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A Pilot Study Comparing Effects of Bifrontal Versus Bitemporal Transcranial Direct Current Stimulation in Mild Cognitive Impairment and Mild Alzheimer Disease

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Objective: While transcranial direct current stimulation (tDCS) can enhance aspects of memory in patients with mild cognitive impairment (MCI) and Alzheimer disease (AD), there has been wide variability in both the placement of tDCS electrodes and treatment response. This study compared the effects of bifrontal (anodal stimulation over the dorsolateral prefrontal cortices), bitemporal (anodal stimulation over the temporal cortices), and sham tDCS on cognitive performance in MCI and AD.

Methods: Seventeen patients diagnosed with MCI or mild AD received 3 sessions of anodal tDCS (bifrontal, bitemporal, 2 mA for 20 minutes; and sham) in random order. Sessions were separated by 1 week. The Alzheimer's Disease Assessment Scale–Cognitive Word Recognition Task, Alzheimer's Disease Assessment Scale–Cognitive Word Recall Task, 2-back, and Montreal Cognitive Assessment were used to assess cognition.

Results: There was a significant effect of stimulation condition on 2-back accuracy ($F_{2,28} = 5.28$ $P = 0.01$, $\eta^2p = 0.27$), with greater improvements following bitemporal tDCS compared with both bifrontal and sham stimulations. There were no significant changes on other outcome measures following any stimulation. Adverse effects from stimulation were mild and temporary.

Conclusions: These findings demonstrate that improvements in specific memory tasks can be safely achieved after a single session of bitemporal tDCS in MCI and mild AD patients.

Key Words: Alzheimer disease, mild cognitive impairment, transcranial direct current stimulation

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One of the earliest and most common clinical manifestations of Alzheimer disease (AD) is impairment of episodic memory with diminished ability to encode new material into long-term memory.[1] The temporal lobes of the brain are key structures in learning, recognition, and recall and are damaged in mild cognitive impairment (MCI) and AD.[2] Evidence has shown that impairment of free recall and recognition memory predicts conversion to Alzheimer dementia in MCI subjects.[3,4] The frontal lobes are also impacted in both MCI and AD, leading to difficulties with attention, processing speed, executive functioning, and expressive language.[5] Patients with AD demonstrate reduced activation of both the temporal cortices and the dorsolateral prefrontal cortices (DLPFCs).[6] Quantification using electron microscopy and immunohistochemical staining for synaptic markers has documented significant decreases in synaptic density and a loss of both presynaptic and postsynaptic components.[7] In recent years, biochemical analysis of the AD brain has revealed a robust correlation between soluble amyloid-β levels and the extent of synaptic loss and severity of cognitive impairment.[8] In experimental models, it has been shown that transsynaptic delivery of amyloid-β increases synapse loss, results in neuronal death, and blocks long-term potentiation.[9] As such, evidence suggests that increased synaptic dysfunction results in hypoactivity and impairs memory formation and cognitive performance in patients with MCI and AD.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that consists of applying a constant, low electric current between electrodes over the scalp to modulate cortical excitability.[10] Anodal stimulation, considered an excitatory stimulation, reduces the threshold required for neuronal firing and has been shown to improve neural efficiency, mood, and cognition.[11] Cathodal or inhibitory stimulation causes a hyperpolarization of the resting membrane potential and decreases neuronal excitability.[11] Based on this ability of tDCS to modulate synaptic transmission, anodal tDCS has been proposed as a therapeutic to improve mood and cognitive functions.[12] For example, tDCS has been found to be efficacious at reducing depressive symptoms in patients with depression.[13] Studies have also demonstrated improved working memory performance and enhanced episodic verbal memory with anodal tDCS in a variety of populations, including Parkinson disease,[14] as well as in depressed[15] and healthy individuals.[16–19]

However, parameters for the use of tDCS as a therapeutic intervention remain unstandardized in patients with cognitive impairment.[12]

