Converging Evidence That Neural Plasticity Underlies Transcranial Direct-Current Stimulation

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Abstract

■ It is not definitely known how direct-current stimulation causes its long-lasting effects. Here, we tested the hypothesis that the long time course of transcranial direct-current stimulation (tDCS) is because of the electrical field increasing the plasticity of the brain tissue. If this is the case, then we should see tDCS effects when humans need to encode information into long-term memory, but not at other times. We tested this hypothesis by delivering tDCS to the ventral visual stream of human participants during different tasks (i.e., recognition memory vs. visual search) and at different times during a memory task. We found that tDCS improved memory encoding, and the neural correlates thereof, but not retrieval. We also found that tDCS did not change the efficiency of information processing during visual search for a certain target object, a task that does not require the formation of new connections in the brain but instead relies on attention and object recognition mechanisms. Thus, our findings support the hypothesis that direct-current stimulation modulates brain activity by changing the underlying plasticity of the tissue. ■

INTRODUCTION

Stimulating the brain with weak direct current for several minutes has long been known to trigger changes in brain function that can last for hours (Bindman, Lippold, & Redfearn, 1962, 1964). How several minutes of electrical stimulation can result in hours of perturbed brain function is far less clear (Reinhart, Cosman, Fukuda, & Woodman, 2017). An early hypothesis proposed that the changes in brain function persist for hours after direct-current stimulation is delivered because the electrical field induced by stimulation promotes protein synthesis and synaptic plasticity (Gartside, 1968). This hypothesis has received support from rodent work in brain slices and in vivo (Kronberg, Bridi, Abel, Bikson, & Parra, 2017; Jackson et al., 2016; Podda et al., 2016; Sun et al., 2016). Here, we tested predictions of the plasticity hypothesis in the human brain using a variety of methods to provide converging evidence.

If transcranial direct-current stimulation (tDCS) is changing the short-term plasticity of the tissue in the human brain, then we should see the following predictions confirmed. First, tDCS should influence the encoding of an episode into long-term memory (i.e., when new connections are made to store information) but should have minimal affects at retrieval (i.e., when those connections are used). The literature suggests that this is an unsettled question. One set of existing studies suggest that this prediction should be supported (Gaynor & Chua, 2017; Smirni, Turriziani, Mangano, Cipolotti, & Oliveri, 2015), with many of these studies using language or auditory memory tasks (Boroda, Sponheim, Fiecas, & Lim, 2020; Rivera-Urbina, Mendez Joya, Nitsche, & Molero-Chamizo, 2019; Vorobiova, Pozdniakov, & Feurra, 2019; Brunyé, Hussey, Gardony, Holmes, & Taylor, 2018; Fiori, Kunz, Kuhnke, Marangolo, & Hartwigsen, 2018; Kucewicz et al., 2018; Payne & Tainturier, 2018; Westwood, Olson, Miall, Nappo, & Romani, 2017; Brasil-Neto, 2012; Ross, McCoy, Coslett, Olson, & Wolk, 2011; Ross, McCoy, Wolk, Coslett, & Olson, 2010; Boggio et al., 2009). However, there are sufficient contradictory findings that a recent meta-analysis suggested that tDCS does not significantly change performance on memory tasks (Galli, Vadillo, Sirota, Feurra, & Medvedeva, 2019), as a number of empirical studies have also concluded (Lang, Gan, Alrazi, & Monchi, 2019; Vorobiova et al., 2019; de Lara, Knechtges, Paulus, & Antal, 2017; Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013; Jacobson, Koslowsky, & Lavidor, 2012). Next, tDCS should change performance in long-term-memory-demanding tasks, but not other difficult tasks that tax mechanisms that do not involve the storage of new information, like shifting the focus of selective attention to find a target object among distractor objects (Wolfe, 2007). Finally, tDCS should change electrophysiological indices of memory encoding but have little effect on brain activity measured during retrieval, as existing synaptic connections are used. Here, we tested this set of predictions of the plasticity hypothesis by targeting the cortex of the temporal lobe. This portion of the brain is an ideal locus in which to test our predictions because empirical work has shown that this region participates in a host of functions, including object recognition (DiCarlo, Zoccolan, & Rust, 2012), auditory perception (Hickok, 2009), semantic analysis (Tsapkini, Frangakis, & Hillis, 2011), memory for

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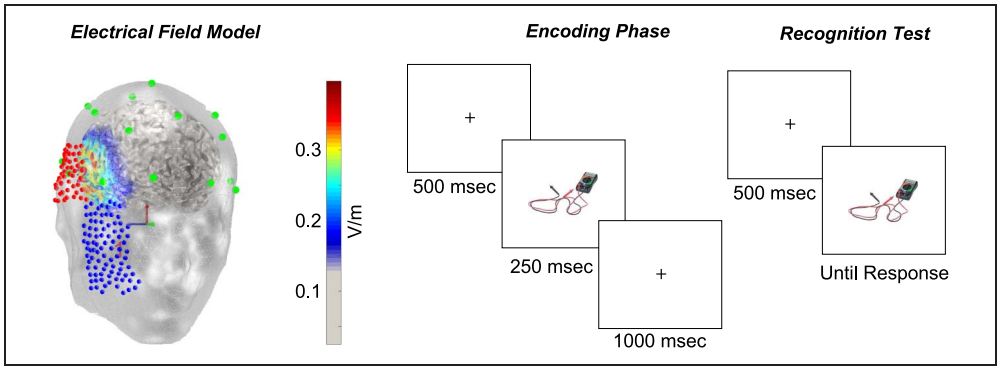

Figure 1. The current distribution of the stimulation and examples of encoding and test phase trials. (Left) The current flow model illustrating right anodal stimulation. The anodal electrode was at T3/T4; and the cathodal electrode, on the ipsilateral cheek (this model is for a right hemisphere montage). (Center) Encoding phase trials began with the presentation of the fixation cross for 500 msec, followed by a 250-msec object presentation and a 1000-msec poststimulus break. This was repeated for all 500 stimuli. (Right) For the recognition test, we presented each picture on the screen until the participant pressed a response button to indicate whether the picture was a new or an old stimulus and his or her confidence rating.

episodes (Ezzyat et al., 2017), and memory for objects we experience visually (Cichy, Pantazis, & Oliva, 2014). Thus, stimulation of this hub structure could change memory storage if the plasticity hypothesis is correct but could also plausibly have other effects, such as improving the efficiency of object recognition, which would be observable in making visual search more efficient and improving recognition memory when tested after a retention interval.

