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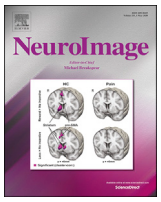

Transcranial direct current stimulation (tDCS) elicits stimulus-specific enhancement of cortical plasticity

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ABSTRACT

Background: Deficits in plasticity underlie many severe psychiatric disorders. Transcranial direct current stimulation (tDCS) is a promising method for modulating plasticity. However, given its non-focal nature, there are open questions as to how targeting and outcome specificity can best be achieved.
Objective: Understanding how tDCS interacts with concurrent brain activity is necessary for the rational advancement of tDCS. In the present study, we use an event-related potential (ERP) paradigm to assess the stimulus-specific effects of tDCS on cortical plasticity.
Methods: 22 healthy volunteers underwent a blinded, sham-controlled plasticity paradigm in a crossover design. High frequency presentation of auditory stimuli was used to induce potentiation in specific components of the ERP. We investigated whether anodal tDCS targeting the auditory cortex would modulate plasticity induction across time. Two pure tones were used as stimuli, only one of the tones, the target tone, was used for plasticity induction. Plasticity was quantified as change in the mean amplitude of the N100 component relative to baseline.
Results: TDCS significantly modulated plasticity in the target tone compared to sham ($p = 0.02$) but had no effect on the control tone ($p = 0.73$). This effect was time dependent, with tDCS effects no longer apparent 30 min after stimulation.
Conclusions: Our results indicate that tDCS can modulate cortical plasticity in the auditory cortex in an activity-dependent manner. These findings bolster the idea that tDCS can be an effective tool to target and modulate plasticity both for research and therapeutic purposes.

1. Introduction

Experience dependent plasticity refers to the brain's ability to dynamically shift functional or structural states in response to internal or external events. This property enables us to learn, make predictions and guides response selection for adaptive behavior (Cooke and Bliss, 2006; Ganguly and Poo, 2013). Given its fundamental role in brain dynamics, maladaptive neuroplasticity often leads to debilitating conditions (Johnston, 2004; Kays et al., 2012). Disrupted plasticity is thought to play a role in the pathophysiology of several psychiatric disorders, including schizophrenia and bipolar disorder (Elvsåshagen et al., 2012; Normann et al., 2007; Stephan et al., 2006). Given the implication of disrupted plasticity in psychiatric disease, tools which can modulate plasticity have great clinical potential (Thickbroom and Mastaglia, 2009).

Non-invasive neuromodulation via transcranial direct current stimulation (tDCS) is a promising method for modulating plasticity. With tDCS, a low-intensity direct current is applied using two or more electrodes placed in a specific orientation over the scalp. The current enters the brain via the positively charged anode, and flows towards the negatively charged cathode, leading to modulation in neuronal excitability. Polarity-dependent modulation of cortical excitability was first demonstrated in animal studies which measured enhanced neuronal firing rates after anodal tDCS and decreased firing rates after cathodal tDCS (Bindman et al., 1962, 1964; Gartside, 1968). More recent investigations using modern electrophysiology have demonstrated the capacity of externally applied currents to modulate classical models of Hebbian plasticity such as Long Term Potentiation and Depression (LTP/D) (Kronberg et al., 2017; Podda et al., 2016; Ranieri et al., 2012). The ability of tDCS to interact with these mechanisms, which are thought to serve as a substrate

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for learning and memory, has been used to explain the positive effects of tDCS on learning and cognitive enhancement in both animal and human models (Reis and Fritsch, 2011; Jahshan et al., 2017; Fritsch et al., 2010). In addition, tDCS has been used to treat deficits in a variety of clinical populations with demonstrated plasticity defects (Jahshan et al., 2017; Player et al., 2014).

Due to its safety and tolerability (Woods et al., 2016), the use of tDCS has grown substantially. Over the last decade, tDCS has been used to modulate a wide range of motor and cognitive processes, as well as to treat various psychiatric disorders (Reis and Fritsch, 2011; Mervis et al., 2017; Reinhart and Nguyen, 2019). Nevertheless, tDCS-induced effects appear to be mediated by a large number of both stimulation and subject-specific factors, often resulting in highly variable responses (Brunoni et al., 2012; Laakso et al., 2019; Li et al., 2015; Vorobiova et al., 2019). The complex parameter space of tDCS presents a challenge when seeking to develop best-use practices and highlights the need to improve on our still rudimentary understanding of the biological mechanisms supporting tDCS-related brain changes.

A crucial question when it comes to the rational development of tDCS is how to achieve *specificity* (Bikson et al., 2013). TDCS induces a low electrical field in the brain, producing only a subthreshold level of membrane polarization which is diffused across wide brain areas (Radman et al., 2009; Ruffini et al., 2013), making it difficult to achieve anatomical targeting (Datta et al., 2009; Bikson et al., 2012; Neuling et al., 2012). However, the low spatial resolution of tDCS contrasts with its focal effects on cognitive performance (Nitsche and Paulus, 2011; Jacobson et al., 2012) and electrophysiological measures (Keeser et al., 2011; Zaehle et al., 2011), indicating that controlling stimulation parameters alone cannot fully explain how this specificity is achieved.

