9-1-2015

Contribution of Far Field Effects of Cortical tDCS in the Cerebellum to Learning in an Object Detection Paradigm

Aaron P. Jones

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Aaron Paul Jones
Candidate

Psychology
Department

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Eric Ruthruff, Ph.D.

CONTRIBUTION OF FAR FIELD EFFECTS OF CORTICAL TDCS IN THE CEREBELLUM TO LEARNING IN AN OBJECT DETECTION PARADIGM

by

AARON P. JONES
B.A., Psychology, The University of New Mexico, 2005

THESIS

Submitted in Partial Fulfillment of the
Requirements for the Degree of

**Master of Science
Psychology**

The University of New Mexico
Albuquerque, New Mexico

July, 2015

ACKNOWLEDGEMENTS

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ABSTRACT

Transcranial direct current stimulation (tDCS) has been shown to enhance many cognitive and motor functions, and has been used in many areas, including rehabilitation of speech after stroke, cognitive enhancement, and treatment of mental illness. Our lab has demonstrated that, paired with training, anodal tDCS over electrode site F10 as well as cathodal tDCS over site T5 both increased the ability to detect hidden objects in a complex visual environment in a discovery learning paradigm. Stimulation of F10 has further been shown to enhance perceptual sensitivity selectively, without a change to response bias, and this effect was further enhanced when images presented during training were repeated in a post-training, post-stimulation test (Clark et al., 2012; Coffman et al., 2012; Falcone et al., 2012). Furthermore, this increased ability to detect hidden objects persisted for at least 24 hours Falcone et al., 2012). It has also been shown to increase measures of attention, using the Attention Network Task (ANT; Fan, 2002). Specifically, alerting network scores were increased in participants receiving active anode F10 stimulation compared to sham. Since both F10 anode as well as T5 cathode stimulation both resulted in increased learning the object detection task, potential additive effects were inferred, and an F10 anode/T5 cathode

electrode montage was investigated. Surprisingly, this montage had an effect of about half of the other two montages (F10 anode/shoulder, T5 cathode/shoulder). Finite element current modeling studies were conducted to investigate more precisely where in the brain the electricity is traveling during these different stimulation protocols. Results suggested that both cephalic/extra-cephalic electrode placements exhibited far-field effects in subcortical areas, bilateral temporal poles, as well as in the cerebellum, albeit with opposite polarities. During F10 anode/shoulder cathode stimulation, a negative electrical field effect was seen in the cerebellum. During T5 cathode/shoulder anode stimulation, the opposite was true: there was a positive field effect in the cerebellum. However, the montage with a bi-cephalic placement showed no such effect in the cerebellum. Based on these modeling data, the difficulty of reaching subcortical areas with tDCS, and the evidence that the cerebellum is not only involved in motor behavior, but cognition as well, the cerebellum was chosen for direct stimulation with tDCS and was hypothesized to be contributing to the learning and attention effects reported in previous studies. Thirty-six participants received either anodal, cathodal, or sham stimulation of the medial posterior cerebellum during training to detect hidden objects in a complex visual environment. Measures of learning, signal detection, and interactions with stimulus type were investigated. Regression models were also built to investigate the contribution of each electrode placement in the two different montages. Measures of attention assessed with the ANT were also investigated. To our surprise, neither anodal nor cathodal stimulation of the cerebellum led to an increase in learning compared to sham stimulation. Furthermore, no effects were observed between groups on signal detection measures, nor was there an effect of group on stimulus type, all of which had previously been reported with F10 stimulation. Likewise, neither anode nor cathode stimulation led to an

improvement on measures of attention compared to sham. The conclusion is that the

cerebellum does not appear to be involved in the network contributing to learning and

performing the object detection task. Although there were no direct effects of anodal or

cathodal tDCS of the cerebellum on learning or attention, this study is an important step in

elucidating the network involved in the robust finding of increased ability to detect hidden

objects after administration of tDCS paired with training, as it rules out one potential

contributor.

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Introduction

Scribonius Largus, physician to Emperor Claudius, first documented using electricity to affect human health when he used the torpedo fish to relieve headaches by placing them on the foreheads of the afflicted in 46 AD (Brunoni et al., 2012). Giovanni Aldini described the first clinical use of direct current stimulation in 1801, when he studied the effects of stimulation in those stricken with melancholy. By applying direct current, he was able to improve the mood of these patients (Parent, 2004). Elbert et al. (1981) conducted the first modern study using transcranial direct current stimulation (tDCS) to investigate performance enhancement in humans. 0.3 milliamps (mA) of positive (anodal) current stimulation over the vertex of the skull lead to an increase in response speed in a task where participants had to press a button as quickly as possible to avoid hearing an unpleasant hissing noise. Since 1981, the rate of publications examining the effects of brain stimulation on a variety of targets, including the enhancement of cognition, is increasing exponentially (Coffman, Clark, & Parasuraman, 2014).

Using electricity to improve human health and functioning has enjoyed a long history, but has recently exploded in academic and industrial research as a means to influence the way in which the human brain operates. For the better part of two decades now, the use of non-invasive brain stimulation technologies have emerged as inexpensive, safe and effective ways to exogenously modulate brain activity. These technologies, including transcranial direct current stimulation (tDCS), have proven themselves repeatedly as a way to excite or inhibit cortical neuronal populations (Nitsche & Paulus, 2000). tDCS has been used in myriad clinical and research settings, including areas of cognitive remediation and neurorehabilitation (Miniussi et al., 2008), enhancement of cognitive function (Coffman,

Clark, & Parasuraman, 2014; Ditye, Jacobson, Walsh, & Lavidor, 2012; Mulquiney, Hoy,

Daskalakis, & Fitzgerald, 2011), and clinical populations (Brunelin et al., 2014; Ferrucci et

al., 2009; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). Furthermore, tDCS has

facilitated improvement of motor functioning following injury (Hummel, 2005) and recovery

of speech after stroke (Baker, Rorden, & Fridriksson, 2010; Fiori et al., 2010; Monti et al.,

2008).

Our lab has demonstrated that the use of tDCS has led to an increase in the ability to

detect hidden objects in a complex visual environment (Clark et al., 2012; Coffman et al.,

2012a, b; Clark, Coffman, Trumbo & Wegele, 2014). Further, associated studies have

suggested that the effect of tDCS on learning in this paradigm lasts up to 24 hours (Falcone

et al., 2012), and leads to an increase in perceptual sensitivity and is more robust when

repeated versus novel images are tested (Coffman et al., 2012a). tDCS leads to increased

measures of attention, and the magnitude of these increases are associated with the degree of

learning to detect hidden objects (Coffman et. al., 2012b). Each of these studies will be

discussed in more detail in following sections, as they lay the foundation for the current

study. First, though, a brief discussion of the mechanisms by which tDCS is hypothesized to

work is presented.

Mechanisms of tDCS

Traditional tDCS involves placing two electrodes in various locations, with either two

cephalic placements or one cephalic and one extra-cephalic placement, and then passing a

small electrical current (up to 2.0mA) through the cortex from a battery-powered stimulator.

High definition tDCS systems are becoming more popular and involve multiple electrodes

(similar to those found on an EEG cap), positioned over various parts of cortex, and have

been suggested to allow for more precise targeting of electrical current (Edwards et al., 2013).

Although the exact mechanism by which tDCS works is not yet fully understood, several hypotheses have been posited to explain it. These derive from the finding that tDCS changes the local extracellular environment of neurons. The positive (anodal) pole of the current is thought to slightly depolarize neurons on the average, making them more likely to produce action potentials, whereas the negative (cathodal) pole is thought to hyperpolarize neurons, making them less likely to fire (Nitsche & Paulus, 2000; Poreisz, Boros, Antal & Paulus, 2007). Bikson, Radman & Datta (2006) suggest that through sub-threshold stimulation, populations of neurons can become polarized, allowing for simultaneous processing of afferent synaptic inputs and the modulation of synaptic plasticity.

However, experimental data suggests that the hypothesis that the anode excites cortex underneath the electrode and the cathode inhibits cortex is too simplistic. For example, Creutzfeldt et al., (1962) suggested that the orientation of neurons is important. He demonstrated in the cat that deeper layers in motor cortex were actually excited by cathodal stimulation, and inhibited by anodal stimulation. More recent work found that cortical layers IV and V were most affected by tDCS, but not layers II, III, and interneurons (Radman et al., 2009). However two years later, Stagg and Nitsche (2011) suggested that tDCS does in fact modulate interneurons. It has even been suggested that tDCS modulates activity of glial cells, which could also be contributing to the effects of tDCS (Ruohonen & Karhu, 2012).

Several hypotheses regarding neurotransmitter-modulation effects of tDCS have been described as well. Nitsche et al. (2003a) initially suggested that facilitation of long-term potentiation (LTP) and long-term depression (LTD) via glutamatergic modulation due to

stimulation is the main after-effect and mechanism by which tDCS works. Our lab has data that supports this theory, as we showed there was an increase in combined glutamate and glutamine concentration under the electrode after anodal tDCS stimulation measured with magnetic resonance spectroscopy (MRS), but not in the opposite hemisphere (Clark et al., 2011). Further, Stagg (2009) showed reduced glutamatergic concentration under the electrode following cathodal stimulation.

Another neurotransmitter implicated in the effects of tDCS is dopamine. Increasing dopaminergic tone using the drug L-DOPA reversed excitability of neurons after anodal tDCS (Kuo et al., 2008). Further, selectively blocking D2 receptors abolished after effects of tDCS (Nitsche et al., 2006). Finally, Monte-Silva et al., (2009) showed a dose dependent effect of dopamine on the effects of tDCS. Ropinirole, a dopamine D2/3 agonist administered at either high (1.0mg) or low (0.125mg) doses resulted in an impairment of plasticity in motor cortex after administration of tDCS, but strangely a moderate (0.5mg) dose allowed normal plastic changes to occur.

Yet another neurotransmitter that has been investigated is serotonin. Nitsche et al., (2009) showed that a selective serotonin reuptake inhibitor (SSRI) Citalopram increased the magnitude and duration of the after effects of anodal tDCS. Finally, Brunoni et al. (2013) showed that 5-HTTLPR (a serotonin transporter gene) predicted the effects of tDCS. Long/long homozygotes displayed a larger improvement comparing active stimulation versus sham, while short-allele carriers did not.

tDCS may also be involved in the expression of neurotrophic factors. Fritsch et al. (2010) showed that brain-derived neurotrophic factor (BDNF) expression was increased after the administration of tDCS. Further, patients expressing the Val66Met allele of BDNF

displayed enhanced plasticity after anodal tDCS compared to other expressions (Antal et al., 2010).

Finally, tDCS also has neurovascular effects. Using arterial spin labeling (ASL), Stagg et al. (2013) showed an increase in cortical profusion underneath the anode electrode in dorsolateral prefrontal cortex (DLPFC). Zheng et al. (2011) demonstrated an increase in regional cerebral blood flow (rCBF) of 17.1% underneath the anode electrode and, interestingly, 5.6% underneath the cathode electrode.

Regardless of its mechanism, there is little denying the fact that tDCS is a reliable way to modulate cortical function and cognition, though there is some disagreement regarding this (see Horvath, Forte & Carter, 2015 for a meta-analysis of the lack of effect of tDCS on cognition). In our lab, however, we have shown that tDCS leads to an increased ability to detect hidden objects in a discovery learning task when paired with training. A discussion of our findings is below.

Using fMRI-guided tDCS to Enhance Object Detection

In work from our lab, we have investigated the effects of tDCS in a complex visual object detection paradigm. Stimuli were adapted from the "DARWARS Ambush!" program (Macmillan et al., 2005; Raybourn, 2009), which is used to train soldiers being deployed into combat in the Middle East. Participants were instructed to view a series of images and decide whether or not an object (sniper rifle, shadow indicating an improvised explosive device, etc.) was present in each image (a detailed description of the task can be found in the methods section below). Functional magnetic resonance imaging (fMRI) was used to

determine neural activity elicited by the task as participants progressed from novice to intermediate and then to expert states of performance.

Before any training, novice subjects were scanned while performing the object detection task without receiving feedback regarding their decisions. When comparing images with a target object to those without, results suggested that many brain areas were more metabolically active when target objects were present and accurately detected in the images, including bilateral anterior caudate and putamen, anterior and posterior insulae, parahippocampal gyri, cingulate gyri, superior temporal gyri, and inferior and superior parietal lobules. Subjects were then trained outside of the scanner until they reached an intermediate (>78% accuracy), or for a subset of seven subjects, expert (>95% accuracy) level of performance. Once trained, they were scanned again and results suggested that more anterior brain areas were active, including right middle and inferior frontal cortex and left inferior frontal cortex in the intermediate group, and bilateral inferior frontal cortex, right cingulate, and right inferior parietal lobule in the expert group.

Learning this task (contrasting the difference between novice and intermediate groups) suggested that several brain areas including right middle and medial frontal cortex, right parahippocampal cortex, right cingulate cortex, right middle temporal/inferior parietal lobule and left superior temporal cortex were involved. Dynamic Bayesian Network (DBN) analyses suggested several networks involved in learning the task as well, including one comprised of right fusiform and right inferior parietal cortex.

Based on these fMRI results, two electrode placements were identified: right inferior frontal cortex (site F-10 in the standard EEG 10-10 system, above Brodmann's area 44), which was the most significant using GLM methods, and right inferior parietal cortex (10-10

site P4 above Brodmann's area 39), which was the most significant using DBN analyses. When right inferior frontal cortex location F10 was stimulated for 30 minutes (2.0 mA, with the cathode on the left arm) the results were astonishing. Participants receiving the active dose of stimulation exhibited nearly a doubling in their ability to identify concealed target objects compared to the sham stimulation (0.1mA) group after training combined with tDCS (26.6% for the active group, 14.2% for the sham group). Furthermore, this effect was also observed in a delayed testing condition (21.4% increase in learning for the active group, 10.5% for the sham group), which occurred 1 hour after stimulation, suggesting that the effects lasted at least 90 minutes after the end of tDCS administration (Clark et al., 2012).

Anodal stimulation over site P4 also showed an increase in learning, which was slightly less than the magnitude seen for the F10 placement (22.5% for the active group). The effect of F10 stimulation on learning this task has been replicated twice (Coffman et al., 2012a; Falcone et al., 2012) and has been shown to persist for at least 24 hours after stimulation ends (Falcone et al., 2012).

In a separate study, based on the finding of reduced blood-oxygen level dependent (BOLD) fMRI activity in left occipital-temporal regions when objects were present versus when they are absent (Clark et al., 2012), cathodal stimulation over area this area (10-20 site T5 above Brodmann's area 37) was investigated for its effects on learning. The hypothesis was that reducing activity with cathodal tDCS in areas showing reduced BOLD fMRI activity which are associated with exogenous attentional processes that are easily confounded by camouflage, would reduce distraction by camouflage present in the images. The results suggested learning effects on par with the F10 anode placement (25.4% for the T5 active group, 13.35% for the sham group; Clark, Coffman, Trumbo & Wegele, 2014).

