7-12-2014

INCREASING YOUR BRAIN POTENTIAL: TRANSCRANIAL DIRECT CURRENT STIMULATION FOR ENHANCEMENT OF BEHAVIOR AND EVENT-RELATED POTENTIALS IN TESTS OF ATTENTION AND IMPUSLIVITY

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by

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DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
Psychology

The University of New Mexico
Albuquerque, New Mexico

May, 2014

DEDICATION

I dedicate this dissertation,

all of my endeavors,

and my very being,

to the love of my life,

Robyn Coffman.

I could never have done it without you, Button.

ACKNOWLEDGEMENTS

I would like to acknowledge Vincent P. Clark, my Advisor and Dissertation Chair, who allowed me the opportunity to learn about the most fascinating organ in the body and who always encouraged me to pursue my interests. The guidance provided by Dr. Clark has undoubtedly influenced the way I will mentor others in the future.

I also thank Julia M. Stephen, my mentor and a member of the dissertation committee, who believed in me when others did not, and taught me that I can solve any problem that I put my mind to. In working with Dr. Stephen, I have gained education not only on the many technical and conceptual skills I have learned, but in the extent of my ability as well.

I thank dissertation committee members Eric Ruthruff for providing assistance with many of the pitfalls I have encountered and Piyadassa Kodituwakku for providing insight to many of the questions I have had along the way.

I extend my gratitude to the National Institute of Drug Abuse and Addiction (NIAAA), who provided funding for this project by a Ruth L. Kirschstein National Research Service Award for Individual Predoctoral Fellows (NRSA-F31).

Also to the undergraduate research assistants, Krista Kolodziejski, Bryce Lockmiller, Omar Khan, Tristan Collar, Athena Mayen, and Isabella Estrada, all of whom aided in data collection and preliminary data processing and to my fellow graduate students, Michael Hunter, Michael Trumbo, and Aaron Jones who were always willing to listen to my latest ideas.

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

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ABSTRACT

Cognitive control of attention and decision making is a defining feature of the human intellect. Our ancestors' survival in the past and our success as individuals today is reliant on our ability to respond to stimuli in the environment, learn from our mistakes, and make complex decisions based on cognitive deliberation, rather than impulsiveness. This study examined the effectiveness of Transcranial Direct Current Stimulation (tDCS) for modulation of cognitive control of attention and impulsiveness. It was hypothesized that anodal tDCS of the right VLPFC would enhance cognitive control of attention and impulsiveness, that tDCS would enhance ERP responses related to cognitive control, and that both tDCS conditions would exhibit effects in these domains. Each of these hypotheses was supported by the results of this study, though there are caveats to the interpretation of these findings and further research is warranted. Despite these limitations, basic scientific and clinical implications of this research are significant. This study lends further support to the role of right VLPFC in cognitive control, demonstrates the effectiveness of tDCS for modulation of cognitive control, and suggests an effect of tDCS on impulsive decision making that may be related to effects on cognitive control of attention.

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CHAPTER 1: INTRODUCTION

Cognitive Control of Attention and Impulsivity

The complexity of the human brain is astounding. It decodes our sensory input, drives our behavior, understands and creates language, solves problems, learns from the past, predicts the future, spawns new ideas, and falls in love. This list only touches on the wonders performed by the nearly 100 billion neurons that compose our very being. The astounding complexity of this system, though metabolically costly, has been selected because it has proven adaptive in a very special way. Human beings have the sophisticated ability to adjust behavior to fit the changing demands of the environment using cognitive flexibility and problem solving. We change our behavior dynamically to accommodate current demands and plan for predicted future circumstances. We do this by using past experience to predict outcomes of behavioral choices within the current sensory context and decide what, if any, behavior is relevant (e.g., Montague, King-Casas, & Cohen, 2006). This complex prediction and decision-making process has become highly refined throughout the rapid evolution of the brain, and, in particular, in the prefrontal cortex (Roth & Dicke, 2005; Miller & Cohen, 2001).

