

High-definition transcranial direct current stimulation modulates theta response during a Go-NoGo task in traumatic brain injury



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HIGHLIGHTS

- Frontal midline theta power and inter-trial phase coherence during Go processing increased after active pre-SMA HD-tDCS.
- Theta phase coherence between frontal and posterior regions during Go processing increased after active pre-SMA HD-tDCS.
- Lower baseline frontal theta inter-trial phase coherence predicted more improved Go performance to active HD-tDCS.

ABSTRACT

Objective: High Definition transcranial Direct Current Stimulation (HD-tDCS) has been shown to improve cognitive performance in individuals with chronic traumatic brain injury (TBI), although electrophysiological mechanisms remain unclear.

Methods: Veterans with TBI underwent active anodal ($N = 15$) vs sham ($N = 10$) HD-tDCS targeting the pre-supplementary motor area (pre-SMA). A Go-NoGo task was conducted simultaneously with electroencephalography (EEG) at baseline and after intervention completion.

Results: We found increased theta event-related spectral perturbation (ERSP) and inter-trial phase coherence (ITPC) during Go in the frontal midline electrodes overlying the pre-SMA after active HD-tDCS intervention, but not after sham. We also found increased theta phase coherence during Go between the frontal midline and left posterior regions after active HD-tDCS. A late increase in alpha-theta ERSP was found in the left central region after active HD-tDCS. Notably, lower baseline theta ERSP/ITPC in the frontal midline region predicted more post-intervention improvement in Go performance only in the active group.

Conclusions: There are local and interregional oscillatory changes in response to HD-tDCS modulation in chronic TBI.

Significance: These findings may guide future research in utilizing EEG time–frequency metrics not only to measure interventional effects, but also in selecting candidates who may optimally respond to treatment.

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Abbreviations: Pre-SMA, pre-supplementary motor area; HD-tDCS, high definition transcranial direct current stimulation; ERSP, event-related spectral perturbation; ITPC, inter-trial phase coherence; TBI, traumatic brain injury.

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1. Introduction

In the US, more than 185,000 veterans who use the Veterans Affairs health care system for their health care have been diagnosed with at least one TBI, and the prevalence of TBI has been estimated to be more than 22% among injured service members

[Whiteneck et al., 2015; Warden, 2006]. An estimated 15% of patients with mild TBI and 65% of patients with moderate to severe TBI report cognitive sequelae longer than 6–12 months post-injury [Rabinowitz and Levin, 2014; McInnes et al., 2017]. Cognitive rehabilitation improves verbal communication but its benefits usually decline after the first 6–12 months [Cicerone et al., 2000]. There has been no broadly accepted effective treatment for persistent cognitive impairments [Diaz-Arrastia et al., 2014]. High-definition transcranial Direct Current Stimulation (HD-tDCS) is a cost effective and clinically feasible tool that has been proven to be safe and efficacious in treating impaired cognition and may offer an improved functional prognosis for TBI patients [Motes et al., 2020; Chiang et al., 2021b, 2021a].

The pre-supplementary motor area (pre-SMA), within the superior medial frontal cortex, is a well-recognized cortical hub central to efficient verbal retrieval, with its role in cognitive control (i.e., inhibition, conflict resolution) and domain-general execution of both motor and speech [Hertrich et al., 2016; Alario et al., 2006]. Electrophysiological and functional magnetic resonance imaging (fMRI) evidence indicate the importance of synchronized activity between the pre-SMA, the left inferior frontal gyrus, and subcortical structures (including the thalamus and the basal ganglia) that facilitates memory retrieval [Hart et al., 2013], motivating the targeting of the pre-SMA for electromodulation. Anodal tDCS has been found to increase not only cortical excitability in the frontal regions but also synchronized activity of their underlying neural circuits [Stagg and Nitsche, 2011; Yu et al., 2015]. Previous studies administered anodal HD-tDCS targeting the pre-SMA and found improved verbal retrieval (category fluency) as well as cognitive control (color-word interference) in veterans with a history of TBI [Motes et al., 2020; Chiang et al., 2021a]. Although disrupted structural connectivity and desynchronized brain activity are core features of TBI and may be modulated by HD-tDCS [Cavanagh et al., 2020; Sharp et al., 2014], the mechanisms of modulation have yet to be clarified.

Changes in neuronal activity as a direct result of electromodulation can be measured non-invasively using EEG, including (1) magnitude of change (e.g., event-related spectral perturbation [ERSP]) and (2) phase of change (e.g., inter-trial phase coherence [ITPC], the consistency of relative phase within a neuronal oscillator across trials) [Fries, 2015; Chiang et al., 2016; Bastos and Schoffelen, 2016]. Phase coherence at lower frequencies (such as in the theta frequency band, 4–8 Hz) may indicate transient synchronized activity between discrete regions and allow for facilitating or suppressing selected neuronal populations in response to stimuli during cognitive operations [Cavanagh and Frank, 2014; Nyhus and Curran, 2010]. These EEG measures may help elucidate the link between disrupted structural connectivity due to TBI and subsequent cognitive deficits [Cavanagh et al., 2020; Sharp et al., 2014].

In order to examine EEG oscillatory changes as an outcome measure to the pre-SMA HD-tDCS, we chose a Go-NoGo task that elicits pre-SMA activity during response selection and inhibition [Chiang et al., 2013; DeLaRosa et al., 2020; Brier et al., 2010]. This Go-NoGo task elicits frontal midline theta (increase in ERSP and ITPC, peak around 300 ms) and alpha (decrease in ERSP, peak around 400 ms) oscillatory changes [Brier et al., 2010]. A recent study using neural network classification with source localization methods showed pre-SMA theta and alpha oscillatory activity to be among the best predictors of Go vs NoGo trials [DeLaRosa et al., 2020]. These theta and alpha power signatures have also proved useful to differentiate individuals with mild cognitive impairment (MCI) from their healthy counterparts [Nguyen et al., 2017] as well as those with early vs late MCI [Lydon et al., 2022]. Frontal theta power (i.e. ERSP) and phase coherence (i.e. ITPC) indi-

cate cognitive control and inhibitory response that are closely tied to the pre-SMA function [Cavanagh and Frank, 2014].

We hypothesized that frontal theta ERSP and ITPC would be modulated by the active pre-SMA HD-tDCS delivered through frontal midline electrodes that demonstrated theta oscillatory changes during the Go-NoGo task [Brier et al., 2010]. We also hypothesized that connectivity between the midfrontal (overlying the pre-SMA) and other regions could be modulated, as measured by EEG phase coherence methods between frontal midline electrodes and the rest of the high-density EEG montage. Furthermore, given the evidence that baseline measures predict (HD-)tDCS effects [Chiang et al., 2021a], we hypothesized that certain baseline EEG measures could be predictive of changes in behavioral performance during the Go-NoGo task.

To our knowledge, no one has investigated HD-tDCS effects using EEG dynamics in chronic TBI patients as reported here. We hope to demonstrate the feasibility and significance of using task-based EEG to improve understanding and application of HD-tDCS. Compared to anatomic imaging techniques such as MRI, EEG is a convenient, relatively inexpensive, and clinically readily applicable tool, with few contraindications. Combining electro-modulation with EEG markers can be a promising tool for optimizing stimulation protocols and selecting neurologic patients appropriate for such intervention.