In Experiment 1, participants performed a recognition-memory task in which they viewed 500 pictures of common objects after 20 min of anodal stimulation delivered to the temporal lobe (see Figure 1). These same participants performed the same task, but with new pictures on a different day after sham stimulation (order counterbalanced). This sham stimulation mimicked the sensations felt during active stimulation such that participants were blind to which day we applied active stimulation, with blinding confirmed during postexperiment debriefing. In Experiment 2, we measured the effects of tDCS on visual search performance, a task that does not demand constant memory encoding when the searched-for target remains the same but does demand efficient shifting of attention and the recognition of objects. In Experiment 3, we stimulated before memory retrieval to determine if tDCS could change memory retrieval operations when retrieval was performed immediately after stimulation. Finally, in Experiment 4, we tested the predictions of the plasticity hypothesis by measuring the effects of tDCS on the known electrophysiological correlates of encoding and retrieval from human memory. An overview of the tasks and our methods across experiments is shown in Figure 2.

METHODS

Participants

Unique groups of 32 Vanderbilt University undergraduate students participated in Experiments 1–3, with Experiment 4 using 24 individuals. Our estimate of the necessary power for each experiment was based on previous tDCS experiments targeting other brain regions with anodal versus sham stimulation in which effect sizes ranged from η^2 = 0.9–2.3 (Reinhart, Xiao, McClenahan, & Woodman, 2016; Reinhart, Zhu, Park, & Woodman, 2015a; Reinhart & Woodman, 2014). To achieve 80% power to detect an effect of the same size at the p = .05 level would require approximately 20 participants. We obtained larger samples because these precise tasks and measures have not been

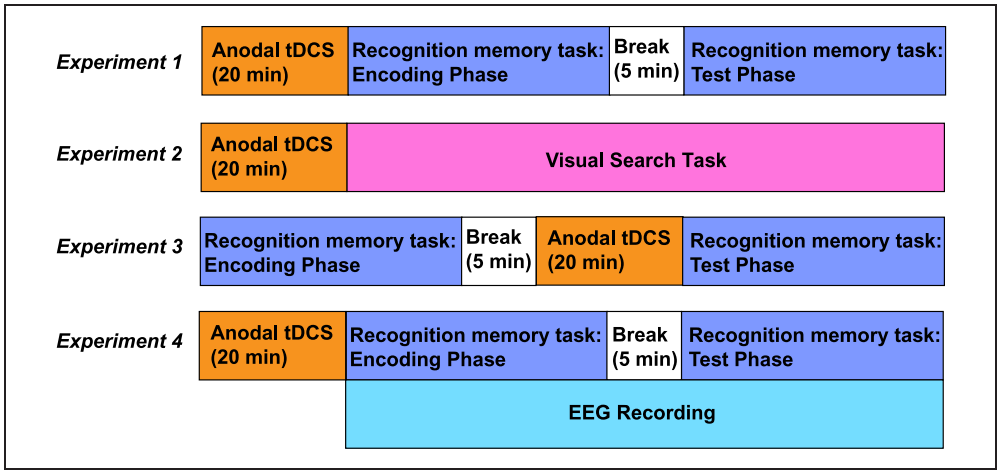

Figure 2. Methodological overview of the experiments. The recognition memory task refers to the paradigm in Figure 1. The visual search task refers to the paradigm in Figure 4.

used in previous work. In exchange for their participation, participants received either $10 per hour or partial course credit for an introductory psychology course. All participants had normal or corrected-to-normal vision, the absence of colorblindness, and no history of neuropsychiatric disorders based on self-report. Participants' data were excluded when they did not return for the second session (four in Experiment 1, zero in Experiment 2, and three in Experiment 3). In Experiment 4, two participants' data were excluded because of excessive ocular artifacts (i.e., more than 25% of trials rejected because of eye movements).

Direct-Current Stimulation

After obtaining informed consent, each session of the experiment began with 20 min of 2-mA tDCS applied to skull over the temporal pole or a single-blind sham procedure that was identical to the active stimulation session. Anodal tDCS was administered using a battery-driven, constant current stimulator (Mind Alive Inc.) and a pair of conductive rubber electrodes (active: 19.25 cm^2; reference: 52 cm^2). The electrodes were placed in saline-soaked sponges and held in place by a headband. The active electrode was placed at T3 or T4 of the International 10–20 system (Jasper, 1958). The anodal electrode at the temporal pole was paired with a cathodal electrode centered over the ipsilateral cheek to avoid confounding effects that occur when the reference electrode is placed over another brain region (Reinhart et al., 2017). We modeled the current flow using COMETS (Jung, Kim, & Im, 2013). Half of the participants were randomly assigned to left-side anodal stimulation (electrode placed at T3), and the other half were assigned to right-side anodal stimulation (electrode placed at T4). Each participant received either right- or left-side anodal stimulation in one of the sessions and an identical sham stimulation procedure during the other session with the exception that the stimulator was turned on for only 20 sec at the beginning and end of the 20-min interval in which the tDCS electrodes where on the participant's head. The side of stimulation and the order for sham and anodal stimulation were counterbalanced across participants.

Participants were given a set of questionnaires at the end of each experimental session to see if they could detect whether the stimulator was on during the 20-min period in which the electrodes were on the participant's head and to determine whether discomfort was felt, using our previous established methods (Reinhart et al., 2017). To evaluate the effectiveness of blinding by the sham procedure, we analyzed the data separately for participants that correctly identified the sham and active stimulation sessions. In Experiment 1, one participant correctly identified both the sham and active sessions, two participants correctly identified both in Experiment 2, four participants identified both in Experiment 3, and one participant correctly identified both sessions in Experiment 4. The pattern of results was identical when these participants are excluded, so the analyses report findings with all of the participants included so as to provide an unbiased sample of all participants.

