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Transcranial direct current stimulation facilitates category learning

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ABSTRACT

Background: After two decades of transcranial direct current stimulation (tDCS) research, it is still unclear which applications benefit most from which tDCS protocols. One prospect is the acceleration of learning, where previous work has demonstrated that anodal tDCS applied to the right ventrolateral prefrontal cortex (rVLPFC) is capable of doubling the rate of learning in a visual camouflaged threat detection and category learning task.
Goals: Questions remain as to the specific cognitive mechanisms underlying this learning enhancement, and whether it generalizes to other tasks. The goal of the current project was to expand previous findings by employing a novel category learning task.
Methods: Participants learned to classify pictures of European streets within a discovery learning paradigm. In a double-blind design, 54 participants were randomly assigned to 30 min of tDCS using either 2.0 mA anodal ($n = 18$), cathodal ($n = 18$), or 0.1 mA sham ($n = 18$) tDCS over the rVLPFC.
Results: A linear mixed-model revealed a significant effect of tDCS condition on classification accuracy across training ($p = 0.001$). Compared to a 4.2% increase in sham participants, anodal tDCS over F10 increased performance by 20.6% ($d = 1.71$) and cathodal tDCS by 14.4% ($d = 1.16$).
Conclusions: These results provide further evidence for the capacity of tDCS applied to rVLPFC to enhance learning, showing a greater than quadrupling of test performance after training (491% of sham) in a difficult category learning task. Combined with our previous studies, these results suggest a generalized performance enhancement. Other tasks requiring sustained attention, insight and/or category learning may also benefit from this protocol.

Introduction

Since the recent re-emergence of transcranial direct current stimulation (tDCS) [1], it has been applied in an effort to improve a range of cognitive functions. Across these applications, tDCS has been shown to be safe, with a minimal number of adverse effects reported over thousands of participants [2,3]. Concomitantly, the technology needed to implement a tDCS protocol is relatively inexpensive and easy to operate compared to other forms of non-invasive brain stimulation. Safety and ease of use have made tDCS a highly versatile and popular tool, but this has led in turn to variable results across studies [4–9], as different experimental protocols interact with individual characteristics in ways that are not fully understood [10–13]. Further work is needed to clearly define the protocols and applications that maximize the potential of tDCS [14].

Numerous meta-analyses have attempted to quantify the effect of tDCS when applied to specific domains. Due to the many experimental and subject moderators that exist across the tDCS literature [15], the findings of these analyses vary, but small to medium effect sizes have been demonstrated for anodal tDCS on tasks requiring sustained attention [16], and learning [17,18]. These two processes were likely critical to the performance improvement

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observed in a study that adapted stimuli from the DARWARS virtual reality-based program designed to train soldiers prior to deployment to the Middle East [19], where participants receiving 30 min of 2.0 mA anodal stimulation over the right ventrolateral prefrontal cortex (rVLPFC) displayed an 87% percent increase in accuracy at identifying and classifying images of concealed threat targets compared to participants receiving sham (0.1 mA) stimulation. The between groups difference in classification accuracy grew to 100% after a 1 hour delay [20]. This intervention attained an effect size of $d = 1.2$, larger than typically observed in tDCS interventions on cognitive outcomes [21], and nearly twice that found in a recent meta-analysis ($d = 0.76$) examining tDCS application during math and language learning [18]. Importantly, two subsequent replication studies found results of a similar magnitude following stimulation with the F10 protocol during this task [22–24].

Understanding the processes underpinning this improvement might provide clues for other laboratory or real-world tasks that would benefit from this tDCS protocol. However, the naturalistic stimuli utilized in the original task [20] make parsing the relative size of tDCS effects on different cognitive mechanisms difficult. Participants were trained to classify images containing threats by learning to identify threat cues within the images. Failure to correctly categorize a threat image led to explicit short movies showing the outcome of the unidentified threat (an explosion in a vehicle or building, someone being shot, etc.). Accordingly, correct categorizations led to videos with positive outcomes. Prior to the task, subjects were not given any specifics about what constituted a threat; rather, in a discovery learning paradigm, they were tasked with engaging in trial and error learning over the course of training.