Making successful decisions can be difficult, and attention to detail is important. What is the current situation? How does it compare to previous experience? What was the outcome of previous decisions in such situations? These questions can take considerable mental effort to answer, and the ability to focus during the decision making process is vital to successful problem solving (Douglas, 1972; Hollenbeck *et al.*, 1995). Attention/working memory capacity is known to mediate decision-making and problem solving in humans (Engle, 2002) and is involved in all realms of cognition. It is also one of the most controversial topics in Cognitive Psychology due

to the nature of what, if anything, controls attention. In the Baddley and Hitch model of working memory (1974), the term "central executive" is used to describe a system of attentional control of behavior. Posner and Snyder (1975) refer to a similar system called "cognitive control" which directs, sustains, and focuses attention. This control mechanism may be intuitive as a concept, but it is difficult to operationalize. Some researchers have used dual-task conditions, assessing the ability to focus attention on multiple events simultaneously (e.g., Norman & Shallace, 1986; Della Sala & Logie, 1993; Logan & Gordon, 2001). Others have used sensory competition as a means of assessing this control mechanism, where one stimulus is meant to be ignored and the other attended (i.e. dichotic listening or flanker tasks) (Conway, Cowan, & Bunting, 2001; Botvinick *et al.*, 1999). Perhaps the most common task type, called the go/no-go task, involves sustained, repetitive responding to frequently occurring stimuli, with occasional withholding of responses to select stimuli. There are many varieties of the go/no-go task, each tailored for sensitivity to different aspects of attention, such as ability to control the spatial direction of attention, speed of attention control, endurance of attention control, or stimulus salience (how well external events can drive attention or exogenous orienting).

In nearly all varieties of go/no-go tasks, electroencephalography (EEG) has been widely used to characterize electrophysiological brain responses associated with attention and cognitive control. One EEG measure in particular, an event-related potential (ERP) called the P3, is arguably one of the most well-characterized EEG responses in the literature (for a review, see Friedman, Cycowicz, & Gaeta, 2001). The P3 is a positive voltage deflection in the ERP waveform peaking at a latency of about 300 – 400 ms after stimulus onset, depending on the stimulus modality and other task specifics; however, the defining factor of this response is the task condition by which it is elicited. The iconic P3 response is found in tasks where participants

attend to and discriminate different types of stimuli, and was first reported nearly 50 years ago in *Science* by Sutton et al. (1965). The authors measured brain responses to cued light flashes and auditory clicks using only a single electrode, and recorded the responses on magnetic tape. By varying the probabilities of flash/click occurrence by cue presentation, they discovered a positive deflection in the EEG signal following stimuli with low predictability. This deflection was later termed the P3 response. Early explanations of the P3 were focused on the sensitivity of the response to the uncertainty of prediction, but recent evidence has suggested that the story is more complex. Current explanations of the P3 suggest that it is related to information processing mechanisms and cognitive control (Polich, 2007). The P3 response is sensitive to task-driven effects on signal detection, indicating its role in information processing (Polich, 2007), and it has been linked to endogenous attentional factors, indicating its role in cognitive control (Polich & Kok, 1995).

The Fixed Sustained Attention to Response Task (F-SART) is particularly well-suited for the evaluation of cognitive control over attention. In this task, like other go/no-go tasks, participants respond to frequently occurring "Go" stimuli, while withholding response to the infrequently occurring "No-Go" stimuli. Like many of the other go/no-go spinoffs, temporal cues are incorporated in the task, but the defining feature of this version is the way in which cues are presented (Robertson *et al.,* 1997). Many other temporal cuing tasks (such as the attention networks test) use single cues with short-duration stimulus onset asynchrony (SOA) around 100 ms (Fan *et al.,* 2002). This is thought to initiate attentional control, preparing a response that may or may not be adaptive in the current task. In the F-SART, stimuli are single-digits (1-9) that are displayed visually, in sequence. Therefore, attention to detail changes rhythmically and cyclically, rather than abruptly and randomly. The F-SART is often paired with the random

SART (R-SART), where order of the stimuli is randomized, changing the task into a simple go/no-go paradigm, and allowing concurrent investigation of standard go/no-go response inhibition measures (Zordan, Sarlo, & Stablum, 2008).

