Cognitive Effects of Transcranial Direct Current Stimulation in Healthy and Clinical Populations

An Overview

Marian E. Berryhill, PhD* and Donel Martin, PhD†

Abstract: Transcranial direct current stimulation (tDCS) is a neuromodulatory approach that is affordable, safe, and well tolerated. This review article summarizes the research and clinically relevant findings from meta-analyses and studies investigating the cognitive effects of tDCS in healthy and clinical populations. We recapitulate findings from recent studies where cognitive performance paired with tDCS was compared with performance under placebo (sham stimulation) in single sessions and longitudinal designs where cognitive effects were evaluated following repeated sessions. In summary, the tDCS literature currently indicates that the effects of tDCS on cognitive measures are less robust and less predictable compared with the more consistent effects on motor outcomes. There is also a notable difference in the consistency of single-session and longitudinal designs. In single-session tDCS designs, there are small effects amid high variability confounded by individual differences and potential sham stimulation effects. In contrast, longitudinal studies provide more consistent benefits in healthy and clinical populations, particularly when tDCS is paired with a concurrent task. Yet, these studies are few in number, thereby impeding design optimization. While there is good evidence that tDCS can modulate cognitive functioning and potentially produce longer-term benefits, a major challenge to widespread translational implementation of tDCS is the absence of a complete mechanistic account for observed effects. Significant future work is needed to identify a priori responders from nonresponders for every cognitive task and tDCS protocol.

Key Words: Cognition, healthy, neuropsychiatric, transcranial direct current stimulation

T he last 2 decades have provided a surge of new noninvasive neuromodulatory techniques offering translational appeal. Included prominently among these is transcranial direct current stimulation (tDCS). In tDCS, low levels of direct current (typically 0.5–0.2 mA; for higher intensity safety testing, see Chhatbar et al1) are applied via scalp-based electrodes (eg, 5 × 5 cm, 5 × 7 cm) to provide diffuse subthreshold stimulation across large areas of the brain. With standard tDCS, 2 electrodes, an anode (+) and cathode (−), are applied to the scalp, and current flows between them. The general logic is that current modulates the resting potential of underlying neural populations, thereby enhancing or suppressing excitability for a limited time period (eg, for an hour2–6 (reviewed in References7–11)). The appeal of tDCS as a neuroscientific and therapeutic tool is that it is comparatively affordable, associated with minor temporary adverse effects (eg, skin irritation, headache), and it holds potential for lasting benefits in healthy and clinical populations (reviewed in References12–14).

Since the first modern report of cognitive enhancement with tDCS in healthy participants,15 there has been substantial interest into tDCS cognitive effects from researchers,16,17 media,18,19 and the public alike.20 This attention likely has been driven by the potential for future tDCS-inspired “thinking caps” for healthy people seeking cognitive advantage and clinical populations seeking to address associated cognitive and functional impairments. In result, there is now a considerable body of research, including studies conducted on diverse clinical populations, cognitive functions, and abilities (eg, see Dedoncker et al21). However, this research has produced controversy (eg, see References22–24), with some commentators raising concerns regarding the validity of reported effects in cognitive domains.25,26 This uncertainty is underscored by substantial deficits in understanding the mechanism(s) underlying reported cognitive effects,27,28 as well as inconsistencies regarding the effects of key stimulus parameters, including current intensity or treatment “dose.” For instance, increasing the stimulation intensity has been associated with superior,21 inferior,29–31 and no difference32 in cognitive outcomes (reviewed in Esmaeilpour et al33).

The aim of the current review is to provide a predominantly clinical audience with a succinct review of research investigating the cognitive effects of tDCS after single and longitudinal applications in healthy and clinical populations. Our aim was not to be comprehensive of the burgeoning tDCS literature, but rather to provide a curated overview of the tDCS field in general. Toward this end, we emphasized the findings from meta-analyses and reviews to maximize consistent patterns and minimize “noise” from individual studies. A secondary aim is to provide a summary of criticisms and limitations of the tDCS approach while casting an eye toward the key gaps in knowledge impeding translational implementation.

EFFICACY OF A SINGLE tDCS SESSION ON COGNITION IN NEUROTYPICAL ADULTS

A commonly used experimental approach is to conduct a single session of active tDCS and compare behavioral measures with performance during placebo (sham) stimulation. The research team applies a particular tDCS montage (eg, anode over a right prefrontal site and the cathode over a left prefrontal site) for 10 to 20 minutes, at low stimulus intensities. Sham stimulation is identical except the current is applied for a brief time period (eg, 30 seconds). Transcranial direct current stimulation can be applied “online,” such that participants perform a cognitive task during stimulation, or “off-line,” usually after completing tDCS.34–36 The single-session approach can be used to address questions related to structure-function relationships, and it permits taking advantage of within-subjects experimental designs. For example, we asked whether providing tDCS during an episodic memory encoding would facilitate the learning rate of verbal information. Participants completed the California Verbal Learning test,37 during left or right parietal anodal tDCS applied during the encoding stage or the retrieval stage. The results showed temporal and spatial specificity such that the
learning rate was faster exclusively during anodal tDCS applied to the left parietal lobe during encoding. 69 Over the last decade, the single-session approach has been used to investigate a wide array of cognitive functions, including perception, memory, attention, creativity, working memory, learning, and episodic memory. 56-62 In other words, for almost every cognitive domain, there is likely to be research using tDCS.

