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Cumulative effects of transcranial direct current stimulation on EEG oscillations and attention/working memory during subacute neurorehabilitation of traumatic brain injury

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HIGHLIGHTS

- Immediate and cumulative increases in cortical excitability were seen among patients with traumatic brain injuries in response to anodal tDCS to the left dorsolateral prefrontal cortex.
- Following 10 consecutive sessions, decreased delta and increased alpha were noted, which extended beyond the region of the anodal electrode, suggesting improved regulation of cortical excitability.
- Study results suggest EEG may provide a useful biological marker for selection of patients likely to benefit from tDCS.

ABSTRACT

Objective: To investigate in a randomized, double-blind design, cumulative effects of anodal tDCS on EEG oscillations and neuropsychological tests among patients with traumatic brain injury (TBI) undergoing subacute neurorehabilitation.
Methods: Twenty-six patients were randomly assigned to active ($n = 13$) or sham ($n = 13$) tDCS groups. EEGs were recorded at 6 different time points, assessing both immediate and cumulative effects of tDCS on EEG oscillations. Twenty minute sessions of 1 mA anodal stimulation to the left dorsolateral prefrontal cortex (F3, cathode placed at right supraorbital site, Fp2), were provided on 10 consecutive days. Neuropsychological tests were administered before and after the series of tDCS sessions.
Results: Theta was significantly reduced for active tDCS patients following the first tDCS session. Delta decreased and alpha increased, both significantly, for the active tDCS group after 10 consecutive tDCS sessions. No significant changes were seen for sham group. Decreases in delta were significantly correlated with improved performance on neuropsychological tests for the active tDCS group to far greater degree than for the sham group. Participants in the active tDCS group who had excess slow EEG activity in their initial recordings showed greater improvement on neuropsychological tests than other groups.
Conclusion: Results suggest that 10 anodal tDCS sessions may beneficially modulate regulation of cortical excitability for patients with TBI.
Significance: EEG-guided tDCS warrants further investigation as a potential intervention for TBI during subacute neurorehabilitation.

1. Introduction

The debilitating consequences often associated with traumatic brain injury (TBI) are all too familiar to many clinicians and neuroscientists. According to the Centers for Disease Control and Prevention, approximately 1.7 million people sustain a traumatic brain injury each year (Faul et al., 2010).

It has been estimated that as many as 3.2–5.3 million individuals in the United States are experiencing lifelong disability as a consequence of TBI (DeGuise et al., 2008). Of the cognitive impairments frequently experienced, problems with attention and working memory are among the most prominent (McCullagh

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et al., 2011). Working memory is regarded as critical for a number of higher level cognitive abilities. As a result, individuals with working memory impairment following TBI are believed to experience problems in a number of related areas, such as executive functions, information processing speed, language, memory and perception (Hoskison et al., 2009). Investigations into novel interventions that may help to ameliorate problems with attention and working memory following TBI are clearly needed.

In recent years, there has been a burgeoning interest in several methods of noninvasive brain stimulation as promising therapeutic interventions for modulating brain activity in beneficial ways (Demirtas-Tatlidede et al., 2011; Villamar et al., 2012). One of these techniques, transcranial direct current stimulation (tDCS) uses weak electrical current applied to the scalp to alter transmembrane potentials of neurons toward either greater depolarization or greater hyperpolarization, depending upon the direction of current flow. Anodal stimulation is known to shift neural membrane potentials toward greater depolarization, resulting in increased neural firing rates and hence increased cortical excitability. Cathodal stimulation, on the other hand, moves the membrane potential toward greater hyperpolarization, thereby decreasing neural firing rates and decreasing cortical excitability (Williams et al., 2009; Zaghi et al., 2010).

Evidence of possible clinical usefulness of tDCS is rapidly accumulating in a number of areas. Recent examples include improvement of motor learning following stroke (Fregni et al., 2005a,b; Boggio et al., 2007), improvement of naming in stroke-related aphasia (Baker et al., 2010), enhancement of working memory in healthy controls (Fregni et al., 2005a,b) patients with Parkinson's disease (Boggio et al., 2006) and stroke (Jo et al., 2009), amelioration of chronic pain (Fregni et al., 2006), treatment of depression (Arul-Anandam and Loo, 2009) and enhancement of planning ability (Dockery et al., 2009).

Given the encouraging results reported in an increasing number of studies of tDCS, several groups have proposed that this technique might have a role in the treatment of traumatic brain injury (Demirtas-Tatlidede et al., 2011; Villamar et al., 2012; DeFina et al., 2009). It has been further suggested that the complex pathophysiology of TBI necessitates identification of biomarkers that could guide the administration of tDCS to appropriate neurological targets (Demirtas-Tatlidede et al., 2011; DeFina et al., 2009).

A number of recent studies have used EEG variables in order to measure the effects of tDCS on brain activity (Keeser et al., 2011; Jacobson et al., 2012a,b; DeRojas et al., 2013; Faria et al., 2012; Wirth et al., 2011). Although the specific aims, subjects and methodologies vary across studies, a general finding emerging from these studies is that of suppression of slow activity, either the delta or theta frequency, in the region of the anodal electrode. These studies indicate that EEG measures are useful in measuring brain activation changes in response to tDCS.

EEG studies have also been shown to be useful in assessing changes in brain activity following TBI. Investigations of EEG changes following TBI have been conducted at various times post-injury, including: immediately upon presentation to the emergency department (Naunheim et al., 2010); during coma (Moulton et al., 1988); in investigating relationships between neuroanatomical measures such as MRI T2 relaxation times and EEG amplitudes during post-acute recovery (Thatcher et al., 1998); and during attention-demanding tasks (Dockree and Robertson, 2011).

Evidence indicates that particular EEG patterns may be associated with different levels of injury severity and different stages of recovery following these injuries. Increases in the power of slow frequencies, particularly delta and theta, and concomitant reductions in high frequency power are commonly reported (Alavarez et al., 2008). Often, slowing of the posterior dominant alpha rhythm is present, shifting it into the theta frequency band, thereby causing an increase in theta spectral power (Nuwer et al., 2005).

In a recent study, our research group recorded serial EEGs, along with serial neuropsychological tests, among a sample of 12 patients as they progressed through inpatient neurorehabilitation for TBI. The same measures were obtained from a group of 13 closely matched healthy controls. This sample of patients was completely separate from the sample recruited for the present study. Patients with TBI differed significantly from controls due to excesses of power in the delta and theta frequency bands, as well as in the mean peak frequency of alpha, which was slower than for controls. Using linear regression, we found EEG spectral power measures to be significantly related to neuropsychological tests such that as power in delta and theta decreased, performance on measures of attention and working memory increased, and as power in the alpha frequency increased, performance on the measures of attention and working memory increased. It was concluded that EEG spectral power measures tracked recovery from TBI in a meaningful way, providing a useful neurobiological marker that could be used to quantify response to rehabilitative interventions, and could potentially become an important predictor of treatment response (Ulam et al., 2013).

Given that tDCS has been shown to effectively modulate cortical excitability in beneficial ways, we set out to undertake an investigation of the potential usefulness of tDCS as an intervention for individuals with moderate to severe TBIs in the acute/subacute phase of recovery. Previous research has indicated that changes in cortical excitability induced by tDCS appear to be reliably indexed by EEG-derived measures. Therefore, we chose to use the resting EEG power spectrum as the primary dependent measure.

