Review

Noninvasive Brain Stimulation with Low-Intensity Electrical Currents: Putative Mechanisms of Action for Direct and Alternating Current Stimulation

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Transcranial stimulation with weak direct current (DC) has been valuable in exploring the effect of cortical modulation on various neural networks. Less attention has been given, however, to cranial stimulation with low-intensity alternating current (AC). Reviewing and discussing these methods simultaneously with special attention to what is known about their mechanisms of action may provide new insights for the field of noninvasive brain stimulation. Direct current appears to modulate spontaneous neuronal activity in a polarity-dependent fashion with site-specific effects that are perpetuated throughout the brain via networks of interneuronal circuits, inducing significant effects on high-order cortical processes implicated in decision making, language, memory, sensory perception, and pain. AC stimulation has also been associated with a significant behavioral and clinical impact, but the mechanism of AC stimulation has been underinvestigated in comparison with DC stimulation. Even so, preliminary studies show that although AC stimulation has only modest effects on cortical excitability, it has been shown to induce synchronous changes in brain activity as measured by EEG activity. Thus, cranial AC stimulation may render its effects not by polarizing brain tissue, but rather via rhythmic stimulation that synchronizes and enhances the efficacy of endogenous neurophysiologic activity. Alternatively, secondary nonspecific central and peripheral effects may explain the clinical outcomes of DC or AC stimulation. Here the authors review what is known about DC and AC stimulation, and they discuss features that remain to be investigated.

Keywords: noninvasive brain stimulation; transcranial direct current stimulation; cranial electrotherapy; electrosleep; cranial AC stimulation; transcutaneous electrical stimulation; tDCS; tACS; CES; TCES; brain polarization

Beginning more than a century ago, neurophysiologists demonstrated great interest in learning about the effects of low-intensity (currents used usually equal to or less than 2 mA) electrical stimulation when applied to the human head. In this age of advanced technology, although relatively little is still known about the mechanism and effects of cranial electrical stimulation, these methods are becoming increasingly explored for their utility in investigating the effect of cortical modulation on various neural networks, and interest in the field remains strong.

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Today we recognize two main forms of low-intensity cranial electrical stimulation: transcranial direct current stimulation (tDCS; a method in which low-intensity constant current is applied to the head) and cranial alternating current (AC) stimulation (in which low-intensity AC is applied to the head). tDCS offers a noninvasive method of brain stimulation and has been shown to be effective in modulating cortical excitability as well as guiding human perception and behavior (Nitsche 2008). In the past two years alone, numerous studies have been published on tDCS demonstrating positive clinical results. Although many groups have studied and reviewed the neurophysiologic and clinical effects of transcranial brain stimulation with direct current using modern techniques of brain research (Lefaucheur 2008 ; Nitsche 2008), less effort in recent years has been dedicated to the study of stimulation with nonconstant and alternating currents. Here we review and discuss the two main techniques of low-intensity cranial electrical stimulation (DC and AC stimulation), and we discuss potential mechanisms of action based on behavioral and neurophysiologic studies, providing new insights for the field of noninvasive brain stimulation.

Methodology of Review

Medline and Scopus databases were searched for English-language articles published between 1980 and 2008, using the following keywords: transcranial direct current stimulation; tDCS; brain polarization; brain, electrical stimulation; brain, direct current; transcranial alternating current stimulation; cranial electrotherapy stimulation; transcutaneous electrical stimulation; brain, alternating current. Articles referenced within these sources were also selected if relevant to this review.

Historical Highlights

Applications of electrical stimulation of the brain, which include invasive and noninvasive modalities, are now burgeoning in the fields of the neurological sciences. On one end, techniques of deep brain stimulation allow for the focal and precise stimulation of deep neural structures (such as thalamic, subthalamic, and pallidal nuclei), which provide remarkable results in controlling undesirable tremors and dystonias, and are used clinically, for example, in the treatment of advanced Parkinson's disease (Limousin and Martinez-Torres 2008). At the level of the cortex, electrodes left implanted at the epidural area above the motor cortex are used for motor cortex stimulation, a technique shown to alleviate many forms of chronic neuropathic pain (Lima and Fregni 2008). Although these methods of brain stimulation have shown marked progress, one limitation in their application is the requirement for the surgical penetration of the scalp, skull, and brain, a costly procedure that carries considerable risk. In this context, methods of noninvasive brain stimulation have regained significant appeal for their capacity to safely modulate brain activity.

Even so, the recent interest in low-intensity transcranial brain stimulation is not new. Low-intensity electrical stimulation probably had its origins in the research thrusts of the 18th century with studies of galvanic (i.e., direct) current in humans and animals by Giovanni Aldini and Alexandro Volta, among many others—based on the work of electrotherapy pioneers Johann Krüger (1715–1759) and Christian Kratzenstein (1723–1795) (Kaiser, 1977)—with a long and interesting history (see Goldensohn 1998; Priori 2003). As early as 1794, Aldini had assessed the effect of galvanic head current on himself (Aldini 1794), and by 1804, he had reported the successful treatment of patients suffering from melancholia (Aldini 1804). Research continued through the early 20th century; yet because DC induced variable results, or sometime none at all, the use of low-intensity DC (i.e., tDCS) was progressively abandoned in the 1930s when Lucino Bini and Ugo Cerletti at the University of Rome proposed the method of electroconvulsive therapy (ECT; Priori 2003), which involves transcranial stimulation at significantly higher intensities. Interesting and imaginative efforts revolving around ECT, particularly between 1938 and 1945, subsequently led to an interest in the application of AC at lower intensities with the first study of "cranial electrotherapy stimulation" (also known as "electrosleep") published by Anan'ev and others in 1957 (Anan'Ev and others 1957). Limoge then identified a specific parameter of low-intensity AC stimulation in 1963 ("Limoges' current"), which was noted to significantly reduce the amount of narcotics and neuroleptics required to maintain anesthesia when stimulation was applied during surgery (Limoge and others 1999). Since the 1960s, a series of studies with low-intensity AC stimulation have been published (Kirsch and Smith 2004; Smith 2007), and cranial AC stimulation devices have become commercially available for personal use (e.g., Alpha-Stim, Fisher Wallace Cranial Stimulator, Transair Stimulator, etc.). However, research in this area has been inconsistent and there remains a lack of solid evidence showing the effects of weak transcranial stimulation with AC.

At the turn of the millennium, interest in a new form of noninvasive brain stimulation, namely transcranial magnetic stimulation (TMS), renewed interest in other forms of noninvasive brain stimulation. Using TMS evoked motor potentials as a marker of motor cortex excitability, Nitsche and Paulus demonstrated the possibility of modulating cortical excitability with tDCS: Weak DC applied to the scalp was associated with excitability changes of up to 40% that lasted several minutes to hours after the end of stimulation (Nitsche and Paulus 2000). In fact, a mathematical model has shown that stimulation with DC could modify the transmembrane neuronal potential (Miranda and others 2006; Wagner and others 2007) and, in turn, influence the excitability of individual neurons without, however, actually eliciting an action potential.

Although recent evidence has been encouraging, the two main challenges for noninvasive methods of brain stimulation with weak currents are the limitations in focality and low intensity (i.e., subthreshold stimulation). In tDCS, the effect of weak currents delivered to the brain may be compensated for by the cumulative time-dependent effects of unidirectional polarizing stimulation (Nitsche and Paulus 2001; Paulus 2003). However, the mechanism of AC remains less understood because the direction of current is constantly changing and so the possibility of polarization with a weak current becomes unlikely. This raises a critical issue as to whether stimulation with weak AC can actually induce significant transcranial CNS effects or whether the clinical effects observed with AC stimulation are manifested through an alternative mechanism of action.

