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Immediate Memory and Electrophysiologic Effects of Prefrontal Cortex
Transcranial Direct Current Stimulation on Neurotypical Individuals
and Individuals with Chronic Traumatic Brain Injury: A Pilot Study

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Running Head: tDCS effects on neurotypical and TBI memory

*We have no commercial relationships of any kind to declare.

Abstract

Purpose/Aim: Memory impairment post-TBI is common, frequently persistent, and functionally debilitating. The purposes of this pilot study were to assess and to compare immediate behavioral auditory working memory and electrophysiologic effects of three different, randomized, conditions of left dorsolateral prefrontal cortex (LDLPFC) transcranial direct current stimulation (tDCS) applied to four neurotypical adults and four adults with chronic traumatic brain injury (TBI).

Materials/Methods: Pre- and post- anodal, cathodal, and sham tDCS auditory memory performance, auditory event-related potentials (P300 amplitude and latency) and power of alpha and theta EEG bands were measured across individuals in each group.

Results: Post-anodal tDCS only, the neurotypical and TBI groups both demonstrated significantly improved immediate auditory memory function. Also post-anodal tDCS, the TBI group demonstrated significantly increased P300 amplitude versus post-sham tDCS. The neurotypical group demonstrated no pre- post tDCS electrophysiologic changes across conditions.

Conclusions: These findings are consistent with findings of other studies of immediate tDCS effects on other types of memory in neurotypical individuals and in individuals with Parkinson's disease, Alzheimer's disease, and stroke and suggest that individuals with memory impairments second to chronic TBI may benefit from LDLPFC anodal tDCS.

Pairing tDCS with traditional behavioral memory interventions may facilitate TBI rehabilitation outcomes and warrants continued investigation.

Key words: tDCS; Memory; Neuroplasticity; Rehabilitation; Traumatic brain injury

Introduction

There is a well established relationship between the prefrontal cortex and working memory, the ability to hold information in mind to recall, manipulate, and associate existing representations with new information [1,2]. Memory abilities are not static and may be enhanced by strategy use and training. The successful use of internal behavioral memory strategies (e.g., semantic association) is associated with improved working memory performance and increased prefrontal cortical activation, especially in left dorsolateral prefrontal cortex (LDLPFC) in neurotypical individuals and individuals with acquired brain injury [3-7].

Transcranial direct current stimulation (tDCS) is a safe, noninvasive method of neuromodulation during which a weak, direct current is applied via anodal and cathodal electrodes strategically placed on the scalp. The current passes through the skull, reaches cortical areas, and modulates the resting membrane potential of individual neurons [8,9]. This impacts cortical excitability (anodal increasing/cathodal decreasing) and synaptic activation strength, in turn enhancing cortical neuroplasticity [10-12]. One 10-minute session of tDCS results in excitability shifts lasting greater than one hour, with multiple sessions resulting in longer-lasting shifts [13-15]. Studies have reported that tDCS enhanced memory function in neurotypical individuals and individuals with Parkinson's disease, Alzheimer's disease, and stroke [16-21].

Results of the three published studies of the effects of anodal LDLPFC tDCS on memory function post-traumatic brain injury (TBI) are mixed. In one of two group studies published, Leśniak and colleagues [22] examined effects of repeated anodal LDLPFC tDCS on attention and memory in a randomized control trial with 23 individuals with severe TBI between 4 and 92 months post-injury.

Following 10 minutes of 1 milli-ampere (mA) tDCS, experimental group participants completed an unspecified amount of time using computerized cognitive software (efficacy of cognitive software not reported) across 15 consecutive days. Post-intervention, although the experimental group presented with larger effect sizes on the majority of neuropsychological tests than the control group, there were no significant between-group differences in attention or memory performance. In the other published anodal LDLPFC tDCS group study of post-TBI memory function, Ulam and colleagues [23] examined effects of 10 consecutive days of 20 minutes of 1 mA repeated anodal LDLPFC tDCS on electroencephalographic (EEG) oscillations, attention, and working memory in a randomized control trial with 26 individuals with moderate to severe TBI participating in subacute rehabilitation. Immediate and cumulative experimental versus control group increases in cortical excitability were identified, supporting tDCS-related enhanced cortical excitability regulation. Following the 10 tDCS sessions, although no significant between-group differences in attention or memory performance were found, decreased experimental group delta correlated with improved neuropsychological testing to a greater degree than in the control group. Additionally, those experimental group participants with excessively slow EEG activity initially demonstrated more improved neuropsychological test performance than all other study participants. A recently published case report examining effects of LDLPFC tDCS on an individual with chronic TBI found that a single 20 minute session of 2 mA anodal tDCS (versus cathodal and sham) significantly enhanced immediate memory function and related cortical activity

(i.e., increased P300 event-related potentials and decreased oscillatory power in alpha and theta bands) [24].

