

Investigating the brain regions involved in tDCS-Enhanced category learning using finite element modeling

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ABSTRACT

Transcranial direct current stimulation (tDCS) influences performance in many cognitive domains. However, the question of which brain networks are involved in these effects is rarely examined. In prior experiments we identified tDCS protocols that produce a large improvement in category learning. Here we examined which brain regions were involved by modelling and comparing the behavioral effects of different electrode placements. In Experiment 1, we placed electrodes at two cephalic sites found to be most effective in our prior studies (F10 and T5/P7), expecting an increased combined effect. However, no effect was found, suggesting that stimulation of additional far field regions using extracephalic electrodes in our prior studies may have been necessary for producing these effects. In Experiment 2, we used finite element modeling (FEM) to compare the E-fields produced by these montages. One region with large differences and that is accessible to tDCS was the cerebellum. We then tested the involvement of the cerebellum by placing electrodes below the inion vs. the left arm in thirty-six participants who received anodal, cathodal, or sham stimulation during training. Neither anodal nor cathodal cerebellar tDCS led to significant changes when compared with sham. These results suggest that neither far-field stimulation of the cerebellum nor nearby cranial nerves played a large causal role in our previous tDCS studies. To our knowledge, this one of the first studies to systematically compare the behavioral and energetic effects produced by different montages to identify the specific brain regions involved in the behavioral responses to tDCS.

1. Introduction

Transcranial direct current stimulation (tDCS) has emerged as an inexpensive, safe, and effective way to exogenously modulate brain activity by increasing or reducing neuronal excitability (Nitsche and Paulus, 2000). The flexibility of tDCS as a potential experimental and therapeutic tool is evident in the breadth of domains to which it has been applied (Polanía, Nitsche, & Ruff, 2018). TDCS has been used in numerous clinical and research settings (Manenti et al., 2012; Nitsche et al., 2009; Kekic et al., 2016; Dedoncker et al., 2016), including the

enhancement of cognitive function (Coffman et al., 2014). In a series of experiments, we showed that anodal tDCS of either right prefrontal cortex or right parietal cortex during training to perform a complex category learning task leads to a 2-4x increase in performance gains ($d = 0.8-1.8$) compared to sham (Clark et al., 2012; Coffman et al., 2012a, 2012b; Gibson et al., 2020). This effect was later replicated by a semi-independent study, which further showed that this effect lasts up to 24 h after stimulation (Falcone et al., 2012), and has been linked to local changes in cortical N-Acetyl Aspartate (NAA) and glutamate/glutamine (Glx) concentrations (Clark et al., 2011), as well as altering activation at

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the network level (Hunter et al., 2015). These effects have largely been characterized as evidence of increased excitability of right-lateralized frontoparietal control systems in the brain, given relationships observed between effects of tDCS on learning and increase in alerting-network measures from the Attention Network Task (ANT) (Coffman et al., 2012b). However, we also found that cathodal tDCS of left temporoparietal cortex also led to enhancement of learning in this task with a similarly large effect size ($d = 1.28$; Clark et al., 2013; see Fig. 1). Category learning has been shown to recruit numerous brain regions, including medial temporal lobe, visual processing areas, and frontal cortex (Aizenstein et al., 2000). Learning to categorize stimuli also has been shown to increase activity in right prefrontal areas (Reber et al., 2003), as well as decrease activity in occipital areas with training (Little et al., 2004). Given the spatial disparity between these stimulation targets, we sought to identify common areas of electric field alterations among the tDCS protocols used for these stimulation targets.

Computational models of tDCS current flow are useful for increasing electrode placement precision and optimizing the electric field distribution (Ciechanski et al., 2018; Rezaee and Dutta, 2019; Unal et al., 2020). To accomplish this, conductivity is modeled for individual tissue types identified within high-resolution structural (T1) magnetic resonance images (MRI), with special attention paid to tissue boundaries with large contrast in electrical resistance (e.g., the inner/outer skull). While the precision of tissue segmentation depends on the resources available and the ultimate aims of a given tDCS application, segments of 1 mm^3 are typically used, allowing for high fidelity modeling of individual brain physiology including gyri and sulci topography (Bikson et al., 2012). Following segmentation, tissue types are assigned resistivity values, which are added to boundary conditions that reflect the physical properties of the electrodes and the specific stimulation intensity to be administered, resulting in meshes with greater than 10 million finite elements (Bikson et al., 2012). Experimental protocols have been improved by computational models (Bestmann and Ward, 2017), such as the finding that the largest current density magnitude is produced between, rather than directly underneath, electrodes (Datta et al., 2009). In addition, recent *in vivo* electrical recordings recorded in epilepsy patients have confirmed the relative accuracy of forward models, demonstrating an $r = 0.81 \pm .12$ between the spatial

distribution of the recorded currents and those predicted by forward computational models (Huang et al., 2017).

While our limited imaging data suggests a local effect close to the cephalic electrode, other brain regions may also be involved in the response, through direct effects of the electrical fields produced by tDCS when using an extracephalic electrode. To better understand the contribution of different neural fields induced by tDCS for enhanced category learning, the present study conducted two experiments. For Experiment 1, we hypothesized that stimulating the union of effective placements (i.e., combining the most effective anodal and cathodal cephalic placements together) would combine and enhance their respective cortical effects reported in previous studies (see Fig. 1). We tested this by placing the anode over F10 and the cathode over T5/P7, with the hypothesis that this tDCS montage would potentially produce an additive effect, resulting in an enhancement of their effects on learning. We also conducted a series of finite element models (FEMs) to determine predicted electric field effects under various montages. Based on the modeling results, Experiment 2 targeted the cerebellum directly as it showed a predicted effect under both successful mono-cephalic montages. We hypothesized that verum stimulation at one site (cerebellum) identified as an intersection of successful montages by FEM would lead to improved learning compared to sham stimulation in this visual category learning task. Based on previous findings investigating the cerebellum as a target for tDCS, we hypothesized that tDCS over the cerebellum would lead to an increase in learning compared to sham stimulation. Based on the FEM results, both anodal and cathodal stimulation was applied over the cerebellum.