Since F10 anodal placement and the T5 cathodal placement both produced significant increases in learning in this task, another study was conducted using those two cephalic placements together in one study (F10 anode vs. T5 cathode) to see if there was an additive effect on learning the task. To our surprise, there was a reduced effect of this montage on learning relative to each of the cephalic/extra-cephalic placements, showing about half of the effect of either of the two other montages (unpublished data; see Figure 1 for a description of all studies, including replications of the effect of stimulation on learning, using this task).
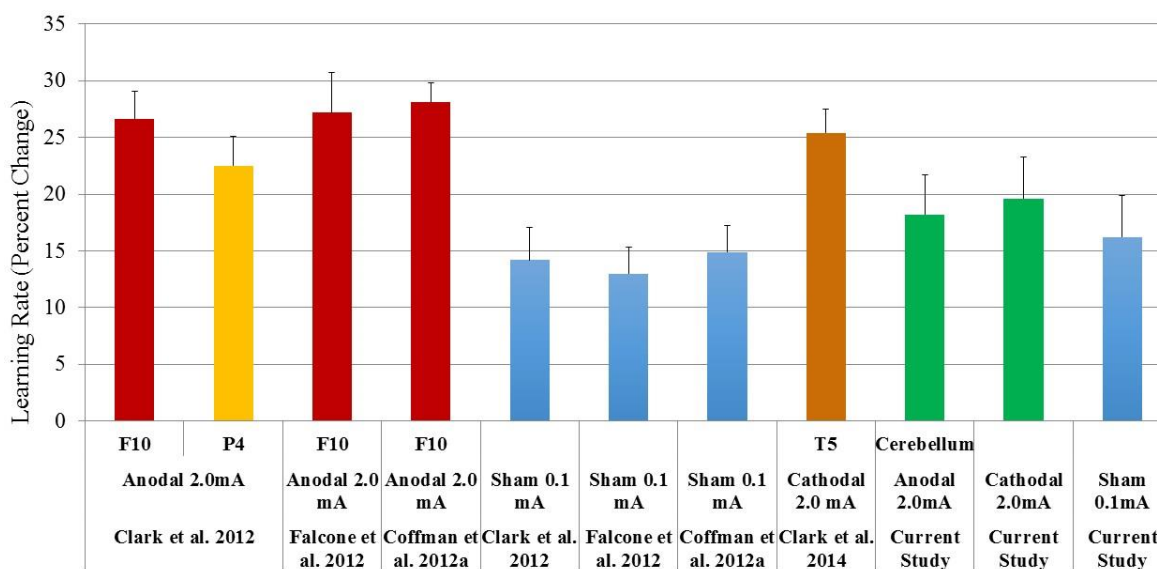
Figure 1. A summary of studies using the object detection paradigm. Note the large effects for the F10 anode placement, as well as the T5 cathode placement, compared to sham. The current study is displayed in green for active conditions, and in blue for the sham condition.

In addition to investigating the effects of tDCS on overall learning in the object detection paradigm, several subsequent studies were conducted to elucidate more precisely the mechanisms by which tDCS was having its effect and are discussed below.

Elucidating the Cognitive Mechanisms by which tDCS Improves Performance in Detection of Hidden Objects

Using the same paradigm described in Clark et al. (2012), Coffman et al. (2012a) investigated the differential effects of tDCS on stimulus type. In the original study, 82% of the testing stimuli were novel (i.e. – had not been presented during training), and only 18% were repeated images. To investigate specifically the impact of tDCS on object detection in repeated versus novel images an experiment was conducted investigating signal detection metrics using the same types of images and procedures, but which was modified to include 50% repeated and 50% novel images.

In signal detection theory, perceptual sensitivity (d') and response bias (β) are used to determine response characteristics in participants. Perceptual sensitivity is a measure indicating how well one discriminates signal from noise (or in terms of this study, objects present and objects absent), and is calculated as the normalized (z-scored) hit rate minus the normalized false alarm rate. Response bias is a measure of how likely one is to respond one way or the other, where values greater than one suggest a bias toward responding "object absent" and values less than one indicating a bias toward responding "object present", and is calculated by raising e to the power of ½ the difference between the squared normalized hit rate and the squared normalized false alarm rate. Ideally, when trying to improve performance on signal detection metrics, one would want to increase a participant's d' while not changing their bias to respond in a certain way.

Data from nine active (2.0mA) and ten sham (0.1mA) participants were included in Coffman et al. (2012a). Results suggest that active tDCS enhanced d' compared to sham without changing the way in which the groups responded to stimuli, evinced by no change in

β across groups. Further, this effect was enhanced when comparing repeated images to novel images.

Active tDCS also showed an improvement on both hit rate (choosing correctly that an object was present in the image) as well as correct rejections (choosing correctly that no object was present in the image) across both stimulus types. There was an interaction observed between stimulus type (object present vs. object absent) and repeated versus novel images, where the active tDCS group showed a greater improvement for repeated images only when objects were present in the image (hits), but not when objects were not present (correct rejections).

Investigation of whether physical sensation during administration of tDCS (itching, tingling, burning) as well as self-reported mood had any effect on performance was conducted as well. Results suggest that neither sensation nor mood had any effect on performance.

Signal Detection Measures and Retention of Performance

Using the same paradigm as Coffman et al. (2012a), a study was conducted by colleagues at George Mason University (Falcone, Coffman, Clark, & Parasuraman, 2012) to examine the validity of the findings obtained in our lab as well as investigate the rate of retention in performance observed after training and tDCS.

Thirty-seven participants took part in the study. In addition to the object detection paradigm procedures outlined in other studies (Clark et. al., 2012; Coffman et al., 2012a,b), participants were asked to return to the laboratory after a 24-hour delay, so retention of performance observed after F10 anodal stimulation could be assessed.

Data suggest that active tDCS over F10 resulted in an improvement of hit rate over sham stimulation (active = 76% peak hit rate; sham = 61% peak hit rate). In addition, false alarm rate was reduced in active participants as well compared to sham (active = 18% false alarm rate; sham = 35% false alarm rate). Perceptual sensitivity scores were also significantly higher in the active group active by the end of training (active = 1.86; sham = 0.73). There were no group differences in response bias, suggesting that tDCS was modulating sensitivity to discriminate images with and without hidden objects, without changing the way in which participants tended to respond. Interestingly, the improvement of the active group over the sham group persisted after a 24-hour retention interval, with only a slight reduction of d' scores, which were reduced in the active group by approximately 8% from the immediate retention condition to the 24-hour retention condition.

Lastly, sensations were compared between groups and results suggest that only tingling, but not heat or itching, was significantly higher in the active group when compared to the sham group. Further, the amount of tingling was moderately correlated with hit rate, but not false alarm rate.

Using tDCS to Improve Measures of Attention

In addition to investigating the effects of tDCS on the object detection paradigm, we have shown that anodal tDCS over site F10 also lead to an increase in alerting attention, measured by the Attention Network Task (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002), and that this increase is associated with the amount of learning in the object detection task (Coffman et al., 2012b). The ANT is a combination of the cued reaction time task and the flanker task. It involves determining the direction of a center arrow amongst distractor (flanker) arrows and has been used to describe three distinct attentional networks: alerting,

orienting and executive (or conflict). The alerting network is calculated as the difference between the no spatial cue condition and the double spatial cue condition, and has been linked to fronto-parietal brain networks (Coull, Nobre, & Frith, 2001).

After receiving 2.0mA of stimulation for 30 minutes to right inferior frontal cortex, participants in the active condition showed improvement in alerting network scores compared to the sham group. Further, the increase in this measure of alerting attention was positively correlated with the proportion of hits in both the immediate and delayed tests, but not with signal detection measures (d' or β) in either group.

Additionally, in this study there was a significant difference in the amount of heat reported between active and sham groups, but no measure of skin sensation was correlated with any attentional measure. Finally, there were no differences in self-reported mood nor was mood associated with any attentional measure. Please see Table 1 for a description of all studies and effects using tDCS to improve target object detection and attentional performance.

Table 1

Summary of effects of tDCS on the object detection and attention network tasks

Study	Anode Electrode Placement	Cathode Electrode Placement	Effects
Clark et al., 2012	F10	Left arm	Doubling of learning rate in the object detection task compared to sham.
Clark et al., 2012	P4	Left arm	Increase in learning the object detection task compared to sham, though the effect was not as large as with the F10 placement.
Coffman et al., 2012a	F10	Left arm	Increase in learning the object detection task compared to sham. d' increase in the active group compared to sham. This effect was stronger for repeated vs. novel stimuli, and was only observed when target objects were present.
Coffman et al., 2012b	F10	Left arm	Active stimulation resulted in increased measures of alerting attention in the ANT. Hit rate on the object detection task was positively associated with alerting attention.
Falcone et al., 2012	F10	Left arm	Increase in learning the object detection task compared to sham. Increase in d' compared to sham. The effect of learning was observed 24 hours after stimulation.
Clark et al., 2014	Right arm	T5	Increase in learning the object detection task compared to sham.
Clark, Unpublished	F10	T5	Increase in learning the object detection task compared to sham. The effect was approximately half that observed with cephalic vs. extra cephalic electrode placements.

tDCS Current Modeling

To elucidate where in the cortex the electrical current was flowing for the electrode montages used in the aforementioned studies (F10 anode/shoulder cathode, T5 cathode/shoulder anode) finite element models (Bikson, Rahman, & Datta, 2012) of electrical field potential were produced.

Results of the modeling studies suggest that both F10 anode/shoulder cathode as well as T5 cathode/shoulder anode placements produced some sub-cortical electrical fields, mainly in the cerebellum and bilateral temporal pole regions, with opposite polarities between these two placements (see Figure 2). The anode placement on the scalp resulted in negative electric current density in the surface of the ventral cerebellum and inferior temporal cortex, and cathodal placement on the scalp produced positive current densities in these same locations. Interestingly, models of the F10 anode/T5 cathode placement predicted no such effects in the cerebellum, though there appeared to be a negative field effect in the right inferior temporal lobe.

F10 Anode/Left Arm Cathode   T5 Cathode/Right Arm Anode   F10 Anode/T5 Cathode

-0.361 V/m   0.361 V/m   -0.372 V/m   0.372 V/m   -0.355 V/m   0.355 V/m
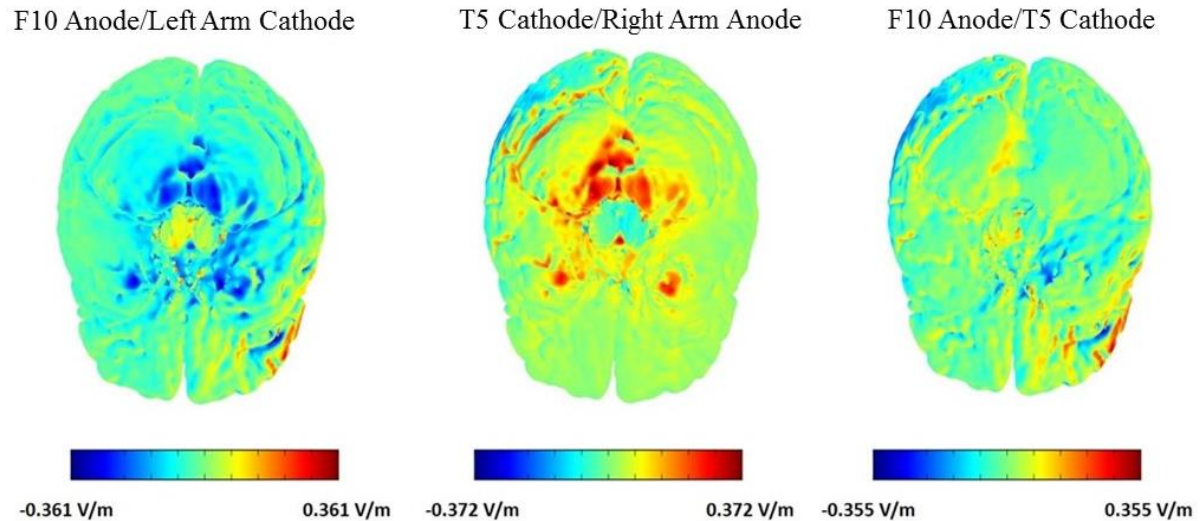
Figure 2: Current modeling. Finite element models show F10 (left) or T5 (middle) vs. shoulder placements produce large effects in the cerebellum with opposite polarities, whereas a bicephalic F10 anode vs. T5 cathode (right) does not.

Evidence of Cerebellar Involvement in Non-Motor Function

Based on the current modeling studies and the improvement in performance associated with the cephalic vs. extra-cephalic placements where activity in the cerebellum was observed, but not in the bicephalic placement where no activity was observed, the cerebellum was an ideal candidate to stimulate directly. It is reasonable to think that the cerebellum could be involved in learning the object detection task as well as in performing the ANT, based on literature describing the cerebellum's role in performance of not only motor tasks, but cognitive tasks as well. Further, modulation of the cerebellum has been accomplished with tDCS. The following discussion provides evidence for these assertions.

The cerebellum has a complicated structure, comprising half of the neurons in the brain, which for a century had been thought only to be involved in the coordination of fine muscle movement, balance, and simple procedural learning. In recent years, however, the

role the cerebellum plays in cognition and other higher order functions like language, working memory and learning has begun to be investigated.

Dolan (1998) defines the cerebrocerebellar pathway, which includes afferent projections from sensorimotor systems and substantial contributions from dorsolateral and medial prefrontal cortices, frontal language regions, posterior inferior and superior parietal cortices, superior colliculus and super temporal cortex to the cerebellum as well as bidirectional connections between the cerebellum and cortical areas specialized for attentional, visuospatial, executive and emotional regulatory functions.

Leiner, Leiner, and Dow (1994) suggest that, using anatomical tracing studies, BA 46 and 9 in the monkey both project to the dentate nucleus of the cerebellum via the thalamus. They further describe the cerebellum as a "versatile information-processing mechanism," which is involved in cognition by both transforming information that it receives as well as orchestrating the delivery of information to other areas of the brain, including frontal cortex, at the appropriate time. Thus, when tasks are performed, the cerebellum works in conjunction with higher-order areas in the frontal lobes to learn execution by practice, eventually becoming a somewhat automatic process, improving the speed at which tasks are accurately performed.

Neuroimaging studies have shown the cerebellum to be activated during many cognitive tasks, but interestingly often that activity declines with practice, suggesting that the cerebellum may be involved specifically in the learning process itself (Friston et al., 1992; Kelly, 2004; Raichle et al., 1994), rather than mere execution of the task. Further evidence supporting this claim comes from Vaina, Belliveau, Roziers, & Zeffiro, (1998), where lateral areas of the cerebellum were involved in the early learning phases of a motion discrimination

task, but this activity diminished by 93% when participants had learned the task. Remarkably, when novel conditions in the form of untrained direction of motion were presented, the activity in the cerebellum returned.