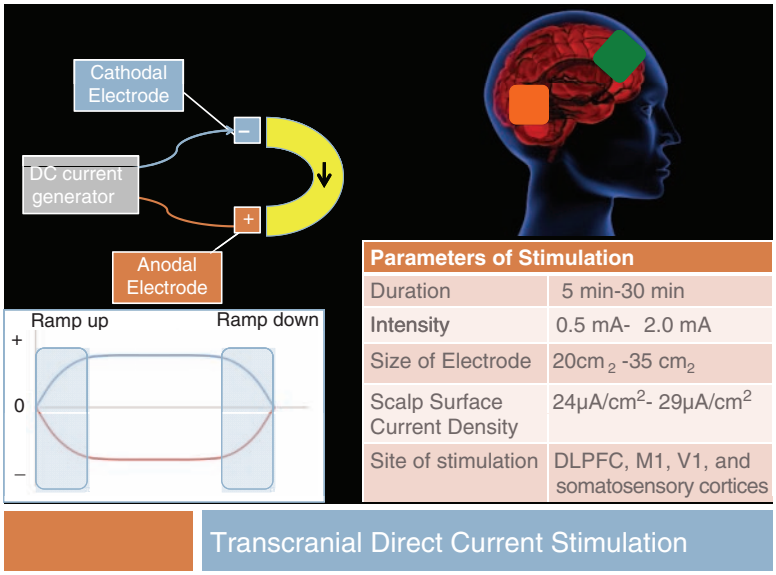

Figure 1. Main characteristics of transcranial direct current stimulation (tDCS). The blue and orange squares represent tDCS electrodes. The graph represents the increase and decrease of electrical current during stimulation.

Noninvasive Brain Stimulation with Low-Intensity Direct Current (tDCS)

Basic Principles

Among the techniques of noninvasive brain stimulation, tDCS stands out as the method of stimulation that is one of the simplest in design. tDCS involves the flow of direct current through two sponge electrodes to the scalp. The device used in tDCS is a battery-powered current generator capable of delivering a constant electrical current flow of up to 2 mA. The device is attached to two electrodes that are soaked in saline (or water) and placed inside sponges (20–35 cm^2); the sponge-electrodes are then held in place by a nonconducting rubber montage affixed around the head (see Fig. 1). Although parameters of stimulation may vary, the current density (i.e., current intensity/electrode size), duration, polarity, and location of stimulation have been shown to have important implications in the neuromodulatory outcome of stimulation (see Table 1).

Neurophysiology of tDCS: Current State of Knowledge and Controversy

tDCS is based on the application of a weak, constant direct current to the scalp via two relatively large anode and cathode electrodes. During tDCS, low-amplitude direct currents penetrate the skull to enter the brain. Although there is substantial shunting of current at the scalp, sufficient current penetrates the brain to modify the transmembrane neuronal potential (Miranda and others 2006; Wagner and others 2007) and, thus, influences the level of excitability and modulates the firing rate of individual neurons. DC currents do not induce action potentials; rather, the current appears to modulate the spontaneous neuronal activity in a polarity-dependent fashion: For example, anodal tDCS applied over the motor cortex increases the excitability of the underlying motor cortex, whereas cathodal tDCS applied over the same area decreases it (Wassermann and Grafman 2005; Nitsche and Paulus 2001). Similarly, anodal tDCS applied over the occipital cortex produces short-lasting increases in visual cortex excitability (Antal and others 2003; Lang and others 2007). Hence, tDCS is believed to deliver its effects by polarizing brain tissue, and although anodal stimulation generally increases excitability and cathodal stimulation generally reduces excitability, the direction of polarization depends strictly on the orientation of axons and dendrites in the induced electrical field (Fig. 2).

Although the polarizing effects of tDCS are generally restricted to the area under the electrodes (Nitsche and others 2003, 2004b), the functional effects appear to perpetuate beyond the immediate site of stimulation. That is, tDCS induces distant effects that go beyond the direct application of current likely via the influence of a stimulated region on other neural networks. For example, anodal tDCS of the premotor cortex increases the excitability of the ipsilateral motor cortex (Boros and others 2008); and, stimulation of the primary motor cortex has inhibitory effects on contralateral motor areas (Vines and others 2008). This supports the notion that tDCS has a functional effect not only on the underlying corticospinal excitability but also on distant neural networks (Nitsche and others 2005). Indeed, fMRI studies reveal that although tDCS has

(Text continues on page 12)

Table 1. Clinical Applications of Transcranial DC Stimulation (tDCS)

Author	Year	No. of Subjects	Focus of Study	Design	Electrode Placement and Polarity	Current Intensity	Session Duration	No. of Sessions	Results
Boggio, Khoury, and others	2008	10	Working memory in Parkinson's disease patients	Randomized sham controlled	Anode over left DLPFC or left temporal cortex (35 cm^2), reference CLSO	2.0 mA	30 min	3 sessions (anodal DLPFC, anodal temporal and sham)	Significant effect of stimulation condition on visual recognition memory task and post hoc analysis showed an improvement after temporal and prefrontal tDCS as compared with sham stimulation.
Mrakic-Sposta S, Marceglia S.	2008	2	Effects on patients with Tourette syndrome	Case report, sham controlled	Cathode over M1 (35 cm^2) contralateral of the most affected side, reference over right deltoid (64 cm^2)	2.0 mA	15 min	10 sessions {5 active, 5 sham)	Cathodal tDCS over the motor areas of the cerebral cortex decreased tics in two patients with Tourette syndrome.
Antal, Lang, and others	2008	26	Cortico-excitability in healthy subjects and migraine patients	Case controlled	Anode or cathode over left S1 (35 cm^2), reference CLSO	1.0 mA	10 min	3 sessions (anodal, cathodal, sham)	5 Hz rTMS after anodal tDCS decreased amplitudes of MEPs in healthy subjects but only had a modest decrease in subjects with migraines. This indicated that short-term homeostatic plasticity is altered in patients with visual auras between attacks.
Boggio, Sultani, and others	2008	13	Decision making behavior	Double blind, sham controlled	Anodal or cathodal over DLPFC (35 cm^2), reference over contralateral DLPFC	2.0 mA	20 min	2 sessions	Anodal left/cathodal right and anodalright/cathodal left significantly decreased alcohol craving compared with sham. And following treatment, craving could not be further increased by alcohol cues.

(*continued*)

Table 1. (continued)

Author	Year	No. of Subjects	Focus of Study	Design	Electrode Placement and Polarity	Current Intensity	Session Duration	No. of Sessions	Results
Fregni, Liguori, and others	2008	24	Decision making behavior	Randomized double blind, sham controlled	Anodal over right or left DLPFC (35 cm^2), reference over contralateral DLPFC (100 cm^2)	2.0 mA	20 min	2 sessions	Smoking craving was significantly increased after exposure to smoking-craving cues. Stimulation of both left and right DLPFC with active, but not sham, tDCS reduced craving significantly when comparing craving at baseline and after stimulation, without and with smoking-craving cues.
Fregni, Orsati, and others	2008	23	Decision making behavior	Double blind, sham controlled	Anode over right or left DLPFC (35 cm^2), reference over the contralateral DLPFC	2.0 mA	20 min	2 sessions	Craving was significantly reduced only after anode right/cathode left. Increased craving after sham and no change after anode left/cathode right. No change in subjects rating of appearance or smell of food after any condition. Calories ingested after active stimulations were significantly lower than sham). Active stimulation showed a decrease of food fixation when sham stimulation had an increase.

