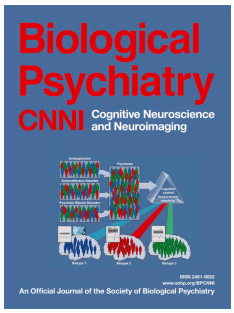

Transcranial Direct Current Stimulation to the left dorsolateral prefrontal cortex improves cognitive control in patients with Attention Deficit Hyperactivity Disorder: a randomized behavioral and neurophysiological study

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Transcranial Direct Current Stimulation to the left dorsolateral prefrontal cortex improves cognitive control in patients with Attention Deficit Hyperactivity Disorder: a randomized behavioral and neurophysiological study

Short title: tDCS modulation of executive functions in ADHD

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ABSTRACT

Background

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder associated with significant morbidity and mortality that may affect over 5% of children and approximately 2.8% of adults worldwide. Pharmacological and behavioral therapies exist, but critical symptoms such as dysexecutive deficits remain unaffected. In a randomized, sham-controlled, double-blind, cross-over mechanistic study, we assessed the cognitive and physiological effects of transcranial Direct Current Stimulation (tDCS) in 40 adult ADHD patients in order to identify diagnostic (cross-sectional) and treatment biomarkers (targets).

Methods

Patients performed three experimental sessions in which they received 30 minutes of 2mA anodal tDCS targeting the left DLPFC, the right DLPFC and Sham. Before and after each session, half the patients completed the Flanker task (EFT) and the other half the Stop Signal Task (SST) while we assessed behavior (reaction time, accuracy) and neurophysiology (event-related potentials, ERPs).

Results

Anodal tDCS to the left DLPFC modulated cognitive (reaction time) and physiological (P300 amplitude) measures in the EFT in a state-dependent manner, but no effects were found in the Stop Signal Reaction Time of the SST.

Conclusion

These findings show pro-cognitive effects in ADHD associated with the modulation of ERP signatures of cognitive control, linking target engagement with cognitive benefit, proving the value of ERPs as cross-sectional biomarkers of executive performance, and mechanistically supporting the state-dependent nature of tDCS. We interpret these results as an improvement in cognitive control but not action cancellation, supporting the existence of different impulsivity constructs with overlapping but distinct anatomical substrates, and highlighting the implications for the development of individualized therapeutics.

Registry: ClinicalTrials (https://clinicaltrials.gov), **Registration number:** NCT04175028

Introduction

Attention-deficit hyperactivity disorder (ADHD) is associated with functional impairment and high morbidity and mortality in youth and adulthood (1). Epidemiologic studies suggest that ADHD may affect over 5% of children and approximately 2.8% of adults worldwide (2, 3). While there is emerging evidence that available psychopharmacology and cognitive behavioral therapy interventions can address executive functioning deficits in individuals with ADHD (4-7), these have been and still remain critical symptoms closely associated with functional impairment yet with suboptimal (or null) response to current therapies; further research could identify the place of transcranial Direct Current Stimulation (tDCS) as an alternative or complementary intervention.

tDCS is emerging as a promising tool in human neuroscience research and for the treatment of neuropsychiatric disorders, and dysexecutive syndromes in particular (8, 9). Previous studies show that tDCS targeting the dorsolateral prefrontal cortex (DLPFC) modulates domains of executive function (10, 11), specifically those affected in ADHD (12). None of these studies, however, combined behavioral and physiological measures.

The Eriksen Flanker Task (EFT) (13) and the Stop Signal Task (SST) (14) are well-established experimental tasks used to assess impaired executive functions in ADHD (15, 16). Although they both capture inhibitory control processes, the EFT primarily assesses interference cognitive control (the ability to resist or resolve distracting interference that is irrelevant to the task), while the SST measures action cancellation (the ability to suppress dominant, automatic, already initiated responses) (17-19).

Human electrophysiological studies assessing event-related potentials (ERPs) have established relevant signatures of executive function during these tasks. Specifically, P200, N200, P300 and ERN/Pe (Error Related Negativity/Positivity) characterize the attentional and inhibitory functions that break down during conflict due to dysexecutive deficits and

impulsivity (20-24). Previous literature also found associations between ADHD symptom scores, event-related potential amplitudes, and poorer task performance in ADHD, which supports the use of these ERPs as correlates of executive function in ADHD (24).

P200 is an early component that usually appears in all trials of the EFT and the SST in the range of 150-275 ms. Although there is a wide range of factors affecting the characteristics of P200, its amplitude usually reflects a more basic level of selective attentional processing of visual stimuli (25, 26). N200 is a negative-going wave that usually peaks in the incongruent trials of the Flanker task in a range of 200-350 ms post-stimulus. Although there are mixed results in the literature for the N200 component in ADHD (27), its amplitude is generally related to the degree of conflict prompted by a given stimulus, or the extent to which individuals are distracted by task-irrelevant (flanker) information compared to task-relevant (target-stimulus) information (20, 28), requiring greater deployment of attentional resources. P300 appears 250 ms to 500 ms after the stimulus and it reflects the conflict post-processing and behavioral inhibition of the incorrect prepotent response in incongruent trials of the EFT and Stop trials of the SST (21, 29, 30). ERN and Pe are response-locked ERPs that appear in both the EFT and the SST. The ERN is a negative deflection in the ERP that occurs following error commission, time-locked to an individual's response. It typically peaks between 0-150 ms after the erroneous response begins and it is thought to be a marker of response conflict that occurs during error commission (22, 31). The ERN is often followed by a positive peak, known as the error-related positivity or Pe, a positive deflection that can peak 100-200 ms after making the incorrect response. The Pe amplitude is thought to reflect the perception or recognition of the error; the more awareness of the error, the larger the amplitude (23, 32).

In this study, we tested 40 ADHD patients during three experimental visits and compared the effect of anodal tDCS targeting the left DLPFC vs. right DLPFC vs. Sham.

