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Transcranial Direct Current Stimulation (tDCS): Modulation of Executive Function in Health and Disease

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Abstract Transcranial direct current stimulation (tDCS) is a noninvasive method of neuromodulation used in human basic and clinical neuroscience. In this article we review its use in the cognitive neurosciences to study executive function, and current preliminary explorations of its therapeutic value as a cognitive enhancer for patients with compromised dysexecutive symptoms. We discuss published studies analyzing their methodology and results. A number of experiments describe improvement in experimental measures of inhibitory control, working memory, and verbal fluency with anodal stimulation over the dorsolateral prefrontal cortex. Positive findings are also described in different clinical populations. Despite the growing promise and interest in tDCS given its safety, simplicity, and low cost, findings are not always consistent across studies due to a host of variables we discuss (study design, stimulation parameters, neuroanatomy, genetics, etc.), highlighting the need for a better mechanistic understanding of the effects of tDCS.

Keywords Transcranial direct current stimulation · tDCS · Neuromodulation · Brain stimulation · Neurotherapeutics · Executive function · Prefrontal cortex · DLPFC · Dysexecutive syndrome · Cognitive enhancement

Introduction

The ability to manipulate and hold information for brief periods of time, to exert control over automatic behaviors, to plan ahead, and to adapt in a competitive and novel environment all fall under the heading of 'executive functions.' [1] These abilities are crucial for wellbeing and optimal performance in personal, social, and professional environments. These functions, once lost, can have devastating consequences as can be seen across multiple diagnostic categories in the entire neuropsychiatric spectrum [2•]. Despite the major functional impact of dysexecutive symptoms, clinicians have limited therapeutic options to address these problems. Cognitive enhancement through pharmacological interventions has demonstrated benefit, but this is limited and not exempt from systemic side effects. There is increased awareness of the need for alternative methods of cognitive enhancement to improve function and quality of life in clinical populations. But this awareness also comes with the identification of possible nonclinical uses and misuses of cognitive enhancers, their potential for abuse [3•], and the ethical problems they raise [4].

Transcranial direct current stimulation (tDCS) is a non-invasive cortical stimulation technique that applies weak electrical currents using surface electrodes [5]. The traditional methodology uses two electrodes, a cathode and an anode, placed over regions of interest on the scalp. The application of weak, continuous electrical current helps facilitate or inhibit particular areas of the brain, and their associated networks [6•]. Initial studies with tDCS focused on the motor system, and proved the capacity of this technique to modulate motor-evoked potentials (MEPs) when applied over the human primary motor cortex [5]. The modulation of the cortico-spinal

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tract is polarity-dependent: when the anode is placed over M1, the contralateral MEPs are facilitated, while if the cathode is used, the opposite effect is achieved, leading to inhibition and reduction of the MEP amplitude [7]. After the initial focus of tDCS research on motor neurophysiology, cognitive neuroscience did not take long to adopt this method to study sensory, cognitive, affective, and behavioral systems. In recent years, translational and therapeutic applications have also focused on investigating the safety and efficacy of tDCS for the treatment of psychiatric and neurological diseases such as major depressive disorder (MDD), chronic pain, tinnitus, epilepsy, stroke, and Alzheimer's disease, among others [8•]. In this paper, we will review the uses of tDCS to study executive function and its underlying brain circuitry in healthy subjects. In addition, we will discuss therapeutic trials to treat clinical populations with dysexecutive deficits across the neuropsychiatric spectrum.

Transcranial Direct Current Stimulation (tDCS)

Compared with other noninvasive brain stimulation tools such as transcranial magnetic stimulation (TMS), tDCS is simpler, cheaper, portable, and safer. It consists of a direct current (DC) stimulator with built-in rechargeable batteries and two sponge electrodes [9••]. The DC stimulator is the source of the current sent to electrodes that are fixed to the scalp using elastic bands or adaptable caps similar to the ones used for EEG [10]. The anode (positive charge) and cathode (negative charge) are typically made of conductive rubber to avoid electrochemical polarization, and inserted in a thin sponge that is in contact with the skin surface. The sponge needs to be soaked with water or NaCl solution to maximize conductivity and limit skin abrasion. The area of the electrode typically ranges from 25 to 35 cm^2, which leads to nonfocal neuromodulatory effects, although novel high definition tDCS approaches use smaller electrodes and more complex montages (with multiple cathodes and anodes) to increase focality and precision [11].

Electrode placement on the scalp determines where and how the current flows, and its effects on cellular and network activity [12•]. Current flows from the cathode to the anode, through the skull, CSF, and brain with current densities that range from 0.029 to 0.08 mA/cm^2 for typical montages [9••]. To avoid local discomfort from the initiation and termination of stimulation, the current is typically increased slowly over the course of a few seconds until the target intensity is reached, and then similarly decreased progressively to the end of the session. A typical session of tDCS lasts 20 min., although other protocols have also been used.