In a case study on an individual with right cerebellar damage, Fiez, Petersen, Cheney, & Raichle (1992) showed that although the patient had normal memory, intelligence, and language as measured with the Wechsler Adult Intelligence Scale, Revised (WAIS-R), he was deficient compared to control subjects in practice-related learning as well as in error detection, using a verb generation task. The task involved reading a common noun, and producing a verb associated with the noun as quickly as possible. The patient was considerably slower in reading the nouns and produced more errors compared to controls. He was also impaired in a concurrent discrimination learning task, where participants had to learn an arbitrarily assigned "positive" stimulus in a word pair. Across 20 repetitions of word pairs, control participants greatly reduced the number of errors committed, whereas the patient with cerebellar damage did not.

In an fMRI study of cerebellar cognitive function, Stoodley, Valera & Schmahmann (2012) showed that the cerebellum exhibits a functional topography, where overt movement activates sensorimotor cortices and contralateral lobules IV, V, VI, and VIII of the cerebellum and cognitively demanding tasks activate lobules VI and VII. They administered a battery of tests to nine healthy participants, including a finger tapping task, a 2-back verbal working memory task, a verb generation task, a mental rotation task, and an image viewing task. Analyses suggest that in addition to various cortical areas, the cerebellum was active as well. For the finger tapping task, right cerebellar lobules IV, V, and VIIIa, b were activated. The 2-back task activated right lobules V and VI, as well as bilateral lobules VI and VII and

the dentate. The mental rotation task activated left lobule VII, extended from lobule VI at the midline. The verb generation task activated lobules VI and VII, as well as lobules VIIb and VIIIa. Viewing emotional images versus neutral images activated right lobule VIIb.

Schmahmann and Sherman (1998) have described a phenomenon called the "cerebellar cognitive affective syndrome," which occurs when individuals incur damage to their cerebellum. They performed neuropsychological, anatomical neuroimaging and mental state tests on 20 patients suffering from cerebellar-specific disease. The deficits of this disorder they describe include impairments of executive function, including planning, set-shifting, abstract reasoning, verbal fluency, and working memory, often with perseveration, distractibility or inattention as well as visual-spatial disorganization and memory. Further problems with emotional blunting and language have also been described in this disorder. They suggest that this occurs because of disruption or damage to the circuits that connect the cerebellum to prefrontal, posterior parietal, superior temporal and limbic cortices.

Popa, Hewitt and Ebner (2014) have proposed that the cerebellum is involved in the encoding of performance errors, and can support associative learning, sequencing, working memory, and forward internal models in non-motor domains. Further, they suggest that the cerebellum both predicts upcoming errors as well as provides error feedback, which would make it an ideal candidate to be included in a learning network responsible for the detection of hidden objects in a discovery learning paradigm, as in the current study, where feedback is given when errors are committed.

Cerebellar tDCS

There have been a number of studies investigating the effect of tDCS on the cerebellum for several different non-motor domains, though none have investigated its effects on a perceptual discovery learning task as in Clark et al. (2102). The results have so far been mixed and several hypotheses have been posited to explain them. For example, Ferrucci (2008) showed that anodal and cathodal stimulation of the cerebellum reduced the practice dependent proficiency improvement in reaction time in the Sternberg working memory task. They concluded that stimulation of the cerebellum resulted in changes in neuronal excitation that impaired normal neuronal function, which was specific to the practice dependent improvement. Boehringer (2012) reproduced these results in a larger sample, showing that cathodal stimulation of the cerebellum reduced forward digit span performance as well as impaired the practice dependent proficiency increase in backwards digit span.

Interestingly however, Pope & Miall (2012) showed that cathodal cerebellar stimulation increased performance on an extremely difficult frontal lobe task, the Paced Auditory Serial Subtraction Task (PASST), whereas anodal or sham stimulation left performance unchanged. He suggested that when stimulated, inhibitory Purkinje cells in the cerebellum lead to inhibition of the dentate nucleus, which then drives frontal regions through ventral-lateral thalamic relays (Pope & Miall, 2014). This is of particular importance to the current study, as the authors suggest that cathodal stimulation of the cerebellum only has a positive effect as task difficulty increases. As the object detection paradigm used in the current study is quite difficult, perhaps the cerebellum is in fact being recruited in the network used to perform the task.

Finally, it is not always clear how the polarity of the current introduced into the cerebellum affects its behavior. In an emotion-recognition task, Ferrucci (2012) showed that both anodal as well as cathodal stimulation of the cerebellum lead to an increased ability to process negative facial expressions, whereas responses to neutral or positive facial expressions remained unchanged. Though not directly analogous to the object detection task, there exists an emotional valence to the stimuli presented in the task that could recruit the cerebellum in identifying or resolving this information.

Objectives and Hypotheses

To summarize the previous work from our laboratory described above, we have shown that both anodal tDCS stimulation over site F10, as well as cathodal stimulation over site T5, improves the ability to detect hidden objects in complex visual environments as judged through significant increases in behavioral accuracy measures with active tDCS vs. sham. Further, this learning could be related to changes in perceptual sensitivity in discriminating scenes where objects are present from those where they are not, as judged by increases in d' with active tDCS vs. sham. F10 stimulation also increases alerting attention network scores, and these scores are associated with the amount of learning observed in the object detection task. Bicephalic placement lead to an increased ability to learn the task as well, but at only about half the observed rate as the other placements. Current modeling of these cephalic/extra cephalic placements suggest electrical fields are present in sub-cortical regions, mainly in the ventral cerebellum and bilateral temporal pole areas, whereas the cephalic/cephalic placement (F10 vs. T5) does not result in electrical fields in these locations.

We therefore concluded from these studies that there may be an effect of tDCS on subcortical structures contributing to the behavioral effects on perceptual learning. In addition, we chose to focus on the cerebellum because it is easily accessible to tDCS and has been successfully stimulated with tDCS in previous studies as described above, and has also been shown to be involved in learning, error correction, and other cognitive functions that may benefit this task.

Based on these findings, the objectives of the current study are: (1) determine if the effects of electrical fields induced by tDCS in the cerebellum are contributing to the behavioral effects of tDCS reported in our previous studies of perceptual learning, including accuracy, learning and d', (2) determine how much of this variance in task performance is explained by electrical modulation of the cerebellum alone, and (3) to determine if electrical modulation of the cerebellum is contributing to the increased measures of attention reported elsewhere.

Given the complicated nature of the literature on the cerebellum's role in cognition and our current modeling studies, it was predicted that both anodal and cathodal stimulation of the cerebellum will lead to an increased ability to detect concealed objects in this task. The second hypothesis is that the cerebellum will be a predictor of variance in learning outcomes, as assessed via regression techniques. The third hypothesis is that anodal and cathodal cerebellar stimulation will lead to increased measures of attention.

Methods

Inclusion/Exclusion Criteria

All participants met the following criteria: English as a first language, no history of head injury with loss of consciousness for longer than five minutes, 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 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 also excluded.

Participants

A total of fifty-seven participants were recruited using the University of New Mexico Department of Psychology's SONA participant management system. They were all undergraduate students that received classroom credit for participating. Of these, 21 participants had to be excluded from the object detection analysis. Of these 21, twelve were excluded after having provided informed consent and beginning the task. Eight were excluded due to experimenter error (i.e. running tasks using incorrect sequences), two because the participants did not understand task instructions, and two because the task was too uncomfortable. Nine were excluded based on preexisting conditions, and never began the experiment. One was excluded for optic surgery using Teflon to correct strabismus which might alter current flow, one for a history of epilepsy, three for a history of post-traumatic stress disorder, one woman who was pregnant, two for a history of anxiety disorder, and one for being left-handed. This left 36 participants (21 female, age = 21.22 years, 5.287 SD). Of

these 36 participants, 12 received active anodal stimulation over the cerebellum, 12 received cathodal stimulation, and 12 received sham stimulation. For the Attention Network Task analysis, six of the subjects excluded from the object detection analysis due to experimenter error were successfully able to complete the task, leaving a total of 42 participants (24 female, age=21.02 years, 4.966 SD). Of these 42 participants, 14 received active anodal stimulation, 13 received active cathodal stimulation, and 15 received sham stimulation. They all provided signed informed consent to participate in the study, which was approved by the University of New Mexico Health Sciences Center Institutional Review Board.

Object Detection Paradigm

Five-second video clips from the training scenarios used in the DARWARS Ambush! virtual reality training environment (MacMillan et al., 2005) were captured for use as feedback in the task. Six-hundred still images were extracted from the videos and edited to include or remove specific objects. Target objects that were hidden in these images included explosive devices concealed by or disguised as dead animals (e.g. – camels), roadside trash, fruit, flora, rocks, sand, or building structures, and enemies in the form of snipers, suicide bombers, tank drivers, or stone-throwers. For each of the images containing target objects, a corresponding image was created which did not contain a hidden target object. There were 1200 total images created, half containing hidden target objects and half not containing them. Of these, 322 images, half containing target objects, were selected for the learning task after review of the images by research associates unaware of the locations or defining features of specific objects. The images were arranged in random order and were not presented to participants in matched pairs (target object present then absent).

Examples of images presented to participants can be found in Figure 3. Participants were instructed that they could stop the task at any time if the stimuli were too uncomfortable, or made them anxious.

Figure 3. Example images from the object detection task. The two upper panels show images where there are no objects present. The complimentary lower panels show images with objects present. Pertinent locations are circled for identification.

Attention Network Task

The Attention Network Task (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002), is a combination of the cued reaction time task and the flanker task. It requires

participants to indicate whether a central arrow, presented either above or below a central fixation cross, is pointed to the left or the right as quickly and as accurately as possible. The central arrow may or may not be surrounded by flankers, and further those flankers could be pointed in the same direction as the central arrow (congruent condition) or in the opposite direction (incongruent condition). Prior to the presentation of the arrow(s) temporal or spatial cues, in the form of an asterisk, may also be presented. These cues either occur 100ms before the stimulus and indicate that the arrow(s) will soon be presented (temporal cue; asterisks presented on the fixation point (center cue) or above and below the center fixation point (double cue)), or indicate spatial information about the arrow(s) (spatial cue; single asterisk presented either above or below central fixation point).

Three separate attentional networks can be described by this task, each relating to the different behavioral outcomes: an alerting network, an orienting network, and an executive network. Fan, McCandliss, Fossella, Flombaum, & Posner (2005) describe three distinct patterns of activation for these three networks using fMRI. For the alerting network, significant activations were found in the superior colliculus, cerebellar vermis, right superior temporal gyrus bilateral thalamus, bilateral inferior parietal lobe, left fusiform gyrus, and inferior frontal gyrus. For the orienting network, activations were found in bilateral fusiform gyri and parietal lobes, left precentral gyrus and right postcentral gyrus. For the executive network, activations were found in the thalamus and cerebellar vermis, bilateral inferior frontal gyri and fusiform gyri, right middle frontal gyrus and anterior cingulate gyrus, and left superior frontal gyrus.

tDCS Stimulation

Direct current stimulation was delivered via two ActivaDoseII Iontophoresis units hooked up to an experimental blinding box. One unit was set to the active dose of 2.0mA, and the other was set to the sham dose of 0.1mA. The blinding box had six switch settings, three set to allow the active dose to pass through to the participant, and three set to allow the sham dose to pass. The blinding box settings were unknown to both the subject as well as the experimenter, thus creating a double blind experimental design.

Two electrodes with saline soaked sponges were affixed to the participant using Coban adhesive bandage. In the active anode condition, the anode electrode was centered 2 cm inferior to the inion along the midline, and the cathode electrode was placed on the upper left arm. In the active cathode condition, the placements were identical, but the electrode polarities were reversed. In the sham condition, the placement and polarities were identical to the active anode placement, but the current was set to 0.1mA instead of 2.0mA.

Physical sensations were recorded three times during tDCS administration, once after current ramp-up (approximately one minute), four minutes following ramp-up before the first training run began (approximately 5 minutes after stimulation had begun), and immediately following the first training run (approximately 17 minutes 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 at all and 10 indicated the worst possible feeling of sensation. Any report of a seven or above resulted in immediate cessation of stimulation and termination of the experiment, without penalty to the participant.

Experimental Procedure

After providing informed consent and HIPPA authorization, participants were administered an initial questionnaire to gather information from them, including demographics, how much sleep they got the night prior to the study, amount of caffeine, nicotine, alcohol and drug consumption, level of education, and military experience. They were also given the Edinburg Handedness Questionnaire to ensure they were right handed. Participants then took a brief personality inventory consisting of 12 questions, and finally a baseline mood questionnaire. The mood questionnaire consisted of nine questions on a 0-5 Likert scale. Items included feelings of nervousness or excitement, tiredness, confusion, sadness, degree of frustration, dizziness, nausea, degree of physical pain or discomfort, and ability to pay attention. After all questions were answered and the participant was deemed eligible, the object detection task was administered.

Participants were seated in front of the computer and instructed how to respond to the stimuli, but were not given specific information about the nature of the hidden objects or any strategies with which to find them. The left keyboard arrow indicated that no object was present and the down arrow indicated that an object was present.

Testing blocks one and two consisted of 100 images each and lasted approximately six minutes. No feedback was given during these blocks, and they were used as baseline measures of the ability to discriminate images with hidden objects from those without. Next, participants completed four training runs, the first two of which (training blocks one and two) were under either active anode, active cathode, or sham tDCS stimulation, followed by two more (training blocks three and four) immediately following administration of tDCS.

The training blocks differed from the testing blocks in that after each choice, the participant was given audiovisual feedback regarding the consequence of their decision. If the participant indicated "object present" and was correct, a short video depicting the mission progressing as planned was shown. A voiceover praising the participant for choosing correctly was played as well. If the participant indicated that there was an object present when there was not, a voiceover chastised them for delaying the mission, or insulted them by indicating they were acting cowardly. If the participant indicated that there was no object present and was correct, feedback was given that the mission was progressing as planned. If they indicated that there was no object present when in fact there was one, a video showing the consequence of missing the object was shown. For example, another member of the participant's platoon was shot by a sniper, or a Humvee was destroyed by an improvised explosive device. Further, a voiceover scolded the participant for missing the object and told them that members of their team had been killed. The training blocks consisted of 60 trials and lasted approximately 11 minutes each. Each image was presented for 2 seconds with an inter-trial interval that varied from 4 to 8 seconds. The audiovisual feedback did not provide specific details of the shape or location of the target object, but enough information was available from the test image and feedback movie that the participant could infer the type and general position of the target object in the image.

Following the four training runs, two more test runs (testing blocks three and four) were administered to gage the immediate effect of tDCS on learning. A portion of the stimuli used in the immediate test had been presented during training, while the remaining stimuli were similar in content and had the same types of target objects, but had not been presented

to the subject during training. Thus, memory for trained images and the generalization of the training to novel images could be examined.