Immediately before and after tDCS, half of the patients performed the EFT and the other half the SST, while we measured behavioral (reaction time and accuracy) and neurophysiological (ERPs) responses. Our previous research showed that tDCS targeting the left DLPFC in healthy adults lead to a significant decrease in reaction time correlated with a modulation of N200 and P300 amplitude in the Flanker task (11). Our aims here are to assess (1) the role of DLPFC laterality in ADHD deficits in interference cognitive control (EFT) and action cancellation (SST), (2) the physiological dynamics sustaining the modulation of executive function by tDCS and (3) the impact of state-dependent dynamics of tDCS effects.

Methods and materials

Trial design

A randomized, sham-controlled, double-blind, cross-over study was performed at the Massachusetts General Hospital (Boston, USA). Recruitment started on July 2015 and ended on March 2018. The study was approved by the Partners Healthcare Institutional Review Board and registered on ClinicalTrials.gov (NCT04175028). The full protocol is available upon request.

Participants

Forty-four adult patients with a primary diagnosis of ADHD were recruited from the Division of Neuropsychiatry, the Behavioral Neurology Unit and the Adult ADHD Research Program at Massachusetts General Hospital and randomized. See Table 1 for demographic and clinical characteristics and Table S1 in Supplement for inclusion/exclusion criteria. All participants gave informed and written consent for participation.

Intervention

For each session, 2mA of anodal stimulation was applied for 30 minutes with Ag/AgCl electrodes (contact area 3.14 cm^2) using the hybrid tDCS-EEG Starstim® system (Neuroelectrics, USA, also used for EEG recording). The duration of the ramp-up and -down at the beginning and the end of the stimulation was set to 15 seconds. During the stimulation period the subject was instructed to sit and relax with eyes open. See Figure 1 for details about the stimulation montage.

The order of stimulation administration (Sham, Left or Right) was randomized across subjects using a permutation-based randomization list generated by a computer to avoid any

confounding order effects across sessions. The experimenter and the subject were blinded by using the double-blind mode in Starstim's software NIC, which blinds the user on the type of stimulation used (active tDCS targeting left/right DLPFC or sham) after a 4-digit password is introduced by the administrator.

Outcomes

Immediately before and after tDCS, half of the patients (n=20) completed the EFT (Figure 2a), in which subjects must respond to the direction of a central arrow that is surrounded ("flanked") by distracting arrows that can either have the same (congruent trials) or opposing orientation (incongruent trials) as the central one. Participants were instructed to press the left or right arrow buttons following the direction of the central arrow, ignoring the flanker arrows. The accuracy of correct/incorrect responses and the reaction time (RT) for each stimulus were measured.

The other half of the patients (n=20) performed the SST (Figure 2b), in which participants had to provide a response as quickly as possible when letters "Z" or "A" appear (Go-trial). However, in some trials the "A" or "Z" stimuli were followed by the Stop Signal "X" (Stop trials), which appeared with varying adaptive delays from the Go stimulus. In these trials, participants must withhold their response. We measured the accuracy of correct/incorrect responses, the RT for Go-trials (GoRT) and the time it takes for the participant to withhold their response in the Stop-trials (Stop-Signal Reaction Time, SSRT). See Supplement for more details.

During the tasks, EEG was recorded from 7 positions (Fp1, Fp2, F3, Fz, F4, P3 and P4) with Ag/AgCl electrodes at a sampling frequency of 500 samples/second. EEG data were referenced to the right mastoid. Offline processing was then performed using EEGlab (version 13.5.4b) (33). Independent component analysis (ICA) was utilized to identify and remove

activity associated with blinks, eye movements, and other artifacts. Data were filtered from 1 to 20 Hz to remove non-neural physiological activity (skin/sweat potentials) and noise from electrical outlets. Trials were epoched within a time frame of 200 ms before and 800 ms after the stimulus onset. The mean of the pre-stimulus baseline [-200,0] ms was then subtracted from the entire ERP waveform for each epoch to eliminate any voltage offset. After rejecting trials that had at least a sample above +/-150 uV, the remaining trials were averaged for each time point and stimulation condition.

Statistical analysis

Based on similar studies (11, 34), we estimated a sample size of 20 subjects for each block of tasks to provide 85% power to detect an effect size of d=0.6 (α=5%), while 25 subjects would provide 90% power, and 30 subjects would provide 95% power for the same estimated effect size and α=5%. We estimated a 20% attrition rate based on previous studies.

Reaction time, accuracy of correct responses, ERP amplitudes, cross-sectional biomarkers and state dependencies were all modeled and analyzed using Generalized Linear Models with Mixed Effects (GLMM). See Supplement and Tables S2-S8 for more details.

Results

As shown in Figure S0 in Supplement, from the 20 patients assigned to each task block for analysis, two patients from the EFT and one patient from the SST were discarded as outliers due to extreme movement artefacts in the EEG data, thus leaving 18 patients in the EFT group and 19 in the SST group. Attrition rate was lower than anticipated. No important harms or unintended side effects were reported.

Flanker task

Cognitive results

There was a significant StimType*TimePoint*TrialType interaction in RT (β=-9.99ms, CI=[3.50, 16.48], p=0.03), indicating that the StimType*TimePoint interaction was significantly different for incongruent vs. congruent trials. After post-hoc tests, we found that this difference is due to the fact that there were no significant changes in congruent trials for any of the stimulation conditions (Figure S2a in Supplement), while for incongruent trials, left-sided stimulation led to a significantly faster RT compared to Sham (Left/Sham*PRE/POST: β=-16.1ms, CI=[-22.8, -9.3], p<0.0001) and right-sided stimulation did not have any significant effect compared to Sham (Right/Sham*PRE/POST: β=-5.3ms, CI=[-13.7, 3.1], p=0.390) (Figure 3a). The effect of left-sided stimulation was also significantly greater compared to right-sided stimulation (Left/Right*PRE/POST β=10.7ms, CI=[1.26, 20.2], p=0.0183). None of the stimulation conditions lead to significant changes in accuracy compared to Sham, both for incongruent and congruent trials (Figure 3b and S2b).