An important factor shaping tDCS specificity may be the state of the brain at the time of stimulation. Indeed, several studies aiming to facilitate cognitive or motor learning have applied tDCS during tasks to leverage a potential synergistic relationship between externally-applied currents and endogenous patterns of brain activity (Reis and Fritsch, 2011; Nienow et al., 2016; Martin et al., 2014). Promising findings from such studies corroborate a recently proposed 'activity-selectivity' hypothesis, which states that tDCS preferentially modulates active over inactive neural populations (Bikson et al., 2013; Fertonani and Miniussi, 2016). However, direct physiological evidence for this model remains limited.

To the best of our knowledge, only two studies have directly examined the physiology of the 'activity-selectivity' model in the human cortex (Hill et al., 2018; Pisoni et al., 2017). These studies utilized electroencephalography (EEG) recordings to investigate tDCS modulation of brain activity. Due to its high temporal resolution, EEG can be an ideal method to probe neuromodulatory changes brought about by tDCS (Miniussi et al., 2012). Pisoni and colleagues (Pisoni et al., 2017) delivered anodal tDCS over the left inferior frontal gyrus during a verbal-fluency task, using TMS-evoked potentials (TEPs) to probe changes in cortical excitability. They found that the amplitude of TEPs was increased after anodal tDCS, but only in specific task related brain regions. Hill and colleagues (Hill et al., 2018) expanded on these findings by comparing the effects of tDCS when paired with a cognitive task, when applied at rest, or when only the cognitive task was performed. This study used event-related potentials (ERP) and resting state electroencephalography (RS-EEG) in addition to TEPs to assess changes in brain activity. In contrast to Pisoni et al., no activity selectivity was observed when analyzing TEPs and RS-EEG. However, changes in ERP amplitudes were observed only in the tDCS + Task condition, providing only limited evidence for the 'activity-selectivity' model. A clearer understanding of the role that brain state plays in shaping tDCS outcomes is crucial in informing the rational use of tDCS.

To better investigate the contribution of brain state to tDCS effects, it would be ideal to utilize paradigms which directly probe the plasticity mechanisms modulated by tDCS. Research in animals demonstrates that tDCS is able to modify synaptic efficacy and learning through modulation of LTP (Podda et al., 2016; Ranieri et al., 2012). Though our ability to investigate LTP in humans is limited, it has recently been demonstrated that high-frequency, repetitive presentation of sensory stimuli, or sensory tetanus (ST), can provide a naturalistic method for inducing LTP-like plasticity in the human cortex (Clapp et al., 2006, 2012; Cooke and Bear, 2010). Studies in rodents show that ST can lead to enhanced sensory evoked potentials in the cortex, similar to the manner in which high frequency electrical stimulation leads to enhanced synaptic efficacy in slice demonstrations of LTP (Clapp et al., 2012). The enhancement in sensory evoked potentials induced by high frequency sensory presentation displays the critical features of LTP, including persistence, input specificity, and N-Methyl-D-aspartate receptor (NMDAR) dependence (Cooke and Bear, 2010; Clapp et al., 2006). In humans, the effects of ST can be observed noninvasively in the EEG as modulations in specific components of sensory ERPs. Indeed, paradigms using ST have been used to induce persistent potentiation of both visual and auditory ERP components in humans (Clapp et al., 2005, 2012; Teyler et al., 2005; Lei et al., 2017), and have been used to identify plasticity deficits in a variety of psychiatric conditions (Elvsåshagen et al., 2012; Mears and Spencer, 2012). ST paradigms provide a valuable window into the mechanisms thought to underlie neural plasticity and are therefore a promising tool with which to probe the effects of tDCS in humans.

We carried out a crossover study featuring 2 sessions, with participants undergoing active and sham tDCS on separate days. Each session utilized an auditory ST paradigm which was designed to induce plasticity in the auditory cortex in a stimulus specific and persistent manner (Clapp et al., 2005; Mears and Spencer, 2012). Previous investigations using variants of this paradigm have shown that the N100 component (a negative deflecting potential peaking approximately 100 ms post stimulus presentation) is potentiated following a short bout of ST (Clapp et al., 2005; Lei et al., 2017; Teo et al., 2014). We utilized two tones of differing pitch, using only one of the tones for ST. ERPs from a pre-ST baseline block were compared to ERPs from two post-ST blocks to assess any plastic changes across time (Fig. 1A). To investigate the impact of tDCS on plasticity, stimulation was applied bilaterally to the auditory cortex, *simultaneous with ST* (Fig. 1A and B). Because the electric fields were present only during the presentation of one of the tones, it allowed us to selectively modulate the neural signal associated with the processing of that stimulus alone. By comparing changes in the N100 amplitude of the two tones, we were able to analyze whether tDCS had any modulatory effect on plasticity, and whether this effect was general, or specific to the stimulus presented during ST. We predicted that active tDCS would enhance plasticity compared to sham (Kronberg et al., 2017; Fritsch et al., 2010; Pisoni et al., 2017). Further, in accordance with the 'activity-selectivity' model of tDCS, we predicted that tDCS effects would be restricted to the stimulus presented during ST (Bikson et al., 2013; Hill et al., 2018; Pisoni et al., 2017).

