control for potential brain state effects whenever behavioral or physiological outcomes are examined during or after tDCS administration. This could be achieved, for example, by requiring subjects to sit at rest for a given period prior to commencement of tDCS and implementing methods to standardize or restrict behavioral activity during and following stimulation.

Blinding, Sham, and Active Control

A relative advantage of tDCS compared to other noninvasive brain stimulation methods is the ability to implement effective blinding. The usual approach for blinding subjects is to apply a "sham" stimulation protocol which typically involves ramping the stimulation up and down similar to active stimulation, although only providing constant stimulation for a few seconds. The advantage of this methodology is while subjects will feel the initial itching/tingling sensation suggestive of active stimulation, the overall stimulation duration is too short to induce aftereffects. For 1 mA tDCS with an electrode size of 25 cm^2, this method has been shown to reliably blind subjects [20]. As stronger stimulation intensities induce larger sensations, providing a brief constant stimulation at the maximum intensity, however, may compromise blinding [21]. An alternative approach is to apply topical anesthetics to abolish skin sensations [22]. Care should be given if this approach is taken, as local anesthetics may reduce cutaneous sensations indicative of skin damage which could in turn increase the risk for adverse side effects. However, a recent paper found no relationship between increased skin sensation and probability of skin burns, suggesting that the use of topical anesthetics may be a safe alternative in the sham procedure [23]. Nonetheless, care should be taken when considering the use of topical anesthetics.

Experimenter blinding is accomplished by use of tDCS stimulators, which include a sham stimulation function that enables the experimenter to remain unaware of the stimulation condition. However, even in this situation it is important to note that the presence of skin erythema due to vasodilation, as well as sensations reported by subjects during and following stimulation can nevertheless compromise experimenter blinding. Skin erythema though can be reliably reduced by acetylsalicylate, or topical application of ketoprofen [24]. Having one experimenter record side effects following tDCS (e.g., skin reddening) while another one only assess efficacy measures can further blind the primary interventionist to study conditions. Hence, for reliable double blinding, several different approaches should be considered.

Alternatively, or in addition, an active control condition may be considered. This may be useful to determine specificity if the overall goal is to demonstrate that stimulation applied over one cortical region induces a particular effect. Application of tDCS to an alternative brain region (i.e., as an active control) therefore may provide a stronger foundation for interpretation of results. For such designs, use of high definition tDCS electrode montages (e.g., 4×1) should be considered, as this enables better localisation the stimulation effects particularly for cortical regions [25–28]. Notwithstanding, the choice of the control (i.e., sham or active) should be hypothesis driven, as this can have a profound impact on study conclusions.

Patient/Participant Screening

Using modern stimulation parameters, tDCS given either over a single treatment session or over several sessions spaced apart, has been safely administered to healthy subjects and patients with diverse psychiatric (e.g., schizophrenia, attention deficit hyperactivity disorder, anorexia) and neurological conditions (e.g., stroke, epilepsy, traumatic brain injury) in experimental protocols. Increasingly, tDCS has also been given over multiple repeated sessions to patients as a therapeutic intervention. Careful screening, however, is critical for minimizing the risk for adverse side effects for all protocols using tDCS in both healthy and patient populations.

Prior to stimulation, it is necessary to conduct formal screening for potential comorbid neuropsychiatric and neurological conditions as well as structural abnormalities. This is important both to accurately characterize the particular patient population being investigated and to determine the relative risk for unexpected side effects for particular subjects. For example, mood switching in patients with major depressive disorder and bipolar disorder have been reported in several case reports [29]. For neuropsychiatric conditions, this can be achieved using published formal structured interviews, for example, the Structured Clinical Interview for DSM-5 (SCID-5: [30]) or the M.I.N.I.6. International Neuropsychiatric Interview (M.I.N.I. 6.0: [31]). Potential neurological conditions can be screened either through either patient interview or self-report questionnaires (e.g., Transcranial magnetic stimulation Adult Safety Screen; TASS; [32]). Due to the potential for local enhancement of current density as a result of anatomical abnormalities (e.g., to the skull), exclusion criteria for tDCS (i.e., metal in the head, pacemaker, no stimulation over fissures, or cranial holes) are also typically implemented.