Event-Related Potentials

Both left-sided stimulation (β=2.15 μV, CI=[0.31, 3.99], p=0.022) and right-sided

stimulation (β=2.37 μV, CI=[0.53, 4.20], p=0.011) led to a significant P300 amplitude increase compared to Sham for incongruent trials (Figure 3c).

There are no significant changes in N200 after left-sided or right-sided stimulation compared to Sham, but the reduction in N200 amplitude after left-sided stimulation is significantly different compared to right-sided stimulation (β=-2.43 μV, CI=[-4.64, -0.22], p=0.027). Note that most P200, N200 and P300 amplitude changes occurred primarily around the area of the anodal stimulation electrode (F3 or F4), matching the laterality of the stimulation, especially for left-sided stimulation (Figure 3d).

There were no significant changes in P200 amplitude for incongruent (Figure 3b) or congruent (Figure S4a in Supplement) trials. ERN and Pe did not show significant differences either (Figure S4b in Supplement).

ERP cross-correlation with reaction time

The amplitudes of P200, N200 and P300 were significantly correlated with RT for incongruent trials in a cross-sectional trial-by-trial basis: the greater P200 (β=-0.26ms/μV, CI=[-0.51, -0.004], p=0.046) and P300 amplitudes (β=-0.25ms/μV, CI=[-0.50, -0.004], p=0.046) the faster the RT, and the smaller the N200 amplitude the faster the RT (β=-0.54ms/μV, CI=[-0.79, -0.29], p<0.0001).

State-dependencies

Table S9 in Supplement shows the effect of variables at baseline (before stimulation) on the change on the same (and other) variables after stimulation (i.e. state-dependent relationships). Figure 5 shows the scatter plots of the significant predictors. The change in P300 and P200 after stimulation is conditioned by the amplitude of P300 and P200 at baseline, while the change in N200 is conditioned by the amplitude of N200 and P300 at baseline. We

also found no significant differences in these relationships before vs. after stimulation, indicating that tDCS did not significantly modulate the relationship between RT and ERP amplitudes: RT*P200: β=0.72, CI=[-0.79, 2.32], p=0.374, RT*P300: β=1.29, CI=[-0.33, 2.91], p=0.121, RT*N200: β=-0.79, CI=[-2.22, 0.87], p=0.295.

Stop Signal Task

Cognitive results

The RT for Go-trials significantly increased after Left stimulation compared to sham (β=8.32 μV, CI=[2.18, 14.47], p=0.0044) (Figure 4a), but there were no significant changes in the SSRT for Stop-trials (Figure 4b). There were also no significant changes in accuracy for any of the stimulation conditions and for none of the trial types (Figure S5 in Supplement).

Event-Related Potentials

For Go-trials, P200 amplitude significantly increased after Left stimulation compared to Sham (β=0.51uV, CI=[0.09, 0.92], p=0.0160) (Figure 4c). For Stop-trials, there were no significant changes in P200, N200 and P300 (Figure 4d). There were no significant changes in ERN or Pe (Figure S6 in Supplement).

ERP cross-correlation with reaction time

The amplitude of P200 was also significantly correlated with RT for Go-trials, i.e., the greater P200 amplitude, the slower the RT (β=1.08ms/μV, CI=[0.69, 1.47], p<0.001).

State-dependencies

No significant state-dependencies were found for the SST (Table S9 in Supplement).

Discussion

Flanker Task

Our results confirmed that anodal tDCS targeting the DLPFC improves RT in the EFT in ADHD patients, similarly to what we previously described in healthy subjects (11). Specifically, we describe that anodal tDCS targeting the left DLPFC results in a significant reduction in RT in incongruent trials, compared to a non-significant change after sham or right DLPFC anodal modulation. Compared to our previous study with HC, the baseline RT (before stimulation) is slower in ADHD patients and the size effect of the improvement in RT after left-sided stimulation is larger for ADHD (β=-16.1ms) than for HC (β=-8.37ms).

The faster RT of incongruent trials in ADHD patients is correlated with a significant increase in P300 amplitude, in this case for both left- and right-sided anodal tDCS. Larger P300 amplitudes are associated with effective conflict post-processing and cognitive control, with the subsequent behavioral inhibition of incorrect prepotent responses (21, 29, 35). We thus interpret the increase in P300 amplitude as a modulation of conflict resolution and interference control processes, leading to more efficient inhibition of distractors and competing responses (i.e., faster RT). Given that P300 increases significantly after left-sided and right-sided stimulation, but behavior (RT) only changes after left-sided stimulation, we hypothesize that the physiological effect of right-sided stimulation is not sufficient to trigger a significant behavioral change, suggesting a greater role for the left DLPFC in the modulation of executive function.

Although in previous research with healthy controls we found a significant decrease in N200 amplitude after left stimulation (11), indicative of an improvement in selective attention in a context of conflict resolution, in the current study the decrease in N200 amplitude was not significant compared to Sham. Similarly, previous studies could not reliably confirm between-group differences for the N200 component as they found heterogeneous results for

N200 alterations in ADHD (27). While this may be partially explained by the higher intra-individual variability in ADHD than in control populations (36), it highlights the need to better understand the underlying physiological differences between ADHD patients and healthy subjects leading to different tDCS effects.

McGough et al. (37) also found executive function improvements using a Transcranial Nerve Stimulation (TNS) protocol designed to primarily target cutaneous nerves. Both this stimulation and our tDCS intervention likely activate the prefrontal cortex (directly or indirectly via activation of brain stem nuclei), although TNS is bilateral and uses a very different temporal pattern, making the direct comparison between TNS and tDCS not trivial. It may be interesting in future studies to test whether these approaches have common mechanisms.

