

Immediate Memory and Electro Physiologic Effects of Prefrontal Cortex Transcranial Direct Current Stimulation on a Chronic Traumatic Brain Injury Survivor: A Case Report

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Abstract

Ongoing memory impairment is a common long-term consequence of traumatic brain injury (TBI) that negatively impacts everyday function. Traditional rehabilitation to improve memory function focuses on use of external and/or internal behavioral memory strategies, the benefits of which are supported by varying levels of evidence. This case report examined immediate behavioral and electrophysiological effects of three conditions of left dorsolateral prefrontal cortex Transcranial direct current stimulation (tDCS) on auditory working memory in a chronic TBI survivor with persisting post-injury memory problems. Pre- and post-tDCS behavioral memory performance was measured, as were auditory event-related potentials (P300 activity) and power of alpha and theta EEG bands. Behavioral and electrophysiological results were specific to tDCS condition, with anodal tDCS, versus cathodal and sham, significantly enhancing memory function and related cortical activity. Rehabilitation implications of these findings are discussed.

Keywords: tDCS; Memory; Rehabilitation; Traumatic brain injury

Introduction

There is a well-established relationship between working memory, those operations that enable an individual to hold information in mind to recall, manipulate, and associate existing representations with incoming new information, and the prefrontal cortex [1-3]. Persisting working memory impairment that limits everyday function is a common consequence of brain injury involving the prefrontal cortex. Rehabilitation to improve memory function using external and/or internal behavioral memory strategies is common and is supported by varying levels of evidence [4-6]. Evidence also supports the ability of internal behavioral memory strategies (e.g. semantic association) to increase prefrontal cortical activation, especially in the left dorsolateral prefrontal cortex (LDLPFC) in individuals with and without brain injury [7-12].

Neuromodulation, the physiologic alteration of brain activity through stimulation or medication, holds great promise as a rehabilitation tool [12,13]. Transcranial direct current stimulation (tDCS) is a safe, noninvasive, portable type of neuromodulation during which a weak, direct current is applied via anodal and cathodal electrodes strategically placed on the scalp [14]. The current passes through the skull, reaches cortical areas, and modulates the resting membrane potential of individual neurons [15,16]. This impacts cortical excitability (anodal increasing/cathodal decreasing) and synaptic activation strength, in turn enhancing cortical neuroplasticity [17]. One 10-minute session of anodal tDCS results in excitability shifts lasting greater than one hour, with multiple sessions resulting in longer-lasting shifts [18]. TDCS has been shown to enhance memory

function in neurotypical individuals and individuals with Parkinson's disease, Alzheimer's disease, and stroke [19-22]. In the only published (pilot) study to date of anodal tDCS and post-traumatic brain injury (TBI) memory, 15 sessions of anodal tDCS (1 milliamperes-mA, 10 minutes) to the LDLPFC followed by computerized cognitive training with 12 individuals with severe TBI who were an average of 19.25 months post-injury did not enhance memory or attention outcomes [23]. Effects of tDCS on brain activity were not measured.

Electroencephalography (EEG) is beginning to be used clinically to measure the effects of tDCS on brain activity [24-28]. In the only in-progress study of the cumulative effects of 10 sessions of anodal tDCS (1 milliamperes- mA, 20 minutes) to the LDLPFC in a randomized group of 13 individuals with TBI who were an average of 57.38 days post-injury (injury severity not reported), EEG oscillations suggested improved control of cortical excitability across tDCS sessions and improved working memory and attention outcomes after the tenth session compared with the first [28]. Impact of individual tDCS sessions on memory and attention was not measured, and information regarding traditional cognitive rehabilitation that these individuals were or were not simultaneously receiving was not reported.

Given the persisting memory impairments of chronic TBI survivors, the potential for tDCS to enhance their rehabilitative outcomes warrants continued study. Here we report immediate behavioral memory and EEG effects of each of three different conditions/sessions of LDLPFC tDCS on a single patient with chronic TBI and persisting memory impairment. EEG effects were measured to examine pre/post-tDCS neuromodulatory changes. These included P300 activity, a reflection of cortical resources allocated for memory and attention [29], and power of EEG bandwidths, a measure potentially linked to stages of cognitive recovery in TBI [28]. This case

study is the first of its kind to explore both behavioral and electro physiologic changes following individual tDCS sessions targeting auditory working memory post-TBI.

