University of New Mexico
UNM Digital Repository

Psychology ETDs | Electronic Theses and Dissertations

2-1-2012

Object detection learning : effects of transcranial direct current stimulation, magnetic resonance imaging, and image novelty

Brian Coffman

Follow this and additional works at: https://digitalrepository.unm.edu/psy_etds

Recommended Citation
Coffman, Brian. "Object detection learning : effects of transcranial direct current stimulation, magnetic resonance imaging, and image novelty." (2012). https://digitalrepository.unm.edu/psy_etds/24

This Thesis is brought to you for free and open access by the Electronic Theses and Dissertations at UNM Digital Repository. It has been accepted for inclusion in Psychology ETDs by an authorized administrator of UNM Digital Repository. For more information, please contact disc@unm.edu.

Brian Coffman

Candidate

Psychology

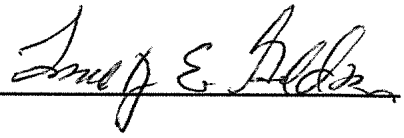
Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

Vince Clark  , Chairperson

Ron Yeo 

Tim Goldsmith 

OBJECT DETECTION LEARNING: EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION, MAGNETIC RESONANCE IMAGING, AND IMAGE NOVELTY

by

Brian A. Coffman

B.S., Psychology, The University of New Mexico, 2008

M.S., Psychology, The University of New Mexico, 2011

THESIS

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Science

Psychology

The University of New Mexico

Albuquerque, New Mexico

December, 2011

ACKNOWLEDGEMENTS

Some of this work was supported by The Defense Advanced Research Projects Agency (Government contract NBCHC070103) and the Department of Energy (Government contract DEFG02- 99ER62764). Special thanks to Elaine Raybourn, Kyle Kenny, Neal Miller, Ron Denny and Alan Rolli, Ranee Flores, Jeremy Bockholt, Elizabeth Browning, Michael Doty, Megan Schendel, Dae Il Kim, Josef Ling, Jing Xu, Mark Skully, Jill Fries, Arvind Caprihan, Claudia Tesche, Sergey Plis, Diane Oyen, Blake Anderson and Francesca McIntire for help in experiment development, data collection and data analysis. The views, opinions, and/or findings contained in this article/presentation are those of the author/presenter and should not be interpreted as representing the official views or policies, either expressed or implied, of the Defense Advanced Research Projects Agency or the Department of Defense.

Special thanks to my parents, David and Carol Coffman, without whom I would not have had the ability, to my brothers, Aaron Coffman, Dustin Oglesbee, Derek Bertrois, Kyle Weinberg, and Ray Quitiquit, without whom I would not have had the dedication, and to my wife, Robyn Coffman, without whom I would not have had the drive to succeed.

OBJECT DETECTION LEARNING: EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION, MAGNETIC RESONANCE IMAGING, AND IMAGE NOVELTY

by

Brian A. Coffman

B.S., Psychology, The University of New Mexico, 2008

M.S., Psychology, The University of New Mexico, 2011

ABSTRACT OF THESIS

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Science

Psychology

The University of New Mexico

Albuquerque, New Mexico

December, 2011

OBJECT DETECTION LEARNING: EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION, MAGNETIC RESONANCE IMAGING, AND IMAGE NOVELTY

By

Brian A. Coffman

B.S., Psychology, The University of New Mexico, 2008

M.S., Psychology, The University of New Mexico, 2011

ABSTRACT

This investigation studied the effects of transcranial direct current stimulation (tDCS) on learning of a difficult visual search task. We also examined the effects of several variables relating to context in which the task was performed, and the relationship of these variables to the effects of tDCS. For this discovery-learning task, participants were trained for one hour to detect objects hidden in a virtual environment. Anodal tDCS was applied over the right inferior frontal cortex at 0.1 mA or 2.0 mA for 30 minutes during training. Participants were tested immediately before and after training and again one hour later. Some test stimuli were repeated during training and testing, while others were novel but contained hidden objects similar to those presented during training. In Experiment 1 we present a reanalysis of our previously published data (Clark et al., 2010) and replication data from an additional group of subjects using an optimized task design. Higher tDCS current was associated with increased test performance for both novel and repeated test

stimuli. In addition, participants' responses were more accurate for repeated than novel test stimuli. An interaction was found between tDCS current and image type, indicating that tDCS performance enhancement was greater for repeated than novel stimuli. These effects were replicated in our second experiment using balanced numbers of novel and repeated test stimuli and a double-blind rather than single-blind design. These results indicate that anodal tDCS over right inferior frontal cortex during training most strongly enhances performance for recognition of objects hidden in images repeated between training and testing, and also enhances the generalization of learned object detection to novel images. In Experiment 2, we examine the effect of high magnetic field on tDCS enhancement of learning by comparing participants tested in active fMRI, at a magnetic field of 3 Tesla, to those tested in a mock MRI scanner, with no active magnetic field. In Experiment 3, we examined the effects of the MRI environment on learning and performance both when participants were trained and received tDCS at a workstation PC and when they were trained and received tDCS in the mock MRI scanner. Results from Experiments 2 and 3 indicate that participants may have been unable or unwilling to perform the task in an MRI environment, and that it is unlikely that either the magnetic field or changed environments from training to test, per se, led to differences in the effects of tDCS present between participants tested inside the MRI scanner environment and those tested at an office workstation PC. The effects of tDCS in these Experiments indicate that learning can be enhanced in participants learning a difficult object detection task when participants are willing and able to perform the task. Enhanced learning in the general population could aid millions of people suffering from disability and could even lead to accelerated advancement of society in general.

TABLE OF CONTENTS

GENERAL INTRODUCTION

Greater understanding of processes involved in learning and memory has potential to aid in the treatment of clinical disorders which compromise memory or the ability to learn. Furthermore, enhancement of normal learning and memory processes in healthy individuals could have many applications in the complex society that exists today. Enhanced learning has been studied using caffeine (Erikson et al, 1985), hormone therapy (Buchanan & Lovallo, 2001), and other drug treatments (McGaugh, 1989). Memory enhancement has been studied by such means as altering the learning environment (Dreyer & Nell, 2003), emotional modulation (LaBar and Cabeza, 2006), and even genetic alteration (Routtenberg et al, 2000; Tang et al, 1999). New methods to enhance the speed and stability of visual learning could offer a number of benefits in learning complicated tasks which take a great amount of time to master. This might also have clinical applications, such as enhanced learning and memory in dementia and other disorders.

In recent years, transcranial direct current stimulation (tDCS) has garnered increasing interest for its application in cognitive enhancement in healthy subjects: tDCS has been shown to facilitate working memory (Fregni et al., 2006), motor learning (Antal et al., 2004; Reis et al., 2008; Reis et al., 2009; Galea & Celnik, 2009), simple somatosensory and visual motion perception learning (Ragert et al., 2008), and memory for word lists (Marshall et al., 2004). The first documented use of tDCS was in 1868, where it was suggested as a potential therapeutic intervention for neuralgia, convulsions, and paralysis (Benedikt, 1868). In the ensuing 140 years, there has been an expansion in ideas about the application of tDCS, and vast improvements in the understanding of the mechanisms which underlie the effects and methods for delivery of tDCS. TDCS is being examined as a

potential treatment for multiple neurological and psychiatric disorders including addiction (Boggio et al., 2008a, 2009a), Alzheimer's disease (Boggio et al., 2009b), anorexia (Hecht, 2010), depression (Boggio et al., 2007, 2008b), epilepsy (Liebetanz et al., 2006), migraine (Chadaide et al., 2007), multiple sclerosis (Mori et al., 2010), pain management (Antal et al., 2008a), Parkinson's disease (Boggio et al., 2006a), and rehabilitation after stroke (Ko et al., 2008). In normal cohorts, tDCS is also being investigated by multiple groups as a method for enhancing learning and memory (Floel et al., 2008), perception (Antal & Paulus, 2008b), cognition (Fertonani et al., 2010), and motor function (Furubayashi et al., 2008). Quantifying the effects of tDCS on brain function is essential to understand and implement treatment and experimentation in this vigorous, growing field.

TDCS is one of several methods (i.e. pharmaceuticals, transcranial magnetic stimulation, intracranial electrical cortical stimulation, etc.) that can be used to exogenously influence brain function. Typical current strengths are 1 - 2 milliamperes (mA) delivered for up to 30 minutes (Nitsche, 2008). Theoretical and empirical evidence suggest that the cortex underlying the anode becomes more excitable during stimulation and for at least a short time after stimulation ends (Liebetanz et al., 2002). In contrast, cathodal stimulation of the brain is thought to reduce the excitability of the cortex (Dieckhofer et al., 2006). The mechanisms of the effects of tDCS in humans have been examined in simulations, as well as studies of electrophysiology, neurochemistry, and neuroanatomy.

Modeling and simulation studies illustrate the current levels and distributions in the brain during the delivery of tDCS (Faria et al., 2009). The current distribution in the brain changes with the arrangement of the electrodes; specific areas of the brain can be targeted for delivery of anodal currents that increase the excitability or cathodal stimulation that

decreases excitability of the underlying cortex (Nitsche et al, 2008; Datta et al., 2009). Additional modeling studies suggest that specific neurons (the long layer IV and V pyramidal cells) are most affected by tDCS (Radman et al., 2009). Animal studies show that DC stimulation of hippocampal slices at low current levels decreases the threshold for neuronal firing (Bikson et al., 2004). When these results are extended to humans, tDCS at the current intensities used in the proposed work is thought to change the resting membrane potential by approximately +1.5 mV with anodal stimulation and -1.5 mV with cathodal stimulation (Radman et al., 2009).

Some hemodynamic and neurochemical effects of tDCS have also been documented. Anodal stimulation resulted in an increase in the concentration of oxyhemoglobin in the cortex near the electrode (Merzagora et al., 2010). The concentrations of the neurotransmitters GABA and glutamate are also altered in the region of the electrodes as measured by magnetic resonance spectroscopy. Our lab has demonstrated increased glutamate activity in participants receiving tDCS using stimulation parameters similar to those in the present study (Clark et al, 2011). Stagg and colleagues (2009) also showed that anodal stimulation reduces GABA, but not glutamate, activity. This change in the ratio of glutamate to GABA activity is thought to relate, at least in part, to the increase in cortical excitability seen with anodal stimulation. Additional evidence suggests that the lasting effects of tDCS are dependent on the NMDA glutamate receptor subtype (Liebetanz et al., 2002; Paulus, 2004). The administration of drugs that alter neuronal sodium and calcium currents have also been observed to modulate the effects of tDCS (Nitsche et al., 2003).