Screening for concurrent medication use is also important, as particular psychoactive medications can interact with tDCS effects. For example, D-Cycloserine, a common treatment for tuberculosis, has been shown to prolong the neuromodulatory effects of tDCS [33]. Other common medications, including selective serotonin reuptake inhibitors (SSRIs; [34]), mood stabilizers (i.e., sodium and calcium channel blockers; [6]), antipsychotics (i.e., dopamine antagonists; [35]), and common pain killers and sedatives (e.g., benzodiazepines; [36]), have also though been shown interact with tDCS. Concomitant medication use should therefore be kept stable throughout the study period and ideally for at least 4–6 weeks prior to tDCS administration in therapeutic interventions. Furthermore, the experimenter should be notified immediately of any medication changes during any tDCS study, as this may affect outcomes.

Lastly, as tDCS is administered using electrodes place upon on the scalp, it is necessary to inspect the skin where the electrodes will be placed. Skin damage to these areas (e.g., disease, irritation, or lesion) during administration of tDCS can potentially increase the likelihood of further skin damage or skin burns [37].

Electrodes and Contact Medium

The role of electrodes in tDCS is to facilitate delivery of current from the stimulation device to the scalp. Teams of clinical trial researchers have reported application of thousands of tDCS sessions without any skin injury using rigorous control of electrode selection and preparation, along with adherence to established tDCS protocols, operator training, and use of certified devices [34, 38–41]. The tDCS electrode assembly most commonly comprises (1) a metal or conductive rubber (e.g., biocarbon) electrode, (2) an electrode sponge, and (3) an electrolyte-based contact medium (e.g., saline, gel, or conductive cream) to facilitate current delivery to the scalp, and (4) any materials used to shape these components or otherwise direct current flow (plastic casing, rivets).

The metal or conductive rubber electrode is the site of electrochemical reactions during tDCS [42], and should never directly contact the skin. An electrolyte must be used as a buffer between the electrode assembly and the skin. Sufficient electrolyte volume prevents chemicals formed at the electrode during the electrochemical reaction occurring during stimulation from reaching the skin [43]. The electrolyte can be placed in a sponge encasing the electrode (i.e., saline) or, in the case of electrode cream, placed directly on the electrode surface. For saline, oversaturation of the electrode sponge can significantly undermine reproducibility of tDCS application and effects. When sponges are oversaturated, saline is evacuated from the sponge and covers an area of the scalp outside of the surface area electrode sponge. Rather than delivering current through a specified surface area on the scalp under the electrode (e.g., 5×5 cm), the electrode surface area and area of current delivery now encompasses the entire area of the scalp that is covered in saline. This creates an unreproducible and amorphous

area of current delivery within and between subjects. It is important to obtain good contact under, and only under, the electrode with the electrode sufficiently, but not overly saturated. Methods allowing quantification of saline (e.g., syringes) can assist in achieving a consistent and appropriate amount of contact medium.

Consistent with issues introduced by oversaturation of sponges, the shape/size of electrodes/sponges significantly alters the distribution of current delivered to the scalp and the brain [44, 45]. At a constant current intensity level (e.g., 1 mA), increases in electrode size or differences in electrode assembly shape result in differences in the distribution of the current across the surface area of the scalp, resulting in differences in the distribution of current throughout the brain [44, 45]. Thus, it is critical for investigators to consistently report not only the current intensity applied and the amount of contact medium used, but also the shape and size of the electrode assembly.