Next, the participants were given a 40-minute break and upon return were given the Attention Network Task (ANT), which consists of one training block and three experimental blocks. Participants were instructed to respond only to the center arrow, and used the "1" key on the numerical keypad to indicate a left-facing arrow or the "2" key on the keypad to indicate a right-facing arrow. A practice block was given first that included feedback to ensure that the participant understood the task. Three experimental blocks followed without feedback, with self-timed breaks in between blocks. The total time required for the ANT was approximately 20 minutes.

After the conclusion of the ANT, participants were given two delayed test blocks of the object detection task (testing blocks five and six; similar to the other testing blocks) approximately 1 hour after the end of testing block 4 to assess the lasting effects of tDCS.

Following the final test block, participants were administered an exit mood questionnaire consisting of the same nine questions in the initial mood assessment. Responses to the mood questionnaire relative to baseline were checked and if they were significantly different (a change of four or more points), the participant was asked to remain

in the lab until their ratings were comparable (typically 15 minutes). See figure 4 for a

graphical description of the experimental procedure.
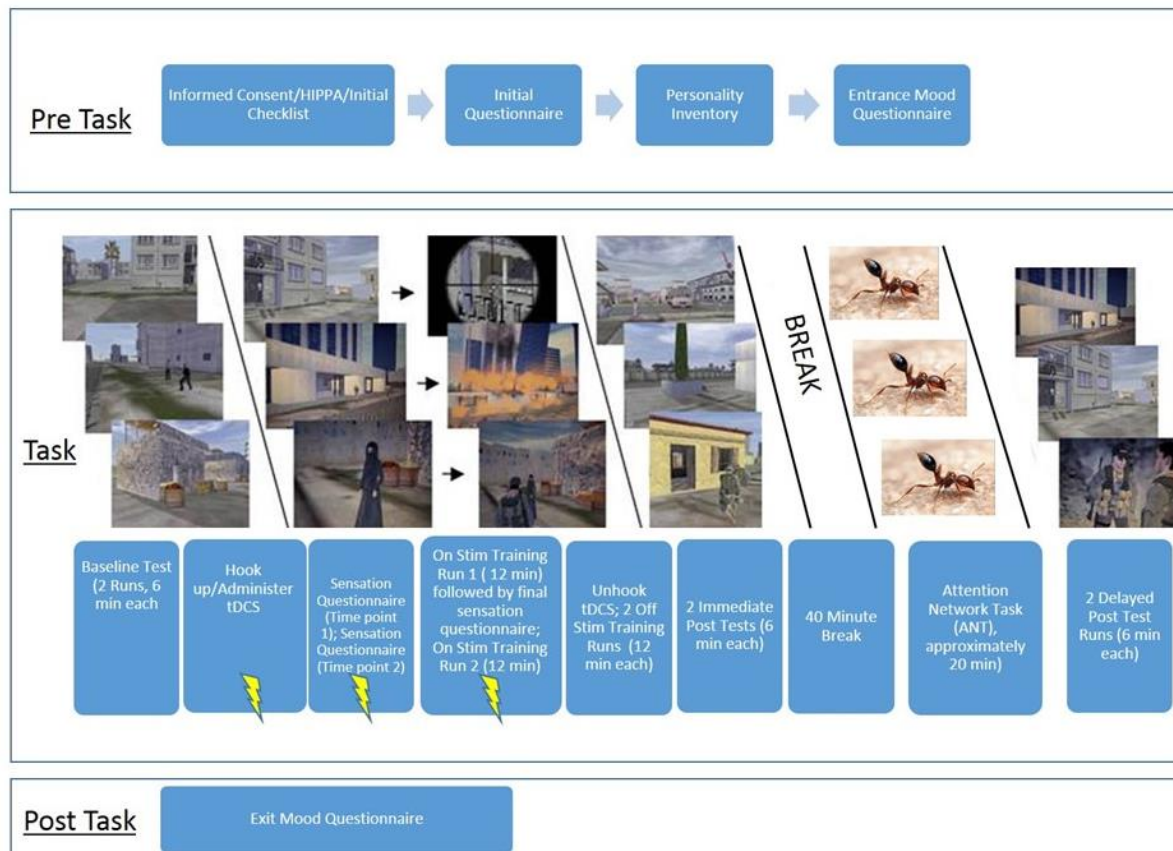
Figure 4. Experimental procedure

Finite Element Modeling

To investigate current flow in the cortex with the cerebellar tDCS montages used in

the current study, colleagues at City College New York conducted finite element modeling

(FEM). FEM of the electric fields produced under both anodal and cathodal cerebellar

stimulation conditions were performed using software developed by Soterix Medical. For a

detailed description of the procedures and assumptions in these models, please see Bikson,

Rahman, & Datta (2012).

Data Analysis: Cerebellum Only Groups

Data were analyzed within an ANOVA framework, comparing three groups (anode active, cathode active, and sham). For analysis of learning in the object detection task, seven dependent variables were calculated: baseline performance, which was the average accuracy of testing blocks 1 and 2, immediate test, which was the average accuracy of testing blocks 3 and 4, delayed test, which was the average accuracy of testing blocks 5 and 6, immediate learning, which was the difference between the immediate test and baseline test, delayed learning, which was the difference between the delayed test and baseline test, as well as the two signal detection measures (d' and β).

For the ANT, three dependent variables were calculated, all of which were based on the reaction time to correct response trials only: executive attention, which was computed as the difference in RT between incongruent and congruent flanker trial types, orienting attention, which was computed as the difference in mean RT between the spatial cue trials (average of the up and down cue trials) and the center cue trials, and alerting attention, which was computed as the difference in mean RT between the double cue trials and no cue trials. Lower scores on the executive network variable indicated better performance, whereas higher scores on altering and orienting networks indicated better performance.

Data Analysis: Regression Models

In order to investigate how much variance in the dependent variables the cerebellum accounted for, two separate regression models were built based on prior electrode arrangements. Electrode placement was dummy coded, with the cerebellum sham group serving as the reference such that in the first model, F10 anode placement and cerebellum

cathode placement were entered as predictors for two dependent variables: immediate learning and delayed learning. Data from the F10 anode placement were reported in Coffman et al., 2012. The second model used T5 cathode and cerebellum anode placements as predictors on the same dependent variables. The T5 data were the same reported elsewhere (Clark, Coffman Trumbo & Wegele, 2014).

Results

Effects of Cerebellar tDCS on Learning in the Object Detection Paradigm

One participant from the sham group had to be 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 (21 female; mean age = 21.29; SD = 5.350) were included in the overall object detection analyses. Of these, 12 received active anode stimulation, 12 received active cathode stimulation, and 11 received sham stimulation.

All participants learned the task, as evidenced by an increase in performance accuracy across time, including the baseline tests, training sessions, and immediate and delayed tests (see Figure 5a).

A 3x3 repeated measures ANOVA comparing group (active cerebellum anode, active cerebellum cathode and sham) by time (repeated measure - baseline, immediate test, delayed test) was run to investigate the effect of stimulation on the ability to detect hidden objects. Mauchly's test of sphericity was violated ($\chi^2_{(2)} = 26.376$, $p < 0.0001$), thus Greenhouse-Geisser correction was used for interpretation of within subject statistics. Results suggest a significant overall effect of time ($F_{(1.272, 40.688)} = 61.399$, $p < 0.0001$; see Figure 5b), but no significant effect of group ($F_{(2,32)} = 0.112$, ns), and no significant interaction of time by group

$(F_{(2.543, 40.688)} = 0.835$, ns). Bonferroni-corrected pairwise comparisons showed a significant increase in performance across groups from baseline between both immediate (mean difference = 0.180, $p < 0.0001$, 95% CI [0.127, 0.233]) and 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 delayed tests (mean difference = -0.027, $p = 0.011$, 95% CI [-0.049, -0.005]).
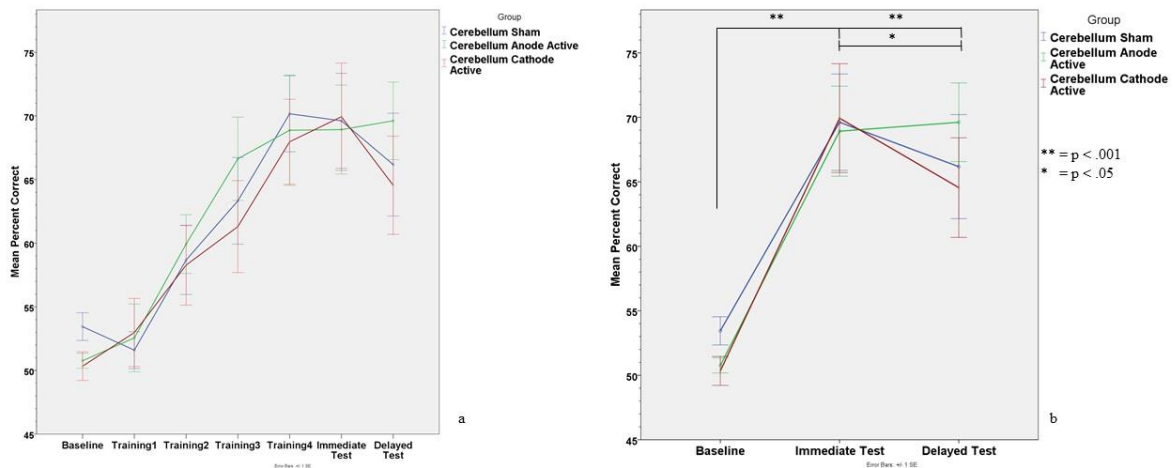

Figure 5. Performance on the object detection task. 5a shows that all groups were able to improve performance on the task, as evinced by increasing scores from baseline, through training, and onto immediate and delayed testing. 5b shows that there was an effect of time, where all groups showed significantly improved performance on both the immediate and delayed tests compared to baseline. There was a significant decrease in performance from the immediate to the delayed test, collapsed across groups. The anode group did not show a significant decrease in performance from the immediate to delayed tests, whereas the other two groups did.

A one-way ANOVA was performed to investigate the effect of group on the two

learning variables (immediate and delayed). Results suggest no effect of group on immediate

learning ($F_{(2,34)}= 0.219$, ns) or on delayed learning ($F_{(2,34)}= 0.847$, ns; see Figure 6). Contrast

tests revealed no significant differences between any two groups on either measure. Please

see table 2 for descriptive statistics from the overall object detection task analyses.
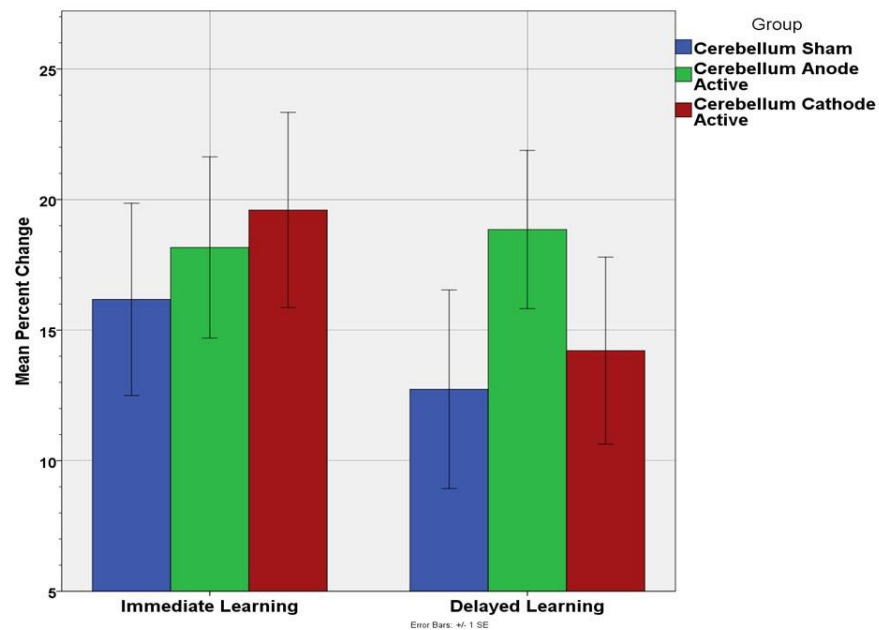

Figure 6. Learning the object detection task. There was no effect of group on either

immediate learning scores (calculated as the difference between the immediate test and the

baseline test), or delayed learning scores (calculated as the difference between the delayed

test and the baseline test).

Table 2

Descriptive statistics for immediate and delayed learning in the object detection task

		Immediate Learning	Delayed Learning
Group	N	Mean (SD)	Mean (SD)
Cerebellum Sham	11	16.9% (11.9%)	13.5% (12.3%)
Cerebellum Active Anode	12	18.2% (12.0%)	18.9% (10.5%)
Cerebellum Active Cathode	12	19.6% (12.9%)	14.2% (12.4%)

Note. There are no significant differences in means between any groups on either variable

Effects of Cerebellar tDCS on Stimulus Type in the Object Detection Paradigm

In order to investigate the effects of cerebellar tDCS on image novelty over time, a 3x2x2 repeated measures ANOVA comparing group (active cerebellum anode, active cerebellum cathode, sham) by image type (repeated measure - repeated, novel) by time (repeated measure - immediate, delayed) was run. The three way interaction (image x time x group) was not significant. The interaction between time and group was significant ($F_{(2,32)} = 4.314$, p= 0.022). Investigation of this interaction with Bonferroni-corrected pairwise comparisons showed that, collapsed across stimulus type, performance decreased between immediate and delay tests for both the sham (mean difference = -0.034, p = 0.036, 95% CI [-0.066, -0.002]) and cathode cerebellum (mean difference = -0.055, p = 0.001, 95% CI [-0.085, -0.024]) groups, but not for the anode cerebellum group (mean difference = -0.006, ns, 95% CI [-0.037, 0.024]). There was no interaction of image and group. However, there was a significant effect of image ($F_{(2,32)} = 25.759$, p < 0.0001). A pairwise comparison showed that participants were more accurate on repeated images (70.8%) compared to novel images (65.4%; mean difference = 0.054; p < .0001, 95% CI [0.032, 0.075]), collapsed across group

and time (Figure 7a). Finally, there was no overall main effect for group, the between subjects factor (Figure 7b).
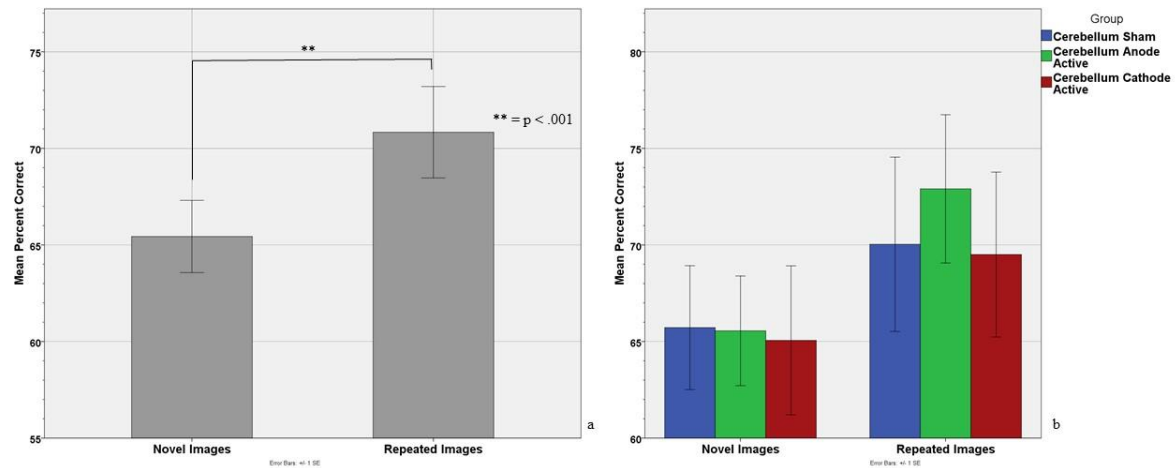

Figure 7. Effect of stimulus type on performance. 7a shows an effect of image type. When collapsed across groups, participants were more accurate on trials where images were repeated from training compared to novel images. 7b shows there was no significant effect of group on performance when images were novel or repeated.