The cyclic, predictable nature of the F-SART allows one to track the regulation of attentional control over the course of the 1-9 number sequence. This is most evident in electroencephalography data from the F-SART, showing modulation of a variety of attentional variables that differ by specific numbers in the sequence (Dockree *et al.,* 2005). ERP components related to cognitive control of attention in the F-SART are closely related to the well-known N2 or N200 that is commonly found in go/no-go tasks. N2 response amplitude is thought to reflect conflict monitoring in the prefrontal cortex and is highly correlated with attention, and the response is higher for stimuli leading up to the "No-Go" trial in this task (Dockree *et al.,* 2005). The N2 response was first proposed as a measure of response inhibition due to its concurrence with response inhibition in go/no-go tasks (Jodo & Kayama, 1992); however, Donkers and van Boxtel (2004) recently found that the N2 reflects change in task demands, as it is also elicited when the goal is response change rather than inhibition. Additionally, the N2 has been found to become more pronounced with increased effort on a cognitive task, such as the stop-signal paradigm (van Boxtel *et al.*, 2001). When conflict is predictable by specific cues, the N2 response to conflict is reduced (Correa, Rao, & Nombre, 2008). In the F-SART the response inhibition trial is easily predictable, so N2 response is decreased (Dockree *et al.,* 2005).

Importantly, the N2 response is correlated with the relevance of a stimulus to task-related goals in studies of decision making in healthy and abnormal cognitive control (Folstein & Van

Petten, 2008). When cognitive control is absent or insufficient, an intuitive/instinctual response might be made rather than one made from careful consideration of the problem. Though instinctual responses are vital when time is short, such as when a threat to survival is detected in the visual field, cognitive decision making is important when complex problems are encountered. Instinctual decision making in this later case is maladaptive. Impulsiveness can be broadly defined as intuitive decision making when deliberative decision making is favorable (Slovic & Peters, 2006). It has been related to cognitive ability (Dohmen *et al.,* 2010) and personality traits (Patton & Stanford, 1995). Within this larger domain, impulsiveness is often studied within one of three classes of impulsive behavior, all of which are related in some way to a deficit in cognitive control.

The most basic of these classes is motor impulsiveness, and is often studied using the go/no-go task described above. Motor impulsiveness, or lack of motor inhibition, occurs when an individual is unable to sustain or dynamically activate cognitive control to inhibit a response within a given time interval (Patton & Stanford, 1995). This type of impulsiveness is very closely related to cognitive control of attention to uncertainty of events, and is measured using similar methods, such as the N2 and P3 ERPs (Ruchsow *et al.,* 2008).

The second class is impatience, or low self-control, which occurs when an individual is unable to delay gratification in some way. This type of impulsiveness is thought to result not from inability to withhold a practiced motor response, but from an inability to sustain cognitive control over internal drives toward immediate gratification. The clearest example of this type of behavior is evident through delay discounting tasks (i.e. Ainslie, 1975; Green & Myerson, 1993; Rachlin & Green, 1972), where participants consistently show devaluation of delayed compared

to immediate outcomes. McClure and colleagues (2004) reported a very influential fMRI result, where brain areas involved in cognitive control were preferentially activated by delayed versus immediate monetary rewards in a gambling task (Ernst *et al.*, 2004). Impatience is somewhat more complex than motor impulsiveness. It involves attention to the process of decision making, rather than attention to the sensory environment, and can be conceptualized as cognitive control over internalized attention.

The third general class of impulsiveness, non-planning impulsiveness, or low risk-adjustment, is often assessed with a probabilistic discounting task, where higher value is placed on outcomes with high likelihood compared to the unpredictable (Richards *et al.*, 1999). This type of impulsiveness is common in problem gamblers (Holt, Green, & Moyerson, 2003). Non-planning impulsiveness is the result of a deficit in predictive modeling. It is not simply a bias in risk preference (i.e., risk aversion or risk seeking), though these are factors in this type of behavior; rather, non-planning impulsiveness is a continuum ranging from instrumental/economic risk taking to stimulating risk taking (Zaleskiewicz, 2001). An instrumental risk-taker is one who uses conscious, controlled deliberation of the choices, based on past experience, and minimizes the dependence of the outcome on chance. A stimulating risk-taker uses a more instinctual strategy, relying on short-term assessment of sensation level and excitement from the decision (Zaleskiewicz, 2001). Non-planning impulsiveness is correlated with reward versus punishment responsiveness in healthy and clinical populations, where negative outcomes are more salient for a stimulating risk-taker, and positive outcomes are more salient for an instrumental risk-taker (Tom *et al.*, 2007). This type of impulsiveness is the most complex, and is quite different from the other two. While motor impulsiveness and impatience are related to cognitive control at the level of the individual event, it can be argued that non-

planning impulsiveness is related to reward responsiveness across the course of experience with a task and perhaps throughout life (Evenden, 1999).