We reported previously that tDCS can increase learning in a complex visual search task involving the detection of objects hidden in a virtual environment (Clark et al., 2010). In this study participants were trained to detect objects hidden in complex images of simulated environments and classify those images as containing or not containing objects. Participants received anodal tDCS during training, which was directed near the 10-10 EEG position F10; over the right sphenoid bone lying above inferior frontal cortex. Large improvements in classification learning occurred in participants receiving tDCS using 10 cm^2 electrodes. Similar to results presented by Iyer et al. (2005), these effects were dose-dependent, with learning increases dependent upon current strength, with those receiving 2.0 mA achieving accuracy scores significantly higher than those receiving 0.6 or 0.1 mA.

In the following three experiments, we present results demonstrating some characteristics and limitations of enhancement of image classification learning using tDCS. In Experiment 1 we examined the effect of tDCS on learned object detection when viewing images which had been repeated from training and when generalizing information during training to object detection in novel images. This experiment was replicated in a different sample of participants using a double-blind tDCS protocol. Interestingly these behavioral results are not consistent with behavioral results obtained from participants who were tested during fMRI. In Experiment 2, we examine the effect of magnetic field on tDCS enhancement of learning by comparing participants tested in active fMRI, at a magnetic field of 3 Tesla, to those tested in a mock MRI scanner, with no active magnetic field. In Experiment 3, we examined the effects of the MRI environment on learning in participants tested in the mock MRI who were trained at a workstation PC and those who were trained and tested in the mock MRI scanner.

EXPERIMENT I: LEARNING EFFECTS OF TDCS

Introduction

Classification learning from exemplars has been demonstrated mathematically to fit Medin and Schaffer's (1978) context theory of classification learning in several studies applying this model to observed classification data (Medin & Florian, 1992; Medin et al., 1982; Medin et al., 1983; Medin & Smith, 1981; Nosofsky, 1984). Context theory states that generalization of learning to a new context is dependent on the retrieval of stored exemplar information and comparison of that exemplar to the context at hand. In this model, stimuli repeated from training to test should be classified at least as easily as novel images to which the exemplar is generalized (Medin & Schaffer, 1978). Other theories of classification learning are similar to context theory, but focus on rule exceptions (i.e., rule-plus-exception (RULEX) theory (Nosofsky et al., 1994)), or do not consistently fit to observed data (i.e., Prototype theory (Reed, 1972)). Regardless of whether participants are detecting objects in the images or classifying the images based on context (using non-object-related components of the images) they are learning to classify images based on features of those images; therefore, we believe the context theory may apply to our object detection task, regardless of how participants reach their decision to classify the images.

In the present investigation, we performed a re-analysis of the effects of test stimulus novelty on test performance accuracy, using data from our previously published study (referred to here as Behavioral Group 1). In addition, we performed a replication of this task in an additional study, using a different sample of participants, with a double-blind, rather than single-blind protocol (Behavioral Group 2). We examined the effects of tDCS current and image type, as well as their interaction, on detection accuracy during

testing after training. We examined generalization of object detection expertise learned in the training sessions by comparing participants' responses to images in which they had previously learned the location of the object (either through successful detection of the object on first presentation or through feedback indicating the location) to responses made to images containing objects they had not seen before. We hypothesized that participants' responses to test images repeated between training and testing sessions would be more accurate than responses to test images not presented during training. We also investigated the effects of tDCS on accuracy of detecting test image type (object-present or object-absent) based on non-object-related components of the images by analyzing the effects of these variables on image classification accuracy for images in which no object was present.

Methods

Inclusion/Exclusion Criteria

All participants met the following criteria: English as a first language, no history of head injuries or concussions resulting in loss of consciousness or hospitalization, right-handedness according to the Edinburgh Handedness Inventory (Oldfield, 1971), no history of psychiatric or neurological disorders, alcohol or drug abuse, or current medication affecting the CNS, and good or corrected vision and hearing.

Behavioral Group 1

Thirty-nine healthy participants gave informed consent and participated in Behavioral Group 1. Three participants with accuracy scores during the immediate test greater than two standard deviations below the mean (2 participants), or above the mean (1 participant) were excluded from analysis. Thus, the results from 36 participants (22 male,

age=24.0 yrs, 4.9 yrs SD) were included in the analyses. Of these 36 participants, 13 received 2.0 mA tDCS, while the remaining 23 received 0.1 mA. One participant did not complete the one hour delay test, but the remaining data for this participant is included in our analyses.

Behavioral Group 2

Twenty healthy participants gave informed consent and participated in Behavioral Group 2. One subject with accuracy scores greater than two standard deviations below the mean was excluded from analysis. Thus, the results from 19 participants (11 male, age=23.4 yrs, 7.7 yrs SD) were included in analyses. Of these 19 participants, 9 received 2.0 mA tDCS, while the remaining 10 received 0.1 mA.

Procedure

Five-second video clips from training scenarios from the DARWARS virtual reality training environment were captured for use as feedback in the task (MacMillan et al., 2005). Six-hundred still images were extracted from these videos and edited to include or remove specific objects. Objects that were hidden in these images included explosive devices concealed by or disguised as dead animals, roadside trash, fruit, flora, rocks, sand, or building structures; and enemies in the form of snipers, suicide bombers, tank drivers, or stone-throwers. For each of the images containing objects, a corresponding image was created which did not contain a hidden person or object. Thus, there were 1200 total images with 50% containing hidden objects. Of these, 322 images, half containing concealed objects, were selected for the learning task after review of the images by research associates ignorant of the locations or defining features of specific objects. The images were arranged

in a random order and were not presented to participants in matched object/no-object pairings.

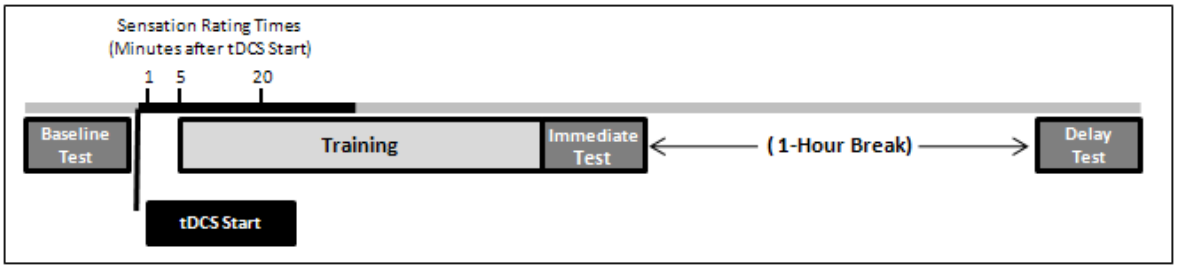


Figure 1. Object detection training and testing paradigm. Training lasted approximately one hour. Tests lasted about 15 minutes for all but MRI Group 1. TDCS was administered 5 minutes before training and lasted for a total of 30 minutes. Participants indicated whether or not tDCS-induced sensation was present at three points during administration. Participants performed baseline, immediate, and delay tests, each consisting of 100 still-image stimuli without feedback. Immediate and delay tests were separated by a one-hour break. Some images in the immediate test had been presented previously, during training, while others had not been seen previously in the task.

Participants were first tested for their baseline ability to detect objects before training, after which participants were trained to detect objects while receiving either 0.1 mA or 2.0 mA tDCS. Following training, participants were tested both immediately (immediate test) and one hour after the end of the immediate test (1 hour delay test; Figure 1). Baseline, immediate, and 1 hour delay tests consisted of 100 images presented with no feedback. Training sessions consisted of four 11-minute blocks of 60 trials, each of which included an image and appropriate audiovisual feedback, with rest periods between blocks.

Each image was presented for 2 seconds with an inter-trial interval that varied across a range of values from 4 to 8 seconds. Participants were instructed to scan the images for objects with no prior information given about the nature of the objects. Thus, the subject discovered the correct and incorrect responses to each image after searching the image, making a decision about the presence of an object, and examining the audiovisual feedback on each training trial. The feedback videos did not provide specific details of the shape or location of the object, but enough information that the subject could infer the type and general position of the object in the image. A correct response was followed by an audio message congratulating the subject on a job well done accompanied by an uneventful video clip. An incorrect response was followed by a disapproving audio message and a movie displaying the consequences of disregarding the object, e.g. a character being shot by a sniper or a bomb detonation. Participants were instructed to respond as accurately as possible when making their responses to the stimuli. No instruction was given to indicate that response time would be a measure of performance, though participants were required to respond within the 3 second response window. Importantly, a portion of the stimuli used in the immediate test had been presented during training, while the remaining stimuli had the same types of objects but had not been presented to the subject during training. Thus, memory for trained images and the generalization of the training to novel images could be examined. The 1 hour delay test was designed to examine retention of learned object detection ability.

Eighteen percent of stimuli in the immediate test of Behavioral Group 1 were repeated from training. This was incidental and not included as a part of the original study design. Following our analysis of the effect of image type on accuracy during post-training

testing, Behavioral Group 2 was recruited to perform a nearly identical task in which the immediate test contained 50% rather than 18% repeated stimuli. All other object learning task-related procedures performed by Behavioral Group 2 were identical to those in Behavioral Group 1.

Anodal tDCS was delivered for 30 minutes near 10-10 EEG location F10, over the right sphenoid bone. The location near F10 was suggested from functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) studies of changes in brain networks associated with the acquisition of expertise in this task (Clark et al., 2010). TDCS was administered through 10 cm2 square water-soaked sponge electrodes. The cathode was placed on the subject's left upper arm. Electrodes were secured to the scalp and upper arm using Coban self-adherent wrap. TDCS was initiated five minutes before training and continued throughout the first two of four training blocks (Figure 1). Current was set to either 0.1 mA or 2.0 mA. Participants, but not experimenters, were blind to tDCS current in Behavioral Group 1 (single blind), while both participants and experimenters were blind to the current delivered in Behavioral Group 2 (double blind). Experimenter blinding was accomplished using a coded switch box, with inputs for positive and negative leads from two current generators and outputs for only two electrodes, one anode and one cathode. One current generator was set to 0.1 mA and the other was set to 2.0 mA. A six-way switch interrupted the circuit, with three settings supplying current to the output leads from one current generator, and the remaining three supplying the output from the other current generator. The inputs which were not actively supplying current to the output leads were routed though a simple circuit loop to maintain the activity of the inactive current generator. The six-way switch was coded by a third party to ensure experimenter blinding.

During tDCS, participants were asked to describe their physical sensations at 1, 5, and 20 minutes after the start of tDCS (Figure 1). For Behavioral Group 1, sensation data were recorded using a list of 10 descriptors including, in order of appearance: no sensation, cold sensation, some tingling, warm sensation, lots of tingling/some itching, very warm, lots of itching, burning (like a sunburn), burning (like scalding water), hurts a lot. TDCS was stopped if participants reported any of the last three descriptors. In Behavioral Group 2, subjects were asked to report sensation on three 10-point Likert scales for itching, tingling, and heat. TDCS was stopped if participants reported a 7 or higher on any scale.