One explanation for the performance benefits seen in Ref. [20] is an increase in attentional capacity. This is supported by behavioral data, where participants receiving 2.0 mA anodal stimulation over F10 demonstrated improved performance on the alerting subscale of the Attention Networks Task (ANT) [25], improvement which itself was positively associated with target detection performance [23]. This coincides with other tDCS interventions that have found similar beneficial effects of F10 stimulation on cognitive control measures, including the stop-signal task [26–30]. Improvement in sustained attention specifically may be a likely antecedent to performance enhancement following F10 stimulation as improvement in sustained attention has been observed following stimulation of the right frontal cortex [31–33]. Sustained attention might be one vehicle through which performance enhancement in the F10 protocol occurs, with consequent improvements in the ability to generalize learned cues and classify new images [20,34], as well as remember previously seen images [23], being mediated by prolonged attentional capacity during training.

A further factor that might contribute to the large effect seen previously is specific to the threatening nature of the pre-deployment training stimuli. Imaging research has linked increased activity in the rVLPFC with the reduction and regulation of the fear response [35,36], and decreased activity with rumination and stress-induced negative affect [37,38]. The reduction of negative affect may thus provide another means by which F10 stimulation enhances attention, as there is evidence that positive affect increases the scope of visual attention while anxiety decreases attentional control [39–41]. Affect-mediated attentional changes are in turn linked to creative problem solving and insight [41–43], factors that might play a crucial role in tasks based on feedback and discovery learning [20,44,45]. Finally, and more applicable to the abstract threats presented in our target detection task [20], the rVLPFC is associated with the semantic representation of stories containing violence [46]. Stimulation of this area might predispose subjects to construct a violence-related narrative of the presented stimulus, making threat-related cues and their consequences more salient.

The aim of the current work was to further elucidate the possible mechanisms through which performance enhancement in the F10 protocol occurs, specifically through the creation of a novel categorization task devoid of threatening stimuli but utilizing a similar discovery learning paradigm. An additional difference was the inclusion of a cathodal stimulation group, the goal of which was to expand on a theoretical account of the neural networks affected by F10 tDCS.

Twenty-first century tDCS research has largely been driven by a stimulation-dependent model of tDCS effects, a de-facto theory that arose from the seminal tDCS motor cortex studies which reintroduced the possibility of noninvasively altering brain function with small direct currents [1,47,48]. However, results have outgrown the dichotomy of anodal excitation and cathodal inhibition [21,49–52], and new theories are needed that provide more nuanced predictions for the interaction between endogenous neural activity and the subthreshold neuromodulation of tDCS. Consistent with a view of cathodal stimulation as a filter of extraneous neural noise [53–56], it was hypothesized that the slope of observed improvement in the cathodal stimulation group would be smaller than that of the anodal group, with any improvement occurring later in the training following initial increases in performance specific neural activity.

Methods

Participants

Potential participants were recruited through the University of New Mexico (UNM) research participation portal and posted advertisements. Participants attended a single experimental session lasting approximately 2 h. Prior to enrollment, participants were screened for the following inclusion criteria: right-handed, English fluency, age 18–55, no history of seizures, no treatment for mood disorders within 2 years, no metal implants or pacemakers, not pregnant, no dependence on alcohol or recent illicit drug use, no recent nicotine consumption, and not taking any other pharmacological agents known to affect nervous system function. At the beginning of the experimental session, participants were informed of the details and goals of the study, including the use of tDCS, and consented. All study materials and procedures were approved by the Advarra IRB and the U.S. Army Research Laboratory's Human Research Protection Program.

Experimental task

In a novel experimental task, participants learned to classify pictures of European streets into two categories, labeled “L” and “R”. Pictures were static street segment views accessed on Google Maps Street View (http://maps.google.com). Each trial consisted of one static street view presented for 2.5 s. Following a baseline, pre-training block of 50 trials without feedback, there were four training blocks, each with 60 trials in which participants received accuracy feedback following each response. Accuracy feedback consisted of a written message indicating a correct or incorrect response accompanied by male voices with European accents reciting a range of verbal responses. Training was followed by two test blocks of 50 trials each, all without feedback (Fig. 1). The baseline set was framed as a practice block during which participants were instructed to become accustomed to the timing of the stimuli and to begin hypothesizing about criteria that might differentiate them. Pictures could be correctly categorized through two arbitrary rules. The first differentiated regions based on how

