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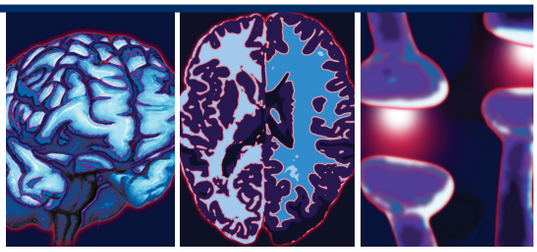

Transcranial direct current stimulation: neurophysiology and clinical applications

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Practice points

- Transcranial direct current stimulation (tDCS) induces an electrical field between an anode and cathode in the brain, thereby shifting the resting membrane potential of pre- and post-synaptic neurons without directly evoking neuronal firing (e.g., as in electroconvulsive stimulation).
- tDCS alters long-term potentiation and associated brain functions, such as learning and memory, largely mediated by the neurotransmitter glutamate via the *N*-methyl-D-aspartate receptor.
- Excitatory and inhibitory effects are dependent on current polarity and limited to the stimulated cortical area.
- tDCS is well tolerated and only induces very minor adverse side effects, such as mild skin irritations at the stimulation site.
- tDCS applied to the prefrontal cortex affects executive function and the strongest evidence in tDCS research suggests clinical improvements in patients with depression.
- Altering excitability with tDCS (e.g., as measured by motor-evoked potentials) has been applied as an experimental intervention for Parkinson's disease and cerebral stroke patients with some promising effects.
- Promising effects have also been reported from tDCS interventions for chronic pain caused by spinal cord injury, fibromyalgia or migraine.
- While reports on tDCS interventions have substantially risen over the past 10 years, the majority of studies are limited by small sample sizes or poor study design (i.e., lacking randomization or long-term outcome measures).

SUMMARY Transcranial direct current stimulation (tDCS) is considered a noninvasive and well-tolerated brain stimulation technique with very few adverse side effects. Importantly, tDCS does not directly evoke neuronal firing (as induced by electroconvulsive or transcranial magnetic stimulation), but instead alters the resting membrane potential of pre- and

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post-synaptic neurons dependent on the current polarity in the stimulated brain region. Animal studies suggest changes in long-term potentiation occur via glutamate release in response to anodal tDCS, thereby affecting learning and memory. In clinical studies, a current not exceeding 2 mA/cm^2 is applied for 20–30 min via sponge electrodes placed above the target brain region. To date, a number of clinical studies have reported some promising effects when treating patients with depression, chronic pain, schizophrenia, dementia, Parkinson's disease and cerebral stroke. However, appropriately designed randomized controlled clinical trials are scarce and reported intervention effect sizes only vary from small to moderate, with little evidence for sustained long-term effects.

Transcranial brain stimulation

Electrical brain stimulation is a well-established form of treatment for various psychiatric and neurological conditions. It ranges from electroconvulsive therapy to treat severe forms of depression and schizophrenia, to deep brain stimulation to treat conditions such as Parkinson's disease via intracranially implanted electrodes. While these forms of interventions are highly effective, their applications are limited by potentially severe adverse side effects, which are associated with general anesthesia and neurosurgery. Hence, the search for less invasive and less costly methods of brain stimulation has been under investigation for a while and has produced two potential alternatives to date: transcranial magnetic stimulation and transcranial direct current stimulation (tDCS). Both methods can be applied without invasive procedures as they use either brief high-intensity magnetic pulses or a low-intensity current to stimulate circumscribed brain tissue via extracranial devices. Both methods are well tolerated and do not have severe adverse side effects. However, are they actually an effective method of intervention? This question will be reviewed here for tDCS in clinical studies that have recently gained significant scientific attention.

How does tDCS work?

Neurophysiologic mechanisms have been predominantly investigated using animal research and *in vivo* brain slice recordings, while human studies have largely relied on measures of tDCS-induced metabolic changes in brain tissue measured via magnetic resonance spectroscopy and associated changes in electroencephalographic recordings of brain activity.

The findings essentially point to a neural mechanism of tDCS, whereby the anodal current shifts the resting membrane potential of pre- and post-synaptic neurons toward depolarization, thus resulting in hyperexcitability, while the cathodal current shifts membrane potentials in the opposite direction, resulting in neuronal hypoexcitability [1]. This notion is supported by the respective changes in response to anodal and cathodal stimulation when altering membrane thresholds by introducing agents acting on calcium or sodium ion channels [1,2].