Effects of Cerebellar tDCS on Signal Detection Measures in the Object Detection Paradigm

To investigate the effects of cerebellar tDCS on measures of signal detection, two separate 3x3x3 repeated measures ANOVAs were run, one for perceptual sensitivity (d'), and another for response bias (β). Both were of similar design, comparing group (active cerebellum anode, active cerebellum cathode, and sham) by image type (repeated measure – novel, repeated) by time (repeated measure – baseline d'/ β, immediate test d'/ β, delayed test d'/ β).

For d', the assumption of sphericity was not met ($\chi^2_{(2)}$ = 22.291, p < 0.0001), thus all within subject effects were Greenhouse-Geisser corrected. Results suggest a significant main effect of time ($F_{1.322,42.306}$ = 51.077, p < 0.0001), but no significant effect of group ($F_{(2,32)}$ = 0.473, ns) nor a significant interaction with time ($F_{(2.644,42.306)}$ = 0.875, ns) was observed. Individual Bonferroni-corrected pairwise comparisons suggest that across groups, participants performed significantly better compared to the baseline test at both immediate (mean difference = 0.936, p < 0.0001, 95% CI [0.626, 1.247]) and delayed (mean difference = 0.806, p < 0.0001, 95% CI [0.529, 1.083]) tests (see Figure 8a for effect of time and 8b for effect of group). However there was no significant difference between the immediate and delayed tests (mean difference = 0.131, p = 0.075, 95% CI [-0.010, 0.271]).
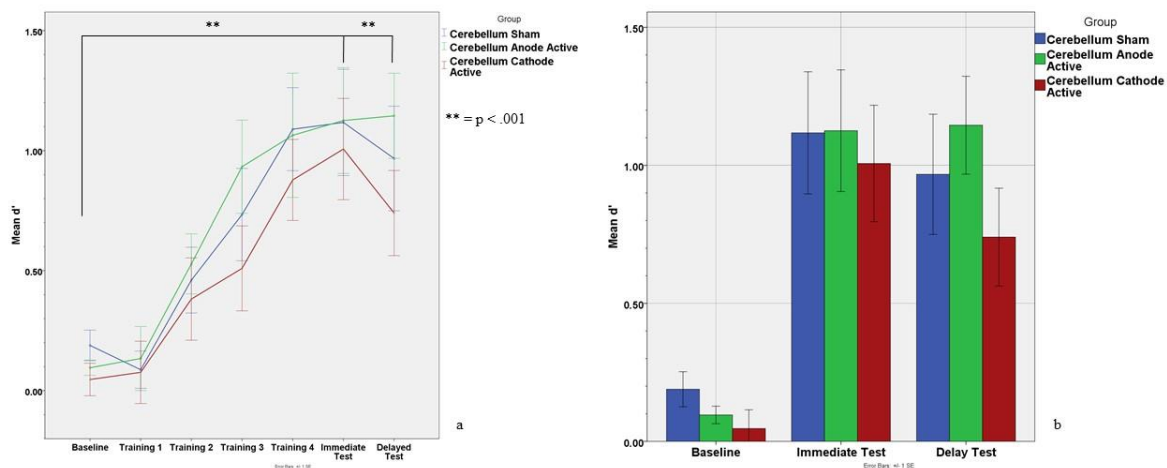

Figure 8. Perceptual sensitivity. 8a shows that perceptual sensitivity (d') improved over time. Collapsed across group, there was a significant increase in d' between both immediate and delayed tests compared to baseline. 8b shows that there was no effect of group on d' for baseline, immediate, or delayed tests.

For β, three participants had to be excluded from the analysis, two for mean scores greater than 3 SD from group means (one for the immediate test and one for the delayed test) and one for incomplete data. This left 33 total participants (20 female, mean age = 21.30, SD = 5.51).

The assumption of sphericity was not met ($\chi^2_{(2)} = 10.530$, p = 0.005) thus all within subject effects were Greenhouse-Geisser corrected. Results suggest a marginal main effect of time ($F_{(1.533, 45.995)} = 3.724$, p = 0.042), but neither group ($F_{(2.30)} = 2.121$, ns) nor their interaction ($F_{3.066, 45.995} = 2.052$, ns) were significant. Bonferroni-corrected pairwise comparisons of time revealed no significant differences between the baseline test and either the immediate or the delayed tests, nor any difference between the immediate and delayed tests (see Figure 9a for effect of time and figure 9b for effect of group).
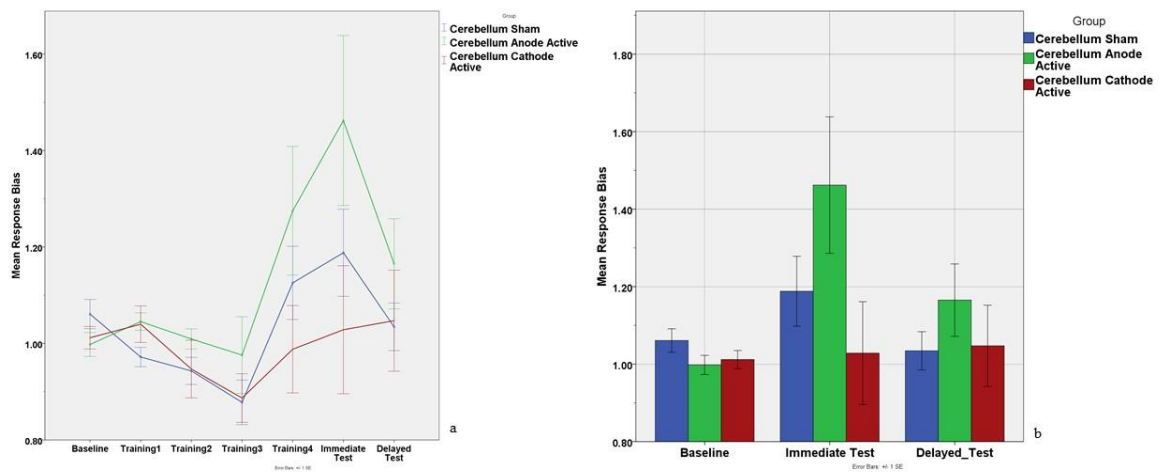

Figure 9. Response bias. 9a shows response bias values from the baseline test, through training, and on the immediate and delayed tests. There was a marginal overall effect of time (p = 0.042), but no individual Bonferroni-corrected pairwise comparisons between the

baseline test and either the immediate or delayed tests were significant. This suggests that participants were slightly more likely to choose the "no object present" option following stimulation and training. 9b shows that there was no effect of group on response bias.

Effects of Cerebellar tDCS on Measures of Attention

Three participants had to be excluded from analysis of the ANT because their accuracy was less than 90%, suggesting they were not engaged in the task. The task is rather uninteresting, but extremely simple in terms of being able to accurately perform it if attention is paid by the participant. Low accuracy scores therefore indicate disengagement from the task, not a difficulty in performing it. Therefore, 38 participants (21 female; mean age = 21.05, SD = 5.204) were included for the ANT analyses. Of these 13 received active anodal stimulation, 12 received cathodal stimulation, and 13 received sham stimulation.

A one-way ANOVA comparing group performance (active cerebellum anode, active cerebellum cathode, sham) on measures of attention (alerting, orienting, and executive attention scores) showed no effect of group for the alerting network ($F_{(2,37)} = 0.882$, ns), the orienting network ($F_{(2,37)} = 1.747$, ns), or the executive network ($F_{(2,37)} = 0.555$, ns). No Bonferroni-corrected pairwise comparisons between groups on the three attention network measures were significant either (see Figure 10 for effect of group on ANT network scores).
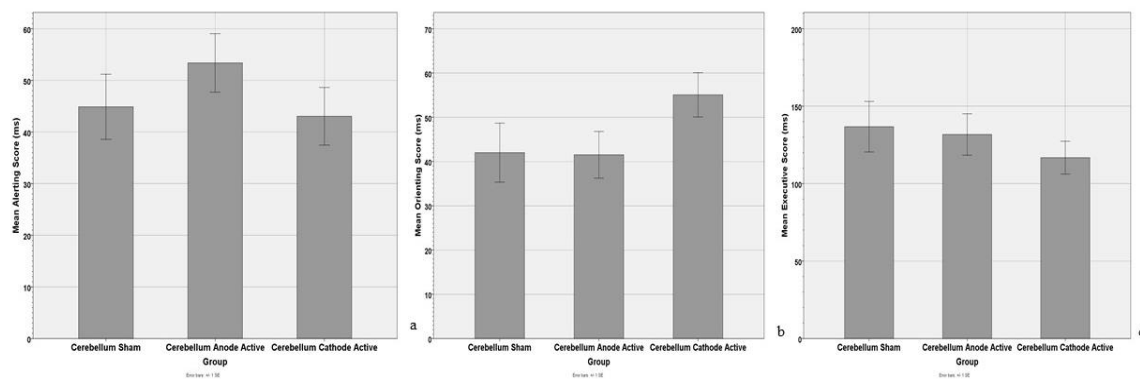
Figure 10. Attention Network Task (ANT) scores. There was no effect of cerebellar anode or cathode stimulation on attentional alerting (10a), orienting (10b), or executive (10c) network scores compared to the sham group.

Regression Models

Electrode placements (F10 anode, T5 cathode, cerebellum anode, cerebellum cathode, cerebellum sham) were dummy coded in SPSS. The reference group for both regression models was the cerebellum sham group.

For the F10/cerebellum cathode regression, 24 participants (16 female, mean age = 23.13, SD = 7.686) were included. Of these, 12 participants received active F10 anodal stimulation and 12 received active cerebellar cathodal stimulation.

Results suggest that the overall model is a significant predictor of immediate learning ($F_{(2,34)} = 5.079$, p = 0.012) and the model predicted 23.5% of the variance. While the F10 anode placement was a significant predictor (b = 0.132, $t_{(33)} = 3.015$, p = 0.005, 95% CI [0.043, 0.221]), cerebellum cathode placement was not (b = 0.027, $t_{(33)} = .612$, ns, 95% CI [-0.062, 0.116]). For the delayed learning variable, the overall model was again significant ($F_{(2,34)} = 5.069$, p = 0.012) and predicted 23.5% of the variance. The F10 anode placement was a significant predictor (b = 0.124, $t_{(33)} = 2.837$, p = 0.008, 95% CI [0.035, 0.212]) but the

cerebellum cathode (b = 0.007, $t_{(33)}$ = .008, ns, 95% CI [-0.081, 0.096]) was not (see Figure

11 for regression plots with the F10 anode vs. cerebellum cathode placements.

Figure 11. Partial regression plots for the F10 anode vs. cerebellum cathode models. 11a,b

show regression plots for the immediate learning outcome. Note that the F10 anode

placement (11a) was a significant predictor, whereas the cerebellum cathode (11b) was not.

11c, d show regression plots for the delayed learning outcome. Again, the F10 anode

placement (11c) was a significant predictor in the model, whereas the cerebellum cathode

(11d) was not.

For the T5 cathode/cerebellum anode model, a 1.5 SD cutoff was used for outlier

removal, because that threshold was used in Clark, Coffman, Trumbo & Wegele (2014).

Further, upon investigation of the data, it was determined that one participant was not right

hand dominant according the Edinburgh handedness questionnaire, and was removed from analysis. Thus, for this regression model, 22 participants (13 women, mean age 23.5, SD = 9.63) were included. Of these, 12 received active cerebellum anode stimulation and 10 received active T5 cathode stimulation.