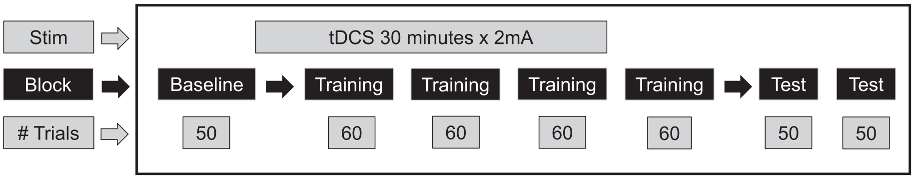

Fig. 1. Study design.

the picture was taken in relation to the road. In region L, pictures were taken on the left hand side of the road with traffic approaching, while in region R, pictures were taken on the right hand side of the road with traffic moving away (Rule 1). Traffic pattern was always on the right. The second rule consisted of symbols added to the pictures (i.e., hidden objects). Two side-by-side dots (umlaut) were added to the pictures for region L, and a curved line (tilde) was added to the pictures in region R (Rule 2). Prior to beginning the study, participants were only told that there were two regions but were not informed about the possible ways to differentiate them. Instead, through discovery learning [45], they gained knowledge of the pertinent criteria via accuracy feedback during the training portion. In each block, Rule 1 was present in all trials, while Rule 2 was present in half of trials. The two rules were always consistent with each other. To ensure uniform difficulty across the task, the saliency of specific criteria (road direction rule, hidden object rule, apparent temperature, signs with written language) in individual pictures was rated by two researchers, and pictures were then evenly distributed across the different blocks according to these ratings.

tDCS

TDCS was applied similarly to previously published studies [20,22,24]. Participants were randomized to receive anodal, cathodal, or sham stimulation over F10, with the "return" electrode placed on the left triceps. TDCS was administered by an ActivaDose II Iontophoresis unit. In a double-blind design, two of these units were connected to a blinding box, with one unit set to deliver an active dose of 2.0 mA (with a ramp-up of 30 s) and the other set to deliver a sham dose of 0.1 mA. Participants were randomized to a specific switch on the blinding box (1–6), with the experimenter implementing the protocol unaware of the dosages associated with each switch. Two saline-soaked Amrex A5 (5 × 5 cm) sponges served as the electrodes, and these were attached to the arm with adhesive Coban and to the head with an Amrex Velcro strap. Stimulation lasted 30 min and began after the baseline block. At 0 and 4 min after the beginning of stimulation, participants completed a sensation questionnaire asking them to rate the degree of itching, heat, and tingling on a 0–10 Likert-type scale. Participants were informed that sensations rated 7 or above would end stimulation and the experiment. After the 2nd sensation questionnaire, participants began the 1st training block, with stimulation ending in the last minute of the 3rd training block.

Profile of Mood States

To explore possible interactions between self-reported affect, tDCS, and performance improvements, participants completed the Profile of Mood States (POMS) prior to stimulation and at the conclusion of the experiment [57,58]. The POMS includes seven unique subscales, Tension, Fatigue, Vigor, Confusion, Esteem-Related Affect, Depression, and Anger.

Statistical analysis

All analyses were conducted in SPSS. Differences in average sensations reported across tDCS conditions were analyzed with analysis of variance (ANOVA). To test the effectiveness of participant blinding, we examined whether individuals correctly guessed their assigned condition at the end of the experiment using a cross-tabulation and χ^2 test. In addition, Bonferroni-corrected paired t-tests were conducted to compare scores on the POMS subscales at the beginning and end of the experiment. One-way ANOVAs were conducted to identify any between-group differences on the POMS subscales at the conclusion of the experiment.

We used linear mixed-effects models to test differences between tDCS conditions on accuracy and reaction time across the experimental blocks. These two separate models were estimated using maximum likelihood. Both models had fixed and random-effects of intercept, condition (anodal, cathodal, or sham tDCS), and block (baseline, 4 training, and 2 test blocks), and used an autoregressive variance-covariance structure to account for decreasing correlations over non-consecutive blocks. Responses occurring later than 2500 ms after stimulus onset were not included in calculation of accuracy or response time. To explicate changes in categorization accuracy and response time between stimulation groups during (online) and after (offline) stimulation, 2 difference scores were calculated, one representing online change (baseline to training block 3) and one representing offline change (training block 4 to test block 2). A linear regression was then performed for each of these difference scores, with stimulation condition as the independent variable. One-way ANOVAs were also conducted to identify any between-group differences in accuracy and reaction time in each of the 2 test blocks.