Another advantage of tDCS is the simplicity and efficacy of its placebo stimulation. Because it is such a benign intervention, subjects do not generally experience any abnormal sensory effects during stimulation, other than mild tingling under the electrode during current ramp up and ramp down [9••]. Placebo stimulation simply applies this current ramp up followed by a quick discontinuation over a few seconds, leading to the typical somatosensory activation without applying any current through the length of a session. [13]. Placebo stimulation is therefore indistinguishable from real stimulation, which is a great asset for controlled studies [14].

Recent progress in cortical electrical stimulation has brought novel technological variations of tDCS such as transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), and high-definition tDCS (HD-tDCS). tACS applies alternating currents to the scalp and is not sensitive to the direction of current flow, so current does not flow unidirectionally from anode to cathode, because the two electrodes alternate their role as positive or negative sources [15]. In most studies, tACS is applied without a DC offset and uses sinusoidal stimulation in a wide frequency range [16]. tRNS, a special form of tACS, distributes random levels of current generated with a frequency spectrum between 0.1 and 640 Hz with white noise characteristics. The modulatory effects of tRNS are related to long-term potentiation (LTP)-like neuroplasticity via its effects on sodium channels [17]. HD-tDCS allows a more focal stimulation using arrays of multiple electrodes [11, 18, 19]. Instead of using the standard sponge electrodes, HD-tDCS uses small, gel-based Ag/AgCl sintered ring electrodes. Electrode configurations include the 4×1-ring montage, which involves the placement of a center ring electrode (anode or cathode) over the target cortical region surrounded by four return electrodes of the opposite sign [20]. This technique has been primarily used in motor neurophysiology studies and therapeutic trials for pain [18, 21]. Similar to tDCS, anodal HD-tDCS (surrounded by four cathodes) leads to facilitation of excitability and MEP amplitude, while cathodal stimulation has the opposite effect [22, 23].

Safety

tDCS is a minimal risk technology. Side effects are mild and acute (i.e., during the course of stimulation). As stated above, currents are usually weak in the range of 1–2 mA. Side effects caused by stimulation, though rare, may include skin irritation, minor heat abrasion, nausea, headache, dizziness, and itching under the electrode. An analysis of 567 tDCS sessions on more than 100 participants reported that the most frequent side effect was the tingling sensation (76 %) and only 17.7 % found the stimulation procedure to be mildly unpleasant [24]. Taking a low dose over-the-counter analgesic and/or resting is sufficient to address most of these side effects. There are no known significant risks of tDCS but it should be applied with precautions, particularly in subjects susceptible to seizures.

Some safety guidelines exclude its use in patients with known epilepsy.

Mechanism of Action

Despite the growing interest of tDCS across basic and clinical neuroscience, the mechanism of action of tDCS remains only partially understood. Nevertheless, there is a growing (though incomplete) understanding of its effects at the cellular, neurochemical, pharmacological, and circuit level.

Although it is generally understood that anodal stimulation is activatory and cathodal inhibitory, anodal and cathodal determine (primarily) the direction of current and not just the direction of physiological modulation [5]. In the motor system, anodal stimulation leads to facilitation of the cortico-spinal pathway and cathodal stimulation leads to inhibition. Attempts to understand the synaptic basis of these physiological effects have pointed to mechanisms similar to LTP and long-term depression (LTD) [5, 25, 26] mediated by intracellular cyclic adenosine monophosphate(cAMP) and calcium levels.

Pharmacological and magnetic resonance spectroscopy studies have established the role of tDCS in regulating different neurotransmitter systems including glutamate [26], GABA [27], dopamine [28], serotonin [29], and acetylcholine [30]. The neuroplastic after-effects of anodal and cathodal modulation have been linked to N-methyl-D-aspartate (NMDA) receptor-dependent plasticity [31•] and can be pharmacologically suppressed by the sodium channel blocker carbamazepine, the calcium channel blocker flunarizine [26], the NMDA receptor antagonist dextromethorphan (DMO) [32], and the β-blocker propranolol [33]. Finally, although neuroimaging studies of the effects of tDCS are still few, computational models are starting to elucidate the effects of tDCS at the systems or circuit level [34].