Stop Signal Task

In the SST, *proactive inhibition* is defined as the advanced preparation to halt action in the anticipation of an imminent Stop Signal in Go-trials, requiring greater selective attention in the visual search for the Stop Signal to appear. *Reactive inhibition* is defined as the performance of outright stopping in response to the appearance of a Stop Signal in Stop-trials (38). In the current study we found that tDCS to the left DLPFC leads to a significant increase on the time patients withhold their response in Go-trials waiting for the Stop Signal to appear, which is correlated with a significant increase in P200 amplitude. There is a wide range and diversity of factors that have been found to affect the characteristics of the P200, but its amplitude is generally associated with selective attention to visual stimuli (25). We thus interpret the increase in P200 amplitude as a modulation in selective attention when searching for the Stop Signal to appear, with the subsequent improvement in proactive inhibition. However, the lack of significant changes in the SSRT suggests no effects on reactive

inhibition. Although there have been positive results in tDCS studies using the SST in a healthy population targeting other areas (39-45), previous tDCS studies with ADHD patients using the SST and targeting the DLPFC have also found a lack of significant effects on the SSRT and accuracy (34, 46). These results support the formulation of inhibitory control and impulsivity as complex multimodal processes with subdomain specificity (e.g. impulsivity of thought, action, affect, etc.) captured by different experimental tasks and with different anatomical representation (47). These findings confirm the hypothesis that that there is a dissociation between action cancellation or the ability of suppressing prepotent responses that have already been initiated, captured by the SST, and interference cognitive control or the ability of resisting distractors and resolving interference between competing responses, captured by the EFT (19, 48-53). From a translational perspective, this also implies that the DLPFC may be a good substrate to improve interference cognitive control and proactive inhibition, but if the goal is to improve action cancellation (e.g. tics, compulsions) one should consider alternative windows into the circuitry (18, 47).

Cross-sectional biomarkers

Our findings indicate that the amplitude of P200, N200 and P300 on a trial-by-trial basis is correlated cross-sectionally with RT in the EFT (as previously described in healthy subjects (11)) and the SST, thus supporting the interpretation of the observed tDCS effects (i.e. small N200 and large P300 are associated with more adaptive responses thus changes in this direction should be therapeutic) and highlighting their value as a potential diagnostic, monitoring or surrogate biomarker (54) for cognitive performance.

State-dependence

Our results indicate that the effect of tDCS in the Flanker task depends on the individual's electrophysiological state at baseline (before stimulation). Specifically, we found that low baseline P300 amplitudes and small N200 baseline amplitudes (associated with impaired cognitive performance) are correlated with greater P300 amplitude increases (and N200 decreases) after tDCS, which are associated with improvement in cognitive performance. This suggests that tDCS leads to greater modulation (improvement) of physiology in subjects with baseline physiological signatures indicative of less adaptive processing, as they allow greater range of modulation. As expected, Sham did not show any significant state dependencies, suggesting that potential effects were not due to regression to the mean. However, we note that these are just correlations and not a definitive proof of causality.

These effects are possibly explained by the principle of state-dependency, a phenomenon by which the response of a system to an external intervention is affected not only by the properties of that intervention (e.g. stimulation parameters) but also by the internal state of the system. The state-dependent characteristics of tDCS have important implications for treatment development: beyond stimulation parameters, clinical trials may benefit from controlling patients' state (before, during or after stimulation) to minimize response variability and maximize the therapeutic effects of tDCS.

Limitations

Our results show modulation of executive function in the context of highly controlled experimental tasks, and therapeutic benefits should be confirmed in future clinical trials using relevant clinical and functional outcome measures after several repeated tDCS sessions aiming to induce longer-lasting pro-cognitive and pro-executive plastic changes. Since we did not control for handedness, a remaining question is whether stimulation to the dominant

hemisphere in left-handed individuals would be a confound in the results, which should be addressed in future studies. In addition, future trials should also assess the effects of the duration of stimulation as well as changes in executive functions and ERP with ADHD symptom outcomes.

We also acknowledge a significant age difference (EFT: 43.85±14, SST: 31.2±13, p=0.0073) between the EFT and the SST groups, which was an artifact caused by the fact that the two cohorts were recruited prospectively in different time frames (though with the same exact protocol and hardware) and then analyzed together retrospectively to address the proposed questions, hence the lack of appropriately age-matched groups. While mean ages are well after periods of brain maturation when myelination patterns and ADHD symptoms are thought to be persistently established, and well before a geriatric threshold when other type of biological changes (including normal aging) may affect cognition, the wide age range (18-67 years) may also introduce some heterogeneity in the results. Thus, future prospective validation studies should use larger homogeneous cohorts, with more restricted age ranges and randomized age-matched groups.

Since there is a modest correlation between neuropsychologically determined executive deficits and molar measures such as the BRIEF, the sample is likely to include patients with less impairments in those functions measured by the EFT and SST tasks, which may obscure therapeutic effects in those with cognitive impairments. Future clinical trials should include a more homogeneous simple of individuals with impairments in those functions measured by EFT and SST, as tDCS effects were most significant for those.

We did not perform any assessment of the effectiveness of the patient blinding as the Sham protocol used in the current study has been proven to be effective (55), but we acknowledge the need to include this type of assessment in future trials.

For the EFT group it is also worth to note that, although the 16 ms decrease in RT after Left-sided stimulation compared to sham is significant (p=0.0001) and greater than the 8 ms we found in healthy controls (11), we acknowledge that it may still be considered small and could be affected by the ADHD heterogeneity, estimation errors and transformations to the data. While the timing precision of the Presentation software is <0.1 ms and thus should not introduce significant estimation errors, we plotted the effects at the individual level (Figure S7 in Supplement) to discard other sources of errors. This figure shows that while there was a high between-subject variability (as expected due to the inherent ADHD heterogeneity), within-subject standard errors were very small for most patients and there was a relatively reliable individual-level effect that is not outlier-driven, thus supporting our conclusions. However, further studies with larger samples should be carried out in order to minimize between-subjects variability and other potential sources of errors.