Recent studies have investigated underlying physiological mechanisms of tDCS more directly by using epidural recordings of corticospinal activity in response to transcranial magnetic stimulation before and after tDCS [3,4]. Di Lazzaro *et al.* suggest that tDCS works via increased excitability of corticospinal axons, thereby increasing activity levels in cortico–cortical projections onto pyramidal tract neurons, thus resulting in motor cortex excitability modulation with both synaptic (I wave) and nonsynaptic (D wave) mechanisms [3].

Hence, tDCS is considered a 'noninvasive' brain stimulation technique that influences neuronal excitability by altering membrane thresholds but without evoking neural firing directly as occurs with electroconvulsive stimulation, for example. Directly evoking neural firing is also highly unlikely given the low intensities of the currents employed, usually not more than 2 mA/cm^2 [5], which is significantly below action potential thresholds [6].

Excitability changes can also be recorded as motor-evoked potentials from peripheral muscles. Consistent with the notion of tDCS-induced response threshold modulation, anodal stimulation of the motor cortex increases and cathodal stimulation decreases response magnitude [7]. This also affects motor skill learning, as reported in the largest study conducted to date investigating tDCS effects on motor skill learning in 93 healthy right-handed subjects in response to left, right and sham stimulation of the primary motor cortex [8]. The authors found improved motor skill learning following three sessions of anodal stimulation of the left (dominant) motor

cortex versus sham stimulation, with intermediate effects for anodal stimulation over the right motor cortex.

These findings exemplify tDCS effects on learning and memory, and point to changes in synaptic functions (i.e., long-term potentiation or depression) in response to anodal (more responsive) or cathodal (less responsive) neural networks [9–12]. A crucial neurotransmitter for long-term potentiation and learning is glutamate acting via the *N*-methyl-D-aspartate receptor [13]. Magnetic resonance spectroscopy studies have confirmed an increase in glutamine/glutamate signal in brain tissue with anodal stimulation [14], which would explain some of the beneficial effects on learning as well as its therapeutic potential for neuropsychiatric conditions that are characterized by 'hypofunctional' brain regions (e.g., due to reduced cortical metabolism and/or abnormal neurotransmission as in the frontal and prefrontal cortex of patients suffering from depression [15]).

Dockery *et al.* examined the effects of tDCS of the left dorsolateral prefrontal cortex on planning function by using the Tower of London task to evaluate performance during and after anodal, cathodal (15 min of 1 mA) and sham tDCS in 24 healthy volunteers [16]. Better performance was reported for cathodal tDCS applied during acquisition and early consolidation when preceding anodal tDCS, but not in the later training session. By contrast, anodal tDCS enhanced performance when applied in the later sessions following cathodal tDCS. These findings suggest that both anodal and cathodal tDCS can improve executive performance but with training phase-specific results. The authors concluded that their findings were due to excitability-decreasing cathodal tDCS producing noise reduction of neuronal activity in the early training phase, whereas a further adaptive configuration of specific neuronal connections is supported by excitability-enhancing anodal tDCS in the later training phase, thus enhancing the efficacy of active connections. This improvement in function was sustained at 6 and 12 months after training.

Iyer *et al.* studied the effects of tDCS of the left prefrontal cortex in 30 healthy participants using different intensities of tDCS [17]. The authors reported no effect on emotion, psychomotor speed and global measures of processing compared with sham stimulation. Improvement, however, of verbal fluency performance was detected with anodal tDCS (20 min of 2 mA) whereas cathodal tDCS had the opposite effect [17].

The findings of this brief review of tDCS studies in healthy subjects are consistent with preclinical data, which suggests a modulatory and polarity-dependent effect on the neural responsiveness in stimulated brain tissue. However, hemispheric specialization of cognitive functions, as well as the interplay of the left and right brain, has to be taken into account when applying tDCS. Chi and Snyder, for example, investigated the effect of tDCS polarity in 60 healthy participants by stimulating the anterior temporal lobes while participants conducted a demanding insight problem-solving task that could only be solved by 20% of the study participants when receiving sham stimulation [18]. The authors reported that only the combination of left-hemispheric cathodal tDCS and right-hemispheric anodal tDCS improved cognitive performance, whereas switching polarities did not change performance [18].