2. Materials and methods

2.1. Participants

US military veterans were referred for intervention due to TBI-related cognitive symptoms. Those eligible for the study had to have a complaint of word finding difficulties verified by neuropsychological measures (see [Motes et al., 2020]). Exclusion criteria included recent seizures, substance abuse, severe visual or hearing impairment, and intracranial implants. Our patients were veterans with military related TBIs, meeting the criteria for mild to moderate TBI [VA/DoD guidelines], and did not have encephalomalacia or evident brain lesions on MRI at the time of study (visual inspection by two neurologists, H.-S.C and J.H., and one neuroradiologist, M.K., based on MPRAGE [Magnetization Prepared - Rapid Gradient Echo] and T2W-FLAIR [T2-weighted-Fluid-Attenuated Inversion Recovery] scans), other than for scattered non-specific T2W-FLAIR white matter hyperintensities. Overall normal brain MRI findings did not indicate regional (e.g., lateralized) structural brain injury as a potential factor to be considered. Eligible participants were assigned to receive active versus sham intervention with a 1.5:1 ratio between the two cohorts. A total of 28 participants underwent HD-tDCS intervention. However, the data from three participants were not included due to missing data at one time point. Thus, the data from 25 participants were included in our EEG analyses ($N = 15$ in the active group, mean age of 39.9 ± 8.4 years; $N = 10$ in the sham group, mean age of 42.8 ± 8.5 years) (Table 1). History of TBI based on retrospective recall, using the Ohio State TBI Identification Method [Corrigan and Bogner, 2007], did not significantly differ between the groups; neuropsychological data were also collected and did not show significant group difference at baseline (Table 1). We summarized baseline data regarding pre-morbid IQ, medication (particularly stimulant and psychotropic medicine), comorbid psychiatric conditions (diagnosis of depression and PTSD, ADD/ADHD), history of neurologic disorders (history of migraine and seizure), socioeconomic status (marital and work status) and ethnicity (Table 1). Written informed consent was obtained, and the study was conducted in accordance with the ethical standards of the Helsinki declaration (1964) and

Table 1
Baseline demographics and baseline neuropsychological measures.

	Active (N = 15)	Sham (N = 10)
Demographics: mean (SD) or subject number		
Age at test (year)	39.9 (8.4)	42.8 (8.5)
Sex	13 M/2F	8 M/2F
Race	All white	9 white/1 mixed race
Ethnicity	14 non-Hispanic/1 Hispanic	9 non-Hispanic/1 Hispanic
Education (year)	15.7 (2.1)	15.1 (2)
TBI history: subject number (percentage)		
+ TBI w/LOC	14 (93.3%)	9 (90%)
+ TBI w/LOC > 30 min	5 (33.3%)	4 (40%)
+ blast TBI	11 (73.3%)	7 (70%)
Medical history/Socioeconomic status: subject number		
Depression ⁺	6	3
PTSD ⁺	1	1
ADD/ADHD ⁺	1	1
History of migraine ⁺	1	2
History of seizure ⁺	1	0
On stimulant	1	1
On psychotropic medicine	4	1
Marital status	1 never married/11 married/2 separated/1 divorced	1 never married/6 married/3 divorced
Work status	7 employed/8 retired	4 employed/3 retired/3 other
Depression/Anxiety measures: mean (SD)		
BAI [†]	10.9 (6.7)	10.3 (8.4)
BDI-II	21.1 (12.6)	15 (10.9)
Neuropsychological measures at baseline: mean (SD)		
Verbal IQ (AMNART) [#]	117.7 (4.8)	117.25 (3.3)
COWAT (total)	43.3 (14.5)	40.1 (10.4)
Category fluency (total)	20.6 (7.1)	21.9 (5.6)
BNT total	56.3 (2.7)	56.2 (3.1)
Digit span-forward (longest)	6.7 (1.8)	6.5 (1.2)
Digit span-backward (longest)	5.3 (1.4)	5.2 (1.5)
TMT A (sec)	32 (12.5)	30 (7.9)
TMT B (sec)	76.1 (28.8)	93.7 (75)
D-KEFS naming (sec)	33.9 (8.5)	32 (10.7)
D-KEFS reading (sec)	26.7 (7.5)	24 (6.1)
D-KEFS inhibition (sec) [*]	56.5 (12.4)	68.4 (22.2)
D-KEFS inhibition-switch (sec)	70.9 (17.4)	73.4 (40.5)
RAVLT total (item)	43.7 (12.5)	45.1 (11.3)
RAVLT delayed recall (item)	8.7 (4.7)	8.1 (4.8)

Group comparisons in all measures at baseline with $p > 0.05$ using two-tailed independent t tests (continuous variables) or chi-squared tests (categorical variables). SD: standard deviation.

ADD/ADHD: attention deficit disorder/attention deficit hyperactivity disorder; AMNART: American National Adult Reading Test [Uttl, 2002]; BAI: Beck Anxiety Inventory [Steer and Beck, 1997]; BDI: Beck Depression Inventory-II [Beck et al., 1996]; BNT: Boston Naming Test [Kaplan et al., 1983]; COWAT: Controlled Oral Word Association Test & Category Fluency [Benton et al., 1994]; D-KEFS: Delis-Kaplan Executive Function System [Delis et al., 2001]; Digit span [Wechsler, 2008]; TBI: traumatic brain injury; LOC: loss of consciousness; MOCA: Montreal Cognitive assessment [Nasreddine et al., 2005]; PTSD: post-traumatic stress disorder; RAVLT: Rey Auditory Verbal Learning Test [Rey, 1941]; TMT: Trail Making Test [Reitan, 1958].

[†] No data in N = 4 sham subjects.

^{*} No data in N = 6 sham subjects.

[#] No data in N = 10 active subjects, N = 4 sham subjects.

[%] No data in N = 1 active subjects.

approved by the Institutional Review Boards of the University of Texas at Dallas and the University of Texas Southwestern Medical Center.

2.2. Study design and HD-tDCS protocol

This was a prospective, single-blinded (to subjects) design. Study candidates were first screened and examined at baseline to ensure their eligibility (see [Motes et al., 2020] for more detail). This current study constitutes a secondary analysis of the preliminary study [Motes et al., 2020] looking for underlying neural changes to support the treatment effect. Thus the study and its hypotheses were not pre-registered. Neuropsychological assessment and EEG acquisition were performed at baseline. Starting within 5 days after baseline assessment, eligible participants received 10 daily sessions of 20-minute HD-tDCS over 2 weeks. Neuropsychological and EEG assessments were re-performed

within a week after completion of HD-tDCS. The HD-tDCS montage consisted of one anodal electrode (Fz) and four cathodal electrodes (FP1, FP2, F7, and F8) (five circular Ag/AgCl electrodes 1 cm radius with conductive gel) which was configured to target the pre-SMA and its surrounding regions, including dorsal anterior cingulate cortex (dACC) (see [Supplementary Fig. 1](#)). Previous studies have shown that HD-tDCS effects using similar electrode sizes are effective in modulating brain responses [Esmaeilpour et al., 2018; Kuo et al., 2013]. The size of electrodes is not the only deciding factor for how much dosing of electric current is delivered using tDCS in general [Giordano et al., 2017]. The electrode positions were based on the international standard 10–10 system. A battery-driven, wireless multichannel device delivered the electric current (Neuroelectronics, Starstim®). During each active session, electric current was ramped up over 60 seconds until it reached 1 mA, stayed at 1 mA for 20 minutes, and ramped down to 0 mA over 60 seconds. During each sham session, current was first ramped

up over 60 sec until it reached 1 mA, then ramped down to 0 mA over 60 seconds until being turned off at 0 mA for 20 minutes. Participants were instructed to sit and stay alert. Napping was not allowed. Please see [Chiang et al. \(2021a\)](#) for simulated electric fields and for detailed discussions regarding the rationale for choosing these stimulation parameters.

2.3. EEG task and procedures

Participants completed a Go-NoGo task, during which they made Go-NoGo decisions based on a line drawing of a single exemplar of a car (Go, with a button push) or a single exemplar of a dog (NoGo, withholding response). This task consisted of 200 trials: 160 (80%) Go trials requiring response through button pressing and 40 (20%) NoGo trials that required inhibition and withholding of response, respectively. Each stimulus was presented for 300 ms followed by a 1700 ms fixation period (with '+' presented in the center of the display). The total duration of the task was about 7 minutes. A button box was situated under the right thumb or index finger to register Go responses and record reaction times (RT). The details regarding the development of this task can be found in [Maguire et al. \(2009\)](#).