Interestingly, both self-control and risk-adjustment are correlated with responsiveness to feedback in gambling tasks. In addition, delay and probability discounting are negatively correlated with each other, and these measures are both correlated with cognitive control, suggesting the cognitive control of reward responsiveness may be a common thread between the two (Richards *et al.,* 1999; Reynolds *et al.,* 2003). Two separate ERP responses are relevant in the assessment of responsiveness to wins and losses: the medial-frontal negativity (MFN) is an amplified N2 response to losses compared to wins, and the win-loss positivity is a differential P3 response to positive vs. negative feedback, termed the P3b. The MFN is sensitive to violations of expected reward probability (Potts *et al.,* 2006; Hajcak *et al.,* 2007) and has even been found when participants watch others receiving feedback on a task (Yu & Zhou, 2006). The P3b is generally found in response to reward (Holroyd, Krigolson, & Lee, 2011) and has been related to general sensitivity to reward and punishment (Lole *et al.,* 2013). In general, the MFN is thought to reflect the attention to and internalization of feedback for later risk assessment, while the P3b is related to individual variance in subjective responsiveness to losses versus wins and, therefore, may differentiate stimulating versus instrumental risk-takers. Both of these responses, however, have been related to motivation to succeed in the task (Yeung, Holroyd, & Cohen, 2005). Additionally, both of these responses are enhanced when the outcome results from an action performed by the participant, suggesting that they are related to the decision making process (Zhou, Yu, & Zhou, 2010).

The Cambridge Gambling Task (CGT) is well-suited for the behavioral examination of impatience and non-planning impulsiveness, as it incorporates both delay discounting and probabilistic discounting measures (Rogers *et al.,* 1999). Unfortunately, the CGT uses stimuli and a response style that are not compatible with EEG. A task similar to both the CGT and Iowa gambling task was recently developed for use in EEG by Van Leijenhorst and colleagues (2008); however, this task was developed for small children and uses a restricted range of available probabilities and delays. To limit eye movement (in the yaw and pitch directions) and touch-screen related limb movement while maintaining the probability assessment/binary *selection* of outcome prediction, delay-based confidence determination by point *wager*, and outcome/feedback *evaluation* which characterize the CGT, the Select, Wager, and Evaluate, Electroencephalography-Tailored, Yaw- and Pitch-Invariant (SWEETYPI) gambling task was developed for use in this study.

Enhancement of Cognitive Control

In recent years, fMRI research has suggested a network of cortical areas subserving the implementation of cognitive control. Though specifics are still a matter of debate, cognitive control is generally thought to be mediated by orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), medial frontal cortex (MFC), and ventrolateral prefrontal cortex (VLPFC) (Hopfinger, Buonocore, & Mangun, 2000; Krain *et al.,* 2006, Cole & Schneider, 2007). MFC activity, including the anterior cingulate cortex (ACC), is generally associated with conflict monitoring and alerting of attention by external stimuli (Rushworth *et al.,* 2004). Activity in this region is linked to the MFN response to unexpected losses in gambling tasks (Herrmann *et al.,* 2004; van Noordt & Segalowitz, 2012). Orbitofrontal regions (as well as with anterior temporal lobes) have been linked to stimulus-reward association and memory retrieval processes involved

with outcome prediction and response selection (Young & Shapiro, 2011). This is not surprising, given the spatial proximity of this region to the hippocampal structures of the temporal lobe and the known involvement of OFC in emotional processing (Bechara, Damasio, & Damasio, 2000). DLPFC has often been linked with selection of the appropriate response and the maintenance of consistent responses over time (MacDonald *et al.*, 2000). Much of the cognitive control literature focuses on the role of DLPFC activity in response selection or the interaction between DLPFC (particularly right DLPFC) and parietal perceptual areas in visual attention (Huettel, Song, & McCarthy, 2005). VLPFC, in contrast, has received substantially less attention in the extant literature, though its role in the frontal cognitive control network is quite important. VLPFC is seen at times when a high level of control over attention and working memory are required in decision making, suggesting a role in direction and coordination of these other regions (Corbetta & Shulman, 2002). The VLPFC is seated in a perfect area for this, and is highly connected with the rest of the network, as well as sensory areas in the superior temporal lobes (Aron *et al.*, 2007). On the left, the VLPFC is most notably associated with language production and the generation of the internal monologue, while the right VLPFC has taken on the role of orchestrating non-verbal cognitive control (Levy & Wagner, 2011).