The prominence of attention/working memory impairments among persons with TBI in this stage of recovery prompted us to target the left dorsolateral prefrontal cortex for anodal tDCS treatment, which has already been shown to improve working memory in healthy controls, patients with Parkinson's disease, and individuals who have suffered strokes (Fregni et al., 2005a,b; Boggio et al., 2006; Jo et al., 2009). Based on previous research showing that anodal tDCS can result in decreases in delta and theta power (Keeser et al., 2011; Jacobson et al., 2012a,b), and our findings that these frequencies decrease over the course of recovery in association with improvements in attention and working memory (Ulam et al., 2013), we hypothesized that active anodal tDCS would result in decreases in delta and theta to a greater degree than for sham tDCS. Our observation that recovery of attention and working memory was significantly associated with higher spectral power of alpha during TBI recovery led us to further hypothesize that anodal tDCS would be associated with an increase in alpha power. We hypothesized that the changes in EEG power specified above would also be associated with greater improvement on measures of attention and working memory for the active anodal tDCS group as compared to the sham group. Given that attention and working memory are fundamental to a number of cognitive functions, we also predicted that the active tDCS group would show greater improvement on neuropsychological tests of immediate and delayed memory and emotional recognition, as compared to the sham group.

2. Methods

2.1. Participants

Participants in this study were recruited from a population of patients undergoing inpatient neurorehabilitation in the acute to subacute stage of recovery from traumatic brain injuries, at a university-based specialty hospital. All aspects of this study were

reviewed and approved by the university institutional review board and all aspects of the study were conducted in compliance with the Declaration of Helsinki. Inclusion criteria for participation in the study were as follows: patients were between 18 and 65 years of age, did not have a previous history of neurological disorder (stroke, TBI, anoxic brain injury) or major, professionally diagnosed psychiatric illness, did not have significant skull defects, had Auditory Comprehension and Verbal Expression FIM (Functional Independence Measure) scores of at least 4, and were able to tolerate the EEG recordings and cognitive assessment procedures. All participants had well documented traumatic brain injuries. All patients had loss or significant alteration of consciousness at the time of injury. All but three patients had documented traumatic neuropathology confirmed by neuroimaging. Injury characteristics of the subjects are listed in Supplementary Table S1. Thirty-three patients were approached for participation. Twenty-six adult patients who met inclusion criteria participated in the study. After enrollment, subjects were randomly assigned to either the active or sham groups. Three potential participants declined, two were dropped from the study due to earlier than projected discharge from the hospital (one active, one sham), and one subject (sham) was dropped from analysis when it was learned after completion of the study that the subject had a prior diagnosis of schizophrenia. No statistically significant differences were present between the active and sham groups for the variables of age, or level of education. In order to test whether the active and sham groups were reasonably matched for cognitive level at the beginning of the study, the groups were compared on the mean of 19 neuropsychological tests administered just prior to the initiation of tDCS, which will be described later. Using an independent samples *t*-test, no significant difference between groups was found on this neuropsychological summary score. Table 1 summarizes patient characteristics.

In order to assess possible medication effects, a count of the number of medications each patient was taking within 8 different classes of neuroactive medications was taken. Use of actual dosages was not feasible due to the fact that patients were on multiple medications, often within a particular class of medication, each with its own potency and specific dosages. Dosages between medications were often not comparable when using milligrams as a unit. Medications taken by the patients were recorded for the day of each EEG recording. The active and sham groups were tested for differences in the mean number of medications taken within each class. Table 2 summarizes this information, including Mann–Whitney *U* tests between the active and sham tDCS groups. One significant difference was found between active and sham groups, with the shams taking a greater number of antipsychotic medications at the time of the first and last EEG recordings. All other differences were non-significant.

2.2. Neuropsychological testing

The near ubiquitous role of attention and working memory in cognitive function prompted us to assess a fairly broad range of neuropsychological functions. While our primary interest was in attention and working memory, we recognized that these abilities are essential to many other neuropsychological functions. Therefore, we also included measures of inhibitory control, cognitive flexibility, immediate and delayed memory for both verbal and visual-spatial material, and a measure of emotion recognition. Supplementary Table S2 summarizes the neuropsychological measures used in the study.

Neuropsychological tests were administered by either a licensed Speech/Language Pathologist with greater than 5 years experience assessing cognitive functions, a licensed neuropsychologist, also with greater than 5 years experience in cognitive assessment, or a graduate student in neuropsychology who was directly supervised by the neuropsychologist. All examiners were blind to subject assignment to active or sham tDCS at both the pre and post treatment assessments. The pre-treatment evaluation took place within 1–2 days of the initial EEG evaluation, and 2–3 days prior to the first tDCS treatment. The post-treatment evaluation took place within 1–3 days after the final tDCS treatment and final EEG. When available, tests were used that have at least two parallel equivalent versions, with the first version being administered prior to treatment, the second being administered after treatment. The Digit Span subtests from the WAIS-IV and the subtests from the Color-Word Interference Test of the Delis-Kaplan Executive Function System, do not have parallel equivalent forms. However, random assignment of subjects to the active and sham tDCS groups should have controlled for possible unequal distribution of any practice effects that might be present. Neuropsychological tests were scored by the same examiners, who continued to be blind to subject assignment at the time of scoring.

2.3. EEG acquisition and analysis

EEG's were recorded in standardized manner using 19 active scalp locations placed according to the International 10/20 system of electrode placement. Linked ears were used as a reference, with the ground placed between the Fpz and Fz locations. Each electrode site was abraded and electrodes were affixed with conductive paste. Impedances were maintained at or below 5 Kohms. A Brainmaster Discovery 24E EEG acquisition system was used (Brainmaster Technologies, Inc., Bedford, OH).

EEGs were digitized at 1024 samples per second and stored to the computer hard drive at the rate of 256 samples per second. Each subject was asked to close their eyes and sit quietly. EEG activity was recorded for 10–15 min. Stringent artifact management techniques were used during the recording to assure the best quality data possible. When excess artifact was noted during a recording, subjects were given verbal instructions and/or physical guidance to reduce the artifact. If a subject could not control eyelid flutter, cotton balls were gently taped over the eyelids, which successfully eliminated this type of artifact.

Following EEG data acquisition, each subject's digital EEG file was imported into the Neuroguide EEG analysis software (Applied Neuroscience, Inc., St. Petersburg, FL). The raw digital tracings were visually inspected for residual artifact. EEG segments selected for analysis were of good quality for quantification purposes. A minimum of 1.5 min of EEG data was obtained for each subject, with all subsequent calculations being based on the average EEG

Table 1
Patient characteristics.

Patient characteristic	Active tDCS ($n = 13$)	Sham tDCS ($n = 13$)	*t*-Test
Age: $\bar{x}(\sigma)$	31.34 (9.8)	35.70 (14.7)	(24)-0.896, $p = 0.38$
Education: $\bar{x}(\sigma)$	11.61 (1.8)	12.15 (2.19)	(24)-0.684, $p = 0.50$
Gender	$M = 12$, $F = 1$	$M = 10$, $F = 3$	n/a
Race	12 C, 1 AA	12 C, 1 H	n/a
Mean neuro ψ *z* score: $\bar{x}(\sigma)$	−1.97 (1.1)	−1.50 (0.85)	(36)-1.53, $p = 0.14$
Days since onset: $\bar{x}$ (σ)	57.38 (37.8)	41.08 (20.87)	(24)1.36, $p = 0.19$

Table 2
Medications.