2.4. EEG data acquisition and processing

While the subjects performed the tasks, EEG was continuously recorded from a 64-electrode EEG cap (Neuroscan Quickcap) via a Neuroscan SynAmps2 amplifier using Scan 4.5 software (Compumedics Neuroscan, USA; sampling rate: 1 kHz, DC–200 Hz). The reference electrode was placed in between Cz and CPz at midline. Bipolar vertical electro-oculogram (VEOG) was recorded for the left eye. EEG leads with impedance exceeding 10–20 k Ω were discarded from further processing and most impedances were less than 5–10 k Ω . Poorly functioning electrodes were also excluded manually by visual inspection of the raw data. Data from fewer than 5% of electrodes were rejected: the number of rejected electrodes did not differ significantly between the active and the sham groups. The continuous EEG data were high-pass filtered at 1 Hz followed by low-pass filtered at 30 Hz using a finite impulse response filter. The filtered EEG data then underwent independent component analysis (ICA) processing to identify artifacts (muscle, eye, and heart) using EEGLab [[Delorme and Makeig, 2004](#)] and those components with >70% probability of representing artifact were automatically removed (ICLabel [[Pion-Tonachini et al., 2019](#)]). Subsequently, ICA components of each individual's data were visually examined and artifacts not identified previously by the algorithm were removed manually to complete data cleaning. After this step, EEG data were segmented per each trial into multiple EEG epochs (–500 to 1500 ms, time-locked to the stimulus onset). Epochs having peak amplitude of more than 75 μ V (highly associated with artifacts) were rejected and epochs with extreme values were excluded by rejection algorithms in EEGLAB. In both active and sham groups, more than 85% of the Go trials and 95% of the NoGo trials were entered for analysis without significant group difference. An algorithm computing the average based on spherical splines fitted to the data was then applied to interpolate EEG data to the sites of the bad electrodes [[Ferree et al., 2009](#)]. [Supplementary Fig. 2](#) depicts group event-related potentials (ERP), ERSP, and ITPC at the frontal midline electrodes.

2.5. EEG Time-Frequency analysis

Fast Fourier Transformation (FFT) was performed to extract power and phase data for frequencies from 4 to 30 Hz (with 1 Hz intervals), using Hanning window tapering that divided the entire epoch into 100 time windows. The length of the sliding time win-

dow was 250 ms, resulting in temporal gaps (between two successive windows) of 17–18 ms. We used a padding ratio of 4, resulting in frequency resolution of 1 Hz. To extract data for frequencies between 1 and 4 Hz, the sliding time window was 500 ms in duration, results in temporal gaps of 22–23 ms. Scalp EEG is not well suited for recording gamma-band EEG data given the large number of artifacts within that frequency range (such as muscle artifact). For this reason, we band-passed filtered our data between 1 and 30 Hz, so gamma range (>30 Hz) EEG signals was excluded from our analysis. Baseline correction within each 1 Hz frequency interval was performed for each single trial by subtracting the average power between –500 and –100 ms pre-stimulus onset from each time point post-stimulus onset to calculate event-related spectral perturbation (ERSP) using a gain model [[Grandchamp and Delorme, 2011](#)]. The power data were then logarithmically converted to decibel (dB) for further statistical analysis. Inter-trial phase coherence (ITPC) within each 1 Hz frequency interval at each electrode was calculated at the same time, again using the above parameters (using EEGLab function `newtimef.m`). Briefly, phase coherence between two signals is calculated as the square of the cross spectrum of the electrodes divided by the product of the power spectra of the individual electrodes, a measure of the consistency of a phase relationship between two signals, ranging from 0 to 1 (phase locking value, PLV, as in [[Delorme and Makeig, 2004](#)]). In order to calculate interareal/interregional phase coherence between two electrodes, identical processing steps and parameters were applied (while using EEGLab function `newcrossf.m`) as described above so the same frequency and temporal resolution were maintained across analyses. Similar to ITPC, the absolute values of interareal phase coherence between electrodes ranged from 0 to 1.

2.6. Statistical analysis

For EEG task performance, we performed mixed generalized linear modeling (mixed GLM) using restricted maximum likelihood (REML) method (IBM SPSS Statistics 26.0) to include a random factor (subject) and two fixed factors (Time – pre vs post and group – active vs sham) with their 2-way interaction. These analyses were performed separately for Go RT, Go accuracy, and NoGo accuracy. All estimates were examined based on Kenward-Roger approximation due to smaller and unbalanced sample conditions, at a confidence level of 95% (IBM SPSS Statistics 26.0). First-order autoregression was used to account for co-variance structure for repeated measures. Significant results were reported when $p < 0.05$.

EEG data analysis was performed on delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (13–25 Hz) frequency bands with mean values (both ERSP and ITPC) calculated from each frequency range. We analyzed the theta frequency band according to our hypothesis, but also included other frequency bands (delta, alpha, and beta) as part of the exploratory analyses and reported them separately. Permutation tests were then performed to compare pre- to post-intervention data using two-tailed paired t-tests (for each group separately) for all electrodes for separate time windows spanning from –4 ms to 583 ms (for theta, alpha, beta) and from –8 ms to 583 ms (for delta) after stimulus onset. We chose this time window based on the Go-NoGo task literature, which shows that most effects occur within this time frame [[Brier et al., 2010](#)]. Within each time window, all electrodes were included (not chosen *a priori*) for analysis. False Discovery Rate (FDR) < 0.05 from permutation tests were considered significant, which is a robust statistical approach commonly adopted in function imaging studies so we did not further apply corrections for multiple comparisons to avoid excessive false negative results. The reason that we used separate time frames for FDR testing was to better disso-

ciate earlier versus later effects that might not be detected if all time windows were included. In order to discount spurious effects, we also only included those significant effects spanning over at least four time windows (in theta/alpha/beta for at least $17\text{--}18 \times 4 = 68\text{--}72$ msec, in delta for at least $22\text{--}23 \times 4 = 88\text{--}92$ msec). Interareal phase coherence was then analyzed based on the significant findings from ITPC, to further test our hypothesis that there was direct phase correlation between the electrodes that had shown increased ITPC. We sought evidence for direct phase correlation between the midline frontal electrodes (based on the findings from ITPC) and all the other electrodes (not a subset chosen *a priori*). The same permutation tests were then applied to the data matrix using the same statistical threshold. We did separate analyses for each group and also separated conditions (Go vs NoGo) due to a possible bias in EEG time–frequency analysis when comparing conditions with different number of observations [Bastos and Schoffelen, 2016]. For the above analyses, permutations reached $N = 1000$ for both the active and sham groups. Effect sizes (Hedges' g) were calculated *post hoc* using paired- t tests (IBM SPSS Statistics 26.0) from mean scores across the time frame at specific electrodes that showed significant results.

In order to examine baseline predictors, we focused on frontal midline electrodes (averaged across Fz, F1, F2, FCz, FC1, FC2) that approximately overlie the pre-SMA target. Specifically, we performed correlational analyses to examine how baseline frontal midline theta ERSP and ITPC (averaged between 0 and 300 ms post stimulus onset) in Go trials were associated with percent change ($100 \times [\text{post-pre}]/\text{pre}$) in Go RT and accuracy, and how baseline frontal midline ERSP and ITPC in NoGo trials were associated with percent change in NoGo accuracy. Given the smaller number of subjects and skewed distribution, we used nonparametric correlations, and results were considered significant if the Kendall's tau b (as well as Spearman's for comparison) correlation coefficient reached a $p < 0.05$ (two tailed). Because the sham group also was small, we performed separate analyses for each group.

Post-hoc power analyses [G*power 3.1; Faul et al., 2007] supported the use of sample sizes ranging from $N = 12$ (with Hedges' $g = 0.90$) to $N = 19$ (with Hedges' $g = 0.70$), based on Power = 0.80, $\alpha = 0.05$, effect size estimates from the actual study data, with Hedges' $g = 0.70\text{--}0.90$, and an estimated correlation between groups (matched pairs), with $r = 0.5$, given that both arms are TBI with no baseline differences.