Cognitive control is impaired in many neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD; Barkley, 2005; Castellanos *et al.*, 2006), and fetal alcohol spectrum disorders (FASD; Fryer *et al.*, 2007). Enhancement of cognitive control can be achieved pharmacologically, using amphetamines such as methylphenidate (Campbell, Douglas, & Morgenstern, 1971); however, there are many undesirable side-effects that go along with the intended pharmacodynamic effects of these drugs (Barkley *et al.*, 1990). Brain stimulation is a fast-emerging method for non-pharmacological treatment of brain dysfunction and shows

promise for treatment of disorders such as depression and tinnitus (Boggio *et al.*, 2008; Garin *et al.*, 2011). Interestingly, enhancement of cognitive control has been reported with electrical stimulation of frontal cortical areas using transcranial direct current stimulation (tDCS). In the first study to report this type of effect, only 10 minutes of anodal tDCS of the left DLPFC resulted in significantly fewer false alarms and greater number of correct responses in a 3-back working memory task, where participants continuously maintain and update items held in working memory (Fregni *et al.*, 2005). Due to the many possible clinical applications of working memory enhancement, new research began investigating the application of tDCS to ameliorate cognitive dysfunction associated with neurological and psychological disorders. One such study investigating the use of tDCS for the treatment of working memory deficits associated with Parkinson's disease (PD) was the first to use a current strength of 2.0 mA in a published research study (Boggio *et al.*, 2006).

Recent studies of tDCS effects on working memory have focused both on behavioral manipulation and the physiological bases of these effects. Research by Zaehle et al. (2011) characterized the effects of tDCS on working memory performance by measuring EEG responses. Anodal tDCS of the left DLPFC resulted in polarity-dependent changes (anodal increases and cathodal decreases) in EEG alpha and theta frequency over occipitotemporal regions, which has been previously implicated during learning and memory research, and is thought to reflect hippocampal-dependent learning processes in the brain (Cashdollar, Duncan, & Duzel, 2011). It should be noted that no behavioral effects of anodal or cathodal tDCS versus sham were seen in the Zaehle et al. study (2011), only effects of anodal versus cathodal stimulation. No other behavioral or neuroimaging studies of tDCS enhancement of working memory have utilized a reference electrode over the mastoid. Nonetheless, these results are

compelling and further research into the effects of tDCS using a mastoid reference electrode is warranted. In a recent study of the effects of tDCS on the N-back (2-back and 3-back) working memory task, Andrews et al. (2011) reported an interesting result, in which increased digit span (forward, but not backward) was found after anodal tDCS of the left DLPFC, but only when tDCS had been previously delivered concurrently with an N-back working memory test, as compared to tDCS alone or sham tDCS with N-back testing. In short, using tDCS with a working memory task subsequently increased cognitive control performance as assessed by a different working memory test.

TDCS effects on cognitive control of vigilant attention have been examined only recently. Nelson et al. (2013) had participants perform a simulated air traffic control task requiring them to detect infrequent collision paths of aircraft (targets) over a prolonged period of time (40 minutes) while not responding to the more frequent non-collision flight paths (non-targets). TDCS at 1 mA was applied for 10 minutes either to the left or right DLPFC and either early (10 minutes) or late (30 minutes) into the task. In addition to behavioral effects of tDCS, Nelson et al. (2013) also examined effects on cerebral blood velocity (using Transcranial Doppler Sonography) and cerebral oxygenation (using Near Infrared Spectroscopy). There was a significant decrement in vigilance over time on task in the sham condition, as reflected by a lower target detection rate, slower reaction times, and a reduction in blood flow velocity, which are typical effects seen in vigilance tasks (Helton *et al.*, 2010; Warm *et al.*, 2008). Active tDCS lead to an improvement in target detection rate, reduced decrement in blood flow velocity over time on task, and increased cerebral oxygenation. These results are encouraging with respect to the potential use of tDCS to mitigate performance decrements arising from the need to sustain attention over long periods of time. More recently, Gladwin et al. (2012) used anodal tDCS of

the left DLPFC to enhance selective attention in normal healthy participants. The authors of this study used a Sternberg task to evaluate selective attention and working memory in participants receiving anodal tDCS of the DLPFC. Anodal tDCS in this study improved reaction time only when the incorrect choice had been a distractor stimulus, indicating that effects of tDCS of the left DLPFC on working memory was mediated by an effect on cognitive control of response selection.