2. Experiment 1: F10 anode vs. T5/P7 cathode

2.1. Methods

2.1.1. Participants

All participants met the following criteria: English as a first language, no history of head injury with loss of consciousness for longer than 5 min, right-handedness according to the Edinburgh Handedness Inventory (Oldfield, 1971), no history of neurological or psychiatric disorder, no history of alcohol or drug abuse, not currently taking any

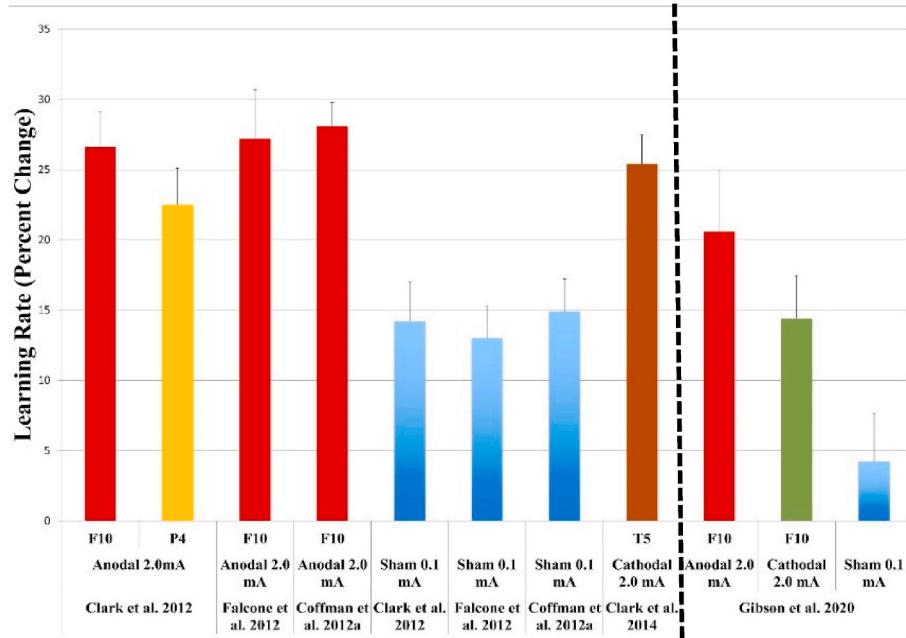


Fig. 1. A summary of studies using the threat category learning paradigm (left of dashed line) and non-threat category learning (from Gibson et al., 2020; right of dashed line) showing large effects for the F10 anode placement, as well as the T5/P7 cathode placement, compared to sham. Colors indicate stimulation condition: red for anode F10, yellow for anode P4, Brown for cathode T5/P7, green for cathode F10, and blue for sham. Error bars = $\pm 1 \text{ SEM}$.

medication affecting the central nervous system, no implanted metal, no sensitivity or allergy to latex, and good or corrected hearing and vision. Women who were or thought they may be pregnant were excluded.

A total of 48 participants (23 female, mean age = 21.4 years, 4.51 SD) were recruited to take part in the study. All were undergraduate students who received classroom credit for their participation. This, and all subsequently described studies were approved by the University of New Mexico's Institutional Review Board. After providing written informed consent, participants completed a demographic questionnaire, the Edinburg Handedness inventory (Oldfield, 1971), a brief personality inventory consisting of 12 short questions, and a mood questionnaire. The mood questionnaire included items related to nervousness, excitement, tiredness, confusion, sadness, degree of frustration, dizziness, nausea, degree of physical pain or discomfort, and ability to pay attention, and this questionnaire was administered before and after the experiment to assess tDCS-related changes in mood.

2.1.2. Experimental procedure

Participants were seated in front of a computer screen and given brief instructions about the goal of the task (to detect hidden items that indicate threats in the environment) but were not given specific information about the nature of the hidden objects nor any strategies with which to find them. They were instructed that they could stop the task at any time if the stimuli were too uncomfortable or made them anxious. A total of 10 experimental sessions were completed, lasting approximately 72 min: 2 baseline sessions (6 min each) with no feedback were completed, followed by 4 training sessions with audiovisual feedback regarding the consequence of their decision, giving them an indication of accuracy (12 min each). After training, 2 immediate test sessions (6 min each, no feedback), and 2 1-h delayed test sessions (6 min each, no feedback), which were separated from the immediate test by 1 h, were completed. Half of the testing images were repeated from training images, thus memory for trained images and the generalization of training to novel images could be examined. For a detailed description of the task and procedure, see Clark et al., 2012; Coffman et al. (2012a); Coffman et al. (2012b).

2.1.3. tDCS

Two 3.3 cm × 3.3 cm (11 cm²) electrodes with saline-soaked sponges were affixed to the participants using Coban adhesive bandage. The anode electrode was centered at 10–20 location F10, and the cathode electrode was centered at 10–20 location T5, also known as P7. Stimulation was delivered for 30 min during training blocks 1 and 2 via two ActivaDoseII Iontophoresis units connected to a custom-made 6-way switch box, through which either the verum (2.0 mA) or sham (0.1 mA) dose was passed. The switch codes were unknown to both the experimenter and participant, thus creating a double-blind experimental design identical to one effectively employed in prior tDCS studies with similar stimulation parameters (Clark et al., 2012; Coffman et al., 2012a; Falcone et al., 2012). Physical sensations at the electrode sites were recorded three times during tDCS administration: once after current ramp-up (approximately 1 min), 4 min following ramp-up and before the first training run began (approximately 5 min after stimulation had begun), and immediately following the first training run (approximately

17 min after stimulation had begun). Participants were asked to rate three different types of sensations (itching, heat/burning, and tingling) on a 0–10 Likert scale, where 0 indicated no feeling of sensation and 10 indicated the most intense feeling of sensation. Any sensation rating of a seven or above resulted in immediate cessation of stimulation and termination of the experiment, without penalty to the participant. Please see Fig. 2 for a timeline of the experimental procedure.