(*continued*)

Table 1. (continued)

Author	Year	No. of Subjects	Focus of Study	Design	Electrode Placement and Polarity	Current Intensity	Session Duration	No. of Sessions	Results
Knoch, Nitsche, and others	2008	64	Decision making behavior	Randomized sham controlled	Cathode over right DLPFC (35 cm^2), reference CLSO (100 cm^2)	1.5 mA	<14 min	1 session	Cathodal stimulation reduces significantly the subjects' propensity to punish unfair behavior.
Ferrucci, Mameli, and others	2008	10	Memory in Alzheimer's patients	Sham controlled	Anode and cathode temporoparietal (25 cm^2) simultaneously and references over the right deltoid	1.5 mA	15 min	3 sessions (anodal, cathodal, and sham)	Recognition memory significantly increased after anodal. No change after sham. No changes in any condition for attention.
Boggio, Rigonatti, and others	2008	40	Depression	Double blind, sham controlled	Anode over DLPFC or occipital cortex (35 cm^2), reference CLSO	2.0 mA	20 min	10 sessions	Stimulation of DLPFC cortex showed significantly reduced depression scores compared with occipital and sham tDCS. The beneficial effects of tDCS in the DLPFC group persisted for 1 month after the end of treatment.
Ko, Han, and others	2008	15	Visual neglect improvements in stroke patients	Double blind, sham controlled	Anode over right posterior parietal cortex (25 cm^2), reference CLSO	2.0 mA	20 min	2 sessions	Significant improvement of percent deviation scores of the line bisect test and the number of omissions were for active stimulation only. For the letter-structure cancellation test was not significant after active or sham. Visual neglect improved.

(*continued*)

Table 1. (continued)

Author	Year	No. of Subjects	Focus of Study	Design	Electrode Placement and Polarity	Current Intensity	Session Duration	No. of Sessions	Results
Monti and others	2008	8	Language improvement in stroke patients	Sham controlled	Anode or cathode over Broca's area (35 cm^2), reference over the shoulder, or cathode over occipital cortex, same reference	2.0 mA	10 min	4 sessions (for both experiments, 2 each)	Cathodal stimulation significantly improved the accuracy of the picture-naming task, anodal and sham produced no response.
Boggio, Bermpohl, and others	2007	26	Working memory in depressive patients	Sham controlled	Anode over left DLPFC (35 cm^2) or occipital cortex, reference CLSO	2.0 mA	20 min	10 sessions	Anodal stimulation of the left DLPFC was the only condition that induced a significant improvement in task performance as shown by the increase in the number of correct responses. This effect was specific for figures with positive emotional content.
Boggio, Nunes, and others	2007	9	Motor function in stroke patients	Experiment 1: double blind, sham controlled; experiment 2: open label	(1) Anode over the affected M1 (35 cm^2), reference CLSO; (2) cathode over the unaffected M1 (35 cm^2) and same reference	1.0 mA	20 min	(1) 12 sessions (4 each: anode affected, cathode unaffected and sham) (2) 5 consecutive sessions of cathode unaffected.	Cathodal stimulation of the unaffected hemisphere and anodal of the affected one showed significant motor improvement and there was no significant difference between them ($P = .56$). For experiment 2 a significance in effect of time was found. The effect of 5 consecutive treatments lasted 2 weeks.

(*continued*)

Table 1. (continued)

Author	Year	No. of Subjects	Focus of Study	Design	Electrode Placement and Polarity	Current Intensity	Session Duration	No. of Sessions	Results
Hesse, Werner, and others	2007	10	Motor function in stroke patients	Open label	Anode over affected M1 (35 cm^2), reference CLSO	1.5 mA	7 min	30 sessions	Fugl-Meyer motor scores improved significantly over time. Three patients profited markedly, starting from an initial score of 6, 10, and 11, they gained +22, +39, and +37 FM scores, respectively. The other 7 patients either did not improve or gained no more than 5 FM scores.
Huey, Probasco, and others	2007	10	Effects of tDCS on verbal fluency of patients with dementia	Double blind, sham controlled	Anode over left M1 (25 cm^2), reference CLSO	2.0 mA	20 min	2 sessions (active or sham)	There was no significant improvement in verbal fluency in active stimulation relative to sham. There was a significant effect of atreatment, independent of type, apparently related to practice.
Roizenblatt, Fregni, and others	2007	36	Fibromyalgia	Sham controlled	Anode over left M1 or left DLPFC (35 cm^2), reference CLSO	2.0 mA	20 min	5 sessions	M1 stimulation significantly increased sleep efficiency and decreased arousals. DLPFC stimulation significantly decreased sleep efficiency, increased rapid eye movement (REM) and sleep latency.

(*continued*)

Table 1. (continued)

Author	Year	No. of Subjects	Focus of Study	Design	Electrode Placement and Polarity	Current Intensity	Session Duration	No. of Sessions	Results
Quartarone, Lang, and others	2007	16	Effects of tDCS on patients with amyotrophic lateral sclerosis (ALS)	Pseudo-randomized for anodal and cathodal stimulation	Anode or cathodal over left M1 (35 cm^2), reference CLSO	1.0 mA	7 min	2 sessions (anodal and cathodal)	The healthy volunteers showed a transient polarity-specific change in corticospinal excitability of about ±45%, anodal had facilitatory effects and cathodal had inbitiory effects. For subjects with ALS no change was induced by either cathodal or anodal tDCS.
Fregni, Marcondes, and others	2006	7	Effects of tDCS in chronic tinnitus	Randomized sham controlled	Anode or cathode over left temporal area (35 cm^2), reference over CLSO	1.0 mA	3 min	6 sessions (2 of each: anodal, cathodal, and sham)	Anodal tDCS of LTA resulted in a significant reduction of tinnitus.
Boggio, Ferrucci, and others	2006	18	Working memory in patients with Parkinson's disease	Single blind, sham controlled	Anode over left DLPFC (35 cm^2) or M1, reference CLSO	1 or 2 mA	20 min	3 sessions (sham, M1, or DLPFC)	Reaction time was significantly decreased in anodal stimulation of M1 but not for DLPFC or sham. For DLPFC the number of correct responses was significantly higher than baseline and significantly different than sham stimulation and M1 stimulation. Although M1 stimulation was associated with an increase in the correct responses and a decrease in the errors it was not significantly different when compared with baseline and sham stimulation.

(continued)

Table 1. (continued)

Author	Year	No. of Subjects	Focus of Study	Design	Electrode Placement and Polarity	Current Intensity	Session Duration	No. of Sessions	Results
Fregni, Boggio, and others	2006	10	Depression	Double blind, sham controlled	Anode over left DLPFC (35 cm^2), reference CLSO	1.0 mA	20 min	5 sessions	Patients that received active stimulation had more of a decrease in Hamilton Depression Rating Scale scores and Beck Depression Inventory Score from baseline than those patients who received sham.
Hummel, Voller, and others	2006	11	Motor function in stroke patients	Double blind, sham controlled	Anode over M1 (25 cm^2), reference CLSO	1.0 mA	20 min	2 sessions (active and sham)	Reaction time had a significant reduction with tDCS (and a nonsignificant trend to lengthening with sham).
Fregni, Gimenes, and others	2006	32	Fibromyalgia	Sham controlled	Anode over left M1 or DLPFC (35 cm^2), reference CLSO	2.0 mA	20 min	5 sessions	Anodal stimulation of M1 had significant improvements in pain compared with sham and stimulation of DLPFC. Improvement decreased but still was significant 3 weeks after stimulation. A small positive impact on quality of life was observed among patients who received anodal M1 stimulation. Cognitive changes were the same over the 3 groups.
Fregni, Thome-Souza, and others [1]	2006	19	Epilepsy	Sham controlled	Cathode over the epilogenic focus (35 cm^2) and anode over the epilogenic focus	1.0 mA	20 min	1 session	Active compared with sham was associated with a significant reduction in the number of epileptiform. A trend ($P = .06$) was noted for decreases in seizure frequency after active compared with sham.

