USING SIMULTANEOUS TDCS AND FMRI TO INVESTIGATE HOW BRAIN STIMULATION ENHANCES COMPLEX PERCEPTUAL LEARNING THROUGH MODULATION OF TASK-RELEVANT BRAIN NETWORKS

by

Brian L. Falcone
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Committee:

_____   Director

_____

_____

_____   Department Chairperson

_____   Program Director

_____   Dean, College of Humanities
                                             and Social Sciences

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                                          George Mason University
                                          Fairfax, VA

Using Simultaneous TDCS and FMRI to Investigate How Brain Stimulation Enhances Complex Perceptual Learning through Modulation of Task-Relevant Brain Networks

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at George Mason University

by

Brian L. Falcone
Master of Arts
George Mason University, 2014
Bachelor of Arts
New Mexico State University

Director: Matthew S. Peterson, Professor
Department of Psychology

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George Mason University
Fairfax, VA

DEDICATION

I would like to thank my friends, family, and colleagues for supporting me through a sometimes arduous path. This work is dedicated to my wife Brooke, who never doubted me for a moment, and would not allow me to doubt myself. I also want to thank my mentor Raja Parasuraman for his valuable guidance and for giving me the opportunity to succeed in something I love.

ACKNOWLEDGEMENTS

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ABSTRACT

USING SIMULTANEOUS TDCS AND FMRI TO INVESTIGATE HOW BRAIN STIMULATION ENHANCES COMPLEX PERCEPTUAL LEARNING THROUGH MODULATION OF TASK-RELEVANT BRAIN NETWORKS

Brian L. Falcone, Ph.D.

George Mason University, 2016

Dissertation Director: Dr. Matthew S. Peterson

The purpose of this series of experiments was to determine whether transcranial direct current stimulation (tDCS) accelerates perceptual learning on complex visual attention tasks and what neural mechanisms underlie this cognitive enhancement. The first experiment showed that tDCS augmented both skill acquisition and retention in a complex detection task and that the benefits are rooted in an improvement in sensitivity (d'), rather than changes in response bias (ß). The second experiment used simultaneous functional magnetic resonance imaging (fMRI) and tDCS to identify a link between active tDCS-modulated brain activity during learning and modulated brain activity following training that was found to be correlated with visual search improvement. The final experiment investigated changes in resting state brain activity and improvement-related functional connectivity immediately following visual search training as a result of tDCS. This study found that tDCS increases resting state brain activity but did not result in any changes in functional connectivity.

PREFACE

The field of neuroergonomics (Parasuraman & Rizzo, 2008) seeks methods to improve cognitive functions that are important in real-world tasks at work and everyday life. One such method is Transcranial Direct Current Stimulation (tDCS). TDCS is a non-invasive and low-cost technique that has been shown to enhance many different cognitive components by affecting cortical excitability changes in the neurons in the brain. Much of the earlier research involving tDCS was primarily focused on its effects on motor memory. The results of these studies showed that tDCS can facilitate motor functions and these positive results led to the broadening of this research to other areas of human cognition such as memory, working memory, attention, planning, language, and mathematical performance in both healthy and non-healthy participants (for reviews, see Brunoni et al., 2014; Coffman et al., 2013; Jacobson et al., 2011; Utz et al., 2010). The general trend of these studies has shown cognitive performance enhancements when applying anodal stimulation through an electrode placed on the scalp over specific cortical brain areas and a performance decrement when applying cathodal stimulation. One of the most recently researched tDCS applications is the possibility of enhancing visuo-spatial attention.

Recent studies have found that anodal tDCS can improve performance on a variety of visuo-spatial attention tasks (Bolognini, Fregni, Casati, Olgiati and Vallar,

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2010; Tseng et al., 2012; Clark et al., 2012) which has promising implications with regard to real-world settings. For example, experts who carry out difficult visual search tasks, such as detecting and identifying tumors in radiological images or scanning satellite images for threats, typically require many hundreds of hours practice to develop mastery (Ericsson, Krampe & Tesch-Romer, 1993). The consequences of a failed perception in situations like these can be quite severe, which is why it is important to develop techniques that will accelerate and improve the quality of visual perceptual learning. The results of previous behavioral studies implicate tDCS as a viable method by which to accomplish this. However, the mechanism by which tDCS improves performance on visual-spatial attention tasks is unclear. It is well known that tDCS can cause itching, tingling, and/or burning sensations at the site of the electrode in most study participants (Poreisz et al., 2007). It is possible that non-specific changes in arousal can occur as a result which has been shown to have an effect on response bias (Broadbent, 1971). If tDCS elicits a shift in response bias then this could affect overall percent accuracy when there isn't any actual change in learning. For example, if there is a 75% chance of a target being present in a perceptual detection task and a participant maintains a hard liberal bias, only answering in the positive, this will result in 75% accuracy regardless of the fact that no discrimination is being made. In order to determine whether tDCS is truly improving the rate of learning on visual-spatial attention tasks, perceptual sensitivity and response bias must be investigated rather than percent correct.

Apart from behavioral measures, there remains a lack of neuroscientific understanding about how the effects of tDCS on the human brain lead to cognitive

enhancement on complex tasks. Animal studies have indeed begun to unravel the neural mechanisms of tDCS on the cellular level (Jefferys, Deans, Bikson and Fox, 2003; Radman, Ramos, Brumberg, and Bikson, 2009), but how these mechanisms influence larger neural networks in the human brain during active task performance is much less clear. To that end, many studies have begun to examine the effects of tDCS on recordings of neural activity using various neuroimaging techniques while participants perform various tasks. Functional Magnetic Resonance Imaging (fMRI) is particularly useful for identifying tDCS induced modulations of specific neural networks due to the fact that it provides superior spatial resolution over other neuroimaging techniques (Parasuraman & Rizzo, 2008). In addition to this, a relatively new fMRI method referred to as resting-state fMRI (rsfMRI) can be used to determine functional connectivity between anatomically separate brain regions and whether tDCS can modulate these networks.

Up until recently, fMRI compatible tDCS devices did not exist; making concurrent tDCS application and fMRI data collection impossible due to tDCS induced local magnetic field artifacts being introduced into MRI images. Therefore, researchers had to resort to only investigating the after-effects of tDCS on brain activity by first applying tDCS for a time, then removing the electrodes and having the subject enter the scanner immediately after stimulation (Nitsche et al., 2004; Baudewig, Nitsche, Paulus & Frahm, 2001; Kim et al., 2012; Stagg et al., 2009; Antal et al., 2012; Ellison et al., 2014). However, with the recent advent of MRI compatible tDCS devices, researchers are now able to observe the active effects of tDCS by concurrently applying tDCS while collecting fMRI data in the scanner (Kwon & Jang, 2011; Kwon et al., 2008; Antal,

Polania, Schmidt-Samoa, Dechent & Paulus, 2011). Similar to the early behavioral tDCS literature mentioned previously, only extremely basic motor memory tasks were used in each of these studies. This of course is to be expected in early studies investigating the active effects of tDCS on the brain. To the best of our knowledge, there has only been one study published to date that used a moderately complex picture naming task (Holland et al., 2011).

The purpose of this series of experiments was to apply a neuroergonomic approach in order to determine whether tDCS can be used as a viable method to improve perceptual learning in the search and detection of targets on complex visual attention tasks as well as what effect tDCS is having on the human brain that results in cognitive enhancements during task performance.

Experiment 1

The first study that we conducted investigated whether anodal tDCS over the right inferior frontal cortex (rIFC) would improve performance on a realistic threat detection task and if this effect was due to enhanced perceptual sensitivity rather than changes in response bias due to arousal. Perceptual sensitivity, as measured by the signal detection theory metric d' (Green & Swets, 1966) and related indexes (Macmillan & Creelman, 2005), is a basic measure of perceptual capability. We observed a significant increase for d' in the real stimulation group over the sham group and no significant difference in response bias between groups. Improvement in perceptual sensitivity without change in bias suggests that participants who received real stimulation performed better because they are more efficiently able to encode stimulus features that distinguished targets from

distracters. These findings were consistent with the theory that tDCS enhances visual attention, which is shown to influence performance on perceptual detection tasks (Posner & Peterson, 1990). It is possible that improved visual attention assists perceptual learning by reducing the effect of distracter items which in-turn enhances the detection of targets. In an initial study by Clark et al. (2010), participants performed the same threat detection task while collecting fMRI data. This was done in order to locate the brain areas that are recruited during task performance as one gains expertise in threat detection. In expert performers, the regions with the strongest increase in BOLD activation were indeed a part of the attentional network: the right inferior frontal cortex (rIFC) and right posterior parietal cortex (rPPC). The rIFC was chosen as the site of stimulation for our experiment due to the previous neuroimaging and behavioral results showing this area to be playing a larger role than the rPPC for this task by Clark et al. (2012).

Experiment 2

The purpose of this study was to observe both active and after-effects of tDCS on brain activation by applying anodal brain stimulation and collecting fMRI data concurrently during task performance. We also hoped to replicate and extend the findings of the previous paper and show that tDCS will improve learning on a different complex visual perceptual detection task, specifically, a high fidelity UAV visual search simulation.

According to Corbetta and Schulman (2002), there are two distinct attention networks: a dorsal fronto-parietal network that processes top-down or exogenous attention and primarily includes the frontal eye fields (FEFs) and posterior intraparietal

sulcus (IPS) and a right lateralized ventral fronto-parietal network that processes bottom-up or endogenous attention and primarily include temporal-parietal junction (TPJ) and right inferior frontal cortex (rIFC). The rPPC along with the FEFs might be responsible for creating the saliency maps that are used in visual search which combine bottom-up and top-down information from both of these networks to represent visual objects of interest. Activation of these areas is strongest during search and detection and decreases after the target has been located.

In addition to the evidence from neuroimaging studies, previous behavioral tDCS studies have demonstrated the relationship between the rPPC and visual attention. Stimulation of the rPPC results in performance improvements on a variety of spatial attention tasks. Tseng et al. (2012) applied anodal tDCS to the rPPC while subjects performed on a visual change detection task and found that tDCS improved performance for individuals who originally did poorly. Another study found that stimulation of the rPPC during multisensory visual field exploration training resulted in improved performance on a variety of basic visual tasks including visual search (Bolognini et al., 2010). In a follow-up experiment it was also observed that tDCS had a direct effect on cognition where brain stimulation of the rPPC resulted in an immediate improvement in visual search performance without the need for prior multisensory training paired with brain stimulation. In addition to improvements observed in healthy subjects, other studies have found that stimulation of the rPPC can also improve spatial attention in an unhealthy population. A study conducted by Ko, Han, Park, Seo and Kim (2008) found that anodal stimulation improved visual scanning in stroke patients suffering from spatial neglect.

Due to the strong neuroimaging evidence for the importance of the rPPC in visual search, as well as the behavioral results seen in prior tDCS studies, we chose this area as the site of stimulation for this experiment instead of the rIFC used in the previous experiment. Unfortunately, we did not observe any behavioral differences between the real and sham stimulation groups for any of the measures on the UAV visual search simulation. It is possible the task was not sensitive enough to bring out differences in behavioral performance in the 30 minute training block which only consisted of 60 trials. Some participants complained in the practice session that they could not distinguish between the target and distractor even when the target was pointed out to them. Perhaps with more trials or an extended training period we would have begun to observe positive results.

Despite the lack of behavioral effects, we observed modulation of brain activity elicited by anodal tDCS over the rPPC that might be responsible for cognitive enhancement observed in previous behavioral studies. This also suggests that with more time we might have begun to observe behavioral differences between stimulation groups.

First, we observed significant differences in brain activation patterns specific to target feedback resulting from active tDCS during the training session where participants received stim or sham stimulation while receiving visual and auditory feedback following their responses (target "present" or target "absent"). We found four clusters of significant differential activation for the real stimulation group which included the right post- and pre-central gyrus (somatosensory, premotor, and primary motor cortices), the ACG, the left cerebellum, and the right cerebellum. The ACG (Holroyd et al., 2004; Kiehl, Liddle

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and Hopfinger, 2000; Hester, Fassbender, & Garavan, 2004) and cerebellum (Callan et al., 2011; Diedrichsen, Hashambhoy, Rane, & Shadmehr, 2005) are both areas known to be involved with target feedback processing. This suggests that tDCS had a moderating effect on target feedback learning during training. As predicted, we also found significant differences in brain activity between stimulation groups in areas associated with the visuospatial attention network. Previous neuroimaging research has shown a heavy overlap between oculomotor and attention networks (Corbetta et al., 1998) with the precentral (premotor/motor) areas being strongly associated with the dorsal goal-directed fronto-parietal network (Corbetta et al., 1998; Coull & Nobre, 1998; Petit et al., 1996; Simon et al., 2002). Finally, the somatosensory cortex has recently been linked to visuospatial attention (Balslev, Odoj, & Karnath, 2013) through proprioceptive gaze input (Wang et al, 2007; Balslev & Miall, 2008).

Next, we found an after-effect of tDCS on brain activity which was positively correlated with improvement in visual search performance. This was accomplished by using the percent correct change from pre-training to post-training as a covariate of interest in a between stimulation groups analysis that contrasted post-training brain activation relative to pre-training activation (before and after tDCS/feedback training). Effects were found primarily in the somatosensory cortex and premotor cortex, again showing that tDCS modulated areas associated with visual attention. Greater improvement related activity in this region for post- relative to pre-training for the real stimulation group over the sham group may reflect modulation of these networks by tDCS. This modulation might be related to mechanisms responsible for cognitive

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enhancement effects elicited by tDCS on other behavioral tasks such as those observed in paper #1.

Finally, we investigated the conjunction of activity that is present for active tDCS during target feedback learning and improvement related activity for the after-effects of tDCS during visual search. The results of this analysis showed shared activation in an area including the right pre- and post-central gyrus. This suggests that active tDCS-elicited modulation of this cluster during feedback training moderated the improvement related activity seen post-training during visual search. A region of interest analysis provided further evidence for this by showing that individuals that had high modulatory activity during feedback training also displayed increased brain activity in this area post-training.

Overall, our fMRI results showed that anodal tDCS of the right posterior parietal cortex resulted revealed a link between active tDCS-modulated brain activity during learning and modulated brain activity following training that was found to be correlated with visual search improvement. While our study shows how tDCS modulates networks relevant to our task resulting in enhanced learning, it can be assumed that a similar mechanism should be observed within networks relevant to other types of cognitive learning.

Experiment 3

This study used resting-state fMRI (rsfMRI) data collected during the experiment from Paper #2. The purpose of this study is to compare the effects of tDCS between stimulation and sham conditions on resting-state brain activity and functional

connectivity. Resting state fMRI data was collected before, during, and after anodal

stimulation (3 sessions) over the rPPC while participants observed a black screen for a

period of 5 minutes per session.

Resting-state functional connectivity analysis uses fMRI to look at the temporal

synchrony of low frequency fluctuations (LFF) in BOLD signal between different brain

regions. It is suggested that when LFF is highly temporally correlated between regions,

these regions are tightly coupled within a functional network (Biswal, Yetkin, Haughton,

& Hyde, 1995; Greicius, Krasnow, Reiss, & Menon, 2003). Using this technique it is

possible to explore changes to functional connectivity elicited by anodal tDCS which

might contribute to augmented cognition observed in previous behavioral studies. A

study conducted by Keeser et al. (2011), applied anodal stimulation over the left

dorsolateral prefrontal cortex (DLPFC) with resting-state brain connectivity being

assessed before and after a 20 minute tDCS session. The left DLPFC is a popular area

used in many previous behavioral tDCS studies as it has been shown to affect working

memory, attention, and executive control (Coffman et al., 2014). This study found that

anodal stimulation resulted in the modulation of resting-state functional connectivity in

the default mode network (DMN), and the left and right frontal-parietal networks (FPNs).

It has been posited that the function of resting-state networks such as these are to

maintain a preparatory alertness in order to react to incoming stimuli more effectively

(Fransson, 2005). It is also suggested that increased strength of spontaneous functional

connectivity in resting-state networks also affects behavior and cognition during task

performance (Keeser et al., 2011).

Using a seed-driven functional connectivity analysis we were able to investigate tDCS induced changes in functional connectivity with brain regions correlated specifically with our region of interest, the rPPC (stimulation site). Simultaneous fMRI and tDCS allowed us to determine areas of modulated spontaneous resting state activity induced by active tDCS using fractional amplitude of low frequency (0.01-0.08 Hz) fluctuation (fALFF). Specifically, fALFF has revealed a region in the rPPC with significant resting-state activation over the sham condition. This is beneficial because it shows that this region of interest is not only theoretically important, but it is also supported by the data to be significantly modulated by active anodal tDCS during resting-state.

We selected a region found from the fALFF analysis within the superior parietal lobule to be used as seed for the functional connectivity analysis as this region is a critical node within the dorsal attention network found to be modulated by tDCS for this visual search task. In addition to a lack of tDCS-induced cognitive enhancement, there were no significant increases in improvement related functional connectivity between a seed voxel selected from an activated region within the right superior parietal lobule and any other brain regions over the sham condition.

TRANSCRANIAL DIRECT CURRENT STIMULATION AUGMENTS PERCEPTUAL SENSITIVITY AND 24-HOUR RETENTION IN A COMPLEX THREAT DETECTION TASK

Brian Falcone[1], Brian A. Coffman[2], Vincent P. Clark[2], Raja Parasuraman[1*]

[1]George Mason University, Center of Excellence in Neuroergonomics,

Technology, and Cognition (CENTEC), Fairfax, Virginia

[2]University of New Mexico, The Mind Research Network and Lovelace

Biomedical and Environmental Research Institute, Albuquerque, New Mexico

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Abstract

We have previously shown that transcranial direct current stimulation (tDCS) improved performance of a complex visual perceptual learning task (Clark et al. 2012). However, it is not known whether tDCS can enhance perceptual sensitivity independently of non-specific, arousal-linked changes in response bias, nor whether any such sensitivity benefit can be retained over time. We examined the influence of stimulation of the right inferior frontal cortex using tDCS on perceptual learning and retention in 37 healthy participants, using signal detection theory to distinguish effects on perceptual sensitivity (d') from response bias (β). Anodal stimulation with 2 mA increased d', compared to a 0.1 mA sham stimulation control, with no effect on β. On completion of training, participants in the stimulation group had more than double the perceptual sensitivity of the sham control group. Furthermore, the performance enhancement was maintained for 24 hours. The results show that tDCS augments both skill acquisition and retention in a complex detection task and that the benefits are rooted in an improvement in sensitivity (d'), rather than changes in response bias (β). Stimulation-driven acceleration of learning and its retention over 24 hours may result from increased activation of prefrontal cortical regions that provide top-down attentional control signals to object recognition areas.

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Introduction

Perceptual sensitivity, as measured by the signal detection theory metric *d'* (Green & Swets, 1996) and related indexes (Macmillan & Creelman, 2005), is a basic measure of perceptual capability. It has long been used to assess perceptual performance and learning (Swets & Pickett, 1982). For example, perceptual sensitivity measures can be used to evaluate acquisition of the ability to detect obscured or concealed objects of the type encountered in naturalistic scenes. This is an important skill that typically develops only after extensive training (Goldstone, 1998). Examples include radiologists identifying tumors in MRI scans or security officers examining surveillance videos of people for suspects. Perceptual sensitivity is also diminished in many sensory disorders, as in hearing-impaired individuals or those with low vision (Coren, Ward, & Enns, 1994). Reduced perceptual sensitivity can also contribute to functional deficits in brain disorders such as head injury (Parasuraman, Mutter, & Molloy, 1991), schizophrenia (Nuechterlein, 1983), and Alzheimer's disease (Parasuraman & Haxby, 1993).

Identifying methods that can increase perceptual sensitivity in both healthy and clinical populations can have significant applications for clinical assessment, training, and research. Unfortunately, few methods exist to enhance perceptual sensitivity reliably and consistently. Many techniques only serve to alter participants' response bias, so that correct target detections (hits) may increase but at the cost of more false alarms, without a change in sensitivity (Druckman & Swets, 1998). Stimulant drugs such as amphetamine (Mackworth, 1965) and physostigmine (Warburton & Brown, 1972) can increase sensitivity, but possess significant drawbacks, such as reduced effectiveness due to

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tolerance, the potential for addiction, and ethical issues raised by the use of pharmacological agents in healthy adults (Farah, Illes, Cook-Deegan, Gardner, & Kandel, 2004).

A newly emerging alternative is to use non-invasive brain stimulation to modulate neuronal activity, in particular transcranial direct current stimulation (tDCS). A number of tDCS studies have shown that it is possible to enhance human performance through the application of low-level DC current to the scalp while participants are engaged in simple perceptual, cognitive, and motor tasks. Examples include studies of motion discrimination (Antal et al., 2004), visual attention (Stone & Tesche, 2009), working memory (Luber et al. 2008), and exploratory behavior (Bolognini, Fregni, Casati, Olgiati, & Vallar, 2010). For a recent review of these and other tDCS studies, see Ref (Utz, Dimova, Oppenländer, & Kerkhoff, 2010). However, it is unclear whether tDCS can reliably enhance perceptual sensitivity in detection tasks, particularly those involving complex targets and naturalistic scenes. Moreover, the duration of this sensitivity benefit is unknown. For tDCS to be a viable training technique, it would be desirable if its effects can be retained for hours, if not days.