3. Results

3.1. EEG task behavioral data

Group average data are presented in Table 2a and Fig. 1. Mixed GLM did not reveal significant results (main effects of Time and Group, Time $\times$ Group interaction, all $p > 0.05$) for either Go RT, Go accuracy, or NoGo accuracy (Table 2b). Based on the means, there seemed to be group difference in NoGo accuracy, but this

Table 2a

Task performance: mean (standard deviation).

	Active ($N = 15$)	Sham ($N = 10$)
Pre-intervention		
Go RT (ms)	371.8 (133.3)	329.8 (103.8)
Go Accuracy (%)	90.5 (12.1)	93.8 (9.8)
Nogo accuracy (%)	82.2 (12.1)	70.6 (18)
Post-intervention		
Go RT (ms)	335.7 (55.4)	329.5 (98.5)
Go Accuracy (%)	91.8 (10)	89.9 (14)
Nogo accuracy (%)	83.9 (12.6)	74.4 (22.7)

RT: reaction time.

was not significant, likely due to high variability among individuals (Tables 2a and 2b, Fig. 1).

3.2. Hypothesis based analysis: EEG theta (4–8 Hz) ERSP and ITPC

For theta ERSP, there was a significant increase in the mid-frontal cluster in the Go condition during 173–243 ms post stimulus onset only in the group that received active HD-tDCS (Fig. 2a; *post hoc* Hedges' $g = 0.303$). There was a significant increase in the NoGo condition near left central electrodes (C5) during a later time window 455–526 ms post stimulus onset only in the active group (Fig. 2b; *post hoc* Hedges' $g = 0.868$). Results for the rest of the time windows are reported in Supplementary Fig. 5.

For theta ITPC, there was a significant increase in the Go condition post active HD-tDCS within the frontal midline (FCz; *post hoc* Hedges' $g = 0.393$) and left posterior (PO5; *post hoc* Hedges' $g = 0.703$) electrodes (Fig. 3), from 173 to 279 ms post stimulus onset. No significant change in theta ITPC was found in the sham group (Fig. 3). There were no significant effects in the NoGo condition (Supplementary Fig. 6).

Interareal phase coherence linked to FCz (pre-selected based on the theta ITPC results) was shown to increase in PO5 in the Go condition after active HD-tDCS between 137 and 243 ms post stimulus onset (Fig. 4; *post hoc* Hedges' $g = 0.579$), providing evidence for increased connectivity between FCz and PO5. We did not analyze interregional phase coherence linked to other electrodes or for the NoGo condition, as there was no significant change within other electrodes nor in NoGo based on the theta ITPC results. Results for the rest of the time windows are reported in Supplementary Fig. 7a.

3.3. Exploratory analysis: EEG delta (1–4 Hz) ERSP and ITPC

For delta ERSP, there was a significant increase in the midfrontal cluster during 129–265 ms post stimulus onset in the Go condition only in the group that received active HD-tDCS (Fig. 5; *post hoc* Hedges' $g = 0.34$). There were no significant effects in the NoGo condition (Supplementary Fig. 3).

For delta ITPC, there was a significant increase in the Go condition post active HD-tDCS within the frontal midline (Fig. 5), from 174 to 310 ms post stimulus onset (*post hoc* Hedges' $g = 0.349$), while no significant effects were found in the sham group. There were no significant effects in the NoGo condition (Supplementary Fig. 4).

Following results from delta ITPC, interareal phase coherence was tested between FCz and other electrodes. However, no significant change after intervention was found after either active or sham stimulation.

3.4. Exploratory analysis: EEG alpha (8–12 Hz) ERSP and ITPC

For alpha ERSP, there was no significant change post stimulation in the Go condition (Supplementary Fig. 8). In contrast, there was a significant increase in alpha ERSP in the NoGo condition near the left central electrodes (C5) between 455 to 526 ms post stimulus onset (Fig. 6; *post hoc* Hedges' $g = 0.838$).

For alpha ITPC, there were no significant effects in either the Go or the NoGo condition (Supplementary Fig. 9).

3.5. Exploratory analyses: EEG beta (13–25 Hz) ERSP and ITPC

There were no significant regional effects of beta ERSP and ITPC (Supplementary Figs. 10 and 11, respectively).

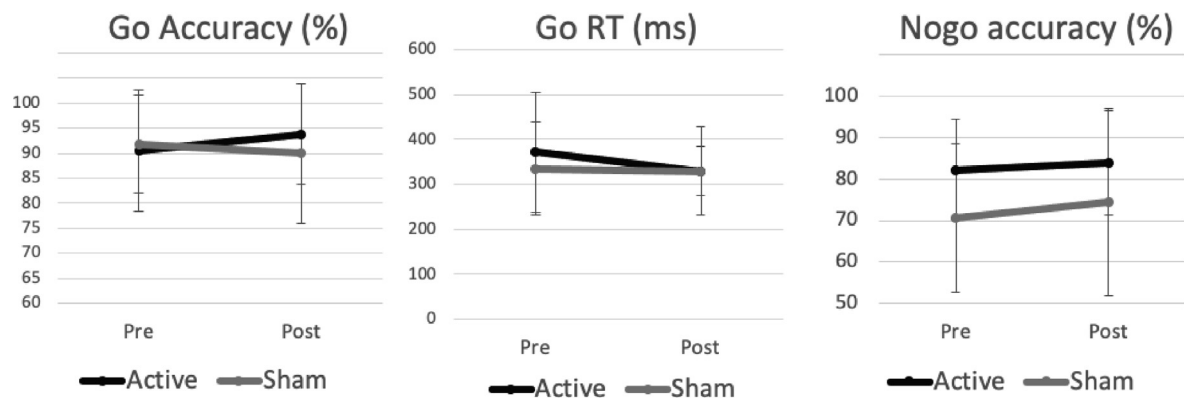


Fig. 1. EEG task performance. Error bars: standard deviations.

Table 2b
Statistical Results based on mixed Generalized Linear Modeling.

	Group	Time	Group $\times$ Time
Go RT (ms)	$F(1,23) = 0.434, p = 0.517$	$F(1,23) = 0.738, p = 0.399$	$F(1,23) = 0.719, p = 0.405$
Go Accuracy (%)	$F(1,23) = 0.041, p = 0.84$	$F(1,23) = 0.211, p = 0.65$	$F(1,23) = 1.336, p = 0.26$
Nogo accuracy (%)	$F(1,23) = 3.533, p = 0.073$	$F(1,23) = 1.672, p = 0.209$	$F(1,23) = 0.007, p = 0.932$

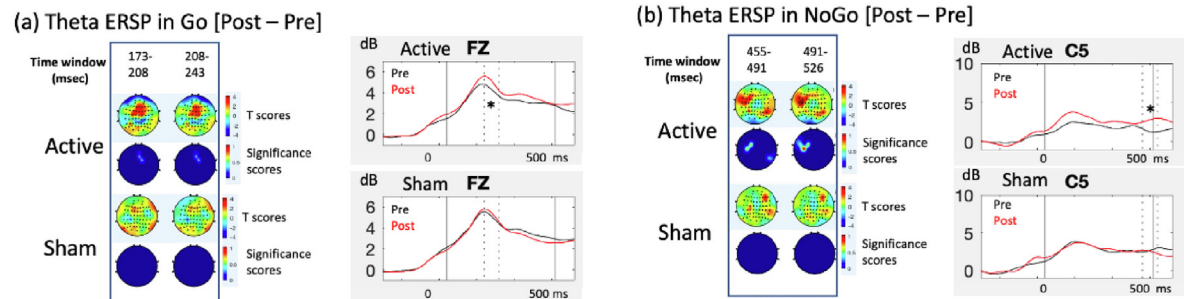


Fig. 2. Theta ERSP results. Permutation results showed a significant increase in the frontal midline theta ERSP around 173–243 ms post stimulus in the active group during Go, while no significant effects were found in the sham group (a, Left). Frontal midline theta ERSP (at Fz) during Go is represented separately for pre- and post-intervention data, showing difference (*) in the active group within this window (indicated by the dotted lines), but not in the sham group (a, Right). There was also a significant increase in the left central theta ERSP around 455–526 ms post stimulus in the active group during NoGo, while no significant effects were found in the sham group (b, Left). Left central theta ERSP (at C5) during NoGo is represented separately for pre- and post-intervention data, showing difference (*) in the active group within this window (indicated by the dotted lines), but not in the sham group (b, Right). In the depiction for each group, topography on top represents T scores (based on 2-tailed paired t tests within each group comparing post to pre data) averaged within each time window, while topography on bottom represents only those electrodes with significant difference (FDR < 0.05) within each corresponding time window. ERSP: event-related spectral perturbation; dB: decibel (unit of power).