While the field has established differences between the constructs captured by the EFT and the SST, the nomenclature used to define the overlap and differences at the cognitive and behavioral level remain equivocal and often contradictory. This seems more than a simple problem with semantics and reflects deficits in the core formulation of the subtleties across executive constructs. We have opted for descriptive terms previously used in the literature (e.g. interference cognitive control and action cancellation), but acknowledge that other terminologies may be considered.

Conclusions

This study indicates that anodal tDCS over the left DLPFC using a simple bipolar montage has pro-cognitive effects in dysexecutive patients with ADHD associated with the modulation of physiological signatures of cognitive control (i.e. treatment target), supporting specific hypotheses and strategies for neuromodulation treatment development under an

experimental therapeutics framework aiming to link target engagement (cognitive and physiological) with clinical benefit. In addition, we provide mechanistic support for the state-dependent nature of the effects of tDCS, highlighting the importance of controlling (or at least measuring) the neural states before (and possibly during) stimulation as a relevant therapeutic strategy beyond choices regarding the neuromodulation parameter space. We also provide empirical evidence supporting the value of the P200, N200 and P300 as cross-sectional biomarkers of cognitive performance across tasks, and across populations if taken together with our previous similar report in healthy subjects (11). Last, we interpret these results as an improvement in interference cognitive control (captured by the EFT) but not in action cancellation (assessed by the SST), supporting the hypothesis of the existence of different impulsivity constructs with overlapping but distinct anatomical substrates and therapeutic strategies.

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Disclosures

GR is a co-founder of Neuroelectrics, a company that manufactures the tDCS technology used in the study. LDV is an employee at Neuroelectrics. JAC is a member of the scientific advisory board for Apex Neuroscience Inc. AW has patent applications pending related to cognitive enhancement through brain stimulation and new methods of transcranial electrical stimulation. CS reports that, within the past 12 months, he has received research support from Shire/Takeda Pharmaceuticals, has served as a consultant to Adlon, Shire, Sunovion,

Supernus and Teva pharmaceuticals, and has received book royalties for “Fast Minds – How to Thrive If You Have ADHD [or Think You Might],” as well as “ADHD in Adults – A Practical Guide to Evaluation and Management”. The remaining authors declare no biomedical financial interest or potential conflicts of interest.

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Figure Legends

Figure 1. Modeling of the normal component of the electrical field (V/m) created by the montage targeting the left DLPFC and right DLPFC. Specifically, the anodal electrode was placed on the scalp at the F4 (for Right DLPFC stimulation) or F3 (for Left DLPFC stimulation) positions, according to the international 10-20 EEG system. The cathode was placed in the contralateral supraorbital region (Fp1 or Fp2). The four electrodes were always placed at both sides for all stimulation conditions (left, right and Sham) to ensure the blinding of the patient and the operator. For the sham condition, the current was applied only for the 15-second ramp up phase at the beginning and the end of a 30-minute sham-stimulation period, to simulate the potential experience of local tingling sensation that real stimulation produces but without sustained effect on cortical activity. The stimulation is usually not noticeable between the ramp up and the ramp down for either active or sham tDCS, thus ensuring the blinding of the patient. The modeling is based on a finite element model included in the Starstim's software NIC (Neuroelectrics, USA).

Figure 2. Flanker and Stop Signal task scheme. A) The Flanker task consisted of 140 trials in two blocks of 70. Each subject had a different, fully random sequence of congruent and incongruent trials, with 2 congruent trials for each incongruent trial, in order to build a tendency towards congruent responses and thus increase the difficulty of conflict detection in incongruent trials. The task had a total duration of 10 min, with 1 minute of training before the task started. The flanker arrows were first presented alone for duration of 136 ms, 114 ms, 92ms, 70 ms or 48 ms, and were then joined by the target arrow for 62 ms, 52 ms, 42 ms, 32 ms or 22 ms, respectively (values were adjusted to the psychometric "sweet spot" in which each patient achieved a performance in the range of 80-85%). These values were calibrated just once at the first session for each participant to avoid confounding the outcomes, so the same values were used for all sessions within participants. Stimulus presentation was followed by a black screen for 500 ms. The time-window for participants' response was 600 ms after target onset. If the participant did not respond within the response window, a screen reading 'TOO SLOW!' was presented for 300 ms. Participants were told that if they saw this screen, they should speed up. If a response was made before the deadline, the 'TOO SLOW!' screen was omitted, and the black screen remained on screen for the 300 ms interval. Finally, each trial ended with presentation of the fixation cross for an additional randomly chosen duration (200, 300 or 400 ms) in order to avoid any habituation or expectation by the subject. Thus, trial durations varied between 1070–1400 ms. **B)** The SST consisted of 160 Go-trials (80%) and 40 Stop-trials (20%). There were only two types of Go trials: "A" and "Z". The "A" or "Z" stimuli were first presented for 100 ms and they were followed by a black screen for 500 ms. Patients had to press the left mouse button whenever the "A" stimulus was presented, and the right mouse button whenever the "Z" stimulus was presented. For the Stop-trials, the Stop Signal initially appeared 400 ms after the "A" or "Z", and was adjusted dynamically according to the subject's performance, increasing or decreasing by 50 ms respectively after a successful or unsuccessful answer, within a range of 50 to 500 ms in order to yield approximately 50% successful inhibition of the Stop-trials (Figure S1 in Supplement).

Figure 3. **Flanker results. A)** Mean reaction time and **B)** accuracy for incongruent trials and p values with 'mvt' correction. Error bars indicate confidence intervals. Significance indicated as (*) = $p<0.05$, (**) = $p<0.01$, (***) = $p<0.001$. **C)** Grand average ERPs time-locked to incongruent stimuli. Waveforms correspond to the average of F3, Fz and F4 positions. The red circle indicates the significant amplitude changes compared to Sham. See Figure S3 in Supplement for ERPs at individual electrodes. **D)** Scalp topographies of POST-PRE difference of P200, N200 and P300

amplitude (uV). Averaging time window for P300=[260, 360] ms. Averaging time window for N200=[180, 230]ms.