Executive Function: an Introduction

Executive function is an umbrella term which encompasses a number of cognitive processes including attention, inhibitory control, working memory, and cognitive flexibility. Within this framework, other high-order processes are also included such as planning, problem solving, and reasoning. There is evidence that executive function is related to physical health, academic performance, job performance, and psychosocial wellbeing [2•]. Meanwhile, executive functioning is impaired in a number of neuropsychiatric diseases such as mood disorders (both depression and bipolar illness), anxiety disorders, schizophrenia, addictions, obsessive-compulsive disorder (OCD), attention deficit and hyperactivity disorder (ADHD), traumatic brain injury (TBI), epilepsy, and neurodegenerative conditions such as dementias and movement disorders.

The neuroanatomy of neural circuits underlying executive function is complex, but the prefrontal cortex (PFC) with its different functional subunits is the central hub of these networks. Its rich connections with cortical and subcortical regions allow the homeostatic 'top-down' control over complex behaviors, integrating information from internal and external environments. The PFC is also responsible for the inhibition of automatic behaviors and affective states, allowing an organized and adaptive (yet plastic and dynamic) set of responses to environmental needs [35••].

Specific functional subunits within the PFC selectively process its different cognitive operations. The dorsolateral prefrontal cortex (DLPFC) is most closely related to executive functions. The caudal DLPFC is involved in the selection among competing responses and the allocation of attention to them. Rostrally, the mid-DLPFC is involved in working memory. There are also rich connections with posterior association cortical neurons [36]. Since the PFC does not act in isolation, the integrity of its white matter connections with other brain regions is also important and has been found to be associated with cognitive performance [37]. This highlights the circuit-based nature of the computations required for executive function, beyond a single node or anatomical structure [38].

Review of tDCS Studies Assessing Executive Functions

A review of studies assessing tDCS functions in healthy subjects and patient populations is summarized in Tables 1 and 2. Only the relevant tests of executive function were included when the test was part of a battery of neuropsychological tests.

Frequently Used Tests for Executive Functions in tDCS

As can be seen from Tables 1 and 2, a number of neuropsychological, cognitive, and behavioral metrics have been used to monitor the effects of tDCS on executive functions. A basic description is provided below, but different variations of these tests are used throughout the studies mentioned.

The *digit span forward and backward test* [39] consists of giving the subject a list of numbers of increasing length, and then asking them to repeat it in the same or in the reverse order. In the *letter number sequencing test* [40], the subject is given a random set of numbers and letters and then asked to organize the numbers and letters in ascending order. In part A of the *trail making test*, the subject is asked to connect circles containing numbers in ascending order; for part B of the test, the subject alternates numbers and letters in ascending order [41]. The performance of the subject in parts A and B are timed. In the *symbol digit modalities test*, the subject is asked to pair numbers with abstract symbols within a 90-sec. period. Tests of *verbal fluency* [42] involve giving the subject a specific time period, usually 60 sec., to generate as many

Table 1 Studies looking at the effect of transcranial direct current stimulation (tDCS) on executive functions in healthy subjects

Study	Amp/electrode area (mA/cm²)	Duration (min)	Montage	n	Age (mean or range)	Measures	Protocol (Session no./interval between sessions/design/follow up)	Findings
Nelson et al., 2014 [55]	1/35	10	A: F3 C: F4 A: F4 C: F3	19	Military	Vigilance task	3/2 d/parallel/none A/C/sham, stim at 10 or 30 min after start of task	Improved target detection with both compared to sham but more prominent with anodal F3 stim
Park et al., 2014 [60]	2/25	30	A: F3,F4 C: arm	40	69.7	DSF/B, TMT A,B n-back, tests of attention	10/1 d/RCT/7 d,28 d 20 A, 20 sham Training during stim	With anodal stimulation, improvement in accuracy and decrease in RT on n-back at 1 and 4 wks, while improvement in DS was only at 1 wk
Filmer et al., 2013 [61]	0.7/25	10	A: 1 cm post to F3 C: RSO A: RSO C: 1 cm post to F3	18	22	Auditory, visual, or dual stimuli task	3/5 d/cross-over/20 min A/C/sham	Cathodal stimulation over the posterior L DLPFC decreased performance
Hoy et al., 2013 [48]	1 and 2/35	20	A: F3 C: RSO	18	24.7	n-back	3/1 wk/cross-over/20 and 40 min A 1 mA/A 2 mA/Sham	Improvement in RT with 1 mA >2 mA at T0 and 40 min
Kwon and Kwon, 2013 [65]	1/35	10	A: R pre-SMA C: L cheek	80	23.0	SST	1/-/parallel/no 40: A, 40: sham	Improved inhibition with anodal stimulation
Leite et al., 2013 [49]	2/35	30	A: F3 C: F4 A: F4 C: F3	16	24	Letter/digit naming Vowel/consonant pairing	3/1–2 d/cross-over/none Testing during stim A F3/ A F4/sham	On letter/digit task, anodal F3 stimulation improved RT, while cathodal stimulation improved accuracy. For the vowel consonant task, F3 anodal stimulation decreased switching performance but increased accuracy compared with sham
Martin et al., 2013 [59]	2/35	30	A: AF3 C: R deltoid	52	21.7–23.2	Adaptive n-back DSF/B, L/N seq VF, TMT A,B Serial 7	10/1 d/parallel/4 wks Training during tDCS with n-back 21 tDCS + training: 21 sham + training: 10 tDCS only	Improvement in accuracy on n-back during tDCS. At last follow up, the group with tDCS + t training performed better on DS
Motohashi et al., 2013 [62]	1/35	20	A: F3 C: RSO	11	22	Computerized battery including a one back test	4 or 4/1 d/cross-over/none 4A, 3 d washout, 4 sham vs 4 sham, 3 d, 4 A	Slight improvement in visual recognition, no effect on one back test
Plewnia et al., 2013 [63•]	1/35	20	A: F3 C: RSO	46	25.9	Parametric GoNoGo	2/2 d/cross-over/none A/sham	Decreased performance in individuals with COMT Met/Met allele. No effect otherwise
Berryhill and Jones, 2012 [57]	1.5/35	15	A: F3 C: R cheek A: F4 C: L cheek	25	63.7	Verbal n-back Visual n-back	3/>1 d/cross-over/none A: F3/A: F4/sham	Improvement in both tasks with tDCS in the high education group regardless of side. In low education group, F4 tDCS worsened performance on visual task