	Anti-epil		Ant-psych		Anti-anx		Neuro-stim		Anti-spas		Anti-depress		Hypnotic		Narcotic	
	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG
Active tDCS $\bar{x}(\sigma)$	.54 (.78)	.54 (.78)	.15 (.38)	.15 (.38)	.54 (.66)	.15 (38)	.54 (.52)	.46 (.52)	.38 (.96)	.38 (.96)	.77 (.93)	.77 (.93)	0	.54 (.52)	.69 (.48)	.69 (.48)
Sham tDCS $\bar{x}(\sigma)$	.61 (.96)	.54 (.78)	.85 (.38)	.54 (.52)	.15 (.38)	.15 (.38)	.54 (.88)	.54 (.88)	.38 (.87)	.31 (.85)	.69 (.85)	.69 (.85)	0	.23 (.44)	.61 (.96)	.61 (.96)
Mann–Whitney *U*	83.5	84.5	26.0	52.0	111.5	84.5	94.0	88.0	79.5	85.0	87.5	87.5	n/a	110.5	101.5	101.5
Expected	84.5	84.5	84.5	84.5	84.5	84.5	84.5	84.5	84.5	84.5	84.5	84.5	n/a	84.5	84.5	84.5
p-Value (two tailed)	.98 ns	1.0 ns	.001	.047	.092	1.0	.60	.86	.74	1.0	.89	.89	n/a	.12	.34	.34

spectrum from this 1.5 min (or greater) sample. Test–retest reliability coefficients were generated for each of the 19 electrode locations by the Neuroguide software. These were calculated as the ratio of variance of the data points within the time series associated with the epochs selected from the first half of each recording divided by the variance of the epochs selected from the second half of each recording. All test–retest reliability coefficients for electrode locations used in the analysis (F3 and Fp2), were above .85. Split-half reliability coefficients were calculated in a similar manner by the Neuroguide software, using the variance of odd versus even selected epochs in the equation. Again, all split-half coefficients for the electrodes used in the analysis were above .85. These coefficients suggest that EEG activity selected for analysis for each subject was obtained in a single state, without major transitions between states.

A Fast Fourier Transform was used to compute the EEG power spectrum in the five frequency bands considered in the Neuroguide software. IIR Butterworth filters were applied, with the low pass setting at 40 Hz and the high pass setting at 1 Hz. The frequency bands were defined as follows: Delta = 1.0–4.0 Hz; Theta = 4.0–8.0 Hz; Alpha = 8.0–12.0; Beta = 12.0–25.0 Hz; High Beta = 25.0–30.0 Hz. The Neuroguide reference database was used for calculation of relative power Z scores in each frequency band. For these database comparisons, each subjects' raw score was converted to a *z* score based upon comparison to the mean of an age-appropriate segment of the normative database. EEGs were reviewed and quantified by an investigator with board certification in quantitative EEG analysis techniques (FAU), who was blind to subject status at the time of review.

EEGs were recorded at 6 different time points: EEG #1 – one day prior to the first tDCS session, EEG #2 – immediately before the first tDCS session, EEG #3 – immediately following the first tDCS session; EEG #4 – immediately before the 10th and final tDCS session, EEG #5 – immediately following the final tDCS session, EEG #6 – one day following the final session of tDCS. This sequence of EEG recordings allowed a specific analysis strategy, with the comparison of EEG #1 and #2 facilitating assessment of the short term stability of the EEG activity, the comparison of EEG #2 and #3 permitting an assessment of immediate effects of tDCS, and the comparison of EEG #1 and #6 assessing cumulative effects of the stimulation.

2.4. tDCS

After participants were enrolled in the study, they were randomly assigned to receive either active anodal tDCS or sham tDCS. Subjects were blind to tDCS group assignment. A Magstim Eldith direct current stimulator was used (NeuroConn, Llmenau, Germany). A research assistant (LD) who was unblinded set up the stimulation for each subject at each session, without discussing this with either subjects or other investigators. The display window of the stimulator was covered with an opaque sheet of paper throughout each session. Electrode impedances were recorded by the research assistant in 4 min intervals throughout each session, to assure stimulation was being delivered appropriately. This recording procedure was followed for both active and sham groups, although the research assistant recorded made-up numbers for the sham group. The impedance sheets were not viewed by the blinded investigators or the participants.

For the active group, anodal tDCS was delivered to the left dorsolateral prefrontal cortex (F3 electrode location according to the International 10/20 System) with cathode placed over the right supraorbital area (Fp2 electrode location). For the sham group, the electrodes were placed in the same locations. Electrodes were 3.8 cm × 4.4 cm carbon/rubber electrodes placed within 5.0 cm × 5.60 cm saline soaked sponge covers. The active group received 20 min of continuous direct current stimulation at 1 mA intensity. For the sham group, current gradually faded in over a period of 8 s, followed by 30 s of stimulation, with current then fading out over an additional 8 s. Subjects sat quietly while receiving stimulation, with the research assistant present, monitoring and recording tDCS electrode impedances. The tDCS treatments were always scheduled between the hours of 9:00 a.m. and 2:00 p.m., depending on open times in each participant's schedule.

2.5. Data analysis

2.5.1. EEG data

Separate repeated measures analyses of variance were conducted for each of the four traditional EEG frequencies, at different time points, with relative power as the dependent measure, and tDCS as the independent variable, with two levels, active and sham. The F3 and Fp2 electrode locations were used, as these correspond to the placement of the tDCS anode and cathode, respectively. Analyses were conducted for EEG #1 versus #2, #2 versus #3, and #1 versus #6. Post hoc *t*-tests were conducted when significant findings were present in the ANOVA.

2.5.2. Neuropsychological data

The primary analysis of neuropsychological data consisted of repeated-measures analyses of variance for each test, involving between-groups comparisons and pre versus post treatment comparisons. Post hoc *t*-tests were conducted when significant results were obtained.

Given that neuropsychological improvements were expected in both the active tDCS group and the sham group, efforts were made to distinguish those improvements that might reasonably be attributed to the tDCS. A correlational analysis was conducted to determine if meaningful relationships were present between change scores in alpha power and delta power from EEG # 1 to EEG #6, and change scores found in the pre to post treatment neuropsychological tests. These correlational analyses were conducted separately for the active tDCS group and sham group.

Another exploratory post hoc analysis was performed based on the significant changes in brain oscillations that were found. It was hypothesized that the effects of tDCS might be influenced by the degree to which EEG slowing was present in the pretreatment EEG. Therefore, both the active and sham tDCS groups were divided

into those with and without EEG slowing. Inclusion in an EEG slowing subgroup required the presence of at least two contiguous electrode locations showing power within the delta or theta frequencies of two standard deviations or higher, relative to the Neuroguide normative database. With this grouping of subjects, repeated-measures analyses of variance were conducted for each neuropsychological test, with the standardized score for each test prior to and after treatment being the dependent variable, EEG-based group designation being an independent variable with two levels – with or without slowing, and tDCS being the other independent variable, with two levels – active or sham. Post hoc *t*-tests were conducted for each neuropsychological test and each EEG-based group. The results of the *t*-tests were then treated as a categorical variable for each EEG-based group. Neuropsychological tests showing significant pre versus post treatment improvement were assigned 1 and those not showing improvement 0. These results were then examined for all neuropsychological tests between EEG- based groups using a Chi^2 test of proportions.