3.6. Hypothesis based analysis: Baseline frontal midline theta as predictors for behavioral changes

Lower baseline frontal midline Go theta ERSP (average across 0 and 300 ms post stimulus onset) predicted a greater increase in Go accuracy after active HD-tDCS (Kendall's tau_b $R = -0.464, p = 0.017$; Spearman's rho $R = -0.645, p = 0.009$), but not after sham (Kendall's tau_b $p = 0.325$) (Fig. 7b). No significant correlations were found in using theta ERSP to predict Go RT percent change (Kendall's tau_b $R = 0.333, p = 0.083$ and $R = -0.156, 0.531$ for active and sham, respectively, Fig. 7a). On the other hand, lower baseline frontal midline Go theta ITPC (average across 0 and 300 ms post stimulus onset) predicted a larger reduction in Go RT (Kendall's tau_b $R = 0.448, p = 0.02$; Spearman's rho $R = -0.636, p = 0.011$) and a greater increase in Go accuracy (Kendall's tau_b $R = -0.464, p = 0.017$; Spearman's rho $R = -0.538, p = 0.039$) after active HD-tDCS (Fig. 7c and d). Such predictions were not significant in the sham group (Kendall's tau_b $R = -0.111, p = 0.655$ and $R = -0.244, p = 0.325$, respectively, for Go RT and accuracy).

In contrast, frontal midline NoGo theta ERSP and ITPC (average across 0 and 300 ms after stimulus onset) did not show any significant correlations with change in NoGo accuracy, in either active or sham groups (all $ps > 0.1$, see Rs in Fig. 7e and f).

4. Discussion

By using a Go-NoGo EEG task to investigate interventional effect of active vs sham HD-tDCS modulating the pre-SMA in veterans with TBI, we found that active HD-tDCS increased theta/delta power and inter-trial phase coherence in the frontal midline region, as well as theta phase synchrony between the frontal midline and left posterior regions, during Go trials. In addition, baseline frontal midline theta oscillations were predictive of Go performance only when active HD-tDCS was applied. There was also a late increase in theta/alpha power near the left central region during NoGo trials. We had previously found improved verbal retrieval performance in the active group lasting until 8 weeks post-treatment completion [Motes et al., 2020; Chiang et al.,

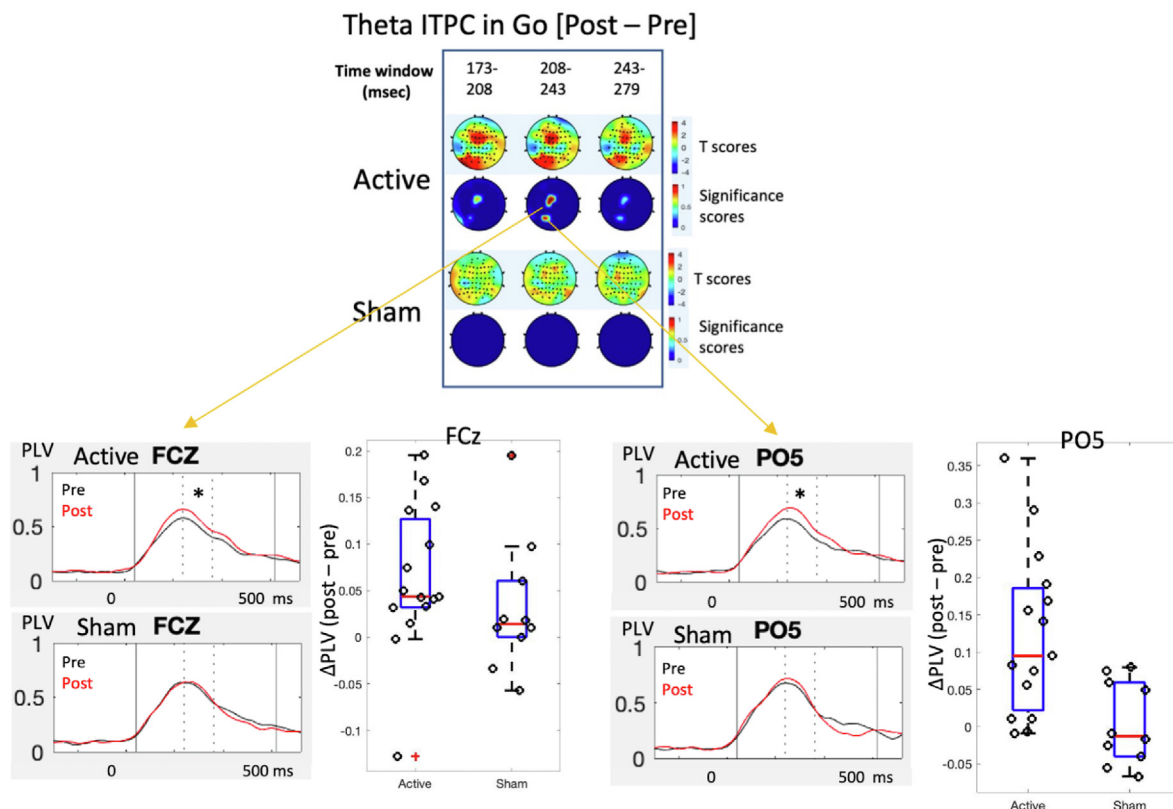


Fig. 3. Theta ITPC results. Permutation results showed a significant increase in the frontal midline and left posterior theta ITPC around 173–279 ms post stimulus in the active group during Go, while no significant effects were found in the sham group (Top). Frontal midline and left posterior theta ITPC (at FCz and PO5, respectively) during Go is represented separately for pre- and post-intervention data, showing difference (*) in the active group within this window (indicated by the dotted lines), but not in the sham group (Bottom). Individual phase locking values (ΔPLV , difference between post and pre data) at these electrodes (FCz and PO5) during the time window of 173–279 ms post stimulus onset are represented in the boxplot separately for the active and sham groups (Bottom). In the depiction for each group, topography on top represents T scores (based on 2-tailed paired t tests within each group comparing post to pre data) averaged within each time window, while topography on bottom represents only those electrodes with significant difference ($FDR < 0.05$) within each corresponding time window. In these boxplots: the horizontal line (in red) inside of each box represents the sample median; the top and bottom edges of each box (in blue) represent the upper and lower quartiles, respectively; the whiskers represent the minimum and maximum values that are not outliers; outliers (>1.5 interquartile range away from the top or bottom of the box) are plotted individually with a cross; black circles represent individual scores. ITPC: intertrial phase coherence; PLV: phase locking value (unit of phase coherence).

2021a], compared to sham, and in the current study we primarily focused on the EEG task to examine electrophysiologic mechanisms of such intervention.