In the present study we examined both of these issues by applying tDCS to scalp regions overlying the inferior frontal cortex of participants learning to perform a complex threat detection task. We hypothesized that tDCS would improve encoding of stimulus features during training and thereby accelerate learning. Signal detection theory analysis was used to examine effects of brain stimulation on perceptual sensitivity independently

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of response bias. We also investigated whether the effect of tDCS on sensitivity, if found, would be retained over a 24-hour period.

tDCS uses small DC electric currents (typically 1 to 2 mA) that are applied to the scalp. The technique is considered to be safe for experimental use in healthy subjects for up to about 30 minutes of stimulation (Bikson, Datta, & Elwassif, 2009). The mechanism by which tDCS influences brain function is not precisely known, but is thought to involve alteration of the electrical environment of cortical neurons, specifically small changes in the resting membrane potential of neurons, so that they fire more readily to input from other neurons (Bikson, Radman, & Datta, 2006). In vitro studies have shown that DC stimulation of rat hippocampal slices at low current levels decreases the threshold for neuronal firing (Bikson et al., 2004). We have also shown, using magnetic resonance spectroscopy in humans, that tDCS results in increased levels of glutamate, glutamine, and N-Acetylaspartic acid that remain elevated after current is turned off (Clark, Coffman, Trumbo, & Gsaparovic, 2011). A positive (anodal) polarity is typically used to stimulate neuronal function and enhance behavioral performance. Conversely, a negative (cathodal) polarity is used to inhibit neuronal activity, although this has also been found to result in behavioral improvements under certain conditions Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009).

Neuroimaging studies can help identify the key brain networks that are associated with the performance of a perceptual detection task and thereby help locate the scalp targets for anodal tDCS application. We used this approach in a functional magnetic resonance imaging (fMRI) study of a complex perceptual learning task requiring

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participants to identify concealed and camouflaged objects representing threats in a simulation of naturalistic warzone environments (Clark et al., 2012). The task was modeled on the "DARWARS Ambush" virtual reality environment MacMillan et al., 2005), which has been used to familiarize and train personnel prior to deployment to areas of military conflict. The objects that participants had to detect included bombs that were concealed by or disguised to look like everyday objects. Other threats involved people who were either enemy combatants in concealed locations or dressed to look like ordinary civilians, with subtle clues as to their identity. Participants performed the object detection task without feedback while undergoing fMRI scanning. Subsequently, they underwent training sessions with feedback outside of the MRI scanner on sequential days. MRI scans were repeated when they reached an intermediate level of performance and again when they attained expert level performance. Activation of brain regions associated with scenes containing concealed objects was compared to that for scenes without such targets at novice, intermediate, and expert stages of performance. Based on these findings, as well as on a Bayesian network analysis of the activated brain regions, the right inferior frontal cortex and the right parietal cortex were identified as areas with significant activation associated with performance and learning of the threat detection task and which are accessible using tDCS on the scalp. In a separate group of participants, anodal 2.0 mA tDCS was applied to the scalp areas overlying these regions. Task performance was significantly enhanced compared to a group receiving 0.1 mA tDCS ("sham" stimulation control group).

These results indicate that tDCS might provide an effective technique for efficient training of high-performance perceptual and cognitive skills in complex tasks. However, additional questions must be addressed before a firm conclusion can be reached on the training potential of tDCS. One issue that needs further examination in tDCS studies, especially those involving perceptual detection tasks, is whether brain stimulation enhances perceptual sensitivity as opposed to making participants more liberal or conservative in responding. The latter could result from non-specific changes in arousal, which can influence response bias (Broadbent, 1971). For example, if tDCS only shifts response bias in a liberal direction so that participants are more likely to respond positively in a detection task, the hit rate will increase, even though there may be no change in the participant's ability to detect the target. Clark et al. (Clark et al., 2012) reported that tDCS increased the rate of correct responses in a threat detection task. However, a change in response bias could also lead to a larger rate of correct responses and cannot be distinguished from a change in perceptual sensitivity using a measure of correct response rates alone (Green & Swets, 1966; Macmillan & Creelman, 2005; Swets, 1982).

A second important issue is the degree of retention of performance benefits. That is, how long does the benefit of tDCS last? If performance improvement only last as long as stimulation or for a short time after, it would not be useful for producing long-term improvements in perceptual sensitivity. Accordingly, in the present study we examined whether a tDCS-related performance benefit in a complex threat detection task would, if obtained, be retained over a 24-hour period. A positive finding would then represent a

starting point for exploring retention over longer periods of time and examination of other issues, such as transfer of training.

In summary, we used signal detection theory to examine whether tDCS applied to the scalp over right inferior cortex during acquisition of a complex threat detection task affects perceptual sensitivity (d') as opposed to response bias (β). We also investigated whether there would be retention of any performance benefit over a 24-hour period. We hypothesized that participants receiving 2.0 mA tDCS would show an increase in d' but not in β, relative to participants receiving 0.1 mA, and that this effect would be significant immediately after training and again 24 hours later.

Materials and Methods

Ethics Statement

All human participants provided written informed consent to take part in the study, which was approved by the George Mason University Institutional Review Board.

Participants

Participants were 37 adults (21 males, 16 females) aged 18-25 years (mean = 20.1 years). Prior to enrollment in the study, participants were screened and excluded for having a primary language other than English, a history of head injuries or concussions, left-handedness, current or previous history of mental, neurological, alcohol or drug abuse disorders, current prescription medication affecting central nervous system function, or uncorrected hearing or visual impairments. The participants were randomly assigned to one of two groups, a real stimulation group (N=19) and a "sham" control group (N=18).

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Threat Detection Task

Short movies showing naturalistic scenes containing objects and people as well as still images extracted from those movies were taken from the "DARWARS Ambush" virtual reality software for presentation to participants (Clark et al. 2012; MacMillan et al., 2005). Participants were only told that they were to determine whether or not there was a threat present in the image, without being provided specific details as to what types of possible threats were present. Half of the scenes included specific concealed objects that indicated possible threats that participants had to detect, while the other half did not contain concealed objects. Examples of images with and without objects indicating possible threats are shown in Figure 1. Target objects that signified threats included concealed objects such as bombs that were hidden by, or disguised as, trash, deceased animals, fruit or other objects such as oil barrels, boxes, cars, toys. Bombs could also be indicated by trip wire or appear as a conspicuous unattended package. People could also signify threats and included enemy combatants such as snipers in various concealed locations, plainly-clothed suicide bombers, plainly-clothed individuals carrying a concealed weapon, or non-military personnel in conspicuous locations (e.g. sneaking up behind military personnel). In each case, similar scenes without target objects were created that differed by discernable characteristics indicating threat presence. The concealed target objects were subtle enough to be missed on first viewing but could be more readily identified after training. Therefore, detection accuracy was expected to be at chance levels during the initial phases of task performance. A discovery-learning paradigm was used in which participants were only told that they were to determine

whether or not there was a threat present in the image, without being provided specific details as to what types of possible threats were present. With experience and interaction with the task during training, however, participants could learn what to look for in the images.

During the training blocks, still images were presented for 2 s each, followed by a 1 s inter-stimulus interval (ISI) consisting of a blank screen with a crosshair fixation. Participants were required to make a button press within 3 s of stimulus onset to indicate whether the scene contained a threat or a non-threat. After each response a short feedback video was presented indicating whether or not the participant responded correctly. Feedback was given for all four stimulus-response outcomes: hit, miss, false alarm, or correct rejection. If a threat was present and the participant reported a threat (a hit), the movie showed the scene progressing without harm and simultaneously a computer-generated voice-over complimented the participant for correct response. If a threat was present in the image but the participant reported a non-threat (a miss), the feedback movie showed the consequence of the failure to detect the threat (e.g. vehicle explosion, friendly casualty, building being destroyed) while playing a voice-over indicating that a threat had been missed. On a non-threat trial, if the participant responded that a threat was present (false alarm), the voice-over chastised the subject for the false alarm. Finally, if the participant correctly indicated that no threat was present on a non-threat trial (correct rejection), the voice-over praised the participant for correct response. None of these feedback videos provided specific information as to the identity of the threats, although they did allow participants to infer location and object type (e.g., bomb, sniper,

or hidden gun). Training trials each lasted an average of 12 s. Each training block contained 60 trials, approximately half of which contained threats, and lasted 12 minutes. Participants completed four of these training blocks.

Test blocks were given before and after training and were similar to training blocks, except that no feedback was given after each response. Stimuli were presented for 2 s with a jittered ISI of 4-8 s. The ISI was a gray background with a crosshair fixation in the center of the screen. Participants had to respond within 3 s of stimulus onset or their response was not counted. Each test block included 50 stimuli, approximately half of which contained threats, and lasted 5 minutes.
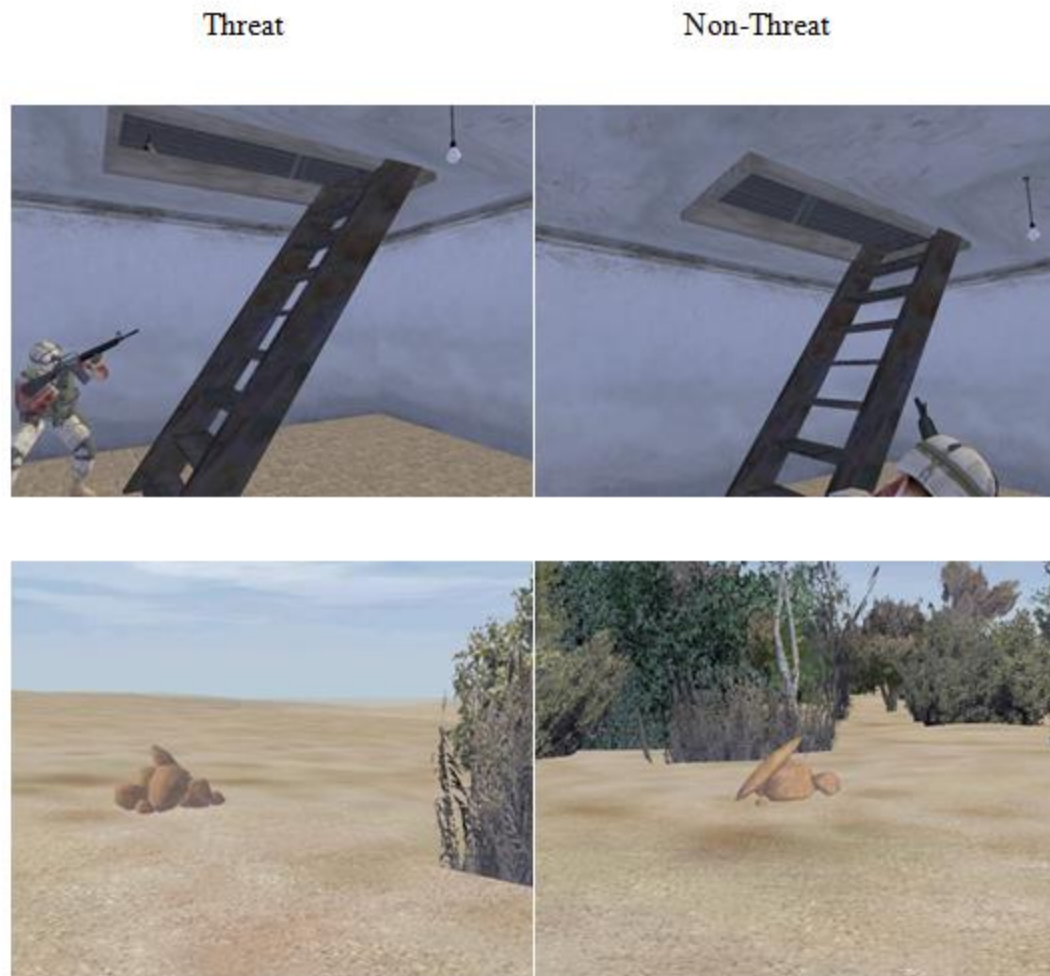
Figure 1: Examples of the concealed threat in images used for both test and training blocks.
Similar scenarios could be repeated throughout the experiment but the presence of a threat varied from trial to trial. Top row, left image: an example of a concealed enemy combatant scenario, indicated by the barely visible tip of a firearm in the room at the top of the ladder. No threat is present in the right image. Bottom row, left image: example of a bomb that has been concealed by a stack of rocks. The bomb is indicated by a tiny object that is barely visible through the space between the rocks. No threat is present in the right image.

Transcranial Direct Current Stimulation Procedures

TDCS was applied using an ActivaDose II Iontophoresis Delivery Unit, which provides for delivery of a constant low level of direct current. Square-shaped ($11cm^2$) saline-soaked (0.9% sodium saline solution) sponge electrodes were attached to the

participant with self-adhesive bandage strips. The anode was placed near electrode site F10 in the 10-10 EEG system, over the right sphenoid bone. The cathode was placed on the contralateral (left) upper arm. The site of the anode was selected based on our previous fMRI results showing that this brain region was the primary locus of neural activity associated with performance this task (Clark et al., 2012).Participants in the real stimulation group received 2 mA current from the tDCS unit for a total of 30 minutes during the first two training blocks, beginning 5 minutes before the training started. Participants in the sham stimulation (control) group received 0.1 mA current over the same time period. The 0.1mA current was used as a control condition, rather than the absence of stimulation, so as to equate aspects of the procedure (preparation and application of electrodes, attachment with adhesive strips, etc.). Another reason was to give the participant a degree of physical sensation that was somewhat similar to that of the 2mA stimulation group while not reaching the level sufficient to affect brain function and behavior. Thus, the goal was to keep participants unaware as to which condition they were in, but we recognize that this represents only an approximation of a "single-blind" test procedure.

Participants first performed two pre-tDCS test blocks to determine baseline performance on the threat detection task (total duration about 10 minutes). After this, they performed two training blocks while receiving either real or sham tDCS stimulation (total duration about 25 minutes). Immediately after the completion of the second training block, the tDCS electrodes were removed and the participant continued on to complete two more training blocks without stimulation (total duration about 25 minutes). Thus,

participants completed a total of six blocks of trials lasting a total of about 60 minutes in the baseline and learning phase of the experiment. To examine retention, we examined performance on an additional two test blocks, the first pair given immediately at the end of the first day of training (immediate retention condition), and the second pair given the next day (24-hour retention condition). Total participation time, including completing informed consent, entry questionnaires, participant instruction, task completion, and tDCS procedures, was about 1 hour 40 minutes on the first day and about 10 minutes on the second day.

Sensation Questionnaire

A sensation questionnaire was administered at three different time points throughout the tDCS application. The first was given after the onset of the stimulation, the second after 5 minutes, and the third immediately after the first training block (approximately 17 minutes after the onset of stimulation). Participants were asked to rate their perceived sensations of itching, heat/burning, and tingling on a 10-point Likert scale; a response of 1 indicated that no sensation was being detected and 10 indicating extreme sensation. Stimulation was to be stopped immediately if participants reported a 7 or above on any of the sensation measures (This did not occur with any of the participants.)

Data Analyses

The hit and false alarm rates for the learning phase of the threat detection task were computed for each of the six blocks of trials (two test, four training) for the real (2

mA) and sham stimulation (0.1 mA) groups. The hit and false alarm rates were then used

to compute the parametric signal detection measures d' and β. (The non-parametric signal

detection measures A' and C were also computed and subjected to the same analyses, but

are not reported here because the results were very similar to those for the d' and β

measures.) Each of the dependent measures was analyzed in 2 (group: real or sham) x 6

(blocks) mixed analyses of variance (ANOVAs). All four performance measures were

also computed for the immediate and 24-hour retention conditions (averaged over the two

blocks in each condition) and subjected to 2 (group: real or sham) x 3 (delay condition:

baseline, immediate, or 24-hour retention) ANOVAs. The degrees of freedom for all F

tests involving repeated measures factors were corrected for violations of the sphericity

assumption by using the Greenhouse-Geisser procedure, and the alpha level was set at

$p<0.05$.

Results

Learning

Figures 2 and 3 show hit rate and false alarm rates for the six blocks of the

learning phase of the study, including the first two baseline test blocks through the four

training blocks. For hit rate, there was a significant effect of group, $F(1,35)=14.584$,

$p=0.001$), blocks, $F(3.179,111.279)=23.139$, $p<0.0001$, and the group x blocks

interaction, $F(3.179,111.279)=4.109$, $p<0.01$. As Figure 2 shows, the mean hit rate was

about 50%—chance level performance—for both groups in the initial two baseline

blocks, but the real stimulation (2 mA) group had significantly higher hit rates than the

sham stimulation (0.1 mA) group in the subsequent training blocks, with the real

stimulation group showing markedly better performance. Participants receiving real stimulation reached 76% hit rate at the end of training while the hit rate in the control (sham stimulation) group peaked at 61%.

For the false alarm rate, there were significant effects of group, $F(1,35)=7.050$, $p<0.05$), blocks, $F(2.577,90.180)=34.854$, $p<0.001$, and their interaction, $F(2.577,90.180)=5.314$, $p<0.01$. As Figure 3 shows, the false alarm rate was about 50% for both groups in the initial baseline blocks, but declined thereafter during training. However, the real stimulation group showed a greater reduction, ending at 18% as opposed to 35% for the control group.
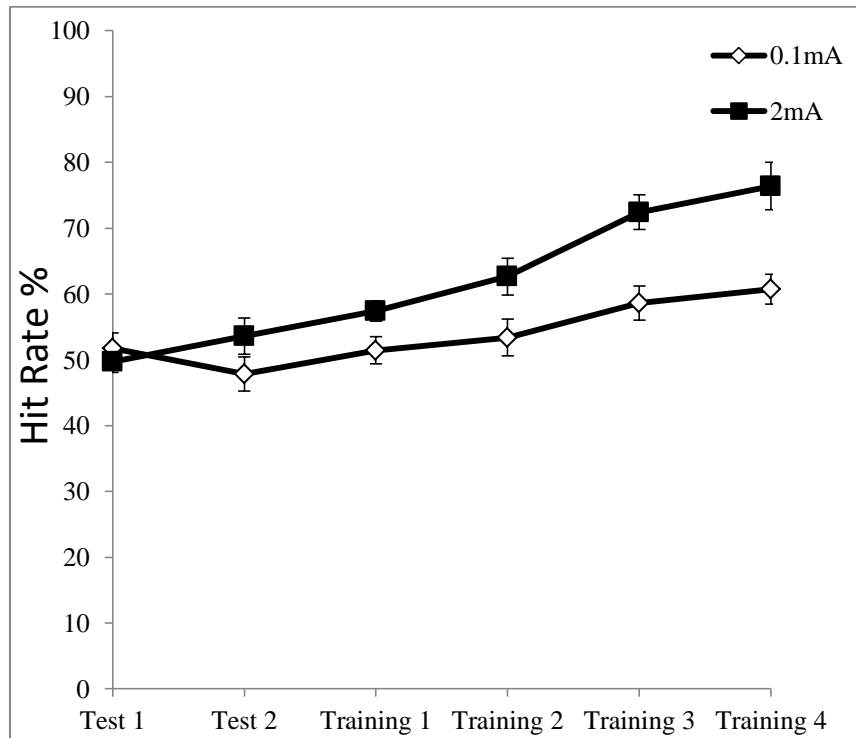
Figure 2: Mean percentage of correct responses on threat trials (hit rate) across the test and training blocks for the anodal (2 mA) and sham (0.1 mA) stimulation groups.
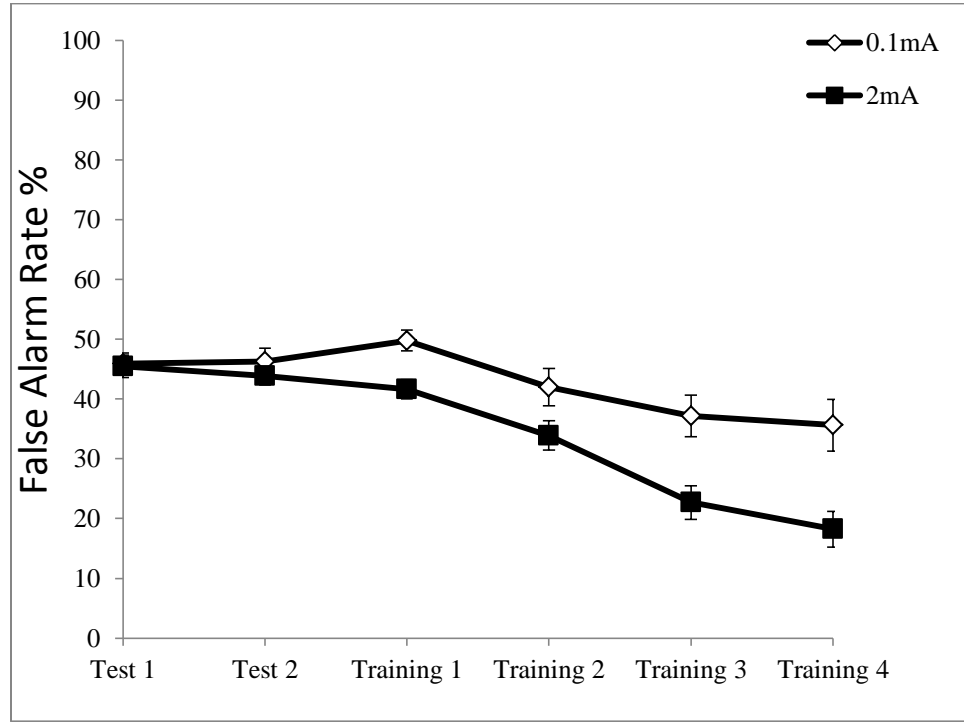
Figure 3: Mean percentage of falsely identified threats on non-threat trials (false alarm rate) across the test and training blocks for the anodal (2 mA) and sham (0.1 mA) stimulation groups.