Results

Participants

Six participants were excluded from the final analysis. Two were excluded due to technical issues with the computer program during data collection. An additional three participants, one in each experimental group, were excluded for insufficient task engagement. Insufficient task engagement was defined by two criteria: average response time during the training blocks was less than 1 s, and pattern of response was consistent 1's or 2's or alternating 1, 2, 1, 2 …. No participants reported sensation ratings of 7 or above, however one subject receiving cathodal stimulation reported a metallic taste and chose to leave the study during the first minutes of stimulation. The final analysis included 54 participants, 18 in each group (Table 1). A one-way ANOVA found no significant differences between groups in sex or age.

Participant blinding & POMS

One-way ANOVAs indicated significant differences for reported sensations between groups. Participants in the anodal (M = 3.07, SD = 1.87) and cathodal groups (M = 2.50, SD = 2.22) reported

Table 1
Subject demographics.

		Age			Male		Female	
Condition	N	Mean	SD	Range	N	%	N	%
Anodal	18	22.85	7.59	30	9	50%	9	50%
Cathodal	18	24.59	11.35	38	9	50%	9	50%
Sham	18	22.16	5.19	17	5	28%	13	72%
Total	54	23.20	8.34	38	23	43%	31	57%

greater tingling than those in the sham group (M = 0.67, SD = 0.72), ($F(2, 43) = 7.821$, $p = 0.001$). Additionally, participants receiving anodal stimulation (M = 2.47, SD = 1.92) reported significantly greater itching than participants receiving sham stimulation (M = 0.87, SD = 1.19), ($F(2, 43) = 3.353$, $p = 0.044$). Despite these differences, a chi-square test of independence did not indicate a significant association between assigned condition (verum or sham) and condition guessed by participants after the experiment (χ^2 (1) = 0.35, $p = 0.554$). Results from the Bonferroni-corrected paired t-tests for the POMS subscales found that participants reported significantly more confusion and fatigue, and significantly less vigor and esteem-related affect after the experiment (Table 2). One-way ANOVAs were conducted to describe differences in the POMS subscales attributable to stimulation group membership, none of which approached significance (all p's > 0.05).

Categorization accuracy and reaction time

One-way ANOVAs confirmed that there were no significant differences between groups on number of no-response trials in any of the blocks (all $p > 0.12$). The mixed-model examining accuracy indicated a significant fixed-effect of experimental block ($F(6, 36.77) = 10.12$ $p < 0.001$) and condition, ($F(2, 47.65) = 7.99$, $p = 0.001$), but not the interaction between condition and block ($F(12, 36.77) = 1.46$, $p = 0.184$) (Fig. 2). For the online change in categorization, anodal group membership significantly predicted improvement ($\beta = 0.427$, $p = 0.006$), while cathodal group membership did not ($\beta = 0.070$, $p = 0.641$). Contrastingly, cathodal stimulation significantly predicted offline improvement ($\beta = 0.314$, $p = 0.049$), while anodal stimulation did not ($\beta = 0.169$, $p = 0.284$). Post-hoc tests indicated that there were significant mean differences between anodal (M = 71.8%, SD = 16.9%) and sham (M = 55.1%, SD = 12.6%) stimulation in test block 1 ($p = 0.002$) and 2 (anodal: M = 70.5%, SD = 15.3%; sham: M = 54.4%, SD = 10.8%; $p < 0.001$), and between cathodal and sham groups in test block 1 (cathodal: M = 70.5%, SD = 15.3%; $p = 0.025$) and 2 (cathodal: M = 65.2%, SD = 11.8%; $p = 0.007$). However, there were no significant differences between anodal and cathodal groups in test block 1 ($p = 0.15$) or 2 ($p = 0.25$). From baseline to test (test block average), anodal tDCS increased average categorization accuracy by 20.6% (SD = 16.1%), cathodal tDCS by 14.4% (SD = 11.8%) and sham by 4.2% (SD = 11.7%). The improvement in performance equated to an effect size of $d = 1.71$, 95% CI [0.95, 2.47] in the anodal group and $d = 1.16$, 95% CI [0.45, 1.86] in the cathodal group [59].