Adverse side effects of tDCS

tDCS is a safe procedure with many studies not reporting adverse side effects at all; although this could be a result of 'absence of evidence rather than evidence of absence' [19]. When reviewing 102 participants who underwent a total of 567 tDCS sessions, mild tingling sensations at the stimulation site (70.6%), moderate fatigue (35.3%) and itching (30.4%) were reported as the most common side effects, followed by headaches (11.8%), nausea (2.9%) and insomnia (<1%) as less common adverse events [20]. These rates do not appear to be different to sham stimulation according to a review of reports published between 1998 and 2010 [19]. However, the authors of this review also noted that adverse side-effect profiles may differ dependent on electrode placements and type of neuropsychiatric condition, but the published data do not support more detailed analyses in this respect [19].

Clinical applications of tDCS

A PubMed search in December 2012 identified 804 publications when using the search phrase 'transcranial direct current stimulation' **(Figure 1)**. However, the methods and study designs vary considerably, and do not support a comprehensive meta-analytical approach other than perhaps for intervention in depression [21]. Hence, this qualitative review will focus on clinical studies

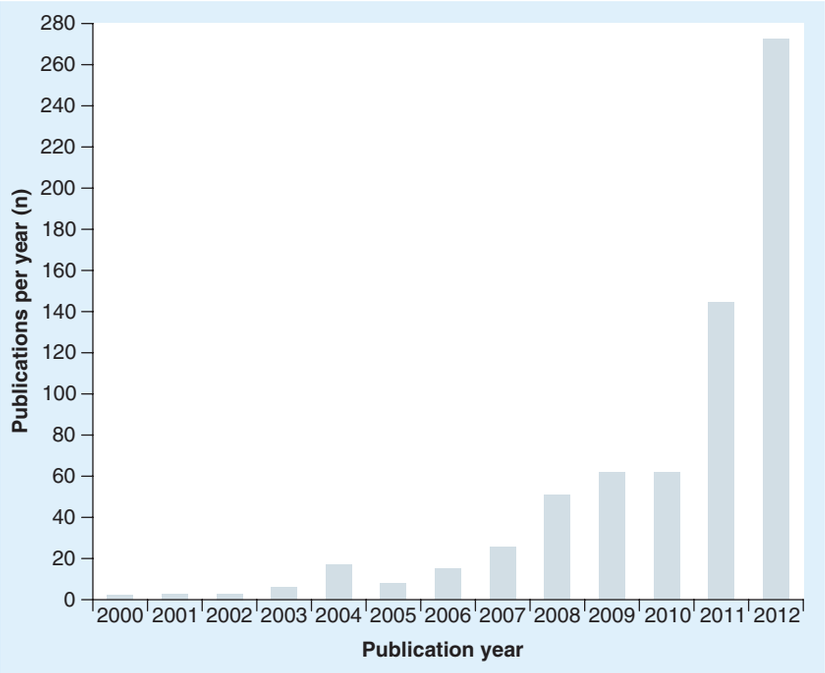

Figure 1. PubMed identified 804 publications when using the search phrase 'transcranial direct current stimulation'. Publications per annum are given between 2000 and 21 December 2012.

published in the past 5 years (i.e., 2007–2012) with a sufficient sample size to detect at least moderate effects and a single- or double-blind study design when comparing tDCS effects to sham stimulation. When applying these criteria, identified studies were relevant to depression, pain, cerebral stroke, neurodegenerative brain disorders (e.g., Parkinson's disease) and schizophrenia. In addition, anecdotal evidence from studies not meeting these inclusion criteria will be reported where relevant.

■ Depression

The first tDCS studies on mood, dating back to the 1960s and 1970s, reported mood elevation, giddiness and talkativeness following bifrontal stimulation in depressed patients [22–25]. By contrast, emotional state, affect, emotional decision-making, arousal and psychomotor functions remained unchanged with bi-frontal anodal and cathodal tDCS in mentally healthy volunteers (n = 25) when tested in a double-blind crossover study [25]. These findings suggest that mood-elevating effects of frontal tDCS are more likely to occur in patients suffering from a depressive disorder.

We identified 93 publications from 2007 to 2012 when entering the search phrase 'major depressive disorder' OR 'depression' AND 'transcranial direct current stimulation' OR 'tDCS'. Most studies apply the anode to the left dorsolateral prefrontal region and the cathode to the right supraorbital region, aiming to re-establish a 'balance' between left and right frontal cortex activation when assuming a link between depression, executive impairment and hypoactivity in the left dorsolateral prefrontal cortex [26,27].