Increased frontal midline theta ERSP and ITPC suggest more recruitment and better phase synchrony, respectively, as a result of active pre-SMA HD-tDCS. Delta ERSP and ITPC effects also showed topographic and temporal distribution similar to theta effects. We posit that these delta and theta findings both reflect slower oscillatory activity underlying enhanced cognitive control during Go trials. In contrast, there were no significant effects in the delta/theta frequency bands in NoGo trials or after sham. Theta and delta oscillations referable to this region are thought to reflect cognitive control, conflict monitoring, and predicting responses [Cavanagh and Frank, 2014; Nigbur et al., 2011]. Even though the pre-SMA has been found to be activated and play a causal role during response selection and inhibition [Chiang et al., 2013; DeLaRosa et al., 2020; Obeso et al., 2013; Allen et al., 2018], our findings suggest that electrically modulating the pre-SMA in this patient population affects theta responses during only response selection (Go) but not evidently response inhibition (NoGo). We posit that the Go response in the frontal midline regions is more easily influenced by HD-tDCS because its baseline response is smaller and more variable, particularly in the theta frequency range, as opposed to NoGo that usually elicits much larger and more coherent activity and likely reaches the ceiling activity, as previously shown [Brier et al., 2010]. Although prior research has

shown that anodal tDCS can (1) modulate theta power and phase coherence in healthy populations ([He et al., 2014; Mangia et al., 2014]; in a Go-NoGo task [Miller et al., 2015]) and (2) decrease pathological theta/delta frequency EEG activity in subacute TBI patients [Ulam et al., 2015], none of the prior studies targeted the pre-SMA or focused on chronic TBI. Here we demonstrate that it is possible to induce frontal midline theta/delta oscillatory changes by modulating the pre-SMA, even in individuals with persistent cognitive sequelae from chronic TBI.

Theta phase synchrony was increased between the frontal midline and left posterior regions as a result of active pre-SMA HD-tDCS. This finding demonstrates that not only inter-trial coherence was increased within these discrete regions, but there was increased connectivity between them, suggesting that pre-SMA HD-tDCS can also affect long-range (fronto-posterior) communication. We showed that this effect was only found in the theta frequency, suggesting selective modulation of theta phase coherence that mediates this long-range communication. There was a consistent pattern of increased theta phase coherence between FCz and PO5 in the active versus the sham group (Fig. 5), indicating this was not simply due to the group mean influenced by a few subjects. Interregional theta phase coupling has been proposed as a mechanism through which neurons in different regions establish coherence in order to execute cognitive operations, especially those that require involvement of multiple subsystems such as language and working memory [Fries, 2015;

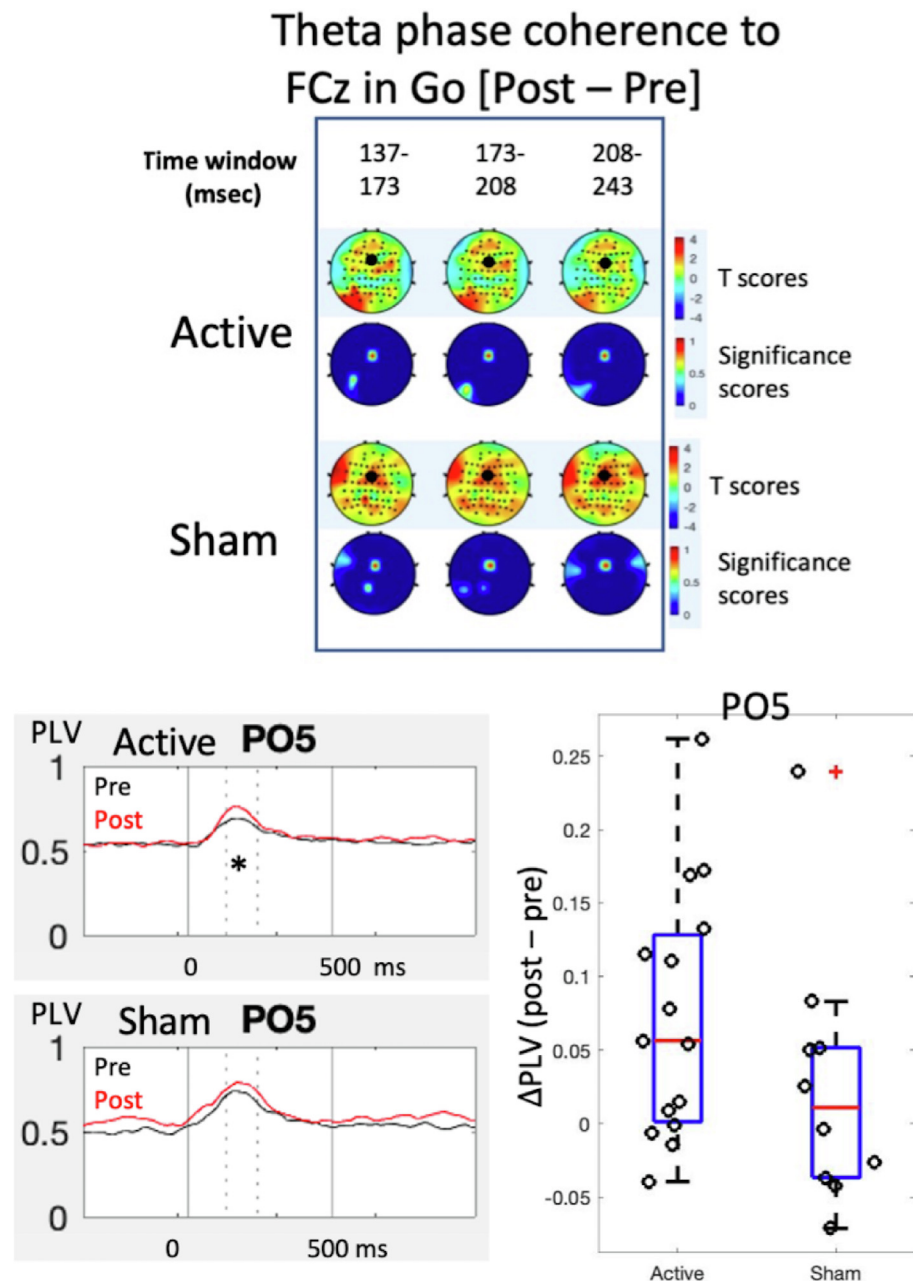


Fig. 4. Theta phase coherence to FCz results. Permutation results showed a significant increase in the theta (interareal) phase coherence between FCz (Top, indicated by the black dot in the topography) and the posterior electrodes (PO5) around 137–243 ms post stimulus in the active group during Go, while no significant effects were found in the sham group (Top). Left posterior theta (interareal) phase coherence to FCz (at PO5) during Go is represented separately for pre- and post-intervention data, showing difference (*) in the active group within this window (indicated by the dotted lines), but not in the sham group (Bottom Left). Individual phase locking values (Δ PLV, difference between post and pre data) at PO5 during the time window of 137–243 ms post stimulus onset are represented in the boxplot separately for the active and sham groups (Bottom Right). In the depiction for each group, topography on top represents T scores (based on 2-tailed paired t tests within each group comparing post to pre data) averaged within each time window, while topography on bottom represents only those electrodes with significant difference (FDR < 0.05) within each corresponding time window. In these boxplots: the horizontal line (in red) inside of each box represents the sample median; the top and bottom edges of each box (in blue) represent the upper and lower quartiles, respectively; the whiskers represent the minimum and maximum values that are not outliers; outliers (>1.5 interquartile range away from the top or bottom of the box) are plotted individually with a cross; black circles represent individual scores. ITPC: intertrial phase coherence; PLV: phase locking value (unit of phase coherence).