2. Methods

2.1. Participants

22 healthy adults (8 females) completed the study (Table 1). Our sample size was based on a power calculation derived from similar reports (Zaehle et al., 2011; Clapp et al., 2005). Individuals who reported a history of neurological illness were not enrolled. The mean age of our sample was 24.9 years (range 19–42, s.d = 5.6), 20 of the participants were right-handed. All participants had auditory thresholds <25 dB in both ears. Prior to the start of the study, participants were informed of the study procedures and signed an informed consent form. The study was approved by the institutional review board at the University of Minnesota.

2.2. Experimental design

Study participation involved a crossover design, with each subject

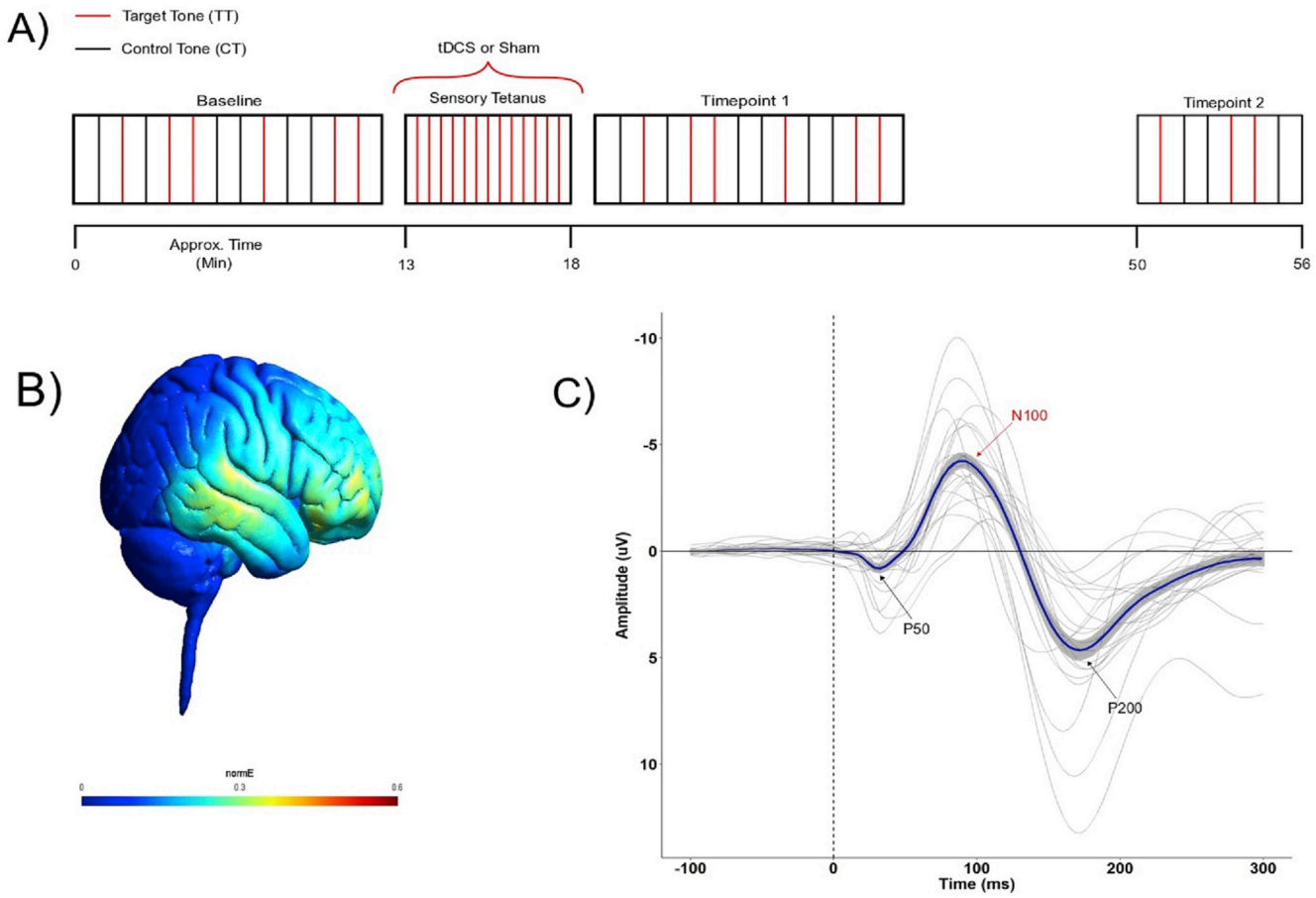

Fig. 1. Experimental Manipulations. **A)** Schematic depicting the timeline of events in a single study session involving the auditory sensory tetanus paradigm and tDCS. The paradigm consisted of three recording blocks, baseline, timepoint 1 and timepoint 2. Two pure tones of differing pitch were presented in these recording blocks at a slow and variable rate. For sensory tetanus, one of the tones (target tone) was presented at a high rate (~13 Hz) for a brief period. TDCS was applied simultaneously with sensory tetanus. **B)** Finite-element model of the normalized electric field produced in the brain by our tDCS montage. Anodal electrodes were placed at T7 and T8 (according to the standard 10–20 electrode placement system). Return electrodes were placed over the supraorbital bone at Fp1 and Fp2. 1 mA of current was delivered through each anode for the duration of the stimulation period. **C)** Grand average ERP recorded over an average channel encompassing 4 fronto-central electrodes (Fz, Cz, F3, F4). The grand average ERP shown in blue is collapsed across all subjects and conditions, prominent ERP components are labeled. Grey ribbon represents 95% within-subject confidence interval. Thin grey traces are derived from single subject grand average ERPs.