Table 1 (continued)

Study	Amp/electrode area (mA/cm²)	Duration (min)	Montage	n	Age (mean or range)	Measures	Protocol (Session no./interval between sessions/design/follow up)	Findings
Coffman et al., 2012 [54]	0.1 or 2/11	30	A: F10 C: arm	19	23.4	Attention network tasks	1/-/parallel/40 min 9 at 2 mA, 10 at 0.1 mA	Improvement in alert attention, but not orienting or executive attention at 2 mA compared with 0.1 mA
Ditye et al., 2012 [93]	1.5/35	15	A: RIFG C: LOFC	22	23.6	SST	4/1 d/parallel/1 d 10 tDCS/12 control	Improved response inhibition with tDCS + training vs control after session 3 and 4, but 24 h after stimulation the difference was gone
Gladwin et al., 2012 [56]	1/35	10	A: F3 C: RSO	14	22	Sternberg	2/50 min/cross-over/none A/Sham	Improvement in selective attention in anodal stimulation when distracter had been included as an incorrect choice
Jeon and Han, 2012 [50]	1/35	20	A: F3 C: RSO A: F4 C: LSO	32	37.3	DSF/B Stroop	1/-/parallel/2 wk 8: A F3, 8: A F4, 8: F3 sham, 8: F4 sham	Improvement on DSB and Stroop with F3 stimulation, improvement on Stroop with F4 stimulation. Results persisted at 2 wk
Sandrini et al., 2012 [68]	1.5/35	13	A: P3 C: P4 A: P4 C: P3	27	25	1 and 2 n-back	1/-/parallel/none 9: A P3, 9 A P4, 9 sham	With P3 as anode, there is loss of improvement compared with sham in RT at 1 n-back, while with P4 as anode, the loss is at 2 n-back
Andrews et al., 2011 [58]	1/35	10	A: F3 C: RSO	10	28.1	DSF/B	3/1 wk/cross-over/none tDCS + n-back/tDCS/sham	tDCS+n-back improved DSF performance compared with sham and tDCS only
Dockery et al., 2009 [84]	1/35	15	A: F3 C: RSO A: RSO C: F3	24	24	TOL	3/1 wk/cross-over/6 mo or 1 y with sham A/C/sham	Improved performance when cathodal applied during acquisition/consolidation and precedes anodal stimulation. Anodal tDCS improved performance only after being applied after cathodal stimulation. RT was still improved at last follow up
Hsu et al., 2011 [64]	1.5/16	10	A: Pre-SMA C: L cheek A: L cheek C: Pre-SMA A: M1 C: L cheek A: L cheek C: M1	28	22.1	SST	2/1 d/RCT + cross-over/none 14 Pre-SMA: A/C/no tDCS 14 M1: A/C/no tDCS	Improved inhibition with anodal stimulation of pre-SMA, and decreased inhibition with cathodal stimulation. No effect with M1 stimulation
Jacobson et al., 2011 [66]	1/25	10	A: RIFG C: LSO C: LSO C: RIFG A: RIFG C: LIFG A: LIFG C: RIFG A: R AG C: LSO	22	28.3	SST	5 vs 2/1 wk/cross-over/none 11: A IFG/C IFG/sham/bil IFG 11: AG/sham	Improvement in inhibition with anodal RIFG stimulation