Cavanagh and Frank, 2014; Meyer, 2018; Pu et al., 2020]. It has been suggested that interregional theta coupling between the frontal midline and posterior regions plays a general integrative role in organization and top-down control of brain activity not limited to working memory, memory encoding and memory retrieval [Cavanagh and Frank, 2014; Sauseng et al., 2010]. More specifically, it has been shown that both frontal and posterior regions (occipital and temporal cortices involved in processing visual stimuli) are

recruited to categorize stimuli while maintaining rule-based criteria for goal-directed responses during the Go-NoGo task [Chiang et al., 2013; Simmonds et al., 2008]. These cross regional communications during cognitive control and response selection/inhibition (e.g., Go-NoGo) have been shown to be affected by chronic TBI due to disruption in structural and functional connectivity [Stephens et al., 2017; Xu et al., 2017]. It has not been previously shown that this frontal-posterior communication is potentially

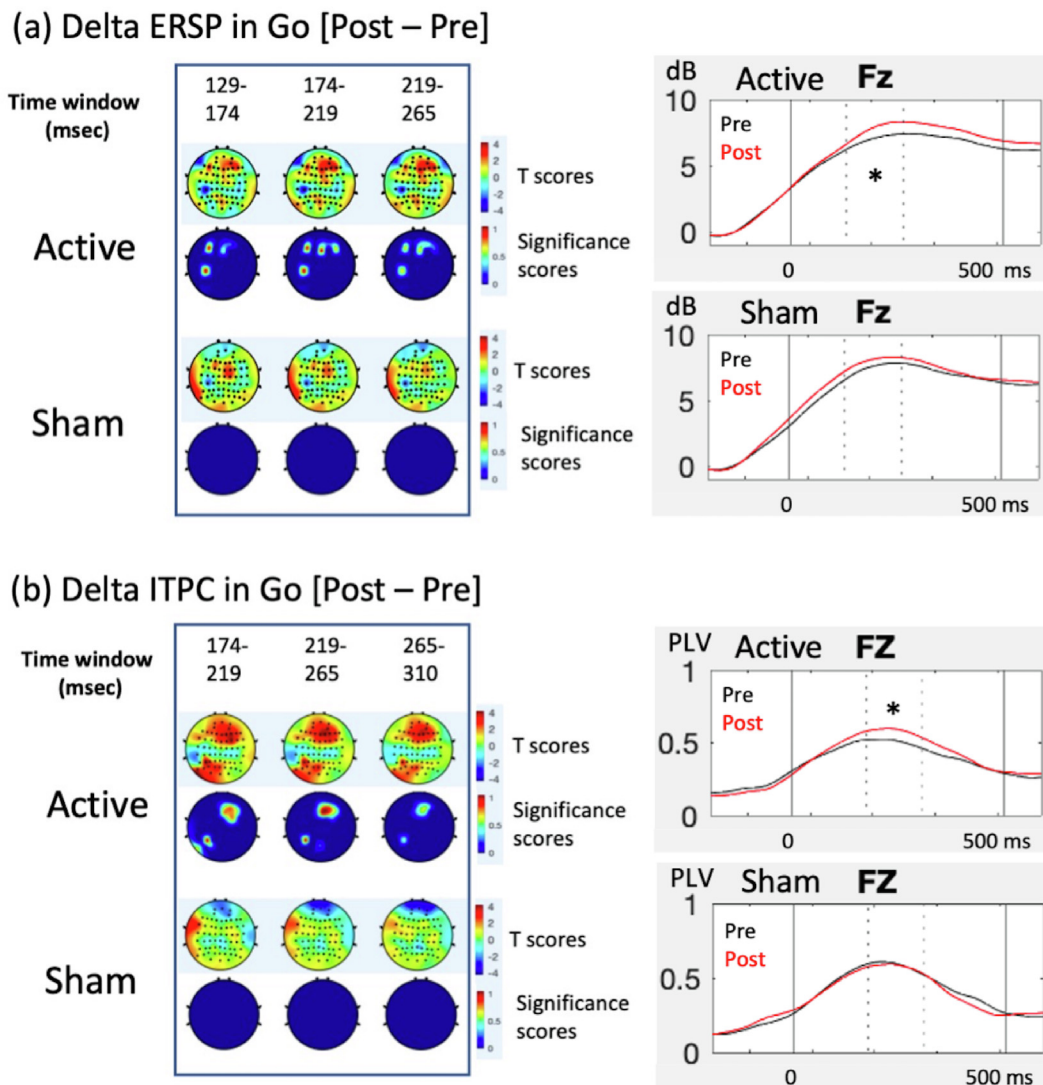


Fig. 5. Delta frequency results. Permutation results showed a significant increase in the frontal midline delta ERSP around 129–265 ms post stimulus in the active group during Go, while no significant effects were found in the sham group (a, Left). Frontal midline delta ERSP (at Fz) during Go is represented separately for pre- and post-intervention data, showing difference (*) in the active group within this window (indicated by the dotted lines), but not in the sham group (a, Right). There was also a significant increase in the frontal midline delta ITPC around 174–310 ms post stimulus in the active group during Go, while no significant effects were found in the sham group (b, Left). Frontal midline delta ITPC (at Fz) during Go is represented separately for pre- and post-intervention data, showing difference (*) in the active group within this window (indicated by the dotted lines), but not in the sham group (b, Right). In the depiction for each group, topography on top represents T scores (based on 2-tailed paired t tests within each group comparing post to pre data) averaged within each time window, while topography on bottom represents only those electrodes with significant difference (FDR < 0.05) within each corresponding time window. ERSP: event-related spectral perturbation; ITPC: intertrial phase coherence; dB: decibel (unit of power); PLV: phase locking value (unit of phase coherence).

modifiable by electromodulation in chronic TBI. Our finding therefore highlights the potential application of anodal HD-tDCS to improve long-range communication between the frontal and posterior regions in chronic TBI to facilitate better performance in response selection by modulating the pre-SMA. Future research is warranted to examine how underlying TBI-related structural disruption may constrain modularity of such interregional phase coherence.

Importantly, we found that baseline theta ITPC in the frontal midline region predicted change in both Go RT and accuracy—lower ITPC was associated with more reduction in Go RT and more improvement in Go accuracy post active HD-tDCS. Similarly, lower baseline theta ERSP was associated with more improvement in Go accuracy. In contrast, these theta EEG markers did not predict change in NoGo accuracy. We posit that lower baseline theta ERSP and ITPC may be a proxy of underlying structural injury and disrupted neuronal activity within the frontal midline region due to

TBI. We hypothesize that these baseline theta EEG markers reflect each individual's homeostatic balance between excitatory and inhibitory neurons/circuits/neurotransmitters [Krause et al., 2013]. Those individuals with baseline over-inhibition due to chronic TBI may benefit more from anodal HD-tDCS, which would increase excitation and therefore optimize excitation-inhibition balance [Krause et al., 2013]. This finding also highlights a potential way to individualize and select better candidates for electro-modulation. Even though there were no overall behavioral effects in this particular task related directly to active stimulation, it is plausible that group level analysis for behavioral performance was unable to capture individual behavioral change due to greater heterogeneity in TBI populations. Therefore, our analyses provide a potential approach to study this heterogeneity of response to electro-modulation across individuals.

Compared to Go response, only a late effect was found in the NoGo condition near the left central region in both theta and alpha

Alpha ERSP in NoGo [Post – Pre]

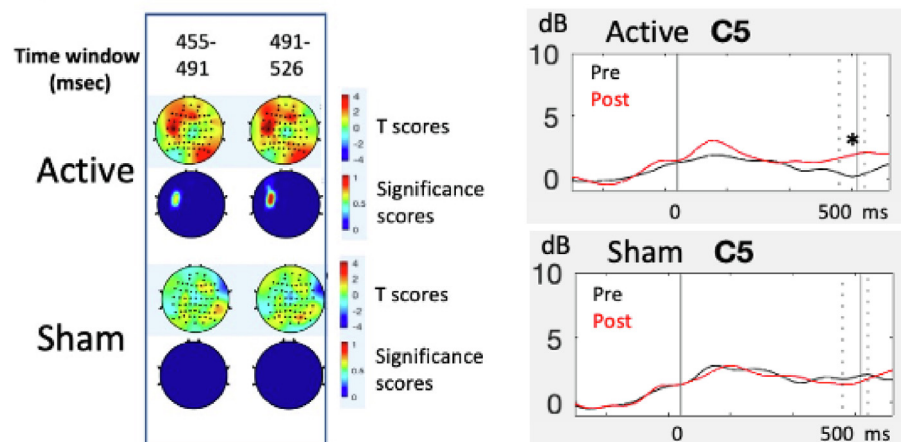


Fig. 6. Alpha ERSP results. Permutation results showed a significant increase in the left central alpha ERSP around 455–526 ms post stimulus in the active group during NoGo, while no significant effects were found in the sham group (Left). Left central theta ERSP (at C5) during NoGo is represented separately for pre- and post-intervention data, showing difference (*) in the active group within this window (indicated by the dotted lines), but not in the sham group (Right). In the depiction for each group, topography on top represents T scores (based on 2-tailed paired t tests within each group comparing post to pre data) averaged within each time window, while topography on bottom represents only those electrodes with significant difference (FDR < 0.05) within each corresponding time window. ERSP: event-related spectral perturbation; dB: decibel (unit of power).