Table 1
Subject demographics.

Age (yrs)	24.9 ± 5.6
Gender (M/F)	14/8
Handedness (R/L)	20/2
Time Between Sessions (days)	8.8 ± 8.2

undergoing two experimental sessions, separated by at least one day (mean = 8.7 days, s.d = 7.9). Each session involved EEG recording and ST with concurrent tDCS. Study sessions were identical except for the nature of tDCS applied, either active or sham. The order tDCS treatment was counterbalanced across participants. Participants were blind to tDCS condition.

2.3. Auditory ST paradigm & EEG recording

The auditory ST paradigm presented two pure tones in three recording blocks (Fig. 1A). A ST block featured the presentation of one of the two tones at a high rate for a brief period. Sinusoidal tones of 1900 and 3000 Hz were used as stimuli (50 ms duration). Tones were constructed using a sine wave function at 44,000 samples/sec and were delivered binaurally at an intensity level of 70 dB through a pair of insert headphones (ER-3C, Etymotic Research).

During the baseline block, each tone was presented 150 times in a random distribution (ISI jittered between 1800 and 2600 ms; duration ~12min). For ST, one of the tones was presented 4000 times at a rate of 13.3 Hz (duration: 5min). The tone selected for ST was designated the target tone (TT) while the other tone served as the control tone (CT). The identity of the TT was pseudo-randomly determined and was counterbalanced between participants. Immediately after ST, participants were asked to sit in silence for 45sec to allow aural ringing to dissipate. Timepoint 1 (T1) recording was identical to the baseline block and commenced after ST. Timepoint 2 (T2) started 30min after the end of ST in order to assess persistence of any plasticity effects across time. To reduce participant fatigue, each tone was presented only 90 times in T2. Participants were instructed to either sit in silence or quietly read during the time between T1 and T2.

During the paradigm, participants were seated in front of a computer monitor in a dimly lit, electrically shielded room and were instructed to remain still, limit eye blinks and focus their gaze on a white fixation cross. EEG was recorded using the Starstim8 tDCS/EEG system (Neuroelectrics, Barcelona, Spain) using 8 channels which were placed at Fz, Cz, Pz, Oz, F3, F4, T7 and T8 (10–20 electrode placement system). Impedances were maintained below 10 kΩ. EEG signal was sampled at 500 Hz, analog band passed between 0.1 and 100 Hz and referenced to the right earlobe.

2.4. TDCS administration and electrical field modeling

TDCS was targeted to the primary auditory cortex bilaterally with anodes at T7 and T8 and return electrodes at Fp1 and Fp2. Past studies targeting the auditory cortex have used similar montages (Zaehle et al., 2011; Royal et al., 2018; Rahimi et al., 2019). Stimulation was delivered using 3.14 cm^2 PiStim electrodes. In the active condition, stimulation was delivered at 1 mA per anode for a duration of 5min, with a current density of 0.318mA/cm2. The timing of stimulation was such that it coincided with ST. In the sham condition, the current was ramped up to 1 mA over 30sec, but was then ramped down to 0 mA over the next 30sec.

We used electric field estimation (SimNIBS 2.1.1 (Thielscher et al., 2015),) to simulate tDCS current flow from our montage. Electric-field models were based on the extended MNI head model derived from 152 structural MRIs taken from normal participants. The parameters used for model simulation mimicked those used in the study. Induced electrical fields were visualized using Gmsh (Geuzaine and Gmsh, 2009) (Fig. 1B).

2.5. ERP processing

EEG data were preprocessed and analyzed in MATLAB R2018b (MathWorks, Inc., MA) using the EEGLAB toolbox (Delorme and Makeig, 2004) and the ERPlab toolbox extension (http://erpinfo.org/erplab). Raw EEG was down-sampled to 250 samples/sec and filtered using a bandpass of 0.1–20 Hz and a roll-off of 12dB/octave. Data were segmented into 800 ms epochs using a 200 ms pre-stimulus period. The mean of the pre-stimulus interval was used as a 0-μV baseline. A moving window peak-to-peak function was used to detect and mark individual epochs for rejection. Data files that produced >25% rejected trials were excluded from further analysis. Using the grand average ERP from all participants, the N100 component was identified (time window: 75–108 ms) and the four electrodes with the highest N100 amplitudes were selected for further analysis (Fz, Cz, F3, F4).

Single session N100 amplitudes and latencies were calculated over an averaged signal encompassing the 4 fronto-central electrodes. For each session, a custom MATLAB script was used to determine fractional peak latencies where the amplitude of the N100 dropped to 75% of its peak. These fractional latency values were used as a time-window to calculate the mean amplitude of the N100 component for each ERP. The latency of the local peak identified within the window was used as the peak latency measure. N100 difference values (Δ-values) for amplitude and latency were calculated within each session by subtracting baseline values from T1 and T2 values. Measures for the P50 and the P200 components were derived in the same manner as for the N100.

2.6. Fatigue and blinding

At baseline and following T2, participants completed a questionnaire designed to assess the level of fatigue ranked on a scale of 0 (alert) to 3 (very tired). To assess blinding, participants were asked to guess which treatment they had received at the end of each session.