(*continued*)

Table 1. (continued)

Author	Year	No. of Subjects	Focus of Study	Design	Electrode Placement and Polarity	Current Intensity	Session Duration	No. of Sessions	Results
Fregni, Boggio, and others [2]	2006	17	Effects of tDCS on patients with Parkinson's disease	Double blind, sham controlled	Anode over left M1 OR DLPFC (35 cm^2), reference CLSO	1 mA	20 min	2 sessions (active and sham)	Anodal stimulation of M1 was associated with a significant improvement of motor function compared with sham stimulation in the Unified Parkinson's Disease Rating Scale and simple reaction time. This effect was not observed for cathodal stimulation of M1 or anodal stimulation of DLPFC.
Hummel and Cohen	2005	1	Motor function in stroke patient	Double blind, sham controlled	Anode over affected M1 (25 cm^2) and reference over contralateral supraorbital area	1.0 mA	20 min	3 sessions (1 sham, 2 active)	Active but not sham applied in a double-blind protocol to motor regions of the affected hemisphere led to improvements in pinch in the paretic hand that outlasted the stimulation period for at least 40 min.

Note: The table is a review of studies that investigate the use of low-intensity (subthreshold) constant DC stimulation with respect to clinical outcomes. Search criteria was published in English within the last 10 years, as indexed on Medline or Scopus using the following key words: transcranial direct current stimulation; tDCS; brain polarization; brain, electrical stimulation; brain, direct current. CLSO = contralateral supraorbital area. DLPFC = dorsolateral prefrontal cortex; LTA = left temporal area; MEPs = motor evoked potentials; rTMS = repetitive transcranial magnetic stimulation. 10–20 EEG system. Reference and active electrodes are of the same size unless otherwise indicated.

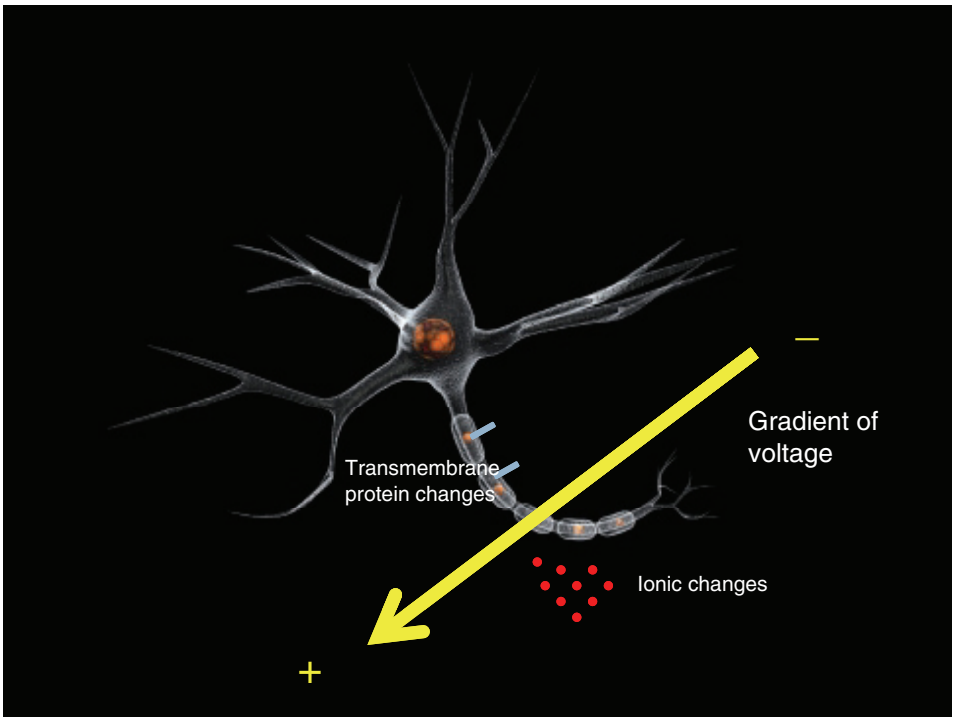

Figure 2. Putative mechanisms of action of transcranial direct current stimulation. The constant gradient of voltage induces ionic shifts and transmembrane protein changes that result in changes to cortical excitability.

the most activating effect on the underlying cortex (Kwon and others 2008), the stimulation provokes sustained and widespread changes in other regions of the brain (Lang and others 2005). EEG studies support these findings showing that stimulation of a certain area (e.g., frontal) induces changes to oscillatory activity that are synchronous throughout the brain (Marshall and others 2004; Ardolino and others 2005). Hence, this evidence suggests that the effects of DC stimulation are site specific but not site limited; that is, stimulation of one area will likely have effects on other areas, most likely via networks of interneuronal circuits (Lefaucheur 2008). This phenomenon is not surprising given the neuroanatomic complexity of the brain, but it raises some interesting questions as to 1) how the effects are transmitted, and 2) whether the observed clinical effects (e.g., pain, depression alleviation) are mediated primarily through the area of the cortex being stimulated or secondarily via activation or inhibition of other cortical and/or subcortical structures (Boggio and others 2008, 2009).

Although it is generally well agreed that DC stimulation can affect cortical excitability, there is controversy as to whether the observed changes are the result of alterations in membrane excitability, synaptic transmission, or other molecular effects. That is, does tDCS render its effect by directly changing the physiology of the neuronal membrane (thereby making a given neural network more or less likely to reach threshold); or, does tDCS function to induce diffuse local changes (such as inducing ionic shifts) throughout the brain that results in a facilitation or inhibition of spontaneous neuronal activity indirectly (Ardolino and others 2005)? On a molecular level, many additional questions remain: Can tDCS indeed change ion conductance at the neuronal membrane, and if so, how? Perhaps tDCS induces the migration and collection of transmembrane proteins by establishing a prolonged constant electric field, but it is also possible that stimulation causes steric and conformational changes in these proteins inducing functional effects (Ardolino and others 2005). Are the long-term effects of tDCS indeed mediated by the activation of N-methyl-d-aspartate (NMDA) channels as previously proposed (Nitsche and others 2004a), and, if so, could we then induce cortical effects that persist for weeks and months with repeated stimulation? Further mechanistic studies are needed to increase our understanding of the neurophysiological basis of tDCS.

Noninvasive Brain Stimulation with Low-Intensity Pulsed and Alternating Current

Basic Principles

Given the remarkable effects of transcranial stimulation with low-intensity constant direct current (tDCS), the use of low-intensity nonconstant current may also prove to be an attractive option. Nonconstant current

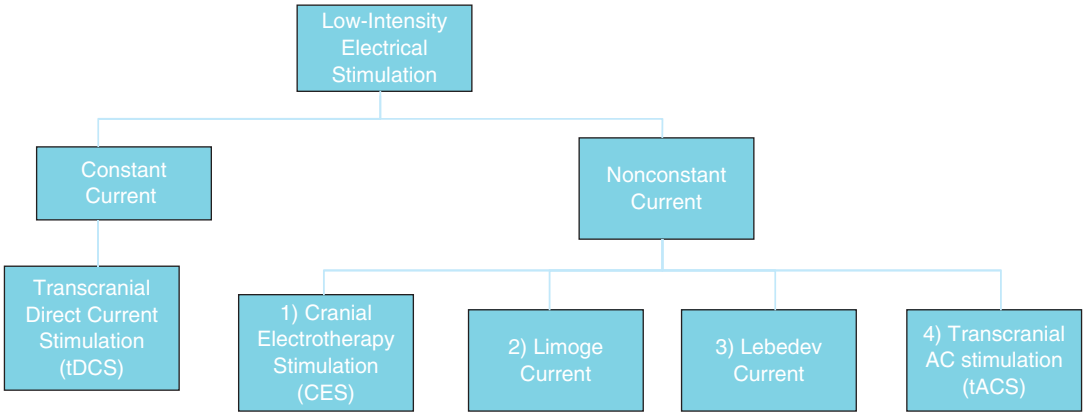

Figure 3. Classification scheme for noninvasive brain stimulation with low-intensity electrical currents.