Case Report

The patient was a 34 year 11 month old right-handed female who sustained a severe TBI (initial Glasgow Coma Scale [30] score of 5 and 30-day loss of consciousness) as a result of a motor vehicle accident 14 years prior to case study participation. Initial neuroimaging revealed diffuse injury and significant right hemisphere front temporal damage. She had no history of neurologic dysfunction, psychological/psychiatric impairment, diagnosed attention deficit disorder or learning disability, and was not on any prescribed psychoactive medications. The patient had a high school diploma, was fluent in English, and was able to read single words. She reported post-TBI memory problems that continued to interfere with her daily function and for which she attempted to use external memory strategies (e.g., calendar) to compensate. She had not been involved in any memory improvement program or therapy in the previous 12 years. The patient reported living with her parents and having a part-time retail job. She provided informed consent to participate in this case study, which was approved by the Institutional Review Boards at North-eastern University and Spaulding Rehabilitation Hospital.

Methods

Procedure

The patient completed three 90-minute sessions, a minimum of 48 hours apart and all at the same time of day. Procedures were the same across sessions: baseline tDCS adverse effects questionnaire; EEG 10-minute eyes open, eyes closed, and completion of auditory task with working memory demands; pre-tDCS behavioral working memory word list testing; 20-minute tDCS; post-tDCS behavioral working memory word list testing; EEG 10-minute eyes open, eyes closed, and completion of auditory task with working memory demands; and end-of-session completion of tDCS adverse effects questionnaire.

The EEG auditory task consisted of an oddball paradigm in which two 70 decibel 150 millisecond (msec) auditory tones (standard at 1000 Hertz and deviant at 500 Hertz) were repeatedly presented through headphones using a randomization schedule of five "usual" to one "odd" tone stimuli and an inter-stimulus interval of 1500 msec. Total duration of the paradigm was 10 minutes, and the total number of events was 400, of which 80 were odd tone stimuli appearing in random order. The patient was instructed to activate one button after every usual tone and a different one after every odd tone. Accuracy and reaction time data were collected using E-Prime software and exported to Microsoft Excel for further analysis.

EEG was recorded continuously using a vertex-referenced 64-electrode saline-soaked HydroCel Geodesic Sensor net (Electrical Geodesics Inc., EGI) and the software Net Station (EGI). Electrodes were placed in accordance with the International 10-20 system for EEG electrode placement [31]. The amplifier's high and low pass filters were set to 70 Hertz (Hz) and 0.3 Hz respectively, with a sampling rate of 250 Hz. Responses and reaction times were recorded by E-Prime 2.0, through which each event was automatically marked on the concurrent EEG data.

Pre/post-tDCS working memory was behaviorally tested based on the Hopkins verbal learning test [32] paradigm and used different auditorily presented word lists per session. Each list consisted of 32 randomly ordered stimuli, with 8 of the 32 words belonging to each of four different semantically related groups (e.g., animals, parts of a house, personal hygiene goods, and sporting goods); stimuli within and across lists were balanced based on frequency of occurrence in the English language. After hearing a list of words, the patient was asked to recall the words as best as possible, in any order, allowing her the opportunity to spontaneously manipulate word order and strategically organize/re-organize the presented stimuli.

The randomized schedule of tDCS conditions across the three sessions was: 2 mA cathodal tDCS to LDLPFC with reference electrode to the right supraorbital area; anodal tDCS to the LDLPFC with reference electrode to the right supraorbital area; and sham tDCS (30 seconds of current) to LDLPFC with reference electrode to the right supraorbital area. The LDLPFC was identified by the F3 electrode position of the 10/20 EEG electrode system. TDCS was delivered by a battery-driven constant current stimulator using a pair of rubber electrodes in 5 × 7 centimeter saline-soaked synthetic sponges.

Behavioral Memory Analysis

Pre-post change in number of words recalled per tDCS condition was determined. Consistent with reports of HVLIT test-retest reliability in healthy adults and chronic TBI survivors, pre-/post-change of three or more words was considered significant [33].