2.1.4. Data analysis

Data were analyzed within an ANOVA framework, comparing two groups (anode verum from the present study, and n = 23 with 0.1 mA sham previously reported in Clark et al., 2012). Data were inspected for normality and outliers, all variables were normally distributed, and no outliers were identified. Greenhouse-Geisser correction was used in the interpretation of within-subject effects if sphericity was violated and all pairwise comparisons were Bonferroni-corrected. For analysis of learning over time in the category learning task, three dependent variables were calculated and used in a 3x2 repeated measures ANOVA (time (within subjects; baseline, immediate test, 1-h delayed test) x condition (between subjects; (verum, sham)), including the following variables: (1) baseline test performance, (2) immediate test performance, and (3) 1-h delayed test performance. Training performance was not entered into this analysis. For analysis of group effects two learning scores were calculated (1) immediate learning, which was the difference between the immediate test and baseline test, and (2) 1-h delayed learning, which was the difference between the 1-h delayed test and baseline test. These learning scores were entered into one-way ANOVAs separately, for a total of 3 ANOVAs run. All analyses were performed in IBM SPSS Statistics (version 22.0).

2.1.5. Finite element modeling

The modeling procedure implemented here is the same as that used elsewhere previously by (Seibt et al., 2019). Segmentation of an exemplary magnetic resonance imaging (MRI) scan of a template human head into six tissue masks namely scalp, fat, muscles, skull, cerebrospinal fluid (CSF), gray matter, white matter, and air was performed using Simpleware software (Synopsys Inc, CA, USA) to develop a high-resolution (1 mm³) MRI derived FEM model. Computer aided design (CAD) models of electrodes with exact dimensions (from experiment) were first modeled in designed in Solidworks 2016 (Dassault Systems Americas Corp., MA, USA), imported into the human head model, and positioned over the respective brain region as per the montages. We generated an adaptive tetrahedral mesh using built-in voxel-based meshing algorithms in Simpleware. The mesh density was refined until additional model refinement produced less than 1% difference the voltage and current density at the brain (gray matter). The resulting volumetric meshes were later imported into COMSOL Multiphysics 5.1 (COMSOL Inc., MA, USA) to computationally solve the model. For each model domain, we assigned the following electrical conductivity values based on prior literature: scalp: 0.465 S/m; fat: 0.025 S/m; muscles: 0.16 S/m; skull: 0.01 S/m; CSF: 0.85 S/m; gray matter: 0.276 S/m; white matter: 0.126 S/m; air: 1x10⁻¹⁵ S/m; electrode: 5.99x10⁷ S/m (Bikson et al., 2015). A quasistatic approximation was implemented for electrical stimulation (Laplace equation ($\nabla \cdot (\sigma \nabla V) = 0$, where V is potential and σ

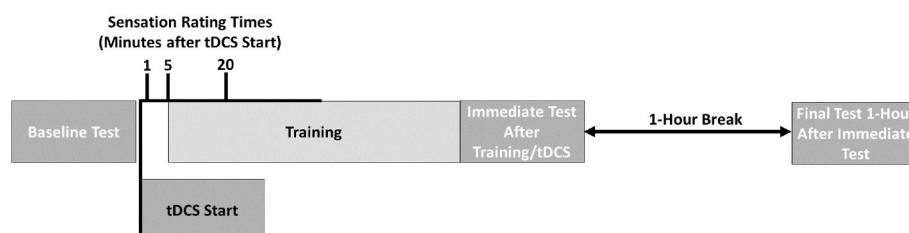


Fig. 2. Experimental procedure timeline for both Experiment 1 and Experiment 2.

is electrical conductivity), and the boundary conditions were applied as normal current density (inward current flow: J_{norm}) at the top exposed surface of anode electrode (2 mA) and ground at the top surface of return electrode (0 mA) to represent different head montages. The other remaining external surfaces of the model were electrically insulated. The final FEM head assembly had $>30,000,000$ tetrahedral elements. To improve the solution accuracy, we set the relative tolerance to 1×10^{-6} . Electric field was calculated for each montage, including F10 vs. left arm, P4 vs. cathode, T5/P7 vs. right arm, F10 vs. T5, and cerebellum vs. left arm, to illustrate the distribution of field intensity across the brain tissues.

2.2. Results

2.2.1. Effects of tDCS on learning

The results for Experiment 1 with F10 anode and T5/P7 cathode suggest a main effect of time $F_{(2,92)} = 54.844$, $p = 2.08 \times 10^{-16}$, but no time*task condition interaction, or between subjects effect of stimulation condition was observed (see Fig. 3). One-way ANOVAs comparing learning scores between verum and sham stimulation revealed no significant effect for immediate learning ($F_{(1,47)} = 0.410$, $p = 0.525$) or 1-h delayed learning ($F_{(1,47)} = 1.443$, $p = 0.236$). Effect sizes (Cohen's d) for immediate and 1-h delayed learning were $d = 0.21$ and $d = 0.40$ for immediate and 1-h delayed learning, respectively (see Fig. 4). The F10/T5 placement showed an effect on learning that was much smaller than the previously reported mono-cephalic montages.

2.2.2. Finite element modeling results

Results from the current and previously used electrode montages suggest that F10/arm, P4/arm, and T5/arm placements all predicted electric field effects located in multiple brain regions. Specifically, electric fields were most apparent in the cerebellum and left occipital cortex. This was the case for the F10 anode montage (the most successful behavioral montage; Fig. 4 left), as well as for the P4 anode montage, and the cathode T5 montage, a field effect was predicted in the cerebellum. However, the bi-cephalic montage in Experiment 1 produces relatively small fields in the cerebellum (see Fig. 5 right for comparison).

Current modeling of the cerebellar montage revealed a similar, albeit reduced predicted field effect in the cerebellum compared to the F10 montage (see Fig. 6 for comparison). These data led us to hypothesize a causal role for the cerebellum in improvement on the threat detection task, which was tested in the second experiment by directly stimulating the cerebellum during training with both anodal and cathodal tDCS.