can be delivered with pulses of unidirectional current in rectangular waves (intensity rapidly increased to a certain amplitude, held at the peak without change, and then interrupted by zero current) or sinusoidal waves (intensity constantly varies as a function of time), or modifications thereof. Moreover, nonconstant current can be delivered with unidirectional current (in which pulses share the same polarity) or AC (in which the pulses of current alternate with opposite amplitude). Indeed, stimulation with nonconstant current is the preferred parameter of neural stimulation in other domains of nervous system stimulation: It is the method used in deep brain stimulation, motor cortex stimulation, spinal cord stimulation, transcutaneous nerve stimulation, vagal nerve stimulation, TMS, and ECT. Of the variety of methods of low-intensity nonconstant current that have been explored, here we will discuss the few specific methods of AC stimulation that have been purported to have clinical effects: cranial electrotherapy stimulation (CES), transcutaneous electrical stimulation (TCES) with Limoge's current, transcranial electrical stimulation (TES) with Lebedev's current, and transcranial alternating current stimulation (tACS; Fig. 3). Table 2 includes a summary of the most recent studies with AC as published in the past 10 years.

Methods of AC Stimulation

With respect to the application of low-intensity AC, there are several methods of AC stimulation that have been tried in the past and are being explored at the present. Because these methods are significantly different regarding parameters of stimulation, we will discuss them separately, as below.

CES is a form of AC stimulation that involves the application of current to infra- or supra-auricular structures (e.g., the ear lobes, mastoid processes, zygomatic arches, or maxillo-occipital junction; Fig. 4). CES is a nonstandardized and often indistinct method of delivering cranial AC stimulation; indeed many studies cite the method of stimulation simply as "cranial electrotherapy stimulation" without identifying the specific site or other parameters of stimulation (e.g., duration, current density, intensity, electrode size) calling into question existing reviews of this method. Even so, CES has been suggested to be effective in the treatment of anxiety, depression, stress, and insomnia (Kirsch and Smith 2004; Smith 2007), and the following parameters of stimulation have been reported: frequency (0.5 Hz to 167 kHz), intensity (100 μA to 4 mA), and duration of stimulation (5 min to 6 consecutive days). Of note, although AC is applied to the head in these circumstances, the current may or may not be delivered directly to the underlying brain structures and thus the term "transcranial" may not apply; we therefore select the term "cranial" AC stimulation to include applications of low-intensity AC in this context. Indeed, CES might more accurately be considered a form of peripheral nerve stimulation.

The term TCES ("transcutaneous electrical stimulation") is mostly associated with a very specific protocol of AC stimulation, called Limoge's current, in which current is applied by utilizing three cutaneous electrodes: one negative electrode (cathode) that is placed between the eyebrows and two positive electrodes (anode) that are placed in the retromastoid region. Stimulation carries a voltage (peak to peak) of 30 to 35 V and an average intensity of 2 mA. In the application of "Limoge's current," wave trains are composed of successive impulse waves of a particular shape: one positive impulse (S1) of high intensity and short duration, followed by a negative impulse (S2) of weak intensity and long duration (see Fig. 5). The impulse waves are delivered at 166 kHz bursts (4 mS "ON" + 8 mS "OFF"). This form of transcranial stimulation has been suggested to decrease the amount of narcotics required to maintain anesthesia during surgical procedures (Limoge and others 1999).

Table 2. Clinical Applications of Cranial Alternating Current (AC) Stimulation

Author	Year	n	Focus of Study	Design	Electrode Placement	Current Intensity	Frequency	Session Duration	Treatment Duration	Results
Kanai and others	2008	8	Visual phosphene induction in healthy subjects	Randomized, single blind, condition control	Occipital cortex (12 cm^2) and vertex (54 cm^2)	250 μA to 1500 μA	5–30 Hz	60–90 min	5–10 sec per trial, each separated by 30 sec	Induction of phosphenes: 20 Hz most effective in light, 10 Hz in dark.
Antal and others	2008	36	Cortical excitability in healthy subjects	Randomized double blind sham control	Left M1 (size of 16 cm^2) and supraorbital (50 cm^2)	400 μA	1, 10, 30 and 45 Hz	5–10 min	— —	No significant interactions, except for improvement in implicit motor learning task with 10 Hz frequency.
Bystritsky and others	2008	12	Effects in patients with generalized anxiety disorder diagnosis	Open label	Earlobe	Below perception threshold (all below 300 μA)	0.5 Hz	60 min/day	6 weeks	50% of the patients met the criteria response for improvement in anxiety.
Tan and others	2006	40	Pain in spinal cord injury patients	Randomized double blind placebo control and an open label phase	Earlobe	100 μA	—	60 min/day	21 days	No significant difference between groups regarding pre- and posttreatment means, but significant difference in the average pain change between groups in the daily ratings.
Scherder and others [*AQ]	2006	20	Rest activity rhythm and cortisol levels in AD patients	Randomized double blind sham-control	Earlobe	10–600 μA	100 Hz	30 min/day	5 days/week for 6 weeks	No interaction between treatment cortisol levels or rest-activity rhythm.
Scherder and others	2006	21	Cognition, mood and behavior in AD patients	Randomized double blind sham control	Earlobe	10–600 μA	100 Hz	30 min/day	5 days/week for 6 weeks	No significant difference in any of the outcomes.
Childs and others	2005	9	Effects on patients with aggressive behavior	Open label	Earlobe	Below perception threshold (max 600 μA)	0.5–100 Hz	60 min/day or 45 min × 2/ day	Daily for 3 months	59% decrease in aggressive episodes.
Markina	2004	90	Effects on adaptative	Comparison of measurements	—	—	—	20 min/day	10 days	Trancranial electrostimulation

(continued)

Table 2. (continued)

Author	Year	n	Focus of Study	Design	Electrode Placement	Current Intensity	Frequency	Session Duration	Treatment Duration	Results
			response of healthy medical students	before and after treatment. Only 13 controls						influences the adaptative state and its effects depend of individual features
Capel and others	2003	30	Pain in subjects with spinal cord injury	Randomized double blind placebo control	Earlobe	Pulses with positive amplitude of 12 μA	50 Hz	53 min × 2/day	4 days	Significant decrease in pain scores as compared with sham.
Gabis and others	2003	20	Pain in β-endorphine subjects with chronic back pain	Randomized double blind placebo control	Mastoids	4 mA (sham was 0.75 mA)	77 Hz	30 min/day	8 days	No significant difference between treatment in pain scores, but significant difference in β-endorphin levels.
Scherder and others	2003	16	Rest activity rhythm and cortisol levels in AD patients	Randomized double blind sham control	Earlobe	10–600 μA	0.5 Hz	30 min/day	5 days/week for 6 weeks	No interaction between treatment cortisol levels or rest-activity rhythm.
Scherder and others	2002	18	Cognition and behavior in AD	Randomized double blind sham control	Earlobe	10–600 μA	0.5 Hz	30 min/day	5 days/week for 6 weeks	No significant interaction in any of the outcomes.
Lichtbroun and others	2001	60	Objective and subjective measures in fibromyalgia patients	Randomized double blind sham control and open label phase	Earlobe	100 μA	0.5 Hz	60 min/day	3 weeks	Significant improvement of the treated group as compared with sham
Schroeder and others	2001	20	EEG alterations in HS	Randomized double blind sham control	Earlobe	10–100 μA	0.5 and 100 Hz	20 min/session	3 sessions (sham, 0.5–100 Hz)	Relative to sham control, 0.5, and 100 Hz caused the alpha band mean frequency to shift downward. Additionally, 100 Hz also caused a decrease of the alpha band median frequency and beta band power fraction.