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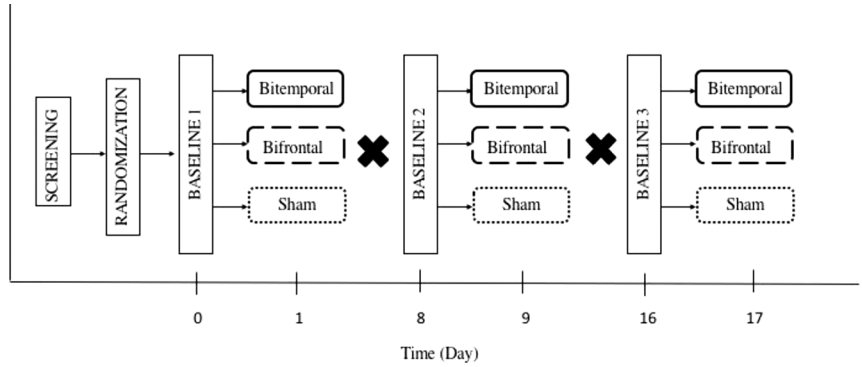

FIGURE 1. Study design. Assessments were conducted at each baseline and stimulation visit. On days 1, 9, and 17, only 1 type of stimulation was administered. The order of stimulations was randomized and counterbalanced.

In MCI and AD studies, there has been significant variability in the placement of the electrodes. Some studies have stimulated over the DLPFC,[20–24] whereas others stimulated over the temporal lobes.[25–28] To date, a single study evaluated the efficacy of temporal versus frontal lobe electrode placement on cognition in MCI or AD patients. Boggio et al[29] demonstrated improved recognition memory following both left temporal and left DLPFC stimulation compared with sham, with no significant differences between electrode locations. Typically, the anodal electrode has been placed over only the left hemisphere, although neuroimaging evidence has demonstrated bilateral hypoactivity in AD.[6] Two studies[25,26] have stimulated both the left and right temporal lobes with anodal electrodes (bitemporal) demonstrating improved recognition memory, yet no prior study has stimulated the left and right DLPFCs (bifrontal). These differences in tDCS target sites may contribute to the variability in outcomes.[12] It remains unknown whether bifrontal stimulation is efficacious in MCI or AD patients, and it is unclear if stimulating the frontal lobes compared with the temporal lobes affects cognitive domains differently. This pilot study aimed to address those knowledge gaps by evaluating the effect of electrode location, specifically bilateral tDCS over the frontal lobes compared with the temporal lobes, on cognitive performance in MCI and mild AD patients.

MATERIALS AND METHODS

Subjects

Eligible participants were 50 years or older and met criteria for mild or major neurocognitive disorder due to AD or mixed AD/vascular dementia as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.[30] We included fluent English-speaking patients of mild severity, scoring 12[31] or higher on the Montreal Cognitive Assessment (MoCA).[32] Patients were excluded if they had a pacemaker or any other metal implants that would preclude the safe use of tDCS, another significant neurological condition (eg, stroke, seizure disorder, multiple sclerosis, Parkinson disease, Lewy body spectrum disorders), a history of psychiatric disorders (eg, schizophrenia, bipolar disorder, psychosis, obsessive-compulsive disorder, generalized anxiety disorder), or current substance abuse disorder, except those with a history of major depressive disorder and currently in remission. Prior to study initiation, patients remained stable on psychotropic and cognitive-enhancing medications for at least 4 and 12 weeks, respectively. This study was approved by the Sunnybrook Research Ethics Board and was adherent to ethical standards. Informed consent was obtained from all participants.

Experimental Protocol

At screening/baseline, we assessed patients for eligibility and collected demographic and clinical information. Eligible patients were randomized to receive tDCS with 2 anodes over the temporal cortices (bitemporal), 2 anodes over DLPFC (bifrontal), and sham in a counterbalanced order. Cognitive assessments were administered before and immediately after each stimulation. This pair of assessments occurred over 2 days, with the first day including assessments only and the second day including stimulation and assessments. Following a 1-week washout period, participants returned for another pair of assessments. Each week, participants received a different type of stimulation (Fig. 1). Assessments were performed during the same time of day for each participant. With the exception of the interventionist, all patients, caregivers, physicians, and psychometrists were blinded to stimulation order.