Despite the widespread range of reported cognitive benefits, the results are modest, and there is controversy surrounding the usefulness of single sessions of tDCS in healthy participants. Several recent meta-analyses demonstrate null or limited effects of tDCS performance in healthy populations, whereas others report some benefits under isolated conditions or report methodological concerns with particular meta-analyses. 66 One key observation is that some genetic and behavioral measures of individual differences are predictors of behavioral responses to single tDCS sessions. Heterogeneous patterns of response are particularly evident for tasks assessing higher-level "executive" abilities, including working memory. For example, after the identical experimental protocol targeting right parietal regions, we observed that only the participants with high working memory capacity showed tDCS-linked improvement, whereas participants with low working memory capacity showed no effect or were impaired. Thus, collapsing across heterogeneous samples contributes to observations of null effects or small effect sizes. A growing literature confirms participant heterogeneity in tDCS effects across a range of cognitive tasks. To optimize tDCS protocols, a more complete understanding of how individual differences predict outcomes is essential.

A related consideration is the age of the population. Not surprisingly, there are efforts to use tDCS to stabilize or maintain cognitive performance in healthy and abnormally aging populations. Age-related changes in brain connectivity provide additional targets for tDCS including resting-state and functional connectivity (reviewed in References 64-66). Several studies comparing young and older adult responses to tDCS indicate there are age-related differences in terms of responsiveness to tDCS. To optimize tDCS protocols, a more complete understanding of how individual differences predict outcomes is essential.

A further methodological factor that may account for heterogeneity in outcomes between studies is diversity in methods for administering "sham" stimulation. Various methods have been used to conceal blinding. Most commonly applied are the fade-in, short-pulse stimulation (eg, 30 seconds), fade-out methods because participants reliably remain blinded to condition. A confound of these stimulation methods is that the sham machine produces a small current while on, which is common for commercial machines as a means to continuously assess impedance. In a recent study, we assessed both the cognitive and neurophysiological effects of 3 different "sham" conditions (0.034, 0.016, and 0 mA with the machine off). Importantly, results showed that, following a single tDCS session, neurophysiological results on electroencephalogram showed that the very low "sham" stimulation (ie, 0.034 mA) elicited biological effects similar to standard active stimulation intensities. 32

Efficacy of a Single tDCS Session in Neuropsychiatric Conditions

An increasing number of controlled studies have investigated the acute cognitive effects of a single tDCS session in clinical samples with associated cognitive impairment. Major depressive disorder (MDD) is associated with cognitive and affective dysfunction, including impairments in processing speed, sustained attention, working memory, memory, and executive functions, as well as negative attentional biases for emotional information. 59,60 The left dorsolateral prefrontal cortex (LDLPFC) is a key node in the dysfunctional "cognitive control" network in depression considered associated with depression-related cognitive and affective symptoms. 61 A number of randomized controlled trials (RCTs) have investigated the effects of a single session of anodal tDCS administered to the LDLPFC in MDD (Table 1); for a comprehensive list of RCTs involving tDCS, see References 62-64; for consensus perspective, see Lefaucheur et al 65). Significant improvements relative to sham stimulation were observed for speed of information processing, working memory, and affective processing. 66 These findings are consistent with enhanced functioning of the DLPCF and "cognitive control" network, thus supporting a potential role for anodal tDCS targeting LTDLPFC to ameliorate MDD-associated cognitive and affective symptoms. While neuroimaging suggests that normalization of this network activity is related to antidepressant response, the acute effects of tDCS have not been associated with mood effects thus far (eg, see Boggio et al 67). As mood response has previously been associated with acute cognitive changes in divided attention with high-frequency repetitive transcranial magnetic stimulation administered to the LTDLPFC, this association remains a promising area for future research.

Interestingly, although the majority of studies have investigated only short-term cognitive effects, Gogler et al 68 recently showed significant cognitive effects at 24 hours poststimulation, an effect that was not evident immediately after tDCS treatment. To our knowledge, this was the first demonstration of delayed cognitive effects following a single tDCS session in patients with MDD. A major methodological difference with that study compared with others was that the task involved detailed examination of visual attention processing over the course of an hour both at posttreatment and follow-up. Therefore, a likely interpretation of this effect is that active tDCS facilitated learning on the task at posttreatment. The implication is that learning conducted around a single tDCS session in MDD may potentially be maintained over time.