Given the lack of evidence of an additive effect, or any significant behavioral effect of verum tDCS compared to sham with this montage, FEM was utilized as a tool to investigate the predicted field effects under

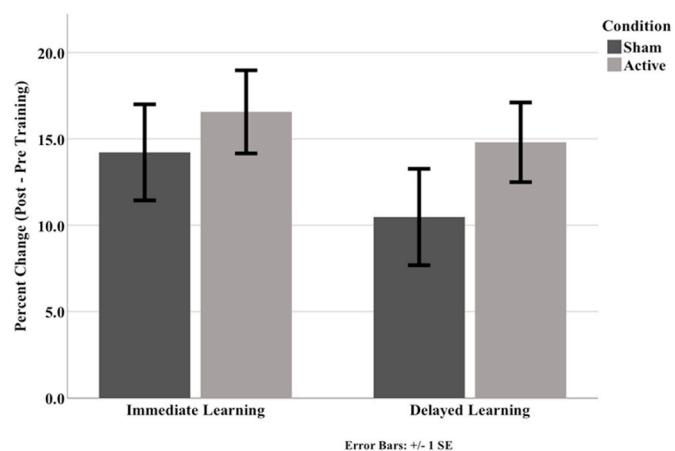


Fig. 4. Immediate and 1-h delayed learning in the category learning task. There were no significant effects of verum tDCS on either learning measure compared to sham. Error bars denote ± 1 SEM.

various montage configurations. We aimed to then use the results from these models to target additional cortical areas with tDCS based on the FEM predictions.

3. Experiment 2. cerebellar tDCS

3.1. Cerebellar tDCS background

Several studies have investigated the effect of cerebellar tDCS on cognitive processes, though none have examined the effects on learning a complex visual category learning task (like that first used in Clark et al., 2012). In the last few decades, an increasing number of studies have emerged regarding the role of the cerebellum in higher order cognition (Maldonado et al., 2019; Mannarelli et al., 2019; for review, see Schmahmann, 2019).

The cerebellum has direct topographic connections with several cortical areas, including sensorimotor, temporal, dorsolateral, and medial prefrontal cortices (Dolan, 1998; Leiner et al., 1994). The cerebellum has also been implicated in the encoding of performance errors (Popa et al., 2014) and other cognitive functions, including language, learning, and working memory (Desmond and Fiez, 1998), as well as visuo-motor learning and error correction (Flament et al., 1996) and associative learning (for review, see Stoodley et al., 2012; Timmann et al., 2010).

Some studies investigating anodal tDCS targeting the cerebellum found no effect of stimulation compared to sham (Ballard et al., 2019; Ferrucci et al., 2019; Mannarelli et al., 2019; Seyed Majidi et al., 2017; Verhage et al., 2017), while Miall et al. (2016), found a better performance in the anodal group for linguistic prediction which was in line with their hypothesis that anodal tDCS would facilitate linguistic prediction. Their investigation also suggests that cathodal stimulation had a degrading effect or no effect depending on the type of task. Other studies investigating cathodal tDCS in cognitive function, also presented mixed results that could be dependent on task complexity, electrode size and placement, as well as ceiling effects. A study conducted by Maldonado et al. (2019) investigating the effects of cathodal HD-tDCS and performance on attention did not find an effect as initially predicted. On a verb generation task (Spielmann et al., 2017) found no direct (short-term) contribution of cathodal stimulation over the cerebellum, but their results demonstrated less improvement in the cathodal group after a week suggesting that cathodal stimulation could have long-term effects. Activity in the cerebellum is reduced after practice of a task or when the task is learned, suggesting that the cerebellum may be involved in the learning process itself (Friston et al., 1992; Kelly, 2004; Raichle et al., 1994; Vaina et al., 1998). The cerebellum is directly accessible via tDCS

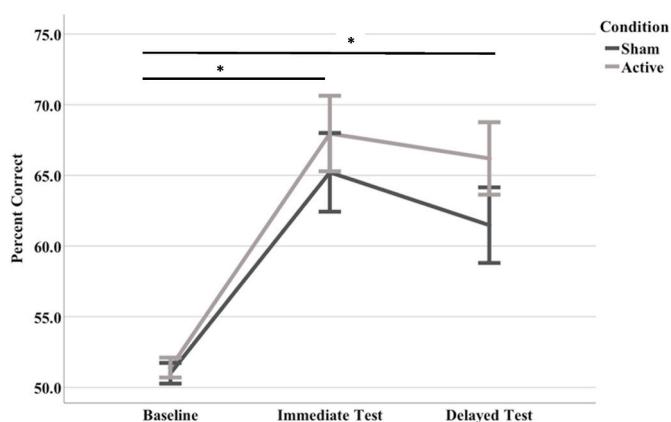


Fig. 3. Percent correct performance over time. A significant main effect of time was observed, however, no significant effects for immediate or 1-h delayed tests were observed. * = $p < 0.05$. Error bars denote ± 1 SEM.

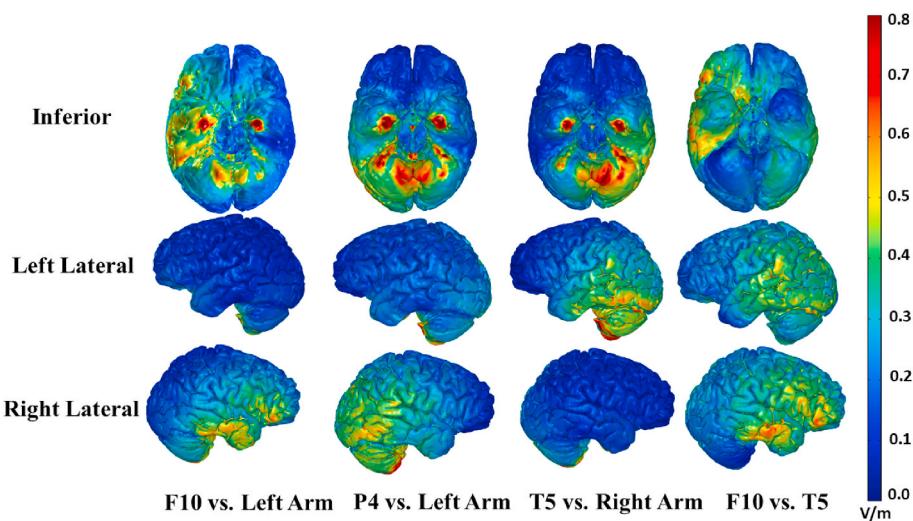


Fig. 5. FEM of electrode placements used in previous studies (left 3 columns), and experiment 1 of the current study (rightmost columns). The first row shows an inferior view for each montage. The second row shows a left lateral view. The third row shows a right lateral view. Note that behavioral effects of tDCS were observed in the first three montages, but not in the fourth.