The purposes of this pilot study were to assess and compare immediate behavioral auditory working memory and electrophysiologic effects of three different conditions of LDLPFC tDCS applied to a group of neurotypical adults and a group of adults with chronic TBI. This study is the first to explore **immediate** behavioral and EEG changes pre- post tDCS targeting auditory working memory in both groups. Measuring these effects may help inform **the mixed results of previously reported repeated LDLPFC tDCS TBI memory studies** and the design of future **group studies and** interventions to maximize TBI survivors' rehabilitation outcomes.

Materials and Methods

Participants

Participants were recruited via study flyers posted at Northeastern University and Spaulding Rehabilitation Hospital. To be eligible, individuals had to 1) be 19 years of age or older; 2) be right-handed, fluent in English, and able to read single words; 3) have no documented history of neurologic dysfunction, psychologic/psychiatric impairment, diagnosed attention deficit disorder or learning disability; 4) be on no prescribed psychoactive medications; and 5) be in no kind of memory improvement program or therapy during study participation. Individuals with TBI additionally had to 1) have had a single TBI, at least one year prior to study enrollment and 2) have no medication changes during study participation. Four neurotypical individuals (one male; mean age, 51.6 years; range, 44-59 years) and four individuals with chronic TBI (two males; mean age, 43 years;

range, 35-53 years) were confirmed eligible for study participation and consented to be in this study. Mean years of education was 16.5 (SD 2) for the neurotypical group and 13 (SD 2) for the TBI group. Each TBI group participant sustained a severe TBI based on documented Glasgow Coma Scale [25] scores ranging from 3-8, and each reported post-TBI memory problems that interfere with their everyday function. **Detailed injury-related characteristics per TBI group participant are provided in Table 1.** All participants provided informed consent to participate in this study, which was pre-approved by the Northeastern University and Spaulding Rehabilitation Hospital Institutional Review Boards.

(Table 1)

Procedure

Each participant completed three 90-minute sessions, a minimum of 48 hours apart and 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 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 auditory task with working memory demands; and end-of-session 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. Participants activated one button after every usual tone and a different one after every odd tone.

EEG was recorded continuously using a vertex-referenced 64-electrode saline-soaked HydroCel Geodesic Sensor net (Electrical Geodesics Inc., EGI) and Net Station (EGI). Electrodes were placed in accordance with the International 10-20 system for EEG electrode placement [26]. 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.

Pre- /post- tDCS working memory was tested based on the Hopkins Verbal Learning Test [27] paradigm and used different auditorily presented word lists per session. Each list consisted of 32 randomly ordered stimuli, with 8 words belonging to each of four different semantically related groups; stimuli within and across lists were balanced based on frequency of occurrence in the English language. After hearing a list of words, participants were asked to recall the words as best as possible, in any order.

Using a randomized cross-over design (see Table 2 for randomization schedule), participants completed three different tDCS sessions (anodal, cathodal, sham), all with the reference electrode to the right supraorbital area: 2 mA cathodal tDCS to LDLPFC; anodal tDCS to the LDLPFC; and sham tDCS (30 seconds of current) to LDLPFC. 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 x 7 centimeter saline-soaked synthetic sponges.

(Table 2)

Analysis

Behavioral Memory. Pre- post change in number of words recalled per tDCS condition was determined per participant per group. Repeated measures ANOVA compared

participants' pre-post change scores across the three tDCS conditions per group. Given significant F values, post-hoc paired *t*-tests were completed for each pair of tDCS conditions (i.e., anodal-cathodal, anodal-sham, cathodal-sham). Unpaired *t*-test analysis compared baseline performance of the two groups (neurotypical versus TBI). Because this was a pilot study with four participants per group, statistical significance was set at $p < 0.05$.