Fewer studies have examined acute effects in other clinical samples with associated cognitive impairments (ie, schizophrenia, bipolar disorder, mild cognitive impairment [MCI]). Schizophrenia is commonly associated with significant cognitive impairment, particularly in the domains of verbal memory, attention, speed of processing, and executive functioning. 69 Deficits considered to be associated with illness-related functional deficits. 10 Cognitive enhancement with tDCS in patients with schizophrenia therefore has potentially important therapeutic implications and is known to reduce auditory hallucinations. 10 Current evidence for acute cognitive effects, however, is limited. Hoy et al 10 similarly investigated off-line effects of anodal tDCS administered to the LDLPFC, finding that only the higher current intensity (ie, 2 mA) significantly improved accuracy on a 2-back working memory task, with effects maintained at 40 minutes after stimulation. In contrast, Vercammen et al 10 similarly administered 2 mA to the LDLPFC but found no overall effect for improving performance on a difficult implicit learning task. These contrasting findings in relation to stimulation intensity may suggest that tDCS efficacy in schizophrenia may be more related to interindividual differences as mentioned in the previous section.

Similarly, bipolar disorder has been associated with cognitive impairment, with prominent deficits in sustained attention, memory, and executive function. 101 Evidence for acute cognitive effects is similarly limited. Martin et al 102 found no overall benefit of anodal tDCS administered to the LDLPFC for sustained attention or working memory in euthymic patients. Interestingly, analysis of individual responses showed that only approximately 30% of patients gained substantial cognitive benefit with active tDCS.
in both active conditions (ie, with different cathode placements). Further, these patients showing benefit were found to be the poorest performers during sham stimulation. This study thus highlighted the role of interindividual factors rather than methodological factors (ie, montage) in affecting tDCS efficacy.

Lastly, another clinical population where acute cognitive effects have been studied is patients with MCI, who are at increased risk of dementia.118,119 There is a high prevalence of MCI in older adults120,121 and currently no effective intervention for improving cognition.121 One RCT so far has investigated tDCS acute effects, showing improved semantic retrieval associated with concomitant reductions in regional blood flow in processing specific regions on functional magnetic resonance imaging.123 Further investigation of the efficacy of tDCS in this clinical population is therefore warranted.

## Efficacy of Repeated tDCS Sessions in Neurotypical Adults

Very little work has examined the cognitive consequences of repeated application of tDCS to healthy adult populations when tDCS is not paired with a specific task. This may be surprising given the level of media exposure afforded tDCS and the claims of “supercharging” brain function, because the do-it-yourself community may be less likely to incorporate a task during self-tDCS, yet would benefit from guidance.123,124 There is conflicting evidence for cognitive enhancement in healthy adults following repeated tDCS when given alone. Motohashi et al125 found no effects on a battery of cognitive tasks following 4 daily tDCS sessions in which the anode was placed over the LDLPFC and cathode over the right supraorbital area. Similarly, there was no effect on response inhibition following 3-second daily tDCS sessions where the anode was placed over the LDLPFC and cathode over the right cerebellum.126 In contrast, another group found that 6 sessions of anodal tDCS over LDLPFC, cathode over right dorsolateral prefrontal cortex (DLPFC), improved response inhibition, and these effects lasted for at least 1 month after the final session.127 It is difficult to reconcile these findings in the context of methodological differences between studies, including the number of sessions, tDCS montages, and cognitive outcome measures. The potential for biological effects from the sham stimulation condition given over repeated sessions is another potential confound, as discussed above. As we will discuss in a later section, the majority of longitudinal designs implementing tDCS pair it with a specific cognitive task.

### Table 1. Summary of Recent Studies Investigating the Effects of a Single tDCS Session on Cognition in Neuropsychiatric Samples