(continued)

Table 2. (continued)

Author	Year	n	Focus of Study	Design	Electrode Placement	Current Intensity	Frequency	Session Duration	Treatment Duration	Results
Southworth and others	1999	52	Memory and attention in HS	Randomized double-blind placebo control	Temples	—	15 kHZ	20 min	1 session	Attention improved significantly in comparison with sham stimulation.

Note: The table is a review of studies that investigate the use of low-intensity (subthreshold) AC stimulation with respect to clinical outcomes. Search criteria—published in English within the last 10 years, as indexed on Medline or Scopus using the following key words: transcranial alternating current stimulation; cranial electrotherapy stimulation; transcutaneous electrical stimulation; brain, electrical stimulation; brain, alternating current. AD = Alzheimer's disease; EEG = electroencephalogram; HS = healthy subjects.

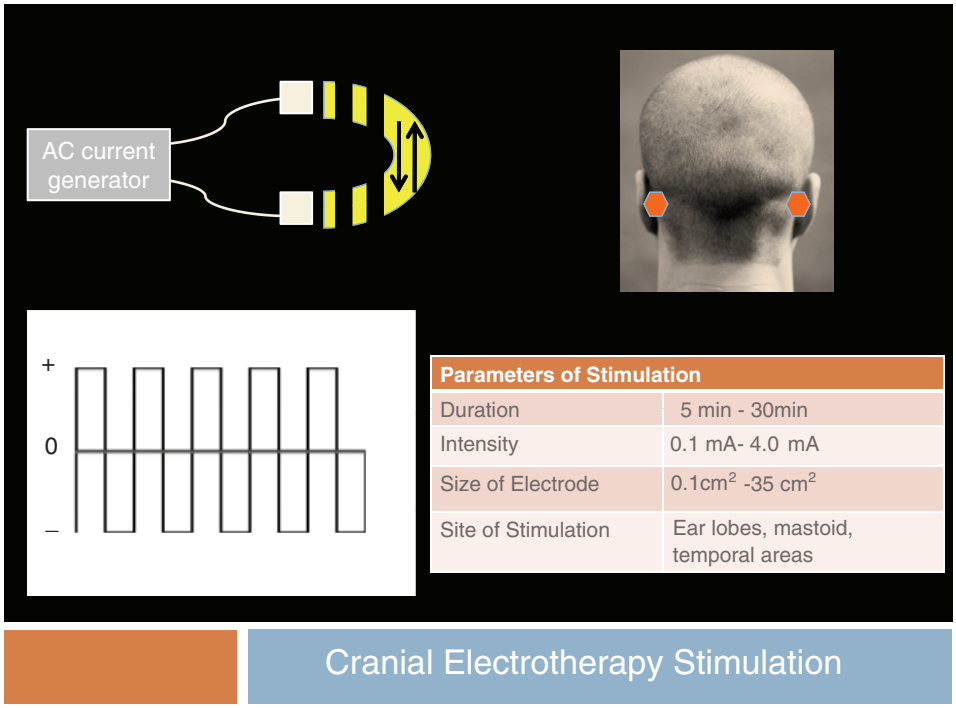

Figure 4. Main characteristics of cranial electrotherapy stimulation (CES). The orange polygons represent AC electrodes (usually placed on mastoid process or ear lobes). The graph represents electrical current polarity changes over time.

Lebedev describes a method of transcranial electrical stimulation that is based on electrode positions similar to Limoge, but instead includes a combination of AC and DC current at a 2:1 ratio. A pulse train of AC is delivered at the optimal frequency of 77.5 Hz for 3.5 to 4.0 msec separated from the next train by 8 msec. Two trains of AC stimulation are followed by a 4-msec stream of constant DC. Lebedev's current has been suggested to be effective for the treatment of stress and affective disturbances of human psychophysiological status (Lebedev and others 2002).

Recently, Antal and others have used alternating currents with a similar montage as in tDCS and appropriately referred to it as transcranial alternating current stimulation (tACS; Antal and others 2008). In their experiments, electrical stimulation was delivered with the same type of device used to deliver tDCS, that is, a battery-driven constant-current stimulator (NeuroConn GmbH, Ilmenau, Germany) with conductive-rubber electrodes, enclosed in two saline-soaked sponges affixed on the scalp with elastic bands. The stimulation electrode was placed over the left motor cortex, and the reference electrode was placed over the contralateral orbit. tACS was applied for 2 and 5 min with a current intensity of 250 to 400 μA using a 16-cm^2 electrode (current density = 25 μA/cm^2) at the following frequencies: 1, 10, 15, 30, and 45 Hz (Antal and others 2008). Antal and colleagues were unable to show robust effects on cortical excitability, but they did show that 5-min tACS at 10 Hz applied at the motor cortex could improve implicit motor learning.

Similarly, Kanai and colleagues have more recently applied tACS to the visual cortex at 5 to 30 Hz and 250 μA to 1000 μA and induced visual phosphenes. This group demonstrated that stimulation over the occipital cortex could induce perception of continuously flickering light; these effects were most prominent at 1 mA and, interestingly, the AC stimulation had differential effects in a light versus dark room. tACS was most effective in inducing phosphenes at 20 Hz (beta frequency range) when applied in an illuminated room and 10 Hz (alpha frequency range) in darkness. In this way, Kanai and colleagues showed that tACS could indeed be used to interact with ongoing oscillatory activity (Kanai and others 2008).

Neurophysiology of Cranial AC Stimulation: Current State of Knowledge and Controversy

As with the technique of tDCS, one of the main conceptual issues for the understanding of cranial AC stimulation is whether the applied electric current can overcome the resistance of skin, soft tissues, and the skull to penetrate the brain. Although part of the current