Electrode Location

Another critical consideration for tDCS is determining where to place electrodes on the head. Studies monitoring physiological changes following tDCS and computational modeling studies of predicted current flow demonstrate that the relative location of electrodes results in significant differences in where and how much current is delivered to the brain [4, 27, 46]. For example, Nitsche and Paulus [1] demonstrated that relative differences in electrode locations altered whether or not tDCS impacted TMS generated motor-evoked potentials (MEPs). Numerous modeling studies have demonstrated significant differences between relative locations of electrodes, with results varying from stimulation of the whole brain to more selective stimulation of particular lobes of the brain [4, 27, 46]. Woods et al. [4] further demonstrated that as little as 1 cm of movement in electrode position significantly altered the distribution of predicted current flow in the brain, as well as the intensity of stimulation in specific brain regions. Computational modeling of electric current through the brain can be a useful tool for the a priori design of tDCS electrode positions for a given study. In this same context, the importance of electrode location also highlights yet another critical consideration, preparation of a stable electrode placement on the head.

Head size and shape vary from person to person. Thus, it is necessary to use a method for common localization of electrode position. There are several methods for addressing this issue: (1) International 10–20 (or 10–5) Electrode Placement System [47, 48], or another gross anatomical coordinate system [49], (2) neuronavigation systems (e.g., MRI guided), or (3) physiology-based placement (e.g., TMS generated MEPs). These methods can be used to consistently center each electrode on the head, accommodating varied head shape or size.

Electrode Placement

Once desired locations are identified based on specific study design needs, the electrode assembly must be affixed to the head for delivery of current. Nonconductive headgear used to position the electrodes on the body or scalp (e.g., elastic straps) are not typically included in the electrode assembly but are critical for appropriate electrode placement [4]. For tDCS using sponge-covered electrodes, elastic straps are the most commonly used headgear for electrode placement. If these straps are undertightened or overtightened, electrodes have a strong tendency to move over the course of a tDCS session. Thus, the distribution of current delivery changes over the duration of a tDCS session [4]. This too undermines tDCS replicability. Furthermore, if electrode straps are overtightened, there is an increase in the probability of evacuation of saline from the electrode sponges. Regardless, the contour at the base of the skull below the inion and the flat of forehead provide for stable placement of a strap around the head. For participants with long hair, placement of the back of the strap under the hairline also improves stability of the strap preparation, whereas placement over the

hair leads to a high probability of upward drift of the strap and the electrodes placed on the head. Use of cross-straps over the head should also avoid overtightening of the cross-strap to avoid this same issue. Use of a cross-strap under the chin can counteract this tendency, but may be uncomfortable to participants. If under-chin straps are used, these should be used for all participants to maintain consistency of participant experience in the study.

tDCS Stimulator Selection

A limited set of certified tDCS-stimulators are currently available (e.g., produced/distributed by Brainstim, Magstim, Neuroconn, Neuroelectrics, Newronika, and Soterix Medical). These devices are designed to deliver constant current through two or more electrodes [50, 51]. Available stimulators differ based on specific features, such as: suitability for alternative stimulation protocols (e.g., transcranial alternating current stimulation, transcranial random noise stimulation, transcranial pulsed current stimulation), custom programming capabilities, number of stimulation channels, available stimulation intensity level, stimulator size, stimulator weight, stimulator portability, compatibility with magnetic resonance imaging (MRI), blinding options, and sham options. Certified tDCS-stimulators provide the basic features required to deliver tDCS. Thus, selection of a stimulator depends on the planned application and study protocol (number of electrodes, requirements for blinding, desired stimulation intensity, sham options, etc.). In any case, exactness of delivered current, as programmed, is of crucial importance, and should be tested at a regular interval (e.g., by aid of an oscilloscope), as minor deviances can result in prominent alterations of experimental outcomes. Thus, while a certified stimulator from a manufacturer may be delivered performing to exact specifications, repeated stimulation may result in alteration of the exactness of delivered current (i.e., delivery of less than or more than 2 mA when stimulator set to 2 mA) and should be tested for consistent delivery of tDCS to patients and participants. Certified tDCS-stimulators also have the advantage of limiting the intensity of current to, typically, less than 3 mA. In contrast, many stimulation devices repurposed for tDCS (e.g., iontophoresis stimulators) provide the ability to deliver stimulation up to and beyond 1 Amp—a significant safety concern regarding skin lesions/burns. Stimulators should be chosen that provide optimal safety for participants and patients, as well as based on the specific features required for a given stimulation protocol.