Data Analysis

We first compared the overall accuracy results from our initial study, as reported in Clark et al. (2010), and those of the replication study (Behavioral Group 2) using a 2 x 2 x 3 repeated measures ANOVA, comparing experiment (Behavioral Group 1 and Behavioral Group 2), tDCS current (0.1mA and 2.0mA), and test (repeated measure; baseline, immediate test, and 1 hour delay test). The overall proportion of correct responses was used as a measure of accuracy for this analysis.

We then compared the results of our reanalysis of Behavioral Group 1 with those of Behavioral Group 2 using a separate 3-way ANOVA. This 2 x 2 x 2 ANOVA compared accuracy for images containing objects in the immediate test between Behavioral Group (Behavioral Group 1 and Behavioral Group 2), image type (repeated measure; repeated and novel) and tDCS current level (0.1mA and 2.0mA). The proportion of correct responses to images in which an object was present was used as a measure of accuracy.

A final 2 x 2 x 2 ANOVA compared accuracy for images not containing an object in the immediate test between Behavioral Group (Behavioral Group 1 and Behavioral Group 2), image type (repeated measure; repeated and novel) and tDCS current level (0.1mA and 2.0mA). The proportion of correct responses to images in which no object was present was used as a measure of accuracy in this analysis to examine the extent to which non-object-related image classification, rather than object detection, was dependent on these within- and between-subject variables.

The influence of sensation on accuracy in the immediate test was examined using two different methods, depending on the way the data was collected. Sensation data from Behavioral Group 1 was treated as a binary variable (sensation present or sensation absent), given that the ratings were descriptors, not ordinal or interval level scales. Accuracy was contrasted between participants who did and did not report sensations using Student's T-Test to determine the degree to which sensation influenced performance. Sensation data from Behavioral Group 2 was analyzed using linear regression in order to determine the effect of tDCS-induced sensation on learning and performance in the task. Sensation ratings from all three measures (itching, heat, and tingling) were first entered into a stepwise multiple regression. When this model was determined non-significant, individual linear regression analyses were performed on each measure to determine the proportion of variance accounted for by each of the different measures of sensation.

Results

TDCS Effects on Learning and Retention

Participants performance increased significantly across the three test sessions (F (2,100) =125.377, p=7.73e^{-20}, Figure 2a). Delay test scores (68.3±1.8%) were slightly, though significantly lower than immediate test scores (73.1±1.7%; F (1, 50) =27.914, p=2.77^{e-6}, Figure 2a), but participants performed significantly better than baseline (52.9±0.5%) in both of these tests (immediate test vs. baseline, F (1, 51) =177.170, p=3.21e^{-18}; delay test vs. baseline, F (1, 50) =105.109, p =6.90e^{-14}, Figure 2a).

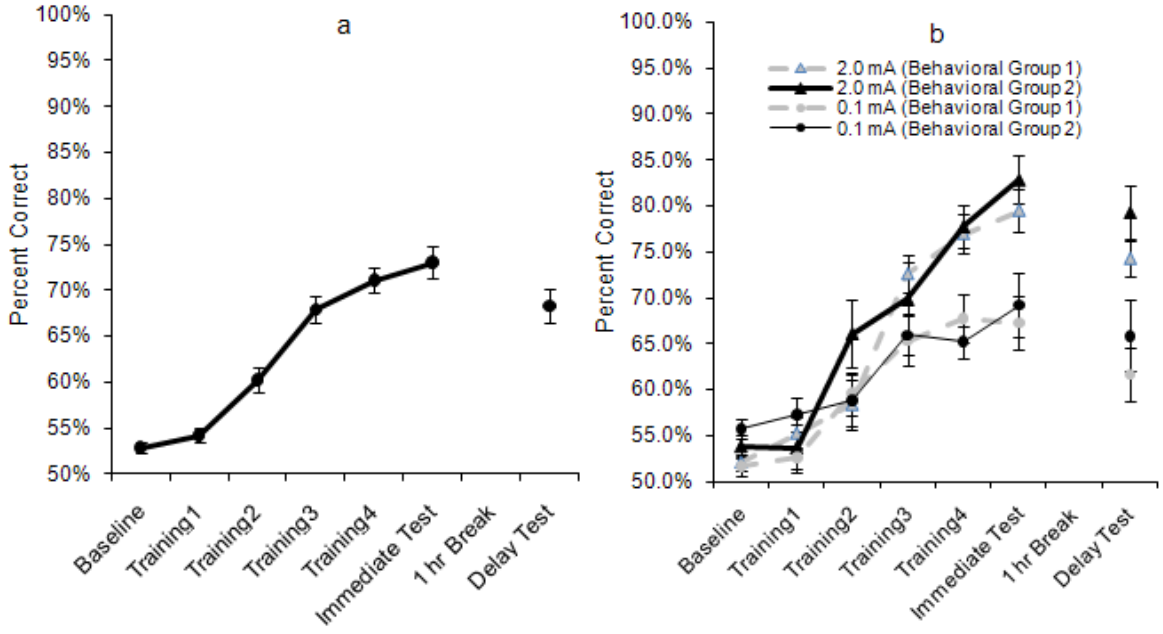


Figure 2 Shows percentage of correct responses during different phases of training and testing. a.) Participants' performance increased significantly with training. Performance decreased somewhat following the one-hour break but remained significantly different from baseline. b.) Participants in Behavioral Group 2 (solid lines) performed in a similar manner

as those in Behavioral Group 1 (broken lines; Clark et al, 2010). In both behavioral groups, participants receiving 2.0 mA (triangles) significantly outperformed those receiving 0.1 mA (circles) in the immediate and delay tests. Rates of forgetting over the one hour break were similar for sham and active groups in both behavioral groups.

	Baseline		Immediate Test		Delay Test	
	Mean	SD	Mean	SD	Mean	SD
Behavioral Group 1						
2.0 mA	52.1%	3.5%	79.5%	8.4%	74.3%	6.6%
0.1 mA	51.7%	4.9%	67.3%	14.0%	61.7%	13.6%
Behavioral Group 2						
2.0 mA	53.8%	3.4%	82.9%	6.9%	79.3%	7.6%
0.1 mA	55.8%	2.8%	69.2%	11.1%	65.9%	3.9%

Table 1. Means and standard deviations (SDs) for baseline, immediate test, and delay test for groups included in our analysis of tDCS effects on learning and retention.

The degree to which performance increased with training depended on current (test x current, F (2,100) =15.075, p=4.82^{e-5}, Figure 2b). Both 0.1 mA and 2.0 mA groups performed significantly better as training progressed (0.1 mA F (2, 62) =24.069, p =3.27^{e-6}, 2.0 mA F (2, 38) =221.415, p =2.80^{e-17}, Figure 2b); however, participants receiving 2.0 mA tDCS performed significantly better than those receiving 0.1 mA, and we believe that differences seen in the 0.1 mA were the result of training alone and that the 0.1 mA condition served as a placebo here. Simple effects of current were significant for the immediate test (2.0 mA 80.9±1.7% , 0.1 mA 67.8±2.3%, F (1,50)=14.864, p=3.27e-4,

Figure 2b) and the delay test (2.0 mA 78.4±1.6%, 0.1 mA 63.0±2.3%, F (1,50)=14.803, p=3.31e-4, Figure 2b), but not for baseline performance (2.0 mA 52.8±0.7%, 0.1 mA 52.9±0.8%, F (1,50)=0.435, p=0.512, Figure 2b), indicating that this effect was not due to baseline differences in image classification.

The 3-way interaction between Behavioral Group, test, and current was not significant (F (2,100) =0.340, p=0.830) and was not considered in Bonferroni adjustments of α for analyses of two-way interactions or simple effects within these analyses. No main effect (F (1,50)=2.140, p=0.158), two-way interaction (Behavioral Group x test, F (2,100)=0.184, p=0.746; Behavioral Group x current, F (11, 50)=0.002, p=0.994), or 3-way interaction (F (2, 100)=0.340, p=0.830) involving Behavioral Group as an independent variable was identified in our analyses, indicating that the results of Behavioral Group 2 were not significantly different from those of Behavioral Group 1. Simple effects were corrected using Bonferroni adjustments of α=.025 (.05/2) for simple effects of test and α=.017 (.05/3) for simple effects of tDCS current. Individual contrasts between tests were Bonferroni-corrected at α=.008 (.05/6).

	Repeated Stimuli		Novel Stimuli	
	Mean	SD	Mean	SD
Behavioral Group 1				
2.0 mA	96.2%	9.4%	72.4%	9.4%
0.1 mA	72.3%	24.4%	65.4%	9.6%
Behavioral Group 2				
2.0 mA	86.5%	7.9%	76.4%	9.5%
0.1 mA	66.2%	16.2%	65.7%	8.6%

Table 2. Means and standard deviations (SDs) for the effects of image type and tDCS current on hidden object detection in images containing objects.

Effects of Image Type and tDCS Current on Hidden Object Detection

The 3-way interaction between Behavioral Group, current, and image type was not statistically significant (F (1, 51) =0.522, p =0.473) and was not considered in Bonferroni adjustments of α for analyses of two-way interactions or simple effect within these interactions. Main effects of current (0.1mA 66.1±1.7%, 2.0mA 77.9±1.8%; F (1, 51) =21.003, p =3.0e-5; Figure 3a) and image type (repeated 79.1±2.8%, novel 68.9±1.4%; F (1, 51) =17.417, p =1.17e-4; Figure 3b) were statistically significant. The 2-way interaction between current and image type achieved significance in this analysis as well (F (1,51) =7.219, p=9.71e-3), with simple effects of tDCS current present for repeated images (0.1mA 70.4±3.9% , 2.0mA 92.2±2.1%; F (1,51) =17.820, p =1.0e-4; Figure 3c), as well as images which had not been seen previously (0.1mA 65.5±1.6% , 2.0mA 74.0±2.0%; F (1,51) =10.762, p=1.87e-3; Figure 3c). A simple effect of image type was present only in the 2.0mA group, with responses to repeated images (92.2±2.1%) greater than those to novel (74.0±2.0%; F (1, 51) =48.008, p=9.96e-7; Figure 3c). Simple effects of image type were not present in the 0.1mA group (repeated 70.4±3.9%, novel 65.5±1.6%; F (1, 51) =0.934, p=0.341, Figure 3c). All simple effects of image type and tDCS current were corrected using Bonferroni adjustments of α=.025 (.05/2).