Table 2
POMS results.

	Pre	Post		
Subscale	M (SD)	M (SD)	t	p
Confusion	1.75 (2.18)	3.59 (2.91)	−4.782	<0.001
Fatigue	2.88 (2.94)	3.80 (2.86)	−3.084	0.003
Esteem Related Affect	15.33 (3.06)	12.55 (3.87)	5.504	<0.001
Vigor	7.25 (4.22)	4.84 (4.46)	6.087	<0.001

For the mixed-effects models of reaction time, there was significant fixed-effect of experimental block ($F(6, 894.95) = 11.75$, $p < 0.001$), while the fixed-effect of condition approached but did not reach significance, ($F(2, 963.67) = 2.94$ $p = 0.053$). The interaction between condition and experimental block also did not reach significance ($F(12, 894.68) = 2.94$, $p = 0.293$). Both anodal ($\beta = 0.374$, $p = 0.017$) and cathodal group ($\beta = 0.330$, $p = 0.034$) membership predicted increases in online reaction times, but stimulation group membership did not predict changes in offline reaction time. Similarly, none of the post-hoc tests for reaction time differences between groups approached significance for test block 1 or 2 (all p's > 0.10). Reaction time changes across the task are shown in Fig. 3.

Discussion

When compared with sham stimulation, anodal tDCS improved categorization accuracy by 20.6% (vs. 4.2% in sham), while cathodal tDCS improved categorization accuracy by 14.4%. Described another way, anodal tDCS at F10 (over rVLPFC) led to a 391% improvement in performance relative to sham, and cathodal tDCS led to a 243% improvement relative to sham. Both the magnitude of performance improvement and corresponding effect size described here were larger than in the previous threat-learning paradigm [20], indicating that the benefits derived from the F10 tDCS protocol are not specific to learning to identify and classify threats, but rather to more generalizable tDCS-mediated improvements in classification learning, sustained attention and/or insight.

Explicating the similarities between this and previous studies that have demonstrated promising behavioral effects from F10 tDCS is crucial for understanding its cognitive effects, and for defining other applications that might benefit from this protocol. Beyond neuronal changes in neurotransmission and metabolism previously noted [60], both tasks capitalized on two factors that have been shown to moderate the effects of tDCS: experimental differences in the timing of stimulation during exposure to a task, and individual differences in neural activity related to task performance. Both of these moderators can be accounted for within the same theoretical framework, one which views the current flowing from the anode as increasing neuronal noise, and the current returning to the cathode as reducing neuronal noise. Depending upon the strength of endogenous signal, the addition or filtering of neuronal noise can be facilitative or detrimental to performance [56,61]. In timing effects, the addition of neuromodulatory noise near first exposure to a task allows anodal stimulation to have the greatest potential impact, as it interacts with yet unorganized task related neural activity. In this way, online anodal tDCS is able to maximize tDCS-mediated plasticity changes [18,60,62,63] within task-specific networks [64–68]. This has been demonstrated elsewhere [69,70], and in our original target detection task, where anodal stimulation applied during the first hour of training led to significantly better classification accuracy than anodal stimulation applied during the second hour of training [71].

Similarly, an individual's level of proficiency or familiarity on the task performed during tDCS has also been shown to moderate the effectiveness of tDCS, with initially lower performers or novices often benefiting more from anodal stimulation than initially higher performers or experts [72–75]. The design of the current study could be maximizing the effect of tDCS by utilizing a paradigm, discovery learning [45], that explicitly introduces an undefined problem space. This too might allow the neuromodulatory effect of the tDCS to have the greatest positive impact by adding noise to a relatively disorganized neural signal. The location of stimulation is critical in this regard, with fMRI work explicitly associating the rVLPFC activity with the initial ability to correctly identify targets