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Design</th>
<th>Online/Off-line</th>
<th>Montage (A/C)</th>
<th>Current Density, mA/cm²</th>
<th>Task</th>
<th>Performance Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boggio et al103</td>
<td>Dep</td>
<td>Parallel</td>
<td>Offline</td>
<td>F3/FP2</td>
<td>0.057</td>
<td>Affective go/no go</td>
<td>Improved correct responses</td>
</tr>
<tr>
<td>Loo et al104</td>
<td>Dep</td>
<td>Parallel</td>
<td>Offline</td>
<td>F3/F8</td>
<td>0.057</td>
<td>SDMT</td>
<td>Improved correct responses</td>
</tr>
<tr>
<td>Brunoni et al105</td>
<td>Dep</td>
<td>Parallel</td>
<td>Online</td>
<td>F3/F4</td>
<td>0.080</td>
<td>PCL</td>
<td>Absence of practice effect</td>
</tr>
<tr>
<td>Oliveira et al106</td>
<td>Dep</td>
<td>Parallel</td>
<td>Offline</td>
<td>F3/F4</td>
<td>0.080</td>
<td>2-back</td>
<td>Improved correct responses</td>
</tr>
<tr>
<td>Wolkenstein et al107</td>
<td>Dep</td>
<td>Crossover</td>
<td>Online</td>
<td>F3/ConEX</td>
<td>0.029</td>
<td>DWM</td>
<td>Faster reaction times</td>
</tr>
<tr>
<td>Brunoni et al98</td>
<td>Dep</td>
<td>Parallel</td>
<td>Offline</td>
<td>F3/F4</td>
<td>0.080</td>
<td>WEST</td>
<td>Faster reaction times</td>
</tr>
<tr>
<td>Moreno et al99</td>
<td>Dep</td>
<td>Parallel</td>
<td>Offline</td>
<td>OLE</td>
<td>0.080</td>
<td>2-back, IST</td>
<td>Improved residual score change on 2 back</td>
</tr>
<tr>
<td>Gogler et al100</td>
<td>Dep</td>
<td>Parallel</td>
<td>Offline</td>
<td>F3/RSO</td>
<td>0.057</td>
<td>TVA</td>
<td>Increased elements processed/second</td>
</tr>
<tr>
<td>Brennan et al101</td>
<td>Dep</td>
<td>Crossover</td>
<td>Online and offline</td>
<td>F3/RSO</td>
<td>0.043</td>
<td>TT, TMT, DST, ERT</td>
<td>Improved recognition of anger and happy</td>
</tr>
<tr>
<td>Vercammen et al102</td>
<td>Sz</td>
<td>Crossover</td>
<td>Online</td>
<td>F3/RSO</td>
<td>0.057</td>
<td>WPT</td>
<td>No effect</td>
</tr>
<tr>
<td>Ribolisi et al103</td>
<td>Sz</td>
<td>Crossover</td>
<td>Offline</td>
<td>P4/ConEX, F3/ConEX</td>
<td>0.029</td>
<td>Line bisection, MNL</td>
<td>Left attention bias on line bisection task, no effect MNL</td>
</tr>
<tr>
<td>Hoy et al104</td>
<td>Sz</td>
<td>Crossover</td>
<td>Offline</td>
<td>F3/RSO</td>
<td>0.029, 0.057</td>
<td>2 back</td>
<td>Improved discriminability</td>
</tr>
<tr>
<td>Knechtle105</td>
<td>Sz</td>
<td>Crossover</td>
<td>Offline</td>
<td>F3/RSO</td>
<td>0.057</td>
<td>Auditory go/no go</td>
<td>No effect</td>
</tr>
<tr>
<td>Martin et al106</td>
<td>BP</td>
<td>Crossover</td>
<td>Online</td>
<td>F3/ConEX, F3/cerebellar</td>
<td>0.057</td>
<td>3 back, CPT</td>
<td>No effect</td>
</tr>
<tr>
<td>Meinerz et al107</td>
<td>MCI</td>
<td>Online</td>
<td>BA44/45/RSO</td>
<td>0.029</td>
<td>Semantic word retrieval</td>
<td>Decreased errors</td>
<td></td>
</tr>
</tbody>
</table>

The electrode montage indicates anode (A) and cathode (C) sites using the 10–20 system for EEG.

BP indicates bipolar; CPT, continuous performance task; Dep, depression; DST, Digit Span Test; DWM, delayed-response working memory task; ERT, Emotion Recognition Test; IST, internal shift task; MNL, mental number line bisection test; PCL, probabilistic classification learning task; RSO, right supraorbital; SDMT, Symbol Digit Modalities Test; Sz, schizophrenia; TVA, theory of visual attention; TMT, Trail Making Test; TT, Tapping Test; WEST, word emotional Stroop task; WPT, weather prediction test.
### TABLE 2. Summary of Studies Investigating the Effects of Repeated tDCS Sessions on Cognition in Neuropsychiatric Samples

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Design</th>
<th>Sessions</th>
<th>Electrode Montage (Anode/Cathode)</th>
<th>Current Density, mA/cm²</th>
<th>Tasks</th>
<th>Performance Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fregni et al¹²⁸</td>
<td>Dep</td>
<td>Parallel</td>
<td>5</td>
<td>F3/RSO</td>
<td>0.028</td>
<td>MMSE, SDMT, DSp, Stroop, FPT</td>
<td>Improved DSp forward and back</td>
</tr>
<tr>
<td>Loo et al¹²⁹</td>
<td>Dep</td>
<td>Parallel</td>
<td>5</td>
<td>F3/F8</td>
<td>0.028</td>
<td>RAVLT, TMT A and B, DSp, COWAT letter and category</td>
<td>No effect</td>
</tr>
<tr>
<td>Loo et al¹³⁰</td>
<td>Dep</td>
<td>Parallel</td>
<td>15</td>
<td>F3/F8</td>
<td>0.057</td>
<td>RAVLT, DSp, Stroop, COWAT letter</td>
<td>No effect</td>
</tr>
<tr>
<td>Palm et al¹³⁰</td>
<td>Dep/BP</td>
<td>Crossover</td>
<td>10</td>
<td>F3/RSO</td>
<td>0.028/0.057</td>
<td>MMSE, RAVLT, LNS, RWT</td>
<td>No effect</td>
</tr>
<tr>
<td>Brunoni et al¹³¹</td>
<td>Dep</td>
<td>Parallel</td>
<td>12</td>
<td>F3/F4</td>
<td>0.080</td>
<td>MoCA, DSp, Stroop, TMT A and B</td>
<td>No effect</td>
</tr>
<tr>
<td>Bennabi et al¹³²</td>
<td>Dep</td>
<td>Parallel</td>
<td>10</td>
<td>F3/RSO</td>
<td>0.057</td>
<td>MMSE, TMT A and B, COT, IST, PNT</td>
<td>No effect</td>
</tr>
<tr>
<td>Brunoni et al¹³³</td>
<td>Dep</td>
<td>Parallel</td>
<td>22</td>
<td>OLE</td>
<td>0.080</td>
<td>MoCA, DSp, DSST, COWAT letter and category</td>
<td>No effect</td>
</tr>
<tr>
<td>Loo et al¹³⁴</td>
<td>Dep/BP</td>
<td>Parallel</td>
<td>20</td>
<td>F3/F8</td>
<td>0.071</td>
<td>MoCA, CVLT-II, DSp, SDMT, Ruff 2&amp;7, DKEFS verbal fluency</td>
<td>Improved category switching</td>
</tr>
<tr>
<td>Smith et al¹³⁵</td>
<td>Sz</td>
<td>Parallel</td>
<td>5</td>
<td>F3/Fp2</td>
<td>0.394</td>
<td>MATRICS battery</td>
<td>Improved global composite, working memory, attention</td>
</tr>
<tr>
<td>Palm et al¹³⁶</td>
<td>Sz</td>
<td>Parallel</td>
<td>10</td>
<td>F3/Fp2</td>
<td>0.057</td>
<td>SOPT, TMT A and B</td>
<td>No effect</td>
</tr>
<tr>
<td>Bersani et al¹³⁷</td>
<td>BP</td>
<td>Parallel</td>
<td>15</td>
<td>F3/R cerebellar</td>
<td>0.057</td>
<td>TMT A and B, WCST, RCFT</td>
<td>Improved TMT B</td>
</tr>
</tbody>
</table>