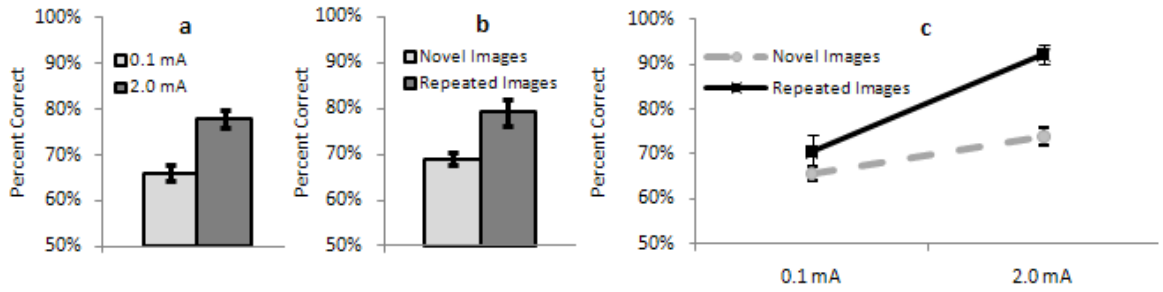


Figure 3. Proportion of correct responses made during the immediate test in both behavioral groups. *a*) Effect of tDCS current. Participants accuracy increased significantly with tDCS current, with participants receiving the 2.0 mA (dark) outperforming those who received 0.1 mA (light). *b)* Effect of stimulus type. Participants were significantly more accurate in detecting objects in repeated stimuli (dark) than in novel stimuli (light). *c)* Interaction of tDCS current and image type on accuracy for the immediate posttest. This interaction was significant, with greater tDCS effect on repeated stimuli (solid line) than in novel stimuli (broken line).

No main effect (F (1, 51) =0.725, p=0.388) or 3-way interaction (Behavioral Group x image type x current, F (1, 51) =0.522, p =0.473) involving Behavioral Group as an independent variable was identified in our analyses. Also, the two-way interaction between Behavioral Group and current was nonsignificant (F (1, 51) = 1.04e-6, p =0.999). There was a significant interaction between Behavioral Group and image type (F (1,51)=4.095, p=0.048), with a slightly greater difference between repeated and novel stimuli in Behavioral Group 1, though both simple effects of Behavioral Group were non-significant (repeated images: Behavioral Group 1, 67.9±1.7%, Behavioral Group 2, 70.8±2.4%, F

(1,54) =0.719, p =0.400; novel images: Behavioral Group 1, 80.9±3.9%, Behavioral Group 2, 75.8±3.8%, *F* (1,54) =0.970, p =0.329; Figure 4).

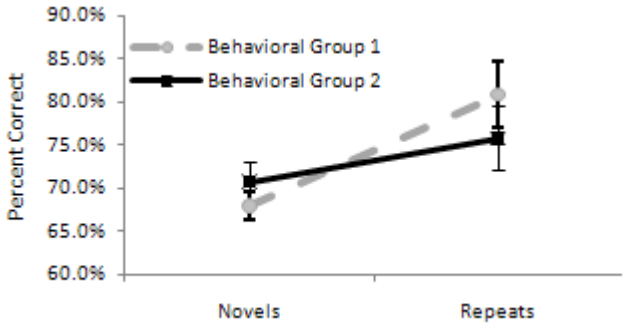


Figure 4. Accuracy during the immediate test for both behavioral groups and image types (repeated or novel). Although the interaction between behavioral group and image type reached statistical significance, neither participants' accuracy in detecting objects in repeated images nor novel images significantly differed between Behavioral Group 1 (solid line) and Behavioral Group 2 (broken line).

Effects of Image type and tDCS Current on Classification of Images without Hidden Objects

Main effects of current (0.1mA 70.6±3.5%, 2.0mA 84.4±2.6%; *F* (1, 51) =7.334, p =0.009; Figure 5a) were statistically significant. Interestingly, no main effect (*F* (1, 51) =0.034, *p*=0.854; Figure 5b), two-way interaction (image type x current, *F* (1, 51) = 0.154, p =0.696; Figure 5c, image type x Behavioral Group, *F* (1, 51) = 0.001, p =0.979), or 3-way interaction (Behavioral Group x image type x current, *F* (1, 51) =0.005, p =0.943)

involving image type as an independent variable was identified in our analyses, indicating that image type did not affect image classification in images without hidden objects.

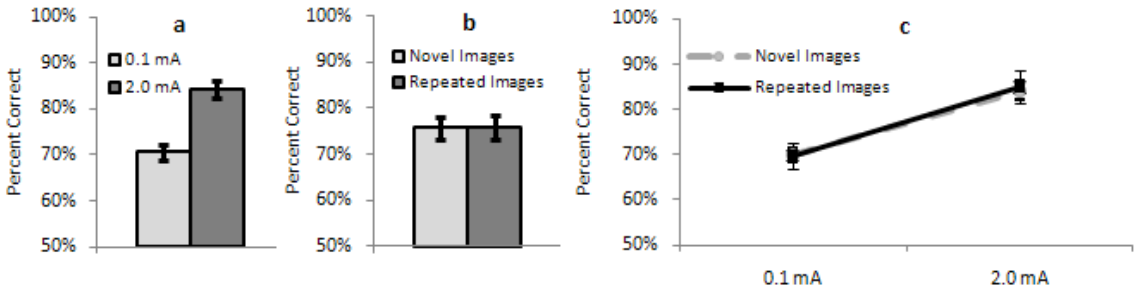


Figure 5. Proportion of correct responses made for images without objects present during the immediate test in both Experiments. *a*) Shows the effect of tDCS current. Participants accuracy increased significantly with tDCS current, with participants receiving the 2.0 mA (dark) outperforming those who received 0.1 mA (light). *b)* Shows the effect of stimulus type. There was no difference in accuracy in detecting objects in repeated stimuli (dark) vs. novel stimuli (light). *c)* Shows the interaction of tDCS current and image type on accuracy for the immediate posttest. This interaction was nonsignificant; the tDCS effect was nearly identical for repeated stimuli (solid line) and novel stimuli (broken line).

No main effect (F (1, 51) =0.009, p=0.706), two-way interaction (Behavioral Group x current, F (1, 51) = 0.154, p =0.696, Behavioral Group x image type, F (1, 51) = 0.001, p =0.979), or 3-way interaction (Behavioral Group x image type x current, F (1, 51) =0.005, p =0.943) involving Behavioral Group as an independent variable was identified in our

analyses, indicating that training and tDCS effects in Behavioral Group 2 are consistent with those of Behavioral Group 1 for images without hidden objects.

	Repeated Stimuli		Novel Stimuli	
	Mean	SD	Mean	SD
Behavioral Group 1				
2.0 mA	85.0%	12.7%	84.1%	15.2%
0.1 mA	68.5%	24.0%	68.8%	21.4%
Behavioral Group 2				
2.0 mA	84.8%	11.5%	84.2%	10.1%
0.1 mA	72.6%	17.6%	72.7%	18.3%

Table 3. Means and standard deviations (SDs) for effects of image type and tDCS current on classification of images without hidden objects

Effect of tDCS-Induced Sensation on Image Classification

All participants completed the training and testing phases of Behavioral Group 1; however, sensation data were collected on only 18 of the 36 participants. For the 18 participants who completed the sensation questionnaire, there was no significant difference in accuracy (sensation present 65.0±4.7%, sensation absent 71.3±3.7%; T=1.056, p=0.306, Figure 6a), indicating that sensation did not significantly influence performance.

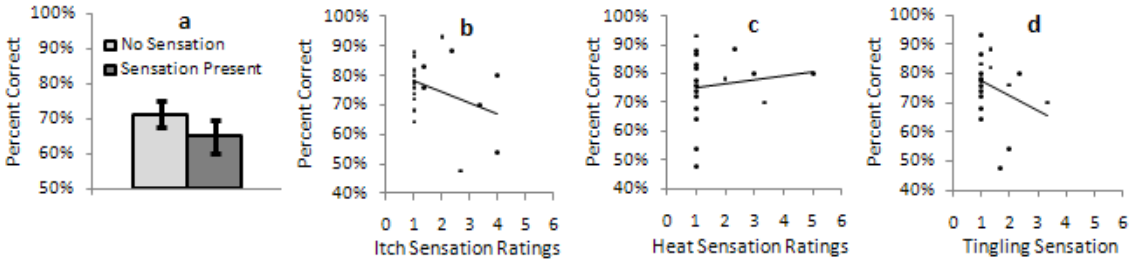


Figure 6 a.) Proportion of correct responses made during the immediate posttest in Behavioral Group 1 relative to skin sensation. There was no difference in accuracy between participants who did (dark) or did not (light) report sensation from tDCS. b-d.) The y axis in each graph represents the proportion of correct responses made during the immediate test in Behavioral Group 2. The x axes represent itching (b), heat (c), and tingling (d) sensation experienced by participants during tDCS. No measure of sensation was found to significantly predict accuracy in the immediate test.

Regression analyses indicated that there was no significant linear relationship present between sensation and accuracy in the immediate test in Behavioral Group 2 for any of the three sensation measures collected indicating that sensation did not significantly influence performance. Itching sensations accounted for 11.7% of the variance in accuracy (β= -0.037, p=0.151 Figure 6b). Heat sensations accounted for 1.9% of the variance in accuracy (β=.014, p=0.571 Figure 6c). Tingling sensations accounted for 8.1% of the variance in accuracy (β= -0.052, p=0.297, Figure 6d).

Discussion

We reported previously that anodal tDCS applied over right inferior frontal cortex facilitated learning to detect hidden objects in a dose-dependent manner (Clark et al., 2010).

This was successfully replicated in a separate group of participants (Behavioral Group 2). In addition, our analysis of data from both Behavioral Groups showed that images presented during training were classified more accurately during testing performed immediately after training than were novel images (images not presented during training), when collapsing across tDCS current levels. Interestingly, the interaction between tDCS current and stimulus repetition was also statistically significant, indicating that the effect of tDCS was larger for repeated than novel test images. Furthermore, no difference was found in participants' accuracy between repeated and novel test images that did not contain objects, while the overall effect of tDCS was comparable to that for images containing objects. Finally, the performance-facilitating effect of tDCS did not appear to be linked to sensation produced by the current in either Behavioral Group.

We found similar patterns of test performance in Behavioral Group 2 as those reported previously for Behavioral Group 1 (Clark et al., 2010). Specifically, neither main nor interaction effects of Behavioral Group (1 or 2) were present, indicating successful replication of our previous findings. Subjects in each of the two tDCS current groups (0.1 mA and 2.0 mA) performed similarly across the two Behavioral Groups. Furthermore, retention over the 1 hour break was nearly identical in the two Behavioral Groups, indicating that the effects of tDCS in enhancing learning is not at the cost of retention, at least over a 1 hour rest period between test sessions.