Stimuli and Tasks

Stimuli were presented on an Apple Macintosh computer running MATLAB (Mathworks Inc.) and the Psychophysics Toolbox (Brainard, 1997). Participants viewed the stimuli from approximately 80 cm in front of an LED monitor with a black background of 0.6 cd/m^2 in Experiments 1–3; for Experiment 4, the stimuli were presented on a CRT monitor inside a Faraday cage, with a black background of 1.2 cd/m^2. The data for Experiments 1–3 were collected from participants seated in a small, dimly lit running room with a peephole so that the experimenters could verify compliance with instructions. The data for Experiment 4 were collected in a dimly lit, sound-attenuated, and electromagnetically shielded room (ETS-Lindgren) using EEG electrodes and a camera to verify compliance with instructions.

In Experiments 1, 3, and 4, the task consisted of a picture study phase and a recognition-memory test phase (see Figure 1) after anodal stimulation or sham. The recognition-memory task involved presenting pictures of 500 real-world objects during a study phase in which each picture was shown individually at the center of the screen for 250 msec, followed by a 1000-msec ISI (Fukuda & Woodman, 2015). The stimuli were adapted from a published set of photographs (Brady, Konkle, Alvarez, & Oliva, 2008). For Experiments 1–3, the mean size of each picture was approximately 6.4° × 6.4° of visual angle. Participants were instructed to study each item while holding central fixation so that they could recognize them later. In Experiment 4, the mean picture size was approximately 4.6° × 4.6° of visual angle. After a 500-msec preencoding period, in which the screen was blank except for a central fixation dot (0.5° of visual angle, drawn in white, 268 cd/m^2 in Experiments 1 and 3 and 75.2 cd/m^2 in Experiment 4), each picture was presented for 250 msec. Each picture was followed by a 1000-msec encoding period, during which the computer screen remained blank. In Experiment 4, the participants were encouraged to blink during this 1000-msec interval so that their eyes did not dry out. After the encoding task, the participants were given a 5-min break between the encoding phase and the recognition test.

During the test phase of the recognition-memory task, participants were shown 750 pictures of real-world objects (i.e., the 500 pictures shown during the encoding phase and 250 new pictures, with the order randomized). Each test-phase trial started with the onset of a central fixation cross for a 500-msec duration (1.5° of visual angle, drawn in white, 268 cd/m^2 in Experiments 1 and 3 and 75.2 cd/m^2 in Experiment 4). Participants were instructed to maintain central fixation until each trial was over. After the 500-msec fixation period, a picture of a real-world object was presented at the center of the screen, just as at study. Unlike the study

phase, at test, each picture was presented until the participants made a key press to indicate whether they had seen that object during the study phase, as well as their confidence. The number keys 1, 2, and 3 indicated that the item was old, and the larger the number, the lower confidence level the participants had for that response. The buttons 7, 8, and 9 indicated the item was new, and the larger the number, the higher confidence level.

In Experiment 2, participants performed a visual search task in which they looked for a target letter T among a variable number of Ls (each letter was approximately 1.2° × 1.2° of visual angle, drawn in white, 75.2 cd/m^2). Each object was centered 5.0° of visual angle from the center of the screen, with each neighboring object separated by at least 2.6° of visual angle. When the set size was 2, the objects were presented at opposite locations on the imaginary circle of eight possible stimulus locations. When the set size was 4, the locations were equally spaced, and at a set size of 8, all of the possible locations were filled. The position of the target was randomized on each trial, as was the rotation of the target and each distractor. On each trial, the fixation cross appeared for 500 msec (physically identical to the fixation cross in Experiment 1), followed by the visual search array, which remained visible until the participant pressed one of the four direction buttons on the keyboard to indicate the direction that the top of the letter T pointed to on each trial (e.g., the up arrow for an upright T, the right arrow for a T rotated 45° to the right). Each session began with the participant undergoing 20 min of sham or active stimulation, before completing 900 trials of visual search (300 of each set size, with set sizes randomly interleaved).

The two stimulation conditions were completed on different days, separated by at least 48 hr, at the same time of the day. In the recognition memory experiments (Experiments 1, 3, and 4), nonoverlapping sets of pictures were used so that each day used a unique set of pictures. The dependent variable that we measured was d' so that we could verify that memory sensitivity actually changed, instead of stimulation inducing a bias (Wickens, 2001).

In Experiment 2, the dependent variable in the visual search task was mean RT, although we also measured accuracy to verify that no speed–accuracy tradeoff was evident. Stimulation condition was a within-participant variable in that every participant received both sham and active stimulation in two separate sessions. Each participant received right- or left-side anodal stimulation (counterbalanced across participants) and sham stimulation in the other session (order counterbalanced). In each session, all participants performed visual search with three different array sizes (2, 4, or 8) that were randomly interleaved. We excluded responses from the means that were faster than 150 msec or were incorrect, approximately 1.5% of the trials across all participants.

In Experiment 3, tDCS was delivered during the retention interval (i.e., before retrieval), instead of before encoding, as in the other experiments. After viewing all of the to-be-remembered pictures, the participants were briefed about the placement of potentially stimulating electrodes and fitted an elastic band that held on the tDCS electrodes. This took approximately 5 min (as represented in Figure 2), after which the 20-min stimulation period began (with either anodal or sham stimulation delivered, depending on the counterbalanced order of conditions). The memory test began immediately after electrode removal, with removal taking approximately 1 min to complete.

Electrophysiology

In Experiment 4, we recorded EEG data from the 10–20 electrode sites, namely, Fz, Cz, Pz, F3, F4, C3, C4, P3, P4, PO3, PO4, O1, O2, T3, T4, T5, and T6, and a pair of custom sites, namely, OL and OR, which were halfway between O1 and T5 and halfway between O2 and T6, respectively. These EEG data were referenced online to the right mastoid and rereferenced offline to the average of the left and right mastoids. Horizontal eye movements were monitored via a pair of electrodes affixed ~1 cm lateral to the outer canthi of the left and right eyes. Blinks and vertical eye movements were tracked using an electrode placed below the right eye. The impedance of each electrode was kept below 3 kΩ. We amplified the EEG data with a gain of 20,000 using an SA Instrumentation amplifier with a bandpass filter of 0.01–100 Hz and digitized at 250 Hz.