Table 1 (continued)

Study	Amp/electrode area (mA/cm²)	Duration (min)	Montage	n	Age (mean or range)	Measures	Protocol (Session no./interval between sessions/design/follow up)	Findings
Leite et al., 2011 [83]	1/35	15	A: F3 C: RSO A: RSO C: F3 A: M1 C: RSO A: RSO C: M1	30	Univ. stud	Set shifting task	3/90 min/cross-over/none 15: A/C/sham F3 15: A/C/sham M1	Anodal stimulation of F3, M1 improved performance on cognitive switching task
Zaehle et al., 2011 [80]	1/35	15	A: F3 C: L Ma A: L Ma C: F3	16	25	n-back	4/1 d/cross-over/none Sham then A F3/sham then C F3 16 control group no stim	Improved performance with anodal, while decreased performance with cathodal stimulation
Stone and Tesche, 2009 [81]	3/25	20	A: P3 C: R arm A: R arm C: P3	14	NA	Global/local visual task	3/4 d/cross-over/20 min A/C/sham	Anodal stimulation decreased performance on trials requiring a switch from local to global targets, while cathodal degraded attentional switching during stimulation only
Beeli et al., 2008 [67]	1.5/35	5.5	A: FC4 C: R Ma A: R Ma C: R FC4	35	24.9	GoNoGo	2/3 min/cross-over/none A/C/sham	Decreased performance with cathodal stimulation
Ohn et al., 2008 [51]	1/25	30	A: F3 C: RSO	15	26.5	n-back	2/2 wk/cross-over/30 min A/sham Testing during and after tDCS	Improvement of performance with anodal stimulation during and after tDCS
Fregni et al., 2005 [52]	1/35	10	A: F3 C: RSO A: RSO C: F3 A: M1 C: RSO	15	20.2	n-back	2/20 min/cross-over/none A/sham then 7 underwent C/A: M1 6 mo later	Improved performance with anodal stimulation only. No effect with M1 stimulation
Iyer et al., 2005 [53]	1 and 2/35	20	A: F3 C: RSO A: RSO C: F3	103	19–70	VF CalCAP[1]	1/none/parallel/none At 1 mA 10 A/10C/10 sham Tests administered during tDCS: At 1 mA 14 A/14C/15 sham At 2 mA 10 A/10C/10 sham	Improvement in VF but not CalCAP with anodal stimulation at 1 mA. When testing is performed during tDCS, VF is improved at 2 mA not 1 mA. No effect on CalCAP
Marshall et al., 2005 [94]	0.26/NA	15	A/C: F3,F4 C/A: R and L Ma A: F3 C: R Ma A: F4 C: L Ma	12	19–27	Modified Sternberg	5/1 wk/cross-over/no A F3 + F4/A F3/AF4/sham Stim was intermittent on-off for A and C for 15 sec.	Decreased reaction time with both anodal and cathodal stimulation

A anode, *AG* angular gyrus, *Amp* amplitude, *C* cathode, *d* day, *DLPFC* dorsolateral prefrontal cortex, *DSF/B* digit span forward/backward, *IFG* inferior frontal gyrus, *L* left, *L/N seq* letter-number sequencing, *M1* primary motor cortex, *Ma* mastoid, *min* minutes, *n* sample size, *NA* not available, *OFC* oribotofrontal cortex, *post* posterior, *pre-SMA* pre-supplemental motor area, *R* right, *RCT* randomized controlled trial, *RT* reaction time, *SO* supra-orbital, *SST* stop signal task, *TOL* Tower of London, *TmT* trails making test, *univ.* university students, *VF* verbal fluency

Electrode montages are based on the 10–20 EEG system.

[1] California Computerized Assessment Package (Cal-CAP): abbreviated version used in this study measuring attention, reaction time, memory, and psychomotor speed.

Table 2 Studies exploring the effect of transcranial direct current stimulation (tDCS) on executive functions in different patient populations