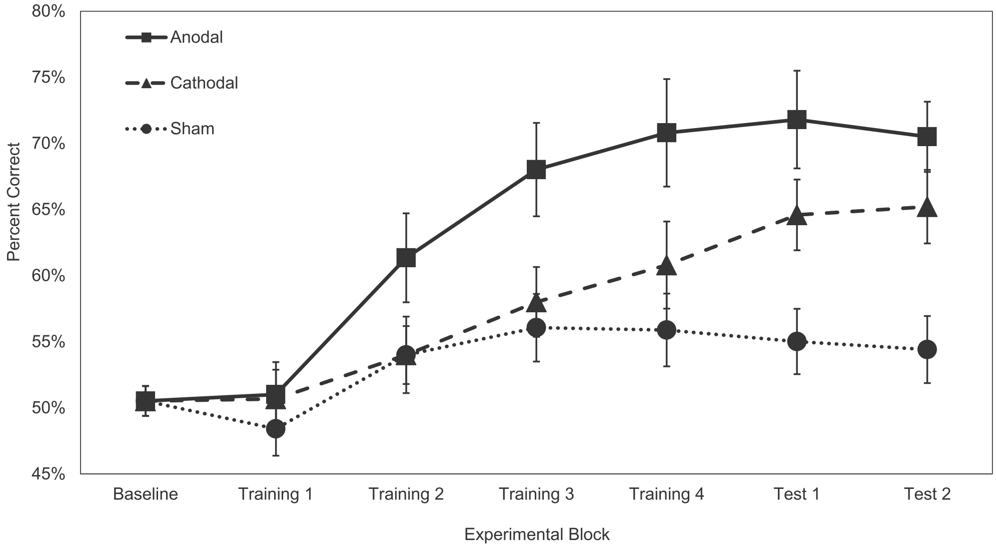

Fig. 2. Between-groups differences in accuracy across experimental blocks. Error bars = ±1 SE.

[20]. This accords with other imaging work, which has connected the generation of hypotheses and insights with the rVLPFC [76–82]. In the current study, online anodal stimulation introduced exogenous noise and accelerated the formation of task related neural networks in the rVLPFC, leading to an increase in categorization accuracy up until the end of training block 3. In comparison, online cathodal stimulation suppressed the functioning of these nascent, task-related networks, by initially filtering both noise and signal alike. The removal of this filter at training block 4 might have led to an immediate increase in relevant excitability in the cathodal subjects, perhaps through a homeostatic mechanism that had adjusted the functional range of neural activity during stimulation [83,84].

The results from this study also support the hypothesis that the F10 tDCS montage promotes sustained attention. This is consistent with fMRI studies, which have found the rVLPFC to be involved in the maintenance of attention and cognitive control [85–89]. Average performance in the sham group peaked during the 3rd training block, while performance significantly increased in the anodal group during stimulation, and in the cathodal group following stimulation. This suggests that verum subjects were better able to maintain engagement with this task, both during and after stimulation. Similarly, increases in fatigue and decreases in vigor were seen across groups following the task, but for those in the anodal and cathodal groups this decrease in self-reported energy was not detrimental to task performance in the test blocks.

The lack of improvement in the sham group is notable, with 9 of the 18 sham subjects displaying average categorization accuracy in the test blocks of <50% (compared to 2 in anodal and 0 in cathodal). In a debriefing questionnaire following the study, sham subjects reported using people and written signs within the pictures as categorization criteria significantly more than those receiving