P300. EEG data was analyzed using EEGLAB and ERPLAB [28,29]. The continuous EEG data was filtered with the high-pass of 1Hz and low-pass of 35 Hz per participant per group. Independent component analysis was performed to remove eye blinks. 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, epochs were baseline corrected (using the first 200ms) and inspected for remaining artifacts. The average of all epochs was 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 Cz as this is a common site from which to obtain P300 measures [26]. A window for P300 was determined manually (300-450 msec) for further measurements of peak amplitude and latency. For amplitude, repeated measure ANOVA compared participants across tDCS conditions per group. For latency, Friedman test compared participants across tDCS conditions per group as the data was not normally distributed. Given significant F values, post-hoc comparisons were made. Unpaired *t*-test analysis compared baseline peak amplitude and latency values of the two groups.

EEG Power. Data recorded during the eyes closed condition was analyzed per participant per group. 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 [30], 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 anatomical locations representing frontal, parietal, and occipital areas. Since EEG power was not normally distributed, statistical analyses were completed using non-parametric tests. Mann-Whitney U test compared baseline alpha and theta power of the two groups. Friedman test compared participants across tDCS conditions per group.

Results

Participants reported no adverse effects from study participation.

Behavioral Memory. Pre- /post- tDCS words recalled under each stimulation condition per **participant per group** are summarized in Table 2. **Number of words recalled post-tDCS increased for each of the four neurotypical group participants in the anodal condition (+5 - +6 words), increased for one neurotypical group participant in the cathodal condition (+1 word) and increased for one participant in the sham condition (+1 word). Number of words recalled post-tDCS increased for each of the four TBI group participants in the anodal condition (+3 - +6 words), increased for none in the cathodal condition, and increased for two in the sham condition (+1 word).**

Repeated measures ANOVA revealed significant differences in pre-post change in number of words recalled across tDCS conditions in both neurotypical and TBI groups ($F_{2,6} = 9.5, p < 0.05$; $F_{2,6} = 6.216, p < 0.05$ respectively). Post-hoc paired *t*-test analysis

of anodal versus cathodal, anodal versus sham, and cathodal versus sham pre-post tDCS change scores revealed that post-anodal tDCS recall improved to a statistically significant extent compared with the other two conditions in both groups and that there were no significant pre-post-tDCS change differences between cathodal and sham conditions in both groups (Table 3). Unpaired *t*-test analysis revealed significant differences in words recalled at baseline between the two groups ($t(6) = 2.46, p = 0.05$).

(Table 2 and Table 3)

P300. Pre-/post-tDCS P300 parameters for oddball task performance per condition per group are summarized in Table 4. For the neurotypical group, mean P300 peak amplitude decreased following all 3 conditions (mean difference; anodal: -1.92 ± 1.86 , cathodal: -0.43 ± 1.1 , sham: -0.08 ± 0.88). P300 latency changes were minimum across all three groups (anodal: -1 ± 25.59 , cathodal: 5 ± 10 , sham: -8 ± 125.77). For the TBI group, average P300s peak amplitude of the difference wave increased most after anodal stimulation ($0.85 \pm 0.93 \mu\text{V}$), and there was a decrease in P300 amplitude after tDCS in cathodal ($-0.51 \pm 0.62 \mu\text{V}$) and sham ($-1.32 \pm 0.86 \mu\text{V}$) conditions. Average P300 latency increased after all 3 conditions anodal (6 ± 36.15), cathodal ($40 \pm 73.10\text{msec}$), and sham tDCS ($35 \pm 59.54\text{msec}$). Figure 1 shows pre- /post- difference waves per tDCS condition.

(Table 4)

(Figure 1)

Unpaired *t*-test analysis revealed no significant baseline differences in mean P300 peak amplitude and mean P300 peak latency between the neurotypical group and (mean P300 amplitude: 4.20 ± 0.55 , mean P300 latency: 367 ± 12.67) and TBI group (mean

P300 amplitude: 3.55 ± 0.86 , mean P300 latency: 377.34 ± 13.88) (*t*-test; P300 amplitude: $p = 0.55$, Mann-Whitney; P300 latency: $p = 0.60$). Repeated measures ANOVA revealed a significant main effect of group for P300 amplitude ($F_{2,6} = 7.89$, $p = 0.008$), indicating a post-tDCS increase in P300 amplitude in the TBI group in the tDCS anodal condition versus sham. No effect of group was found for neurotypical participants for P300 amplitude and latency ($p < 0.05$).