Results suggest that the overall model does not significantly predict scores on the immediate learning variable ($F_{(2,31)}$ = 1.366, ns), nor the delayed learning variable ($F_{(2,31)}$ = 2.183, ns). The T5 placement was only found to be a significant predictor in the delayed learning variable (b = 0.098, $t_{(31)}$ = 2.076, p = 0.046, 95% CI [0.002, 0.194]), but not in the immediate learning variable. Further, the cerebellar anode placement was not a significant predictor in either model (see figure 12 for regression plots with T5 vs. cerebellum anode placements).
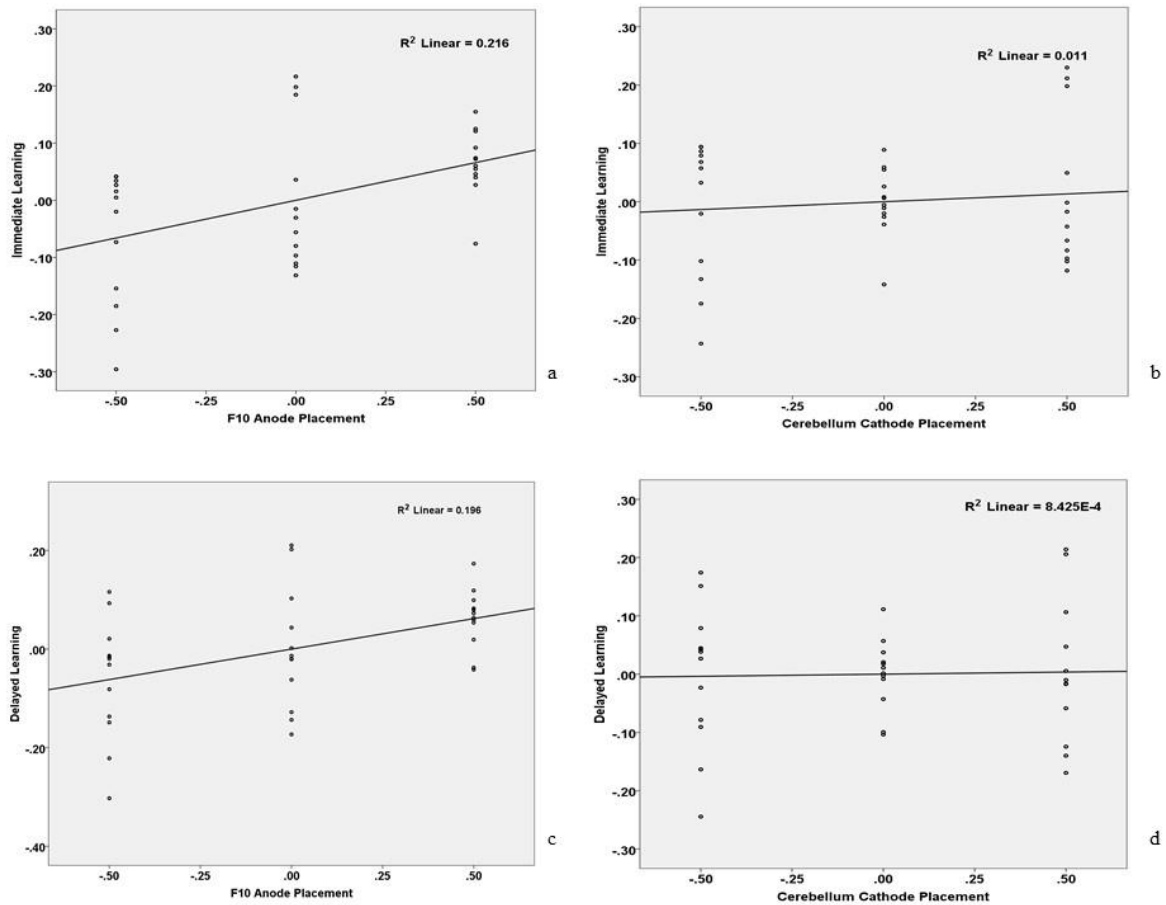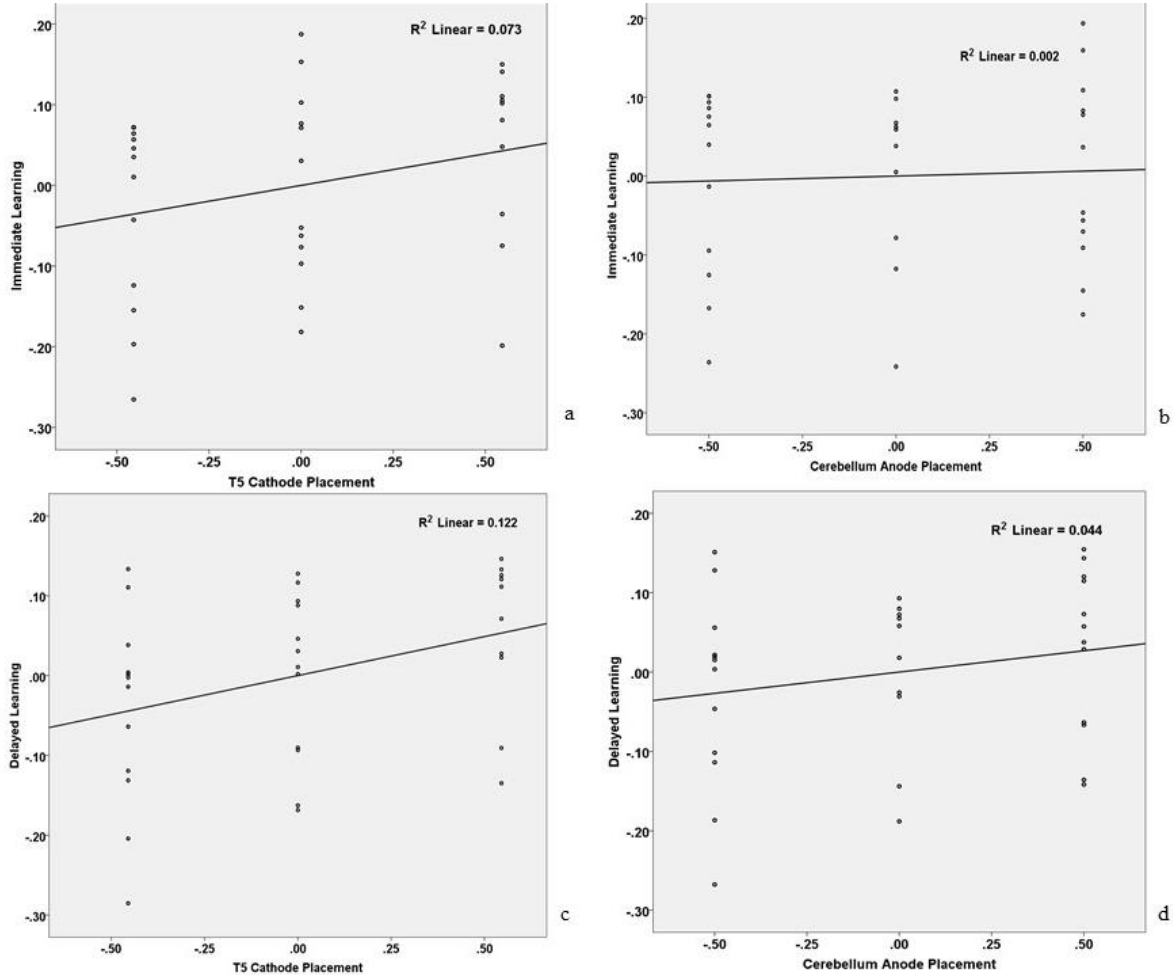
Figure 12. Partial regression plots for the T5 cathode vs. cerebellum anode models. 12a,b show regression plots for the immediate learning outcome. Note that neither T5 cathode (11a) nor cerebellum anode (11b) were significant predictors. 11c, d show regression plots for the delayed learning outcome. Note that the T5 cathode placement (11c) was a significant predictor in the model, whereas the cerebellum anode (11d) was not.

This finding is unexpected, as T5 has been shown to increase learning in this task, however, there were several differences between the current study and the initial report of this finding. One glaring difference is the fact that in the previous report, the sham group had 23 participants and a mean learning score of 13.35% for the immediate learning variable,

whereas for the current study the sham group has only 12 participants and a mean learning score of nearly 17%. This difference is not significant, however, $(t_{(33)} = 0.876, p = 0.3871)$. Also, the removal of an additional subject from the T5 group (due to being right-handed), could also be contributing to this phenomenon, as removing this data resulted in the mean score of the T5 group being reduced slightly.

The disproportionate sample sizes, which effects the ability to detect statistical differences by altering degrees of freedom available, combined with the difference in performance between the two sham groups is hypothesized to be contributing to the lack of replication and difficult interpretation of the regression analyses in the current study.

Physical Sensation during Cerebellar tDCS

To investigate the dynamics of physical sensations experienced during tDCS, a 3x3x3 repeated measures ANOVA comparing group (anode active, cathode active, sham) by sensation rating (repeated measure – itching, heat/burning, tingling) by time (repeated measure – immediately at current ramp up, 5 minutes after the start of administration, after conclusion of the first training run) was run.

Main effects were observed for sensation $(F_{(2,66)} = 5.695, p = 0.005)$, group $(F_{(2,33)} = 8.483, p = 0.001)$ and time $(F_{(2,66)} = 13.997, p < 0.0001)$. The three-way interaction of time, sensation and group was also significant $(F_{(8,132)} = 2.050, p = 0.045)$. Further investigation of the three-way interaction showed significant two-way interactions between sensation and group $(F_{(4,66)} = 10.047, p < 0.0001)$ as well as between time and group $(F_{(4,66)} = 6.544, p < 0.0001)$.

Bonferroni-corrected pairwise comparisons for the sensation by group interaction revealed that collapsed across time, the sham group had lower mean scores for itching compared with both the active anode group (mean difference = -2.139, $p < 0.0001$, 95% CI[-3.187, -1.091]) and the active cathode group (mean difference = -1.111, $p = 0.035$, 95% CI[-2.159, -0.063]). The difference between the two active groups showed higher scores for the anode group compared to the cathode group (mean difference = 1.022, $p = 0.030$, 95% CI[0.077, 1.967]). For heat/burning ratings, the sham group had lower scores compared to the cathode group (mean difference = -1.778, $p = 0.001$, 95% CI[-2.854, -0.702]). The anode group had lower scores compared to the cathode group as well (mean difference = -1.417, $p = 0.007$, 95% CI[-2.493, -0.341]). Finally, the sham group reported lower sensations of tingling than both the anode active (mean difference = -1.084, $p = 0.013$, 95% CI[-1.979, -0.189]) as well as the active cathode (mean difference = -0.976, $p = 0.033$, 95% CI[-1.889, -0.063]) groups.

For the time by group interaction, Bonferroni-corrected individual pairwise comparisons revealed that at the first sensation rating (1 min after current was started), the sham group reported significantly lower sensations than both the anode (mean difference = -2.028, $p < 0.0001$, 95% CI[-3.215, -0.841]) and cathode (mean difference = -1.944, $p = 0.001$, 95% CI[-3.131, -0.758]) groups. There was no difference between the active groups at this time point. At the second time point, the sham group reported lower sensations than the cathode group (mean difference = -1.194, $p = 0.016$, 95% CI[-2.206, -0.183]). No other differences were observed at the second time point. For the third time point, the sham group reported lower sensation than the cathode group (mean difference = -0.750, $p = 0.035$, 95% CI[-1.458, -0.042]). No other significant differences were observed.

Investigation of the main effect of sensation showed that itching was the sensation rated the highest, collapsing across groups and time. It was rated significantly higher than heat (mean difference = 0.537, p = 0.001, 95% CI[0.189, 0.885]) but not tingling. Tingling was rated higher than heat (mean difference = 0.407, p = 0.036, 95% CI[0.021, 0.794]).

The investigation of the main effect of time showed that sensation ratings fell from the initial rating to the second rating (mean difference = -0.380, p = 0.019, 95% CI[-0.790, -0.051]), and again from the second rating to the third (mean difference = -0.296, p = 0.019, 95% CI[-0.553, -0.040]).

Finally, a one way ANOVA was run comparing active groups (both anode and cathode) with the sham group for each of three types of sensation ratings. Results suggest that the active groups rated sensations higher for itching ($F_{(2,39)}$ = 15.447, p < .0001), heat ($F_{(2,39)}$ = 10.362, p < .0001), and tingling ($F_{(2,39)}$ = 5.584, p = .007) compared to the sham group. Please see Table 3 for descriptive statistics of sensation ratings and Figure 13 for effects of condition (13a), group (13b), and time (13 c-e) on reported sensation.

Table 3

Descriptive statistics for sensation ratings

Group	N	Itching	Heat/Burning	Tingling
		Mean (SD)	Mean (SD)	Mean (SD)
Cerebellum Sham	15	0.36 (0.62)	0.11 (0.21)	0.51 (0.71)
Cerebellum Active Anode	14	2.38 (1.04)	0.64 (0.83)	1.59 (0.89)
Cerebellum Active Cathode	13	1.35 (1.22)	1.82 (1.58)	1.48 (1.25)

Note. All mean ratings are well below the threshold to stop stimulation (7). Ratings for the sham group are lower for all sensations compared to both active groups
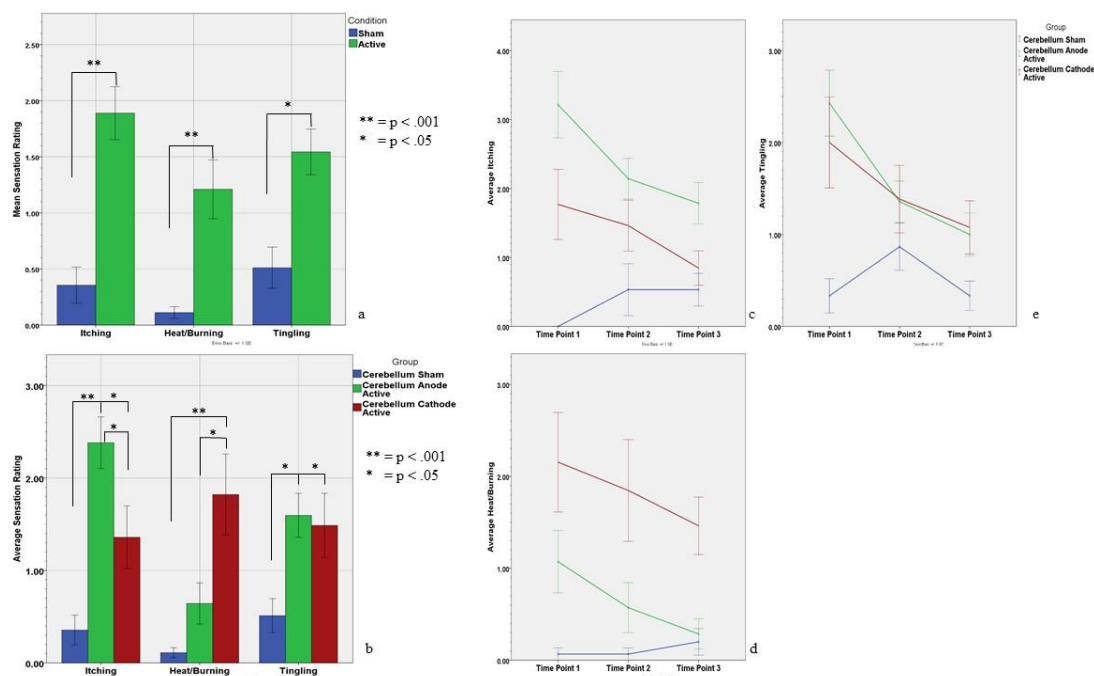
Figure 13. Effects of cerebellar stimulation on sensations of itching, heat/burning, and tingling. 13a shows that there was a significant difference in the reported level of all three sensation types between the active and sham groups. 13b shows that there was a significant difference in itching between the sham group and both anode and cathode active groups, as well as a significant difference between the two active groups. It further shows a significant difference between the sham and cathode group on reported heat/burning, as well as a difference between the two active groups. Lastly, it shows a significant difference between the sham group and both active groups on measures of tingling. 13c-e shows that ratings of sensation generally were reduced from the first to the third time points. 13c shows that the sham group showed an increase in itching from time point one to time point two, while the active groups showed a reduction from time point one to two and from two to three. 13d shows that the sham group showed an increase in report of heating from time point two to time point three, whereas the active groups showed reductions from one to two and from two to three. Finally, 13e shows that the sham group reported an increase in tingling from time

point one to time point two, and a reduction from time point two to three, whereas the active groups showed reductions from time point one to two and again from two to three.