Figures 4 and 5 show the results during the learning phase for d' and β. For d', there were significant effects for group, $F(1,35)=12.676$, $p< 0.001$, blocks, $F(2.126,74.414)=45.392$, $p<0.001$, and the group x blocks interaction, $F(2.126,74.414)=8.396$, $p=<0.001$. As Figure 4 indicates, perceptual sensitivity was near zero in both groups during the baseline blocks but was significantly higher in the real stimulation group than in the control group during training. The significant group x blocks interaction shows that sensitivity increased more rapidly with training in the real stimulation group than in the control group. By the end of training, the 2 mA group had a d' of 1.86 while that for the 0.1 mA group was 0.73.
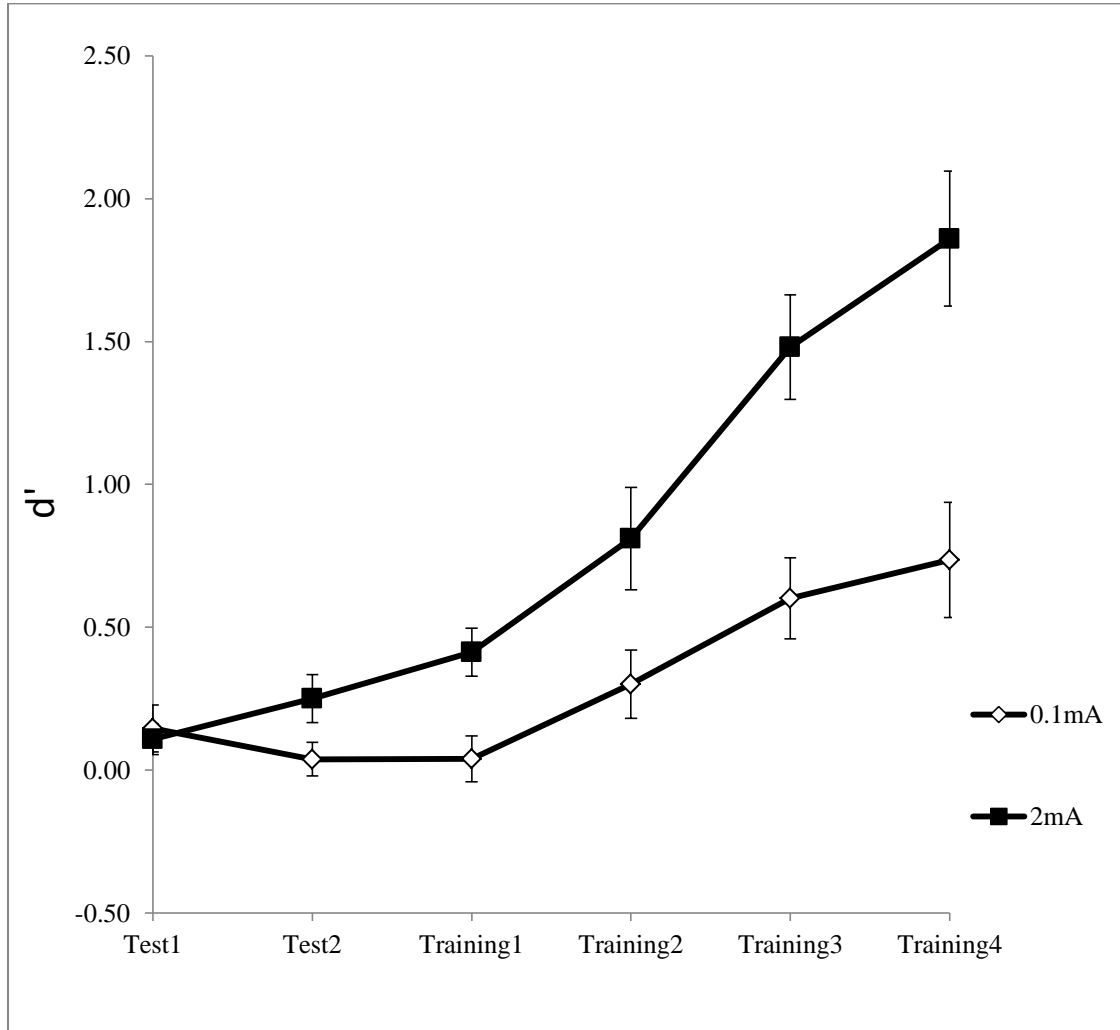
Figure 4: Mean perceptual sensitivity (*d'*) across the test and training blocks for the anodal (2 mA) and sham (0.1 mA) stimulation groups.

For the response bias measure β, the main effect of group was not significant, $F(1,35)=0.133$. The main effect of blocks was significant, $F(1.738,60.844)=5.121$, $p<0.05$. The group x blocks interaction was not significant, $F(1.738,60.844)=1.116$. As Figure 5 shows, there was a slight increase in β over blocks towards the end of training in

both groups—in a more conservative direction—but there were no differences between

the real and sham stimulation groups in response bias.
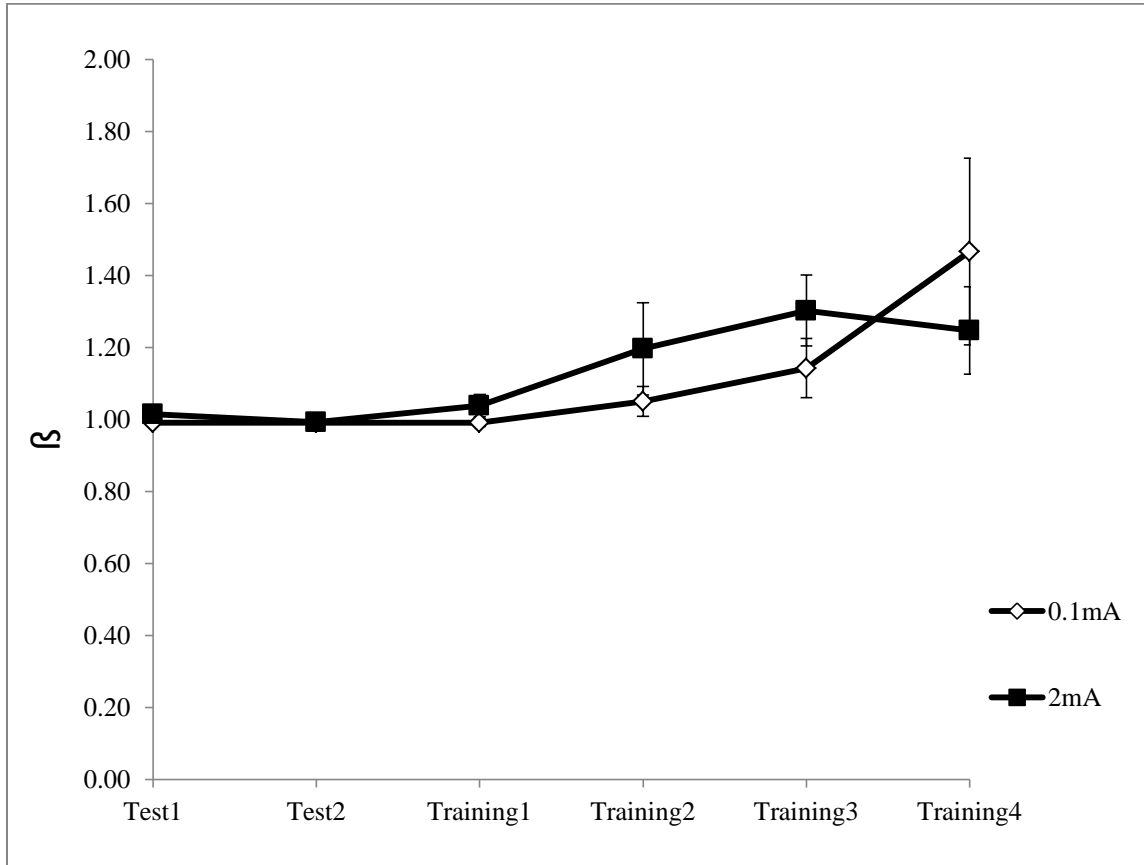
Figure 5: Mean response bias (β) across the test and training blocks for the anodal (2 mA) and sham (0.1 mA) stimulation groups.

Retention

For hit rate, the effect of group, $F(1,35)=15.537$, $p<0.001$, delay condition,

$F(1.229,43.032)=62.598$, $p<0.001$, and the group x delay condition interaction,

$F(1.229,43.032)=6.868$, $p<0.01$, were significant. As Figure 6 shows, hit rates were

higher in both retention periods than the baseline and were higher for the 2 mA group

than for the 0.1 mA group. The 2mA group improved their hit rate by 27.2% across the pre-training and immediate post-training test blocks. The hit rate remained at this relatively high level 24 hours later.
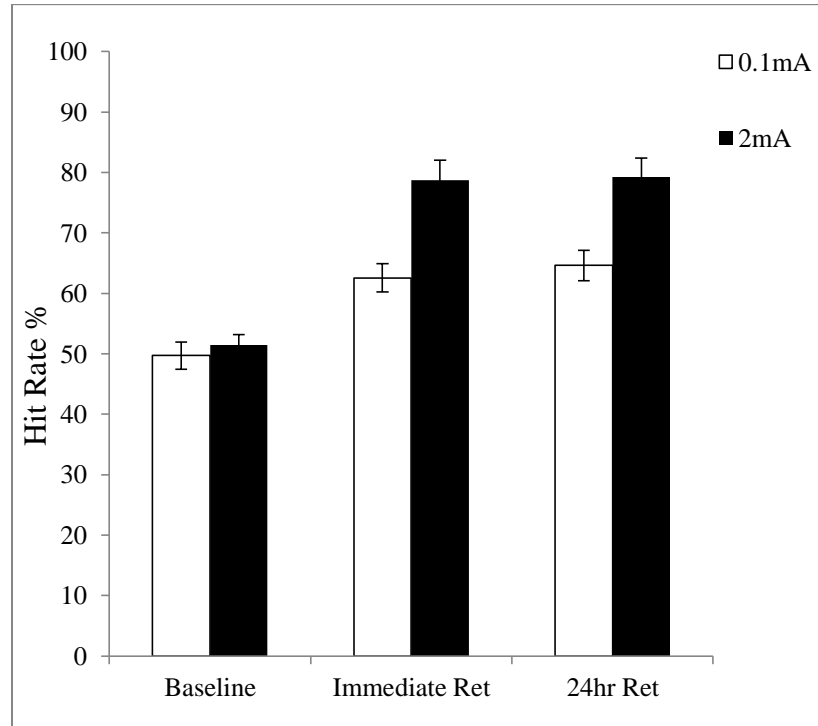
Figure 6: Mean hit rate in the pre-training baseline, immediate post-training retention test, and 24-hour retention test blocks for the anodal (2 mA) and sham (0.1 mA) stimulation groups.

For the false alarm rate, the effect of group, $F_{(1,35)}= 13.747$, $p<0.001$, delay condition, $F_{(1.689,59.116)}=89.787$, $p<0.001$, and the group x delay condition interaction, $F_{(1.689,59.116)}= 13.412$, $p<0.001$, were significant. As Figure 7 shows, there was a reduction in false alarm rate by 27.4% in the 2 mA group from the pre-training to the immediate post-training test blocks. The false alarm rate remained at this level in the 24-hour retention test block.
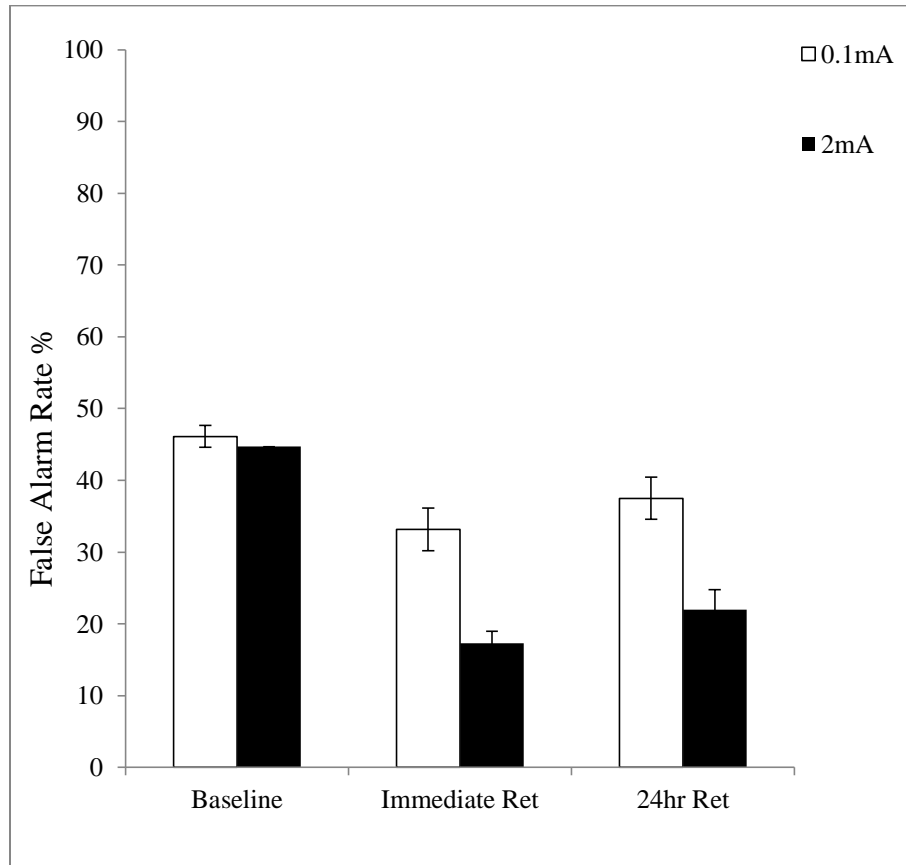
Figure 7: Mean false alarm rate in the pre-training baseline, immediate post-training retention test, and 24-hour retention test blocks for the anodal (2 mA) and sham (0.1 mA) stimulation groups.

For d', the effect of group, $F(1,35)= 19.496$, $p<0.001$, delay condition, $F(1.307,45.738)=84.335$, $p<0.001$, and the group x delay condition interaction, $F(1.307,45.738)=14.065$, $p<0.001$, were significant. As Figure 8 shows, d' values were higher in both retention periods than the baseline and were higher for the 2 mA group than for the 0.1 mA group. There was a slight (~ 8%) reduction in sensitivity in the 2 mA group from the immediate retention to the 24-hour retention periods.

Finally, for β, the effect of group, $F(1,35)=0.040$, delay condition, $F(1.222,42.754)=2.988$, and the group x delay condition interaction, $F(1.222,42.754)=.037$, were all not significant. Thus, there were no significant effects of either training or retention on response bias.
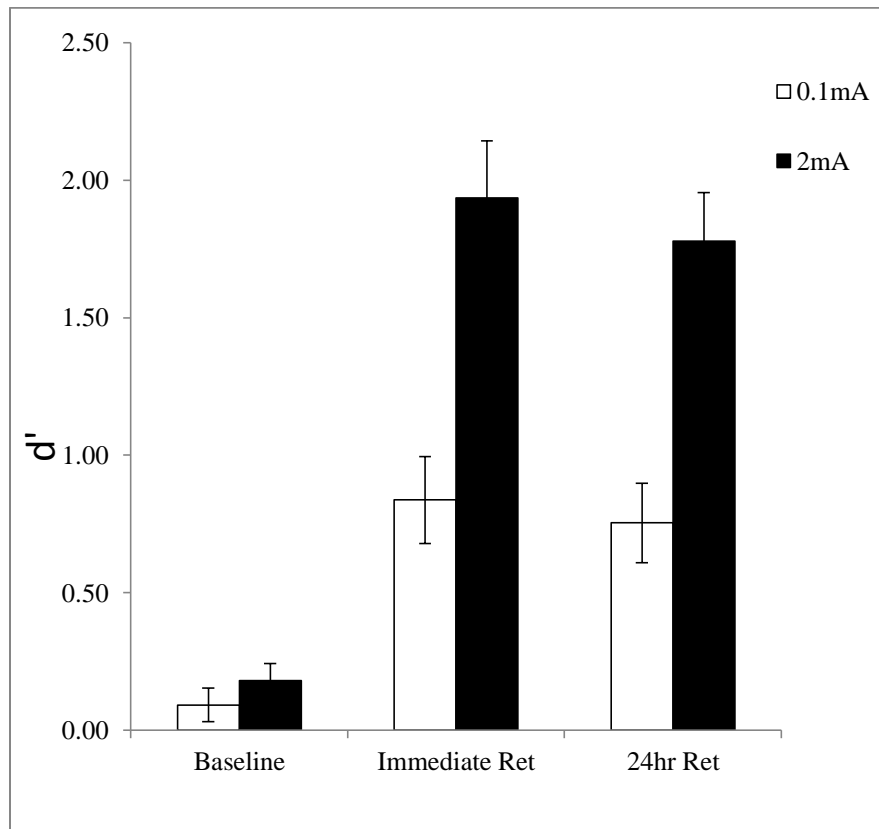
Figure 8: Mean perceptual sensitivity (d') in the pre-training baseline, immediate post-training retention test, and 24-hour retention test blocks for the anodal (2 mA) and sham (0.1 mA) stimulation groups.

Sensation

The results of the sensation survey given at three time points throughout the stimulation procedure were averaged together for an overall sensation score for each

sensation measure of tingling, heat, and itching (see Table 1). A significant difference in self-observed sensation scores between the 2mA and 0.1mA stimulation groups was found only for tingling, $F(1,35)=14.105$, $p<0.01$, but not for heat $F(1,35)=1.084$, nor itching, $F(1,35)=3.418$. As Table 1 shows, however, the mean ratings were near the bottom range of the 10-point scale, and the significant difference between groups for tingling was less than 1 point. To determine if learning was associated with perceived sensation, we conducted a correlational analysis for each sensation measure with the hit and false alarm rates of the two immediate post-training test blocks averaged together. Neither itching nor heat was significantly correlated with either the hit or false alarm rates (r values ranging from -.15 to .27). Tingling was moderately but significantly correlated with hit rate ($r= .35$, p=0.03 uncorrected for multiple comparisons) but not with false alarm rate ($r= -.18$), d' ($r=.24$) or β ($r=.00$).

Table 1: Mean sensation scores (on a 10-point scale, with 1=no sensation and 10=extreme sensation) for tingling, heat, and itching for the sham (0.1 mA) and anodal stimulation (2 mA) groups.

	Sham Stimulation (0.1 mA)	Anodal Stimulation (2 mA)
Itching	1.37	1.81
Heat	1.18	1.44
Tingling	1.57	2.51

Discussion

This study examined whether stimulation of the right inferior frontal cortex using tDCS enhances learning and/or retention of a complex threat detection task, and if so, whether enhancement is based on increased perceptual sensitivity or an alteration in

response bias. We found that, compared to a 0.1 mA sham stimulation control, stimulation with 2 mA tDCS increased perceptual sensitivity in detecting targets and accelerated learning in the task. The performance gain with tDCS was extensive: on completion of training, participants in the real stimulation group had more than double the perceptual sensitivity of the control group. Furthermore, the performance enhancement was maintained for 24 hours. Finally, the performance benefits associated with both skill acquisition and retention were rooted in an improvement in sensitivity (d'), rather than changes in response bias (β).

Anodal 2 mA current was applied to the scalp electrode site F10 in the 10-10 EEG system. The resulting enhancement of performance in the threat detection task is consistent with our previous fMRI results (Clark et al., 2012) showing that the right inferior frontal cortex is a major locus of a distributed brain network that mediates performance on this task. The right parietal cortex is a part of this network and could also be a target for stimulation. One possible explanation for the improvement in detection performance (hit rate) in the threat detection task is that tDCS increases general arousal, thereby leading to a change in response bias in the more liberal direction (Broadbent, 1971), which would increase the hit rate. However, computation of signal detection metrics showed that there were no significant effects of tDCS on the β measure of response bias. Instead, the effect of brain stimulation was to enhance perceptual sensitivity, d'.

The improvement in perceptual sensitivity suggests that participants receiving tDCS were better able to encode stimulus features that distinguished targets and non-

targets, which in turn led to accelerated learning and improved retention. Such effects are also consistent with the view that tDCS enhances attention, which is known to improve performance of perceptual detection tasks, particularly when targets are difficult to distinguish from non-targets (Posner & Peterson, 1990). In particular, attention has been found to improve the ability to detect concealed or obscured objects (Walther, Rutishauser, Koch & Perona, 2005) and the intentional acts of other individuals (Parasurman et al., 2009; Thompson & Parasuraman, 2012) in complex scenes. The mechanism by which attention enhances detection could be through the reduction of the influence of distracter objects that are close to the target (Desimone & Duncan, 1995), thereby enhancing detection of the target threat. This would suggest that stimulation-related enhancement of performance should be associated with increased activation of prefrontal cortical regions that provide top-down attentional control signals to inferior temporal cortical areas that mediate object recognition (Tanaka, 1996). Our previous fMRI findings are consistent with this prediction (Clark et al. 2012).