EEG Power. Comparison of the two groups at baseline showed no significant difference between the neurotypical and TBI groups (Mann-Whitney rank sum; $p > 0.05$). Mean changes in alpha and theta power per tDCS group and scalp localization are summarized in Table 5. No differences were found across tDCS conditions for each of the two groups (Friedman, $p < 0.05$).

(insert Table 5)

Discussion

This pilot study is the first to assess and compare immediate behavioral auditory working memory and electrophysiologic effects of three randomized conditions of LDLPFC tDCS on a group of neurotypical adults and a group of chronic TBI adult survivors. Both groups demonstrated a significant increase in number of words recalled following anodal versus cathodal and sham tDCS. Cortical electrophysiologic activity of the TBI group also increased post-LDLPFC anodal tDCS. These **case series** findings are consistent with findings of other studies of tDCS effects on various types of memory in neurotypical individuals and in individuals with Parkinson's disease, Alzheimer's disease, and stroke [16-21] and are the first to offer **Level 4** evidence suggesting that

individuals with memory impairments second to chronic TBI may also benefit from LDLPFC anodal tDCS [31].

Memory impairment post-TBI is common, frequently persistent, and functionally debilitating. Rehabilitation to improve memory function has traditionally consisted of external and/or internal behavioral memory strategy training, which is supported by varying levels of evidence [e.g., 32-35]. **Given the limited benefits of behavioral memory training**, the well-documented relationship between working memory and the prefrontal cortex, the studies reporting enhancing effects of LDLPFC anodal tDCS on immediate memory, **and the too few published interventional group studies of LDLPFC anodal tDCS effects on memory function post-TBI to date [22,23]**, pairing tDCS with traditional behavioral interventions to enhance TBI rehabilitation outcomes warrants continued investigation.

Compared with the positive TBI findings in this pilot study, the TBI findings in the Leśniak et al. [22] and the Ulam et al. [23] randomized controlled group studies were mixed. In the Leśniak et al. study, although the TBI experimental group presented with larger effect sizes on neuropsychological tests than the TBI control group post- LDLPFC anodal tDCS, which is promising, there were no significant between-group differences in memory performance. In the Ulam et al. study, although decreased experimental group delta correlated with improved neuropsychological testing to a great degree than in the control group post- LDLPFC anodal tDCS, which is also promising, no significant between-group differences in memory performance were found.

Ongoing study of post-TBI combined tDCS-behavioral memory interventions may be informed by possible explanations for the mixed findings in the Leśniak et al. [22] and Ulam et al. [23] TBI studies compared with the positive TBI findings in this study, each warranting investigation of its own. One such possibility is tDCS parameters. For example, evidence across studies of neurotypical individuals and individuals with various neurologic diagnoses supports that current intensity levels and stimulation duration differentially impact cortical excitability responses to tDCS [e.g., 10,15,16,36]. The current intensity level in the Leśniak et al. study was 1 mA, and the stimulation duration was 10 minutes [22]. The current intensity level in the Ulam et al. study was 1 mA, and the stimulation duration was 20 minutes [23]. Keeping safety considerations in mind, perhaps the 20 minutes of 2 mA current used in this study is minimally needed to enhance memory performance post-TBI [10,36].

Another possible explanation for the mixed findings across studies is characteristics of each study's TBI participants, one being time post-injury and another being anatomy of each individual's brain post- injury. Regarding time post-injury, mean time post-injury was 18 months (S.D. = 19.7) in the Leśniak et al. study [22], 1.9 months (S.D. = 1.3) in the Ulam et al. study [23], and 81 months (S.D. = 71.4) in this study. Perhaps the chronicity of the TBI group in this study facilitated their responsiveness to anodal tDCS. A neuroplasticity principle that supports this possibility is timing of tDCS intervention [37]. As has been found in some controlled group studies of constraint induced therapy with and without tDCS with acute and chronic stroke survivors, perhaps tDCS does not enhance

spontaneous recovery that typically occurs acutely post-TBI but, as spontaneous recovery slows/stops, positively impacts functional improvements (e.g., memory) [e.g., 38-40]. Regarding anatomy of each individual's brain post- injury, it is possible that patterns of tDCS current flow are affected by specific sites of incurred brain trauma [22,41-43]. Based on the information provided in the Leśniak et al. and Ulam et al. studies [22,23], meaningful comparisons of the anatomy of their participants' brain injuries with those in this study were not possible. Investigation of individualized computational modeling to predict impact of damaged tissue on tDCS candidacy, optimal electrode placement, and tDCS intervention outcomes post-TBI is needed.