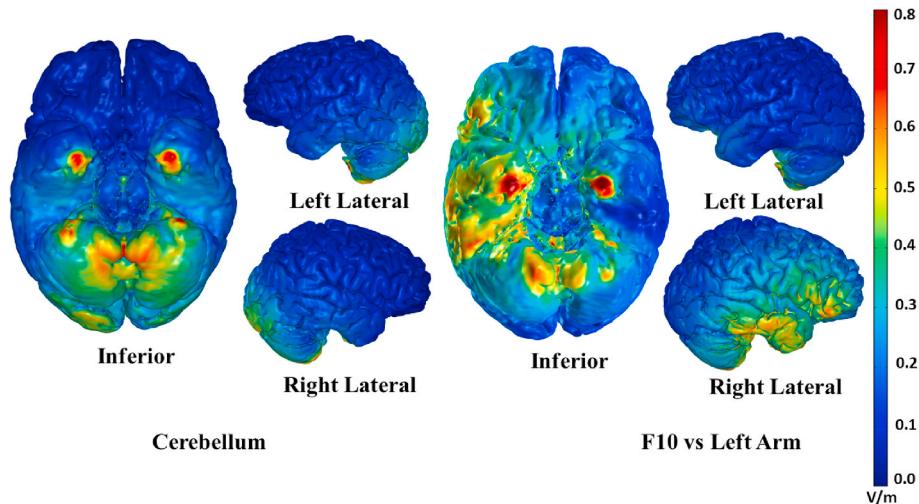


Fig. 6. Finite element models of cerebellar tDCS (left) compared to F10 (right). Larger images are inferior views for each montage. The smaller images are left and right lateral views on top and bottom, respectively.

and stimulation of the cerebellum is known to produce behavioral effects, however the extent to which this area is highly involved in cognitive task remains not well-understood (Maldonado et al., 2019), and stimulation over the cerebellum has led to inconsistent results. Anodal and cathodal stimulation of the cerebellum impaired performance on a working memory task (Ferrucci et al., 2008). Anodal and cathodal stimulation over the right cerebellar hemisphere showed no performance improvement on an N-back task (van Wessel et al., 2016). However, Pope & Miall (2012), showed that cathodal cerebellar stimulation improved performance on an extremely difficult frontal lobe task. Finally, Ferrucci et al. (2012), showed that both anodal and cathodal stimulation of the cerebellum lead to an increased ability to identify negative facial expressions. The mixed results thus far reported could be the result of timing of tDCS, timing of measurements, and, but not limited to, the complexity of the task (for review, see van Dun et al., 2017), or even the polarity-specific effects of cerebellar tDCS (Ballard et al., 2019). The placement of the electrodes can also be a factor associated with the effects of stimulation. However, an optimal placement can be challenging due to the tightly folded layers of the cerebellum and the high conductivity of the cerebrospinal fluid (CSF; Rezaee

and Dutta, 2019).

3.2. Methods

3.2.1. Participants

Criteria for inclusion/exclusion were the same as experiment 1. A total of 36 participants (21 female, mean age = 21.22 years, 5.29 SD) were recruited to take part in the study. All were undergraduate students who received classroom credit for their participation. Participants were randomly assigned to one of three equally sized groups, each with electrodes placed over the cerebellum and left arm: (1) anodal tDCS, (2) cathodal tDCS, or (3) sham tDCS. One participant from the sham group was excluded because of a mean score on the baseline test variable that was greater than three SD from the group mean. Thus, a total of 35 participants (14/21 males/females; mean age = 21.29; SD = 5.35) were included in the overall category learning analyses. Of these, 12 received verum stimulation with the anode placed over the cerebellum, 12 received verum stimulation with the cathode placed over the cerebellum, and 11 received sham stimulation.

3.2.2. tDCS

tDCS procedures were identical to Experiment 1 with the following exception. One electrode was centered 2 cm inferior to the inion along the midline, and the other electrode was placed on the upper left arm. All other procedures were identical to Experiment 1.

3.2.3. Data analysis

Data were analyzed within an ANOVA framework, comparing three groups (anode verum, cathode verum, and sham). For analysis of learning over time in the category learning task, three dependent variables were calculated and used in a 3x3 repeated measures ANOVA (within subjects, time (baseline, immediate test, 1-h delayed test) x between subjects, condition (verum anode, verum cathode, sham)). All other procedures and variables were identical to Experiment 1.

3.3. Results

3.3.1. Effects of cerebellar tDCS on learning

The results for Experiment 2 suggest participants were able to learn the task, as a significant overall effect of time ($F_{(1.2722, 40.688)} = 61.399, p < 0.0001$) was observed. However, no effects of group ($F_{(2,32)} = 0.112, \text{ns}$) or time x group ($F_{(2.543, 40.688)} = 0.835, \text{ns}$) were observed. Simple effects testing was conducted because one of our primary hypotheses was to evaluate the difference between groups in performance from baseline to immediate and 1-h delayed learning even though the time x group interaction was not statistically significant. Bonferroni-corrected pairwise comparisons showed a significant increase in performance across groups from baseline for both immediate (mean difference = 0.180, $p < 0.0001$, 95% CI [0.127, 0.233]) and 1-h delayed (mean difference = 0.153, $p < 0.0001$, 95% CI [0.102, 0.203]) tests. There was a significant decrease in performance across groups between the immediate and 1-h delayed tests (mean difference = -0.027, $p = 0.011$, 95% CI [-0.049, -0.005]; see Fig. 7).