Figure 4. SST results. A) Mean reaction time for Go-trials. **B)** SSRT for Stop-trials. Error bars indicate confidence intervals. Significance indicated as (*) = $p<0.05$, (**) = $p<0.01$. **C)** Grand average ERPs time-locked to Go-trials. The red circle indicates the significant amplitude changes compared to Sham. **D)** Grand average ERPs time-locked to Stop-trials. Waveforms correspond to the average of F3, Fz and F4 positions.

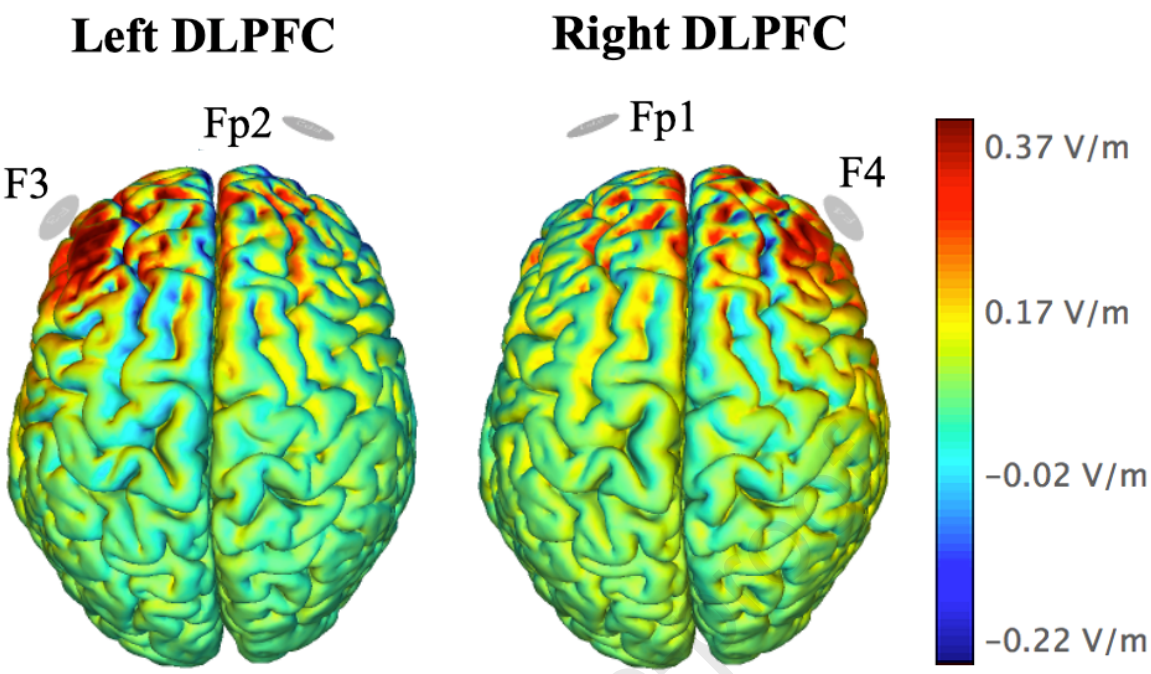
Figure 5. State dependencies. Scatter plots, regression lines and confidence intervals for significant state dependencies in the EFT. **Top row:** change in P300 as a function of P300 (left) and N200 (right) at baseline in the EFT. **Second row:** change in N200 amplitude as a function of P300 (left) and N200 (right) amplitude at baseline in the EFT. **Third row:** change in P200 amplitude as a function of P300 (left) and P200 (right) amplitude at baseline in the EFT.