Two other possibilities are number of tDCS sessions and amount of time between multiple tDCS sessions. In the Leśniak et al. [22] study, participants received 15 tDCS sessions over 15 consecutive days (time of day not reported). In the Ulam et al. [23] study, received 10 tDCS sessions over 10 consecutive days (time of day depending on participant's daily availability). In this study, participants received one tDCS session. Perhaps repeated tDCS does not always have a positive cumulative effect on memory performance post-TBI. Perhaps the interval between repeated tDCS sessions influences whether the impact of repeated applications is positive or negative [39,44]. Testing effects of tDCS on memory after each tDCS application of a repeated tDCS intervention would be one approach to explore both of these possibilities.

Another possible explanation for the mixed findings across studies is absence of a TBI control group in this study. Leśniak et al. [22] and Ulam et al [23] had TBI

control groups who did not receive tDCS with whom to compare experimental group outcomes. It is possible that a TBI control group would have done as well as the experimental group on our outcome measure. However, our outcome measure was based on the Hopkins Verbal Learning Test paradigm [27], which has high test-retest reliability in individuals post-TBI [45]. Therefore, we do not believe that this is a likely possibility.

Electrophysiologically, the neurotypical group of participants in this study demonstrated no significant pre-post-tDCS P300 changes. The TBI group demonstrated significantly increased P300 amplitude post-stimulation in the anodal versus the sham condition. Anodal tDCS has been shown to increase P300 amplitude and working memory in neurotypical adults, and post-tDCS changes in P300 amplitudes in different clinical populations have also been identified [46-48]. One explanation for the lack of neurophysiological changes in the neurotypical group may be their higher level of functioning. Indeed, the TBI group had lower amplitudes on average (though not significant) as compared to the neurotypical group, allowing more room for improvement.

There are multiple limitations to this study, which should inform ongoing research in this area. First, this was a pilot study, with small groups of neurotypical individuals and individuals with chronic TBI. Further studies, powered with adequate numbers of **experimental and control group** participants **matched on such criterion as age**, are needed. Second, this study only examined the immediate effects of a single dose of three randomized tDCS conditions on memory function. The effects of multiple doses of tDCS over time warrant continued investigation to better inform the design of future

interventions combining tDCS and traditional memory therapy to maximize memory outcomes.

Conclusion

In this pilot study, immediate auditory memory function of a group of neurotypical individuals and a group of individuals with memory impairments second to chronic TBI improved post-LDLPFC anodal tDCS. Cortical electrophysiologic activity of the TBI group also increased post-LDLPFC anodal tDCS. Pairing LDLPFC anodal tDCS with traditional behavioral memory interventions may facilitate rehabilitation outcomes of chronic TBI survivors and warrants continued investigation.

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Declaration of Interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References

1. Rypma B, Berger JS, D'Esposito M. The influence of working-memory demand and patient performance on prefrontal cortical activity. *J Cogn Neurosci*. 2002;14:721-731.
2. Wagner AD, Maril A, Bjork RA, Schacter DL. Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. *Neuroimage*. 2001;14:1337-1347.
3. Miotto EC, Savage CR, Evans JJ, Wilson BA, Martins MG, Balardin B, et al. Semantic strategy training increases memory performance and brain activity in patients with prefrontal cortex lesions. *Clin Neurol Neurosurg*. 2013;115:309-316.
4. Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activity after training of working memory. *Nat Neurosci*. 2004;7:75-79.
5. O'Neil-Pirozzi TM, Strangman GE, Goldstein R, Katz DI, Savage CR, Kalka K, Supplant C, Burke D, Rauch SL, Glenn MB. A controlled treatment study of internal memory strategies (I-MEMS) following traumatic brain injury. *J Head Trauma Rehabil*. 2010;25:43-51.
6. Savage CR, Deckersbach T, Heckers S, Wagner AD, Schacter DL, Alpert NM, Fischman AJ, Rauch SL. Prefrontal regions supporting spontaneous and directed application of verbal learning strategies: evidence from PET. *Brain*;2001;124:219-231.
7. Strangman GE, O'Neil-Pirozzi TM, Goldstein R, Kelkar K, Katz DI, Burke DT, Rauch SL, Savage CR, Glenn MB. Prediction of memory rehabilitation outcomes in traumatic brain injury by using functional magnetic resonance imaging. *Arch Phys*