Study	Population	Amp/electrode area (mA/cm²)	Duration	Montage	N	Age (mean or range)	Measures	Protocol (Session no./interval between sessions/design/follow up)	Findings
Oliveira et al., 2013 [69]	MDD	2/25	30 min	A: F3 C: F4	28	18–65	n-back	1/-/parallel/none 14: A, 14: sham	Improved accuracy with anodal stimulation
Pereira et al., 2013 [75]	PD	2/35	20 min	A: F3 C: RSO A: P3–T5 C: RSO	16	61.5	VF	2/2 h/cross-over/none F3/P3–T5	Improved performance with F3 stimulation
Loo et al., 2012 [73••]	MDD	2/35	20 min	A: F3 C: RSO	58	48.6 vs 47.8	DSF/B, VF, L/n seq SDMT	30/1 d/parallel/7 d,28 d 29:15 sham then 15 A 31: 30 A Testing done after session 1, 15, and 30	SDMT improved with anodal stimulation after the first session. No effect otherwise. Trend for improvement on L/N seq after 30 anodal sessions
Loo et al., 2010 [70]	MDD	1/35	20 min	A: F3 C: RSO	34	48.9 vs 45.6	TMT A,B, DSF/B VF, SDMT	10/1–2 d/parallel/none 15: 5 sham then 5A 19: 10 A sessions	Group with 10 anodal stimulation sessions improved on TMT B and DSF/B
Boggio et al., 2009 [79]	AD	2/35	30 min	A: F3 C: RSO A: T7 C: RSO	10	79.1	DSF/B, Stroop	3/2 d/cross-over/none F3/T7/sham	No effect
Ferrucci et al., 2009 [72]	MDD	2/32	20 min	A: F3 C: F4	8	52.4	Sternberg, Posner paradigm	5(×2)/4 h/open label/1 mo	No effect
Kang et al., 2009 [77]	Stroke	2/25	20 min	A: F3 C: RSO	10	69.9	GoNoGo	2/2 d/Cross-over/1 h,3 h A/sham 10 healthy controls	Improved accuracy at 1 and 3 hours in the active group. No effect in controls. No change in RT
Jo et al., 2009 [76]	Stroke	2/25	30 min	A: F3 C: RSO	10	47.9	n-back	2/2 d/cross-over/none A/sham	Improved accuracy with anodal stimulation
Huey et al., 2007 [78]	FTD	2/25	40 min	A: F3 C: RSO	10	61.3	VF	2/NA/cross-over/none A/sham	No effect
Boggio et al., 2006 [74]	PD	1 and 2/35	20 min	A: F3 C: RSO A: M1 C: RSO	18	61.1	n-back	3/2 d/cross-over/none 9: 1 mA F3/M1/sham 9: 2 mA F3/M1/sham	Anodal F3 stimulation at 2 mA improved accuracy but not speed
Fregni et al., 2006 [71]	MDD	1/35	20 min	A: F3 C: RSO	18	46.4	DSF/B, Stroop, SDMT	5/1 d/parallel/none 9: A, 9: sham	Improvement on DS with anodal stimulation

A anode, *AD* Alzheimer's disease, *Amp* amplitude, *C* cathode, *d* day, *DSF/B* digit span forward and backward, *FTD* fronto-temporal dementia, *h* hours, *L/n seq* letter number sequencing, *mo* month, *mA* milliamperes, *MDD* major depressive disorder, *min* minutes, *N* sample size, *P* Parkinson's disease, *R* right, *RT* reaction time, *SDMT* symbol digits modalities test, *SO* supra-orbital, *stim* stimulation, *TMT* trails making test, *VF* verbal fluency, *w* week.

Electrode montages are based on the 10–20 EEG system.

words starting with a specific letter of the alphabet (e.g., phonemic fluency) or belonging to a specific semantic category such as animals or vegetables (e.g., semantic fluency). The *Tower of London* [43] is another test of executive function whereby the subject is asked to problem solve a given task using a set of pegs and tiles. In the *Stroop test* [44], the subject is shown a series of written names of colors (e.g., 'RED') but printed in a different color (printed in blue for example), and asked to report the actual color of the word rather than the word itself. The *n-back test* [45] is one of the most frequently used tests of working memory in behavioral paradigms. The subject is shown a series of letters (verbal) or geometric figures (visual) and asked whether the stimulus currently presented is the same as that presented n (usually 1 or 3) stimuli previously. The *stop signal task* [46] measures response inhibition by measuring an individual's ability to inhibit a prepotent response. The subject is exposed to a series of stimuli and asked to press a key when they see them, but avoid pressing when exposed to another stimuli (a stop auditory signal, for example). The *Go-NoGo test* [47] is similar and again measures the subject's ability to correctly respond to a stimulus, or withhold the response when exposed to another specific stimulus.

Findings in Healthy Subjects and Patients

A significant number of studies (Table 1) found an improvement in impulse control, working memory, attention, and phonemic verbal fluency with tDCS stimulation in healthy subjects.