In addition to examining whether tDCS enhances perceptual sensitivity during the acquisition of a threat detection task, the present study also investigated whether such performance enhancement can be retained over a period of 24 hours. The results were positive: 2 mA tDCS not only increased *d'* by more than a factor of two in the stimulation group compared to the control group, but this benefit was maintained when participants were tested without tDCS the next day.

There are a number of possible mechanisms underlying the retention of performance enhancement over a 24-hour period. First, anodal stimulation with tDCS

may increase neuronal plasticity (Buanoman & Merzenich, 1998; Cotman, 1978), thereby enhancing the rate of learning compared to sham stimulation, and therefore also to retention of learning. A second possibility is the attentional explanation discussed previously with respect to the effects of tDCS on perceptual sensitivity. Attentional modulation with tDCS may increase effective perceptual acuity by allowing participants to detect the visual cues more easily, thereby improving encoding. This in turn may promote better retention, given that stimuli that are better attended and encoded are retained more effectively in memory (Cowan, 1988). However, we found no differences in the rate of forgetting over the 24-hour post-stimulation retention period between the anodal and sham stimulation groups, suggesting that once the threat stimuli were well encoded, performance showed the same (small) decay as in the untrained group. It is possible that differential retention rates could be observed over longer periods than that examined in this study, namely days or weeks. Retention of tDCS-based performance benefits over the long term is an important area for future research.

The results of the present study are encouraging with respect to translational applications. TDCS can be used to enhance sensitivity and accelerate learning of complex detection tasks in healthy individuals. Most previous tDCS studies have examined fairly simple perceptual and cognitive tasks having little ecological validity (Utz, Dimova, Oppenländer, & Kerkhoff, 2010). The use in the present study of tDCS training with a detection task that is more representative of real work environments is consistent with the goals of translational neuroscience (Editorial, 2002) and with the neuroergonomic approach of applying neuroscience research to everyday and work settings (Parasuramn

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& Rizzo, 2007; Parasuraman, Christensen, & Grafton, 2012). Other training techniques aimed at enhancing perceptual sensitivity in learning-impaired or autistic children have used psychophysical techniques such as slowing the rate at which stimuli are presented or increasing their contrast (Merzenich et al., 1996). Training with tDCS can achieve the same goal as these other techniques but with the added advantage that training can be conducted with complex stimuli very similar to those encountered in real settings, thereby reducing concerns about transfer. More generally, tDCS also holds promise as a technique that could be used to remediate diminished perceptual sensitivity in these and other neurological and psychiatric disorders.

TRANSCRANIAL DIRECT CURRENT STIMULATION INDUCES CHANGES IN CORTICAL ACTIVATION MEDIATING LEARNING ON A COMPLEX VISUAL SEARCH TASK REVEALED BY SIMULTANEOUS FMRI

Brian Falcone[1], Atsushi Wada[2,3], Raja Parasuraman[1], Daniel E. Callan[2,3]

[1]Center of Excellence in Neuroergonomics, Technology, and Cognition

(CENTEC), George Mason University, Fairfax, Virginia, USA

[2]Center for Information and Neural Networks (CiNet), National Institute of

Information and Communications Technology (NICT), Osaka University, Osaka, Japan

[3]Multisensory Cognition and Computation Laboratory, Universal Communication

Research Institute, National Institute of Information and Communications Technology,

Kyoto, Japan

Abstract

Transcranial direct current stimulation (tDCS) is a non-invasive technique that has been shown to enhance many different cognitive components by affecting cortical excitability changes in the brain. Studies have recently begun attempting to understand the underlying neural mechanisms by which tDCS leads to cognitive enhancement in humans through various neuroimaging techniques; however, these studies often only observe the effects of residual excitability changes. The purpose of this study was to investigate the active as well as the after-effects of tDCS on brain function by using functional magnetic resonance imaging (fMRI) concurrently with tDCS stimulation in order to observe brain activity during performance of a complex visual search task resembling a real-world search and rescue operation using unmanned aerial vehicles. The experiment consisted of three fMRI sessions: pre-training (no performance feedback), training (performance feedback and either real tDCS or sham stimulation given), and post-training (no performance feedback). We found that active tDCS of right posterior parietal cortex resulted in differential activation during target feedback within networks related to attention and feedback-processing. One area in particular, consisting of the premotor, motor, and somatosensory cortex, showed significant behavioral improvement related to differential activity post- relative to pre- training for the real tDCS over sham group. The degree of differential activity (post- relative to pre- training) in this area was directly related to how strongly it was activated during the training session in which tDCS stimulation was given. These results suggest that tDCS modulates learning in task related functional networks and that performance improvement is reflected by increased

activity even after the cessation of tDCS. However, additional supplementary analyses using non-parametric permutation testing were also conducted to address the risk of false positive findings. These tests did not reveal any significant differences between stimulation conditions which indicate that interpretations of the initial findings should be made with reservations.

Introduction

Experts who carry out difficult visual search tasks, such as detecting and identifying tumors in radiological images or scanning satellite images for threats, typically require many hundreds of hours practice to develop mastery (Ericsson, Krampe, & Tesch-Romer, 1993). Recent findings suggest, however, that skill development in such complex tasks can be accelerated using non-invasive brain stimulation in conjunction with task training (Parasuraman & McKinley, 2014). One such stimulation technique is transcranial Direct Current Stimulation (tDCS), which has been shown in several studies to promote cortical plasticity and enhance performance in such domains as motor skills, working memory, mathematical performance, and attention (for reviews, see Brunoni et al., 2014; Coffman et al., 2013; Jacobson et al., 2011; Parasuraman and Galster, 2013; Utz et al., 2010).

Despite the growing research base of tDCS studies, two major limitations characterize previous work. First, attempts are being made to understand the neural mechanisms by which tDCS leads to cognitive enhancement (Bestmann et al., 2015; Jefferys, Deans, Bikson, & Fox, 2003; Radman, Ramos, Brumberg, & Bikson, 2009). To that end, many studies have examined the effects of tDCS both on behavior and on recordings of neural activity using various neuroimaging techniques. However, less research has been conducted which looked at the active effects of tDCS on the human brain by combining tDCS simultaneously with these techniques such as electroencephalography (EEG) (Faria, Fregni,Sebastiao, Dias, & Leal, 2012; Schestatsky, Morales-Quezada, & Fregni, 2013; Lauro et al., 2014; Roy, Baxter, & He, 2014; Song,

Shin, & Yun, 2014), functional near infrared spectroscopy (fNIRS) (Khan, Hervey, Stowe, Hodics, & Alexandrakis, 2013), and functional magnetic resonance imaging (fMRI). Previous fMRI studies have investigated the after-effects of tDCS on blood oxygen level-dependent signal (BOLD) (Antal et al., 2012; Baudewig, Nitsche, Paulus, & Frahm, 2001; Kim et al., 2012; Nitsche et al., 2004; Stagg et al., 2009) and functional connectivity (Amadi, Ilie, Johansen-Berg, & Stagg, 2014; Keeser et al., 2011; Peña-Gómez et al., 2012; Hunter et al., 2015). In these studies, fMRI data was collected before and after, but not during stimulation. With the use of newer MRI compatible tDCS equipment other studies were conducted to test the active effects of tDCS during fMRI image acquisition by concurrently applying tDCS while collecting fMRI data. Most of these studies were conducted using very basic hand movement tasks (Kwon & Jang, 2011; Antal, Polania, Schmidt-Samoa, Dechent, & Paulus, 2011) or without tasks at all (Kwon et al., 2008). Concurrent tDCS and fMRI studies which used cognitive tasks are even rarer. In fact, to the best of our knowledge, there only exists one such study which used a basic picture naming task while applying tDCS to the left frontal cortex inside the MRI scanner (Holland et al., 2011).

A second limitation of previous tDCS research is that it has mostly been carried out using very basic cognitive tasks. The general implication of many of these studies is that the cognitive improvements elicited by tDCS might lead to improvements in performance in everyday life or in occupations such as radiology or imagery analysis. However, such transfer of enhancement in basic cognitive tasks to everyday performance

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cannot be assumed but must be demonstrated using more complex cognitive tasks that are representative of naturalistic or work tasks.

The present study is an initial attempt to counter both of these limitations by examining the effects of tDCS on performance during a complex visual search task while participants underwent simultaneous fMRI recording. The visual search task we used was based on those typical of Unmanned Aerial Vehicles (UAV) operators. UAVs are being used for a growing variety of applications, including reconnaissance, surveillance, search and rescue missions, firefighting, and homeland security. Effective performance in such settings is dependent on how well the operator can perform a visual search through the UAV video-feed. We used a high fidelity battlefield simulator and training platform to design a realistic UAV task that simulated a search and rescue mission which required participants to perform a visual search for a specific target vehicle hidden in an urban environment through a UAV video-feed.

Recent human and animal studies have provided evidence on the neurophysiological mechanisms of tDCS effect on behavior which suggests that increased excitability in the affected area results in long-term potentiation (LTP) of task relevant neural networks (Coffman et al., 2012; Coffman et al., 2014, Liebetanz et al., 2002; Nitsche et al., 2003). It has been previously posited that on complex visual perceptual detection tasks, such as visual search, tDCS enhances learning mechanisms through an improvement in attention (Coffman et al., 2012) which is facilitated most likely by LTP induced synaptic strengthening of the attentional network. This suggests that increased attention results in more efficient processing of target features and a

suppression of distractor features which in turn leads to enhanced encoding during learning (Coffman et al., 2014; Coffman et al., 2012; Falcone et al., 2012). According to Corbetta & Shulman (2002), there are two distinct neural networks associated with bottom-up (saliency driven) and top-down (goal-directed) attention. Bottom-up attention involves a right lateralized ventrofrontal temporoparietal network and top-down attention involves a bilateral dorsofrontal posterior parietal network. Both networks are involved in visual search as they interact to reorient attention to behaviorally relevant stimuli (Corbetta, Patel, & Schulman, 2008). Further, the right posterior parietal cortex (rPPC) is crucially involved in visual search (Corbetta & Schulman, 2002) as it is involved in both the dorsal fronto-parietal and the right ventrofrontal temporoparietal networks. In a study conducted by Ellison et al. (2014), it was shown that tDCS can be used to reveal the relationship between the critical nodes within these networks during visual search. Cathodal stimulation was applied to the right PPC for 15 minutes before a visual search task was performed by participants during an fMRI scan. Results showed that cortical inhibition of the rPPC induced by cathodal stimulation resulted in a decrease in activation in frontal brain regions, specifically, the frontal eye fields (FEF) in the premotor cortex. These results make it clear that stimulation of the rPPC can result in activation changes in brain areas throughout the entire attention network involved in visual search rather than just the area being stimulated. This suggests that we can expect to see a similar pattern in our own results.

In addition to neurophysiological changes, previous behavioral tDCS studies have shown that stimulation of the rPPC results in performance changes on a variety of spatial

attention tasks. Tseng et al. (2012) applied anodal tDCS to the rPPC while subjects performed on a visual change detection task and found that tDCS improved performance for individuals who originally did poorly. Another study found that stimulation of the rPPC during multisensory visual field exploration training resulted in improved performance on a variety of basic visual tasks including visual search (Bolognini, Fregni, Casati, Olgiati, & Vallar, 2010). In a follow-up experiment it was also observed that tDCS had an active effect where brain stimulation of the right PPC had an immediate positive effect on visual search performance without the need for prior multisensory training paired with brain stimulation. In addition to improvements observed in healthy subjects, other studies have found that stimulation of the rPPC can also improve spatial attention in an unhealthy population. A study conducted by Ko, Han, Park, Seo, & Kim (2008) found that anodal stimulation improved visual scanning in stroke patients suffering from spatial neglect.

Due to the strong neuroimaging evidence which demonstrates the importance of the rPPC in visual search, as well as the behavioral results observed in prior tDCS studies, we chose this area as the site of stimulation for this experiment. While the results of these studies suggest an effect of tDCS on the rPPC or other areas in the visual attention network, very little is understood about the underlying active mechanisms mediating these improvements on visual search capabilities. Towards the comprehensive understanding of the effects of tDCS on complex visual search performance, we devised an integrative experimental design that enables to investigate the active and after-effects of tDCS on neural activity and behavior through three primary goals: 1. To determine the

effect that tDCS has on cortical activity that may enhance the likelihood of learning. In accomplishing this goal we examine the difference in brain activity during target feedback between real tDCS and sham groups while undergoing simultaneous fMRI scanning. It is hypothesized that the tDCS group will show specific differences in activity related to learning via target feedback. We focus on target feedback because of its involvement in learning and potential link in enhancing behavioral performance. 2. Another primary goal is to determine behaviorally related changes in brain activity post-relative to pre- training that is specific to the tDCS over the sham group. 3. The final primary goal is to show that there is a link between increased brain activity for target feedback training during simultaneous tDCS and fMRI and behaviorally related changes in brain activity post- relative to pre- training for the real tDCS group. Fulfilling the goals of this experiment will help elucidate the neural processes underlying behaviorally related modulation in performance by tDCS on a complex visual search task simulating real-world conditions. By using concurrent brain stimulation of the rPPC and fMRI during performance on a high-fidelity visual search task, we hope to answer these questions.

Methods

Participants

The participants consisted of 28 Japanese adults (14 males, 14 females) aged 18-25 years (mean = 20.7) from Osaka University. Participants were screened and excluded for having a history of head injuries or concussions, current or previous history of mental, neurological, alcohol or drug abuse disorders, or current medication affecting central

nervous system function. Subjects without normal vision were given MRI compatible

glasses to correct their vision to normal before the study was conducted and all subjects

were right-handed. Participants were randomly assigned to the real tDCS (which will be

referred to as the "stim group" from this point forward) or sham group. There were 14

individuals (7 females and 7 males) in the tDCS stim group (mean age = 22.1 years) and

14 individuals (7 females and 7 males) in the tDCS sham group (mean age = 21.3 years).

The person giving the instructions was blind with regard to the group membership of the

participant. Subjects gave written informed consent. The experimental procedures were

approved by the NICT Human Subject Review Committee and were carried out in

accordance with the principles expressed in the WMA Declaration of Helsinki.

UAV Visual Search Task

A high fidelity battlefield simulator and training platform, Virtual Battlespace 2

(VBS2), was used to program the UAV visual search task. Participants viewed a 3D

virtual Middle Eastern urban environment on a monitor from the perspective of a video

feed from an MQ-9 Predator unmanned aerial vehicle. In each trial the UAV camera was

locked to the central point of the area to be surveyed as the UAV loitered in a circular

path around this point. The goal of the task was based on a search and rescue mission that

required participants to locate a red pickup truck located in the search area amongst

buildings and other similar looking distractor vehicles. In each trial there were 5 non-

moving vehicles distributed throughout the search area, one of which could be the red

truck. These vehicles were located in a variety of areas such as on roads, in parking lots,

next to walls or buildings or out in the open, away from any man-made structures. The

task was designed so that as the UAV loitered in a circle around the search area, all vehicles would remain in constant view despite a continually changing view angle. Each trial lasted 10 seconds where the participants searched the area looking for the target and were required to make a button press indicating whether the search area contained a target or not. If they did not respond by the end of the trial, these trials were removed from the analysis. The justification for removing these trials was that we were mainly interested in focusing on the time in which the visual search decision was made. We believe that the button response is a good indicator of this time. There was a 2 second interstimulus interval (ISI) before the start of each trial, which consisted of a black screen and white crosshair fixation.

All distractor vehicles in this task were chosen to share one particular feature with the target vehicle, which is the color red (see Figure 9A for pictures of the target and distractor vehicles). This allowed us to easily manipulate the difficulty of the task based on the flying altitude of the UAV because at higher altitudes it becomes exceedingly difficult to distinguish between vehicles of the same color. Through initial pilot testing, the permanent flying altitude of the UAV for the experiment was chosen based on the altitude that yielded an average of ~66% performance accuracy with no prior visual search training and also when sitting at a distance of 1.2 meters from the display. This was to ensure that the task was sufficiently difficult with plenty of room for improvement but also not so much that it resulted in chance level performance. The distance of 1.2 meters was used in the pilot study as this was also the distance of the display from the participant in the MRI scanner.

There were three sessions: a pre-training session that did not provide performance feedback, a training session, which provided immediate reinforcement feedback after each response, and a post-training session with no feedback. Each session consisted of 60 visual search trials and 15 baseline control trials in which subjects looked at a black screen. Trials were 10 seconds long. Half of the visual search trials contained a target (red truck) (see Figure 9B for a snapshot picture of a visual search trial). In the feedback trials, a tone would play immediately after the participant responded by button press, which would indicate whether or not they answered correctly (reinforcement feedback). They would hear a 'ding' sound-effect for correct responses and a 'buzz' for incorrect responses. For target present trials only, a transparent white sphere would appear over the target at the end of the 10-second trial (See Figure 9C for a snapshot picture of an example of the target feedback). This sphere was used to draw attention to the actual location of the target, which allowed effective target feedback and also gave the participant the opportunity to study the features of the target and to use this knowledge for future trials. The sphere would remain over the target and the next trial would not begin until the participant responded with a button-press a second time indicating whether or not they saw this target. If they indicated that the target was present with their first response but had actually been looking at a distractor when the sphere appeared highlighting the real target they would respond in the negative with the second button-press. This allowed us to determine true "hits" from guessing. If they had missed the target and indicated that the target was absent with their first response they would simply respond in the negative for the second button-press.

A. Vehicles used in the Visual Search Task

Target

Distractors

B. Snapshot of a Visual Search Trial

C. Snapshot of Target Feedback

Figure 9.

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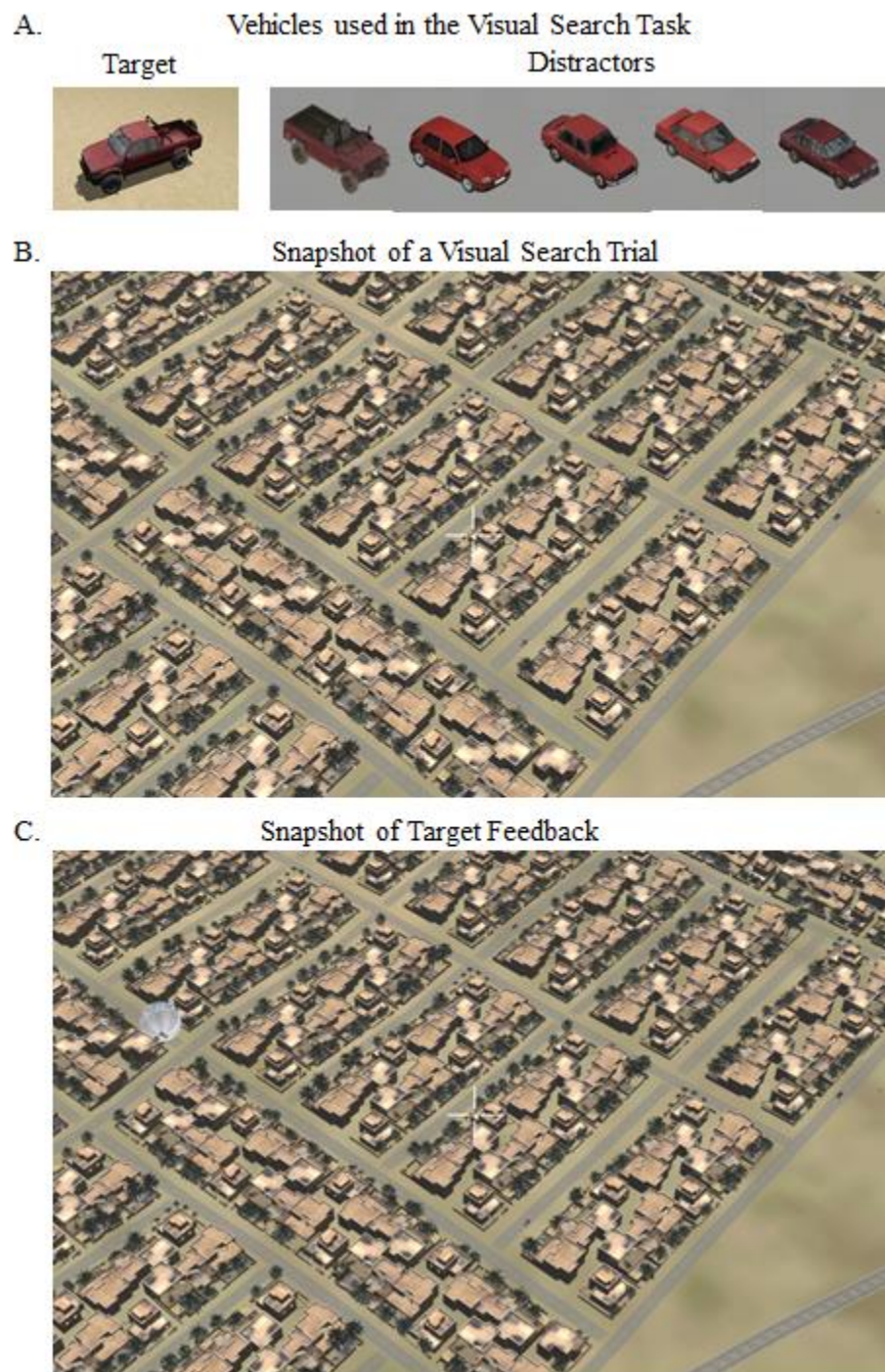
Behavioral Data Analysis

        Performance measures and response times were collected for each of the three sessions. Performance measures included: percent correct, hit rate, and false alarm rate. Hit and false alarm rates were then used to compute the parametric signal detection measures d-prime (*d'*) and beta (ß) (Green & Swets, 1966) in order to assess changes in perceptual sensitivity and response bias (respectively). Using signal detection metrics allowed us to determine whether differences in performance between stimulation groups were due to enhanced perceptual sensitivity rather than through changes in response bias due to an arousal effect from stimulation. Response time measures included: 1. Response time for all trials (RT all search); 2. Response time for hit and correct rejection trials (RT HT&CR Search); 3. Response time for target present trials (RT TP trials Search); 4. Response time to target for target present trials (RT TP trials Target). The "RT TP trials Search" and "RT TP trials Target" measures were only analyzed for the training session to correspond with an fMRI analysis looking at the effects of feedback (see FMRI Data Collection and Analysis below) as visual feedback only occurred in the training session and on target present trials. All measures (excluding RT TP trials Search & RT TP trials Target) were analyzed in 2 (group: stim or sham) x3 (session) mixed analyses of variance (ANOVAs). In addition, between subjects t-tests (stim vs. sham) were also conducted in order to identify any significant differences for all dependent measures that might confound the fMRI results. This was done for each session as well as for gain scores from the pre-training session to the post-training session.