The main effects of tDCS and image repetition are more clearly interpreted in light of their interaction. While present for both repeated and novel images, the effect of tDCS on performance after training for stimuli containing hidden objects was larger for repeated, than for novel, images. This result supports Medin and Schaffer's (1978) context theory of

classification learning. If generalization of learned object detection depends on memory for exemplars learned during training, then performance should be equal or better on classification of repeated than novel images. It is also likely that recognition is more easily enhanced by improved attention or perception than is generalization of learned information to novel situations in this task. Object detection was quite difficult, with participants receiving 0.1 mA current reaching only 67.8±2.3% accuracy in the immediate test. Interestingly, the difference in performance between repeated and novel test images increased with tDCS, but only for images containing objects. This implies that tDCS may have enhanced either encoding or retrieval of hidden object locations in exemplars learned during training.

Because tDCS causes sensation at the site of the electrodes (Furubayashi et al., 2008; Gandiga et al., 2006; Poreisz et al., 2007), we investigated the possibility that sensation itself facilitated performance. In Behavioral Group 1, the performance of participants reporting tDCS-induced sensation was compared to that of participants who reported no sensation. As before (Clark et al., 2010), there was no significant difference in classification performance between groups. In Behavioral Group 2, we used regression to look more quantitatively for effects of sensation. Again, we found that skin sensation was not the basis for increased learning and performance.

Though effects of tDCS in this experiment were consistent between two participant samples using single and double-bind protocols, the effects were are not necessarily robust to large manipulations in the task. Specifically, effects of tDCS were completely diminished when testing during neuroimaging. In Experiment 2 we present an analysis of the behavioral effects of tDCS when participants were tested both during active fMRI at a

magnetic field of 3 Tesla, and in a mock MRI scanner, which was identical to an active MRI.

EXPERIMENT 2: LEARNING EFFECTS OF MRI MAGNETIC FIELD AND tDCS

Introduction

As stated above, we previously found a large effect of tDCS on object detection learning. Surprisingly, however, behavioral results from our fMRI studies of the effects of tDCS on object detection (unpublished observations) are not consistent with those from our published behavioral studies (Clark et al, 2010). Specifically, the enhanced learning effect for this group of participants was not significantly different from our previous results throughout training outside of the MRI scanner, but behavioral data did not support this effect during testing inside the MRI scanner. There are two possible explanations of these results: (1) there is some modulation of the neurophysiological effects of tDCS by the intense magnetic fields generated by MRI. (2) The enhancement of learning by tDCS is specific to the general environment in which it was learned, and dramatically changing one's environment nullifies this effect. This Experiment examined the former hypothesis that magnetic field influences the effect of tDCS, while the latter hypothesis is examined in Experiment 3.

Static magnetic fields produced in MRI at strengths of up to 8 Tesla have not been shown to effect cognitive ability (Sweetland et al., 1987; Chakeres et al., 2003), and have had effects on visual perception and hand/eye coordination only when participants were instructed to move their heads within the magnetic field, although this study was performed at a lower magnetic field (1.8 Tesla) than used in our studies, and only examined static magnetic fields (DeVocht et al., 2007). Static fields at 4 Tesla, similarly, do not affect brain metabolism (Volkow, 2000). Therefore, it is unlikely that participants' memory processes were directly altered by the static magnetic field present in our studies. It is likely, however,

that the varying magnetic fields that are generated during echo-planar imaging (EPI), the standard technique used in fMRI, induce electric fields within the brain and body (Glover and Bowtell, 2008; Volkow, 2010). These electric fields are generated in the same process that drives the effects of transcranial magnetic stimulation (TMS), which has been shown to decrease cortical excitability at the frequencies that are commonly used in EPI (Todd, 2006). This inhibitory effect of EPI has been demonstrated in polar regions of the brain (occipital cortex, orbito-frontal cortex, and superior parietal cortex) by the use of positron emission tomography (PET), a measure of metabolic activity in the brain (Volkow, 2010). Interestingly, these areas encompass those which were active during learning to detect concealed objects in our previous fMRI study (Clark et al. 2010). This could mean that the electric fields generated by EPI inhibited the very areas whose activity were necessary in performance of learned threat detection processes, particularly those that may have been effected by previous electrical stimulation during training.

We examined the effect of MRI magnetic field by comparing behavioral results from our previous work with tDCS during active fMRI (MRI Group 1) to those obtained using a similar protocol in the mock MRI scanner (MRI Group 2). This mock MRI scanner resembles a real MRI in every way (e.g. external appearance, sound, visual projection system, subject response methods) except the induced magnetic field is absent. This comparison allowed us to directly compare performance with the magnetic field to performance in the absence of the magnetic field.

Methods

Inclusion/Exclusion Criteria

All participants met the same inclusion/exclusion criteria as those in Experiment 1.

MRI Group 1

Nineteen healthy participants gave informed consent and participated in MRI Group 1. One participant with accuracy scores during the immediate test that was greater than two standard deviations below the mean was excluded from analysis. Thus, the results from 18 participants (10 male, age=24.5 yrs, 1.0 yrs SD) were included in analyses. Of these 18 participants, 8 received 2.0 mA tDCS, while the remaining 10 received 0.1 mA.

MRI Group 2

Twenty-one participants gave informed consent and participated in MRI Group 2. One participant with accuracy scores greater than two standard deviations below the mean and one participant with accuracy scores greater than two standard deviations above the mean were excluded from analysis. Also, one participant informed us at debriefing that she thought during testing the mock MRI may not have been real. Thus, the results from 18 participants (12 male, age=21.8 yrs, 1.4 yrs SD) were included in analyses. Of these 18 participants, 10 received 2.0 mA tDCS, while the remaining 8 received 0.1 mA.

Procedure

Task-related procedures in Experiment 2 were similar to Experiment 1. The only difference between the two protocols was that participants in Experiment 2 were tested inside either an active or mock MRI scanner. MRI Group 1 performed the baseline and

immediate test inside the active (3T) MRI scanner and MRI Group 2 performed the baseline and immediate test inside the mock MRI scanner. Baseline and immediate tests completed by MRI Group 2 were similar to those completed by Behavioral Group 2, though MRI Group 1 completed longer (~30 min) tests. Tests in the active MRI were lengthened so that they would be long enough that a sufficient number of averages could be acquired for fMRI analysis. MRI Group 2 completed tests identical to those performed by the Behavioral Groups rather than MRI Group 1 because we predicted that magnetic field effects would be less likely to affect performance than environmental effects of the MRI (see Experiment 3). All participants in Experiment 2 were trained outside of the scanner, in the same office environments as participants in Experiment 1.

Because participants were tested inside the MRI scanners, they were required to remove any metal from their person and change into hospital nurse's scrubs prior to baseline testing. Participants remained in these clothes for the entire duration of the experiment. Participants viewed the images in both the mock and active MRI scanners through a mirror affixed to the head coil, which reflected the image displayed projected on a wall either behind or in front of the scanner. Viewing angle of the images in both the mock and active MRI scanners was 18^{o} x 18^{o}. Luminance was similar between the two environments. Participants responded using buttons beneath their pointer and middle fingers, and were instructed to press the button beneath their pointer finger if they discovered a hidden object, or the button beneath their middle finger if they did not.

All participants were told that the mock MRI scanner was an actual MRI scanner prior to participation and were debriefed about this deception following completion of the experiment. This deception component of the study was essential to study the effect of the

MRI environment on tDCS enhancement of learning in this study, particularly as many participants in both MRI Groups had never had an MRI before, and any anxiety or apprehensiveness experienced due to the thought of the MRI scan may be important in our results.

All tDCS related procedures in Experiment 2 were identical to those in Experiment 1. Participants in MRI Group 1 received tDCS in a single-blind protocol, while those in MRI Group 2 received double-blind application of tDCS. This was accomplished using the same switch device described in Experiment 1.

Data Analysis

Image classification learning in Experiment 2 was measured by accuracy (% correct) in the baseline and immediate tests. We examined the effects of tDCS and magnetic field on learning using a 2x2x2 repeated-measures ANOVA, comparing baseline and immediate test scores between participants receiving 2.0 mA and 0.1 mA tDCS in MRI Groups 1 and 2.

Results

There was a significant main effect of test (baseline vs. immediate test; F (1, 32) =56.402, p=1.5e^{-8}), indicating that participants ability to classify images as containing or not containing hidden objects increased with training. The change in performance between baseline and the immediate test was not significantly affected by tDCS current (test x current; F (1, 32) =0.007, p=0.933, Figure 7a) or magnetic field (test x magnetic field; F (1, 32) =15.956, p=3.56e^{-4}, Figure 7b). Also, the degree to which learning was enhanced by tDCS was not affected by the magnetic field present in the MRI, as evidenced by the non-

significant three-way interaction between test, tDCS current, and magnetic field (F (1, 32)=0.951, p=0.337, Figure 7c).

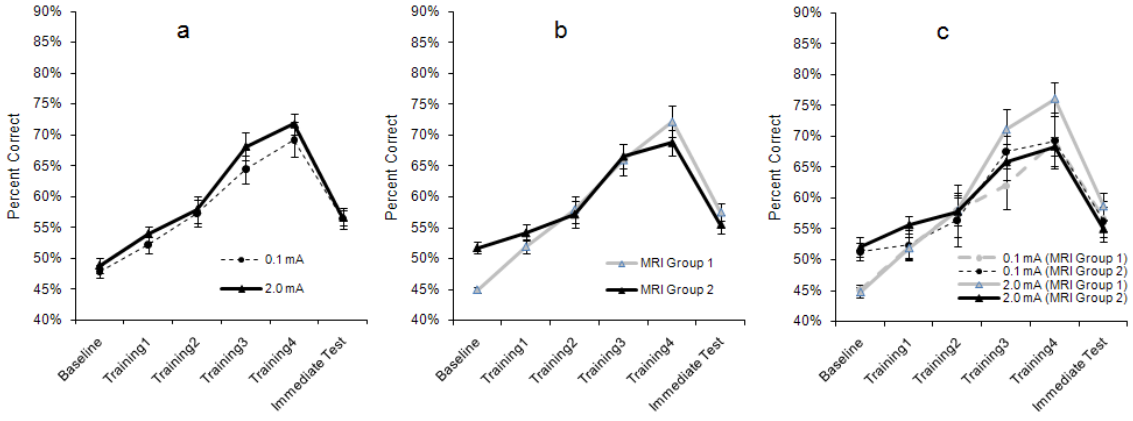


Figure 7 a.) Effect of tDCS when participants were tested in an MRI environment. There was no difference in learning between participants receiving 0.1 mA tDCS (dashed line) and those receiving 2.0 mA tDCS (solid line). b.) Effect of magnetic field collapsed across participants receiving both tDCS currents. There was no difference in learning between participants tested in the active (3T) MRI scanner (grey line) and those tested in the mock MRI scanner (black line). c.) Effects of tDCS and magnetic field on learning to detect objects. The interaction was non-significant.