3. Results

3.1. EEG #1 versus EEG #2: short-term stability of EEG measures

3.1.1. Delta

F3 Electrode: No significant differences between groups were present for the F3 site in the delta frequency. No differences in delta relative power between EEG #1 and EEG #2 were present. *Fp2 Electrode:* At the Fp2 site, in the delta frequency, a difference was present, ($F(1, 24) = 6.02$, $p = 0.02$) between groups. Post hoc *t*-tests revealed that the active tDCS group had greater delta at Fp2 than the sham group for EEG#1 (active $m = -.53$, sd = 1.08; sham $m = -1.55$, sd = 1.33; $t(24) = 2.15$, $p = 0.042$) and EEG #2 (active $m = -.88$, sd = .97; sham $m = -1.81$, sd = 1.11; $t(24) = 2.29$, $p = 0.031$). No significant differences between EEG #1 and EEG #2 in delta power were noted.

3.1.2. Theta

F3 Electrode: No significant between groups differences were present in the theta frequency for the F3 electrode site. No differences in theta at this site were present between EEG #1 and #2. *Fp2 Electrode:* No between groups differences were present in the theta frequency for the Fp2 site, and no differences in theta were noted between EEG #1 and #2 at Fp2.

3.1.3. Alpha

F3 Electrode: No differences between active tDCS and sham groups were present in the alpha frequency, at the F3 electrode site. No differences between EEG #1 and #2 were present in alpha at this location. *Fp2 Electrode:* No between group differences were present in the alpha frequency at Fp2, and no differences in alpha were found between EEG #1 and #2.

3.1.4. Beta

F3 Electrode: No differences between groups were present at the F3 electrode for the beta frequency. No differences between EEG #1 and #2 were identified for beta at this electrode location. *Fp2 Electrode:* Between groups differences were not present for the beta frequency at Fp2. No differences between EEG #1 and EEG #2 were present for the beta frequency at this location.

3.2. EEG # 2 versus EEG #3: immediate effects of the first tDCS session

3.2.1. Delta

F3 Electrode: A significant difference between active tDCS and sham groups was present for the delta frequency at F3 ($F(1, 24) = 4.57$, $p = .043$). Post hoc *t*-tests revealed greater delta at F3 for the active tDCS group compared to the sham group, at EEG #3 (active $m = -1.02$, sd = 1.06; sham $m = -2.32$, sd = 1.82; $t(24) = 2.22$, $p = 0.04$). No significant differences between EEG #2 and #3 were found for delta at F3. *Fp2 Electrode:* For the between groups comparison in the delta frequency at Fp2, a significant difference was also present ($F(1, 24) = 4.28$, $p = 0.05$). Post hoc *t*-tests identified greater total delta for the active tDCS group at EEG #2 and #3 compared to the sham group (active $m = -.85$, sd = .93; sham $m = -1.69$, sd = 1.20; $t(24) = 2.82$, $p = 0.007$). No significant differences were present between EEG #2 and #3 for the Fp2 location in the delta frequency.

3.2.2. Theta

F3 Electrode: No significant between group differences were present in theta frequency at F3. A significant difference between EEG #2 and #3 ($F(1) = 4.04$, $p = 0.05$) was present. Post hoc *t*-tests identified a significant decrease in theta between EEG #2 and EEG #3 for the active tDCS group (EEG #2 $m = 1.13$, sd = 1.43; EEG #3 $m = .88$, sd = 1.56; $t(12) = 2.13$, $p = 0.03$) but not the sham group (EEG #2 $m = .55$, sd = 2.0; EEG #3 $m = .51$, sd = 2.0; $t(12) = .46$, $p = .65$). *Fp2 Electrode:* No significant differences were present in the theta frequency at Fp2 for either between groups or between EEG #2 versus #3 comparisons.

3.2.3. Alpha

F3 Electrode: No significant between group differences were identified for the F3 electrode in the alpha frequency. A trend toward a difference in the comparison between EEG #2 and #3 was found ($F(1) = 3.81$, $p = 0.057$), which did not reach statistical significance. *Fp2 Electrode:* For the Fp2 electrode location, no between group differences were present in the alpha frequency, nor were differences present between EEG #2 and #3.

3.2.4. Beta

F3 Electrode: For the F3 electrode location, in the beta frequency, no between group differences were present. No differences were present at this electrode site between EEG #2 and #3. *Fp2 Electrode:* No differences were found at the Fp2 electrode for the between groups comparisons or for the comparisons between EEG #2 and #3.

3.3. EEG # 1 versus EEG #6: cumulative effects of tDCS

3.3.1. Delta

F3 Electrode: No significant differences were present in the between groups comparison at the F3 electrode. Although no significant difference was present between EEG #1 and EEG #6 for this electrode site, a significant group × EEG interaction was noted ($F(1) = 7.5$, $p = .009$). Post hoc *t*-tests revealed a significant decrease in delta between EEG #1 and #6 for the active tDCS group (EEG #1 $m = -1.08$, sd = 1.08; EEG #6 $m = -1.74$, sd = .99, $t(12) = 3.20$, $p = 0.004$), but not for the sham group (EEG #1 $m = -2.20$, sd = 1.58; EEG #6 $m = -1.86$. sd = 1.18; $t(12) = -1.13$, $p = .28$). *Fp2 Electrode:* Between groups comparisons at the Fp2 electrode location were not significant. No significant difference was identified in the comparison between EEG #1 and #6. However, a significant group × EEG interaction was present ($F(1) = 4.63$, $p = 0.005$). The post hoc *t*-tests showed a significant decrease in delta for the active tDCS group (EEG #1 $m = -.53$, sd = 1.08; EEG #6 $m = -1.27$, sd = 1.03; $t(12) = 1.79$, $p = 0.043$), but not for the sham group (EEG #1 m = −1.55, sd = 1.33; EEG #6 m = −1.10, sd = 0.97; $t(12) = -.99$, $p = .33$).

3.3.2. Theta

F3 Electrode: The between groups comparison at the F3 electrode site revealed no significant differences. Similarly, the comparison between EEG #1 and #6 was without significant differences. *Fp2 Electrode:* No significant differences were present in the between group comparison at Fp2, or in the comparison between EEG #1 and #6.

3.3.3. Alpha

F3 Electrode: Between groups comparisons were not significant at the F3 electrode for the alpha frequency. No significant differences were present in the comparison between EEG #1 and #6. A significant group × EEG interaction was present ($F(1) = 6.57$, $p = .014$). The post hoc *t*-tests revealed a significant increase in alpha from EEG #1 to #6 for the active tDCS group (EEG #1 $m = -.032$, sd = .91; EEG #6 $m = .52$, sd = .77; $t(12) = -3.68$, $p = 0.002$), but not for the sham group (EEG #1 $m = 0.012$, sd = 1.27; EEG #6 m = −0.20, sd = 1.04; $t(12) = 0.83$, $p = .42$). Additionally, a significant difference was identified between the active tDCS and sham groups at EEG #6, with the active group having greater alpha relative power than the shams (active $m = .52$, sd = .77; sham $m = -.20$, sd = 1.04; $t(24) = 2.00$, $p = 0.028$) (see Fig. 1). *Fp2 Electrode:* No significant differences were present in the between groups comparison, or the EEG #1 versus EEG #6 comparison at the Fp2 electrode location. A significant group × EEG interaction was present ($F(1) = 5.60$, p = 0.022). Post hoc t-tests revealed a significant increase in alpha for the active group (EEG #1 $m = 0.027$, sd = .95; EEG #6 $m = .44$, sd = .94, $t(12) = -2.87$, $p = .007$) but not for the sham group (EEG #1 $m = -0.007$, sd = 1.18; EEG #6 $m = -.28$, sd = 1.13, $t(12) = 1.09$, $p = .30$). Additionally, the difference in alpha relative power at EEG #6, between the active and sham groups was significant (active EEG #6 $m = .44$, sd = .94; sham EEG #6 $m = -.28$, sd = 1.13, $t(24) = 1.75$, $p = 0.046$) with the active group showing greater power.