The electrode montage indicates sites using the 10–20 system for EEG.

BP indicates bipolar; COWAT, Controlled Oral Word Association Test; Dep, depression; CVLT II, California Verbal Learning Test—second edition; DKEFS, Delis-Kaplan Executive Function System; DSp, Digit Span; DSST, Digit symbol substitution test; FPT, Five-Point Test; LNS, Letter Number Sequencing; MATRICS, MATRICS Consensus Cognitive Battery; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test; Ruff 2&7, Ruff 2 & 7 Selective Attention Test; SDMT, Symbol Digit Modalities Test; SOPT, Self-ordered Pointing Task; Sz, schizophrenia; TMT A, Trail Making Test Part A; TMT B, Trail Making Test Part B; WCST, Wisconsin Card Sorting Test.

Cognitive improvement.¹³⁸ Nevertheless, evidence to date suggests no beneficial effect.⁴⁴,¹²⁹,¹³⁰,¹³¹,¹³²,¹³³,¹³⁴,¹³⁵,¹³⁶,¹³⁷,¹³⁸,¹³⁹,¹⁴⁰ reviewed in Martin et al.¹⁴¹. This is corroborated by mixed (eg, schizophrenia) or limited (ie, bipolar disorder) findings from controlled studies in other clinical conditions and in healthy samples (described above).

One relevant methodological factor for these null results could be that in the majority of these trials tDCS treatment was given alone, with no specified cognitive task or activity during stimulation. During tDCS treatment, patients’ “online” brain activity was thus uncontrolled, potentially leading to both reduced cognitive efficacy and/or increased interindividual variability in outcomes. Future tDCS treatment studies involving repeated sessions should attempt to standardize patients’ brain activity during stimulation. This was done in the study of Smith et al. using a PowerPoint presentation of pleasant images shown during treatment (personal communication, electronic communication to author Donel Martin).

**Efficacy of Repeated tDCS Sessions Combined with Cognitive Training**

There is growing enthusiasm for longitudinal tDCS designs using a combined approach in which tDCS is paired with a task occurring during stimulation. The rationale is that because tDCS modulates resting membrane potentials in a subthreshold manner, concurrent brain activity is required during tDCS to produce lasting neuroplastic changes beyond the period of stimulation.¹⁴² Importantly, some data show durable (>1 month) cognitive effects using this approach. These effects may facilitate concurrent task-induced effects due to repeated tDCS-induced long-term potentiation-like neuroplastic changes.¹⁴³–¹⁴⁸ However, our understanding is incomplete. We begin this section by summarizing the small collection of studies pairing tDCS and cognitive training in healthy populations before turning to the smaller literature involving clinical populations.

The enthusiasm surrounding combined tDCS plus cognitive training counters the general view that cognitive training is ineffective. Cognitive training research¹⁴⁹ and commercial brain training software¹⁵⁰,¹⁵¹ primarily show null or disappointing results. The data reveal practice-related task-specific performance benefits that show little generalization in the minority of cases where transfer to untrained tasks is measured.¹⁴⁹,¹⁵²–¹⁵⁶ Importantly, under certain conditions, there are significant benefits of cognitive training, including when there is a theoretically grounded protocol¹⁵⁷–¹⁵⁹ and when tailored to a specific population’s needs, such as in older adults.¹⁶⁰,¹⁶¹ Combining cognitive training with tDCS in healthy or clinical populations shows promise in extending and enhancing performance improvements. Importantly, compared with the mixed findings from single-session tDCS paradigms, the small number of longitudinal studies appears to be more robust to individual differences and show benefits across healthy participants,¹⁶²,¹⁶³ although higher baseline performance still predicts greater gains.¹⁶⁴ Going forward, systematic collection of independent baseline cognitive and physiological measures will be needed to clarify the extent of impact that individual differences have on longitudinal designs.