Kalu *et al.* identified six randomized trials and four open-label studies published from 1998 to May 2011 for their meta-analysis [21]. The authors concluded that depression symptom severity is significantly reduced with frontal tDCS versus sham stimulation, while four studies [28–31] also reported sustained effects or further symptom improvement over a 4-week follow-up period. However, a lack of homogeneity following meta-regression points to patient sampling bias due to the absence/presence of medication or inter-individual differences in symptom severity at study inclusion.

Since then, and following on from an earlier study [32], the largest controlled clinical trial using tDCS as a treatment for depression was performed on 64 patients by an Australian team and published in 2012 [29]. Patients underwent 15 sessions of anodal left prefrontal stimulation versus sham, followed by 3 weeks of open-label treatment. Clinical ratings on the Montgomery–Asberg Depression Rating Scale significantly improved in the active treatment versus sham stimulation arm, as did processing speed (Symbol Digit Modalities Test) after the first session. However, other mood ratings did not confirm an advantage of active tDCS versus sham stimulation, whereas an advantage has been demonstrated for various other neuropsychological tests across multiple cognitive domains after the initial 15 sessions. In addition, the number of actual responders was small, as was the overall intervention effect size. However, the open-label phase suggests more benefits of repeated tDCS on mood but no additional cumulative effects on cognition.

While more sustained and larger effects with repeated tDCS on mood have also been reported by others [31,33] – including trials without concurrent antidepressant treatment [31,32] – the published findings to date are still limited. In particular, randomized and controlled clinical trials comparing tDCS (active vs sham) with other established forms of intervention (e.g., pharmacotherapy and cognitive behavior therapy) are missing. Therefore, tDCS as a treatment for

depression should be considered in line with other forms of physical intervention, such as light-exposure therapy for seasonal depression or sleep-deprivation therapy, until findings from larger clinical trials become available. While the lack of serious adverse side effects seems to favor tDCS – even without unequivocal evidence of its effectiveness – caution should be exerted with respect to suicidality as with any other mode of intervention.

■ Pain

Pain and depression symptoms often present as concurrent phenomena [34]. Moreover, antidepressant pharmacotherapy (i.e., in the multimodal treatment of chronic pain [35]) also offers additional benefits via modulatory effects on central pathways associated with pain processing [36,37]. Therefore, tDCS may also offer an alternative method of intervention by modulating pain processing in these central pathways.

Various studies have investigated this approach in a variety of chronic pain conditions, such as spinal cord injury [38], fibromyalgia [39,40] and migraine [41,42]. For example, Fregni *et al.* investigated anodal motor cortex stimulation in a small group of 17 patients suffering from chronic pain following traumatic spinal injury [38–40]. Patients were randomly assigned to active (n = 11) and sham stimulation (n = 6), which was performed in a double-blind fashion. The authors reported a significant cumulative decrease of pain rating scores in response to successive anodal tDCS versus sham stimulation.

Repeated anodal stimulation of the motor cortex also appears to be beneficial for fibromyalgia patients (n = 32) [39]. The reported effect was side specific for the motor cortex and tDCS was not effective when stimulating the dorsolateral prefrontal cortex. Finally, repeated cathodal stimulation (n = 13) of the visual cortex (vs sham; n = 13) over 6 weeks appears to reduce the intensity and duration but not the frequency of migraine attacks when comparing 2 months pre- versus 2 months post-treatment [41].

While the reported preliminary findings are promising, sample sizes were very small and often heterogeneous in respect of baseline pain measures, treatment history and other concurrent treatment or coexisting morbidities. Furthermore, pain is a very complex phenomenon and it remains unclear how tDCS interferes with central pain processing. Hence, more systematic research is required to draw firm conclusions on the effectiveness of tDCS for chronic pain treatment.

These previous clinical applications of tDCS are largely passive in their nature; that is, patients are not required to perform tasks while receiving tDCS. This approach, however, neglects the potential benefits of tDCS on learning and memory, which has applications for brain injury, cerebral stroke and degenerative brain disorders.

■ Cerebral stroke

Cerebral stroke usually affects unilateral circumscribed brain regions. This often results in a functional interhemispheric imbalance that hinders rehabilitation efforts. tDCS may be used to selectively down- and/or up-regulate affected brain regions in the respective hemisphere in order to support neural reorganization in combination with active rehabilitation therapy after stroke or traumatic brain injury.