Discussion

Based on the lack of significant findings in Experiment 2, we conclude that magnetic field generated during EPI did not lead to our behavioral results during fMRI. Participants in MRI group 1 performed no differently than those in MRI group 2 during the

immediate test, in either the 2.0 mA or 0.1 mA tDCS condition. Importantly, tDCS administered during training outside the MRI did not enhance performance when tested in the MRI in either MRI group. This indicates that some other factor or factors that differ between the laboratory and MRI environments may have led to the lack of changes in learning and performance between these groups. These results are explored further in Experiment 3.

EXPERIMENT 3: LEARNING EFFECTS OF MRI ENVIRONMENT AND tDCS

Introduction

The environment in an MRI scanner differs from that of an office workstation on various contextual variables including: postural position (supine vs. sitting), ambient lighting, display presentation, ambient sound, openness of the environment (~800ft^3 room vs. ~55ft^3 tunnel), and response methods. It is also possible that the effects of tDCS in this study are somewhat context-dependent, and that the testing environment (a Siemens TIM Trio 3T MRI with rear projector display and response glove) was too far removed from the training environment (a well-lit workstation environment with a standard CRT monitor display and keyboard response device) in our fMRI study of tDCS-enhanced object detection. In this Experiment we examined our second hypothesis from Experiment 2: that tDCS enhancement of learning to detect objects in images is affected by changes in testing environment between training and test.

Evidence of context-dependent learning has been found reliably in studies of the effects of incidental background environment on memory (for a review see Smith, 1988). Meta-analyses of environmentally-dependent learning have demonstrated significant effects of context manipulations on memory (Smith and Vela, 2001). It is plausible that when participants were trained to detect hidden objects at an office workstation PC, this learning did not transfer to the context of the MRI environment. Furthermore, participants are more likely to experience context effects on recognition memory (Smith, 1994). This may play a role in the results of these Experiments as participants receiving 2.0 mA tDCS were more likely to recognize repeated images than those receiving 0.1 mA (see Experiment 1).

This Experiment examined the effects of tDCS on learning when participants were trained and/or tested in an MRI scanner environment. Participants tested in the mock MRI scanner were compared to those tested at the workstation PC. We also included another group of participants (MRI Group 3) who were trained and tested in the mock MRI in order to examine the effects of tDCS and training when training is performed in the mock scanner.

Methods

Inclusion/Exclusion Criteria

All participants met the same inclusion/exclusion criteria as those in Experiments 1 and 2.

Behavioral Group 2

See Experiment 1.

MRI Group 2

See Experiment 2.

MRI Group 3

Nineteen healthy participants gave informed consent and participated in MRI Group 3. One subject with accuracy scores greater than two standard deviations below the mean was excluded from analysis. Thus, the results from 18 participants (9 male, age=20.8 yrs, 1.2 yrs SD) were included in analyses. Of these 18 participants, 9 received 2.0 mA tDCS, while the remaining 9 received 0.1 mA.

Procedure

Object detection learning in Experiment 3 was similar to Experiments 1 and 2. Experiment 3 included 3 groups of participants: participants who were trained and tested at an office workstation (Behavioral Group 2), participants who were trained at an office workstation and tested in a mock MRI (MRI Group 2), and participants who were both trained and tested in a mock MRI (MRI Group 3). Participants in MRI Group 3 performed all training and testing inside the mock MRI scanner and were only removed from the scanner to place tDCS electrodes and use the restroom, if needed.

Just as in Experiment 2, participants were told that the mock MRI scanner was an actual MRI scanner prior to participation and were debriefed about this deception following completion of the experiment. All other MRI-related procedures were identical to Experiment 2 as well.

All tDCS-related procedures in Experiment 3 were identical to those in Experiments 1 and 2. Participants in the 3 groups included in this Experiment received double-blind application of tDCS. This was accomplished using the same switch device described in Experiment 1. Participants in MRI Group 3 received tDCS while inside the mock MRI scanner.

Data Analysis

Our first analysis of data from Experiment 3 focused on the effect of changed environment from training to test on tDCS enhancement of image classification in the absence of magnetic field. Here we examined the learning effects of tDCS and testing environment by comparing baseline, immediate, and 1 hour delay test scores for

participants receiving 2.0 mA or 0.1 mA tDCS who were trained and tested at an office workstation PC (Behavioral Group 2) to those who were trained at an office workstation PC and tested in the mock MRI scanner (MRI Group 2). This was performed using a 2x2x3 repeated measures ANOVA.

Our second analysis examined the effect of MRI environment on the ability to learn to detect objects during training and the effects of tDCS on learning while in the MRI. This was performed using a 2x2x4 repeated measures ANOVA which compared participants responses in each of the 4 training runs between those receiving 0.1 mA and 2.0 mA tDCS who were trained in the mock MRI scanner (MRI Group 3) or at a workstation PC (Behavioral Group 2)

Results

Effects of tDCS and Test Environment on Learning and Retention

The results from our first analysis of the effect of tDCS during testing in an MRI environment vs. the same environment where training had occurred were consistent with data from our active fMRI study. Main effects of testing environment (mock MRI scanner vs. workstation PC; F (1, 33) =51.678, p=3.06e^{-8}), tDCS current (0.1 mA vs. 2.0 mA; F (1, 33) =5.158, p=0.030), and learning (baseline vs. immediate test vs. 1 hr delay test; F (2, 66) =58.998, p=6.26e^{-13}) were identified. Also, learning was significantly better at higher tDCS current (F (2, 66) =6.528, p=0.005, Figure 8a) and when tested in the same environment as training (learning x testing environment; F (2, 66) =28.625, p=1.93e^{-8}, Figure 8b). Simple effects of learning were present for participants receiving both levels of tDCS current (2.0 mA: F (2, 36) =19.372, p=1.27e^{-4}; 0.1 mA: F (2, 34) =10.336, p=0.001, Figure 8c) and

participants tested at a workstation PC (F (2, 36) =45.384, p=4.10e^{-7}, Figure 8c), but not for participants tested in the mock MRI scanner (F (2, 34) =3.110, p=0.058, Figure 8c). The interaction between tDCS current and testing environment was also significant (F (1, 33) =4.210, p=0.048), although this interaction is not very meaningful without consideration of the effect of learning.

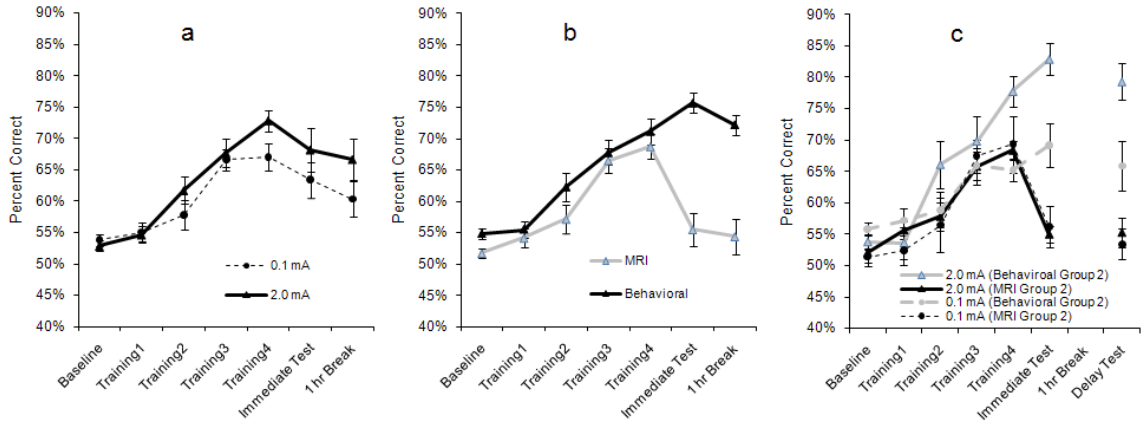


Figure 8 a.) Effect of tDCS collapsed across both testing environments. There was a significant difference in learning between participants receiving 0.1 mA tDCS (dashed line) and those receiving 2.0 mA tDCS (solid line). b.) Effect of MRI magnetic field collapsed across participants receiving both tDCS currents. There was a large difference in test performance between participants tested in the mock MRI scanner (grey line) and those tested at a workstation PC (black line). c.) Effects of tDCS and testing environment on learning to detect objects. The interaction was significant, with effects of tDCS on learning present only for participants tested at a workstation PC. Simple effects of testing environment were present both within groups receiving 0.1 mA and groups receiving 2.0 mA tDCS.

These results are more clearly examined when taking into consideration the three-way interaction, which indicated that the difference in learning between participants receiving 0.1 mA and 2.0 mA tDCS was effected by the testing environment (learning x tDCS current x testing environment; F (2,66)=7.281, p=0.003, Figure 8c). This interaction was such that effects of tDCS on performance change throughout testing were present when participants were tested at a workstation PC (tDCS x learning; F (2, 34) =11.731, p=0.001, Figure 8c), and not when tested in the mock MRI (F (2, 32) =0.485, p=0.610, Figure 8c). Also, testing environment significantly affected learning for participants receiving 2.0 mA tDCS (F (2, 34) =52.581, p=3.57e^{-9}, Figure 8c), but not those receiving 0.1 mA (F (2, 32) =2.684, p=0.098, Figure 8c). Simple-simple effects of learning were present for participants receiving 2.0 mA tDCS, who were tested at a workstation PC (F (2, 16) =125.134, p=9.16e^{-9}, Figure 8c), and for participants receiving 0.1 mA in the same testing environment (F (2, 18) =10.639, p=0.006, Figure 8c), but not for those receiving the 2.0 mA tDCS who were tested in the mock MRI (F (2, 18) =1.730, p=0.217, Figure 8c). Individual contrasts for this group of participants receiving 2.0 mA tDCS who were tested at a workstation PC revealed significant differences between baseline and immediate test (F (1, 8)=182.418, p=9.67e^{-7}, Figure 8c) and between baseline and 1 hour delay test (F (1, 8)=121.097, p=4.14e--6, Figure 8c), but not between immediate and 1 hour delay tests (F (1, 8)=6.218 p=0.037, n.s. at Bonferroni corrected α of 0.004, Figure 8c).