Although there was not a significant group x time interaction, we examined planned post-hoc comparisons between tests within each group. The anodal and sham tDCS groups did not show a significant difference in performance from the immediate to 1-h delayed tests ($p > 0.10$), the cathode group displayed a significant decrease in performance ($p = 0.002912$). A one-way ANOVA was performed to investigate the effect of group on immediate and 1-h delayed learning. Results suggest no effect of stimulation on immediate learning ($F_{(2,34)} = 0.219, \text{ns}$) or on 1-h delayed learning ($F_{(2,34)} = 0.847, \text{ns}$; see Fig. 8) compared to sham. For immediate learning, effect sizes (Cohen's d, adjusted for unequal group size) were 0.17 and 0.27 for the anode and cathode groups,

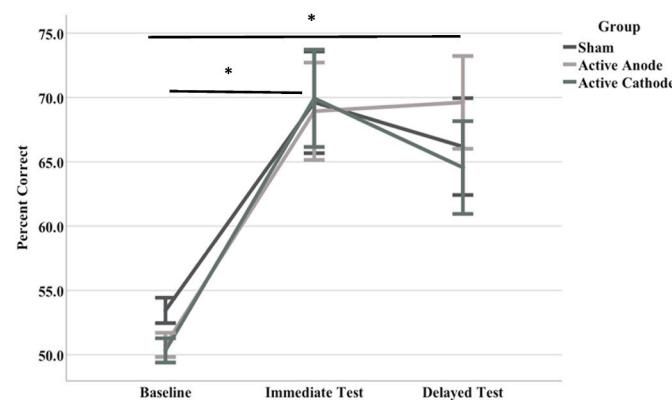


Fig. 7. Overall performance on the category learning task using cerebellar stimulation. Performance was significantly improved in both the immediate and 1-h delayed tests compared to baseline; however no significant effect of group was observed. Note that while performance declined from immediate to 1-h delayed test for both cathode and sham groups, no such effect was observed for the anode group. * = $p < 0.05$. Error bars denote $\pm 1 \text{ SEM}$.

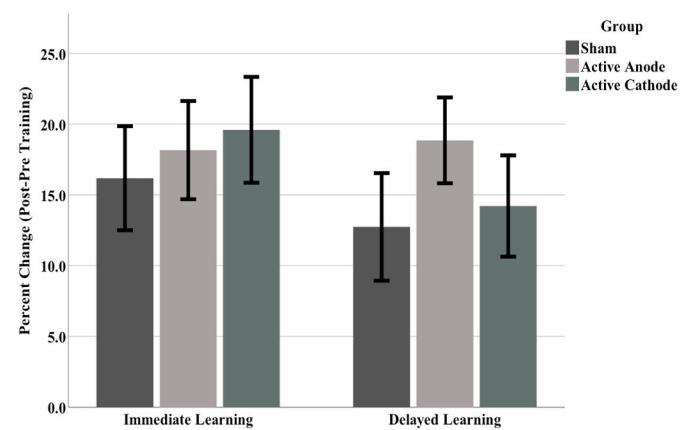


Fig. 8. Immediate and 1-h delayed learning. The black, dark gray, and light gray bars represent the sham, anode, and cathode groups, respectively. No significant group differences were observed in either immediate nor 1-h delayed learning. Error bars represent $\pm 1 \text{ SEM}$.

respectively. For 1-h delayed learning, effect sizes were 0.53 and 0.12 for the anode and cathode groups, respectively. Contrast tests revealed no significant differences between any two groups on either measure. To investigate experimental blinding, participants were asked at the end of the experiment to guess if they had been assigned to the verum or sham condition, and then a chi-square test was run on these responses. Participant blinding appeared to be accomplished, as evidenced by a non-significant ($\chi^2_{(1)} = 0.287, \text{ns}$) result from this test, suggesting that the group to which participants thought they were assigned, and their actual assignments, were independent.

4. Discussion

The present study investigated the effects of targeted tDCS on category learning. To our knowledge, this is one of the first studies to systematically compare tDCS montages and their corresponding electric fields on anatomical regions distant from tDCS electrodes. Moreover, the present study identified brain regions likely involved in a behavioral response to tDCS and used this information to guide electrode placement.

Our prior experiments showed that when the anode electrode was placed at position F10 (right inferior frontal gyrus), and the cathode on the left arm, or when the cathode was placed at position T5/P7 (left temporal-occipital area) and the anode on the left arm, a large effect was found on performance of a category learning task. In Experiment 1, we combined these two cephalic electrode placements (F10 anode vs. T5/P7 cathode), expecting a large effect, but instead found that there were no effects of this tDCS protocol on category learning. One interpretation of this unexpected finding is that the use of one extracephalic lead on the arm may have been critical to the large behavioral effects observed from both tDCS protocols previously. Those results led to an investigation of the electrical current distributions imposed by these different montages using finite element modeling. The results of this investigation predicted an electric field effect in the cerebellum and spinal cord for each montage for which there was a significant behavioral response to tDCS, but not in the montage for Experiment 1. Thus, Experiment 2 aimed to test the hypothesis that the cerebellum or spinal cord was involved in enhancing performance on this task, and that performance could be improved by stimulating the cerebellum directly.

The results of Experiment 2 suggest that the cerebellum and/or spinal cord are not significantly involved in performance of the category learning task used here. We therefore conclude that verum stimulation (either anodal or cathodal) over the cerebellum does not significantly affect performance on this task compared to sham. Several other possibilities are suggested by the FEM. One is that the tDCS effects

previously reported could be due to a complex interaction within and across a variety of brain networks and does not result from changes in activity any single brain region (Miall et al., 2016). Alternatively, one or a small number of regions may be responsible for these effects. One possibility are the medial and inferior portions of the temporal lobes, which were also observed in our FEM modelling but were relatively unaffected by the cerebellar-targeted montage. Our prior findings across studies of enhanced performance when images repeated from training are presented, relative to novel images (Coffman et al., 2012a), which is consistent with the functional characteristics of these brain regions in long-term memory encoding. This effect might be expected to be mediated by medial temporal lobe networks.

Computational modeling currently relies on a stimulation-dependent account of tDCS effects that conceives of the stimulated brain as passive (Fertonani and Miniussi, 2017; Schroeder and Plewnia, 2017). As such, brain tissue is subject only to the broadly inhibitory influence of cathodal stimulation or the excitatory influence of anodal stimulation. While this model has driven much of the tDCS research over the past few decades, it has become clear that new theories of tDCS effects are needed (Au et al., 2017; Harty et al., 2017; Jacobson et al., 2012; Schroeder and Plewnia, 2017; Tremblay et al., 2014). In modeling studies, the “quasi-uniform assumption” (Bikson et al., 2012) is the theoretical derivative of the stimulation-dependent account, and its assumption is that tDCS current flow and tDCS effect are interchangeable. This assumption is the result of the realization that, currently, we do not know enough about the *in vivo* effects of tDCS to proffer more nuanced predictions. As a subthreshold neuromodulator (Radman et al., 2009) that alters membrane potential without eliciting action potentials (Bindman et al., 1964; Creutzfeldt et al., 1962), endogenous neuronal activity is thought to account for much of tDCS’ effects, and yet current modeling techniques are unable to account for the ongoing, dynamic activations of the brain.