Assessment of Safety/Adverse Events and Monitoring During Stimulation

It is important to make the distinction between tolerability and safety aspects in relation to tDCS. Whilst tolerability refers to the presence of uncomfortable and unintended effects (e.g., tingling, and itching sensation under the electrodes), safety refers to damaging effects. Using modern protocols, comfort ratings for tDCS have generally shown a favorable tolerability profile [52]. The most frequently reported side effects are tingling and itching sensations under the electrodes, headache, and tiredness [41]. The sensation of phosphenes elicited by abrupt current onset or offset is avoided by ramping current intensity in both active and sham conditions. Erythema under the electrodes is caused by tDCS-induced vasodilation, and hence is not a safety issue [53].

In relation to safety aspects, no structural damage of brain tissue as examined with diffusion-weighted and contrast enhanced MRI [54], or neural damage as assessed using neuron specific enolase [54, 55] have been reported using the modern protocols introduced by Nitsche and colleagues. To date only one seizure, which potentially may be attributed to tDCS, has been reported since the introduction of modern tDCS protocols. This occurred when repeated tDCS sessions in combination with administration of escitalopram was given to a 4 year old boy who had a prior history of epileptic activity and a recent adjustment to his antiepileptic medication

regime [56]. This report thus further highlights the importance for careful patient screening and monitoring, as well as titration with the use of both novel tDCS protocols and established protocols used in different clinical populations.

Another potentially relevant aspect to safety is the application of tDCS using an extracephalic reference electrode based on adverse side effects reported in an early study [57]. Computer modeling of the use of an extracephalic electrode placed upon the shoulder suggests that cardiac or brainstem activities should not be affected [58, 59]. Data in healthy subjects suggests that using an extracephalic electrode reference does not modulate brainstem autonomic activity [60]. Notwithstanding, this assumption does not necessarily apply for any tDCS protocol, independent from current intensity, and stimulation duration, and without regard for inclusion/exclusion criteria. Hence, careful patient monitoring to demonstrate safety is recommended particularly for novel protocols.

The most immediate safety risk for tDCS is the potential for skin lesions or burns following repeated treatments [23, 61]. Risk to subjects, however, can be substantially ameliorated through the implementation of several previously outlined recommendations [37]. (1) Subjects should be screened for skin disease, irritation or lesions underneath where the electrodes will be placed to minimize focalisation of current density. Skin should also be checked prior to every tDCS administration. (2) A single-use sponge should be placed between the electrode and the scalp, as repeated use of sponges may lead to the build-up of substances, which could cause electrochemical reactions [61]. (3) Sponges should be evenly saturated with contact medium (e.g., saline) so that no dry portion of the sponge is in contact with the skin. If using electrolyte cream directly on an electrode, the thickness of the cream application should be consistent (~3 mm) and should cover the electrode completely, preventing direct contact of the electrode with the skin. (4) Care should be taken to ensure adequate and even contact of the electrode skin interface is achieved. (5) Finally, standardized monitoring of patient comfort (e.g., discomfort/pain during stimulation) and side effects following stimulation should be implemented [37, 62], to regularly assess subjects' skin condition and risk for burns.