We preprocessed the EEG data using custom MATLAB scripts and EEGLab (Delorme & Makeig, 2004). After we rereferenced the EEG data, we segmented the continuous EEG data into epochs that included the activity 200 msec before stimulus onset until 1200 msec after trial onset. For the study phase, we only measured until 1000 msec after the stimulus onset because of the stimuli only being shown for 250 msec, with this slightly shorter measurement window avoiding excessive contamination by blinks and eye movements. We then used threshold rejection followed by visual inspection to manually reject trials containing eye movements, muscle activity, amplifier saturation, and other artifacts. This artifact rejection protocol resulted in the removal of a mean of 6.97% of trials across the 24 participants.

We sorted the data from each trial into bins based on the participants' memory responses: high-confidence old, low-confidence old, and miss (old, but said new). We then time-locked the data to the stimulus onset from the study and test phases to compute the mean voltages of the EEG signals to obtain the ERPs with which to measure the frontal positivity. Following previous studies (Fukuda & Woodman, 2015), we focused our ERP analyses on midline electrodes and show data from Fz, where this effect is maximal in our data and the previous work.

To measure alpha power, we decomposed the single-trial EEG data using *spectopo.m* in MATLAB with a fixed window size of 400 msec and a window overlap of 360 msec to obtain Fourier coefficients at 8–12 Hz in 1-Hz steps. The function provided the average of alpha power within the time window for each channel. Next, we slid the

measurement window across the epoch of interest from 400 to 1000 msec in 40-msec steps to generate the averaged alpha power for each electrode of interest (following Fukuda & Woodman, 2015). Finally, we used the alpha power as an input to the *topoplot.m* function to generate the topographical map of alpha power to visualize the distribution of effects.

RESULTS

Figure 3 shows the findings from Experiment 1. We saw that anodal stimulation delivered to the temporal pole improved recognition memory, regardless of which hemisphere was stimulated. The psychophysical measurement of memory sensitivity (d') was higher after anodal stimulation, compared to the sham stimulation baseline, $F(1, 30) = 16.50$, $p < .001$, consistent with the predictions from the account that anodal tDCS increases short-term plasticity. We found neither a main effect of hemisphere, $F(1, 30) = 0.14$, $p = .71$, or an interaction of Stimulation Condition × Hemisphere, $F(1, 30) = 0.09$, $p = .75$. Figure 3 demonstrates that this improvement in recognition memory was observed across the receiver operating characteristic curve, indicating that it was not only low confidence judgments that benefited from direct-current stimulation.

In Experiment 2, we tested the plasticity hypothesis of tDCS by stimulating the temporal pole, as in Experiment 1, but followed by an attention-demanding visual search task in which observers searched for a target letter among similar distractor letters (see Figure 4 for example stimuli). Visual search tasks tax selective attention, as attention needs to be deployed to possible target objects that are then recognized, but do not require the formation of new memories when the target remains the same across trials (Woodman, Carlisle, & Reinhart, 2013; Horowitz & Wolfe, 1998). We found no change in the efficiency with which people could search the visual arrays, as measured with the slope of the function relating RT to set size in preplanned analyses, $t(31) = 0.55$, $p = .59$, but we did find a trend toward anodal stimulation speeding RT generally,

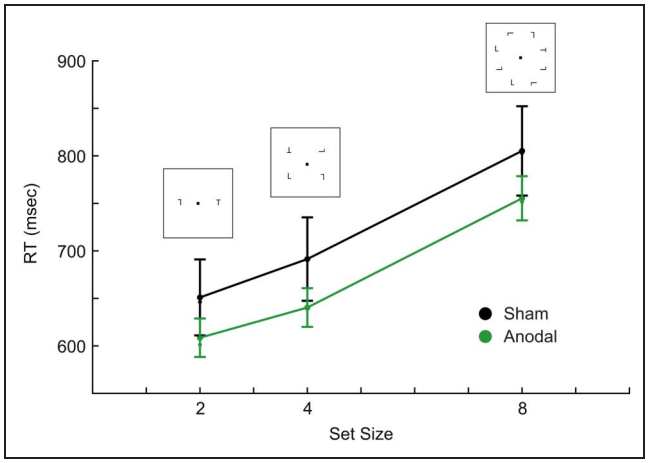

Figure 4. Example arrays and results from the visual search task used in Experiment 2. Participants searched for the letter T among Ls, 500 msec after the fixation point appeared (letter identity counterbalanced across participants and letter rotation randomized). Error bars reflect *SEM*s. Participants' search accuracies under sham (mean = 98.8%, *SE* = 0.24) were not different ($p > .5$).

$t(31) = 1.69$, $p = .10$, suggesting that tDCS changed a process that occurred before or after the attention-demanding search process, following the additive factors logic of interpreting RT effects (Sternberg, 2001). We note that the absence of an effect in Experiment 2 relative to Experiment 1 is not simply because of measuring RTs in the former as visual search tasks using accuracy as the dependent variable show the same sensitivity to independent variables as RTs (Wolfe, 1998) and learning tasks that measure RTs show robust tDCS effects (Reinhart & Woodman, 2014, 2015).[1] Our ANOVA with the factors of Stimulation condition (anodal vs. sham), Set size (2, 4, or 8 objects), and Hemisphere (left vs. right) was consistent with our preplanned comparisons of slope and y intercept of the search functions, in that we obtained a significant effect of Set size, $F(2, 29) = 227.78$, $p < .001$, but did not yield a main effect of Stimulation, $F(1, 30) = 2.18$, $p = .15$, Hemisphere, $F(1, 30) = 0.05$, $p = .83$, or any interactions of these factors ($p > .30$). Thus, we did not find that tDCS changed the rate of