FMRI Data Collection and Analysis

All 3 sessions were conducted within a Siemens 3T Trio Scanner using a 32-channel head coil at the Center for Information and Neural Networks NICT Osaka University. The functional T2* weighted images were acquired using a gradient echo-planar imaging EPI sequence with a repetition time of 2 seconds (TR=2). Each scan consisted of 30 interleaved axial slices (3x3x4mm) covering the brain and cerebellum. For both sessions 1 and 3, 454 scans (~15 minutes) were taken for each session. For session 2 approximately 475 scans (~16 minutes) were taken that varied depending on the participant's response time on the feedback trials. An additional 150 scans (5 minutes) measuring resting-state activity were collected after each experimental session. The analysis and results of the resting state activity will be presented in a separate study. Images were preprocessed using programs within SPM8 (Wellcome Department of Cognitive Neurology, UCL). Images were realigned, unwarped, spatially normalized to a standard space using a template EPI image (2x2x2 mm voxels), and were smoothed using an 8x8x8 mm FWHM Gaussian kernel. Regional brain activity for the various conditions was assessed using a general linear model employing an event-related design in which a modeled hemodynamic response function (HRF) was convolved with the event onset predictors. Auto-regression was used to correct for serial correlations. High pass filtering (cutoff period 128 s) was carried out to reduce the effects of extraneous variables (scanner drift, low frequency noise, etc.).

Fixed effect contrasts of interest were conducted for each subject. These contrasts consisted of the following: 1. The first contrast consisted of target feedback relative to

visual search: This contrast was from data collected during the second session in which subjects were trained on the visual search task during real stimulation or sham stimulation. During this training session an auditory feedback signal was presented with regards to their response. In addition, feedback of the true position of the target was given at the end of the trials in which it was present. The contrast under investigation was based on the onset of the target feedback (at the end of the trial) relative to two-seconds after the onset of the trial when visual search was underway (feedback relative to visual search). Trials without a button response as well as trials with false hits (button response was a hit but the subject was attending to a distractor instead of the true target) were not included in the analysis. This contrast was designed to specifically focus on activity related to training feedback that is not related to general processes related to visual search. Therefore, only the target present trials, in which target feedback was given, were included for this contrast. 2. The second contrast consisted of post- relative to pre-training for the visual search trials compared to baseline control trials (post- relative to baseline minus pre- relative to baseline). The event onset of the visual search trials was taken as the time of the subject's button response. The onset of the event for the baseline control trials was randomly taken from 4.1 to 7.1 seconds after trial onset. This onset time corresponded to plus or minus 1.5 seconds around the mean button response time of the visual search trials, which was approximately 5.6 seconds. Visual search trials without a button response were not included in the analysis. This contrast was designed to determine differences in brain activity after relative to before training. The baseline

control condition was used to ensure that differential activity post- relative to pre-training was not related to session effects.

Between subjects random-effects analyses (between subjects t-tests) were conducted to determine differences in brain activity between the tDCS stim and sham groups. The first contrast was to determine differential brain activity between the two groups during the training session specifically related to target feedback that is hypothesized to be modulated as a result of tDCS stimulation. Because it was later found that the ratio of true hits to the total number of target present trials included in the analysis statistically differed (T = -2.22; p < 0.05) between tDCS stim (mean = 0.470; SE = 0.04) and sham (mean = 0.594; SE = 0.01) groups, an additional analysis was conducted in which this ratio for each subject was entered as a covariate of non-interest. While this analysis may control for between group differences in performance it may at the same time mask important between-group differential processing related to feedback. The results of both analyses are given and we focus on activity that is found to be present in both. The second contrast of interest was to determine improvement-related changes in brain activity post- relative to pre- training that differs between the tDCS stim and sham groups. This was accomplished by using percent correct performance on the visual search task as a covariate of interest in the between subjects analysis of the contrast of post- relative to baseline minus pre- relative to baseline. Using improvement in performance as a covariate of interest allowed us to compare the relationship between performance improvement and brain activity between stimulation conditions. This allows us to investigate the effects of tDCS on learning mechanisms despite a lack of behavioral

enhancement via tDCS between stimulation conditions. Only trials containing responses were included in the behavioral and brain activity analyses. The third contrast of interest was conducted within the region of overlapping brain activity found for the first two contrasts. The purpose of this third contrast was to determine if between group differential activity (post- relative to baseline minus pre- relative to baseline) within this defined region of interest (ROI) shows modulation related to the degree of activity in this same region for the target feedback relative to visual search contrast. To conduct this analysis, we first determined the activity present in the peak voxel (contrast estimate for each subject) of the target feedback contrast within the ROI (that was also present for the contrast in which the ratio of hits to total trials was included as a covariate of non-interest). We then conducted a between group ROI analysis using these target feedback related activity measures as a covariate of interest for the contrast of post- relative to baseline minus pre- relative to baseline. This contrast is meant to provide additional support that the improvement related differences post- relative to pre- training are induced within this brain region by modulation of target feedback processing by tDCS. Correction for multiple comparisons ($p < 0.05$) across the entire brain was carried out using Monte-Carlo simulation of the brain volume to define a voxel contiguity threshold at an uncorrected significance level of $p < 0.005$ (Slotnick et al., 2003; Ellison et al., 2014). Using 10000 Monte-Carlo simulations a cluster extent of 146 voxels thresholded at $p < 0.005$ uncorrected, is necessary to correct for multiple comparisons across the whole brain at a threshold $p < 0.05$.

Because we only included trials in which responses were given, it is possible that the number of trials between groups may differ and confound the brain imaging results. Analyses were conducted to ensure that there were no between group differences with regards to the number of trials included for each contrast of interest. For the target feedback contrast no significant differences ($T = -1.28$; $p > 0.1$) in the number of trials were present between the tDCS stim (mean = 26.86 trials out of 30; SE = 0.69) and sham (mean = 27.93; SE = 0.53) groups. For the post- relative to pre- contrast there were no significant differences for the following: 1. The post- session ($T = -1.66$; $p > 0.1$) between the tDCS stim (mean = 59.07 out of 60; SE = 0.48) and sham (mean = 59.86; SE = 0.10) groups. 2. The pre- session ($T = -0.41$; $p > 0.1$) between the tDCS stim (mean = 58.71; SE = 0.47) and sham (mean = 58.93; SE = 0.28) groups. And 3. The difference in the number of trials included for the post- minus the pre- session ($T = -0.88$; $p > 0.1$) between the tDCS stim (mean = 0.36; SE = 0.60) and sham (mean = 0.93; SE = 0.30) groups. Based on these results it is unlikely that the difference in the number of trials between the groups for the various contrasts confounded the brain imaging results.

Finally, supplementary non-parametric permutation testing was conducted using SnPM13 (http://warwick.ac.uk/snpm) to identify FWE $p < .05$ corrected clusters of activation in addition to the Monte-Carlo simulation mentioned above. This was done in order to address an unacceptably high risk of false positive results found to be associated with cluster-extent thresholds determined from the software we used to perform the Monte-Carlo simulations. Around the time of this manuscript being written, Eklund et al. (2016) reported that some cluster analyses might have unacceptably high false positive

rates. Specifically, a bug was found to exist in the code which results in a reduction in the size of the image being used to calculate the cluster-extent threshold leading to "underestimating the severity of the multiplicity correction and overestimating significance" (Eklund et al., 2016). Non-parametric permutation testing has been shown to deliver the most reliable results when using cluster-extent thresholding as this method does not rely on as many assumptions as parametric methods because the null distribution is constructed using the actual data rather than a theoretical distribution (Nichols & Holmes, 2001). For these analyses, the voxel-height or cluster-defining threshold (CDT) was set at $p < .001$ and only clusters that are significant at a FWE $p < .05$ will be reported. This CDT was selected as it was found to reliably produce results with false positive rates below 5% (Eklund et al., 2016). In addition, no variance smoothing was needed as the degrees of freedom for these analyses were sufficiently high to allow for accurate variance estimation (Nichols & Holmes, 2001).

Transcranial Direct Current Stimulation

TDCS was applied using a NeuroConn DC-Stimulator MR, which is a certified MRI compatible device, which allows for DC stimulation during magnetic resonance imaging. Conductive paste was applied to two (5.3 x 7.2 cm) rectangular-shaped MRI compatible rubber electrodes which were attached to the participant. The anode was placed over the right P4 (posterior parietal cortex (PPC)) according to the 10-20 International EEG System and held in place using a padded headband. The cathode was placed contralaterally on the back half way between the shoulder and neck (trapezius

muscle) that was held in place by the conductive paste and the weight of the participant

as they lay in the supine position in the MRI scanner.

Participants in the real stimulation group received approximately 1mA current for

a total of 30 minutes during the training session. Stimulation was started 5 minutes before

the task in order to ensure that the full modulatory effect of tDCS was active during task

performance. Participants in the sham stimulation (control) group also received

approximately 1mA current but only for 30 seconds and then the unit was shut off.

Behavioral Results

Table 2 shows the results of the mixed ANOVAs for each of the dependent

measures. While there was a significant main effect of session for all dependent

measures, except for hit rate and "RT HT&CR", there was no significant main effect for

stim group or stim group $\times$ session interaction for any of the performance or response

time measures (see Table 2).

Table 2: Mixed Anova Behavioral Results.
* = statistically significant at $p < 0.05$; RT = Response Time; HT = Hit; CR = Correct Rejection.

Performance Measure	Stim Group		Session		Stim X Session	
	Degree of Freedom	F Value p<0.05	Degree of Freedom	F Value p<0.05	Degree of Freedom	F Value P<0.05
Percent Correct	1,26	.317 n.s.	2,52	12.468 *	2,52	.303 n.s.
Hit Rate	1,26	3.878 n.s.	1.58,41.109	.894 n.s.	1.581,41.109	.534 n.s.
False Alarm Rate	1,26	1.362 n.s.	2,52	34.366 *	2,52	.004 n.s.
d-prime	1,26	-0.45 n.s.	2,52	27.247 *	2,52	.444 n.s.

Beta	1,26	3.409 n.s.	2,52	26.150 *	2,52	.319 n.s.
RT all Search	1,26	.180 n.s.	2,52	12.288 *	2,52	2.901 n.s.
RT HT&CR Search	1,26	.120 n.s.	2,52	9.798 n.s.	2,52	2.548 n.s.

The between subjects t-test results for all dependent measures for the training session are given in Table 3. Only the hit rate was found to be statistically significant between the tDCS stim and sham groups. The t-test results for the pre-training session, the post-training session, and the post- minus the pre- training session are given in Table 4. No statistically significant differences were found between tDCS stim and sham groups for any of the behavioral measures (see Table 4). It is important to note that differences in response time between the tDCS stim and sham groups that could serve as a potential confound can be ruled out. This is because there were no statistically significant differences in any of the response time measures for the training session, the pre-training session, the post-training session, nor the post- minus pre- training session (see Tables 3 and 4). As indicated by the significant main effect of session in the mixed ANOVA analyses (see Table 2), there was a significant improvement in overall performance measures (percent correct and d'). Percent correct performance post-training (mean = 72.06%; SE = 2.36) was significantly better relative to pre-training (mean = 64.26; SE = 2.64) for the tDCS stim group (t = 4.05; p < 0.05) (see Figure 10). There was also a significant improvement in percent correct performance post-training (mean = 73.02%; SE = 1.99) relative to pre-training (mean = 64.98%; SE = 2.47) for the sham

group (t = 3.15; p < 0.05) (see Figure 10). However, there was no statistically significant difference in percent correct performance post- relative to pre- training between the groups as is reported in Table 4. Post-training d' performance (mean = 1.50; SE = 0.16) was significantly better relative to pre-training (mean = 0.78; SE = 0.15) for the stim group (t = 5.74; p < 0.001). There was also a significant improvement in d' performance post-training (mean = 1.50; SE = 0.16) relative to pre-training (mean = 0.88; SE = 0.15) for the sham group (t = 3.78; p < 0.01). Similar to percent correct, there was no significant difference in perceptual sensitivity (d') post- relative to pre-training between stim and sham conditions as seen in Table 4. All of the behavioral results reported above excluded trials in which there was no button response given. If we included these no responses as misses the results were essentially the same. There was a significant increase in percent correct performance post-training (mean = 70.95%; SE = 2.02) relative to pre-training (mean = 62.86%; SE = 2.56) for the tDCS stim group (t = 3.85; p < 0.05). There was also a significant improvement in percent correct performance post-training (mean = 72.86%; SE = 2.02) relative to pre-training (mean = 63.81%; SE = 2.42) for the sham group (t = 3.53; p < 0.05).

Table 3: The behavioral results for various performance measures for the training session for the tDCS stim and sham groups.
The between subjects t-tests were assessed using p < 0.05 with 26 degrees of freedom. * = statistically significant at p < 0.05; SE = standard error; RT = Response Time; HT = Hit; CR = Correct Rejection; TP = Target Present. The Beta is the criterion value for the d-prime analysis. The RT for the Target trials is the time spent observing the feedback before the button was pressed to continue to the next trial.

Performance Measure	Mean (SE) Stim	Mean (SE) Sham	T p<0.05

Percent Correct	64.86 (2.70)	67.94 (2.74)	-0.825 n.s.
Hit Rate	0.5178 (0.0382)	0.6262 (0.0337)	-2.21 *
False Alarm Rate	0.2227 (0.0284)	0.2672 (0.0403)	-0.94 n.s.
d-prime	0.8566 (0.1616)	1.0384 (0.1763)	-0.79 n.s.
Beta	1.4667 (0.1543)	1.5417 (0.3338)	-0.21 n.s.
RT all Search	5.47 (0.260)	4.98 (0.230)	1.45 n.s.
RT HT&CR Search	5.40 (0.254)	4.94 (0.240)	1.36 n.s.
RT TP trials Search	5.03 (0.247)	4.48 (0.226)	1.705 n.s.
RT TP trials Target	1.29 (0.099)	1.13 (0.078)	1.27 n.s.

Table 4: The behavioral results for various performance measures for the pre- and post- training sessions (and their difference post-pre) between the tDCS stim and sham groups.

The Beta is the criterion value for the d-prime analysis. The between subjects t-tests were assessed using $p < 0.05$ with 26 degrees of freedom. * = statistically significant at $p < 0.05$; SE = standard error; RT = Response Time; HT = Hit; CR = Correct Rejection

Performance Measure	Pre Mean (SE) Stim	Pre Mean (SE) Sham	Pre T p<0.05	Post Mean (SE) Stim	Post Mean (SE) Sham	Post T p<0.05	Post-Pre Mean (SE) Stim	Post-Pre Mean (SE) Sham	Post-Pre T p<0.05
Percent Correct	64.26 (2.64)	64.98 (2.47)	-0.21 n.s.	72.06 (2.36)	73.02 (1.99)	-0.33 n.s.	7.80 (2.00)	8.04 (2.65)	-0.08 n.s.
Hit Rate	0.5682 (0.0397)	0.6238 (0.0310)	-1.15 n.s.	0.5277 (0.0391)	0.5929 (0.0374)	-1.25 n.s.	-0.0465 (0.0399)	-0.0310 (0.0323)	-0.19 n.s.
False Alarm Rate	0.2813 (0.0270)	0.3234 (0.0521)	-0.74 n.s.	0.0900 (0.0168)	0.1337 (0.0294)	-1.34 n.s.	-0.1913 (0.0312)	-0.1896 (0.0464)	-0.03 n.s.
d-prime	0.7841 (0.1479)	0.8761 (0.1526)	-0.45 n.s.	1.5016 (0.1619)	1.5005 (0.1600)	0.01 n.s.	0.7176 (0.1297)	0.6244 (0.1715)	0.45 n.s.
Beta	1.1849 (0.0864)	1.4129 (0.2170)	-1.01 n.s.	3.1411 (0.4617)	2.7979 (0.4843)	0.5322 n.s.	1.9562 (0.4544)	1.3850 (0.4438)	0.93 n.s.
RT all Search	5.84 (0.314)	6.07 (0.221)	-0.61 n.s.	5.61 (0.272)	5.50 (0.179)	0.36 n.s.	-0.23 (0.212)	-0.57 (0.204)	1.20 n.s.
RT HT&CR Search	5.73 (0.324)	5.97 (0.259)	-0.59 n.s.	5.49 (0.266)	5.39 (0.191)	0.31 n.s.	-0.24 (0.232)	-0.57 (0.230)	1.07 n.s.
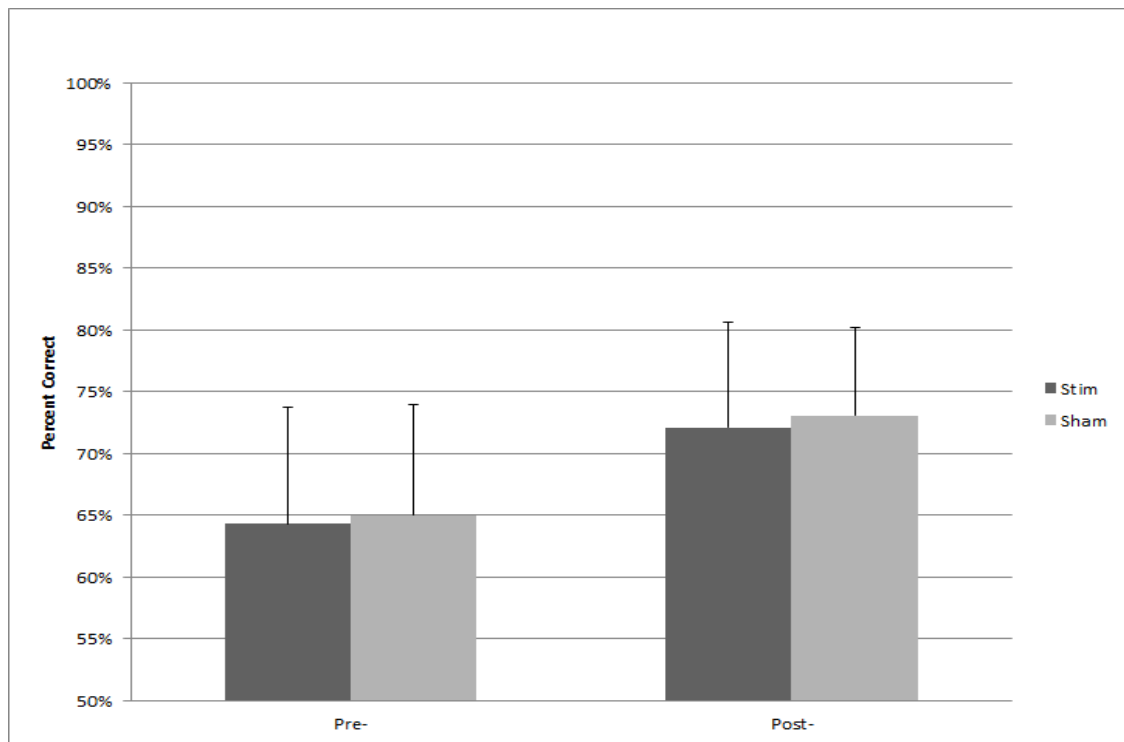
Figure 10: Shows change in behavioral performance (percent correct) before and after training for both stim and sham tDCS groups.

Brain Imaging Results

The brain imaging results for all the contrasts of interest are reported in Figures 11-14 and Tables 5-9. Correction for multiple comparisons (p < 0.05) was accomplished using Monte-Carlo simulation to determine the voxel contiguity threshold over uncorrected thresholds of p < 0.005. This contiguity threshold was found to be 146 voxels within a single cluster. Please see methods section for more details. This correction method for multiple comparisons is the same for all brain imaging contrasts presented unless otherwise stated. Activated brain regions were identified using the SPM Anatomy Toolbox v1.8 (Eickhoff et al., 2005).