Specifically, a single session of anodal tDCS stimulation over the left PFC has been shown to improve working memory [48–52], verbal fluency [53], and attention [54–56]. One of the first studies looking at working memory was performed by Fregni et al. [52]. They were able to show an improvement in performance on the n-back test with a 1-mA, 10-minute stimulation session with the anode over F3 and the cathode on the right supraorbital region. These findings were not replicated when the montage was reversed or when anodal stimulation occurred over the left motor region. A similar protocol was adapted by Ohn et al. [51], this time with 30 min. of stimulation. The improvement was noted both during and after the stimulation sessions. A single study then compared varying stimulation intensities (1 mA vs 2 mA) and found that with 1-mA anodal stimulation there was a faster reaction time on the n-back test as compared with 2 mA, which challenged the notion that higher currents lead to stronger behavioral effects [48]. Berryhill and Jones [57] analyzed whether stimulation had domain-specific effects on working memory in an elderly population: a verbal n-back test consisting of consonants and a visual n-back test consisting of shapes. They found an improvement in performance with anodal stimulation over F4 or F3 in the highly educated subjects, but surprisingly a worsening of performance on visual n-back in the subjects with lower education and anodal stimulation over F4

(F3 in this subgroup showed no effects). Two studies showed that training on one working memory task (n-back test) during tDCS improved performance on another working memory task (digit span) after stimulation [58, 59]. Consistent with other findings in the neuromodulation literature, repeated sessions (a total of 10) of anodal tDCS have shown long-term improvement in working memory performance, lasting up to 4 weeks [59, 60].

Filmer et al. [61] assessed multi-tasking abilities by exposing subjects to auditory, visual, or auditory and visual stimuli. The subjects' reaction times to these stimuli where most enhanced with cathodal stimulation. In this experiment, the electrode was specifically placed 1 cm behind F3 to target the DLPFC region. Nelson et al. [55] tested military recruits on a vigilance test consisting of an air traffic control computer simulation with a bifrontal tDCS montage. The recruits were instructed to monitor whether the orientation of four airplanes was suggestive of an imminent collision. Performance was most improved with anodal stimulation over F3. Coffman et al. [54] used an attentional task consisting of responses to alerting cues, spatial cues, and flankers. The response times were then calculated for alerting, orienting, and executive attention. They found an improvement of alerting cues only with anodal stimulation over F10 (over the right sphenoid bone). The alerting performance also correlated with the subjects' performance on target identification in a virtual environment.

The positive results described above were not always consistent across studies as other single-session studies using similar (though not identical) parameters did not find an effect on working memory [58, 62], multi-tasking [61], or inhibition[63•].

Studies on cognitive control and impulsivity have described how anodal stimulation over the pre-supplemental motor area (pre-SMA) and the right inferior frontal gyrus improves response inhibition and decreases impulsivity as assessed by the stop signal task [64–66]. A single session of anodal stimulation over the right PFC showed a slight improvement in attention [55] and working memory [57], while cathodal stimulation led to increased impulsivity [67]. Anodal stimulation of the left posterior parietal lobe led to worsening of performance on working memory [68].

Table 2 summarizes studies on clinical populations. In patients with MDD, anodal stimulation over the left DLPFC showed an improvement in tests of working memory after a single [69] or repeated sessions [70, 71], while others reported no effect [72]. Loo et al. [70, 73••] performed two experiments assessing repeated stimulation in MDD. In the first experiment, they administered 1-mA stimulation over ten sessions in one group and five sham then five anodal sessions in another. A battery of neuropsychological tests was administered at baseline, after five sessions, and after ten sessions. There was no effect of stimulation on mood between groups after the first five sessions, but an effect was seen at ten sessions.

On neuropsychological measures, and after ten sessions, an improvement in the digit span backward and trail making B tests was noted, but there was no effect on verbal fluency. In their second experiment, subjects either received 30 active daily sessions or 15 sham followed by 15 active sessions. An effect on mood was also seen, but no improvement in neuropsychological measures after the 30 sessions, except for a trend towards improvement with letter number sequencing.

Anodal stimulation over F3 was shown to improve accuracy on the n-back test as well as verbal fluency in Parkinson's disease [74, 75]. In stroke patients, and using the same montage, improvements in accuracy on n-back and the GoNoGo test were noted [76, 77]. A single study [78] tried to assess tDCS in fronto-temporal dementia patients and did not find any benefit on verbal fluency. Finally, Boggio et al. [79] used tDCS in Alzheimer's disease patients, placing the anode over F3 or T7 and the cathode on the right supraorbital region. They only found an effect on visual memory but not on executive functions.

A Comment on Study Parameters and Design

An increasing number of studies are attempting to enhance cognition using tDCS. Discrepancies between published experiments can be explained by variability in stimulation parameters, number of sessions, study design, and psychometric measures. The intensity of stimulation across studies ranged from 0.26 to 2 mA, and the electrode surface area from 11 to 35 cm^2. This creates a wide range of charge densities and distributions, which will naturally have different modulatory effects of neurons and networks. Montages were also different, with the most common placement situating the two electrodes over the F3 and F4 position on the international 10–20 EEG system. However, the paired electrode location differs across studies with the use of ipsilateral reference electrodes [67, 80] or extra-cephalic arm electrodes [54, 59, 60, 81]. These different montages also lead to important differences in the distribution of charge across studies.