2.7. Statistical analysis

2.7.1. ERP amplitude and latency analysis

Statistical analyses were carried out in R software. We analyzed ERP component Δ-values using a hierarchical linear modeling (HLM) approach. In the final model, treatment (Active/Sham), tone (TT/CT), and timepoint (T1/T2) were considered as main effects, as well as an interaction between treatment x tone and between treatment x timepoint. Random effects were included to account for repeated measures across timepoints for each subject within tone and within treatment. A timepoint x tone fixed effect interaction was also considered but the interaction was not significant, nor did it improve model fit. Time between sessions (in days), treatment order, pitch (whether the TT was the high or low pitch tone) and change in fatigue were included as covariates, but dropped from the final model as they did not sufficiently improve model fit (based on akaike information criterion (Akaike, 1974)).

Planned contrasts were used to further explore significant main effects and interactions. Contrasts were computed using the least-square mean approach. We focused on two contrasts, (1) comparing active vs. sham Δ-values for the TT and (2) for the CT. These contrasts were applied at both timepoints; Bonferroni-Holm correction was used to account for multiple comparisons. Effect sizes (Cohen's d) were computed for any significant treatment effects.

2.7.2. Analysis of fatigue and blinding efficacy

An HLM was used to analyze change in fatigue. We tested for the main effects of treatment and time as well as their interaction.

To assess the blinding, we categorized participant responses as either "correct" or "incorrect" after each session. A general linear model was used to assess any significant effect of treatment on blinding.

Data from this study are available at Mendeley Data (https://doi.org/10.17632/5n4wvd285d.2). Scripts used to analyze data can be made available upon reasonable request.

3. Results

3.1. Baseline amplitude and latency

Comparisons were first performed to assess differences in baseline amplitude and latency for the major mid-latency ERP components (P50, N100, P200). No significant baseline differences were found between any of the conditions for any ERP component ($p > .05$ for all comparisons), indicating consistent amplitudes and latencies prior to ST and tDCS.

3.2. Amplitude and latency modulation across time

3.2.1. ST induces stimulus-specific plasticity in the N100

When analyzing N100 Δ-values, we found a significant effect of tone ($t_{21} = 5.53$, $p < .001$), indicating that N100 amplitude was differentially modulated depending on tone identity. Irrespective of tDCS, the TT N100 was potentiated compared to baseline, whereas the CT N100 did not significantly differ from baseline (Table 2 & Fig. S1). This finding reinforces the idea that ST can be used to induce a stimulus-specific modulation of cortical plasticity in the human brain (Clapp et al., 2012; Mears and Spencer, 2012).

3.2.2. TDCS Modulates Plasticity in an activity-selective manner

We next asked whether tDCS modulated the induced plasticity. We observed a significant effect of treatment ($t_{42} = 2.84$, $p = .007$), and a significant interaction between treatment and tone ($t_{42} = -2.62$, $p = .012$).

A significant main effect of timepoint ($t_{86} = 3.30$, $p = .001$) revealed that plasticity modulation was time dependent. At T1, active tDCS resulted in a greater potentiation in the TT compared to sham ($p = .023$; Fig. 2), and the effect size of this result was large ($d = 0.821$). Importantly, tDCS had no discernible effect on CT amplitude ($p = .613$; Fig. 2), implying a stimulus-specific effect. These findings were corroborated by a *post-hoc* analysis of baseline adjusted difference-waves, where t-tests were used to identify timepoints at which active and sham ERPs significantly differed[1] (Fig. 3). Significant differences were identified only in the TT waveforms, in a time region corresponding to the N100 peak (Fig. 3B).

At T2 we no longer observed a tDCS effect (Fig. 4), with no significant difference between active and sham in the TT ($p = .192$) or in the CT ($p = .201$). No significant effects were revealed for N100 latency.

[1] Multiple comparisons were accounted for using the false discovery rate method.

Table 2
N100 Amplitude and Latency. Mean and standard deviation for the amplitude (microvolts) and latency (milliseconds) of the N100 component at each timepoint. Values were computed across individual subject grand average waveforms.

	Baseline				Timepoint 1				Timepoint 2			
	Target Tone		Control Tone		Target Tone		Control Tone		Target Tone		Control Tone	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
ACTIVE tDCS												
Amplitude (μV)	−3.92	1.97	−4.39	2.26	−5.02	2.05	−4.32	1.89	−4.70	2.15	−3.60	1.59
Latency (ms)	98.4	14.5	97.5	15.5	96.4	11.0	95.8	10.8	92.2	14	91.6	14.1
SHAM tDCS												
Amplitude	−4.38	2.01	−4.21	2.59	−4.73	2.10	−4.27	2.35	−4.71	2.08	−3.85	2.09
Latency	91.6	13.4	93.3	15.3	91.1	12.1	91.2	14.5	89.8	11.1	89.6	13