Brain Regions Showing Modulation in Feedback Processing by tDCS

The results of the random effects analysis for the contrast of target feedback relative to visual search for the tDCS stim over the sham group is presented in figure 11A-C and Table 5. Four clusters of brain activity were found to show statistically significant differential activity between the tDCS stim and sham groups. These clusters were located in the following brain regions: 1. The right post- and pre- central gyrus including the somatosensory cortex, premotor cortex, and primary motor cortex; 2. The anterior cingulate gyrus ACG; 3. The left cerebellum lobules V and VI; 4. The right cerebellum lobules V and VI (See Figures 11A-C and Table 5). It should be noted that there was no significant differential activity when correcting for multiple comparisons for the sham over the stim group for this contrast.

The difference in the hit rate between the tDCS stim and sham groups in the training session could potentially confound the results. In order to find brain regions that are not confounded by differences in hit rate between the stim and sham groups, this variable was used as a covariate of non-interest in the same contrast. The results of this analysis correcting for multiple comparisons are given in figure 18 and table 12 in Appendix A. The brain regions showing significant differential activity for target feedback relative to visual search for the stim over the sham group with and without using hit rate as a covariate of non-interest are given in Figure 11D-E and Table 6. This activity was in 1. The right post- and pre- central gyrus including the somatosensory cortex, premotor cortex, and primary motor cortex; and 2. The ACG. The non-parametric

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permutation testing for the stim over the sham group did not result in any clusters

significant at k>220 using a CDT of p < .001 and a cluster correction of FWE p < .05.

Table 5: Target feedback relative to visual search (stim-sham).
Brain Regions showing significant differential activity corrected for multiple comparisons at the cluster level (p < 0.05) using Monte-Carlo simulation (corrected cluster extent threshold = 146 contiguous voxels over uncorrected significance threshold of p < 0.005). BA = Brodmann area; PMC = Premotor Cortex; M1 = Primary Motor Cortex; ACG = Anterior Cingulate Gyrus. Negative 'x' MNI coordinates denote left hemisphere and positive 'x' values denote right hemisphere activity.

Brain Region	MNI Coordinates x,y,z	T	Cluster Size
Post- and Pre- central Gyrus Somatosensory Cortex, PMC, M1 BA1,3,4,6	56,-14,52 52,-20,58	4.14 3.92	151
ACG BA 24,32	-4,28,20	4.5	376
Left Cerebellum Lobule V,VI	-8,-54,-10 -10,-56,-24	3.46 3.23	182
Right Cerebellum Lobule V,VI	10,-54,-18 10,-48,-24	3.88 3.47	177

Table 6: Overlap of Brain Regions showing significant (p < 0.05 corrected) differential activity for target feedback relative to visual search with and without using hit rate as a covariate of non-interest.
BA = Brodmann area; PMC = Premotor Cortex; M1 = Primary Motor Cortex; ACG = Anterior Cingulate Gyrus. Negative 'x' MNI coordinates denote left hemisphere and positive 'x' values denote right hemisphere activity.

Brain Region	MNI Coordinates x,y,z	T	Cluster Size
Post- and Pre- central Gyrus Somatosensory Cortex, PMC, M1 BA1,3,4,6	54,-14,54	3.85	36
ACG BA 24,32	-2,28,18	4.31	115
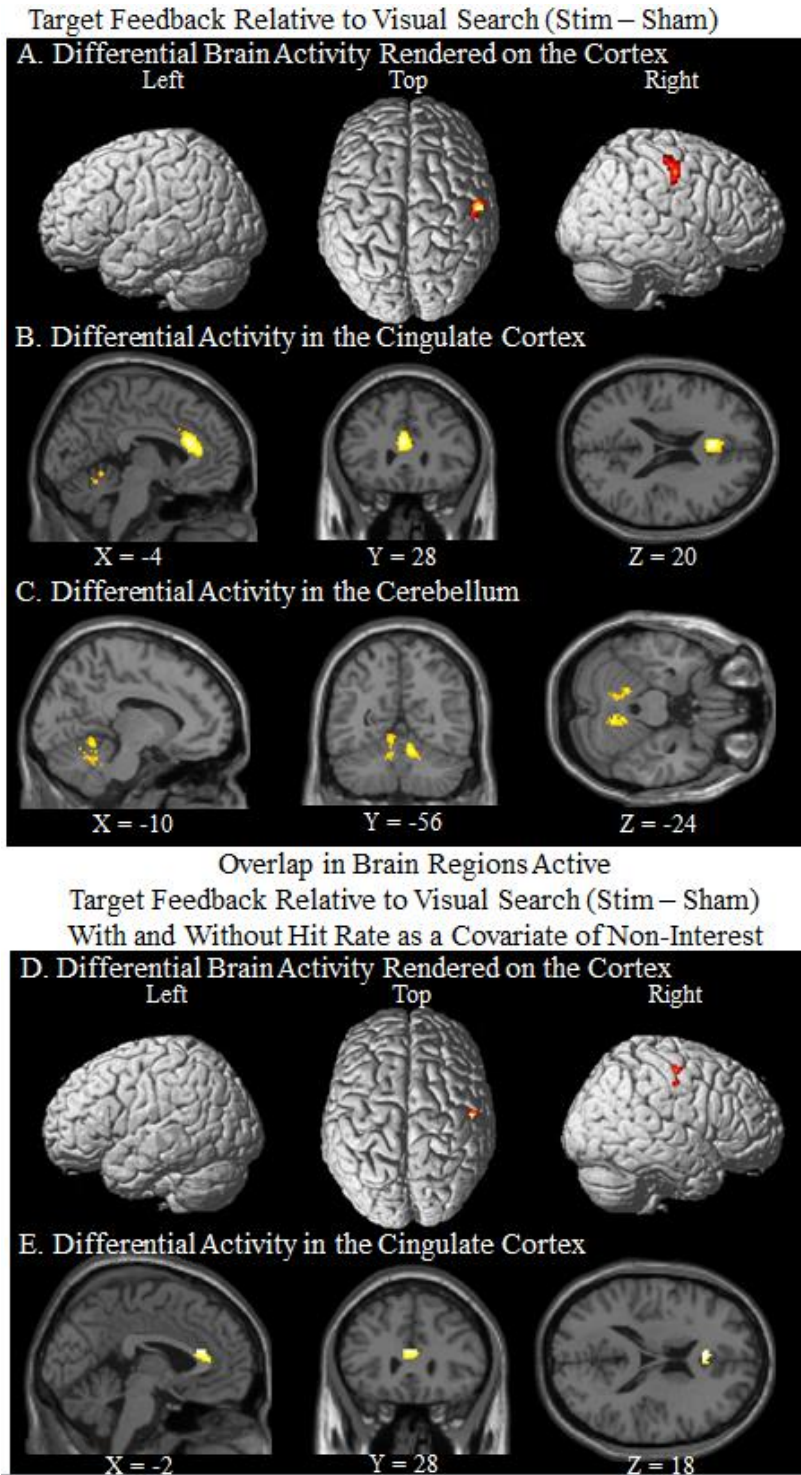
Figure 11: Brain activity unique to the stim group over the sham group during target feedback in the training session (activetDCS).
A) Differential activity in post and pre-central gyrus including the somatosensory cortex, primary motor cortex, and pre-motor cortex. B) Differential activity in the anterior cingulate gyrus. C) Differential activity in the left and right cerebellum. D) Differential activity remains after taking into account group differences in hit rate during the training

session in post and pre-central gyrus including the somatosensory cortex, primary motor cortex, and pre-motor cortex. E) Differential activity remains after taking into account group differences in hit rate during the training session in anterior cingulate gyrus.

Brain Regions Showing Differential Behavioral Improvement Related Activity Post- relative to Pre- Training

The random effects analysis investigating improvement related activity for the contrast of visual search post- versus pre- training relative to baseline for the tDCS stim over sham groups was determined by using as a covariate of interest each subjects differential percent correct performance for post- minus pre- training. Differential activity correcting for multiple comparisons is given in figure 12 and Table 7. There were three clusters of activity located in 1. The right post- and pre- central gyrus including the somatosensory cortex, premotor cortex, and primary motor cortex; 2. The left post- and pre- central gyrus including the somatosensory cortex, premotor cortex, and primary motor cortex; and 3. The superior and middle temporal gyrus STG/MTG. The linear regression fit for behavioral performance in relation to the contrast estimates of post- minus pre- brain activity for each of the peak voxels in the three clusters is also given in Figure 12. It should be noted that there was no significant differential activity when correcting for multiple comparisons for the sham over the stim group for this contrast. The non-parametric permutation testing for the stim over the sham group did not result in any clusters significant at k>292 using a CDT of $p < .001$ and a cluster correction of FWE $p < .05$.

Table 7: Improvement Related Activity Post- relative to Pre- Training (Stim – Sham).
Brain Regions showing significant differential activity corrected for multiple comparisons at the cluster level (p < 0.05) using Monte-Carlo simulation (corrected cluster extent threshold = 146 contiguous voxels over uncorrected significance threshold of p < 0.005). BA = Brodmann area; PMC = Pre Motor Cortex; M1 = Primary Motor Cortex; STG = Superior Temporal Gyrus; MTG = Middle Temporal Gyrus. Negative 'x' MNI coordinates denote left hemisphere and positive 'x' values denote right hemisphere activity.

Brain Region	MNI Coordinates x,y,z	T	Cluster Size
Right Post- and Pre- central Gyrus Somatosensory Cortex, PMC, M1 BA 1,6,3,4	48,-14,62 54,-16,56 46,-8,44	4.13 3.96 3.35	319
Left Post- and Pre- central Gyrus PMC, Somatosensory Cortex BA 6,1,4,3	-46,-16,62 -30,-26,74 -40,-20,66 -58,-4,38	5.26 4.54 4.38 3.65	604
STG/MTG BA 22,21	-64,-14,-4 -58,4,-16	3.32 3.14	190

Figure 12: Improvement related activity post- relative to pre- training unique to the stim group over the sham group (residual tDCS).
Areas of differential activity included: left and right post/pre-central gyrus (somatosensory cortex, primary motor cortex, and pre-motor cortex), left superior temporal gyrus, and left middle temporal gyrus. Graphs demonstrate that within the stim group, participants with increased activation also showed greater improvement in behavioral performance post- relative to pre-training. Abbreviations: SS = somatosensory cortex; M1 = primary motor cortex; PMC = pre-motor cortex; STG, superior temporal gyrus; MTG, middle temporal gyrus.

Brain Regions Showing a Link between Improved Behavioral Performance and tDCS Modulated Feedback Processing

To determine brain regions that are present for both the target feedback relative to visual search contrast for stim over sham groups and the contrast of improvement related activity post- relative to pre- for stim over sham the intersection of active voxels was determined. The overlap in brain regions for these two contrasts is given in figure 13 and Table 8. Overlapping activity was present in the right post- and pre- central gyrus including the somatosensory cortex, premotor cortex, and primary motor cortex. To further provide evidence that tDCS-induced change in feedback processing is indeed modulating increases in improvement related activity post- relative to pre- training, a ROI analysis was conducted within the cluster of voxels showing overlapping activity for the two contrasts of interest (Figure 13, Table 8). The contrast estimate of brain activity in the peak voxel (MNI 54,-14,54) in the target feedback relative to visual search for stim over sham (that was also present when using hit rate as a covariate of non-interest (Figure 11D, Table 6)) was used as a covariate of interest for the contrast of visual search relative to baseline post- minus pre- training for the stim over sham group. Significant modulation (using a small volume correction for multiple comparisons $p < 0.05$) was found in our ROI between target training feedback activity and post- relative to pre- training activity (Figure 14, Table 9). The difference in the modulatory effects can be seen in the positive linear regression fit that is significant only for the tDCS stim group (Figure 14).

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Table 8: Target Feedback Relative to Visual Search (Stim – Sham) that is also present for Improvement Related Activity Post- relative to Pre- Training (Stim – Sham).
Overlap in significant differential activity (p < 0.05 corrected) for target feedback relative to visual search and improvement related activity post relative to pre- training for stim over the sham group. BA = Brodmann area; PMC = Pre Motor Cortex; M1 = Primary Motor Cortex. Positive MNI 'x' coordinates denote right hemisphere activity.

Brain Region	MNI Coordinates x,y,z	T	Cluster Size
	56,-14,52	3.96	84

Table 9: Region of Interest Analysis. Brain Activity Post- Relative to Pre- Training (Stim – Sham) Modulated by SS/PMC/M1 Activity for Target Feedback Relative to Visual Search.
The region of interest consisted of activity that was present for target feedback relative to visual search and improvement related activity post relative to pre- training for stim over the sham group (Figure 13, Table 8). Within this region a small volume correction for multiple comparisons analysis revealed significant (p < 0.05 corrected) brain activity post- relative to pre- training for the stim over sham group that is modulated by Somatosensory/PMC/M1 activity for feedback relative to search. BA = Brodmann area; SS = Somatosensory Cortex; PMC = Pre Motor Cortex, M1 = Primary Motor Cortex. Negative 'x' MNI coordinates denote left hemisphere and positive 'x' values denote right hemisphere activity.

Brain Region	MNI Coordinates x,y,z	T	Cluster Size
Right Post- and Pre- central Gyrus Somatosensory Cortex, PMC, M1 BA 1,6,3,4	52,-12,54	3.18	44
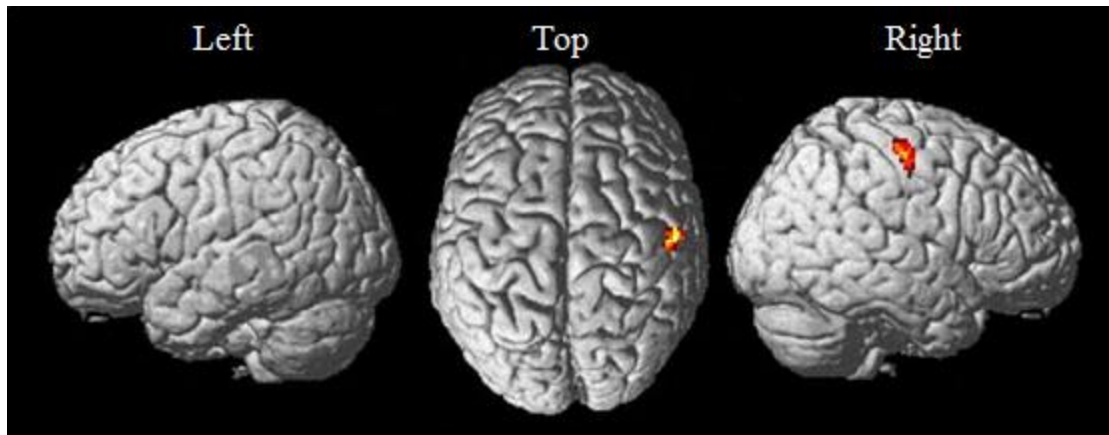
Figure 13: Target feedback relative to visual search (stim – sham) that is also present for improvement related activity post- relative to pre- training (stim – sham). The overlap (conjunction) of active and after-effect tDCS analyses.
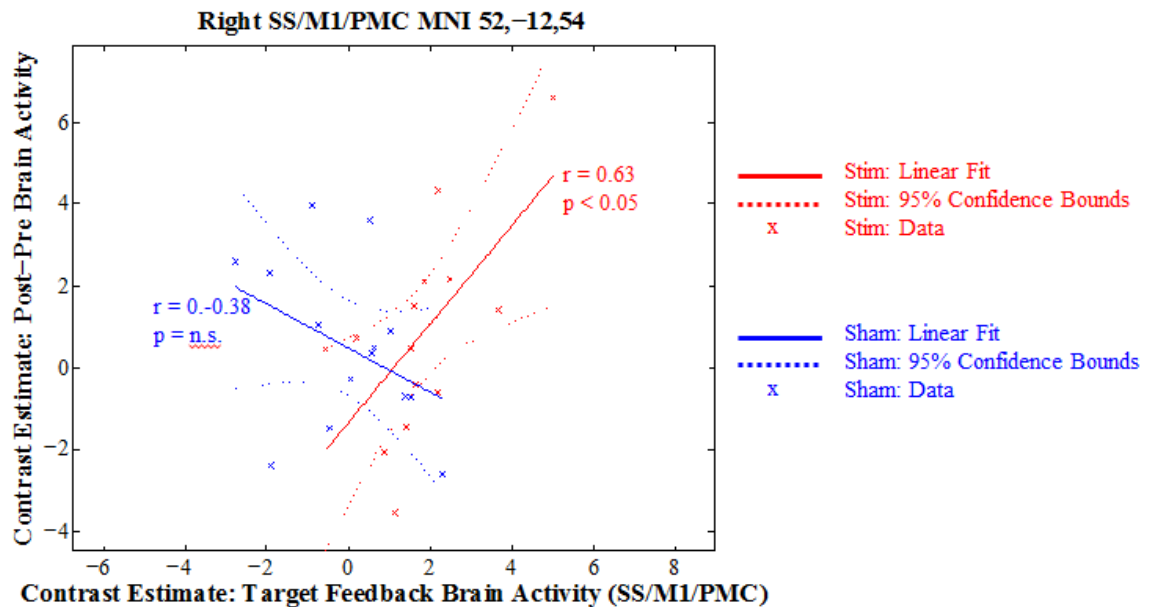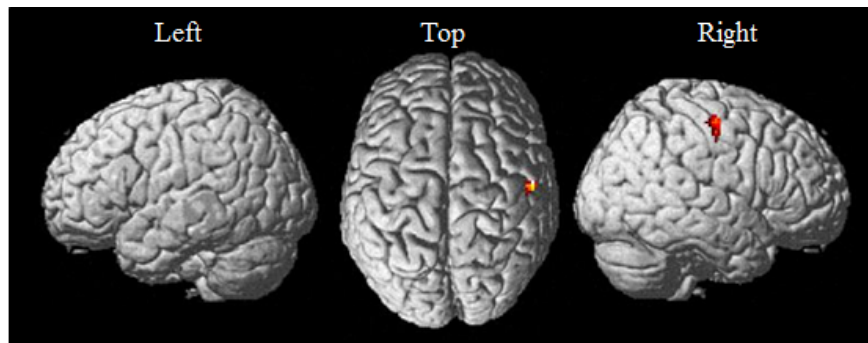
Figure 14: Region of Interest Analysis – improvement related brain activity post- relative to pre- training (stim – sham) modulated by post- and pre-central gyrus activity for target feedback relative to visual search.
Analysis included right somatosensory cortex, primary motor cortex, and premotor cortex. The graph illustrates that as activity during active tDCS increases during target feedback, improvement related activity post- relative to pre-training also increases in the stim group, but not sham. Abbreviations: SS = somatosensory cortex; M1 = primary motor cortex; PMC = pre-motor cortex.

Discussion

The results of this study elucidate potential neural modulatory mechanisms involved with task related enhancement of performance by tDCS observed in previous studies. In accordance with the goals of this research significant task related differences in brain activity between the stim and sham groups were identified (despite a lack of

enhanced behavioral performance between the two groups). Specifically, a right hemispheric region on the border of the pre- and post- central gyrus including the somatosensory cortex, premotor cortex, and primary motor cortex was found to show the following: 1. Greater activity is present in this brain region during target feedback processing for the tDCS stim over the sham group. This result is consistent with the hypothesis that tDCS could be modulating mechanisms of learning which results in enhanced behavioral performance that has been typically observed in other studies. In the case of this experiment the processes are specific to feedback (See Figure 11A and Table 5). 2. This brain region also shows greater improvement related activity post- relative to pre- training for the tDCS stim over the sham group (See Figure 12 and Table 7). The degree of improvement in task performance was positively correlated with greater differential brain activity post- relative to pre- training only for the tDCS stim group (See Figure 12). 3. A link in this brain region is present between the degree of target feedback process increased activity and the improvement related differential activity post- relative to pre- training for the tDCS group (See Figure 13 and Table 8). The positive correlation between activity present during tDCS stimulation and activity post- relative to pre-training (See Figure 14) in the same brain region showing task related improvement is suggestive of a potential underlying neural mechanism. Together the results of our experiment imply that task related behavioral improvement in the tDCS stimulation group is mediated by modulation of activity (specific in this case to target feedback) that induces long-term increases in brain activity during visual search.

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While we might have expected the locus of differential activation to be centered over the rPPC located directly beneath the electrode, the site showing behaviorally related modulatory effects of tDCS in our study was a region in the pre- and post- central gyrus including the somatosensory cortex, premotor cortex, and primary motor cortex. This region was also found to be implicated in other tDCS fMRI studies involving visual search tasks when stimulating over the rPPC (Ellison et al., 2014). This is ascribed to network effects resulting from tDCS stimulation. It is entirely possible to observe effects of stimulation on brain activation for other areas within the attention network while not showing any effect for the area underneath the tDCS electrode. Alteration in functional connectivity as a result of tDCS has been identified using EEG (Polania et al., 2011a) and fMRI (Polania et al., 2011b, 2012). Despite these findings, we must also acknowledge an alternative possibility. There is evidence to suggest that the peak current density does not occur at the center of the electrode as might be expected, but rather on the edges of it (Wagner et al., 2007). The right pre- and post-central gyrus is located just anterior to the edge of the electrode, which could also explain why our stimulation group showed differential activation in this area.