Related results were reported in a recent study of the effects of tDCS on alerting, orienting, and executive attention (Coffman *et al.*, 2012a), which found that alerting measures of the attention networks test (ANT) were enhanced more than an hour after anodal tDCS directed at right VLPFC. Alerting attention in the ANT refers to the advantage in response time when a temporal warning cue is presented; therefore, this effect indicates that responsiveness of attention to external temporal cues was enhanced in this study. The effects of tDCS were also related to enhancement of a feedback-based discovery learning task in this study, where participants showing greater enhancement of attention measures were also better able to detect objects hidden in a computerized virtual environment. Importantly, task performance increase was highly dependent on learning from positive and negative feedback. This effect on complex decision making about presence of hidden objects has now been shown in multiple tDCS studies, and further exploration of right VLPFC tDCS effects on different aspects of cognitive control and decision making are warranted (Clark *et al.*, 2012, Coffman *et al.*, 2012b, Falcone *et al.*, 2012, Bullard *et al.*, 2011).

The first peer-reviewed research studies examining tDCS effects on problem solving and decision making were published nearly seven years ago in two multinational collaborative papers

by Fecteau et al. (2007a, b). The authors of these two studies examined the effects of tDCS on impulsive behavior and found an interesting, but perplexing effect of tDCS using a left-right polarization method. Effects of tDCS were strongest when left and right DLPFC were simultaneously stimulated with opposite current polarity (anodal or cathodal), regardless of the direction of current polarity (Fecteau *et al.*, 2007a). No effects of tDCS were present during unilateral stimulation of the left or right DLPFC. Effects of tDCS in these studies were substantial. In the first study, an approximate 25% decrease in risk-taking measures was found when participants performed the Balloon Analog Risk Task (BART) during 2 mA tDCS (Fecteau *et al.*, 2007a). In their follow-up experiment using the same stimulation parameters with a different task, right anodal/left cathodal DLPFC stimulation again led to an approximate 25% decrease in impulsiveness measures (Fecteau *et al.*, 2007b). The task used in this study ("The Risk Task"; Rogers *et al.*, 1999) involves "gambling" on probabilistic outcomes by wagering points, similar to the CGT and SWEETYPI. Participants receiving right anodal/left cathodal DLPFC stimulation earned more than 800 points, while those receiving sham tDCS earned just over 550.

Effects of tDCS on motor impulsiveness were explored by Liron Jacobson and colleagues of Bar Ilan University in Isreal nearly four years later (Jacobson, Javitt, & Lavidor, 2011). The stop signal task used in this study is a variant of the go/no-go task, in that participants are required to respond to frequent stimuli and withhold responding to infrequent stimuli; however, in the stop signal task, a measure of the time needed to inhibit a committed response is calculated by presenting a "stop" (withhold response) cue at a variable delay after a "go" (respond) cue. In a result similar to findings by Fecteau et al. (2007b), the authors found a more than 10% (30 ms) decrease in the amount of time needed to inhibit responding when participants received 10 min

of 1 mA anodal tDCS of the right, but not left DLPFC. A year later, Jacobson published another study examining the neurophysiological correlates of this effect using EEG (Jacobson *et al.*, 2012). The authors found that theta power was significantly reduced following tDCS delivered using the same protocol as their previous study. This is particularly interesting given recent results by Lansbergen, Kenemans, & van Engeland (2007), who reported that lower theta power is associated with a higher probability of response inhibition. Taken together, these results suggest that stimulation of the right DLPFC may decrease theta band activation, resulting in greater response inhibition and less risky decision making.