EEG Analysis

ERP analysis

The continuous EEG data was filtered with the high-pass of 1Hz and low-pass of 35 Hz. Independent component analysis was performed to remove eye blinks. The EEG data was divided into 1000 msec segments or "epochs". Each epoch began 200 msec before the onset of either a deviant ("odd" tone) or standard ("usual" tone) auditory stimulus. As per standard ERP processing protocols, the epochs were baseline corrected (using the first 200 ms) and inspected for remaining artifacts. The average of all epochs was then obtained for each category (deviant and standard). A third category showing the difference wave between standard and deviant stimuli was created to calculate peak amplitude and peak latency. Measurements for P300 were obtained from an average signal of two known electrode localizations (Cz and Pz) as these are common sites from which to obtain P300 measures [32]. A window for P300 was determined manually (300-450 msec) for further measurements of peak amplitude and latency.

EEG power

Data recorded during the eyes closed condition was analyzed. Absolute power (μV^2) was calculated using Fast Fourier Transformation (FFT). Given that alpha and theta power are known to be related to memory function [34], mean power for alpha (8-13 Hz), and theta (4-8 Hz) band were calculated. A value from each electrode was obtained and then grouped according to the anatomical locations representing frontal, parietal, and occipital areas.

Results

The patient reported no study-related adverse effects.

Pre- /post-tDCS word list task performance

Pre- /post-tDCS behavioral word list performance per condition is summarized in Table 1. Across pre-tDCS conditions, number of words recalled ranged from 13 (anodal) to 16 (cathodal). Across post-tDCS conditions number of words recalled ranged from 13 (cathodal) to 19 (anodal). Post- versus pre- tDCS, number of words recalled decreased by three in the cathodal condition and increased by six in the anodal condition and by one in the sham condition.

tDCS Condition	Pre-tDCS Recalled	Words	Post-tDCS Recalled	Words
Cathodal	16		13	
Anoda	13		19	
Sham	15		16	

Table 1: Pre-/Post-tDCS word list task performance. Note Maximum recallable words=32.

EEG oddball task performance

Pre-/post- tDCS EEG oddball task performance per condition is summarized in Table 2. Post- versus pre-tDCS, accuracy increased in the cathodal and anodal conditions (by 19% and 5% respectively) and decreased in the sham condition (by 2%). Reaction time decreased in the sham condition (by 6.64 msec) and increased in the cathodal and anodal conditions (16.28 and 22.11 msec respectively).

EEG parameter	Pre-cathodal	Post-cathodal	Pre-anodal	Post-anodal	Pre-sham	Post-sham
Task accuracy (%)	76	95	92	97	88	86
Mean reaction	364.09	380.37	340.16	362.27	380.75	374.11
Time (msec)	(± 96.47)	(± 101.58)	(± 100.84)	(± 102.95)	(± 78.80)	(± 86.37)

Table 2: Pre-/Post- EEG oddball task performance per tDCS condition.

P300

Pre-/post-tDCS P300 parameters for oddball task performance per condition are summarized in Table 3. Average P300 peak amplitude of the difference wave over the two pre-determined channels increased most after post- anodal stimulation (+1.69 μ V). There was minimum pre- /post- tDCS change in the cathodal (+0.43 μ V) and sham (-0.74 μ V) conditions.

Average P300 latency over the identified channels increased after cathodal tDCS (52m sec) and sham tDCS (52m sec). There was minimum change in average P300 latency after anodal stimulation (+12m sec). Figure 1 shows pre-/post-difference waves for each tDCS condition.

tDCS Condition	Pre-tDCS P300 Peak amplitude (μ V)	Pre-tDCS P300 Latency (msec)	Post-tDCS P300 Peak amplitude (μ V)	Post-tDCS P300 Latency (msec)
Cathodal	2.00	336	2.43	388
Anodal	2.67	392	4.37	404
Sham	3.68	340	2.93	392

Table 3: Pre-/Post-P300 difference wave ERP neurophysiologic oddball task performance per tDCS condition.