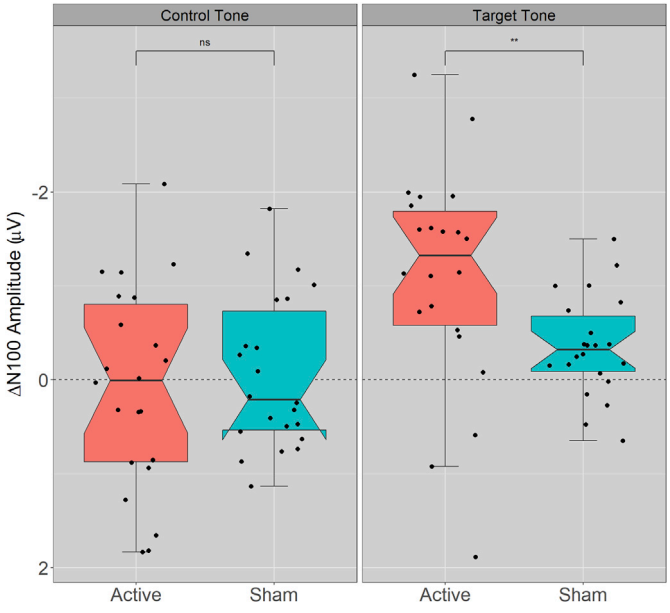

Fig. 2. TDCS Modulates Plasticity in an Activity-Selective Manner Immediately Following Stimulation. Boxplots showing distribution of N100 amplitude difference values (Δ-values) at timepoint 1. Δ-values were computed by subtracting baseline amplitude form amplitude at timepoint 1 for each subject. A negative shift compared to baseline would indicate enhanced N100 amplitude. Distribution of Δ-values for the control tone are shown on the right panel. There was no significant effect of tDCS on amplitude change in the control tone. In contrast, tDCS had a robust effect on target tone N100 amplitude modulation (left panel), with active stimulation leading to enhanced plasticity compared to sham.

3.2.3. No amplitude and latency modulation in secondary ERP components

No significant effects or interactions were revealed for P50 amplitude or latency (Supplementary Tables 3 and 4). A significant main effect of timepoint (t_{86} = 2.75, p < .001) was observed for P200 amplitude, indicating increased amplitudes over time (Supplementary Table 1).

3.3. Fatigue and blinding

TDCS had no effect on participant fatigue (t_{63} = 2.75, p = .713), both groups became more fatigued over time (t_{63} = 5.27, p < .001). TDCS did not influence ability to guess treatment condition correctly (t_{21} = −0.961, p = .333) as participants were close to chance when guessing treatment condition (59% accuracy).

4. Discussion

We used a unique ERP-based plasticity paradigm to explore whether tDCS could be used to modulate cortical plasticity in a stimulus-specific manner. Our manipulation allowed us to ascertain whether tDCS effects would be altered by the functional state of the brain during stimulation, as postulated by the 'activity-selectivity' hypothesis (Bikson et al., 2013). The current results provide strong physiological evidence that anodal tDCS can modulate plasticity and that these effects are sensitive to brain-state. We also find that the effect of tDCS on plasticity potentially degrades over time.

4.1. Induction of stimulus-specific plasticity via ST

Our ST paradigm was designed to induce plasticity in the auditory cortex (Zaehle et al., 2007; Chen et al., 2011; Krumbholz et al., 2003). Previous reports have demonstrated that ST with auditory stimuli leads to a stimulus-specific potentiation in the amplitude of the N100 component (Clapp et al., 2005; Lei et al., 2017; Mears and Spencer, 2012). The N100 is evoked in response to a wide array of sensory stimuli (Näätänen and Picton, 1987) and though the functional implications of modulating the N100 are still unclear, the presence of this potential across diverse stimulation conditions and sensory modalities suggests that the N100 is a general electrophysiological marker of cortical activation, indexing the brain's response to a particular input (Näätänen and Picton, 1987; Du et al., 2017). In the case of auditory stimulation, the cortical sources for the N100 have been localized to the superior and middle temporal gyri (Chen et al., 2011; Ford et al., 2016), resulting in a dipole which is best observed in the EEG over fronto-central electrodes.

Irrespective of tDCS, we showed that N100 amplitude was potentiated in response to the target tone following ST. This potentiation was not present in the control tone (Fig. S1), reinforcing the idea that ST can induce stimulus-specific plastic changes within the human cortex. Though we can only speculate as to the mechanism of these plastic changes, it seems plausible that presenting auditory tones at a rapid rate activates synapses within the auditory system in a manner similar to what is seen in cellular studies of LTP, where high frequency electrical stimulation is used to induce plasticity in neuronal tissue. Animal studies have shown that plasticity can be driven by persistent exposure to a sensory stimulus, and can lead to stimulus-specific and NMDAR dependent changes in the neocortex of rats and mice (Cooke and Bear, 2010; Clapp et al., 2006). These studies demonstrate that ST can indeed induce neuronal changes which feature the cardinal properties of Hebbian plasticity. Nevertheless, because we recorded non-invasively with scalp electrodes, we cannot be certain that we are inducing the same sort of neuronal modifications as in the previously mentioned animal studies. Further investigation using more spatially precise methods would serve to greatly complement our current findings.