Wu *et al.* investigated tDCS in 90 inpatients suffering from upper limb spasticity after cerebral stroke [43]. Twenty sessions of cathodal stimulation were applied to the primary sensory and motor cortex area of the stroke-affected hemisphere while the patients concurrently underwent conventional physiotherapy. The authors found a better response in patients receiving active tDCS versus sham stimulation. This advantage was maintained at follow-up after 4 weeks. By contrast, early intervention in acute stroke does not appear to benefit from tDCS [44]. While these findings are promising, they still require replication in sufficiently large controlled clinical trials.

More recently, Meinzer *et al.* investigated tDCS effects on language function in 20 healthy volunteers using functional MRI [45]. Anodal stimulation of the left inferior frontal gyrus significantly improved semantic word retrieval while resting-state functional MRI showed increased connectivity [43]. Further research using a combination of repeated functional and structural brain imaging may be helpful to better understand the potential effects of tDCS on neuroplasticity.

Animal research is equally important to systematically investigate the potential effects of an electrical current on neural repair.

■ Neurodegenerative & neurodevelopmental brain disorders

The loss of dopamine-synthesizing neurons in substantia nigra characterizes Parkinson's disease.

Motor symptoms such as rigidity, tremor, bradykinesia and gait instability are the defining neurological symptoms. However, reduced processing speed and impaired executive function (i.e., attention and working memory), along with mood and vegetative symptoms, complicate the complex clinical presentation of Parkinson's disease.

tDCS applied to various cortical regions (i.e., to the motor, frontal and prefrontal cortex) may be beneficial in treating some of the motor and cognitive symptoms as they occur in this disorder; for instance, via retrograde cortical stimulation of the dopamine-depleted midbrain structures. Moreover, working memory performance correlates with prefrontal dopamine levels [46]. Dopamine release in the caudate nucleus can be facilitated by high-frequency repetitive transcranial magnetic stimulation of the prefrontal cortex [47]. Hence, prefrontal tDCS may mediate similar mechanisms.

However, the available data from sufficiently large clinical trials are still scarce and largely limited to investigating effects on motor performance. Benninger *et al.* undertook a randomized double-blind and sham-controlled study on 25 Parkinson's disease patients, stimulating motor and prefrontal cortices [48]. They reported small effects on gait and bradykinesia versus sham stimulation, but no effects on self-assessed mobility, physical and mental wellbeing, nor in reaction time or symptoms as rated on the Unified Parkinson's Disease Rating Scale.

Increasing prefrontal dopamine may also be beneficial when targeting 'hypofrontality' and associated cognitive and negative symptoms in schizophrenia (via increased caudate dopamine release in response to prefrontal cortex stimulation [47]). However, reports are still scarce or have revealed limited effects [49]. More promising effects have been reported by Brunelin *et al.* when targeting medication-refractory auditory hallucinations with tDCS in 30 schizophrenia patients [50]. The authors placed the anode left prefrontally and the cathode left temporoparietally and stimulated twice a day over 5 consecutive days. They were able to find a significant reduction of auditory verbal hallucinations versus the sham condition along with improved negative and other positive symptoms. These beneficial effects lasted for up to 3 months. These findings are awaiting replication.

It has also been shown that anodal tDCS increases the activity of cortical cholinergic interneurons, increasing short latency afferent inhibition [51] but also decreasing excitatory aftereffects [52]. This may represent a promising therapeutic target for patients diagnosed with Alzheimer's disease, which is associated with decreased cholinergic function, in particular when combining tDCS with cognitive training. However, study populations to date remain too small and heterogeneous to support a critical review.

Conclusion & future perspective

tDCS is inexpensive, safe to administer and based on plausible biological mechanisms. However, its effects on brain functions associated with mood and cognition are still poorly understood. Nevertheless, our review suggests small-to-moderate effects when treating some neuropsychiatric conditions. Hence, tDCS may be considered a complementary form of treatment, specifically targeting mood and executive function, and perhaps auditory hallucinations in schizophrenia. However, large-scale randomized controlled clinical trials are still required to evaluate its effectiveness in comparison to other more established forms of intervention. Also, a more systematic approach comparing stimulation sites, altering polarity, and varying duration, current intensity and number of repeats is critical. These investigations should consider adding functional brain imaging, magnetic resonance spectroscopy and EEG-based tools to further our understanding of tDCS effects in clinical populations. In particular, tDCS effects on learning and memory, and its clinical applications in cognitive remediation and stroke recovery, are promising and warrant further research.

Disclaimer

The contents of the manuscript are solely the responsibility of the authors and do not necessarily represent the official views of any of the funding agencies.

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