Transcranial Direct Current Stimulation

Direct current was transferred by saline-soaked sponge electrodes (35 cm^2) and delivered by a battery-driven, contact current stimulation (Magstim Co Ltd, Whitland, UK). To stimulate the left and right DLPFCs, the anodes were placed over F3 and F4 according to the 10-20 international system for electroencephalogram electrode placement. The left and right temporal cortices were stimulated with anodes placed over T3 and T4 in accordance with the 10-20 electroencephalogram system. For both conditions, the reference, cathode electrode was placed over the inion (Iz) (Fig. 2). Participants received 2 mA tDCS for 20 minutes (with 30 seconds of ramp-up). The same procedure was used for sham stimulation, but current was applied only for the first 30 seconds. This procedure has been used previously

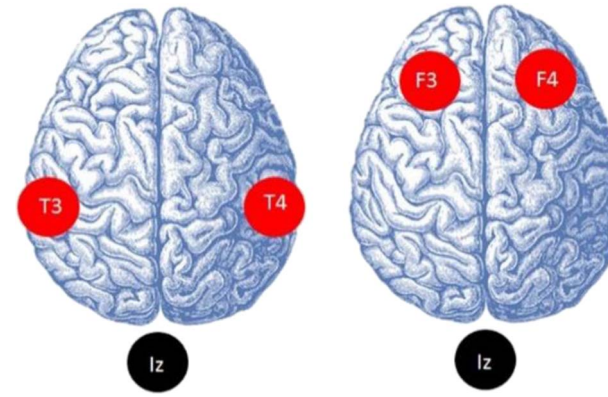

FIGURE 2. Schematic of electrode placements. Red and black circles indicate anodal and reference (cathodal) electrodes.

and is reliable to blind participants for the respective stimulation condition.[33]

Cognitive Assessments

Recognition memory was measured using the Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog) Word Recognition Task.[34] Previous AD studies have consistently found improvements following a single session of tDCS with the same assessment.[25,28,29,35] The Word Recall Task from the ADAS-Cog was used to assess recall memory.[34] The 2-back was used to measure reaction times (in milliseconds) and accuracy (d prime) of working memory.[36] The MoCA was used to assess global cognitive changes, including orientation, short-term memory, executive function, language abilities, attention, and visuospatial ability.[32] Alternative versions of all tasks were used to avoid learning effects.

Data Analysis

We performed a repeated-measures analysis of covariance (ANCOVA) to test whether there was an overall effect of the intervention (stimulation condition) on each cognitive assessment. We individually controlled for age, years of education, and diagnosis (mild versus major neurocognitive disorder due to AD or mixed AD/vascular disease) as these variables significantly affect cognitive performance.[37–39] When appropriate, we performed post hoc paired comparisons using Fisher least significant difference test to compare the 3 approaches. Statistical significance refers to $P < 0.05$ with no adjustments for multiple comparisons as this was a pilot study.

RESULTS

Efficacy of Single-Session tDCS

Of 19 patients assessed for eligibility, 2 were excluded as they did not meet minimum MoCA scores, and 17 were randomized to treatment. Four participants received treatment in a bifrontal-sham-bitemporal order. There were 3 participants for each of the following treatment orders: sham-bitemporal-bifrontal, sham-bifrontal-bitemporal, bifrontal-bitemporal-sham, bitemporal-sham-bifrontal. One participant received treatment in a bitemporal-bifrontal-sham order. Two patients refused to complete the 2-back memory task but completed all other assessments. Demographics and clinical characteristics are summarized in Table 1.