4.2. Stimulus-specific effects of tDCS on plasticity

TDCS modulated ST induced plasticity in a stimulus-specific manner. We observed a greater degree of potentiation in the TT N100 under active tDCS compared to sham, bolstering the idea that tDCS can modulate plasticity in the human cortex. Further, we found that the effects of tDCS were restricted to the TT, with the CT showing no stimulation dependent modulation. This indicates that tDCS did not cause a general

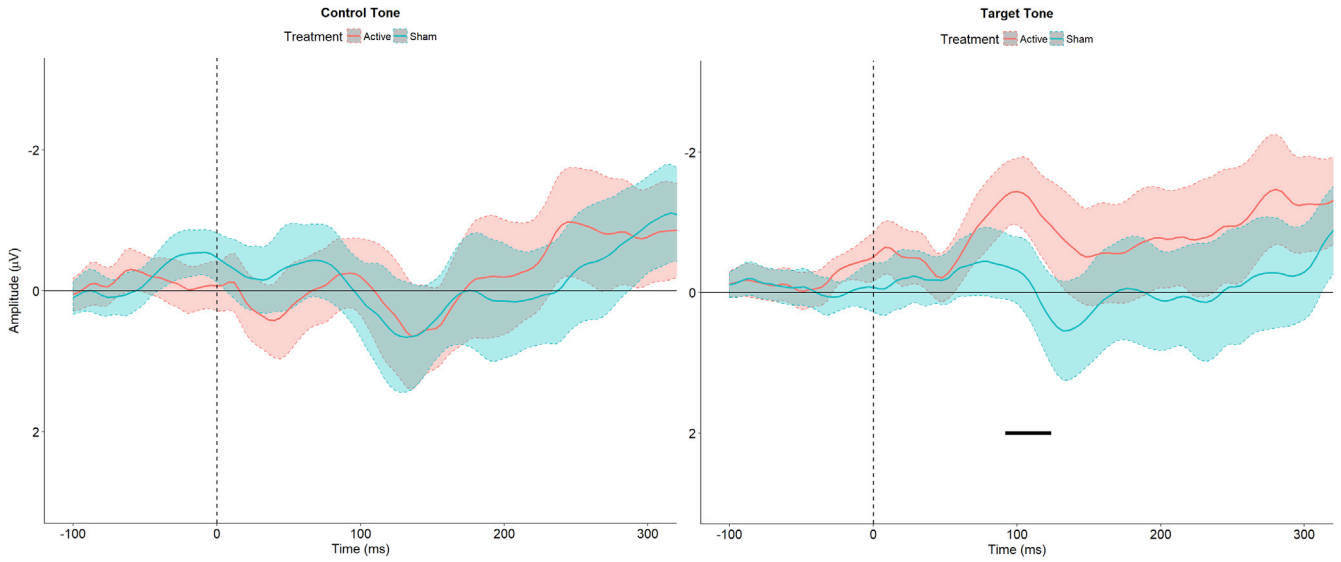

Fig. 3. Grand Average Difference Waves at Timepoint 1 Showing TDCS Activity-Selectivity. The grand averages were recorded over an average channel encompassing 4 fronto-central electrodes (Fz, Cz, F3, F4). Waveforms were constructed by subtracting the baseline waveform from the waveform at timepoint 1. Ribbon around the waveforms indicates within-subject 95% confidence interval. As a post-hoc confirmatory analysis, we ran t-tests at each timepoint, comparing active vs. sham difference waves to identify timepoints at which the waves significantly differed (FDR corrected for multiple comparisons). The black bar underneath the waveforms (seen in right-hand panel) shown times at which the two waves were significantly different. Significant differences were identified only between the target tone difference waves at timepoints corresponding to the N100 component.

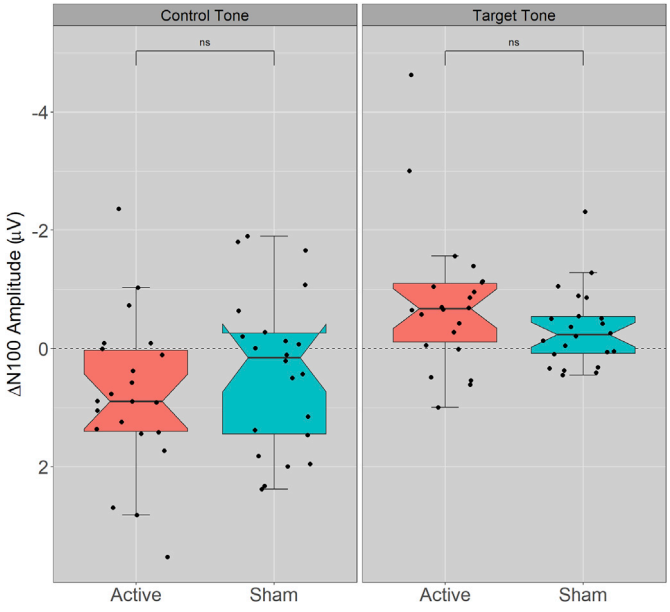

Fig. 4. TDCS Effects No Longer Significant 30min Post Stimulation. Boxplots show the distribution of N100 amplitude difference values at timepoint 2. Δ-values were computed by subtracting baseline amplitude form amplitude at timepoint 2 for each subject. Distribution of Δ-values for the control tone are shown on the right panel. There was no significant effect of tDCS on amplitude change in the control tone or in the target tone 30min post stimulation and sensory tetanus.

enhancement of cortical excitability, but rather *an alteration in cortical excitability that was dependent on stimulus-specific brain state.*