Falcone, Coffman, Clark, and Parasuraman (2012) suggested that the degree of sensation of tingling was positively associated with hit rate, but not false alarm rate. Further, Coffman et al. (2012 a, b) did not report any association of sensation with measures of performance on the object detection task or on measures of attention, respectively. In the current study, correlations revealed that both ratings of heat/burning and tingling were positively associated with measures of orienting attention ($r = 0.328$, $p = 0.045$; $r = 0.376$, $p = 0.020$ respectively; see Figure 14). However, no other significant correlations were observed for any other metric in this manuscript.
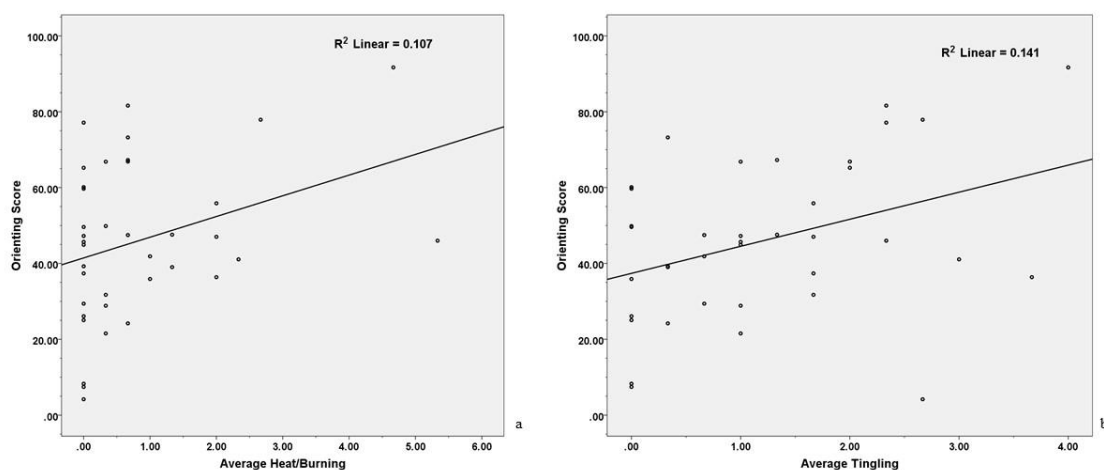
Figure 14. ANT orienting scores were positively and significantly correlated with self-reported measures of heat/burning (14a) as well as measures of tingling (14b) collapsed across group.

The last question on the exit mood questionnaire asked participants to indicate what group they thought they were assigned to, and to describe in their own words their experience with tDCS. They had three options: "active," "sham," or "unable to tell." To investigate

whether or not participants were able to accurately predict what condition they were in, two chi-square tests were run, one including only those participants who ventured a guess to which group they had been assigned, and another including those who responded "unable to tell" as well.

Results suggest that, for those participants who guessed either "active" or "sham," the groups were independent from each other and thus no group was better at prediction than any other group ($\chi^2_{(1)} = 0.287$, ns). After including the "unable to tell" respondents, the pattern of results was similar ($\chi^2_{(2)} = 2.544$, ns). Thus, the switch box provided blinding of both the participant as well as the researcher to the experimental condition to which the participant was assigned. Further, though there were group differences between active and sham conditions, the degree of physical sensation reported did not allow participants to infer the group to which they had been assigned.

Ratings of Mood Preceding and Following Cerebellar tDCS

To investigate any effects tDCS had on self-reported mood questions, a 3x9x2 repeated measures ANOVA was run comparing group (anode active, cathode active, sham) by question (repeated measure - nine questions in the questionnaire) by time (repeated measure – baseline and follow-up). One additional subject had to be removed from analysis because baseline mood questionnaire data were lost. This left a total of 35 subjects, 12 in the sham group, 11 in the active anode group, and 12 in the active cathode group.

 Results suggest no main effects of group nor of time. No significant mood by group or time by group interactions were observed. A significant interaction of mood by time ($F_{(4.674, 149.566)} = 25.231$, $p < 0.0001$; Greenhouse-Geisser corrected for within subject

comparisons) was observed, however. Bonferroni-corrected pairwise comparisons showed

that across groups, participants rated feelings of being nervous or excited higher before

receiving tDCS and completing the experiment than after (mean difference = 1.841, p <

0.0001, 95% CI[1.386, 2.296]). Ratings of feeling tired or fatigued increased from baseline to

follow-up assessments (mean difference = 1.003, p < 0.0001, 95% CI [.592, 1.413]).

Participants showed a slight, but significant, increase on feelings of lightheadedness or

dizziness from baseline to follow-up (mean difference = 0.301, p = 0.042, 95% CI [.011,

0.590]). Finally, ratings of inattentiveness were significantly higher at the follow-up

assessment (mean difference = 0.793, p < 0.0001, 95% CI [0.415, 1.171]; Figure 15). These

results suggest that stimulation did not influence any self-reported measures of mood.
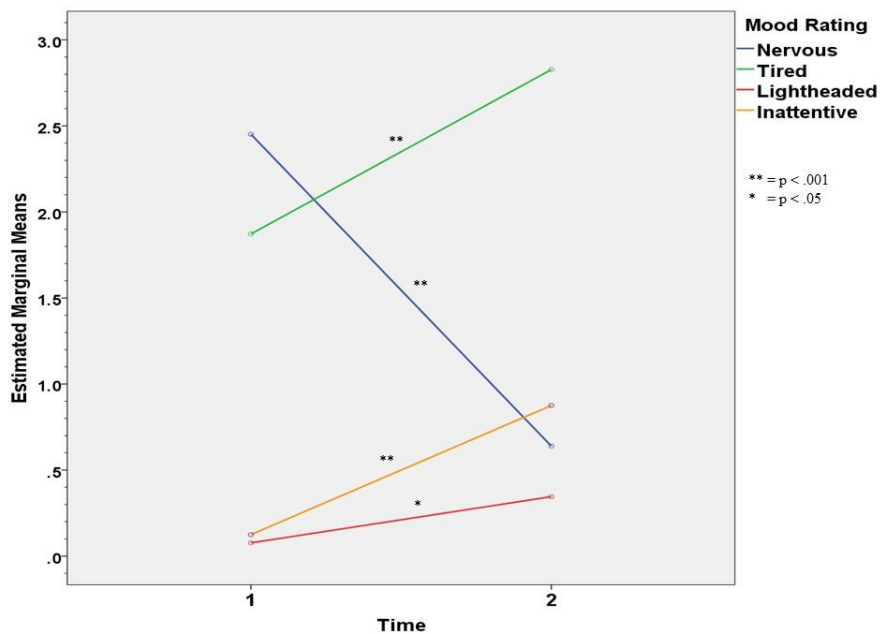
Figure 15. Changes in self-reported mood ratings. Feelings of nervousness were significantly

higher before training and stimulation than after, collapsed across groups, while feelings of

tiredness, lightheadedness and inattentiveness were significantly increased after training and

stimulation compared to baseline.

Finite Element Models

Results of finite element modeling of cerebellar tDCS are presented in Figure 16. Results suggest that during active stimulation of 2.0mA, there is an electric field effect in the cerebellum as well as left occipital cortex. Under 0.1mA sham stimulation, no electric field effect was observed in the cerebellum.

Figure 16. Finite element modeling of cerebellar tDCS. The top row shows active (2.0mA) anode stimulation over the cerebellum. The bottom row shows sham (0.1mA) stimulation. The first column is an inferior axial view of the cortex, and the second column is a posterior coronal view. Further, there appear to be no effects in the cerebellum nor any other region under sham stimulation.

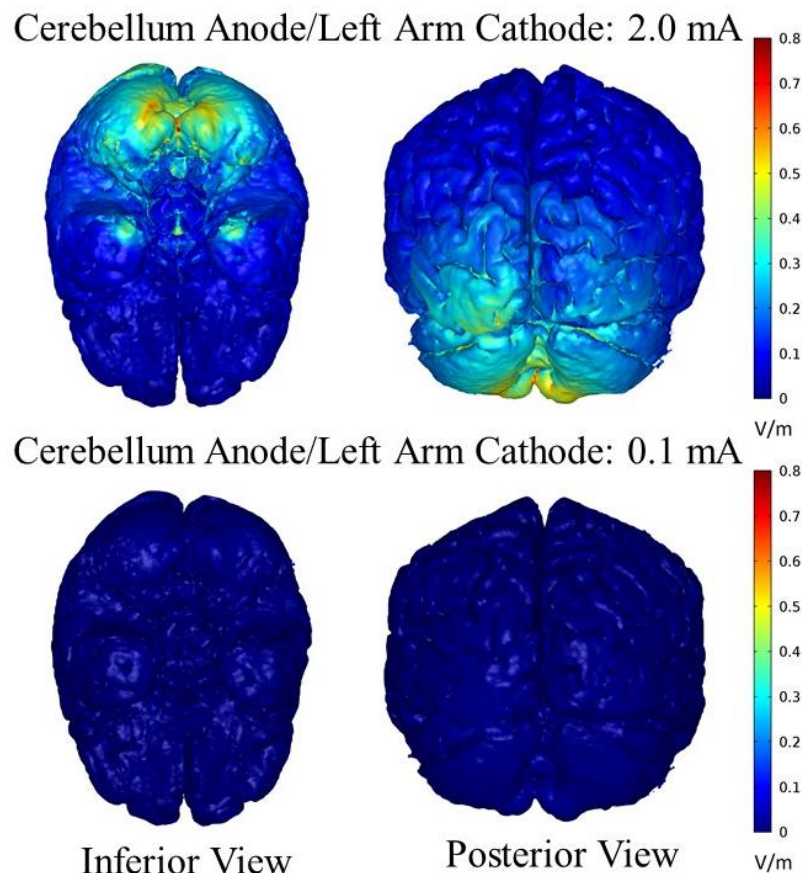Figure 17 shows a comparison of F10 anode/left arm cathode, cerebellum anode/left arm cathode, and the F10 anode/T5 cathode placements. Results of these models suggest that similar areas of the cerebellum show an electric field effect during F10/left arm stimulation as well as cerebellum anode stimulation, whereas the F10/T5 model suggests no effect in the cerebellum.
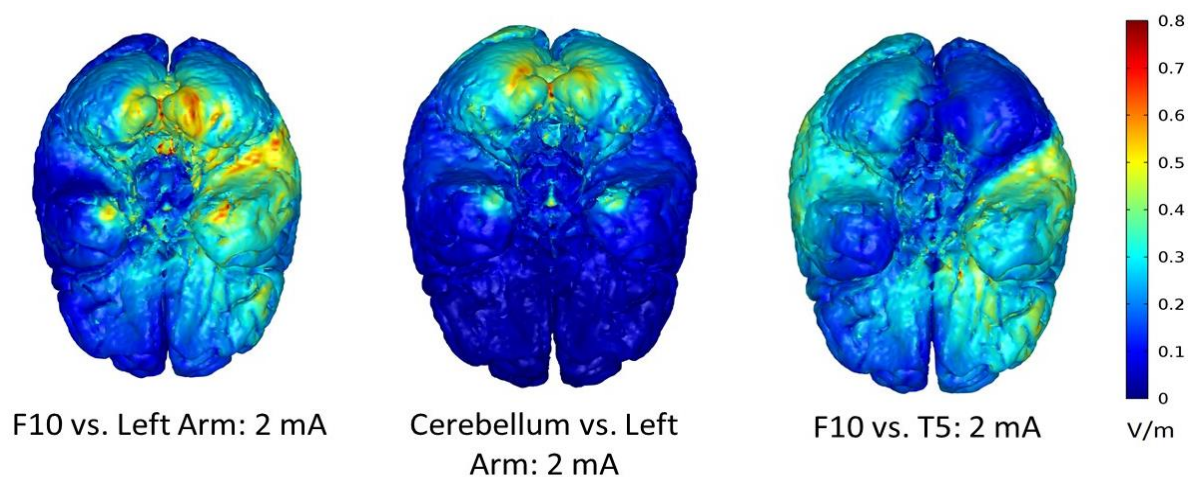
Figure 17. Finite element modeling of prior tDCS montages. The left image shows active (2.0mA) anode stimulation over F10. The middle image shows the placement for the current study. The right image shows the F10 anode/T5 cathode placement. Note that similar areas in the cerebellum show an effect during both F10 and direct cerebellar stimulation, whereas the F10 anode/T5 cathode placement shows no such effect.

Finally, Figure 18 shows subcortical effects of tDCS under both F10 anode/left arm cathode and cerebellum anode/left arm cathode stimulation. Results of these models suggest that anodal F10 stimulation produces larger field effects in subcortical areas, namely in the striatum, basal ganglia, amygdala, as well as brain stem structures including the pons.
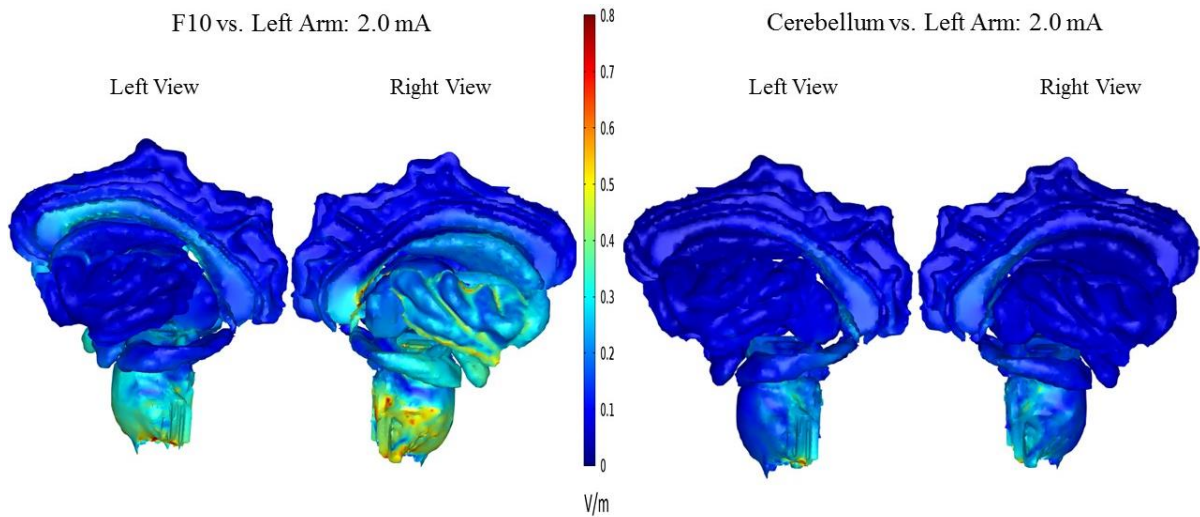
Figure 18. Finite element modeling of subcortical structures under F10 anode/left arm cathode and cerebellum anode/left arm cathode placements. Note that in the F10 model (left), there are large electric field effects predicted in subcortical areas, including basal ganglia, amygdala, striatum, and brainstem structures including the pons. These areas do not appear to show an effect during anodal cerebellum stimulation (right).