Monitoring Functional Effects of tDCS

There are several possible approaches to monitoring the functional effects of tDCS. Effects on motor cortex plasticity and motor cortex excitability, for example, are typically examined through experimental designs which involve firstly determining the motor cortex hotspot for a targeted muscle (e.g., first dorsal interosseous) using single pulse TMS, obtaining a measure of baseline excitability, and then measuring physiological changes following tDCS stimulation [55, 63]. Another commonly used approach is to examine cognitive effects either during or following tDCS administration (for review see [64]).

Increasingly, investigators are additionally employing neuroimaging tools (e.g., EEG and fMRI) to further explore functional effects. EEG, whilst lacking the spatial resolution of other techniques, has the advantage of allowing for enhanced temporal resolution for assessing tDCS related functional effects. EEG measures voltage fluctuations resulting from ionic current flow via scalp recorded activity and thus is useful for elucidating changes in processing over time within specific regions or across circuits [18]. Similarly to the assessment of functional cognitive changes, functional effects can be measured "online" or "offline" following stimulation. Both methods, however, are associated with methodological challenges. Firstly, the tDCS electrodes will need to be integrated together with the EEG electrodes, so as to avoid both types of electrodes being in direct contact and potential bridging between tDCS and nearby EEG electrodes via spreading of the conductive medium. The latter can be potentially avoided through the use of small sized electrodes, similarly to those used with HD-tDCS [25]. Secondly, for "online" protocols, as tDCS involves the application of an electrical current

and EEG directly measures very small electrical changes within the brain, there is the potential for direct interference from tDCS. This can thus result in saturation of an EEG recording amplifier that does not have sufficient range. Artifacts related to the tDCS device can also introduce external noise. Such effects may potentially be accounted for by the use of a phantom head so as to identify potential artifacts introduced by the tDCS device [65].

Functional effects may further be investigated using magnetic resonance imaging (MRI), which incorporates several methods including Blood Oxygen Level Dependent (BOLD) fMRI [15, 66], Arterial Spin Labeling [12], as well as proton and non-proton MR Spectroscopy [67]. tDCS can be applied within the bore of the magnet, with the option of assessing effects either during "online" stimulation, and "offline," where subjects are removed from the scanner, have tDCS applied, and then are returned in the scanner. There are several methodological considerations in regard to the use of tDCS within the MR bore. Firstly, due to the potential for premature drying out of the electrodes during concurrent scanning (which may last up to or over an hour), biocarbon electrodes should be attached to the participant using thick electrical conductance paste (e.g., Ten-20 paste), rather than saline soaked sponges or low viscosity electrode gel. Secondly, electrodes should be marked with oil-capsules so their position can be checked on the resulting images. It is also very important that electrodes are not in contact with the head coil, or headphones, to prevent electrode displacement and unexpected interactions between the stimulator and the scanner. Specially designed MRI compatible (nonferrous or appropriately shielded) tDCS cables and electrodes passed through the magnet suite waveguide and into the magnet bore are also necessary, with loops avoided and placed away from subjects to avoid the risk of eddy current induction and potential RF burns. Lastly, when analyzing data, consideration should also be given to the potential warping of the magnetic field due to the introduction of tDCS resulting in false-positive findings.

Concluding Remarks

In this chapter, we deliver guidance for technically sound application of tDCS. Although the technique is seemingly simple and easy to apply, specific aspects must to be taken into careful consideration to perform reproducible application and obtain reliable results. In the absence of careful consideration for the topics covered in this chapter, it is difficult, if not impossible, to interpret study findings, and difficult to facilitate attempts to replicate prior findings. In addition to other available technical guides to tDCS [68], this chapter will arm researchers and clinicians new to tDCS with insight into methodological considerations necessary for consistent application of tDCS in both clinical and research settings. For experienced researchers, this chapter provides a critical review of methodological aspects of tDCS important for consideration in attempts to replicate existing effects in the literature and important for inclusion in reports of tDCS effects. In summary, with careful consideration of the topics covered in this chapter, clinicians and researchers should be well equipped to perform consistent and reproducible tDCS in clinical and research settings.

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