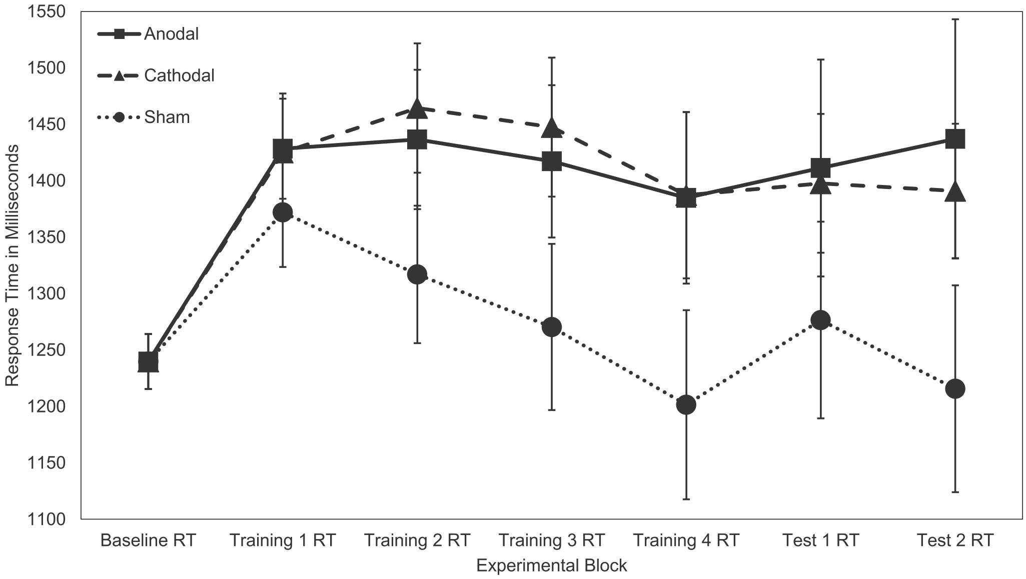

Fig. 3. Between-groups differences in response time across experimental blocks. Error bars = ±1 SE.

verum stimulation. It is possible that the failure of these and similar candidate objects within the pictures themselves represented an exhaustion of the *set size* subjects brought to the pictures [90,91], where set size can be thought of as a framework for thinking about a problem. Contrastingly, subjects receiving verum stimulation were able to go beyond this original set size, either driven by augmented sustained attention, allowing them to continue looking following the exhaustion of an initial set, or by enhanced insight, allowing them to more quickly see beyond the confines of the initial set.

Several limitations within the design of the current study should be considered. Beyond the use of new stimuli and categorization criteria, there were three other differences between the task used in the current study and our original target detection task [20]. First, stimulus presentation time was increased from 2.0 to 2.5 s. Second, half as many baseline trials were presented in the current study, as no participants were significantly above chance at baseline when piloting the stimuli, likely related to the arbitrary cues used here. Finally, the visual feedback was different. In Ref. [20], a computer animated video showed the consequences of a subject's classification choice, while in the current study, the visual feedback was a non-specific "Correct" or "Incorrect." Given the larger effect found here compared to these prior studies, it is unlikely that any of these differences weakened the magnitude of tDCS effects. While verum vs. sham stimulation was double-blinded, an additional limitation here was a lack of double-blinding between the cathodal and anodal conditions. Finally, while stimulation of the rVLPFC might have directly impacted cortical networks involved in attention and insight, the extracephalic electrode placement might have led to far field effects in other brain areas. Indeed, unpublished finite element modeling done on this protocol demonstrated that large field effects occur in the basal ganglia, amygdala, brain stem, and especially in the cerebellum [92]. While no significant improvement in target detection was found following cerebellar anodal stimulation with the return on the left arm, it is still possible that remote effects contribute to performance improvements resulting from F10 stimulation.

Conclusion

Our prior work examining the impact of rVLPFC tDCS on threat-target categorization and detection [20], coupled with recent fMRI studies implicating the rVLPFC in processing violence-related semantic stimuli, suggested that tDCS of the rVLPFC may have been effective due to the threat-related content. This was not supported by findings in the current study, wherein learning to categorize stimuli without violent imagery benefited to a relatively larger degree from this tDCS protocol. This in turn suggests that the F10 tDCS protocol provides a general benefit to category learning, and is not related to threat detection.

The behavioral differences between tDCS groups observed here, with participants receiving sham tDCS tending to "give up" sooner than those receiving either anodal or cathodal tDCS, implies that this protocol may be associated with greater perseverance, an attribute that is associated with greater learning and performance [93]. Future work should specifically test the effects of this protocol on perseverance during tedious tasks, and perceptual and declarative learning within a discovery learning paradigm. If this protocol provides resilience during tedious and difficult tasks, or helps hypothesis generation and insight in the face of an undefined problem space, it may ultimately prove beneficial for a variety of real-world tasks.

Author contributions

Conceptualization, B.G. and V.C.; methodology, B.G. and V.C.; software, B.G. and T.M.; formal analysis, B.G., M.H., and K.W.; investigation, B.G; resources, A.Y., J.H. and V.C.; writing—original draft preparation, B.G.; writing—review and editing, all authors; supervision, B.G. and V.C.; project administration, V.C.; funding acquisition, V.C.

Declaration of competing interest

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.11.010.

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