Effects of tDCS and Training Environment on Learning and Retention

Participants trained in the mock MRI performed significantly worse during training than those trained at a workstation PC (F (1, 33) =75.296, p=7.97e^{-10}). This effect was largely driven by the difference in learning between these groups of subjects (learning x

training environment; F (3, 99) =8.492, p=8.91e^{-5} Figure 9). The effects of tDCS on learning during training were also different between groups trained in different environments (tDCS current x learning x training environment; F (3, 99) =2.839, p=0.047 Figure 9). This interaction was such that effects of tDCS current on learning were significant for participants trained at a workstation PC (F (3, 51) =6.408, p=0.002 Figure 9), but not for those trained in the mock MRI (F (3, 48) =0.010, p=0.995 Figure 9). Importantly, large effects of training environment on performance during training were present at both levels of tDCS current (0.1 mA: F (1, 17) =25.157, p=9.63e^{-5}; 2.0 mA: F (1, 16) =46.288, p=4.25e^{-8} Figure 9).

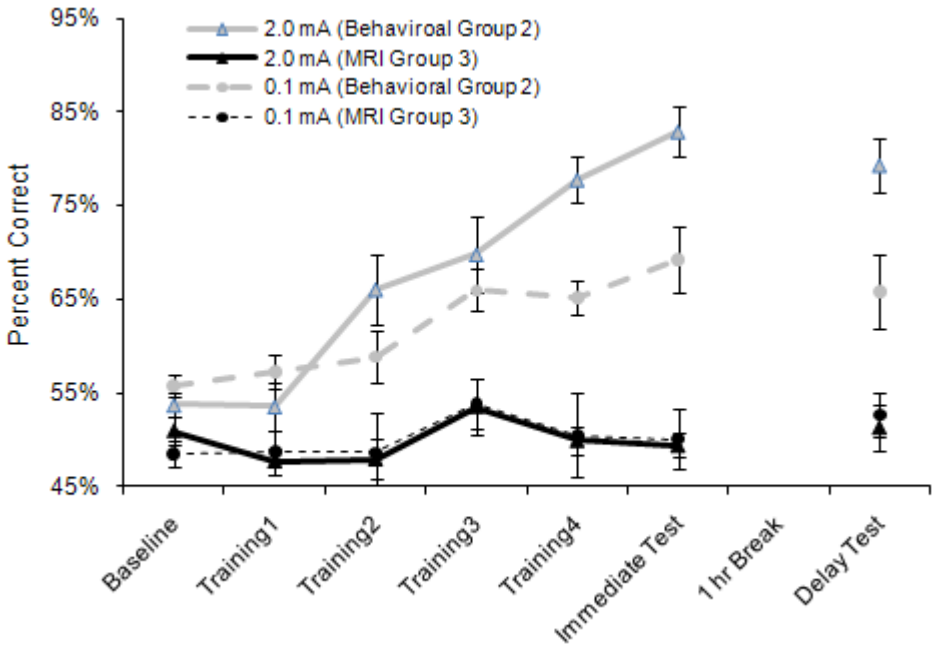


Figure 9) Effects of tDCS and training environment on learning to detect objects. The interaction between tDCS and training environment was significant, with effects of tDCS on learning present only for participants tested at a workstation PC. Simple effects of test

environment were present both within groups receiving 0.1 mA and groups receiving 2.0 mA tDCS. There was no learning effect for participants trained in the MRI in either tDCS current group.

Discussion

The results of Experiment 3 suggest that participants may have been unable to perform the task in the MRI environment, regardless of the environment in which training occurred or the tDCS current. Average test performance was not greater than 57% in either group tested in the MRI environment, at either tDCS current. Furthermore, average training scores were not greater than 54% for participants trained in the mock MRI, receiving either tDCS current. Participants seem to have been unable to perform the task in the scanner, which may be related to factors associated with stimulus properties, distractions, or apprehensiveness associated with performance of the task in the scanner.

The difference in visual angle manipulation between the testing environments may have played a role in these results. The visual angle of the images when performing the task in the MRI scanner environments was fixed at 18°, while the visual angle when performing the task at the workstation PC was variable, depending on the distance of the participants head from the monitor. The monitor was positioned at a distance of 2 feet from the edge of the desk on which it sat, which helped to limit the maximum visual angle at which the image could be viewed. Even so, we estimate that the visual angle when performing the task at the workstation PC may have ranged from as small as 10° (if the participant were to lean back as far as possible and had relatively long arms) to as large as 32° (if the

participant were to lean over the desk by approximately 6 inches). It is possible that the hidden objects contained in the images were simply too small to be detected at a viewing angle of 18°. Viewing angle of the objects contained in the images ranged from 0.10° to 1.99° in the MRI scanner environments, and from 0.19° to 3.72° at the closest possible distance in the workstation PC environments. As a form of reference, a person with 20/20 vision can discriminate spatial patterns on the Snellen chart, which are separated by 0.017° visual angle (Snellen, 1862). Visual acuity as determined by Snellen chart, however, is likely a liberal estimate of visual specificity when one is searching complex images for hidden or camouflaged objects. Perhaps this small difference in visual angle between images in the two environments was enough to lead to the differences seen in learning between the two environments.

The MRI environment is quite different from the workstation PC at which participants in Behavioral Groups 1 & 2 performed the object detection task. Performing the task while dressed in unfamiliar clothes and remaining completely still in supine position with little ambient light and a very distracting, loud sounds could lead to drastic differences in behavior when compared to the comparably comfortable office workstation environment. Differences in mood variables, such as nervousness or frustration, or cognitive variables, such as ability to focus attention on the task, may have led to the results seen in this Experiment, although we did not see any differences in participants' change in mood throughout the course of testing, as measured by self-report mood questionnaires.

GENERAL DISCUSSION

In Experiment 1 we demonstrated that tDCS can enhance object detection both when viewing images which had been repeated from training and when generalizing information during training to object detection in novel images. Behavioral results in this Experiment were not consistent with behavioral results obtained from participants who were tested in an MRI. In Experiments 2 and 3 we found that this was likely the result of participants' inability to perform the task in the MRI scanner environment, due to differences between the MRI and workstation environments such as visual angle of the images and ambient light and sound. It is evident from the results of these 3 experiments that the effects of tDCS on object detection are genuine and replicable.

The physiological effects of anodal tDCS are thought to include increased excitability in the neocortex (Liebetanz et al., 2002). This hypothesis supported by our recent findings of increased glutamatergic activity with anodal tDCS (Clark et al 2011). Therefore, it is possible that anodal tDCS in this study enhanced activity in specific brain regions, which may have facilitated the cognitive functions that support performance of this task, such as object recognition and attention, or may also have facilitated learning. Increased glutamatergic levels could have resulted in enhanced memory formation through a Hebbian mechanism in which cells become more readily active in a synchronous manner (Kelso et al., 1986; Kirkwood & Bear, 1994; Song et al., 2000).

Enhancing the excitability of the right frontal cortex could facilitate image detection performance for several reasons: Lateral frontal cortex has been suggested by Posner and Peterson (1990) to be a key component of the fronto-parietal attention network, a brain network active in attention requisition during target detection. Greater attention requisition

during visual search may lead to a greater probability of noticing objects in the images, enhanced encoding of the image and, therefore, greater accuracy. While we targeted the right frontal cortex, it is unlikely that tDCS resulted in focal stimulation of this area of the brain. While there are no modeling studies that simulate the placement of the anode on the right frontal cortex with a cathode on the left upper arm, other studies indicate that even with two electrodes placed on the scalp the stimulation is diffuse and unpredictable (Sadleir et al., 2010; Datta et al., 2009; Wagner et al., 2007; Miranda et al., 2009). Realistic, finite element, head models suggest that a large fraction of the current passes into the brain via low resistance paths including the orbits and nose (Sadleir et al., 2010). While there are no currently accepted empirically-based methods to identify the precise path of tDCS current through the brain, magnetic resonance spectroscopy based methods to image tDCS induced changes in glutamatergic activity and other metabolites are currently being developed (Clark et al 2011). This may help to better understand the brain networks and cognitive functions most affected by tDCS.

CONCLUSION

In summary, tDCS produced a dose-dependent increase in the accuracy of image classification for hidden objects after training, which was not related to the amount of skin sensation and was not different between single- and double-blind experimental designs. This was greatest for test images containing objects, which were also presented during training, although tDCS also facilitated detection of objects hidden in novel images and classification of images without objects. The replication of these effects across experiments indicates that tDCS enhanced recognition memory for training images facilitated object recognition during testing. Interestingly, effects of tDCS were not present when participants were trained or tested in an MRI environment, though this was found to be the result of general inability to perform the task in the scanner. This process involved in tDCS enchantment of object detection in these Experiments may be due to the alteration of some combination of attentional, perceptual, visual search, memory encoding or retrieval processes by tDCS, although we have insufficient data at present to determine which of these processes may be involved. What we can determine is that tDCS can have large effects of learning. The effects of tDCS on specific neural and cognitive processes are being examined in additional studies.

REFERENCES

Antal A, Nitsche MA, Kincses, TZ, Kruse W, Hoffmann KP, & Paulus W (2004) Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans. *European Journal of Neuroscience* **19**: 2888–2892.

Antal A, Brepohl N, Poreisz C, Boros K, Csifcsak G, & Paulus W (2008a) Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clinical Journal of Pain* **24**:56-63.

Antal A & Paulus W (2008b) Transcranial direct current stimulation and visual perception. *Perception* **37**:367-374.

Benedikt, M (1868). Elektrotherapie. Tendler

Bikson M et al (2004) Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *The Journal of Physiology* **557**:175-179.

Boggio PS et al (2006) Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. *Neuroscience Letters* **404**:232-236.

Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, & Fregni F. (2006) Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *Journal of Neurological Science* **249**:31-38.

Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, & Fregni F (2007) Repeated sessions of noninvasive brain DC stimulation is associated with motor

function improvement in stroke patients. *Restorative Neurology and Neuroscience* **25**:123-129.

Boggio PS et al (2008a) A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology* **11**:249-254.

Boggio PS, Rocha RR, da Silva MT, & Fregni F (2008b) Differential modulatory effects of transcranial direct current stimulation on a facial expression go-no-go task in males and females. *Neuroscience Letters* 447:101-105.

Boggio PS et al (2008c). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind, sham-controlled study. *Drug and Alcohol Dependence* **92**:55-60.

Boggio PS, Zaghi S, Lopes M, Fregni F. (2008d). Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *European Journal of Neurology* **15**:1124-1130.

Boggio PS, Zaghi S, Fregni F. (2009a). Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). *Neuropsychologia* **47**:212-217.

Boggio PS, Liguori P, Sultani N, Rezende L, Fecteau S, Fregni F. (2009b). Cumulative priming effects of cortical stimulation on smoking cue-induced craving. *Neuroscience Letters* **463**:82-86.

Boggio PS, Khoury LP, Martins DC, Martins OE, de Macedo EC, Fregni F. (2009c). Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. *Journal of Neurology Neurosurgery and Psychiatry* **80**:444-447.

Buchanan TW & Lovallo WR (2001). Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology* **26**:307-317.