A few prior studies of cerebellar tDCS used larger electrodes (Nitsche et al., 2009; Ferrucci et al., 2008, 2012), or lateralized electrode placements (Boehringer et al., 2013; van Wessel et al., 2016; Pope & Miall, 2012) allowing for more complete coverage of lateral areas of the cerebellum than obtained in the current study. The lateral cerebellum is thought to contribute to higher-order cognitive functions and have denser connections with frontal areas (Stoodley and Schmahmann, 2010) when compared to medial cerebellum, which has dense connections to motor cortex (Coffman et al., 2011) as well as prelimbic ventromedial prefrontal cortex (Watson et al., 2014). Future investigation could be conducted using similar setups during the category learning task. Targeting the temporal lobe directly is an important next step for this line of research. Along with the cerebellum, FEMs suggest that more effective tDCS protocols exert stronger electric fields in this area. It is reasonable to hypothesize that medial temporal cortex may be involved in this perceptual learning task. In addition, prior studies suggest that tDCS over the temporal lobe improves visual memory (Boggio et al., 2008, 2012; Chi et al., 2010).

While computational models have informed and improved tDCS methodology (Bestmann and Ward, 2017), they are only able to provide a provisional account of the biophysical properties underlying any tDCS induced electric field on brain anatomy, and not the accompanying behavior itself. Indeed, some of the successes of computational modeling come with caveats. While the spatial accuracy of modeling studies has been supported, the amount of current reaching specific brain areas is less than predicted (Huang et al., 2017; Vöröslakos et al., 2018), and that neuroimaging data find brain activation is greatest underneath the anode, not between electrodes as predicted by FEM (Datta et al., 2009; Galletta et al., 2015; Kim et al., 2014; Polaná et al., 2018). Improving the predictive power of forward computational models is a difficult prospect. Increasing the precision with which tissues are measured and circumscribed within an individual, leads to a model that is less generalizable, a tradeoff which must be assessed on a case-by-case basis (Bikson et al., 2012). Moreover, a model can only be as accurate as its inputs, and there is inconsistency in the field when it comes to the

conductivity values assigned to specific tissue types (Opitz et al., 2015; Parazzini et al., 2014; Shahid et al., 2014). Some of this discrepancy is due to the use of ex-vivo animal models to derive tissue impedance values, while some is due to the type of current used, with many studies utilizing values derived from alternating current (Huang et al., 2017; Rahman et al., 2015). Differences in input values might be a particularly relevant problem in modelling the electric current on the cerebellum, which has roughly half the impedance of the cortex (Parazzini et al., 2014), and where intricately folded tissue makes the direction of current flow (and subsequently, the direction of neuronal polarization) highly variable (Rahman et al., 2015; Rezaee and Dutta, 2019). Additionally, for extra-cephalic electrode placement, accurate modeling of the neck might be essential, as its inclusion has been shown to increase model accuracy (Huang et al., 2017).

While it remains an informative tool, future tDCS research involving FEM must be aware of the technique’s limitations. Interpretation of finite element modeling should be done with caution. There are many assumptions that must be made in such models, from thickness and conductivity properties of tissues to the anatomy of gyri and sulci, all of which may be different from one individual to the next (Bikson et al., 2012). The FEM results of the cerebellar vs. left arm electrode placements suggest that similar areas in the ventral cerebellum may be affected as in the F10, P4 and T5 vs. contralateral arm placements. Empirical investigation of this assertion, whereby tDCS currents are empirically mapped in the living brain with high precision, are beyond the capabilities of modern imaging technology. There exists no way to quantify the difference in electric field magnitude between montages with the software currently available. Having such information would be important in determining the similarity between the cephalic vs. extra cephalic placements and the placements used in the current study.

However, this leaves the question of why an extracephalic electrode produces a much larger effect on category learning when compared with two cephalic electrodes. This lack of cerebellar effects also refutes the possibility that spinal cord stimulation or cranial nerve stimulation resulting from the extracephalic electrode stimulating these nerves in the head and neck may be involved in the benefit of tDCS. If true, then any combined cephalic and extracephalic combination would produce an effect, but cerebellar stimulation did not. A further possibility is that other regions are involved in the effects produced by extracephalic electrodes. Further review of neuroimaging and FEMs suggest that other brain regions such as inferior temporal lobe/temporal pole may be involved in category learning that could explain these results (see Fig. 9. Likely candidates are medial and inferior temporal cortex. Both are known to be primarily involved in memory formation and visual categorization, respectively, both of which are likely to be involved in category learning (Seger and Miller, 2010). However, these regions are difficult to target using tDCS without simultaneously stimulating more superficial regions and complicating the analysis. Further understanding of the contribution of deep brain regions such as these to category learning using neuromodulation may require other modalities, such as ultrasound (Gibson et al., 2018), Temporal Interference (TI; Grossman et al., 2017), or Intersectional Short Pulse (ISP; Vöröslakos et al., 2018; see Fig. 10 for deep brain/brainstem FEM images).