Subject variables such as age and gender also differ, with the majority of the studies evaluating healthy university students and a few focusing on the elderly. Differences in the subject's anatomy (e.g., brain volume and cortical gyri-sulci morphology such as contours, folding patterns, functional localization) also contribute to the variability of effects in healthy and clinical populations [82]. The individual anatomy and physiology determines the amount and distribution of current reaching different brain regions [12•]. In clinical and translational studies with patients, disease-specific parameters including stage of the disease and concomitant psychotropic medications are also important sources of variability.

Study designs were also different in terms of randomization, control groups, blinding, number of sessions, and washout periods. Some studies evaluated single sessions, while others

repetitive daily sessions (up to 30) [73••], or twice-daily sessions [72]. The exact washout period between studies varied, with some studies relying on a washout period of up to 90 min. only [52, 67, 83] while others relied on a time difference of days to weeks between sessions. The sequence of the sessions also has to be taken into account, as there is evidence that it may impact test performance [84]. The time when cognitive assessments occurred changed as well, with some studies assessing during tDCS stimulation and other after the stimulation was finished. As a result, not all subjects were passive during the stimulation, as some were either being tested or were being trained on another task [49, 51, 52, 54, 55, 59, 61, 69, 74, 76, 78, 79, 81, 84]. A few studies also included long-term follow up to 1 year, to determine whether the changes persisted beyond the immediate post-stimulation period [50, 59, 60, 70, 72, 84]. Finally the nature of the tests used also varied and executive functions were tested as a primary outcome, or as part of a battery of tests.

Conclusions

tDCS represents an appealing opportunity for cognitive enhancement. It is an inexpensive and relatively simple method with the potential to help compromised patients.

Studies in healthy subjects and patient populations have shown improvement in a number of tests of executive function. Improved performance on tests of impulse control, working memory, phonemic verbal fluency and attention has been described. The exact mechanism of this effect is unclear, but alterations in the neurotransmitter concentrations beneath stimulation sites [85] and widespread perfusion changes have been shown [86].

Results, however, were not consistent and were sometimes contradictory across studies. Inconsistencies are more pronounced in clinical studies. The variability in the population being studied, the study protocol, stimulation parameters, montage used, timing and method of testing all may play a role in these discrepancies. For example, a montage using an extra-cephalic or ipsilateral electrode pair would not be expected to affect the brain region similar to one using contralateral electrodes. A review of the studies also highlights that, against common belief, more may not always be better: stimulation intensity does not necessary have a linear relationship with neural or behavioral modulation, and 2 mA may not lead to stronger effects than 1 mA, but can actually reveal weaker or qualitatively different changes [48].

Genetic and neuroanatomical differences also play a role. Plewnia et al. [63•] noted that in catechol-O-methyltransferase (COMT) Met/Met allele carriers, tDCS actually worsened their performance on a set-shifting task, highlighting the importance of the subjects' genetic profile in their performance. The interaction of the genetic profile and gender and their impact on executive function has also been demonstrated in

other studies [87]. There is evidence that subjects with higher education benefited more from stimulation than those with lower levels of education [57]. Anatomical differences are also important; they impact the current density over specific brain regions, and may impact performance [88]. Along the same lines, future studies in dementia should also account for the amount of brain atrophy in their analysis of performance [89]. Computational models of the charge density are being used and integrated in tDCS studies [82, 90]. In addition, the use of neurostimulation, functional imaging, and connectivity analysis may also improve our ability to predict how subjects may benefit from this treatment [6•, 91].

There is a need for replication of the prior studies using similar protocols to confirm the benefits of tDCS and their duration. But, perhaps more importantly, we need to better understand the mechanism of action of tDCS and the differences among the most commonly used protocols. The safety of repeated sessions and whether enhancing one brain region is at the expense of another should also be studied more carefully [92]. There is an urgent need to ameliorate executive functions in a host of diseases. Patients with schizophrenia, epilepsy, dementias, stroke, and ADHD, among others, would greatly benefit from cognitive enhancement. Whether tDCS can provide them this opportunity and whether the improvement affects clinical and day-to-day functioning remains unknown, but it is a possibility worth pursuing.

In conclusion, the use of tDCS represents an exciting opportunity for researchers and clinicians to enhance executive functions in different patient populations. Further studies on its efficacy and safety are needed.

Compliance with Ethics Guidelines

Conflict of Interest Joan Camprodon declares no conflicts of interest. Navneet Kaur declares no conflict of interest. Rani Sarkis declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author(s).

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