Chadaide Z, Arlt S, Antal A, Nitsche MA, Lang N, & Paulus W (2007) Transcranial direct current stimulation reveals inhibitory deficiency in migraine. *Cephalalgia* **27**:833-839.

Chakeres DW, Bornstein R, & Kangarlu A (2003) Randomized comparison of cognitive function in humans at 0 and 8 Tesla. *Journal of Magnetic Resonance Imaging* **18:**342-345.

Clark VP et al (2010) tDCS guided using fMRI significantly accelerates learning to identify concealed objects. *Neuroimage* in press doi:10.1016/j.neuroimage.2010.11.036

Clark VP, Coffman BA, Trumbo MC, Gasparovic C (2011) Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: A 1H magnetic resonance spectroscopy study. *Neuroscience Letters* **500**:67-71.

Datta A, Bansal V, Diaz J, Patel J, Reato D, & Bikson M (2009) Gyri-precise head model of transcranial DC stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimulation* **2**:201-207.

De Vocht F, Stevens T, Glover P, Sunderland A, Gowland P, & Kromhout H (2007) Cognitive effects of head-movements in stray fields generated by a 7 Tesla whole-body MRI magnet. *Bioelectromagnetics* **28**:247-255.

Dieckhofer A, Waberski TD, Nitsche M, Paulus W, Buchner H, & Gobbele R (2006) Transcranial direct current stimulation applied over the somatosensory cortex - differential effect on low and high frequency SEPs. *Clinical Neurophysiology* **117:**2221-2227.

Dreyer C & Nel C (2003) Teaching reading strategies and reading comprehension within a technology-enhanced learning environment. *System* **31**:349–365.

Drew AS, & van Donkelaar P (2007) The contribution of the human FEF and SEF to smooth pursuit initiation. *Cerebral Cortex* **17**:2618-2624.

Erikson, G. C. (1985). The effects of caffeine on memory for word lists. *Physiology & Behavior* **35:** 47-51.

Faria P, Leal A, & Miranda PC (2009) Comparing different electrode configurations using the 10-10 international system in tDCS: a finite element model analysis. *Engineering in Medicine and Biology Society: Conference Proceedings of the IEEE* **2009**:1596-1599.

Fertonani A, Rosini S, Cotelli M, Rossini PM, & Miniussi C (2010) Naming facilitation induced by transcranial direct current stimulation. *Behavioral Brain Research* **208**:311-318.

Fitzgerald PB, Fountain S, & Daskalakis ZJ (2006) A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology* **117**:2584-2596.

Floel A, Rosser N, Michka O, Knecht S, & Breitenstein C (2008) Noninvasive brain stimulation improves language learning. *Journal of Cognitive Neuroscience* **20**:1415-1422.

Fregni F et al. (2006). A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* **122**:197–209.

Furubayashi T et al. (2008) Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. *Experimental Brain Research* 185:279–286.

Galea JM & Celnik P (2009) Brain polarization enhances the formation and retention of motor memories. *Journal of Neurophysiology* **102**:294-301.

Gandiga PC, Hummel FC, & Cohen LG (2006) Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology* **117**:845–850.

Glover PM & Bowtell R (2007) Measurement of electric fields due to time-varying magnetic field gradients using dipole probes. *Physics in Medicine and Biology* **52:**5119-5130.

Hecht D (2010) Transcranial direct current stimulation in the treatment of anorexia. *Medical Hypotheses* **74**:1044-1047.

Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, & Wassermann EM (2005) Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology* **64**:872-875.

Kelso SR, Ganong AH, & Brown TH (1986) Hebbian synapses in hippocampus. *PNAS* **83**:5326-5330.

Kirkwood A & Bear MF (1994) Hebbian synapses in visual cortex. *Journal of Neuroscience* **14**:1634-1645

Ko MH, Han SH, Park SH, Seo JH, & Kim YH (2008) Improvement of visual scanning after DC brain polarization of parietal cortex in stroke patients with spatial neglect. *Neuroscience Letters* **448**:171-174.

LaBar KS & Cabeza R (2006) Cognitive neuroscience of emotional memory. *Nature Reviews Neuroscience* **7**:54–64.

Liebetanz D, Nitsche MA, Tergau F, & Paulus W (2002) Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain* **125**:2238-2247.

Liebetanz D et al (2006) Anticonvulsant effects of transcranial direct-current stimulation (tDCS) in the rat cortical ramp model of focal epilepsy. *Epilepsia* **47**:1216-1224.

MacMillan J et al. (2005) DARWARS: An Architecture That Supports Effective Experiential Training. DARWARS Research Papers, http://www. darwars. com/downloads/2005% 20IITSEC% 20White% 20Paper% 20v2. pdf

Marshall L, Molle M, Hallschmid M, & Born J (2004) Transcranial direct current stimulation during sleep improves declarative memory. *Journal of Neuroscience* **24**:9985-9992.

McGaugh JL (1989) Dissociating learning and performance: drug and hormone enhancement of memory storage. *Brain Research Bulletin* **23**:339–345.

Medin DL & Schaffer MM (1978) Context theory ofclassification learning. *Psychology Review* **85**:207-238.

Medin DL & Smith EE (1981) Strategies and classification learning. *Journal of Experimental Psychology: Human Learning and Memory* **7**.241-253

Medin DL, Altom MW, Edelson SM, & Freko D (1982) Correlated symptoms and simulated medical classification. *Journal of Experimental Psychology: Learning, Memory, & Cognition* **8**:37-50.

Medin DL, Dewey GI, & Murphy TD (1983) Relationships between item and category learning: Evidence that abstraction is not automatic. *Journal of Experimental Psychology: Learning, Memory, & Cognition* **9**:607-625.

Medin DL & Florian JE (1992) Abstraction and selective coding in exemplar-based models of categorization. In A. Healy, S. Kosslyn, & R. Shiffrin (Eds.), From Learning

Processes to Cognitive Processes: Essays in Honor of William K. Estes (Vol. 2, pp. 207-234). Hillsdale, NJ: Erlbaum

Merzagora AC et al (2010) Prefrontal hemodynamic changes produced by anodal direct current stimulation. *Neuroimage* **49**:2304-2310.

Miranda PC, Faria P, & Hallett M (2009) What does the ratio of injected current to electrode area tell us about current density in the brain during tDCS? *Clinical Neurophysiology* **120**:1183-1187.

Mori F et al (2010) Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. *The Journal of Pain* **11:**436-442.

Nitsche MA et al (2003) Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *Journal of Physiology* **553**:293-301.

Nitsche MA et al (2008) Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation* **1**:206–223.

Nosofsky RM (1984) Choice, similarity, and the context theory of classification. *Journal of Experimental Psychology: Learning. Memory, and Cognition* **10**. 104-114.

Nosofsky RM, Palmeri TJ, & McKinley SC (1994) Rule-plus-exception model of classification learning. *Psychology Review* **101**:53-79.

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* **9**:97–113.

Pascual-Leone A, Davey N, Rothwell J, Wassermann EM, Puri BK (2002) Handbook of Transcranial Magnetic Stimulation. New York: Oxford

Paulus W (2004) Outlasting excitability shifts induced by direct current stimulation of the human brain. *Supplementary Clinical Neurophysiology* **57**:708-714.

Poreisz C, Boros K, Antal A, & Paulus W (2007) Safety aspects of transcranial direct current stimulation concerning healthy participants and patients. *Brain Research Bulletin* **72**:208–214.

Posner MI & Petersen SE (1990) The attention system of the human brain. *Annual Review of Neuroscience* **13**:25–42

Radman T, Ramos RL, Brumberg JC, & Bikson M (2009) Role of Cortical Cell Type and Morphology in Sub- and Suprathreshold Uniform Electric Field Stimulation. *Brain Stimulation* **2**:215-228.

Ragert P, Vandermeeren Y, Camus M, & Cohen LG (2008) Improvement of spatial tactile acuity by transcranial direct current stimulation. *Clinical Neurophysiology* **119**:805–811

Reed SK (1972) Pattern recognition and categorization. *Cognitive Psychology* **3**:382-407

Reis J et al. (2008) Consensus: Can transcranial direct current stimulation and transcranial magnetic stimulation enhance motor learning and memory formation? *Brain Stimulation* **1**:363-369

Reis J et al. (2009) Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *PNAS* **106**:1590-1595

Rigonatti SP et al. (2008) Transcranial direct stimulation and fluoxetine for the treatment of depression. *European Psychiatry: Journal of the Association of European Psychiatrists* **23**:74-76

Routtenberg, A., Cantallops, I., Zaffuto, S., Serrano, P., & Namgung, U. (2000). Enhanced learning after genetic overexpression of a brain growth protein. *PNAS* **97:**7657-7662.

Sadleir RJ, Vannorsdall TD, Schretlen DJ, & Gordon B (2010) Transcranial direct current stimulation (tDCS) in a realistic head model. *NeuroImage* **51**:1310-1318

Smith SM (1988) Environmental context—dependent memory. In Davies, GM & Thomson, DM (Ed), Memory in context: Context in memory. Oxford, England

Smith SM (1994) Theoretical principles of context-dependent memory. In Morris P & Gruneberg M (Eds.), Theoretical aspects of memory. New York: Routledge

Smith SM & Vela E (2001) Environmental context-dependent memory: A review and meta-analysis. *Psychonomic Bulletin & Review* **8**:203-220.

Snellen, H. (1862) Test-Types for Determination of the Acuteness of Vision. *Utrecht, van de Weijer*

Song S, Miller KD, & Abbott LF (2000) Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. *Nature Neuroscience* **3**:919–926

Stagg CJ et al (2009) Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *Journal of Neuroscience* **29**:5202-5206.

Sweetland J, Kertesz A, Prato FS, & Nantau K (1987) The effect of magnetic resonance imaging on human cognition. *Magnetic Resonance Imaging* **5:**129-135.

Todd G, Flavel SC, & Ridding MC (2006) Low-intensity repetitive transcranial magnetic stimulation decreases motor cortical excitability in humans. *Journal of Applied Physiology* **101**:500-505.

Tang YP et al. (1999). Genetic enhancement of learning and memory in mice. *Nature* **401**:63–69.

Volkow ND et al (2000) Resting brain metabolic activity in a 4 tesla magnetic field. *Magnetic Resonance in Medicine* **44:**701-705.

Volkow ND et al. (2010) Effects of low-field magnetic stimulation on brain glucose metabolism. *NeuroImage* **51**:623–628.

Webster BR, Celnik PA, & Cohen LG (2006) Noninvasive brain stimulation in stroke rehabilitation. *NeuroRx* **3**:474–481

Wagner T, Valero-Cabre´ A, & Pascual-Leone A. (2007) Noninvasive human brain stimulation. *Annual Review of Biomed Engineering* **9**:527–565