A plausible explanation for the observed stimulus-specific effects can be derived from the fact that tDCS modulation is dependent on endogenous brain activity (Bindman et al., 1964; Kronberg et al., 2017; Fritsch et al., 2010; Rahman et al., 2017). Thus, neuronal populations which are concurrently active with tDCS should be preferentially modulated relative to inactive populations. Studies in animals investigating effects of tDCS on plasticity support this view (Fritsch et al., 2010). For instance, application of DCS alone to cortical slice did not modulate synaptic efficacy as measured by field excitatory postsynaptic potentials. However, when applied concurrently with synaptic input (via afferent stimulation), DCS resulted in a robust change in synaptic efficacy. Furthermore, at the cellular level, DCS is known to modulate the level of potentiation in a specific pathway, but only if that pathway is co-active with stimulation (Kronberg et al., 2017; Ranieri et al., 2012). TDCS modulation of plasticity may be mediated by changing membrane potential and removal of the Mg^{2+} block (Stagg and Nitsche, 2011), but because tDCS fields are subthreshold (Ruffini et al., 2013), only those neuronal populations active during tDCS would experience potentiation.

In the context of our experiment, we were activating a population of neurons responsible for processing a specific stimulus, and then selectively exposing that population to tDCS. The N100 is tonotopically distributed in the auditory cortex (Yamamoto et al., 1992; Woods et al., 1993), and distinct populations of neurons are responsible for processing auditory stimuli of differing pitch (Bitterman et al., 2008). We can then posit that those groups of neurons which were active during tDCS (those involved in processing the TT) were preferentially modulated. These results provide the most robust physiological evidence for the 'activity-selectivity' model to date, demonstrating the ability of tDCS to selectively modulate a neuronal signal associated with processing a specific input (Fritsch et al., 2010; Bikson et al., 2013; Rahman et al., 2017).

It is important to note that while we achieved plasticity modulation, tDCS effects were no longer detectable 30min post-stimulation. Several factors may have contributed to this finding. Previous studies using MEPs have demonstrated that long stimulation durations (>10min) are required to elicit persistent psychological changes from tDCS (Nitsche and Paulus, 2000; Mosayebi et al., 2018). Given our short bout of tDCS (~5min), it is not unexpected to see effects fade over time.

Alternately, a physiological explanation for no effects at T2 may be related to the slow rate of stimulus presentation in the recording blocks. As mentioned previously, it is the high rate of stimulus presentation during ST that leads to plasticity induction. High frequency inputs result in a tight temporal correlation between spikes of pre- and postsynaptic neurons, leading to potentiated postsynaptic functioning. Conversely,

low frequency inputs can have the opposite effect, leading to de-correlation and a reduced level of postsynaptic activity (Gerstner et al., 1996). Given this mechanism, it is plausible that the reduced effects at timepoint 2 were a result of an active depotentiation due to the repeated slow presentation of stimuli, rather than merely a passive decay of plasticity over time. This interpretation is supported by findings from related studies. First, in a study utilizing a visual variant of the ST paradigm, Tyler et al. only found significant potentiation after 1 h if early post-tetanus recording blocks were withheld (Teyler et al., 2005). Second, it has been shown that LTP induced by high frequency electrical stimulation of surgically resected human neocortex can be actively de-potentiated via low frequency electrical stimulation (Chen et al., 1996).

4.3. Limitations

One limitation of this study is that the spread of current from our montage is diffuse, reaching cortical regions outside of our nominal target (Fig. 1B). Thus, off target effects could potentially confound our interpretations. However, unless concurrently activated, it is unlikely that those off target regions were significantly modulated (Pisoni et al., 2017).

Due to the difference in the number of trials used to construct ERPs at baseline and timepoint 1 compared to timepoint 2, we exercise some caution in interpreting timepoint 2 results. Nevertheless, given the prominence of the N100, we believe that the number of trials used for timepoint 2 (90) are usually sufficient to accurately characterize this component (Luck, 2014). Additionally, we used a relatively small number of EEG electrodes in the current study. A higher density of recording electrodes would be useful for better detailing topography of the plasticity effects; however our results indicate that the number of electrodes used were sufficient for the purposes of the study.

The functional implications of modulating the N100 component, and the mechanism by which this modulation relates to plasticity is not clear. It is important to note that we did not include any form of behavioral task to assess functional implications of our manipulation, as we felt this was outside the scope of the present study. It would be interesting for future investigations to include a perceptual discrimination task to determine whether modulating the sensory ERP has some form of functional relevance (i.e. reaction time, sensitivity).

5. Conclusions

We demonstrate that tDCS can modulate a physiological marker of cortical plasticity. Further, we show stimulus-specific modulation, demonstrating that pairing tDCS with a targeted brain-state is a crucial factor in eliciting tDCS effects. These findings support the 'activity-selectivity' hypothesis (Bikson et al., 2013), confirming in humans what has been found in animal models. Together this body of work represents a solid theoretical framework which can aid in the rational advancement of tDCS. The important translational step provided by this study further emphasizes the importance of combining tDCS with concurrent, and specifically targeted brain network activation in order to improve outcomes from tDCS interventions. This research is thus especially informative for future clinical studies which seek to effectively optimize tDCS interventions for remediation of deficits in a variety of brain disorders.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

Elias Boroda: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Scott R. Sponheim:** Methodology, Writing - review & editing, Validation. **Mark Fiecas:** Formal analysis. **Kelvin O. Lim:** Validation, Funding acquisition, Project administration.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116598.

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