The electrode montage indicates sites using the 10–20 system for EEG.

BP indicates bipolar; COWAT, Controlled Oral Word Association Test; Dep, depression; CVLT II, California Verbal Learning Test—second edition; DKEFS, Delis-Kaplan Executive Function System; DSp, Digit Span; DSST, Digit symbol substitution test; FPT, Five-Point Test; LNS, Letter Number Sequencing; MATRICS, MATRICS Consensus Cognitive Battery; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test; Ruff 2&7, Ruff 2 & 7 Selective Attention Test; SDMT, Symbol Digit Modalities Test; SOPT, Self-ordered Pointing Task; Sz, schizophrenia; TMT A, Trail Making Test Part A; TMT B, Trail Making Test Part B; WCST, Wisconsin Card Sorting Test.

SUMMARY OF STUDIES INVESTIGATING THE EFFECTS OF REPEATED tDCS SESSIONS ON COGNITION IN NEUROPSYCHIATRIC SAMPLES

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<td>0.028/0.057</td>
<td>MMSE, RAVLT, LNS, RWT</td>
<td>No effect</td>
</tr>
<tr>
<td>Brunoni et al¹³¹</td>
<td>Dep</td>
<td>Parallel</td>
<td>12</td>
<td>F3/F4</td>
<td>0.080</td>
<td>MoCA, DSp, Stroop, TMT A and B</td>
<td>No effect</td>
</tr>
<tr>
<td>Bennabi et al¹³²</td>
<td>Dep</td>
<td>Parallel</td>
<td>10</td>
<td>F3/RSO</td>
<td>0.057</td>
<td>MMSE, TMT A and B, COT, IST, PNT</td>
<td>No effect</td>
</tr>
<tr>
<td>Brunoni et al¹³³</td>
<td>Dep</td>
<td>Parallel</td>
<td>22</td>
<td>OLE</td>
<td>0.080</td>
<td>MoCA, DSp, DSST, COWAT letter and category</td>
<td>No effect</td>
</tr>
<tr>
<td>Loo et al¹³⁴</td>
<td>Dep/BP</td>
<td>Parallel</td>
<td>20</td>
<td>F3/F8</td>
<td>0.071</td>
<td>MoCA, CVLT-II, DSp, SDMT, Ruff 2&amp;7, DKEFS verbal fluency</td>
<td>Improved category switching</td>
</tr>
<tr>
<td>Smith et al¹³⁵</td>
<td>Sz</td>
<td>Parallel</td>
<td>5</td>
<td>F3/Fp2</td>
<td>0.394</td>
<td>MATRICS battery</td>
<td>Improved global composite, working memory, attention</td>
</tr>
<tr>
<td>Palm et al¹³⁶</td>
<td>Sz</td>
<td>Parallel</td>
<td>10</td>
<td>F3/Fp2</td>
<td>0.057</td>
<td>SOPT, TMT A and B</td>
<td>No effect</td>
</tr>
<tr>
<td>Bersani et al¹³⁷</td>
<td>BP</td>
<td>Parallel</td>
<td>15</td>
<td>F3/R cerebellar</td>
<td>0.057</td>
<td>TMT A and B, WCST, RCFT</td>
<td>Improved TMT B</td>
</tr>
</tbody>
</table>
In healthy neurotypical adults, longitudinal studies typically include 2 to 10 cognitive training sessions during which anodal or sham tDCS is applied to the right DLPFC or LDLPFC during 1 or more training tasks. For example, participants in a working memory training study might perform both visual and spatial working memory task during tDCS. Again, there is a proliferation of experimental paradigms such that each laboratory conducts studies slightly differently. However, despite this diversity, there are a number of reports showing improvements in a range of cognitive areas including visual working memory,171–176 verbal working memory,172,177–179 multitasking,179 attention,180 and decision making.180 (Table 3). Evidence of near transfer to similar untrained tasks has been reported across several studies,174,177,179 and to unrelated tasks in tests of far transfer.168,180,181 In a subset of these studies, follow-up testing after periods of no contact revealed prolonged generalization effects lasting several weeks68,127,167,179 to a year.164

The effect of combined tDCS and cognitive training in clinical samples, however, is scattered, with few studies in any given clinical population. The clinical population contributing the largest number of tDCS studies is those with poststroke aphasia, accompanied by some work in those with primary progressive aphasia. In these populations, paired approaches find enhanced fluency and word-finding abilities.182–186 For example, multiple sessions of anodal tDCS targeting the LDLPFC while practicing a naming task resulted in enhanced verbal fluency in stroke patients with aphasia.187

The remaining studies are diverse and suffer from low power. What is currently reported is that variable forms of cognitive training (eg, PASAT, word naming, attention training) paired with 5 to 10 sessions of tDCS generally over the DLPFC improve performance on those trained tasks beyond the cognitive training alone. This pattern is observed in those with multiple sclerosis (reviewed in References188,189), Alzheimer disease,190 and traumatic brain injury.191 At this point, the data are tantalizing, but it remains to be seen whether these observations translate to meaningful therapeutic interventions.