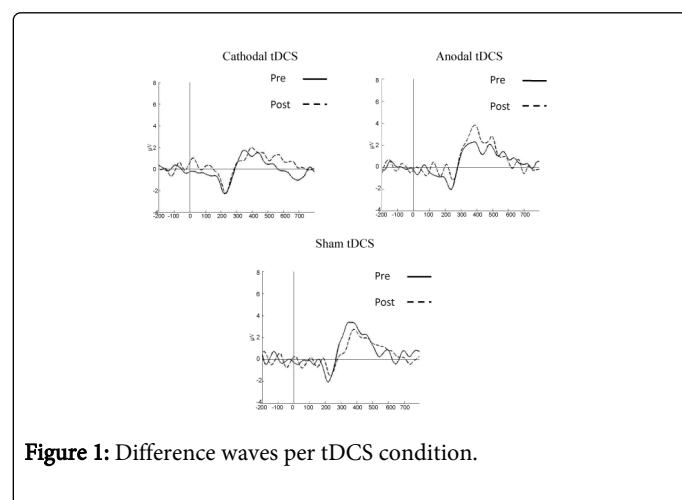


Figure 1: Difference waves per tDCS condition.

EEG alpha and theta bands

Mean theta power decreased after anodal tDCS over occipital (-0.40 μ v²) and parietal (-0.10 μ v²) areas but increased after cathodal tDCS (occipital: + 0.60 μ v²; parietal: +0.24 μ v²; central, +0.16 μ v²). There was a minimal change with sham stimulation over these areas for theta band (occipital, -0.01 μ v²; parietal -0.01 μ v²). For frontal and central areas, the change was similar across groups for theta power (anodal: central, -0.04 μ v²; frontal, -0.06 μ v²; cathodal: frontal, 0.05 μ v²; sham: central, -0.02 μ v²; frontal, -0.02 μ v²). Figure 2 shows topographical maps representing the whole scalp distribution of theta power at 6 and 8 Hz for each tDCS condition, including decreased theta power in the occipital area post- anodal tDCS.

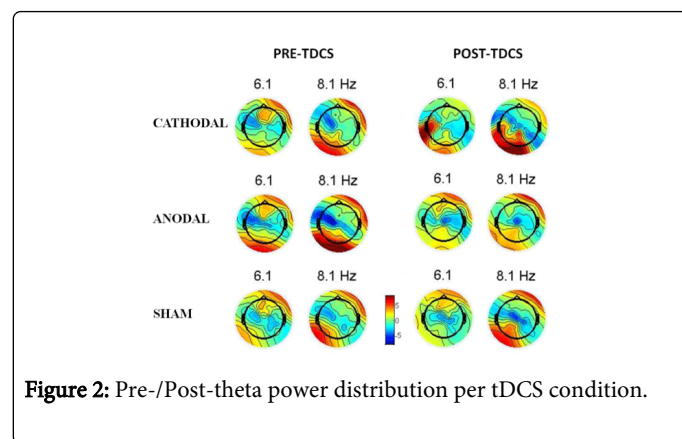


Figure 2: Pre-/Post-theta power distribution per tDCS condition.

In contrast, alpha power increased most after cathodal tDCS over occipital (+ 0.44 μV^2) and decreased after anodal tDCS (occipital, -0.45 μV^2 ; parietal - 0.20 μV^2 ; frontal, -0.15 μV^2). Effects of cathodal stimulation over frontal (-0.06 μV^2), parietal (0.04 μV^2), and central areas (0.04 μV^2) and effects of anodal stimulation over central areas (central, -0.09 μV^2) were similar to sham (occipital, 0.02 μV^2 ; parietal - 0.01 μV^2 ; central 0.014 μV^2 ; frontal 0.01 μV^2).