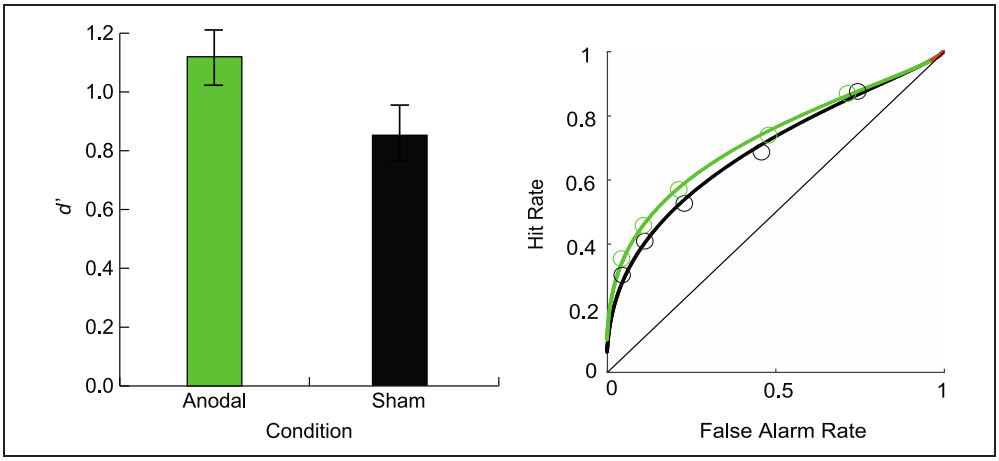

Figure 3. Recognition memory performance from Experiment 1 after sham and anodal stimulation. (Left) The mean d' sensitivity index after sham and anodal stimulation. Error bar represents the *SEM*. (Right) The receiver operating characteristic curves after anodal stimulation (green) and sham (black).

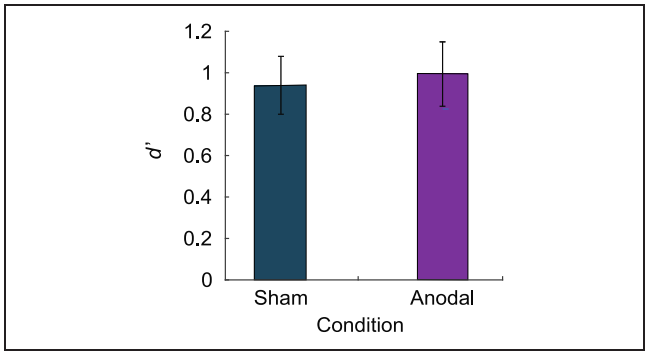

Figure 5. Recognition memory performance from Experiment 3 after sham and anodal stimulation applied after the encoding phase. Error bars represent *SEM*s.

information processing in a difficult task that does not require the human brain to store new information via synaptic connections.

In Experiment 3, we wanted to test an alternative explanation for the results of Experiment 1. Specifically, it is possible that memory was improved in Experiment 1 because anodal stimulation helped retrieval (Crossman, Bartl, Soerum, & Sandrini, 2019; Javadi & Cheng, 2013) and not because tDCS improved encoding through increased plasticity, despite stimulation being delivered closer in time to encoding. To address this possibility, we ran Experiment 3 in which tDCS was applied before retrieval, instead of before encoding. However, we found no evidence that tDCS could improve memory retrieval, as shown in Figure 5.

We found that d' after anodal stimulation before retrieval was not significantly different from the sham baseline, $F(1, 30) = 0.56, p = .46$ (see Figure 5). In addition, we did not find that this effect of stimulation differed as a function of which hemisphere was stimulated (main effect of Hemisphere: $F(1, 30) = 1.34, p = .26$, and the Condition × Hemisphere interaction: $F(1, 30) = 0.88, p = .36$). To verify that there was a significant difference in the effect of stimulation between Experiment 1, in which we stimulated before encoding, and Experiment 3, in which we stimulated before retrieval, we performed a mixed-model ANOVA on d' and found that the interaction of Experiment (1 vs. 3) and Stimulation (anodal vs. sham) was significant, $F(1, 62) = 4.99, p < .03$. Thus, the findings of Experiment 3 rule out the alternative explanation that tDCS failed to alter memory retrieval because of temporal proximity to encoding versus retrieval. This is consistent with previous