3.3.4. Beta

F3 Electrode: No significant between group differences were identified for the F3 site in the beta frequency. Similarly, no differences between EEG #1 and #6 were found. *Fp2 Electrode:* The between groups comparisons for the Fp2 electrode location were without significant differences, as were the comparisons between EEG #1 and #6.

It is important to note that for the examination of the differences between EEG #1 and EEG #6, there were several missing data points. One subject from the active tDCS group and two subjects from the sham group did not have EEG values for EEG #6, due to discharge from the hospital on the day the final EEGs were scheduled. Group means were used to substitute for the missing data. In order to cross check the validity of substituting the mean for this missing data, we also examined differences between EEG #1 versus EEG #5, where there was no missing data. It will be recalled that EEG #5 was recorded immediately following the final tDCS session. The results of independent t-tests of EEG #1 versus EEG #5 are presented in Table 3. As can be seen in Table 3, the active group showed significant decreases in delta and increases in alpha at both the F3 and Fp2 electrode locations, while the sham group showed no significant differences in any frequency at either electrode location. The same pattern seen in the comparison between EEG #1 and EEG #6 was found in the comparison between EEG #1 and EEG #5.

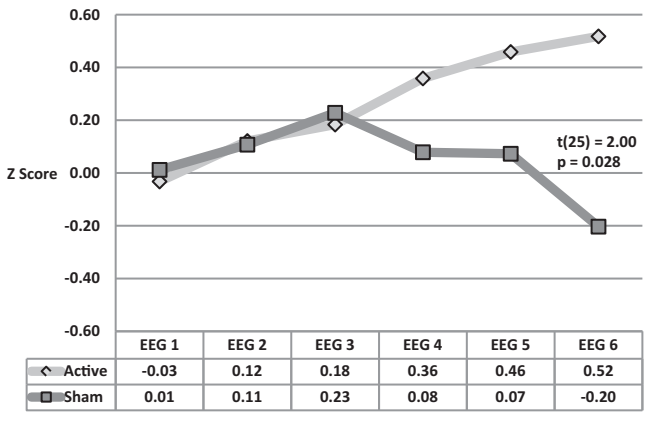

Fig. 1. Alpha relative power *z* scores, active tDCS versus sham, EEGs #1 through #6. Active tDCS $N = 13$; sham tDCS $N = 13$.

3.4. Neuropsychological measures

The results of the repeated-measures ANOVAs comparing neuropsychological tests are shown in Table 4.

Inspection of Table 4 shows that no between-group differences were present for any of the tests administered. Fifteen (15) out of 19 tests (79%) showed significant pre to post treatment changes. However, no tDCS group × pre/post test score interactions were present.

Correlations between change scores for alpha and delta relative power, and pre versus post change scores on neuropsychological tests are shown in Tables 5–8. The active tDCS and sham groups were analyzed separately.

As can be seen in Table 5, the active tDCS group showed significant positive correlations between change scores in the alpha frequency and 3 neuropsychological tests. Table 6 shows that 2 significant positive correlations were present for the sham group between alpha change scores and neuropsychological test change scores.

In the delta frequency, the active tDCS group showed 9 significant negative correlations between delta change scores and neuropsychological change scores (Table 7) while the sham group showed significant negative correlations in the delta frequency for only 2 neuropsychological tests (Table 8). A *z* test comparing the proportion of neuropsychological change scores showing significant negative correlations with the delta change scores for the active tDCS and the sham groups was also significant (difference = 0.37; critical value = 1.96; $p = 0.006$, two tailed).

Our earlier work (Ulam et al., 2013) showing that activity in the delta and theta frequencies predicted poorer performance on neuropsychological tests and that activity in the alpha band predicted better performance, lead us to hypothesize that the reduction of EEG slowing and the increase in alpha associated with active tDCS might be associated with greater improvement on neuropsychological tests. We further reasoned that the degree of neuropsychological improvement might differ depending on the degree of slowing in the EEG that was present prior to treatment. We therefore divided our sample into those with and without slowing in the initial EEG, as explained above. There were 7 individuals within the active tDCS group with slowing, 6 without, and 5 in the sham group with slowing and 8 without.

The results of *t*-tests comparing the pre versus post tDCS neuropsychological test scores by EEG-based tDCS groups are shown in Table 9.

Inspection of Table 9 shows that significant post treatment improvements were present for all groups. The active tDCS group with EEG slowing improved on 10 (53%) tests, the active tDCS group without slowing improved on 2 (10%), the sham group with EEG slowing improved on 4 (21%) and the sham group without slowing also improved on 4 (21%) of tests.

Further analysis was conducted to determine whether or not the number of tests on which significant improvement was present

Table 3
t-Tests, EEG #1 versus EEG #5, (active tDCS $n = 13$, sham $n = 13$).

	Δ		θ		α		β	
	EEG #1	EEG #5	EEG #1	EEG #5	EEG #1	EEG #5	EEG #1	EEG #5
Active tDCS – F3 (mean, SD)	−1.08, 1.08	−1.58, 1.02	1.19, 1.44	1.00, 1.14	−0.03, 0.91	0.46, 1.01	0.025, 1.75	−0.19, 1.62
t(df), *p*	$t(12) = 2.57$, $p = 0.012$		$t(12) = 1.78$, $p = 0.24$		$t(12) = -1.78$, $p = 0.001$		$t(12) = 0.82$, $p = 0.42$	
Sham tDCS – F3 (mean, SD)	−2.19, 1.58	2.18, 1.44	0.68, 2.0	0.33, 1.92	0.01, 1.27	0.07, 1.16	0.42, 1.68	0.75, 1.65
t(df), *p*	$t(12) = 2.18$, $p = 0.99$		$t(12) = 2.18$, $p = 0.25$		$t(12) = -0.43$, $p = 0.67$		$t(12) = -1.67$, $p = 0.12$	
Active tDCS – Fp2 (mean, SD)	−0.53, 1.08	−0.97, 0.97	1.05, 1.10	1.08, 0.97	0.03, 0.95	0.45, 0.88	−0.11, 1.12	−0.11, 0.97
t(df), *p*	$t(12) = 2.20$, $p = 0.024$		$t(12) = 1.78$, $p = 0.55$		$t(12) = -2.92$, $p = 0.006$		$t(12) = -0.015$, $p = 0.99$	
Sham tDCS – Fp2 (mean, SD)	−1.55, 1.33	−1.58, 1.38	0.65, 1.84	0.31, 1.72	−007, 1.18	0.09, 1.22	0.59, 1.63	0.75, 1.58
t(df), *p*	$t(12) = 0.12$, $p = 0.91$		$t(12) = 2.18$, $p = 0.18$		$t(12) = -0.95$, $p = 0.36$		$t(12) = -0.73$, $p = 0.48$	

Table 4
Repeated-measures ANOVAs for neuropsychological measures (active tDCS $n = 13$, sham $n = 13$).