Discussion

The main objective of the current study was to investigate, based on prior imaging, behavioral, and modeling studies, the potential contribution of a far-field effect of tDCS in the cerebellum on learning a difficult object detection task. The second objective was to investigate the effects of cerebellar tDCS on measures of attention. Discussed below are each of the findings of the current study, followed by a general discussion as well as conclusions, limitations, and future directions.

Cerebellar tDCS Effects on Learning in the Object Detection Paradigm

We failed to detect any effects in performcae between groups when stimulating the cerebellum directly using either anodal or cathodal tDCS, contrary to the hypotheses. Participants did learn the task, as they improved their ability to detect hidden objects from the baseline tests through training and on to the immediate and delayed tests, but there were no significant effects of either type of stimulation compared to the sham control group. It could be the case that the effects are so small that a much larger number of subjects would be required to detect a difference. The group numbers for the current study were based on large effect sizes observed with the cephalic (F10 and T5) placements.

To investigate the degree of effect size for the current study, calculations were made using the immediate learning variable, which is the primary measure of learning most often reported in other studies from our lab. The results suggest a very small effect of .10, and thus very large sample sizes would be needed in order to detect any differences between groups.

Cerebellar tDCS Effects on Novel vs. Repeated Images in the Object Detection Paradigm

No significant interactions of stimulation condition and image type were found in the current study. There was an effect of image type collapsed across groups, where participants were more accurate in identifying repeated test images compared to novel test images. There was also an interaction observed between test time and group. When collapsed across stimulus type, the sham and active cathodal groups showed a reduced ability to detect concealed objects when comparing the immediate to delayed tests (6.6% reduction in the sham group and a 5.5% reduction in the active cathode group), whereas the anode group did

not (<1% reduction). This finding suggests that the active anodal group did not lose the ability to detect hidden objects at a similar rate as the other groups. It was expected that participants would be more accurate when detecting objects in images that were repeated compared to novel, but since there was no significant effect of group, the data suggest that direct cerebellar stimulation, regardless of direction, did not influence performance in any significant way, contrary to our hypotheses.

Cerebellar tDCS Effects on Signal Detection in the Object Detection Paradigm

As with other measures, stimulation of the cerebellum with either anodal or cathodal tDCS resulted in a failure to detect differences between groups on signal detection measures. For perceptual sensitivity, there was an effect of time, where d' values were increased at both the immediate and delayed tests compared to baseline, but there was no significant effect of stimulation condition.

Investigation of response bias produced similar results. There was an effect of time, where across all groups β values increased from baseline to immediate and delayed tests, but no corrected comparisons were significant. The increase in β values suggests that over time participants were biased toward responding that no object was present, but again, since there was no significant difference between groups, tDCS did not appear to affect response bias.

Cerebellar tDCS Effects on Measures of Attention

The attention network task (ANT) describes three separate attentional networks: orienting, alerting and executive, each of which have been shown to reflect their own signature neural substrate. We found that neither increasing excitability of the cerebellum with anodal stimulation nor decreasing excitability with cathodal stimulation led to an

improvement in performance in any measure of attention in this task compared to the sham group. This is not entirely surprising, as the brain networks described as being involved in this task include mainly frontal areas, and specifically include right inferior frontal gyrus. Recall that site F10 sits right over this area and the only time we observed an effect of tDCS on the ANT was with that placement. ANT Data for cathodal tDCS over site T5 were never collected. It would be interesting to investigate what, if any, effect this placement has on measures of attention.

Regression Models

In an attempt to describe the amount of variance explained in learning outcome variables in the object detection task with the various electrode placements used in this and previous studies, regression models were utilized. The comparison group for the regressions was the cerebellum sham group, which performed slightly better (about 4%) than other sham groups, which made interpretation of the models slightly more difficult.

For the first model, F10 anode placement and cerebellum cathode placement were included as predictors for both immediate learning and delayed learning variables. The overall model predicted a significant amount of the variance in both the immediate and delayed learning variables. This effect was being driven almost entirely by the F10 placement, as it was a significant predictor in the immediate learning variable, whereas the cerebellum cathode placement was not.

The model overall was significant for the delayed learning variable, which was again being driven by the F10 placement. The cerebellum cathode placement was not a significant predictor.

The second model included the T5 cathode placement and the cerebellum anode placement as predictors of the immediate and delayed learning variables. The overall model was not a significant predictor of either variables, and neither the T5 cathode nor cerebellum anode placements were significant predictors on their own for the immediate learning variable. T5 was a significant predictor in the delayed learning variable. This was an unexpected and puzzling finding, especially since it has been reported that cathodal stimulation over T5 shows an effect on learning. This could be a limitation of the analytic method used or could be due to the high performing sham group from the current study.

Physical Sensation Measures and Relationships with Performance

Experimenter and participant blinding is important when conducting research with brain stimulation. If the researcher is aware of the experimental condition to which a participant is assigned, they could introduce a bias in the way the participant performs the task. In addition, it could be the case that a participant could be aware of which condition s/he is in based on the physical sensations they feel during stimulation.

In the current study, there were significant differences between the active groups and the sham group on the self-reported ratings of sensation, specifically for itching and heat. Although ratings of sensation diminished over time for all groups and for all different types of sensations, the sham group reported less intense feeling of both itching and heat compared to both active groups, but there was no difference on ratings of tingling. However, when the two active groups were collapsed into one group, there was a significant difference in tingling. This finding has implications in terms of experimental blinding as it could suggest that participants could accurately deduce to which condition they had been assigned and performance could be biased accordingly.

Participants were asked to guess to which group they thought they had been assigned prior to ending the experiment, following the exit mood questionnaire. They had the option of indicating they did not know (the question did not require a forced-choice answer). A chi-square test showed that, in fact, participants were not able to guess to which they had been assigned, as there was no relationship between actual group assignment and guesses made by participants, regardless of whether the "unable to tell" responders were included or not.

This suggests that the experimenters as well as subjects were blinded to experimental conditions via a current blinding box. There were significant differences in the level of sensation ratings between groups, and this could have affected performance. This is unlikely, however, because if there were a positive bias introduced by the sensation ratings, one would expect to see a behavioral difference in performance between groups, something that was not observed in the current study. In fact, the only association found between any performance measure and rating of sensation was that higher ratings of heat lead to increased orienting scores, but performance on that measure was not different between groups.

It could also be the case that the level of sensation was distracting the participants, and though tDCS was working to improve the ability to detect objects, the distraction from sensation overpowered that effect. This has not been observed in any other of our studies, and the mean ratings for the three sensation types were well below the 7-point criteria for secession of stimulation. This suggests that though there was a difference between groups on measures of sensation induced by tDCS, these physical sensation did not distract participants from being able to perform the task as optimally as possible.

Changes in Mood Associated with tDCS

There were several changes in mood that were discovered in this experiment as well. Participants were more likely to rate feelings of anxiety or nervousness higher before tDCS than after, which is not unexpected as all participants were tDCS-naïve and would understandably have some apprehension regarding the experiment. Ratings of being tired or fatigued increased from baseline assessment to follow-up. This is also not unexpected, as the experiment lasted a total of 4 hours, thus some degree of fatigue is expected. Interestingly, ratings of both lightheadedness and inattentiveness were higher at the follow-up assessment compared to baseline. Though lightheadedness could be a side-effect of tDCS, ratings were low overall, and there was no significant effect of stimulation condition on mood, which suggests these findings were related to the length of the experiment, not a result of tDCS. There were no indications or reports of these feelings being uncomfortable or worrisome to participants.

Finite Element Models

Finite element modeling approximates how electrical fields are distributed through the skull and into the brain during tDCS. One must interpret the findings with caution, however. 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. The initial models of the F10 anode/shoulder cathode and T5 cathode/shoulder anode placements showed subcortical effects of stimulation, mainly in bilateral temporal poles and ventral medial cerebellum.

The results of the electrode placements for the current study suggest that similar areas in the ventral cerebellum that show an electric field effect in the F10 vs. contralateral upper arm placement were targeted. Empirical investigation of this assertion is beyond the current technology, however. There exists no way to derive an estimate of the difference in electric field effects between the F10 anode/left arm cathode montage and the cerebellar anode/left arm cathode montage with the finite element modeling software used. Having such information would be important in determining just how similar the cephalic vs. extra cephalic placements (F10 and T5 vs. upper arm) are to the placements used in the current study.

Other laboratories conducting cerebellar tDCS research use larger electrodes allowing for more complete coverage of lateral areas of the cerebellum, or use lateralized electrode placements, namely over the right cerebellar hemisphere. Future investigation could be conducted using larger electrodes or lateralized electrode placements during the object detection task, perhaps allowing for stimulation of cognitive areas of the cerebellum.

Areas of the lateral cerebellum are thought to contribute more to higher-order cognitive functions, and have denser connections with associated frontal areas (Stoodley & Schmahmann, 2010), when compared with more medial areas, which have dense connections to motor cortex (Coffman et al., 2011) as well as prelimbic ventromedial prefrontal cortex (Watson, Becker, Apps, & Jones, 2014).

General Discussion

This study sought to combine newly collected data and those from several previous studies conducted in our laboratory and in those of colleagues to further elucidate a network involved in learning an object detection task, as well as in performance of the Attention Network Task. Based on current modeling data, it was suggested that cephalic electrode placements at both site F10 as well as T5, both with extra-cephalic opposite-pole electrode placement, appear to have far-field effects in other brain areas, including bilateral temporal poles and the cerebellum.

The cerebellum, once thought of only to be involved in fine motor coordination and motor sequence learning, now enjoys the attention of researchers from a variety of cognitive domains. It now appears that the cerebellum plays a role in myriad cognitive functions, including language, learning, and working memory (for a review, see Desmond & Fiez, 1998) as well as visuo-motor learning and error correction (Flament, Ellermann, Kim, Uğurbil, & Ebner, 1996) and associative learning (Timmann et al., 2010).

There is no arguing the large role the cerebellum plays in task-related motor behavior. Of particular import to the current study is its involvement in visuo-motor tasks. Perhaps if the object detection task were more video game-like, the cerebellum would play a larger role in the successful execution of the task, and thus could potentially be more malleable using transcranial stimulation techniques like tDCS.

The cerebellum has been successfully stimulated using transcranial stimulation techniques to produce a host of findings in a variety of non-motor domains, from an impairment in the practice dependent increase in the Sternberg working memory task with

anodal stimulation (Ferrucci et al., 2008), to an improvement in performance in the paced auditory serial subtraction task with cathodal stimulation (Pope & Miall, 2012). In many studies, though not all, stimulation of the cerebellum lead to a decrement in task performance (for a review, see Tomlinson, Davis & Bracewell (2013).

The current study suggests that neither the cerebellum nor peripheral nerves are involved in learning the object detection task or in performing the ANT. Regression analyses of two key dependent variables, immediate and delayed learning, suggest that the cerebellum is contributing 1.1% and 0.08% to the effects reported with the F10 anode placement for immediate and delayed learning, respectively. Furthermore, the data suggest a contribution of 0.02% and 4.4% to the effect with the T5 cathode placement on those same variables.

Stimulation of the cerebellum did not significantly impair performance on either the object detection paradigm or the ANT, nor did it improve performance compared to sham, as was expected. Table 4 provides a summary of the null effects of tDCS stimulation condition on key measures in the current study, including 95% confidence intervals.

Table 4

Null effects of stimulation condition on key dependent measures

Measure	Mean Difference	95% Confidence Interval
Immediate Leaning		
Anode Active - Sham	0.019	[-0.086, 0.125]
Cathode Active - Sham	0.034	[-0.071, 0.139]
Delayed Learning		
Anode Active - Sham	0.061	[-0.039, 0.162]
Cathode Active - Sham	0.015	[-0.086, 0.116]
Perceptual Sensitivity (d')		
Anode Active - Sham	0.081	[-0.406, 0.567]
Cathode Active - Sham	-0.110	[-0.608, 0.387]
Alerting Attention		
Anode Active - Sham	8.497	[-8.171, 25.166]
Cathode Active - Sham	-1.832	[-18.844, 15.180]

Note. All active placements refer to direct cerebellar tDCS. Difference scores were calculated as active group mean minus sham group mean for all metrics. All p-values for mean differences are non-significant (all p's >0.20)

Conclusions, Limitations and Future Directions

Though we were unable to detect any significant differences between stimulation conditions on any performance measures in the object detection paradigm or the ANT, the findings from the current study should not merely be tucked away in the file drawer. There was good scientific reason, based on finite element current modeling and literature suggesting a cognitive role of the cerebellum, to hypothesize that it may be involved in learning and executing both of these tasks.

The number of participants suggested per group was based on the large effect size of the F10 anode placement. The current study was considerably underpowered due to the effect size being drastically lower than the F10 and T5 groups. Increasing sample size would improve an ability to detect differences between groups, but given the small effect size (approximately 0.10) such differences are not significant, as they could merely be due to statistical chance.

The static nature the object detection task may not lend itself well to cerebellar involvement. It could be the case that if the task were designed differently, that is, more like a video-game, where there was more of an interaction of movement, decision making, attention and dynamic responding, the cerebellum would be more likely to be involved. Introducing a task as such described would be an interesting avenue for future research.

Investigation of reaction times in the current task could be another possibility for future research. Given the cerebellum's role in visuo-motor operations, error correction, and motor behavior, it could be hypothesized that stimulation would influence reaction times, even if the cerebellum is not involved in the direct identification of hidden objects. Furthermore, the electrode placement in the current study targeted mainly medial cerebellum, an area implicated in motor function.

Modulation of "bottom-up" processes through direct stimulation of the cerebellum is not sufficient to detect any significant change in performance in this task. Performance on this task appears to be modulated by driving cortical areas directly, by either affecting "top-down" executive processes by exciting right inferior frontal areas, or "bottom-up" processes by inhibiting left occipital-temporal areas. The excitation of right inferior frontal gyrus is thought to modulate endogenous attention, allowing for more control in searching for and

detecting hidden objects. The inhibition of left occipital-temporal areas is thought to influence bottom-up, exogenous attentional processing involved in resolving visual scenes with camouflaged objects present, and inhibiting these areas led to less confusion by the camouflage and thus an increased ability to detect concealed objects. Perhaps the cerebellum does not exert enough influence on downstream processing required for this task, or is simply not involved, and thus modulating it with brain stimulation led to the current null effects.

In conclusion, anodal or cathodal direct current stimulation over posterior-medial cerebellum did not significantly improve performance or learning on either the object detection task or the Attention Network Task compared to a sham control group. Furthermore, no significant differences between active and sham groups were detected in measures of signal detection or when comparing accuracy in detecting concealed objects in novel images versus images repeated from training. These findings are an important step in elucidating a network involved in the learning and execution of these tasks, and other areas can now be investigated since the current data suggest no significant cerebellar involvement.

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