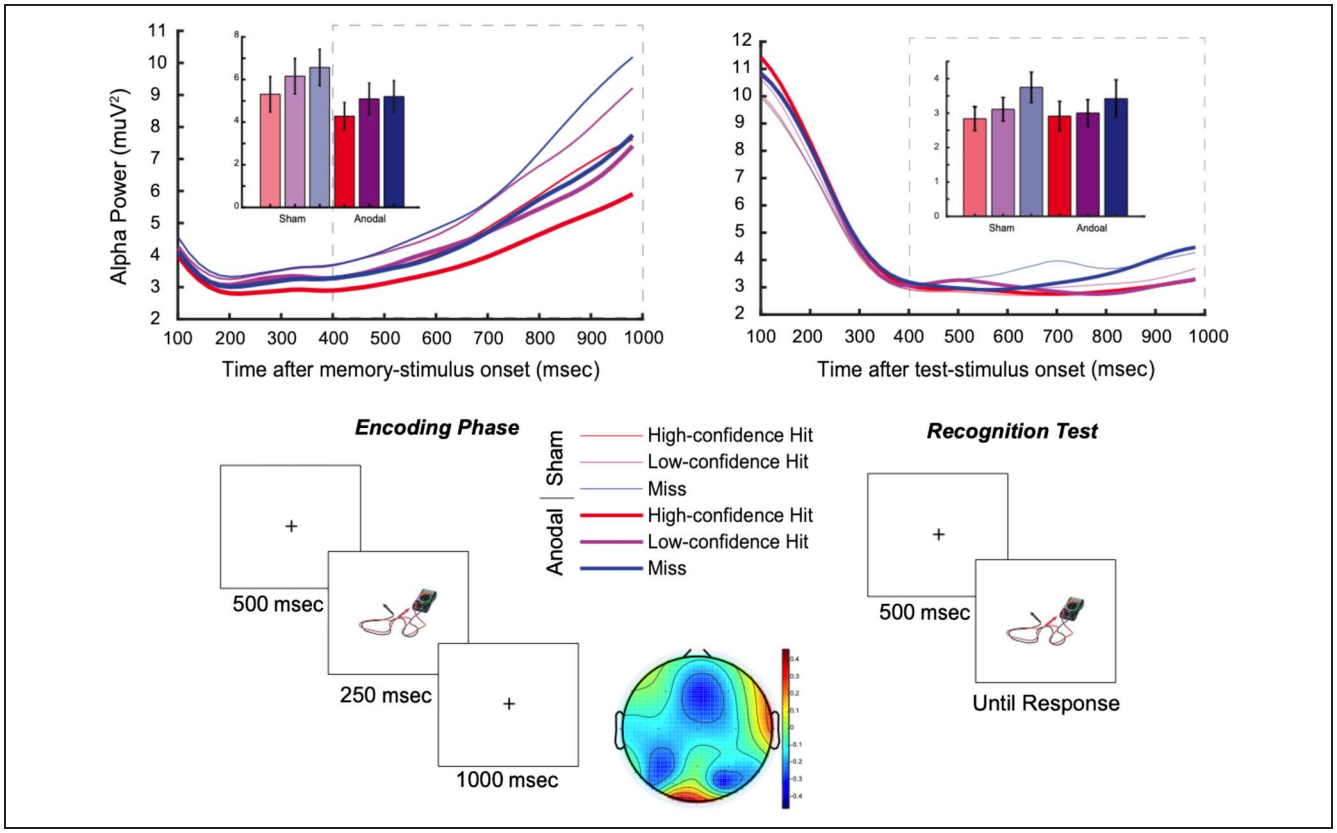

Figure 6. The posterior alpha-band power measured during the encoding and retrieval phases of Experiment 4. (Top left) The alpha power measured after the onset of each stimulus, sorted by whether participants subsequently remembered the item, from electrode PO4 with the dashed box showing the measurement window summarized with the inset bar graph. (Top right) The alpha power measured after the onset of the test stimulus, also sorted by the participants' responses. Error bar represents ±1 *SEM*. (Bottom center) The scalp distribution of the alpha power effect (i.e., the difference between anodal and sham alpha-power from high-confidence hits).

evidence showing an impact lasting hours of tDCS in learning experiments (Reinhart & Woodman, 2014, 2015; Reinhart et al., 2015a; Reinhart, Zhu, Park, & Woodman, 2015b) but, with this previous work, unable to pull apart whether it was encoding versus retrieval that was changing.

In Experiment 4, we recorded electrical brain activity (i.e., the EEG) from our human participants after tDCS to provide converging evidence for our conclusion that tDCS potentiates long-term memory encoding, but not retrieval, as predicted by the plasticity hypothesis. To this end, we had a group of participants participate in two sessions, one that began with 20 min of anodal tDCS delivered to one hemisphere and the other the sham baseline. If the plasticity hypothesis is correct, then we should see that the electrophysiological effects during encoding are changed by tDCS, but not retrieval-related activity measured during our memory task (i.e., Figure 1).

Replicating the behavioral findings of Experiment 1, we again found that anodal stimulation delivered to the temporal pole improved recognition memory performance, $F(1, 22) = 8.88$, $p = .01$, regardless of which hemisphere was stimulated (i.e., we observed neither a main effect of Hemisphere, $F(1, 22) = 0.01$, $p = .94$, nor an interaction of Stimulation condition × Hemisphere, $F(1, 22) = 0.89$, $p = .36$).

Consistent with the plasticity predictions, we found that encoding-related alpha-band oscillations were more strongly suppressed by tDCS, whereas the electrophysiological measures of retrieval were unchanged by the direct-current stimulation (see Figures 6 and 7). Previous work has shown that the suppression of alpha-band oscillations occurs after the onset of an item that is more accurately encoded into long-term memory (Fukuda & Woodman, 2015), and our findings here show that 20 min of anodal tDCS at 2.0 mA increases the strength of this suppression (Jones, Peterson, Blacker, & Berryhill, 2017; Choe, Coffman, Bergstedt, Ziegler, & Phillips, 2016; Spitoni, Cimmino, Bozzacchi, Pizzamiglio, & Di Russo, 2013), resulting in superior memory encoding measured behaviorally. Specifically, anodal stimulation resulted in deeper alpha power suppression after the presentation of a to-be-remembered picture.

The alpha-power measurements that we made after anodal and sham stimulation were entered into an ANOVA with the factors of Subsequent memory response (high-confidence hit vs. low-confidence hit vs. miss) and Stimulation condition (anodal vs. sham). This yielded a significant main effect of Response type, $F(2, 21) = 6.37$, $p = .01$, and a significant main effect of Stimulation condition, $F(1, 22) = 6.38$, $p = .02$. The interaction of these terms was not significant, $F(1, 22) = 0.305$, $p = .740$.