Repeated-measures ANCOVAs for the ADAS-Cog Word Recognition Task ($F_{2,28} = 0.48$, $P = 0.26$), the ADAS-Cog Word Recall Task ($F_{2,28} = 0.30$, $P = 0.97$), 2-back reaction time ($F_{2,26} = 0.36$, $P = 0.70$), and MoCA ($F_{2,28} = 1.22$, $P = 0.31$) did not reveal any significant differences between groups. However, a repeated-measures ANCOVA revealed that the main effect of stimulation condition was significant ($F_{2,28} = 5.28$, $P = 0.01$, $\eta^2p = 0.27$) on change in 2-back accuracy. Post hoc analyses revealed greater improvements on 2-back accuracy following bitemporal tDCS compared with both bifrontal and sham stimulations (Fig. 3). Following bitemporal stimulation, 2-back accuracy improved by 0.91 ± 1.09, whereas scores decreased by 0.40 ± 1.49 and 0.41 ± 1.45 following bifrontal and sham stimulation, respectively. There were no significant declines on 2-back accuracy following sham stimulation ($t_{14} = 0.87$, $P = 0.40$) or bifrontal stimulation ($t_{14} = 1.30$, $P = 0.22$). Performance after bitemporal stimulation was 7.6% higher in comparison to both bifrontal and sham stimulations. There were no differences between those who were and were not taking cognitive enhancing medications on 2-back accuracy performance following bitemporal stimulation ($t_{13} = 0.51$, $P = 0.62$), bifrontal stimulation ($t_{13} = -0.71$, $P = 0.49$), or sham ($t_{13} = -0.24$, $P = 0.81$). Further, a repeated-measures analysis of variance revealed no significant differences between prestimulation performances ($F_{2,28} = 0.26$, $P = 0.78$), suggesting the absence of carryover effects. There was also no significant difference on 2-back performance between stimulation order groups ($F_{5,9} = 0.40$, $P = 0.84$), suggesting the lack of order effects.

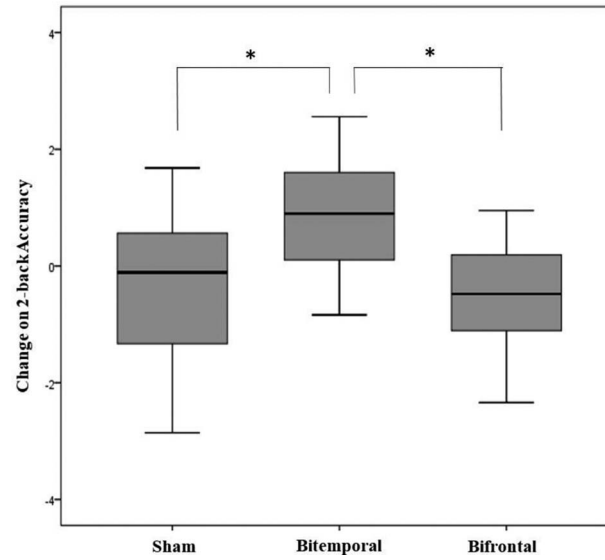

FIGURE 3. Change in accuracy on the 2-back between sham, bitemporal, and bifrontal tDCS (n = 15; mean ± SD). Error bars represent 95% confidence intervals.

TABLE 1. Demographics and Clinical Characteristics at Screening

	Mean ± SD or % (n = 17)
Age, y	77 ± 5
Sex (male), %	59%
Diagnosis of MCI, %	48%
Education, y	16 ± 3
MoCA (total)	20.8 ± 4.0

Tolerability

All 17 participants tolerated treatment well. Common adverse effects included itchiness (52.9%), tingling (31.4%), discomfort (13.7%), and a burning sensation (13.7%) and were mild, temporary, and tolerable in all patients. There were no significant differences between any of the reported symptoms and stimulation type (itchiness [Wald $\chi^2 = 3.20$, $df = 2$, $P = 0.20$], tingling [Wald $\chi^2 = 0.72$, $df = 2$, $P = 0.70$], discomfort [Wald $\chi^2 = 2.10$, $df = 2$, $P = 0.35$], and burning sensation [Wald $\chi^2 = 2.10$, $df = 2$, $P = 0.35$]). There were no dropouts or treating-limiting adverse events related with tDCS.

DISCUSSION

The current study was a pilot randomized, within-participants, sham-controlled trial of single-session tDCS for cognition in MCI and AD patients. There were no reported treating-limiting adverse events related to tDCS. The absence of treating-limiting adverse events is especially important given that our electrode montage used 2 active anodal electrodes. This study found that single-session

bilateral tDCS to the temporal lobes resulted in a significant small improvement in accuracy on the 2-back task, a test of working memory. These results are in accordance with previous studies that have demonstrated improved working memory performance following single-session stimulation over regions of the temporal lobes.[40,41] Our results also remained significant after controlling for age, diagnosis (mild vs major neurocognitive disorder), and years of education. This effect was not seen for sham or bifrontal stimulation. Furthermore, we did not find evidence of order or carry-over effects. These findings suggest that single-session tDCS may be effective at stimulating the temporal lobes and enhancing cortical networks involved in working memory tasks.