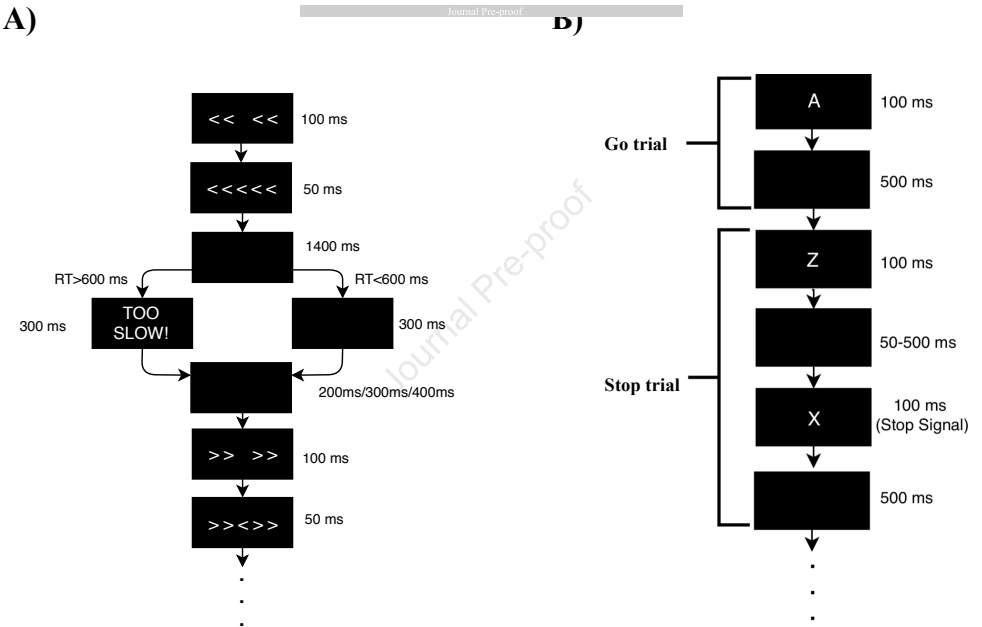
Table 1. Participant characteristics

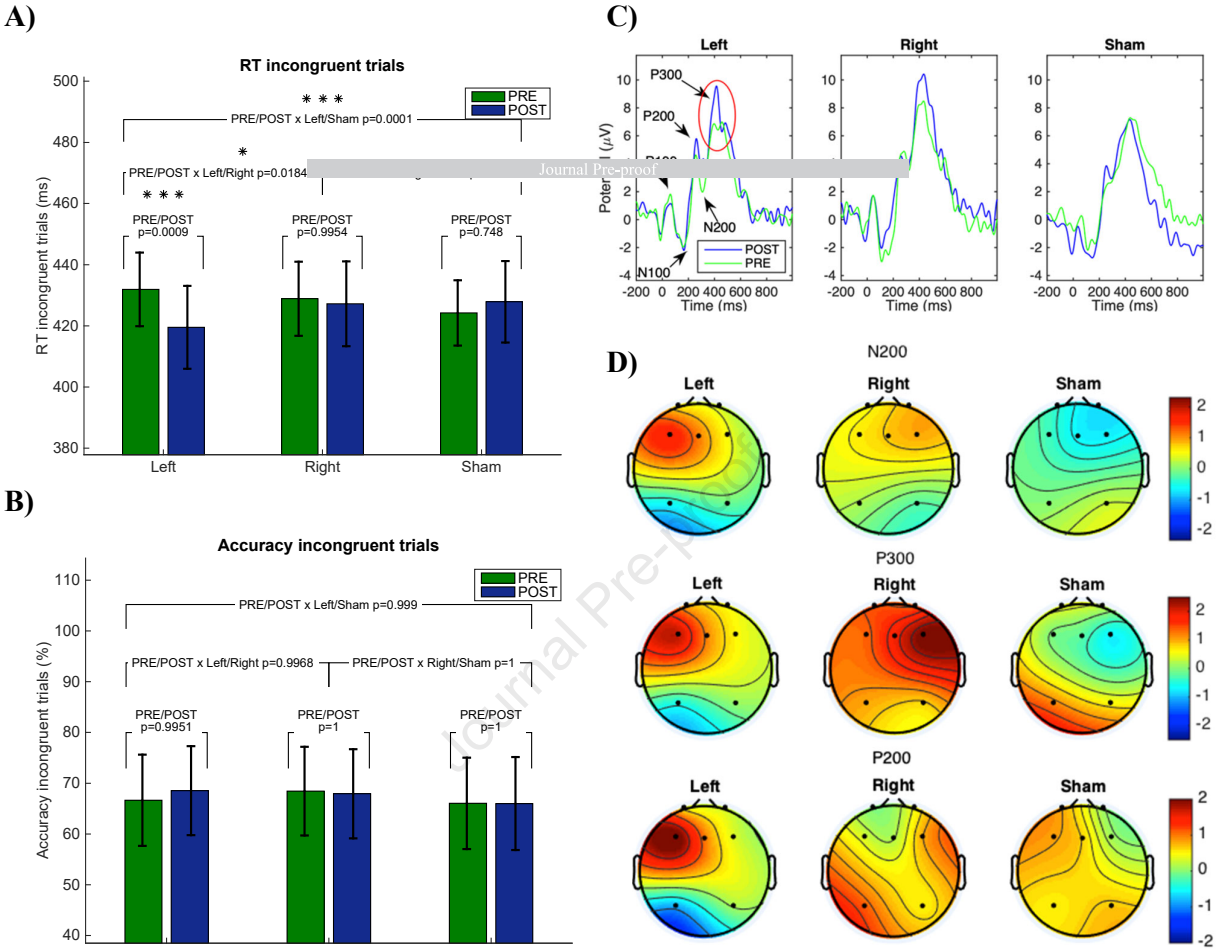
	EFT	SST
Demographic	**mean (SD)***	**mean (SD)***
Age	43.85 (14.78)	31.2 (13)
Females	10 (50%)	10 (50%)
White N (%)	16 (80%)	16 (80%)
Single N (%)	10 (50%)	15 (75%)
Baseline Scores		
CHRT	0.6 (1.89)	0.1 (0.45)
PHQ9	10.05 (8.05)	6.7 (5.6)
QIDS	9.33 (6.14)	10.29 (5.45)
ASRS	62.6 (9.17)	58.20 (19.58)
Prior medications – N (%)**		
No medication	11 (55%)	7 (35%)
Adderall	2 (15%)	4 (20%)
Vyvanse	2 (10%)	3 (15%)
Claritin	0	1 (5%)
Concerta	1 (5%)	1 (5%)
Lisinopril	0	1 (5%)
Lamictal	0	1 (5%)
Nortryptiline	0	1 (5%)
Verapamil	1 (5%)	0
Aspirin	1 (5%)	0
Levothyroxine	1 (5%)	0
Modafinil	1 (5%)	0