- Med Rehabil. 2008;89:974-981.
8. Datta A, Bikson M, Fregni F. Transcranial direct current stimulation in patients with skull defects and skull plates: high resolution computational FEM study of factors altering cortical current flow. *Neuroimage*. 2010;52:1268-1278.
 9. Wagner T, Fregni F, Fecteau S, Grodzinsky A, Zahn M, Pascual-Leone A. Transcranial direct current stimulation: a computer-based human model study. *Neuroimage*. 2007;35:1113-1124.
 10. Nitsche MA, Cohen L, Wasserman, EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, Pascual-Leone A. Transcranial direct current stimulation: state of the art. *Brain Stimul*. 2008;1:206-223.
 11. Miniussi C, Cappa SF, Cohen LG, Floel A, Fregni F, Nitschem MA, Oliveri M, Pascual-Leone A, Paulus W, Priori A, Walsh V. Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimul*. 2008;1:326-336.
 12. Pena-Gómez C, Sala-Lonch R, Junqué C, Clemente IC, Vidal D, Bargalló N, Falcón C, Valls-Solé J, Pascual-Leone Á, Bartrés-Faz D. Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. *Brain Stimul*. 2012;5:252-263.
 13. Brunoni AR, Mitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, Edwards DJ, Valero-Cabre A, Rotenberg A, Pascual-Leone A, Ferrucci R, Priori A, Boggio PS, Fregni F. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul*. 2012;5:175-195.
 14. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by

- weak transcranial direct current stimulation. *J Physiol*. 2000;527:633-639.
15. Ohm SH, Park CI, You WK, Ko MH, Choy KP, Kim GM, Lee YT, Kim YH. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. *Neuroreport*. 2008;19:43-47.
 16. Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, Fregni F. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J Neurol Sci*. 2006;249:32-38.
 17. Boggio PS, Khoury LP, Martins DC, Martins OE, de Macedo EC, Fregni F. Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. *J Neurol, Neurosurg, Psychiatry*. 2009;80: 444-447.
 18. Chi RP, Fregni F, Snyder AW. Visual memory improved by non-invasive brain stimulation. *Brain Res*. 2010;1353:168-175.
 19. Fregni F, Boggio PS, Nitsche M, Berman F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MT, Paulus W, Pascual-Leone A. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Exp Brain Res*. 2005;166:23-30.
 20. Jo J, Kim Y, Ko M, Ohn S, Joen B, Lee K. Enhancing the working memory of stroke patients using tDCS. *Am J Phys Med Rehabil*. 2009;88:404-409.
 21. Marshall L, Mölle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. *J Neurosci*. 2004;24:9985-9992.
 22. **Leśniak M, Polanowska K, Seniów J, Czlonkowska A. Effects of repeated anodal tDCS coupled with cognitive training for patients with severe**

traumatic brain injury: a pilot randomized controlled trial. J Head Trauma Rehabil. 2014;29:E20-E29

23. **Ulam F, Shelton C, Richards L, Davis L, Hunter B, Fregni F, Higgins K. Cumulative effects of transcranial direct current stimulation on EEG oscillations and attention/working memory during subacute neurorehabilitation of traumatic brain injury. Clin Neurophysiol. 2015;126:486-496.**
24. O'Neil-Pirozzi T, Doruk D, Thomson JM, Fregni F. Immediate memory and electrophysiologic effects of prefrontal cortex transcranial direct current stimulation on a chronic traumatic brain injury survivor: a case report. *Int J Phys Med Rehabil.* 2015;3:1-6.
25. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. *Lancet.* 1974;ii:81-84.
26. Klem GH, Luders HO, Jasper HH, Elger C. The ten-twenty electrode system of the International Federation. *Electroencephalogr Clin Neurophysiol Suppl.* 1999;52: 3-6.
27. Brandt J, Benedict RHB (2001) *The Hopkins Verbal Learning Test-Revised.* Lutz, FL: Psychological Assessment Resources, Inc.
28. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics. *J Neurosci Methods.* 2004;134:9-21.
29. Lopez-Calderon J, Luck SJ. ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Front Neurosci.* 2014;8:213.
30. Roux F, Uhlhaas PJ. Working memory and neural oscillations: alpha-gamma

versus theta-gamma codes for distinct MW information? Trends Cogn Sci.
2014;18:16-25.