One emerging pattern across this literature is that in some cases tDCS-linked performance differences are not immediately detectible, but rather they emerge over time when follow-up testing is included. For example, those who received 10 sessions of tDCS paired with visuospatial working memory training showed sustained benefits and near transfer after 1 month of no contact, whereas the sham group had lost ground.192 These observations highlight the need for later follow-up testing to avoid missing significant training effects, which may emerge over a protracted timeline, which may not be present immediately following the intervention.170

The problem of understanding the mechanism of cognitive effects using this combined paradigm is being addressed by studies that have included neuroimaging. For example, by collecting electroencephalogram before and after 4 sessions of tDCS paired with a visual working memory in young adults, the neural correlates of behavioral improvement were isolated. The data indicated that the 4 sessions altered alpha and theta band phase locking between posterior and anterior sites, exclusively in the active tDCS group.166 In the perceptual domain, a second study collected functional magnetic resonance imaging data pre/post and at follow-up from 5 sessions of tDCS to S1 and found lasting differences in the active tDCS group.192 Future studies pairing combined longitudinal designs with neuroimaging techniques will therefore be important to identify the neural correlates of behavioral changes.

### TABLE 3. Summary of Studies Investigating the Effects of Multiple tDCS Sessions Paired With Cognitive Training in Neurotypical Samples

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Design, No. Sessions</th>
<th>On/Offline</th>
<th>Electrode Montage (A/C)</th>
<th>Current Density, mA/cm²</th>
<th>Task</th>
<th>Performance Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephens and Berryhill</td>
<td>OA</td>
<td>Parallel, 5</td>
<td>Online</td>
<td>F4/cheek</td>
<td>0.028, 0.057</td>
<td>Vis, Sp WM</td>
<td>Far transfer at 1 mo f/u</td>
</tr>
<tr>
<td>Jones et al166</td>
<td>YA</td>
<td>Parallel, 5–10</td>
<td>Online</td>
<td>F4-P4/cheek</td>
<td>0.043</td>
<td>Vis WM</td>
<td>Improved accuracy</td>
</tr>
<tr>
<td>Katz et al164, Au et al165</td>
<td>YA</td>
<td>Parallel, 7</td>
<td>Online</td>
<td>F4, F3/Fp1, Fp2</td>
<td>0.057</td>
<td>Vis n-bk</td>
<td>Improved accuracy, sustained at 1 yr f/u</td>
</tr>
<tr>
<td>Brasil-Neto144</td>
<td>YA</td>
<td>Parallel, 10</td>
<td>Online + offline</td>
<td>F3/F4</td>
<td>0.043</td>
<td>Ver/Sp WM</td>
<td>Improved accuracy, near transfer</td>
</tr>
<tr>
<td>Wu et al145</td>
<td>YA</td>
<td>Parallel, 10</td>
<td>Online</td>
<td>F3/R deltoid</td>
<td>0.057</td>
<td>Ver WM</td>
<td>Improved accuracy (borderline), near transfer at 1 mo f/u</td>
</tr>
<tr>
<td>Rohan et al146</td>
<td>YA</td>
<td>Parallel, 3</td>
<td>Online + offline</td>
<td>F3/rSO</td>
<td>0.028</td>
<td>Ver/Sp WM</td>
<td>Day 1 improved accuracy</td>
</tr>
<tr>
<td>Park et al174</td>
<td>OA</td>
<td>Parallel, 10</td>
<td>Online</td>
<td>F3, F4/arm</td>
<td>0.08</td>
<td>Ver WM</td>
<td>Improved accuracy, near transfer post and 1 mo f/u</td>
</tr>
<tr>
<td>Looi et al177</td>
<td>YA</td>
<td>Parallel, 2</td>
<td>Online</td>
<td>F4/F3</td>
<td>0.04</td>
<td>Math</td>
<td>Improved RT and accuracy, transfer to ver WM, post and 2 mo f/u</td>
</tr>
<tr>
<td>Filmer et al179</td>
<td>YA</td>
<td>Parallel, 4</td>
<td>Online</td>
<td>F3/rSO</td>
<td>0.028</td>
<td>Multitasking</td>
<td>Near transfer; post and 2-wk f/u</td>
</tr>
<tr>
<td>Filmer et al180</td>
<td>YA</td>
<td>Parallel, 4</td>
<td>Online</td>
<td>F3/rSO</td>
<td>0.028</td>
<td>Decision making</td>
<td>Improved RT; post and 2-wk f/u, far transfer to visual search post and f/u</td>
</tr>
<tr>
<td>Monte-Silva et al143</td>
<td>OA</td>
<td>Parallel, 20</td>
<td>Online + offline</td>
<td>F3-F5/rSO</td>
<td>0.057</td>
<td>Ver/Vis WM and task switching</td>
<td>No effect</td>
</tr>
</tbody>
</table>

The electrode montage indicates anode (A) and cathode (C) sites using the 10–20 system for EEG.