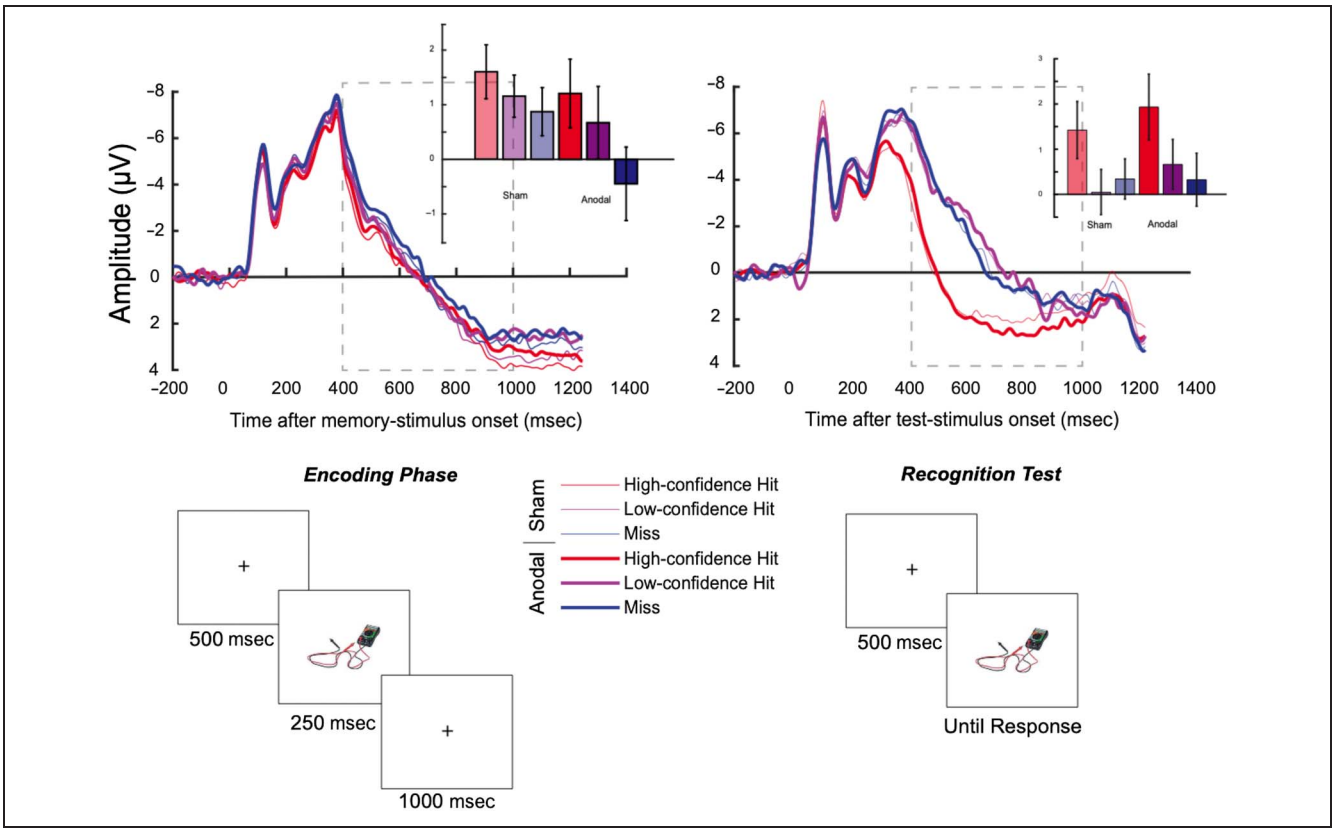

Figure 7. The frontal positivity (also known as the FN400 or frontal old/new effect) measured during the encoding and retrieval phases of Experiment 4, as illustrated with the bottom of the figure. (Top left) The ERPs measured after the onset of each stimulus, sorted by whether participants' subsequently remembered the item, from electrode Fz. (Top right) The ERPs measured after the onset of the test stimulus, also sorted by the participants' responses. Error bar represents the *SEM*.

To further characterize how alpha activity changed after anodal stimulation, we also analyzed the scalp distribution of the difference between anodal and sham stimulation (see Figure 6). Using Bonferroni-corrected paired t tests on activity at each electrode before and after stimulation, we found that stimulation significantly changed alpha-band power across electrodes P3, P4, PO4, C3, C4, Cz, and Fz. Moreover, we analyzed the entire time–frequency space to determine if frequencies other than those previously related to long-term memory encoding showed modulations by tDCS; however, we found these effects were confined to the alpha band (8–12 Hz).

During encoding, we saw that anodal stimulation increased the suppression of alpha-band activity. Demonstrating the selectivity of this effect, we found no modulation of the amplitude of the frontal ERPs associated with memory processes. Prior research has shown that, when a stimulus elicits a more positive frontal potential, that stimulus is remembered better than one that elicits a less positive potential (Fukuda & Woodman, 2015; Paller, McCarthy, & Wood, 1988). The amplitude of the frontal positivity after anodal stimulation and sham is shown in Figure 7. We found that our participants' frontal positivities were larger in amplitude for high-confidence hits, smaller for low-confidence hits, and smaller still for misses, replicating the known effects from the literature we just mentioned. However, we found that stimulation did not significantly change the amplitude of these potentials.

We calculated the mean voltage at electrode Fz from 400 to 1000 msec after the to-be-remembered stimulus onset (see Fukuda & Woodman, 2015). Next, we performed a repeated ANOVA with the factors of Subsequent response type (high-confidence hit vs. low-confidence hit vs. miss) and Stimulation condition (anodal vs. sham stimulation). This yielded a significant effect of Response type, $F(2, 21) = 5.63$, $p = .007$, because of more positive potentials for high-confidence hits than low-confidence hits or misses (see Figure 7). However, we did not observe a significant main effect of Stimulation, $F(1, 22) = 1.01$, $p = .325$, or Hemisphere, $F(1, 22) = 2.62$, $p = .120$, or an interaction of Response type × Stimulation, $F(2, 21) = 0.93$, $p = .403$, Stimulation × Hemisphere, $F(1, 22) = 0.65$, $p = .429$, Stimulation × Response, $F(2, 21) = 1.563$, $p = .221$, or Stimulation × Response × Hemisphere, $F(2, 21) = 0.74$, $p = .299$.

One alternative explanation for our findings that does not rely on us concluding that the plasticity of the tissue was modulated is that tDCS may have made retrieval more efficient (Crossman et al., 2019; Javadi & Cheng, 2013), despite the null results of Experiment 3 in which tDCS before retrieval did not change performance. If people could retrieve the right information from long-term memory more easily, this would improve memory-task performance, without changing the plasticity-dependent memory encoding process. To test this alternative explanation, we analyzed the EEG power and the ERPs elicited during retrieval.

In the time domain, the amplitude of the frontal positivity replicated prior work in that the high-confidence hits exhibited larger-amplitude frontal positivities than the items that were forgotten (i.e., misses, $F(2, 21) = 6.07$, $p = .008$; see Figure 7; e.g., Fukuda & Woodman, 2015). However, the frontal positivity did not change with anodal stimulation, $F(1, 22) = 0.09$, $p = .766$ (see Figure 7). Note that the absence of an effect on the test-phase frontal positivity is not incompatible with the encoding effects we saw in Figure 6. Instead, these findings fit together in that the enhanced processing during encoding elevated more representations into the high-confidence bin from the low-confidence and miss bins, such that more stimuli move into the superior memory group by the time activity was recorded at test. In the frequency domain, we found that the occipital alpha-band power replicated prior work with the high-confidence hits exhibiting stronger alpha-band suppression than the forgotten items, $F(1, 22) = 3.64$, $p = .043$ (see Figure 7; e.g., Fukuda & Woodman, 2015). However, alpha-band power measured during the retrieval phase did not change after anodal stimulation, $F(1, 22) = 0.507$, $p = .484$ (see Figure 7). Consistent with the predictions of the plasticity hypothesis and the findings of Experiments 1–3, we observed that anodal stimulation changed neural activity measured during encoding but did not change the neural signatures of memory retrieval recorded from our human participants.