31. **Jenicek M. Foundations of Evidence-based Medicine. Parthenon Publishing Group; Boca Raton: 2003.**
32. Cicerone KD, Dahlberg C, Kalmar K, Langenbahn DM, Malec JF, et al. Evidence-based cognitive rehabilitation: recommendations for clinical practice. Arch Phys Med Rehabil. 2000;81:1596-1615.
33. Cicerone KD, Dahlberg C, Malec JF, Langenbahn DM, Felicetti T, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. Arch Phys Med Rehabil. 2005;86:1681-1692.
34. Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, et al. Evidence-based cognitive rehabilitation updated review of the literature from 2003 through 2008. Arch Phys Med Rehabil. 2011;92:519-530.
35. O'Neil-Pirozzi TM, Kennedy MRT, Sohlberg MM. Evidence-based practice for the use of internal strategies as a memory compensation technique after brain injury: A systematic review. J Head Trauma Rehabil. 2015;15:32-42.
36. **Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, Edwards DJ, Valero-Cabre An, Rotenberg A, Pascual-Leone A, Ferrucci R, Priori A, Boggio PS, Fregni F. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5:175-195.**
37. **Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Sp, Lang, Hear Res.**

2008;51:S2225-S239.

38. Bolognini N, Vallar G, Casati C, Latif LA, El-Nazer R, Williams J, Banco E, Macea DD, Tesio L, Chessa C, Fregni F. Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabil Neural Repair*. 2011;25:819-829.
39. Holland R, Crinion J. Can tDCS enhance treatment of aphasia after stroke? *Aphasiology*. 2012;26:1169-1191.
40. Rossi C, Sallustio F, Di Legge S, Stanzione P, Koch G. Transcranial direct current stimulation of the affected hemisphere does not accelerate recovery of acute stroke patients. *Eur J Neurol*. 2013;20:202-204.
41. Bikson M, Rahman A, Datta Abhishek. Computational models of transcranial direct current stimulation. *Clin EEG Neurosci*. 2012;176-183.
42. Datta A, Baker JM, Bikson M, Fridriksson J. Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. *Brain Stimul*. 2011;169-174.
43. Li MN, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Front Cell Neurosci*. 2015;9:181.
44. Monte-Silva K, Kuo MF, Liebetanz D, Paulus w, Nitsche MA. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). *J Neurophysiol*. 2010;103:175-1740.
45. O'Neil-Pirozzi TM, Goldstein R, Strangman GE, Glenn MB. Test—re-test reliability of the Hopkins Verbal Learning Test-Revised in individuals with

traumatic brain injury. Brain Inj. 2012;26:1425-1430.

46. Khedr EM, El-Gamal NF, El-Fetoh NA, Khalifa H, Ahmed EM et al. A double-blind randomized clinical trial on the efficacy of cortical direct current stimulation for the treatment of Alzheimer's Disease. *Front Aging Neurosci.* 2014;6: 275-287.
47. Nakumura-Palacios EM, de Almeida Benevides MC, da Penha Zago-Gomes M, de Oliveira DW, de Vasconcellos VF, de Castro LN, da Silva MC, Ramos PA, Fregni F. Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. *Int J Neuropsychopharmacol.* 2012;15:601-616.
48. Polich J, Kok A. Cognitive and biological determinants of P300: an integrative review. *Biol Psychol.* 1995;41:103-146.

Table 1: Injury characteristics for participants with TBI.

Participant	Years post-injury	Initial GCS	Injury mechanism	Radiological findings
1	1.2	5	Fall	L frontotemporal damage
2	2.8	4	MVA	Diffuse injury; L temporoparietal damage
3	9.2	7	MVA	R frontal, L frontotemporal damage
4	14	5	MVA	Diffuse injury; R frontotemporal damage

Note. GCS = Glasgow Coma Scale. R = right. L = left.