Discussion

This case report examined immediate memory and electrophysiologic effects of three different conditions of LDLPFC tDCS on a patient with chronic TBI and subsequent persisting memory impairment. Following anodal tDCS, there was a significant 6-word increase in number of words recalled. This 46.2% pre- /post-tDCS increase is highly promising, especially given the significant 3-word decrease (18.8% pre- /post- tDCS decrease) in words recalled following cathodal tDCS and the 1-word increase (6.7% pre- /post-tDCS increase) following sham tDCS. Relatedly, the fact that the best post-tDCS behavioral memory performance was during the second session versus the third supports the belief that neither learning effects nor tDCS condition order effects explain the patient's performance across the three sessions and that enhanced cortical excitability effects of LDLPFC anodal tDCS do. Further supporting the enhancing anodal tDCS behavioral findings are post-tDCS EEG oddball task accuracy and absolute mean reaction time comparisons across the three conditions.

Consistent with the enhancing behavioral effects of LDLPFC anodal tDCS, electrophysiologic pre-/post-tDCS P300 changes across conditions in this case report largely support the enhancing neuromodulatory effects of LDLPFC anodal tDCS. Anodal tDCS resulted in increased P300 amplitude in addition to improved oddball task performance, with no change in P300 latency compared to cathodal and sham. P300 is known to be related to attention and memory and requires discrimination and conscious detection of external stimuli [29]. Anodal tDCS has been shown to increase P300 amplitude and working memory performance in healthy subjects [35], and changes in P300 amplitudes and latencies following tDCS have been documented in different clinical populations, with magnitudes comparable to those seen in this study [36,37].

Regarding EEG bandwidth findings, another encouraging neurophysiologic change was the patient's decreased resting theta power after anodal stimulation compared to increased theta power after cathodal stimulation. Similar to our findings, Ardolino and colleagues found that cathodal tDCS increased theta power [38], and Jacobson and colleagues found that anodal tDCS decreased theta power [39]. Theta power has been known to relate to cognitive and memory performance, and decreased resting theta power has been linked to increasing cognitive performance [40]. Thus, a decrease in theta power following anodal stimulation might help to explain our patient's improved memory performance. The patient's increase in alpha power after cathodal stimulation and decrease after anodal stimulation is difficult to interpret. Mixed results are reported in the literature regarding the effects of tDCS on alpha power [35,41-43].

Memory impairment post-TBI is common, persistent, and functionally debilitating. Rehabilitation to improve memory function using external and/or internal behavioral memory strategies is common but is supported by varying levels of evidence [4-6]. Consistent with Ulman and colleagues' in-press study findings with

(less chronic) TBI patients [28], this study strongly supports further examination of the potential for long-term, functional impact of LDLPFC anodal tDCS on memory rehabilitation.

There are several points worth noting about this case report. First, the patient was 14 years post-TBI. Rehabilitation typically occurs during acute and sub-acute stages post-injury, which are believed to be "critical periods" for recovery [44]. Perhaps anodal tDCS provided the neuromodulation needed for re-activation of the patient's long dormant, or under-stimulated, LDLPFC [19,20,22,28]. This would be consistent with the growing body of evidence supporting the potential for neuroplasticity-facilitated improvements in chronic neurologically impaired individuals [28,45-47].

Second, given the role of the LDLPFC in memory function and the evidence supporting the enhancing benefits of LDLPFC anodal tDCS to memory function [19-24], this was the site targeted with this patient. Primary right fronto-temporal damage did not prevent the patient from recalling more words post-LDLPFC anodal tDCS. Whether or not the LDLPFC is the best tDCS site to enhance memory function in all patients post-TBI - especially ones with primary LDLPFC damage - is not known and should be examined. Using neuroimaging techniques (e.g. EEG) to measure whole brain activation during pre-stimulation memory tasks may lead to development of candidacy guidelines for clinical tDCS use and identification of patient-specific tDCS electrode placement sites to maximize memory rehabilitation outcomes [28,48].

Finally, this case report explored the immediate impact on memory of LDLPFC tDCS alone. Pairing tDCS with traditional memory strategy training may further enhance the rehabilitative outcome that either of these interventions might achieve individually, thereby maximizing memory function of all TBI survivors.

Conclusion

This case report demonstrates the ability of a single session of LDLPFC anodal tDCS to significantly enhance memory function and cortical activity in a 14 year-post TBI survivor with persisting post-injury memory problems. With post-TBI memory impairment being common and functionally debilitating, clinical use of neuromodulation to enhance the outcomes of traditional rehabilitation approaches has great promise.

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