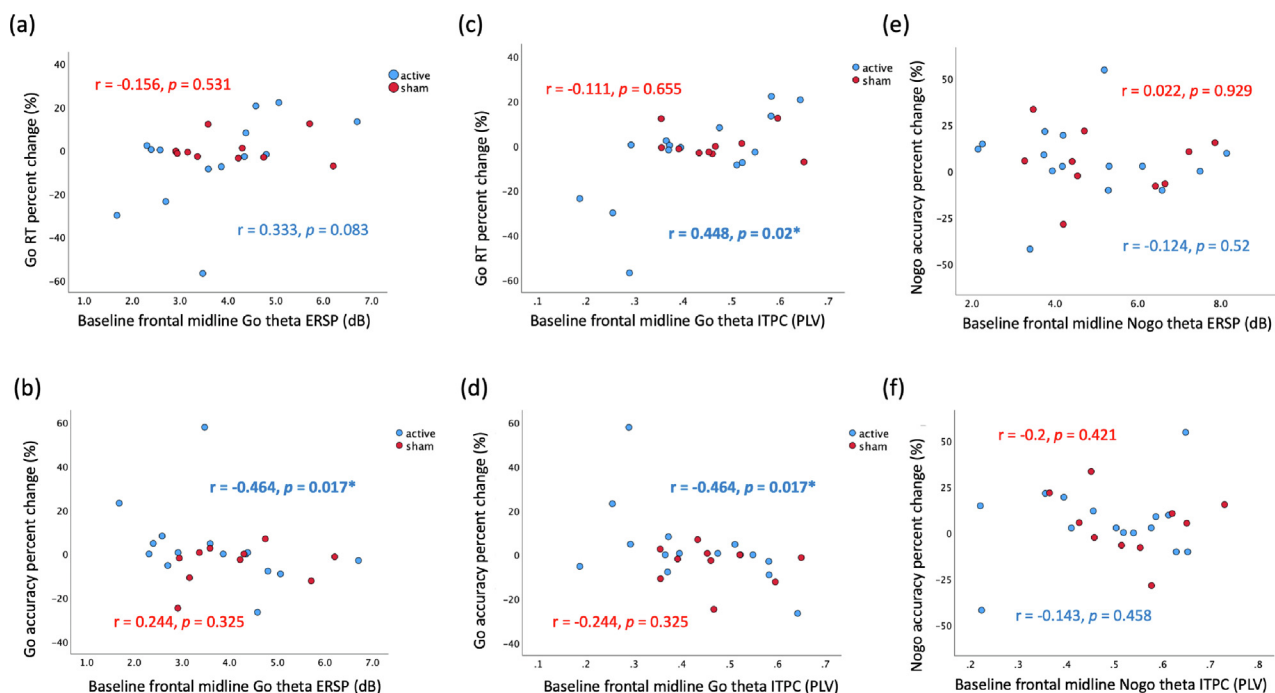


Fig. 7. Correlation results. Baseline frontal midline Go theta ERSP did not show significant correlations with Go RT percent change in either group (a), while it did show a significant correlation with Go accuracy percent change in only active but not sham group (b). Baseline frontal midline Go theta ITPC showed significant correlations with both Go RT and accuracy percent change in the active group, but not in the sham group (c, d). Baseline frontal midline Nogo theta ITPC did not show significant correlations with Nogo accuracy percent change in either group (e, f). All correlation analyses were based on Kendall's tau b correlation coefficient. Of note, correlations were still significant ($p < 0.05$) in the active group after the exclusions of one possible outlier in the active group ($N = 14$), as could be identified in the scattered plots (a–d). ERSP: event-related spectral perturbation; ITPC: intertrial phase coherence; dB: decibel (unit of power); PLV: phase locking value (unit of phase coherence).

ERSP. We posit that both the theta and alpha frequency band EEG activity, appearing to constitute a continuum of neural activity, reflected the same underlying source given their matching topographical and temporal distribution. Although there were no significant effects in the midfrontal region during NoGo processing where the most prominent responses are typically found when using this paradigm, these left central effects suggest modulation of left lateralized (contralateral) activity corresponding to inhibiting

the use of the right hand (all of the subjects used their right thumb or index finger for button push). This increase in the theta-alpha spectral power may indicate more recruitment of neural activity during response inhibition post active HD-tDCS. However, given that a response decision most likely has taken place by the time frame of this effect (455–526 ms post stimulus onset), this heightened activity may reflect change in post-inhibitory monitoring, rather than response inhibition *per se*.

We acknowledge some limitations. The population were middle-aged veterans with military-related TBI, which may reduce the generalizability of the findings. Our TBI cohort was selected to participate only if they demonstrated subjective word finding difficulty, confirmed by objective verbal retrieval deficits. Thus, these results should be interpreted with caution when TBI patients without verbal retrieval deficits are considered. Our sample size was relatively small, and larger cohorts will be obtained to replicate the current findings. However, compared to the TBI tDCS literature, our sample size is within the range of (and not inferior to) that from prior reports [Hara et al., 2021; Ahorsu et al., 2021; Zaninotto et al., 2019; Dhaliwal et al., 2015]. Again, this current study constitutes a secondary analysis of a preliminary study [Motes et al., 2020] looking for underlying neural changes to support the treatment effect. In addition, some of the EEG behavioral results may become significant (e.g., improved Go accuracy and Go RT to the active stimulation) if more subjects are included. We also acknowledge that our HD-tDCS montage does not only stimulate the pre-SMA, but also other surrounding regions. Methodological improvements for more accurately targeting brain regions using tDCS and for better localizing cortical generators of EEG signal are underway (e.g., MRI targeted stimulation and MRI-assisted source localization algorithms) that may well lead to improvement in assessment and treatment [Pellegrino et al., 2018]. However, these methods also have assumptions and limitations and are beyond the scope of this current study.

5. Conclusion

We demonstrated potential neural mechanisms mediated by increased focal and interregional theta oscillatory activity induced by anodal HD-tDCS modulation targeting the pre-SMA in chronic TBI patients. We also showed that baseline theta EEG oscillations may serve as a potential predictor for behavioral outcomes in response to electromodulation. These EEG effects seem to demonstrate better sensitivity than behavioral measures in response to active HD-tDCS and can be used to study how HD-tDCS modulates neurophysiologic brain activity that may underlie behavioral changes. The mechanisms through which TBI-related disruption in structural and functional network (which can vary among individuals) constrains effects of electromodulation remain to be clarified, but EEG markers appear to represent a promising tool for optimizing stimulation protocols and selecting neurologic patients appropriate for such intervention.

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Declaration of Competing Interest

The authors declare no known competing financial interests or personal relationships relevant to the work.

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Author contributions

H.-S. C. designed and implemented the data analysis and wrote the manuscript. J.H., Jr., M.M., and M.K. advised analysis framework. J.H., Jr., M.K., and S.V. designed the HD-tDCS protocol. All authors participated in editing.

Appendix A. Supplementary material

Supplementary material to this article can be found online at <https://doi.org/10.1016/j.clinph.2022.08.015>.

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