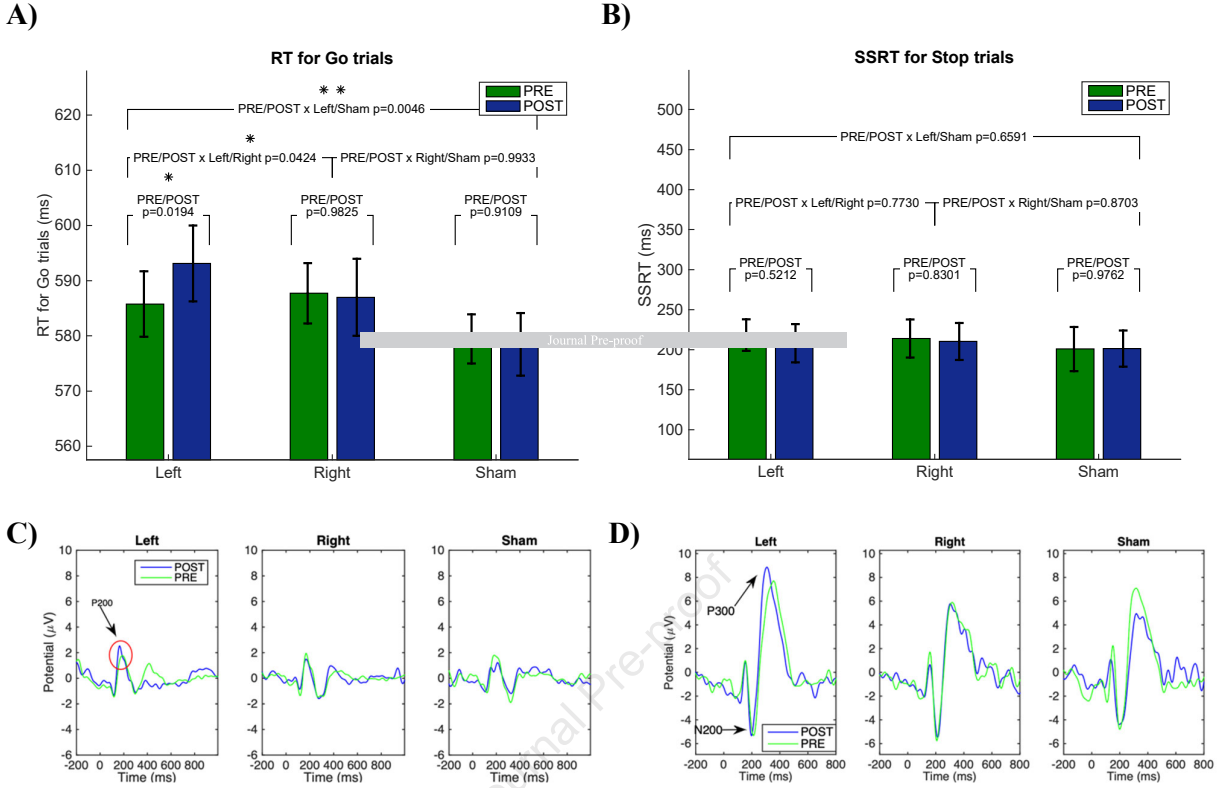
(*) All figures are "Mean (Standard Deviation)" unless otherwise specified.

(**) Patients were either off stimulant medications or, if undergoing treatment with stimulants, were asked to discontinue two days prior to the experiment, under physician-guided protocol, and allowed to resume afterwards.

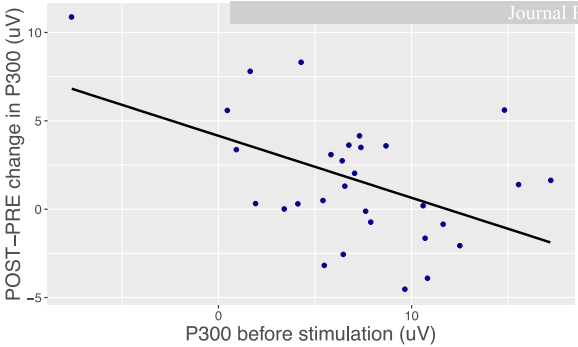




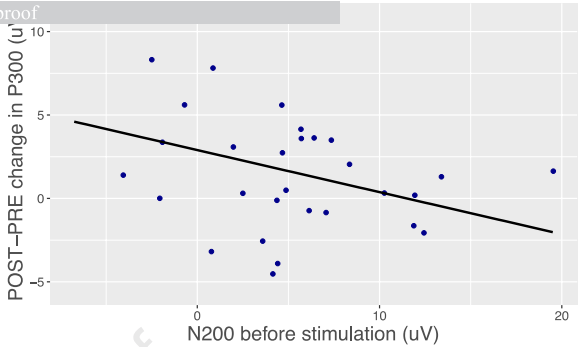




Change in P300 as a function of P300 before tDCS



Change in P300 as a function of N200 before tDCS



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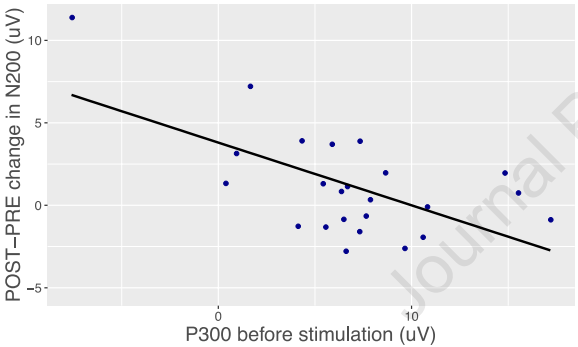

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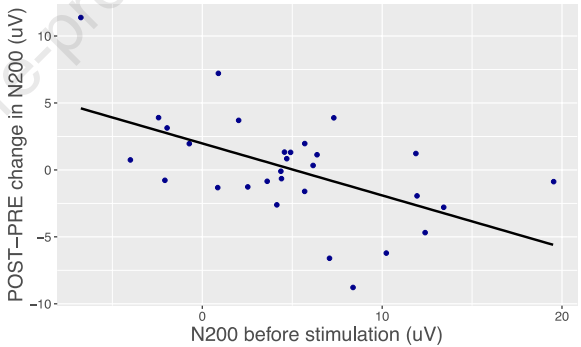

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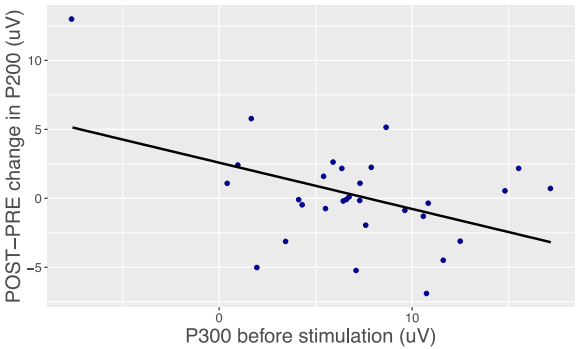

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