	Active versus sham		Pre versus post Tx		Group × pre/post interaction	
	F	*p*	*F*	*p*	*F*	*p*
Elevator count w distraction	1.3 (1, 24)	0.26	.005 (1, 24)	0.945	.005 (1, 24)	0.94
Visual elevator accuracy	1.64 (1, 24)	0.212	**9.78 (1, 24)**	**.003**	.022 (1, 24)	0.88
Visual elevator time	1.58 (1, 24)	0.22	**4.69 (1, 24)**	**.035**	.002 (1, 24)	0.97
Elevator count w reversal	0.127 (1, 24)	0.72	**7.63 (1, 24)**	**.008**	0.153 (1, 24)	0.70
Digit span forward	0.807 (1, 24)	0.38	0.135 (1, 24)	0.71	0.94 (1, 24)	0.34
Digit span reversed	1.06 (1, 24)	0.31	**4.76 (1, 24)**	**0.034**	0.58 (1, 24)	0.45
Digit span sequencing	2.43 (1, 24)	0.13	**26.56 (1, 24)**	**0.0001**	0.026 (1, 24)	0.87
Symbol span	3.30 (1, 24)	0.08	**17.68 (1, 24)**	**0.0001**	0.16 (1, 24)	0.69
Color naming time	1.98 (1, 24)	0.17	**10.66 (1, 24)**	**0.002**	0.88 (1, 24)	0.35
Word reading time	0.65 (1, 24)	0.43	**7.0 (1, 24)**	**0.011**	0.05 (1, 24)	0.82
Inhibition time	1.01 (1, 24)	0.32	**12.93 (1, 24)**	**0.001**	0.36 (1, 24)	0.55
Inhibition accuracy	0.01 (1, 24)	0.91	**18.93 (1, 24)**	**0.0001**	0.1 (1, 24)	0.75
Inhibit/switch time	1.22 (1, 24)	0.28	**9.21 (1, 24)**	**0.004**	0.32	0.57
Inhibit/switch accuracy	0.17 (1, 24)	0.69	**12.26 (1, 24)**	**0.001**	0.03 (1, 24)	0.86
TASIT	2.90 (1, 24)	0.10	**16.94 (1, 24)**	**0.0002**	0.76 (1, 24)	0.39
HVLT total recall	3.07 (1, 24)	0.09	1.29 (1, 24)	0.26	1.01 (1, 24)	0.32
HVLT delayed recall	0.72(1, 24)	0.40	3.71 (1, 24)	0.06	0.51 (1, 24)	0.48
BVMT total recall	0.34 (1, 24)	0.57	**8.36 (1, 24)**	**0.006**	0.12 (1, 24)	0.74
BVMT delayed recall	1.0 (1, 24)	0.33	**4.94 (1, 24)**	**0.03**	0.23 (1, 24)	0.64

Bold = Significant at $p \leqslant 0.05$.

Table 5
Correlation analysis, active tDCS group, alpha relative power change scores between EEG #1 and EEG #6, with pre versus post treatment neuropsychological change scores (active tDCS $n = 13$, sham $n = 13$).

Neuropsych test	Pearson *r*	*p* value
Visual elevator time	**.53**	**0.03**
Visual elevator accuracy	.12	ns
Elevator count w distraction	.30	ns
Elevator count w reversal	.24	ns
Digit span forward	−.40	ns
Digit span reversed	−.15	ns
Digit span sequencing	−.26	ns
Symbol span	.08	ns
Color-word interference – color naming	.10	ns
Color word interference – word reading	.46	0.06
Color word interference – inhibition time	.10	ns
Color word interference – inhibition accuracy	.15	ns
Color word interference – inhibit/switch time	.20	ns
Color word interference – inhibit/switch accuracy	**.74**	**0.004**
TASIT	0.03	ns
Hopkins verbal learning – total correct	.13	ns
Hopkins verbal learning – delayed recall	.27	ns
Hopkins verbal learning – recognition	.30	ns
Brief visual memory – total recall	**.47**	**0.05**
Brief visual memory – delayed recall	**.50**	**0.04**
Brief visual memory – learning	.26	ns

Bold = Significant at $p \leqslant 0.05$.

Table 6
Correlation analysis, sham group, alpha relative power change scores between EEG #1 and EEG #6, with pre versus post treatment neuropsychological change scores (active tDCS $n = 13$, sham $n = 13$).

Neuropsych test	Pearson *r*	*p* value
Visual elevator time	0.21	ns
Visual elevator accuracy	0.36	ns
Elevator count w distraction	0.07	ns
Elevator count w reversal	−0.08	ns
Digit span forward	**0.52**	**0.03**
Digit span reversed	0.24	ns
Digit span sequencing	0.30	ns
Symbol span	0.04	ns
Color-word interference – color naming	0.31	ns
Color word interference – word reading	0.16	ns
Color word interference – inhibition time	−0.19	ns
Color word interference – inhibition accuracy	0.015	ns
Color word interference – inhibit/switch time	0.024	ns
Color word interference – inhibit/switch accuracy	0.01	ns
TASIT	**0.76**	**0.001**
Hopkins verbal learning – total correct	0.45	ns
Hopkins verbal learning – delayed recall	0.14	ns
Hopkins verbal learning – recognition	−.22	ns
Brief visual memory – total recall	0.34	ns
Brief visual memory – delayed recall	0.39	ns
Brief visual memory – learning	0.17	ns

Bold = Significant at $p \leqslant 0.05$.

for the different EGG-based groups could be accounted for by chance. We tallied each instance of statistically significant improvement for each group, assigning such improvements a '1', with each instance where no improvement was present being assigned a '0'. A Chi^2 test showed the distribution of post-tDCS improvements to be unlikely to have occurred by chance ($Chi^2 = 9.771$, critical value = 7.052, $p = 0.021$), thereby prompting rejection of the null hypothesis (see Fig. 2). A Marascuilo procedure

Table 7
Correlation analysis, active tDCS group, delta relative power change scores between EEG #1 and EEG #6, with pre versus post treatment neuropsychological change scores (active tDCS $n = 13$, sham $n = 13$).

Neuropsych test	Pearson r	p value
Visual elevator time	−.23	ns
Visual elevator accuracy	**−.52**	**0.03**
Elevator count w distraction	−.43	ns
Elevator count w reversal	**−.67**	**0.006**
Digit span forward	.49	0.06
Digit span reversed	.12	ns
Digit span sequencing	−.08	ns
Symbol span	−.06	ns
Color-word interference – color naming	**−.53**	**0.03**
Color word interference – word reading	**−.76**	**0.001**
Color word interference – inhibition time	**−.53**	**0.03**
Color word interference – inhibition accuracy	−.13	ns
Color word interference – inhibit/switch time	−.46	0.06
Color word interference – inhibit/switch accuracy	**−.60**	**0.01**
TASIT	**−.53**	**0.03**
Hopkins verbal learning – total correct	−.33	ns
Hopkins verbal learning – delayed recall	−.24	ns
Hopkins verbal learning – recognition	.23	ns
Brief visual memory – total recall	**−.58**	**0.02**
Brief visual memory – delayed recall	**−.74**	**0.002**
Brief visual memory – learning	**−.55**	**0.02**

Bold = Significant at $p \leqslant 0.05$.

Table 8
Correlation analysis, sham group, delta relative power change scores between EEG #1 and EEG #6, with pre versus post treatment neuropsychological change scores (active tDCS $n = 13$, sham $n = 13$).