5. Conclusions

Our prior studies showed that tDCS protocols that target the right fronto-parietal “top-down” executive attention areas with anodal current, or that inhibit activity in occipito-temporal “bottom-up” sensory processing areas targeted using cathodal stimulation, both enhance learning and performance in category learning when hidden or camouflaged objects are used. However, the combination of these two cephalic electrode placements in a single tDCS protocol did not produce significant effects on learning. We concluded that other far-field brain regions or extracephalic nerves such as cranial nerves or the spinal cord may be involved. FEM models suggested that E-fields were greater in the

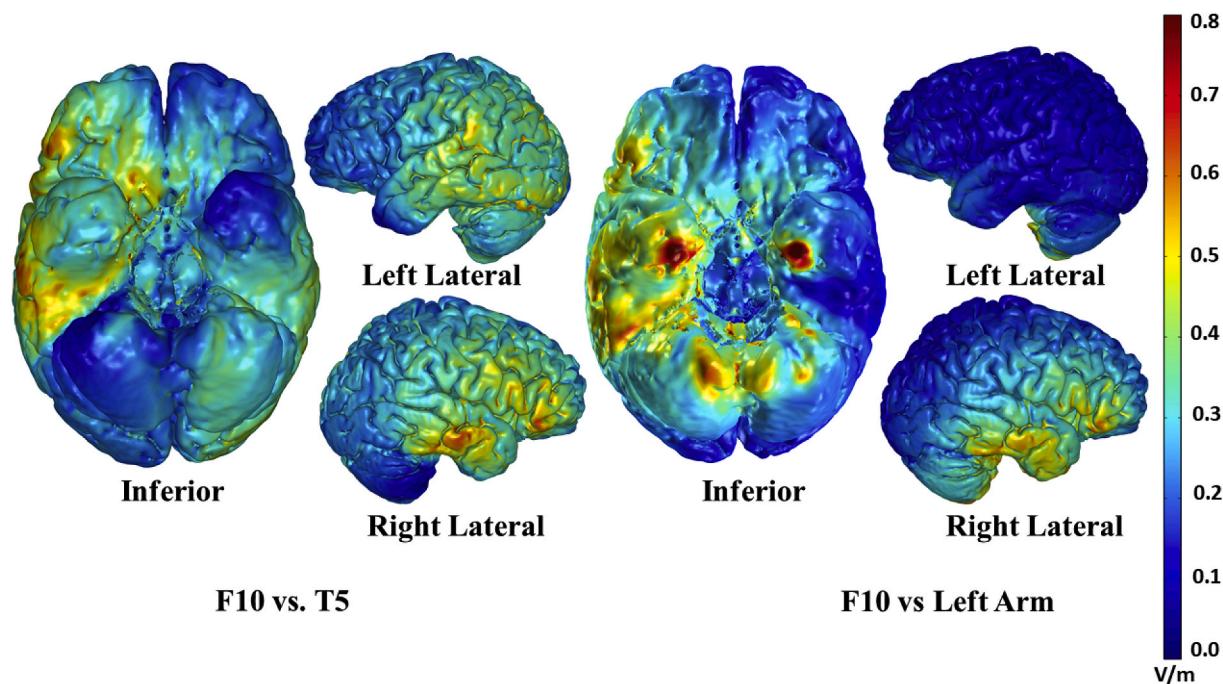


Fig. 9. Finite element models of F10 vs. T5/P7 (left) compared to F10 vs. Left Arm (right). Larger images are inferior views for each montage. The smaller images are left and right lateral views on top and bottom, respectively. Notice the predicted field effect in the temporal lobe under the monocephalic F10 montage compared to the same region in the bi-cephalic F10 vs. T5/P7 montage.

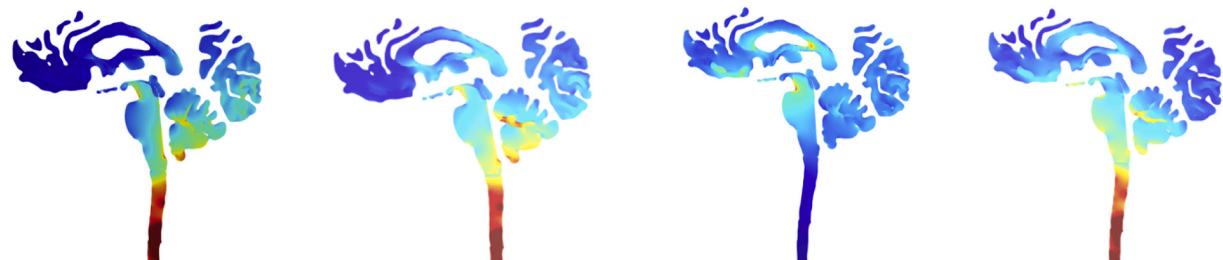


Fig. 10. Models of F10 vs. Left Arm, T5 vs. left arm, F10 vs. T5/P7 and cerebellum vs. left arm for mid-sagittal slices ($x = 0$). Notice the predicted field effect in the cerebellum and spinal cord across montages.

cerebellum and spinal cord when using tDCS protocols that increase performance on category learning tasks. However, focused cerebellar stimulation with an extracephalic electrode, while producing substantial electric fields in these extracephalic nerves, did not significantly influence performance on this task. Neither anodal nor cathodal direct current stimulation over posterior-medial cerebellum improved performance for category learning compared to a sham control group. Furthermore, no significant differences between verum and sham groups were found using measures of signal detection. The small but non-significant effects on learning that were found, when combined with our prior imaging data also showed small but minimally significant BOLD effects during performance of this task (Clark et al., 2012), suggest that the cerebellum may have small involvement, but is not significantly involved in performance of category learning. We conclude that the cerebellum is not an important component of the networks that support category learning.

In summary, the present findings are an important step in elucidating the brain networks involved in category learning, and how tDCS acts to influence these networks and category learning behavior. This study illustrates the combined use of neuroimaging, modelling and neuro-modulation to better understand the brain basis of category learning. Their combined use leads to a greater understanding than when each method is used individually. In general, this multimodal method that

includes neuroimaging, FEM modelling and behavioral comparison of tDCS montages could be applied to a variety of other cognitive tasks to better elucidate the relationships between human brain organization and behavior, and to optimize tDCS protocols to improve performance on these tasks.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The City University of New York holds patents on brain stimulation with MB as inventor. MB has equity in Soterix Medical Inc. MB consults, received grants, assigned inventions, and/or serves on the SAB of Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Halo Neuroscience, X. The City University of New York (CUNY) has IP on neuro-stimulation systems and methods with authors NK and MB as inventors. MB is supported by grants from the National Institutes of Health: R01NS101362 (MB), R01NS095123 (MB), R01NS112996 (MB), R01MH111896 (MB), R01MH109289 (MB). VPC is a scientific advisor of NeuroGeneces LLC. No other authors declare any competing interests.

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