Previous research has shown that there is a heavy overlap of visual attention and oculomotor neural networks in regions found in the temporal, parietal, and frontal lobes (Corbetta et al., 1998; Corbetta, 1998; Nobre, Gitelman, Dias, & Mesulam, 2000). A major node of activation in the frontal lobe found in these studies for both covert shifts in attention and planned saccadic eye movements is the premotor cortex; specifically, the precentral gyrus/sulcus. Within this region, areas of activation are found that respond

selectively to covert attention shifts, planned eye movements, or both. Following these results, Corbetta and colleagues identified the precentral gyrus/sulcus as the human homologue for the frontal eye fields (FEFs) and the most anterior node of the top-down attention network (Corbetta & Shulman, 2002; Corbetta, Patel, & Shulman, 2008). While the location of the human FEFs has been difficult to pinpoint, a recent meta-analysis published by Vernet et al, (2014) also supported this assertion by identifying the human FEFs as being located in Brodmann area 6 somewhere between anterior precentral gyrus and precentral sulcus near the superior frontal sulcus. The premotor regions identified in these previous studies overlap with the cluster of differential activation revealed in our results to be the functionally related to improved learning and performance during visual search. Our results show a significant relationship between activation in this area and visual search performance that occurs during tDCS that does not exist in the absence of stimulation. Specifically, participants who improved the most from baseline following visual search training also displayed larger increases in brain activity within this region. This gives evidence to our theory that tDCS is modulating attentional processes during visual search training. In addition, our identified ROI also included the post-central gyrus which contains the somatosensory cortex. Recently, the somatosensory cortex has also been shown to play a role in visual attention by locating visual objects relative to the body through proprioceptive gaze input (Balslev, Odoj, & Karnath, 2013; Wang et al., 2007; Balslev & Miall, 2008). Admittedly, there is not an abundance of research for us to make a strong case for this theory as these findings are relatively recent. It is unlikely, however, that the activation we observed in the somatosensory cortex is the result of

perceived sensation resulting from active brain stimulation because of our use of within

subject control conditions in which the same degree of tDCS sensation on the scalp are

present.

We should also note that post- and pre-central gyrus activation was bilateral when

looking at improvement related activity post- vs pre-training but was right lateralized

during active stimulation/feedback training. In the aforementioned studies identifying

visual attention and oculomotor networks, brain activity in precentral areas is often

contralateral to the hemi field being attended to. As our task was a high-fidelity visual

search simulation, the visual field being attended was not controlled but due to a rotating

camera angle, attention to a particular hemifield (in this case left) seems highly unlikely.

While we have highlighted the major finding of our experiment above, we will

discuss the results of these analyses delineating the goals of this experiment in more

detail. In the first analysis, we observed significant differences in brain activation

resulting from active tDCS during target feedback in the training session. Before

comparing between stimulation groups, brain activity during visual search prior to

response was subtracted from brain activity during visual target feedback. This was done

in order to ensure that differences in brain activity between stimulation groups were

specific to target feedback processing and not a result of visual search processing or pre-

existing differences. We found four clusters of significant differential activation for the

tDCS stim over sham group including the right post- and pre-central gyrus

(somatosensory, premotor, and primary motor cortices) (See discussion above), the ACG,

the left cerebellum, and the right cerebellum (See Figure 11A-C, Table 5). The ACG

(Holroyd et al., 2004; Kiehl, Liddle, & Hopfinger, 2000; Hester, Fassbender, & Garavan, 2004) and cerebellum (Callan et al., 2011; Diedrichsen, Hashambhoy, Rane, & Shadmehr, 2005) are both areas known to be involved with feedback processing. This suggests that tDCS had a modulating effect on target feedback processing during training which might have resulted from facilitated feature detection and encoding for targets and distractors. One potential mechanism by which this is accomplished is through enhancement of LTP by tDCS in neural networks of attention as has been suggested by previous work (Coffman et al., 2014; Coffman et al., 2012; Falcone et al., 2012). The co-activation of the right post- and pre-central gyrus during target feedback training which includes areas associated with attention provides further evidence for this theory.

In the second analysis, we compared post- relative to pre-training brain activity in order to observe the after-effects of tDCS and found significant improvement related activity during visual search for the real stimulation group over the sham condition. Differential activity between groups was located bilaterally in the post- and pre-central gyrus, as well as the left superior and middle temporal gyrus (STG/MTG). In the real stimulation group, the better a participant performed after training in comparison to their baseline abilities, the greater the increase in brain activity for these areas. This correlation between behavioral performance improvement and increased brain activity is very interesting because, while we did not find an overall significant difference in behavioral performance between groups, it provides insight into the changes in underlying neural activity that result from anodal tDCS when performance is improved. Similar to the previous analysis, the activation of the pre- and post-central gyrus during visual search is

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most likely related to facilitation of visuospatial attention and occulomotor movements; however, the bilateral activation of this area was unique to this analysis. This is not entirely surprising, as this analysis observed brain activity during active visual search rather than during target feedback. During active search, goal-directed attention is engaged which involves a bilateral top-down attentional network (Corbetta & Shulman, 2002). A similar result was also observed by Ellison et al (2014) where they found that cathodal stimulation of the rPPC also resulted in bilateral activation of the pre-motor cortex during visual search. The activity in the STG/MTG is assumed to be related to processing in response to auditory feedback provided during the training session. Curiously, because this analysis compared post- vs. pre-training sessions, differential activation in this area occurred during sessions when there was no auditory feedback provided. This might be due to a tDCS elicited enhancement of conditioned learning such as has been found in previous animal studies (Márquez-Ruiz et al., 2012). The auditory system could display increased activation for participants in the stim group because they are either expecting or simulating an auditory response after the button press more so than the sham group.

In the third analysis, we investigated the conjunction of activity that is present for active tDCS stimulation for target feedback learning and improvement related activity for residual after-effects of tDCS stimulation for visual search. The results of this analysis showed activation in the right pre- and post-central gyrus (again including somatosensory cortex, the premotor cortex, and the primary motor cortex) (Figure 12, Table 8). An ROI analysis provided further evidence for this by showing that individuals that had high

modulatory activity during training also had increased brain activity in this area post-training (Figure 14). This suggests that active tDCS stimulation elicited modulation of this cluster during feedback training moderated the improvement related activity seen post-training for after-effects of tDCS during visual search.

It has been previously conjectured that the active facilitative effects anodal tDCS has on various cognitive components, such as attention, may be a result of overall lowering of local neural firing threshold of areas near the site of stimulation (Coffman et al., 2014). As a result there is an increase in activity dependent synaptic activity which elicits mechanisms of long-term potentiation (LTP) in the affected neural circuits resulting in a strengthening of connection between synapses relevant to task performance (Coffman et al., 2014, Liebetanz et al., 2002; Nitsche et al., 2003). Evidence of long-term effects of tDCS on LTP/LTD is supported by magnetic resonance spectroscopy (MRS) experiments demonstrating that anodal tDCS stimulation increases glutamatergic concentration (Clark et al., 2011) and conversely that cathodal tDCS stimulation reduces glutamatergic concentration (Stagg et al., 2011). Further evidence has shown that this stimulation induced LTP is NMDA receptor dependent and the effects disappear when an NMDA receptor antagonist (D-APV) is introduced before stimulation in mouse brain slices (Fritsch et al., 2010). TDCS induced LTP would also explain the after-effects of tDCS, which results in a continued increased excitability after the cessation of anodal stimulation for at least an hour (Nitsche & Paulus, 2001). In addition, the effects of tDCS do not only occur locally, but can also extend to other areas functionally associated with the site of stimulation (Coffman et al., 2014; Grefkes and Fink, 2011; Ellison et al.,

2014). It has been found previously that tDCS might enhance learning on visual

perceptual detection tasks through an improvement of the alerting component of attention

as revealed by the attention networks task (ANT) which tests the three different

components of attention: alerting, orienting, executive control (Coffman et al., 2012).

This study found that 2mA anodal stimulation over the right inferior frontal cortex

resulted in enhanced learning on a complex hidden object detection task and higher

scores in only the alerting measure on the ANT task. It was also found that alerting scores

correlated positively with performance on the complex hidden object detection task,

providing additional evidence for the importance of attention in tDCS-elicited enhanced

learning on visual perceptual detection tasks. Interestingly, the ANT was given 1 hour

after the cessation of tDCS which suggests long-term excitability changes in the

attentional network consistent with the tDCS-LTP literature. It has been suggested that on

perceptual detection tasks such as this, enhanced attention leads to more efficient

processing of target features and a suppression of distractor features which in turn results

in enhanced encoding during learning (Coffman et al., 2014; Coffman et al., 2012;

Falcone et al., 2012). The results of our current study are in agreement with this theory.

Increased activation in the right pre- and post-central gyrus during feedback training

could possibly be the result of excitability changes in the attentional network through the

reduction of local resting membrane potential thresholds in the rPPC similar to what was

observed by Ellison and colleagues (2014). Increased activation in attentional areas

occurring specifically during target feedback and co-activation of error-feedback

processing regions (ACG and Cerebellum) could also suggest an enhancement in

encoding of stimulus features through improved attention during learning. Additionally, an after-effect of tDCS as evidenced by continued differential improvement related activation of the pre- and post-central gyrus is also in agreement with prior research advocating a role of LTP mechanisms. We feel we should also mention that given the seemingly critical role of the alerting component of attention observed in other visual perceptual learning tasks (Coffman et al., 2012) one might expect to find regions responsible for improved performance on our complex visual search task within the ventral bottom-up attentional network responsible for this function rather than a region within the dorsal top-down attention network. However, it is not entirely surprising considering the different areas of tDCS electrode placement between studies. The right inferior frontal electrode placement used by Coffman and colleagues (2012) would have a higher probability of affecting the ventral attention network and result in changes in alerting. Our area of stimulation over the rPPC could feasibly affect both dorsal and ventral attention networks as this is an area of overlap. Our observed region showing differential activity between tDCS stim and sham groups, on the border of the pre- and post- central gyrus including the somatosensory cortex, premotor cortex, and primary motor cortex, is a critical node within the dorsal attention network and suggested to be the location of the FEFs (Corbetta & Shulman, 2002; Corbetta, Patel, & Shulman, 2008; Vernet et al, 2014) which are responsible for the orienting of attention which might simply be a highly utilized attentional component for our specific visual search task.

Despite strong neuroimaging results suggesting a modulation of the visual attention network through anodal stimulation, we did not find any significant differences

between the stim and sham tDCS groups for the primary behavioral measures of percent correct and d' for the three sessions. It is possible that the task itself was to blame for the lack of improvement. Previous models of visual search based on conjunction visual search paradigms have suggested a two-stage process involving an initial stage that processes features very quickly over a large visual field based on top-down influenced "saliency maps" that selects relevant items to be processed by a following limited-capacity stage that performs more complex operations over the selected visual areas or objects such as object identification, discrimination, and recognition (Wolfe, 1994). In order to maintain a controlled experiment that still simulated the difficulty of realistic visual search we introduced a finite set-size (five) of vehicles into the environment within each trial that were extremely similar, but not exact, in any dimension (color, form, size, etc). This is where we believe there could have possibly been an issue. In order to increase the difficulty of the task the UAV camera was zoomed out from the environment. In addition, due to the MRI bore length, the participants observed the display monitor from a distance of ~1.2 meters away. Unfortunately, this resulted in visual acuity being an extremely important factor and elicited complaints from several participants that they had difficulty to distinguish targets from distracters even after the target was pointed out to them in the practice session. This brought into play an overly difficult discrimination component in the second stage of visual search. It is possible that after the first stage of visual search, participants will have located all candidate vehicles but would essentially become stuck during the second stage of visual search when they needed to determine whether or not a target was present simply because in many cases

they could not see well enough to reliably do so. Due to the lack of other objects, aside from buildings, which were not at all similar to the target or distractors, the initial pre-attentive stage of visual search was most likely relatively easy in comparison to the object discrimination that followed. The difficulty in discriminating between extremely similar features between target and distractors after the imposed perceived distance (both real and virtual) from the stimuli is not dissimilar to that of a difficult sensory perceptual learning task.

TDCS has been shown to improve performance on visual sensory perceptual learning tasks (Pirulli, Fertonani, & Miniussi, 2013; Fertonani, Pirulli, & Miniussi, 2011) and while we did see a slight overall improvement in performance for both groups, we were unable to show that tDCS resulted in greater improvement. Aside from the fact that in our task the target differed from distractors on more than one dimension, our task also presented far less trials during stimulation (60 vs. 320). Following this, it is entirely possible that with an increased training duration we might have begun to see an improvement of the stim group over the sham group. While the task used in the current study was not sensitive enough to reveal behavioral differences between stimulation groups; in the future it might be beneficial to either: 1 . Reduce the length of trials to allow for more feedback during the 30 minute training/stimulation session. 2. To reduce the similarity between target and distractor features and increase set size in order to make the task less difficult which will allow for greater improvement within the limited number of trials in the training block. 3. To increase the starting level task performance by decreasing the distance from the drone to the target by lowering the drone altitude.

SIMULTANEOUS TDCS-FMRI INVESTIGATING RESTING STATE NETWORKS CORRELATED WITH VISUAL SEARCH IMPROVEMENT

Brian Falcone[1], Atsushi Wada[2,3], Raja Parasuraman[1], Daniel E. Callan[2,3]

[1]Center for Information and Neural Networks (CiNet), National Institute of

Information and Communications Technology (NICT), Osaka University, Osaka, Japan

[2]Multisensory Cognition and Computation Laboratory, Universal Communication

Research Institute, National Institute of Information and Communications Technology,

Kyoto, Japan

[3]Center of Excellence in Neuroergonomics, Technology, and Cognition

(CENTEC), George Mason University, Fairfax, Virginia, USA

Abstract

      This study uses simultaneous transcranial direct current stimulation tDCS and fMRI to investigate tDCS modulation of resting state activity and connectivity that underlies improvement in behavioral performance for selective attention. The experiment consisted of three sessions within the fMRI scanner in which participants conducted a visual search task: Session 1. Pre-training (no performance feedback), Session 2. Training (performance feedback given), Session 3. Post-training (no performance feedback). Resting state activity was recorded during the last five minutes of each session after the task. During the 2nd session one group of participants underwent 1mA tDCS stimulation and another underwent sham stimulation over the right posterior parietal cortex. Resting state spontaneous activity, as measured by fractional amplitude of low frequency fluctuations, for session 2 showed significant differences between the tDCS stim and sham groups in the precuneus, right superior parietal lobule, and inferior parietal lobule. From these results a seed voxel was selected from the right superior parietal lobule to be used in a resting state functional connectivity analysis as this region is a critical node within the dorsal attention network. It was hypothesized that individuals who received real tDCS would display increased functional connectivity between these attentional regions, and more so for those who performed better following feedback training. However, no significant differences in improvement related functional connectivity between stimulation conditions was found between this seed region and any other brain regions. Supplementary analyses using non-parametric permutation testing were also

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conducted to determine a more reliable cluster-extent threshold but these analyses also

did not yield any significant findings.

Introduction

In recent years there has been an explosion of research investigating a method by which to augment human cognition by passing a low amplitude direct current (typically in the range of 0.5 to 2mA) through the human brain and enhancing human performance and abilities (Coffman et al., 2014). This technique is called transcranial direct current stimulation (tDCS). TDCS has been shown to enhance such abilities as attention and performance on vigilance, threat detection, and visual search tasks (Falcone et al., 2012; Nelson et al., 2014; Parasuraman and Galster, 2013); to enhance learning and performance on perceptual and cognitive tasks (Clark et al., 2012; Parasuraman and McKinley, 2014); and to improve motor and cognitive function in patients with brain damage, neuropsychiatric, and neurological diseases (Floel et al., 2014; Kuo et al., 2014; O'Shea et al., 2014). The underlying neurological processes that allow for these enhancements in ability are largely unknown. It has been shown that anodal DC stimulation decreases neural firing thresholds, and that glutamatergic modulation of long-term potentiation/depression may be involved with the enduring effects of tDCS (Coffman et al., 2014; Bikson et al., 2004; Liebetanz et al., 2002; Hunter et al., 2015; Nitsche et al., 2003). While one may expect these effects to be localized on the cortex near the stimulating electrode, fMRI studies have also shown modulation in activity in distal brain regions suggesting possible network effects induced by tDCS (Ellison et al., 2014; Weber et al., 2014; Clemens et al., 2014).

It is our goal in this study to use simultaneous tDCS and fMRI to determine modulation in resting state activity and functional connectivity of the brain correlated

with improved performance as a result of stimulation. Studies have shown that resting state activity and connectivity in the brain can predict various characteristics such as attention (Kelley et al., 2008), learning (Baldassarre et al., 2012), memory (Hampson et al., 2006), language processing (Koyama et al., 2011), personality (Adelstein et al., 2011), and IQ (van der Heuvel et al., 2009) (See Stevens and Spreng 2014 for review). Previous studies using tDCS and fMRI have revealed that as a result of stimulation, resting state networks can show widespread changes in activity and connectivity in cortical and subcortical brain regions (Clemens et al., 2014; Saiote et al., 2013).

In our study we investigate improvement related resting state connectivity in response to tDCS. A visual search task was employed before (pre-training), during (training), and after (post-training) tDCS stimulation to determine its facilitative effects on performance. Resting state fMRI was recorded toward the end of each session after completing the visual search task. We placed the stimulating electrode over the posterior parietal cortex as it has been found in previous tDCS studies to modulate visual search performance (Ellison et al., 2014; Bolognini et al., 2010). We used the fractional amplitude of low frequency fluctuations (fALFF) in the BOLD signal, which has been found to be associated with spontaneous neural activity (Biswal et al., 1995; Song et al., 2011; Zou et al., 2008), as a measure of resting state activity. By comparing fALFF across tDCS stimulation and sham groups we intend to show brain regions in which the spontaneous neural activity is being modulated. Unlike most previous neuroimaging studies, we applied tDCS and fMRI concurrently in order to observe the active effects of tDCS on resting state activity in addition to after-effects that exist following the cessation

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of tDCS. A seed was then selected from a brain region determined to show tDCS induced activity to be used for a functional connectivity analysis (Song et al., 2011).

It has been well established from the results of many neuroimaging studies and meta-analyses that there exists two distinct neural networks for attention: a goal-driven dorsal fronto-parietal network which includes the superior parietal cortex (SPL) and frontal eye fields (FEFs), and a right-lateralized ventral fronto-parietal network that responds to unattended behaviorally relevant stimuli which includes the inferior parietal lobule (IPL) and the inferior frontal cortex (IFC) (Corbetta, 1998; Corbetta & Shulman, 2002; Corbetta, Patel, & Shulman, 2008). In a previous fMRI study using the same complex visual search task, we found that 1mA anodal tDCS over the rPPC resulted in differential activity during learning and differential activity related to improved performance following training between real and sham stimulation groups in areas within the goal-driven dorsal fronto-parietal network, specifically the FEFs (Falcone, Wada, Parasuraman, & Callan, 2015). Based on the results of this study, we selected a region found from the fALFF analysis within the superior parietal lobule to be used as seed for the functional connectivity analysis as this region is a critical node within the dorsal attention network found to be modulated by tDCS for this visual search task. It is hypothesized that resting state functional connectivity related to improvement in behavioral performance on the visual search task will be found to exist for this region for the tDCS group to a greater extent than for the sham group.

Methods

Participants

There were 28 participants that took part in this study. All of the participants (14 males, 14 females) were Japanese right-handed adults ranging from 18 to 25 years (mean = 20.7) of age from Osaka University. The participants were pseudo-randomly assigned to the tDCS stim and sham groups such that there were 7 females and 7 males in each group. All participants were screened for exclusion if there was a history of head injury, history of mental, neurological, alcohol or drug abuse disorders, or using medication that affects central nervous system function. The participants gave written and informed consent to take part in this experiment. The experimental procedures were approved by the NICT Human Subject Review Committee and were carried out in accordance with the principles expressed in the WMA Declaration of Helsinki.

Procedure

The experiment consisted of three sessions within the fMRI scanner. During the first part of scanning the participants conducted a visual search task. During the last 4.5 minutes of fMRI scanning, for each session, resting state activity was acquired. In this study we will focus only on the resting state fMRI data from these sessions.

The visual search task was based on a search and rescue mission that required participants to locate a red pickup truck located in the search area amongst buildings and other similar looking distractor vehicles. In each trial there were 5 non-moving vehicles

distributed throughout the search area, one of which could be the red truck. The task was designed so that as the unmanned aerial vehicle UAV loitered in a circle around the search area, all vehicles would remain in constant view despite a continually changing view angle. Each trial lasted 10 seconds where the participants searched the area looking for the target and were required to make a button press indicating whether the search area contained a target or not.

The three experimental sessions consisted of the following: Session 1, a pre-training session that did not provide performance feedback, and Session 2 a training session in which tDCS stimulation or sham stimulation was delivered. In the training session immediate reinforcement target feedback ('ding' sound correct, 'buzz' sound incorrect) after each response. Additionally, for target present trials only, a transparent white sphere would appear over the target at the end of the 10-second trial identifying the target location. The final session, Session 3, was a post-training session with no feedback. After each experimental session resting state activity was recorded for 4.5 minutes. The task for the participants during collection of the resting state data was to visually fixate on a white cross mark presented in the center of the display against a black background.