Neuropsych test	Pearson r	p value
Visual elevator time	−0.40	ns
Visual elevator accuracy	0.15	ns
Elevator count w distraction	0.45	0.06
Elevator count w reversal	0.27	ns
Digit span forward	−0.17	ns
Digit span reversed	−0.35	ns
Digit span sequencing	−0.15	ns
Symbol span	0.02	ns
Color-word interference – color naming	−0.29	ns
Color word interference – word reading	−0.37	ns
Color word interference – inhibition time	0.36	ns
Color word interference – inhibition accuracy	0.09	ns
Color word interference – inhibit/switch time	0.06	ns
Color word interference – inhibit/switch accuracy	−0.006	ns
TASIT	**−0.54**	**0.03**
Hopkins verbal learning – total correct	−0.20	ns
Hopkins verbal learning – delayed recall	−0.26	ns
Hopkins verbal learning – recognition	0.43	ns
Brief visual memory – total recall	−0.28	ns
Brief visual memory – delayed recall	**−0.47**	**0.05**
Brief visual memory – learning	0.05	ns

Bold = Significant at $p \leqslant 0.05$.

for multiple pairwise comparisons indicated that the active tDCS group with slowing was responsible for the rejection of the null hypothesis, due to a greater number of post-tDCS improvements than the other groups.

In order to assess for possible medication effects that might have influenced the neuropsychological results, the EEG-based groups were compared for the total number of medications taken within 8 different classes of neuroactive medications. The Kruskal–Wallis nonparametric test for multiple samples was used. This data was compared for EEG #1 and #6, which would have been prior to and after the course of tDCS treatment. The results of this comparison are shown in Table 6.

As can be seen from Table 10, the EEG-based groups differed only in the number of antipsychotic medications taken. To further understand this difference, the Steel–Dwass–Critchow–Fligner procedure for multiple pairwise comparisons was used. This procedure showed that the significant difference between groups was in fact driven by a difference between the sham with EEG slowing group as compared to the Active tDCS groups with and without slowing at EEG #1, and a difference between the sham group with EEG slowing and the Active group without EEG slowing at EEG #6.

4. Discussion

The present trial of tDCS among a sample of patients with TBI participating in inpatient subacute neurorehabilitation, revealed changes in brain oscillations for the active tDCS group as compared to the sham group. Both immediate and cumulative changes in EEG oscillations were seen for the active group.

First of all, no EEG changes were seen for either group between EEG #1 and EEG #2, both of which were prior to the first tDCS session. This suggests satisfactory stability of the EEG measures used in the study.

The comparison of EEG #2, recorded immediately before the first tDCS session, with EEG #3, recorded immediately after the first session, revealed a significant decrease in theta for the active group only, at the F3 electrode, the same location used for the placement of the tDCS anode. No significant changes were present in other frequencies between EEG #2 and #3. A decrease in theta band activity has been reported in at least one study following anodal tDCS (Jacobson et al., 2012a,b). Earlier, Ardolino et al. (2005) documented increases in delta and theta power of the motor cortex following cathodal stimulation, which they interpreted as reflecting reduced cortical activity. Their results are therefore consistent with the present results, although opposite in direction. The decrease in theta activity seen immediately following the first tDCS session in the present study is consistent with increased cortical excitability in the vicinity of the anodal electrode.

In the comparison between EEG #1, recorded prior to the initiation of tDCS, and EEG #6, which was recorded after the completion of 10 daily sessions of tDCS, several changes in oscillatory activity were detected. First, a decrease in delta was present at both the F3 and Fp2 electrode locations, for the active tDCS group but not the sham group. This is once again consistent with increased cortical excitability. Interestingly, the increase in excitability is not restricted to the location of the anodal electrode, but extends to the area of the cathodal electrode as well. It is important to note that this decrease in activity in the delta frequency was recorded one day following the final tDCS treatment. This change is present beyond the span of time associated with the immediate effects of tDCS. It appears that this may represent a cumulative change in cortical excitability. The fact that it is documented at the locations of both the anodal and cathodal electrodes suggests that the cumulative changes may be more extensive in range, encompassing a larger area of cortex.

Another important change noted between EEG #1 and #6 occurs in the alpha frequency band. Here, the active tDCS group shows a significant increase not seen in the sham group. Additionally, this increase in alpha is again present at both the F3 and Fp2 electrode sites. Bearing in mind that the EEGs were recorded in the eyes closed resting but awake state, this increase in alpha is also consistent with enhanced cortical excitability. The fact that the increase in alpha is once again seen at both the anode and cathode sites suggests a more widespread change in cortical excitability that may be characteristic of cumulative as opposed to immediate effects of tDCS.

With respect to the changes on neuropsychological tests from prior to tDCS treatment to after treatment, both the active tDCS and sham tDCS groups showed an equal number of statistically

Table 9
t-Tests, pre versus post tDCS neuropsychological test scores by EEG-based treatment groups.

	Active tDCS with slowing ($n = 7$)		Active tDCS without slowing ($n = 5$)		Sham tDCS with slowing ($n = 5$)		Sham tDCS without slowing ($n = 8$)	
	t/*p* value		*t*/*p* value		*t*/*p* value		*t*/*p* value	
Elevator count w distraction	−0.525	0.31	1.023	0.35	1	0.37	0.148	0.89
Visual elevator accuracy	−1.35	0.11	**−2.8**	**0.02**	**−3.8**	**0.01**	−0.58	0.29
Visual elevator time	−1.98	0.09	−0.33	0.75	−0.18	0.87	−1.51	0.17
Elevator count w reversal	−1.91	0.053	−1.7	0.15	−1.36	0.12	−0.7	0.5
Digit span forward	1.63	0.15	−1.67	0.16	−0.91	0.41	−0.31	0.77
Digit span reversed	−0.85	0.21	−0.72	0.5	**−3.36**	**0.014**	−0.63	0.56
Digit span sequencing	**−3.35**	**0.006**	−1.54	0.18	−1.51	0.1	**−3.65**	**0.008**
Symbol span	**−3.88**	**0.004**	−1.67	0.16	−1.81	0.14	−1.86	0.1
Color naming time	**−4**	**0.003**	−0.63	0.56	−2.1	0.11	−1.36	0.22
Word reading time	**−2.2**	**0.04**	−0.16	0.88	−0.43	0.34	**−2.8**	**0.03**
Inhibition time	**−2.13**	**0.04**	−1.58	0.17	−1.72	0.16	**−2.9**	**0.02**
Inhibition accuracy	−1.34	0.11	**−2.84**	**0.04**	**3.13**	**0.03**	−1.7	0.14
Inhibit/switch time	**−2.71**	**0.02**	−1.4	0.22	**−3.77**	**0.02**	−0.25	0.81
Inhibit/switch accuracy	**−2.84**	**0.015**	−0.9	0.41	−2.55	0.06	−1.32	0.23
TASIT	**−3.38**	**0.007**	−0.95	0.39	−0.94	0.4	**−5.5**	**0.001**
HVLT total recall	0.48	0.68	−1	0.36	−0.52	0.63	−1.44	0.19
HVLT delayed recall	−1.51	0.09	−0.68	0.53	−1.58	0.19	−0.57	0.59
BVMT total recall	**−2.1**	**0.04**	−1.63	0.16	−0.46	0.67	−0.89	0.4
BVMT delayed recall	**−3**	**0.012**	−1	0.36	−1.11	0.33	−1.1	0.31

Bold = Significant at $p \leqslant 0.05$.