DISCUSSION

Here, we tested the hypothesis that tDCS has long-lasting effects because of it modulating neural plasticity. Consistent with this hypothesis, we found that 20 min of anodal tDCS delivered to the temporal pole of the healthy human brain could improve encoding into visual long-term memory. The plasticity hypothesis also predicts that metrics of cognitive processing that do not require continuous learning of object properties should not show tDCS effects. We confirmed this prediction by showing that tDCS did not change the efficiency with which attention could select a target during visual search, a task that demands attentional selection and object recognition but only requires memory storage when participants are first learning what to look for (i.e., the first several trials; Carlisle, Arita, Pardo, & Woodman, 2011).

Our direct measurements of participants' brain activity provided further support for our conclusions. We found that the alpha-band signature of memory encoding was influenced by the application of tDCS, whereas retrieval-related activity was unaffected, as predicted under the plasticity hypothesis. We note that these findings also contribute to our understanding of the neural correlates of long-term memory encoding. Although previous work had identified multiple neurophysiological correlates of encoding into memory, we did not know whether these were indices of distinct neural mechanisms of encoding, although previous work has shown that the alpha-band

suppression and frontal positivity are uncorrelated (Fukuda & Woodman, 2015). The present findings provide causal evidence that the frontal ERPs measured during encoding and the posterior alpha activity index distinct neural processes during the time that encoding into long-term memory is occurring. On the basis of existing findings in the literature, it appears that the suppression of alpha after stimulus onset may be critical in establishing high-fidelity memory representations. One way this may come about is by filtering out distracting information so that memory consolidation is focused on task-relevant representations (Hakim, Adam, Gunseli, Awh, & Vogel, 2019; Wang, Rajsic, & Woodman, 2019; Klimesch, 2012). This would suggest that encoding into long-term memory was improved by consolidation being better focused on the stimuli, resulting in higher fidelity representations of the objects. This explanation will be tested in our future work.

A recent study of patients with epilepsy found that stimulation of the lateral temporal cortex could improve declarative memory in patients, but only if the brain of the patients was in the right state when stimulation was delivered (Ezzyat et al., 2018). Another study with aging adults suggested that stimulation needed to be delivered at a specific frequency for noninvasive stimulation to improve human memory (Reinhart & Nguyen, 2019). Given these findings, it seemed unlikely that simple, tonic anodal tDCS could systematically improve memory, unless the plasticity hypothesis was correct. Our findings indicate that anodal tDCS applied to the temporal lobe changes the state of the tissue, making it more modifiable by experience. These findings have the important implication that patients with memory disorders should stand to gain the most from the application of this type of noninvasive stimulation.

Controversy has followed the development of tDCS methods for cognitive enhancement, similar to all neuroscientific methods in their infancy (Walter, 1938). Specifically, some researchers have proposed that tDCS rarely results in modulations of cognitive processing (Horvath, Forte, & Carter, 2015). On the basis of the findings from this study, we suggest that a number of these seeming failures may be consistent with the biophysical changes that underlie the long-lasting effects of tDCS. That is, the present findings suggest that it should not be possible to modulate a cognitive process that does not rely on plasticity-dependent learning. For example, anodal stimulation over ventrolateral pFC was shown to improve memory for word lists only if the stimulation was applied before the memory encoding phase (Medvedeva et al., 2019). Similarly, anodal stimulation can improve source memory for experimentally presented words (Westphal et al., 2019) and associative memory with face–name pairs (Leshikar et al., 2017) when delivered before encoding, whereas relatively automatic processes like risk-taking and mood are not consistently modulated by tDCS (Tremblay et al., 2014). Consistent with the plasticity hypothesis supported by the present experiments, tDCS appears to increase functional connectivity in neuroimaging studies (Antonenko, Hayek, Netzband, Grittner, & Flöel, 2019; Yu, Tseng, Hung, Wu, & Juan, 2015).

The present findings might be explained with a slightly more general phenomenon than a direct modulation of synaptic plasticity. Specifically, tDCS researchers have proposed that transcranial electrical stimulation has its effects by modulating the balance of excitatory and inhibitory neurotransmitter available in stimulated regions of the brain. Specifically, spectroscopy studies indicate that tDCS is followed by local reductions in gamma-aminobutyric acid, whereas cathodal stimulation is followed by local reductions in excitatory glutamate in the extracellular matrix (Krause, Márquez-Ruiz, & Cohen Kadosh, 2013). Under this view, learning is a state in which the brain needs more glutamate than gamma-aminobutyric acid to encode new memories, with tDCS setting just such conditions to favor memory encoding.

Our findings support the plasticity hypothesis, but clearly, additional tests of this hypothesis are necessary. For example, it is possible that both the memory improvement and the alpha suppression at encoding point toward a perceptual fluency explanation. That is, existing research suggests that memory improvements can come via more fluid front-end processing of the to-be-remembered information (Jacoby & Dallas, 1981), and a set of previous tDCS effects are consistent with a perceptual fluency explanation (Juan, Tseng, & Hsu, 2017; Tseng, Chang, Chang, Liang, & Juan, 2016; Hsu, Tseng, Liang, Cheng, & Juan, 2014; Tseng et al., 2012). We believe that this is a viable variety of the plasticity hypothesis to test. We also note that our test of the plasticity hypothesis underlying tDCS did not systematically explore multiple areas of the brain, and it is possible that another region of the brain might show tDCS effects that do not conform to the predictions of the plasticity hypothesis. However, we do note that our study is unique in the literature in that it systematically tested a hypothesis regarding the biophysical changes in the brain that underlie tDCS using multiple tasks and multiple measures of brain activity. Thus, although preliminary, the present findings are consistent with the plasticity hypothesis of tDCS and suggest that plasticity-dependent cognitive processes may be those that can be modified by this type of brain stimulation.

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Woodman: Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Validation; Writing - Review & editing.

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Note

1. We note that an optimal design would compare performance in memory and visual search tasks using identical stimuli. That is, perhaps if people were searching for a specific picture of a real-world object, we would see impaired performance. However, this stimulus-based proposal does not explain findings in the literature suggesting that it is possible to manipulate attention mechanisms with tDCS, although we are not aware of an article that has been able to change the rate that people could search an array of objects (see Sung & Gordon, 2018; Reinhart & Woodman, 2015).

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