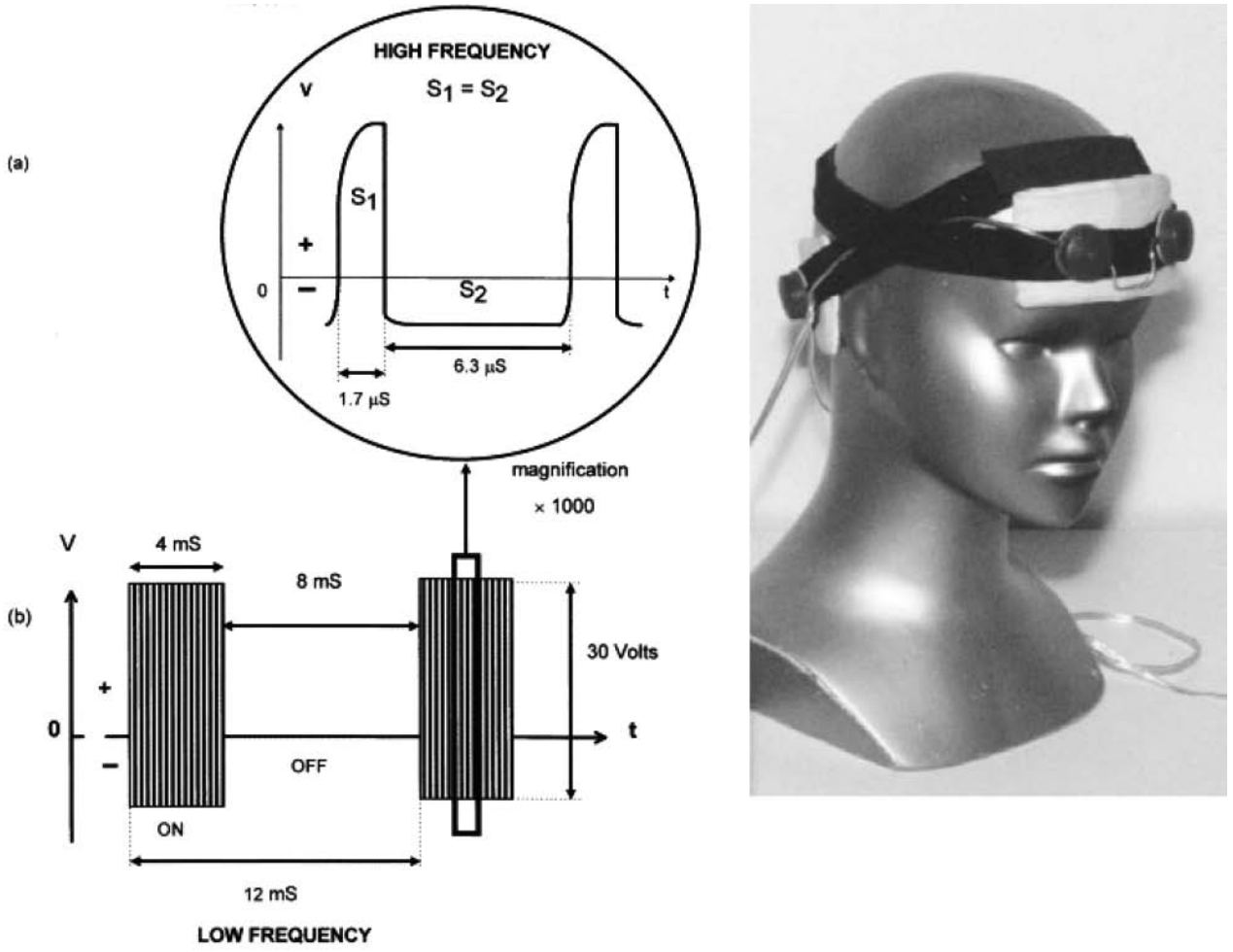

Figure 5. Main characteristics of Limoge and Lebedev current stimulation. a, Wave trains are composed of successive impulse waves of a particular shape: one positive impulse (S1) of high intensity and short duration, followed by a negative impulse (S2) of weak intensity and long duration. The high-frequency current is regularly interrupted by a low-frequency cycle (4 mS "ON" + 8 mS "OFF"). b, Headset positioning of electrodes in Limoge and Lebedev current stimulation (adapted with permission from Limoge and others 1999).

is usually shunted through skin, a significant amount of current can be injected into the brain if the electrodes are positioned adequately. An electrophysiologic mathematical model of cranial AC stimulation shows that, with a 1-mA stimulus applied via standard electrodes behind the ear, the maximum injected current density is about 5 µA/cm^2 at a radius of 13.30 mm (thalamic area) of the model (Ferdjallah and others 1996). This suggests that, indeed, although the vast majority of the applied current is diffused across the scalp, a small fraction of the stimulating current can penetrate brain tissue and even reach deep brain structures, including the thalamic nuclei (Ferdjallah and others 1996). In addition, when CES was applied to the head of primates, it was found that 42% of the current applied externally actually penetrated throughout the entire brain, canalizing especially along the limbic system (Jarzembski 1970; Kirsch and Smith 2004). In addition, the recent modeling studies for DC stimulation (given the limitations inherent to the method of modeling studies and also given that electrode positions and sizes are different) can also be used to show that electric currents can reach the brain tissue (Miranda and others 2006; Wagner and others 2007). Therefore, low-intensity cranial AC stimulation can indeed penetrate the scalp to deliver AC to brain tissue.

Although it is conceivable that electrical stimulation with small currents can reach the cortex, the subsequent critical issue is whether a subthreshold, very small current can induce biological changes. It is known that suprathreshold AC stimulation does induce changes in neuronal activity and can, for instance, induce the phenomenon of LTP and LTD (Habib and Dringenberg 2009). However, for small currents, this is not clear. Although DC currents also use small currents, the effects of this technique are based on cumulative effects affecting

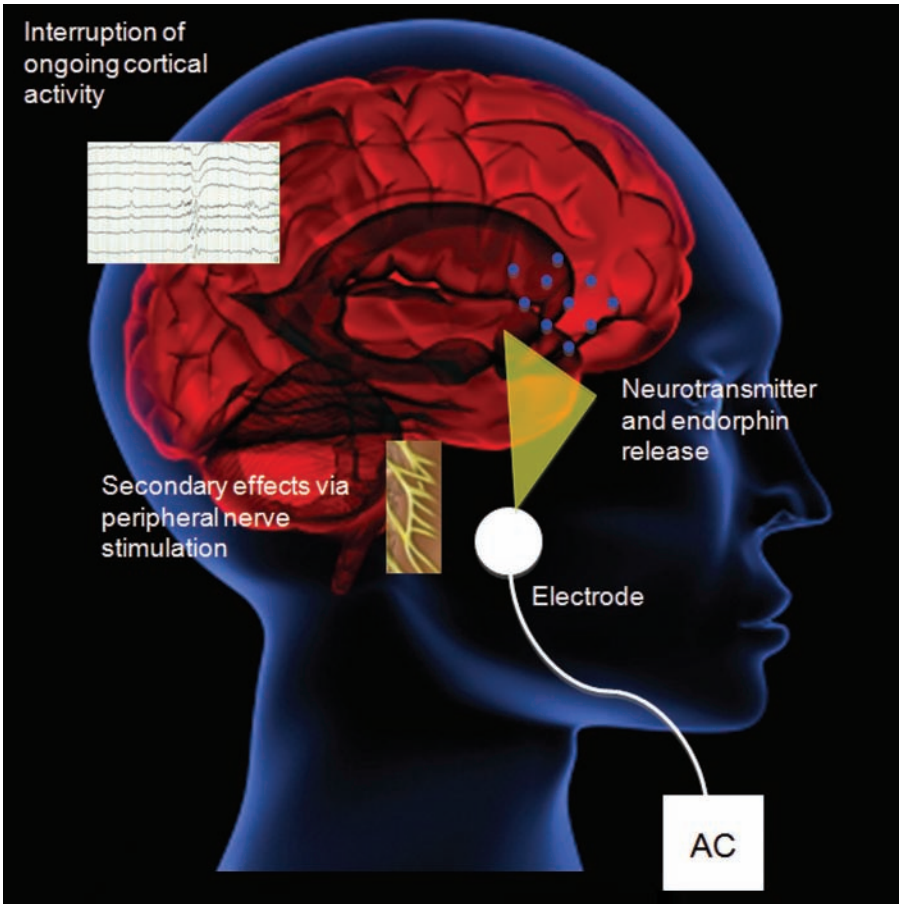

Figure 6. Putative mechanisms of action of alternating current (AC) stimulation. Some potential mechanisms of AC stimulation are 1) release or neurotransmitters, 2) interruption of ongoing cortical activity, and 3) secondary effects via peripheral nerve stimulation.

the area under the constant gradient of voltage. We therefore review evidence regarding the biological effects of low-intensity cranial AC according to different methods to investigate brain activity (Fig. 6).

Cortical excitability changes as indexed by single pulse TMS. Antal and others (2008) recently explored whether transcranial AC stimulation applied for 5 min at the motor cortex could significantly modulate cortical excitability. Using a current density of 25 μA/cm^2 at 1, 10, 15, 30, and 45 Hz, this group showed that AC stimulation did not result in significant changes to cortical excitability as measured by TMS evoked motor potentials. Although the results of this study may be restricted to the parameters of stimulation investigated, these findings suggest that unlike tDCS and repetitive TMS, the effects of cranial AC stimulation might not be due to a modulation of local cortical excitability (Antal and others 2008).