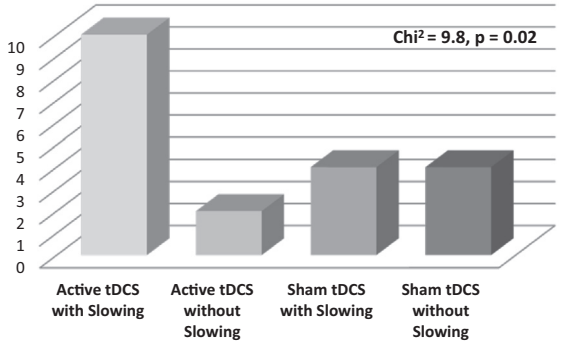

Fig. 2. Number of statistically significant improvements on neuropsychological tests, from pre to post treatment. Patients are grouped by active tDCS versus sham, and by whether or not EEG slowing was present before the initiation of treatment. Active tDCS with slowing, $N = 7$; active tDCS without slowing, $N = 6$; sham tDCS with slowing, $N = 5$; sham tDCS without slowing, $N = 8$.

significant improvements. Both groups showed overlapping improvement on 53% (8 out of 15) tests. In the post acute phase of neurorehabilitation, rapid recovery of neuropsychological functions is frequently seen and expected to some degree. There were 20% of the tests on which only the active tDCS group improved, and a separate 20% on which only the sham tDCS group improved. These results could be partly explained by the fact that a large number of tests were used, with different aspects of attention and working memory measured by each test. In this study, we did not have hypotheses regarding the specific type of attentional or working memory task that might be influenced most by anodal tDCS delivered to the left dorsolateral prefrontal cortex. Rather, our interest was in investigating overall effects of tDCS on attention and working memory, broadly defined, among individuals with traumatic brain injuries.

A correlational analysis between EEG power change scores and neuropsychological test change scores showed several positive correlations between increases in alpha and improvements on neuropsychological tests, for both the active tDCS group and the sham group. However, in the delta frequency, reductions in delta were significantly negatively correlated with improvements on neuropsychological tests on 9 out of 19 tests for the active tDCS group, but only 3 out of 19 tests for the sham group. The difference in the number of significant correlations of delta change with neuropsychological improvement between the active tDCS group and the sham group was itself statistically significant, as noted above. This indicates a meaningful relationship between the decreased delta found in the active tDCS group and improvements on an appreciable number (47%) of neuropsychological tests, a finding that is consistent with increased excitability resulting from the active treatment.

It is widely understood that excesses in slow EEG activity seen in association with various neurological conditions are indicative of decreased cortical excitability (Steriade et al., 1993; Llinas and Steriade, 2006). Given that the changes in the frequency composition of the EEG shown by the active tDCS group are strongly suggestive of increased cortical excitability, and the changes in frequency were meaningfully associated with improved neuropsychological performance for the active tDCS group, we explored whether the amount of slowing in the EEG (reflecting the degree of decreased cortical excitability) present at the beginning of the study would be related to the beneficial effects of tDCS on neuropsychological functions. This adjunctive analysis indeed showed that individuals with TBI who had greater slowing prior to treatment, and who received active tDCS improved on a greater number of neuropsychological tests than the active tDCS group without EEG slowing, and the sham tDCS groups with and without EEG slowing. These findings, although based on numbers too small to allow confident generalization, support the hypothesis that EEG slowing may be a biological marker for identifying individuals with TBI that might benefit from anodal tDCS. Further, decreases in EEG slowing, particularly delta, and increases in alpha, may help to guide the delivery of anodal tDCS in terms of intensity and number of treatments.

In spite of being randomly assigned, one difference between the active tDCS and sham tDCS groups was that a greater number of the sham group was taking atypical antipsychotic medications during the time they participated in the study. This leads to the question as to whether these medications could have played a role in the EEG and cognitive differences between groups that were observed. We could not find relevant scientific articles concerning the effects of neuroactive medications, including atypical antipsychotics, on the EEG among individuals with TBI. We did find some evidence that these medications increase alpha relative power among patients with schizophrenic-spectrum disorders (Hyun

Table 10
Number of neuroactive medications taken at EEG #1 and EEG #6, by EEG-based groups.

	Anti-epil		Anti-psych		Anti-anx		Neuro-stim		Anti-spas		Anti-depress		Hypnotic		Narcotic	
	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG	1st EEG	6th EEG
Active tDCS w slow (∑)	5	5	1	1	2	0	3	3	3	3	3	3	5	4	6	5
Active tDCS no slow (∑)	2	2	1	0	5	2	4	4	2	2	7	6	4	2	3	2
Sham tDCS w slow (∑)	4	4	4	4	1	1	5	5	4	4	3	3	4	1	6	4
Sham tDCS no slow (∑)	3	3	6	3	1	1	2	2	1	0	5	4	4	2	2	3
Kruskal–Wallis – observed	1.70	1.70	12.73	9.06	5.53	2.78	3.07	3.07	1.71	3.47	1.93	0.62	1.37	2.28	5.41	2.78
Expected	7.81	7.81	7.81	7.81	7.81	7.81	7.81	7.81	7.81	7.81	7.81	7.81	7.81	7.81	7.81	7.81
p-Value (two tailed)	0.64	0.64	**0.005**	**0.03**	0.14	0.43	0.38	0.38	0.63	0.32	0.59	0.89	0.71	0.52	0.14	0.43

Bold = Significant at $p \leqslant 0.05$.

et al., 2011). A specific atypical antipsychotic, clozapine, has also been associated with increases in delta and theta power in the above cited report. However, none of our participants were taking this particular medication. Generalizing from the limited evidence from schizophrenic-spectrum disorders, we would have expected higher alpha relative power among the sham group compared to the active tDCS group. Thus, our results are completely contrary to what would be expected if the higher use of atypical antipsychotics among the sham group were influencing the results. Furthermore, the possible association of atypical antipsychotic medications with elevated delta power would lead one to predict higher delta, even at the outset of the study, among the sham group. Again, this is opposite to what was actually found.

Our study has several limitations. First of all, it might be informative if the individuals with TBI could be placed into subgroups based on specific features of their neuropathology, their EEG features, as well as medications taken. The relatively small sample in the present study precludes this. Therefore replication with a larger sample would be useful. The numbers of individuals in our EEG-based subgroups are too small to allow confident generalization. However, the results do lead to specific hypotheses that should be tested with larger samples.

All of the EEG changes seen in the active tDCS group are consistent with increased cortical excitability. Interestingly, the cumulative changes consisting of a reduction in delta and an increase in alpha, were seen both at the site where the anodal electrode was placed, and at the site of the cathode. This suggests widespread neuroplastic changes in the regulation of cortical excitability.

Evidence exists to suggest that many of the cognitive impairments seen in the subacute phase of traumatic brain injury are due, at least in part, to excessive inhibition of cortical circuitry (Kobori and Dash, 2006; Goforth et al., 2011). In light of this, it is reasonable to hypothesize that cortical stimulation that increases excitability, such as with anodal tDCS, should produce beneficial effects for individuals with TBI. In our study, both the active and sham groups showed extensive improvements on neuropsychological tests. An adjunctive analysis appears to have helped clarify the cognitive effects of the tDCS treatment. When we analyzed the neuropsychological results based on a division of our patient sample into subgroups with and without EEG slowing, we found that the active tDCS group with EEG slowing improved on a significantly greater number of tests than the active group without slowing, and the sham groups with and without slowing. This is entirely consistent with the idea that EEG slowing is an indicator of decreased cortical excitability and therefore, individuals with decreased excitability would be expected to benefit most from a treatment that increases excitability.

Overall, the results of this study indicate that anodal tDCS shows great promise as a treatment for neuropsychological impairments among persons that have sustained traumatic brain injuries, even in the subacute stage of recovery. Our results further suggest that resting EEG measures may be very useful as biological markers of dysregulated cortical excitability, and may help in selection of patients likely to benefit from tDCS, as well as in guiding the delivery of stimulation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2014.05.015.

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