Table 2: tDCS condition randomization schedule and pre- /post- stimulation word recall per participant per group.

Group	tDCS condition	Pre-word recall	Post-word recall
Participants			
Control Group			
1	cathodal	17	18
	anodal	13	19
	sham	10	11
2	Sham	23	13
	anodal	22	27
	cathodal	17	15
3	cathodal	18	15
	sham	26	26
	anodal	25	30
4	anodal	15	21
	sham	17	16
	cathodal	21	19
TBI Group			
1	cathodal	14	7
	sham	18	19
	anodal	16	22
2	sham	11	12

	cathodal	10	10
	anodal	12	15
3	cathodal	12	12
	sham	18	13
	anodal	12	18
4	cathodal	16	13
	anodal	13	19
	sham	15	16

Note. Maximum recallable words = 32.

Table 3: Post-hoc pre- /post- tDCS word recall change score *t*- tests for tDCS condition pairs per group.

tDCS pairs	Neurotypical	TBI
Anodal-Cathodal	$t(3) = 9.9$ $p = 0.002^*$	$t(3) = 3.628$ $p = 0.036^*$
Anodal-Sham	$t(3) = 3.361$ $p = 0.044^*$	$t(3) = 5.657$ $p = 0.011^*$
Cathodal-Sham	$t(3) = 0.414$ $p = 0.707$	$t(3) = 2.423$ $p = 0.094$

Note. () = **degrees of freedom**. * = statistically significant.

Table 4: Pre- /Post- P300 difference wave ERP neurophysiologic oddball task mean performance per tDCS condition per group.

EEG parameter	Pre-anodal	Post-anodal	Pre-cathodal	Post-cathodal	Pre-sham	Post-sham
Mean (SD) peak amplitude (μ V)						
Control	4.52 (0.99)	2.60 (1.45)	3.49 (1.81)	3.06 (1.17)	4.60 (1.54)	4.60 (0.90)
TBI	2.52 (1.16)	3.38 (2.04)	3.98 (2.23)	3.47 (2.03)	4.14 (2.01)	2.80 (1.41)
Mean (SD) peak latency (msec)						
Control	354 (10.58)	353 (33.68)	361 (15.10)	366 (12.0)	386 (60.09)	378 (73.07)
TBI	389 (38.14)	395 (47.15)	354 (28.0)	394 (49.58)	396 (63.78)	424 (76.38)

Table 5: Mean Pre- /Post- power oddball task mean performance changes per tDCS condition per group.

Brain area	Frontal		Central		Parietal		Occipital	
tDCS condition	Control	TBI	Control	TBI	Control	TBI	Control	TBI
Anodal mean (SD) (μV)								
alpha	0.012 (0.029)	-0.0049 (0.045)	0.0071 (0.031)	-0.012 (0.024)	0.0042 (0.066)	-0.027 (0.035)	0.055 (0.17)	-0.034 (0.13)
theta	0.0049 (0.023)	0.0087 (0.028)	0.00035 (0.012)	-0.0021 (0.012)	0.00013 (0.0091)	(0.0095) (0.034)	0.0055 (0.011)	0.0049 (0.12)
Cathodal mean (SD) (μV)								
alpha	-0.026 (0.019)	0.00068 (0.017)	-0.015 (0.018)	0.0013 (0.021)	-0.059 (0.057)	0.011 (0.028)	0.12 (0.11)	0.055 (0.15)
theta	-0.0048 (0.0073)	0.025 (0.026)	0.0036 (0.0095)	0.02 (0.045)	-0.0051 (0.017)	0.029 (0.049)	0.0068 (0.038)	0.071 (0.14)
Sham mean (SD) (μV)								
alpha	0.0002 (0.017)	0.0029 (0.0058)	0.0021 (0.018)	-0.0075 (0.006)	-0.019 (0.036)	-0.028 (0.046)	-0.012 (0.11)	0.019 (0.051)
theta	-0.0074 (0.022)	0.00055 (0.012)	-0.0066 (0.023)	-0.003 (0.0058)	-0.015 (0.023)	-0.0064 (0.012)	-0.016 (0.029)	0.022 (0.039)

Figure 1