Although not demonstrated in our study, previous studies have reported improvements in working memory performance following tDCS over the frontal lobes. In healthy and Parkinson disease patients, stimulation of the left DLPFC compared with sham improved accuracy on the 3-back.[14,42] Andre et al[24] also found improvements on the 2-back following repeated left DLPFC stimulation compared with sham in vascular disease and mixed dementia patients. Various observations can help explain why tDCS over the temporal lobes was associated with improved performance on the 2-back in our study. First, patients with AD have selective hypoactivation of the temporal lobes.[43] Evidence has also shown that the 2-back, a particularly high-memory load task,[44] requires the involvement of the temporal lobes.[44,45] Under stressful conditions, working memory processing has been shown to further reduce activity in the medial temporal lobes.[45] As tDCS increases cortical excitability and focally improves cortical function,[46] it is likely that improvements in 2-back accuracy were associated with enhancements in cortical activity within the temporal lobes following bitemporal stimulation.

This study found no significant improvements on the ADAS-Cog Word Recognition Task, the ADAS-Cog Word Recall Task, 2-back reaction times, or the MoCA following any stimulation. Previous studies have demonstrated improvements in word recall and recognition following a single session of tDCS.[25,28,29,35] Those findings may have been due to varying stimulation parameters. For example, Boggio et al[29] also administered 3 single stimulations, but only over 1 hemisphere (left DLPFC, left temporal lobe, and sham) and for 30 minutes at a time. In addition, each stimulation was separated by 48 hours, whereas we separated each stimulation by 1 week. It is also possible that the administration of tDCS combined with cognitive training could have enhanced the effects of stimulation,[17] which resulted in improvements in recall and recognition domains. In our study, we did not combine tDCS with cognitive training.

Furthermore, our lack of significant improvements following tDCS over the DLPFC may be due to anatomical differences between the temporal lobes and the DLPFC. Skin and skull thickness are important factors that determine the flow of current through the brain.[47] Hwang et al[48] reported that the thickness of the human frontal bone is greater than 3 times that of the temporal bone. Those findings may also help explain why peak cortical current density is reduced in the DLPFC compared with the temporal lobes following tDCS.[49] Future studies should consider implementing neuroimaging or computational modeling techniques to help create more personalized treatment methods.

The lack of significant improvements on the MoCA following tDCS may be due to our use of a single stimulation only. It is possible that a single session of tDCS in our population may be able to elicit only subtle changes that can be detected using more sensitive tests, such as the 2-back. Although evidence has shown that tDCS can improve measures of global cognition in AD patients,[21] that study administered 10 sessions of tDCS. It remains unclear whether a single session of tDCS predicts response to subsequent stimulations.[50]

As a limitation, we did not measure whether the effects on the 2-back following bitemporal stimulation were long-lasting by testing cognition at future time points. We also did not collect apolipoprotein E (APOE) genotype data in our patients. The APOE epsilon4 allele has been shown to affect memory and attentional-executive network function in AD patients.[51] Future tDCS studies should consider investigating the effect of APOE genotype on cognitive functions in patients with MCI and AD. We also did not directly examine cortex excitability to identify whether there were differences in cortical current density between the temporal lobes compared with the DLPFC. In addition, as this was a pilot study, the sample size was small, and we did not adjust for multiple comparisons. As a result, findings are preliminary and should be interpreted with caution.

Our findings provide further support for the safety and tolerability of using 2 anodes and suggest that single-session tDCS over the temporal lobes improves working memory in patients with MCI and mild AD. Given the increasingly growing interest in tDCS as a therapeutic device, future studies should investigate the efficacy of bilateral tDCS in controlled studies with larger sample sizes, repeated stimulations, and longer periods of follow-up to better determine safety and efficacy over the longer term. Future studies should also investigate the neurophysiological and neurobiological mechanisms under the effects of tDCS with the goal of identifying more personalized stimulation protocols.

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