f/u Indicates follow-up; OA, older adults; Sp, spatial; rSO, supraorbital; Vis, visual; Ver, verbal; WM, working memory; YA, younger adults.
MODERATIONAL FACTORS

While a large number of moderational factors are associated with tDCS cognitive efficacy, there is no current consensus regarding which are most important or most relevant to outcomes. This is further complicated by inconsistencies in findings between studies (eg, stimulus intensity\textsuperscript{102,104}). As noted above, I consistent theme that has emerged, however, is that interindividual factors are highly relevant. This was confirmed by the most recent meta-analysis of single-session tDCS cognitive effects, which was restricted to crossover sham-controlled studies where tDCS was administered to the DLPFC.\textsuperscript{22} This meta-analysis examined a number of different stimulation factors as predictors of tDCS effects, including current intensity, density, duration, charge, laterality, montage, and timing of stimulation (ie, online or offline). However, interestingly for the outcomes where tDCS was shown to have significant efficacy, only the timing of stimulation was a significant predictor, such that “online” tDCS elicited stronger behavioral effects. This suggests that tDCS cognitive efficacy may be more dependent on both how the stimulus interacts with ongoing brain activity (ie, related to timing of stimulation and task) and other interindividual factors not accounted for in the analysis (ie, other than age and sex). Greater cognitive effects with “online” stimulation are consistent with neuroimaging studies showing greater metabolic,\textsuperscript{193} and blood oxygen level dependent responses\textsuperscript{184} in targeted stimulated regions during compared with after stimulation. With regard to other potentially relevant factors, pretreatment cognitive performance has been found to be important, particularly in clinical populations.\textsuperscript{102,106} Physiological differences between participants are also important, for example, head size that affects the shunting of current between electrodes and other differences in brain morphology.\textsuperscript{78} Another candidate interindividual factor likely important is the relative strength of the tDCS-induced electric field in targeted stimulated regions/networks subserving performance, as this varies between individuals because of physiological differences (eg, see Bai et al\textsuperscript{195}), and as noted above. This remains to be systematically investigated.

SUMMARY AND FUTURE DIRECTIONS

The last decade has seen a tremendous increase in research applying tDCS to study questions of brain structure-function and to develop novel interventions to improve cognitive performance. This review began by revisiting the cognitive effects of single sessions of anodal tDCS, most commonly applied to the DLPFC, in healthy and neuropsychiatric populations. In healthy populations, cognitive tasks are typically conducted “online” during stimulation; this is less consistently the case in clinical populations. The diverse research methodologies used make these findings difficult to encapsulate. Conservatively speaking, a single anodal tDCS session can modestly and temporarily benefit cognitive performance. Emerging results indicate that there are heterogeneous patterns of behavioral effects across participants such that subsets of participants may show cognitive benefits, whereas others experience no effect or impairment. Thus, future work investigating why individual differences matter is urgently needed. For example, using computational modeling to model the individual stimulus pathways and resulting electric fields may be beneficial for understanding the effects of physiological differences. Future work should also ensure that no active stimulation is given during sham, as this may cause biological effects\textsuperscript{32} and thus potentially confound interpretation of outcomes. Apart from the temporary effects afforded by single sessions of tDCS, more durable effects have been associated with repeated tDCS sessions (reviewed in Berryhill\textsuperscript{162}). What is clear from the existing data is that longitudinal tDCS offers more consistent broader cognitive benefits in healthy and neuropsychological populations when tDCS is applied “online” during concurrent task performance. In neuropsychiatric populations, the findings are less robust, particularly when tDCS has been given alone (eg, for treatment of depression). Thus, future research is needed to determine if longitudinal tDCS might provide greater cognitive benefit to neuropsychiatric populations when conducted using combined approaches.

Key knowledge gaps pertain to the mechanism for tDCS cognitive effects of both single-session and longitudinal designs. Physiological and neuroimaging studies have shown that tDCS acute effects involve many neurotransmitter systems,\textsuperscript{196–199} changes in local neurochemistry,\textsuperscript{5,200,201} and neural connectivity.\textsuperscript{74,166,202} Findings from longitudinal studies suggest that the mechanism involves lasting neuroplastic changes that are likely different than acute effects.\textsuperscript{203–207}

It is noteworthy that the mechanism of tDCS is clearer in the motor system where correspondence between input and output is better understood (eg, Fricke and Seeber\textsuperscript{208}). The relationship between each parameter and behavioral outcomes, as with cognitive tasks, however, is far more complex. This is likely due to the large interindividual variability in performance and corresponding neural activity for any given behavioral task. This presents a significant challenge going forward, as the lack of an account for the mechanism currently confounds interpretation of diverse and conflicting findings, which is further underscored by the broad parameter space and lack of consistency between laboratories.\textsuperscript{209} Future work is needed to parametrically modulate these variables to optimize effects, establish convention, and enable apples-to-apples comparisons across laboratories. These measures will further facilitate delineation of mechanistic accounts for observed cognitive effects, for example, with neuroimaging.

REFERENCES


Minniti A, Cason S. No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations. *Cortex*. 2017;94:131–141.