Electrical activity changes as indexed by EEG. Most studies confirm significant EEG changes during cranial stimulation with low-intensity AC. An EEG study by McKenzie and others (1971) found that one 30-min session of cranial AC stimulation each day for five days yielded increases in the amplitudes of slower EEG frequencies with increased alpha wave (8–12 Hz) activity (McKenzie and others 1971). More recently, Schroeder and Barr (2001) measured EEG activity during sham and AC stimulation and showed increases in low alpha (8–12 Hz) and high theta (3–8 Hz) activity; these findings were significant even when controlled for AC stimulation induced electrical noise. Even so, EEG recordings before and after transcranial AC stimulation of the motor cortex (400 μA; 5 min; 1, 10, and 45 Hz) failed to show a difference in effect before and after stimulation (Antal and others 2008). Therefore, cranial AC stimulation may alter EEG patterns toward more relaxed states during stimulation, but current evidence suggests that it is unlikely to leave a lasting effect on EEG patterns at the completion of stimulation; and, in addition, these effects may be highly dependent on the specific parameters of stimulation investigated.

Biochemical changes—neurotransmitter and endorphin release. Several studies suggest that AC stimulation may be associated with changes in neurotransmitters and endorphin release. In this context, subthreshold

stimulation induced by AC stimulation would indeed cause significant changes in the nervous system electrical activity. Briones and others demonstrated changes in urinary free catecholamines and 17-ketosteroids after stimulation (Briones and Rosenthal 1973); Pozos and others showed that cranial AC stimulation can be as effective as L-dopa (and both better than no treatment) in accelerating the re-equilibirum of the adrenergic-cholinergic balance in the canine brain after administration of reserpine and physiostigmine (Kirsch and Smith 2004). In another study, presynaptic membranes were analyzed before, during, and following cranial AC stimulation of four squirrel monkeys (Kirsch and Smith 2004). The results showed that the number of vesicles declined when stimulation first began, increased after five minutes of stimulation, and returned toward normal shortly after cessation of stimulation. Some authors collectively use this evidence to speculate that some forms of cranial AC stimulation may directly engage serotonin-releasing raphe nuclei, norepinephrine-releasing locus ceruleus, or the cholinergic laterodorsal tegmental and pediculo-pontine nuclei of the brainstem (Kirsch 2002; Giordano 2006); however, we believe that there is not enough evidence to fully support this notion. Interestingly, Limoge and others demonstrate significant changes to blood plasma and CSF levels of endorphins during cranial AC stimulation, and they report that naloxone antagonized the analgesic effects of stimulation (Limoge and others 1999). Although it is not possible to determine whether neurotransmitter and endorphin hormone changes are directly or indirectly related to AC stimulation of the brain, these studies do suggest that there is at least an association between cranial AC stimulation and neurotransmitters release. Even so, current evidence is inadequate to suggest that these effects are of central origin, because neurotransmitter changes may also be induced by nonspecific peripheral effects.

Interruption of on-going cortical activity (i.e., introducing cortical noise). It is possible that stimulation of the brain with a constantly varying electrical force could induce noise that would interfere with ongoing oscillations in the brain. Indeed, evidence from in vitro studies of rat brain slices shows that high frequency (50–200 Hz) sinusoidal stimulation with AC suppresses activity in both cell bodies and axons (Jensen and Durand 2007), demonstrating a disruptive effect of stimulation on basic neural processing. In addition, low-frequency (0.9 Hz) alternating electric cortical stimulation applied directly to epileptic foci has been shown to decrease interictal and ictal activity in human epilepsy, further supporting the notion that nonconstant stimulation can interrupt neural activity (Yamamoto and others 2006). Similarly, pulsed stimulation applied over the lateral prefrontal cortex during a working memory task (15 sec on/15 sec off) was shown to impair central nervous processing related to response selection and preparation in working memory (Marshall and others 2005), further suggesting that it is possible for pulsed current to have an interrupting effect on nervous system function.

Secondary effects via peripheral nerve stimulation. Finally, the effects of cranial AC stimulation might be due to a primary effect on the peripheral nervous system that is secondarily transmitted to the CNS. Studies of transcranial electrostimulation in rats suggest that peripheral craniospinal sensory nerves play a critical role in mediating the anti-nociceptive action of pulsed electrical stimulation (Nekhendzy and others 2006). In this study, antinociceptive effects of stimulation were blocked with the application of local anesthetic injected under the stimulation electrodes. This suggests that the effects of low-intensity cranial AC stimulation may be mediated through the activation of brainstem centers (i.e., trigeminal subnucleus caudalis and wide-dynamic range neurons of the solitary nucleus) via stimulation of peripheral cranial (CN V1–V3 and VII) and craniospinal nerves (C1–C3). Similar results have been reported in studies of scalp stimulation with rhesus monkeys (Kano and others 1976). Therefore, cranial AC stimulation may function via a mechanism similar to TENS units (transcutaneous electrical nerve stimulation; devices used to help control pain via application of electric current to peripheral nerves).

Noninvasive Cranial Stimulation with Low-Intensity Electrical Currents—What Have We Learned So Far?

The field of cranial electrical stimulation is developing rapidly—especially with the new attention focused on the techniques of neuromodulation for the treatment of neuropsychiatric diseases. Although these techniques have been used for many years, the recent increased interest in these methods have provided new insight that were discussed in this review and we summarize them in seven points: 1) recent studies using new techniques to index cortical activity (such as single-pulse TMS) have shown that parameters of stimulation such as duration of stimulation and electrode montage play a critical role for the effects of these methods of brain stimulation; 2) modeling and animal studies have shown that electrical currents can be induced in the brain using cranial methods of brain stimulation, and preliminary use in humans has shown that these techniques are associated with relatively minor adverse effects; 3) techniques of cranial electrical stimulation induce changes in central nervous system activation (as indexed by changes in EEG, neurotransmitter

release, and cortical excitability); 4) it is not clear whether the effects of cranial electrical stimulation are specifically due to currents that are induced in the brain as opposed to the modification of peripheral nerve activity that are secondarily transmitted to the brain; 5) DC stimulation has been shown to polarize brain tissue with long-lasting, site-specific effects on CNS activity; and 6) the mechanism of AC stimulation has been understudied; and 7). although limitations certainly exist for the use of cranial electrical stimulation, some studies show encouraging results that at the very least suggest that further research in this area is needed.

Summary

Noninvasive stimulation of the brain with low-intensity direct and alternating currents have both been associated with significant clinical effects, but results from various groups are often mixed, and many studies are limited by small sample sizes and experimental design. tDCS has been shown to induce long-lasting shifts in the polarity of the underlying cortex resulting in large changes in cortical excitability. In tDCS, the effect of weak currents delivered to the brain may be compensated for by the cumulative time-dependent effects of unidirectional polarizing stimulation (Nitsche and Paulus 2001; Paulus 2003). Hence, tDCS is believed to deliver its effects by polarizing brain tissue, and although anodal stimulation generally increases excitability and cathodal stimulation generally reduces excitability, the direction of polarization depends strictly on the orientation of axons and dendrites in the induced electrical field. tDCS can induce effects beyond the immediate site of stimulation because the effects of DC stimulation are perpetuated throughout the brain via networks of interneuronal circuits. On the other hand, recent evidence suggests that the effects of cranial AC stimulation may not be due to a modulation of local cortical excitability (Antal and others 2008): Because the direction of current is constantly changing with AC stimulation, the possibility of polarization with a weak current becomes unlikely. Even so, cranial AC stimulation may function by 1) inducing synchronous changes in brain activity (as indexed by EEG); 2) altering the release of synaptic vesicles (i.e., stimulating neurotransmitter or endorphin release); 3) interrupting ongoing cortical activity by introducing cortical noise; or 4) via secondary effects of peripheral craniospinal nerve stimulation. Despite the differing proposed mechanisms of action, preliminary small studies suggest that both techniques show promising results and should be explored further. Future studies should target an understanding of the mechanisms or neurophysiology of these methods of neuromodulation in addition to well-controlled and well-designed clinical studies also addressing the mechanisms of action.

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