Transcranial Direct Current Stimulation

TDCS was delivered during the training session (session 2) using the MRI compatible NeuroConn DC-Stimulator MR. Two rectangular-shaped (5.3 x 7.2cm) MRI compatible conductive rubber electrodes were placed on the participant before entering the MRI scanner (See Figure 15 for picture of placement of electrode on the head of a participant and a rendered MRI showing the tDCS electrode on the head). The anodal

electrode was placed over the right posterior parietal cortex. It was placed over where the

P4 electrode is located according to the 10-20 International EEG System. The electrode

was held in place by the conductive paste as well as a padded headband. The cathodal

electrode was placed over the contralateral left side trapezius muscle on the back.
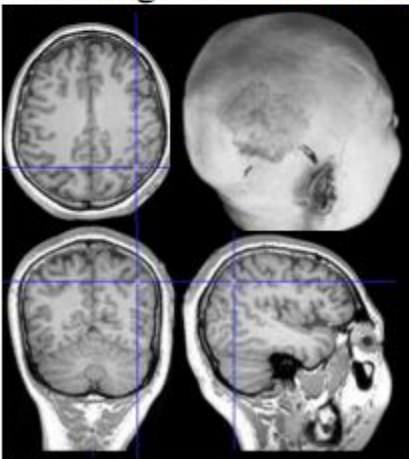

Figure 15: Top: Picture showing the placement of the anodal tDCS electrode on the right posterior parietal cortex of the participant. Bottom: The placement of the tDCS electrode can be seen in the rendered MRI of the participant. Sections are shown through the brain at the site of the electrode. For the MRI sections the right side of the image is the right side of the brain.

Participants in the stim group received 1mA current for a total of 30 minutes. Stimulation was started 5 minutes before the task in order to ensure that the full modulatory effect of tDCS was active during task performance. The participants in the sham group also received 1mA current but only for 30 seconds and then the unit was turned off. This procedure helps to conceal from the participant which group (stim or sham) they belong to as both groups feel the onset of the stimulation. In addition group membership of the participant was not known by the experimenter giving the instructions.

fMRI Data Collection and Analysis

FMRI scanning of resting state activity was acquired for 4.5 minutes at the end of each session (TR=2s; 30 interleaved slices covering the brain and cerebellum, 3x3x4mm voxels; Siemens 3T Trio Scanner; 32 Channel head coil). Preprocessing of fMRI data was conducted using SPM8 (Wellcome Department of Cognitive Neurology, UCL) and included realignment and unwarping, normalization to the template EPI image (2x2x2mm), and smoothing (8x8x8mm). The REST (Song et al., 2011) Toolkit was used to conduct the resting state spontaneous activity (fALFF) and the functional connectivity analyses. The realignment parameters were used as covariates of noninterest and regressed out of the preprocessed EPI data to extract potential confounds related to head movement while scanning. The linear trend was then removed from the data. The parameters for the fALFF analysis included a low frequency fluctuation band of 0.01 Hz to 0.08 Hz (Biswal et al., 1995) compared to the entire frequency range (0 to 0.25 Hz). The fALFF results were normalized by dividing by the mean fALFF values within the

whole brain mask to be used for second level random effects analyses. The functional

connectivity analysis was carried out over the preprocessed covariates removed,

detrended, and filtered (0.01 Hz to 0.08 Hz) data. Prior to analysis, masks included in the

REST Toolkit were used to obtain regressors for white matter (WM) and cerebrospinal

fluid (CSF) from the data. Average BOLD signals for WM, CSF, and whole-brain were

treated as nuisance variables and regressed out. The seed region of interest (ROI), the

superior parietal lobule (MNI, 40,-44,54), was selected from the results of the fALFF

analysis (See Results section). A spherical region with a radius of 8mm at the given

coordinates for this region was used as seed for the functional connectivity analyses. The

Pearson linear correlation was used to determine the functional connectivity between the

mean of the voxels within the seed ROI and the rest of the voxels in the brain according

to the defaults in the REST toolbox (Song et al., 2011). The Fisher's z transform was

used to normalize the correlation coefficients to be used for second level random effects

analyses. SPM8 was used to conduct the random effects analyses. Correction for multiple

comparisons ($p < 0.05$) across the entire brain was carried out using Monte-Carlo

simulation of the brain volume to define a voxel contiguity threshold at an uncorrected

significance level of $p < 0.005$ (Slotnick et al., 2003; Ellison et al., 2014). Using 10,000

Monte-Carlo simulations a cluster extent of 152 voxels thresholded at $p < 0.005$

uncorrected, is necessary to correct for multiple comparisons across the whole brain at a

threshold $p < 0.05$. Activated brain regions were identified using the SPM Anatomy

Toolbox v1.8 (Eickhoff et al., 2005) as well as Talairach Client. The substantia nigra, red

nucleus, and subthalamic nuclei were identified using the regions specified in Keuken et al., (2015).

Finally, supplementary non-parametric permutation testing was conducted using SnPM13 (http://warwick.ac.uk/snpm) to identify FWE p < .05 corrected clusters of activation in addition to the Monte-Carlo simulation mentioned above. See Study #2 manuscript under "fMRI Data Collection and Analysis" for rationale. CDT was set at p < .001 and only clusters that are significant at a FWE p < .05 will be reported. No variance smoothing was used.

Behavioral Results

The behavioral results in terms of percent correct on the visual search task for the tDCS stim and sham groups are as follows: There was a significant enhancement in performance post- relative to pre-training (ANOVA $F(2,52)=12.47$, $p < 0.05$). The enhancement was statistically significant ($t(26) = 4.05$; $p < 0.05$) for the stim group (pre-training mean = 64.26%; SE = 2.64; post-training mean = 72.06%; SE = 2.36) and was statistically significant ($t(26) = 3.15$; $p < 0.05$) for the sham group (pre-training mean = 64.98%; SE = 2.47; post-training mean = 73.02%; SE = 1.99). There was no significant difference between stim and sham groups for either pre- ($t(26)= -0.21$) or post- training ($t(26)= -0.33$) sessions. The interaction between stim and sham groups and pre- and post-training session was not significant (ANOVA $F(2,52) = 0.3$). Additionally there was no significant difference ($t(26) = -0.83$) between stim (mean = 64.86%; SE = 2.7) and sham (mean = 67.94%; SE = 2.74) groups for the training session 2.

Brain Imaging Results
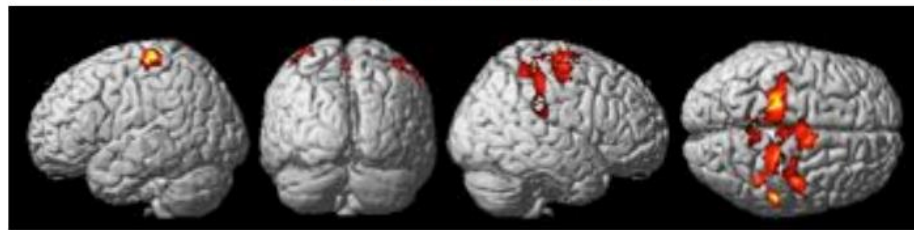
Resting State Activity: fALFF Analysis

The results of the fALFF analysis are given in Figure 16 and Table 10. Clusters with at least 152 voxels are significant ($p < 0.05$) when correcting for multiple comparisons using 10,000 Monte-Carlo simulations (Slotnick et al., 2003; Ellison et al., 2014) across the whole brain. Significant differences in fALFF between the stim and sham groups for session 2 was found to be located in three large clusters of activity: Cluster 1 is located around the right superior parietal cortex (cluster size = 1900 voxels; MNI 24,-32,60, $t(26) = 4.47$) spreading into the left parietal cortex as well as the neighboring regions of the precuneus, post central gyrus, pre-central gyrus, and supplementary motor area; Cluster 2 is located in the right inferior parietal lobule (cluster size = 194 voxels; MNI 58,-30,44; $t(26) = 5.17$); Cluster 3 is located in the premotor cortex BA6 (cluster size = 289 voxels; MNI 46,-14,62; $t(26) = 4.29$) (See Figure 16 Top). Brain regions significant ($p < 0.05$ corrected) for the stim – sham comparison masked by the interaction of Stim (Session 2 – Session 1) – Sham (Session 2 – Session 1) consisted of the right precuneus, the right superior parietal lobule, and the right inferior parietal lobule (See Figure 16 bottom and Table 10). The non-parametric permutation testing for the stim over the sham group did not result in any clusters significant at k>341 using a CDT of $p < .001$ and a cluster correction of FWE $p < .05$.

Table 10: fALFF (Stim – Sham) Session 2 Masked by Interaction.
Brain Regions showing significant differential activity for the stim – sham comparison corrected for multiple comparisons (p < 0.05) that are also present for the interaction of stim (ses2-ses1) – sham (ses2-ses1) thresholded at p < 0.005. BA = Brodmann area; IPL=Inferior Parietal Lobule; SPL=Superior Parietal Lobule. Negative 'x' MNI coordinates denote left hemisphere and positive 'x' values denote right hemisphere activity.

Brain Region	MNI Coordinates x,y,z	T(26)
IPL (BA 40)	50,-30,24	3.82
SPL (BA 40)	40,-44,54	3.99
Precuneus (BA 7)	6,-46,60	3.76

Figure 16: Results of the fALFF SPM random effects analysis rendered on the surface of the brain.
Top: Differential resting state activity as measured by fALFF for the stim – sham groups for session 2 corrected for multiple comparisons at the cluster level (p < 0.05) using Monte-Carlo simulation (corrected cluster extent threshold = 152 contiguous voxels over uncorrected significance threshold of p < 0.005; t=2.78. Activity in the top analysis that is additionally masked by the interaction of stim (ses2 – ses1) – sham (ses2-ses1) with a threshold of p < 0.005.

Resting State Connectivity: Functional Connectivity Analysis

The resting state functional connectivity analyses, using post – pre behavioral

performance as a covariate of interest, was conducted using the superior parietal lobule

region found in the fALFF analysis (Figure 16 Bottom, Table 10) as seed. Due to the lack of a behavioral effect of tDCS, a between group analysis of functional connectivity alone would not be very meaningful with regard to investigating possible underlying mechanisms of tDCS-elicited improved performance observed in previous behavioral studies. Using a performance covariate allowed us to identify significant group differences in the relationship between functional connectivity and changes in performance from baseline, which can then be related to these previously observed effects.

For session 1, improvement-related resting state functional connectivity was not found for the stim-sham contrast for session 1 using a cluster level corrected threshold of $p < 0.05$. The non-parametric permutation testing for the stim over the sham group did not result in any clusters significant at k>353 using a CDT of p < .001 and a cluster correction of FWE p < .05.

For session 2, the stim-sham contrast revealed a cluster located in left superior parietal lobule which fell just short of the 152 voxel threshold at a cluster size of 148 (See Table 11, Figure 17). The non-parametric permutation testing for the stim over the sham group did not result in any clusters significant at k>356 using a CDT of p < .001 and a cluster correction of FWE p < .05.

For session 3, the stim-sham contrast did not reveal any significant clusters of activation. Likewise, the non-parametric permutation testing did not result in any significant clusters for the stim over the sham. The non-parametric permutation testing

for the stim over the sham group did not result in any clusters significant at k>367 using a

CDT of p < .001 and a cluster correction of FWE p < .05.

Table 11: Behavioral improvement related resting state functional connectivity with the seed region for session 2 (during stim).
Brain regions showing differential resting state connectivity during active stimulation. There were no significant clusters that survive correction for multiple comparisons at the cluster level (p < 0.05) using Monte-Carlo simulation (corrected cluster extent threshold = 152 contiguous voxels over uncorrected significance threshold of p < 0.005; t=2.80; spatial extent threshold = 50 voxels). BA = Brodmann area; L=Left; SPL=Superior Parietal Lobule. Negative 'x' MNI coordinates denote left hemisphere and positive 'x' values denote right hemisphere activity.

Brain Region	MNI Coordinates x,y,z	t(24)	Cluster Size
L SPL (BA 5)	-22,-48,38	4.30	148
	-24,-50,50	4.03	
	-28,-42,30	3.42	
R Cerebellum Lobule VI	34,-44,-28	3.39	61
	38,-52,-26	3.21	

Right SPL Improvement Related Resting State Functional Connectivity with Left SPL
Session 2
Stim - Sham

Left Superior Parietal Lobule MNI-22, -48, 38
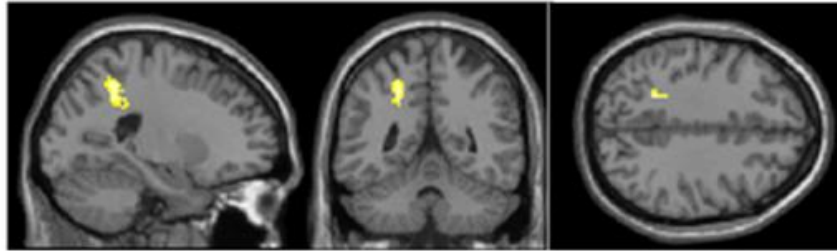
Left Superior Parietal Lobule MNI-24, -50, 50
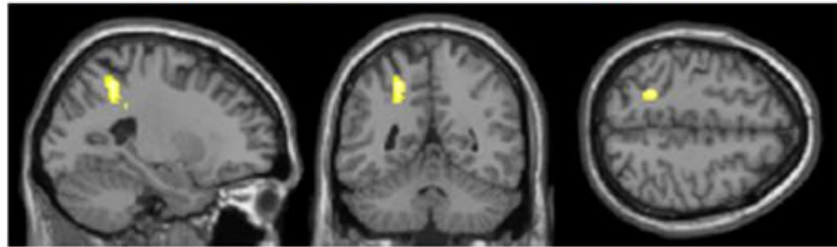
Left Superior Parietal Lobule MNI-22, -42, 30

Figure 17: Session 2 results of the SPM random effects between groups *t*-test for the superior parietal lobule behavioral improvement related resting state connectivity analysis for the stim relative to sham group contrast. Near statistically significant improvement related resting state functional connectivity is rendered on sections of a template T1 MRI scan at MNI coordinates for the peaks in the cluster. Negative 'x' MNI coordinates denote left hemisphere and positive 'x' values denote right hemisphere activity. For the MRI sections the right side of the image is the right side of the brain.

Discussion

This study shows that tDCS affects resting-state brain activity through low amplitude fluctuations in spontaneous brain activity in the region around the anodal stimulating electrode. Specifically, these areas included the precuneus, the superior parietal lobule, and the inferior parietal lobule (See Figure 16, Table 10). However, using the right superior parietal lobule as seed, no significant improvement related differences in functional connectivity were found between this region and any other brain regions.

The mechanisms behind tDCS-induced enhanced cognition have been associated with that of activity-dependent plasticity. The regions revealed by the fALFF analysis to be specifically modulated by anodal tDCS is most likely the result of increased spontaneous neuronal firing due to excitability changes brought on by tDCS. Spontaneous fluctuations in BOLD signal related to cognitive abilities are known to be present at rest (Biswal et al., 1995; Stevens and Spreng, 2014). Furthermore, studies have shown that resting state activity is modulated by tDCS (Clemens et al., 2014; Saiote et al., 2013).

Using a voxel selected from the fALFF analysis as a seed for the functional connectivity analysis we were unable to observe any improvement related differences in functional connectivity associated with tDCS. When corrected for multiple comparisons, resultant clusters must exceed a voxel contiguity threshold of >152 voxels in order to achieve statistical significance. However, the cluster containing the left superior parietal

lobule falls just short with a cluster size of 148. The resting state functional connectivity analysis assumes that, in the absence of ongoing task related activity, two regions that display spontaneous fluctuations in BOLD signal that are highly temporally synchronized are likely within the same functional network. Lacking a significant behavioral enhancement for tDCS, such as was observed in this study, any differences in functional connectivity without some learning component would do little to elucidate the underlying mechanisms that result in tDCS-induced cognitive enhancement similar to that observed in Falcone et al (2012). In this case any differences found in functional connectivity might simply be the result of unspecific current/stimulation factors. Using visual search performance post-training (session 3) relative to pre-training (session 1) as a covariate of interest in this analysis allowed us to be able to identify regions where the relationship between functional connectivity and behavioral improvement is significantly different between real and sham stimulation groups, and what these relationships are. Similar to the event-related fMI results from paper #2 it was expected that individuals who performed better would on average experience larger increases in functional connectivity within attentional regions for the real stimulation group with no such relationship existing for the sham stimulation group. Improvement related modulation of functional connectivity between attentional regions and regions with resting state activity shown to be modulated by tDCS near the site of stimulation would have been consistent with a task-related facilitative effect of tDCS on relevant functional networks carrying over as a result of visual search training just prior to recording of the resting state activity. However, given the failure of the results to survive both, the Monte-Carlo correction, and

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a more conservative permutation testing analysis it is impossible to draw any strong conclusions or implications from these results.

We selected a seed underneath the anodal electrode as this has been established to be an effective method to reveal differences in functional connectivity resulting from tDCS (Keeser et al., 2011). The advantage of using a seed ROI resulting from the fALFF analysis is that we ensure that we are actually utilizing regions that are showing potential modulation as a result of the tDCS for the functional connectivity analysis instead of arbitrarily selecting a region underneath the stimulation electrode. We do not believe that this will unduly bias the results of the functional connectivity analyses for stim over the sham group comparison because the fALFF (fluctuations in low frequency activity in single voxels) and functional connectivity (correlation in time course between voxels) analyses are quite different. Additionally, we employed the use of improvement in behavioral performance post- relative to pre- training as a covariate of interest in the functional connectivity analyses. There is no a priori reason to believe that future improvement in behavioral performance should be predicted by differences in fALFF or functional connectivity unless of course these changes are induced as a result of tDCS. We specifically chose the right superior parietal lobule as our seed ROI instead of other areas revealed by the fALFF because this region is known to be a critical node in the dorsal fronto-parietal attention network and it has been shown to be involved goal-driven visual orienting along with the frontal eye fields (Corbetta, M.,1998; Corbetta, M., & Shulman, G. L., 2002; Corbetta, M., Patel, G., & Shulman, G. L., 2008).

There are at least two differences between this tDCS study and others that may explain why group differences in improved performance between the stim and sham groups were not observed. The first is that the training session was quite short and the number of trials within this session was very low in comparison to other studies (See Study #1). Another difference is that due to safety limitations introduced by concurrent tDCS and fMRI this study only allowed for a 1mA current instead of the much more common 2mA (See Study #1). Given that we did not observe significant improvement related differences in the resting state functional connectivity between real and sham stimulation, it may be the case that given a longer training period, more trials, or a higher current, behavioral enhancement by tDCS may have been observed.

Table 12: Target feedback relative to visual search (stim-sham) using hit rate as a covariate of non-interest.
Brain Regions showing significant differential activity corrected for multiple comparisons at the cluster level (p < 0.05) using Monte-Carlo simulation (corrected cluster extent threshold = 146 contiguous voxels over uncorrected significance threshold of p < 0.005). BA = Brodmann area; PMC = Premotor Cortex; M1 = Primary Motor Cortex; ACG = Anterior Cingulate Gyrus; MTG = Middle Temporal Gyrus; STG = Superior Temporal Gyrus. Negative 'x' MNI coordinates denote left hemisphere and positive 'x' values denote right hemisphere activity.

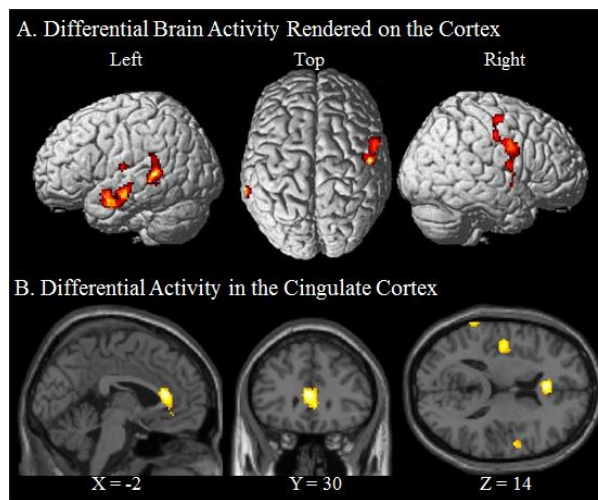| Brain Region	MNI Coordinates x,y,z	T	Cluster Size
Post- and Pre- central Gyrus Somatosensory Cortex, PMC ,M1 (BA 1, 3, 4, 6)	50,-10,58 54,-14,42 58,-2,12	3.95 3.85 3.68	398
ACG (BA 24, 32)	-2,30,14	4.73	308
Left MTG (BA 21)	-62,-12,-14 -54,-2,-22	4.32 3.69	474
Left STG (BA 22)	-66,-44,6	4.27	280
Left Insula (BA 13)	-42,-14,14	3.95	180

Figure 18: Target feedback relative to visual search (stim – sham) using hit rate as a covariate of non-interest.

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BIOGRAPHY

Brian Falcone received his Bachelors of Arts in Psychology from New Mexico State University in 2010. He continued his education at George Mason University and received his Master of Arts in Psychology in 2014. Finally, he received his Doctorate of Philosophy in Psychology with a concentration in Human Factors and Applied Cognition from George Mason University in 2016.