Perhaps the clearest demonstration of tDCS enhancement of problem solving was published only three years ago by a group at the Centre for Mind in Sydney, Australia. In this study by Chi and Snyder (2011), participants performed "matchsticks math problems," a difficult task requiring divergent thinking. In a previous report, only 10% of participants were able to solve the second set of problems, which requires divergent thinking. In the Chi and Snyder study, 60% (12/20) of participants receiving about 17 min of 1.6 mA anodal tDCS of the right anterior temporal lobe were able to solve the problem in under 6 min, compared to 20% (4/20) of participants receiving 30 s sham tDCS, and 25% (5/20) of participants receiving tDCS over the left anterior temporal lobe. The large effect of stimulation in this study is likely related to combined modulation of excitability in the right anterior temporal lobe, associated with greater insight and divergent thinking, and the right VLPFC, associated with cognitive control of attention. Interestingly, the anode placement over right anterior temporal lobe is overlapping with that used in our studies of tDCS effects on cognitive control, implicating a common effect among these results. These findings and results from studies by Fecteau indicating greater reduction of impulsiveness with opposing bilateral tDCS, compared to unilateral anodal tDCS of

the right DLPFC, suggest a need to evaluate the effectiveness of unilateral anodal right VLPFC stimulation compared to opposing bilateral anodal right and cathodal left VLPFC stimulation.

Hypotheses

Based on these findings, four separate hypotheses were examined in the experiments reported herein: (1) Anodal tDCS of the right VLPFC enhances cognitive control of *attention*, as assessed by a multivariate comparison of behavioral measures obtained from the random and fixed versions of the SART; (2) Anodal tDCS of the right VLPFC enhances cognitive control of *impulsiveness*, as assessed by a multivariate comparison of behavioral measures obtained from the random SART and SWEETYPI; (3) Anodal tDCS of the right VLPFC enhances *ERP measures* of cognitive control in the random and fixed versions of the SART and the SWEETYPI. More specifically, it was predicted that P3 response would be enhanced for "No-Go" stimuli in the random SART, N2 response would be enhanced for numbers leading up to the "No-Go" stimulus in the fixed SART (stimuli with the greatest attentional salience), and MFN and/or win-loss P3 would be enhanced in response to feedback in the SWEETYPI; and (4) As anodal stimulation of right frontal lobes is thought to be the primary driving factor of these effects, it was hypothesized that *both unilateral stimulation* (anodal stimulation of right VLPFC) *and bilateral stimulation* (anodal stimulation of the right and cathodal stimulation of the left VLPFC) would be effective for the enhancement of cognitive control using the measures described in the first three hypotheses.

CHAPTER 2: METHODS

Participants

Inclusion/Exclusion Criteria

All participants included in this study met the following criteria (based on self-report): (1) 18-30 years old; (2) English-speaking; (3) no history of head injuries or concussions resulting in loss of consciousness for more than 5 minutes; (4) right-handedness as determined by the Edinburgh Handedness Inventory (Oldfield, 1971); (5) good or corrected vision and hearing; (6) no known exposure to alcohol or other substances prenatally; and (7) no history of major psychiatric, substance use, neurological (e.g. epilepsy), or neurodevelopmental disorders (e.g. dyslexia).

Descriptive Statistics

Forty-three participants met the inclusion criteria, gave written informed consent, and participated in this study. Fourteen of these participants were excluded due to equipment malfunction, high sensation during tDCS, not following instructions in the SART, performance (average reaction time) greater than three standard deviations from the mean in two or more blocks of the SART, or performance (number of strikes) greater than three standard deviations from the mean in all three blocks of the SWEETYPI gambling task (Table 1). Participant demographic information is presented in Table 2. All participants were recruited via the UNM psychology department research credit system.

	Equipment Malfunction	High Sensation	Not Following Instructions	Outliers	Total
Active (A)	1	1	0	2	***4***
Active (B)	4	3	0	0	***7***
Sham	1	0	1	1	***3***

Table 1. Participant exclusions listed by tDCS group

	N	# Males	Age ($\bar{X}$±SD)
Active (A)	11	2	20.9 ± 3.2
Active (B)	6	0	22.1 ± 3.4
Sham	12	3	20.2 ± 1.9

Table 2. Participant demographics by tDCS group. Differences in gender and mean age were not statistically significant by χ^2 and *t*-tests, respectively.

Procedures

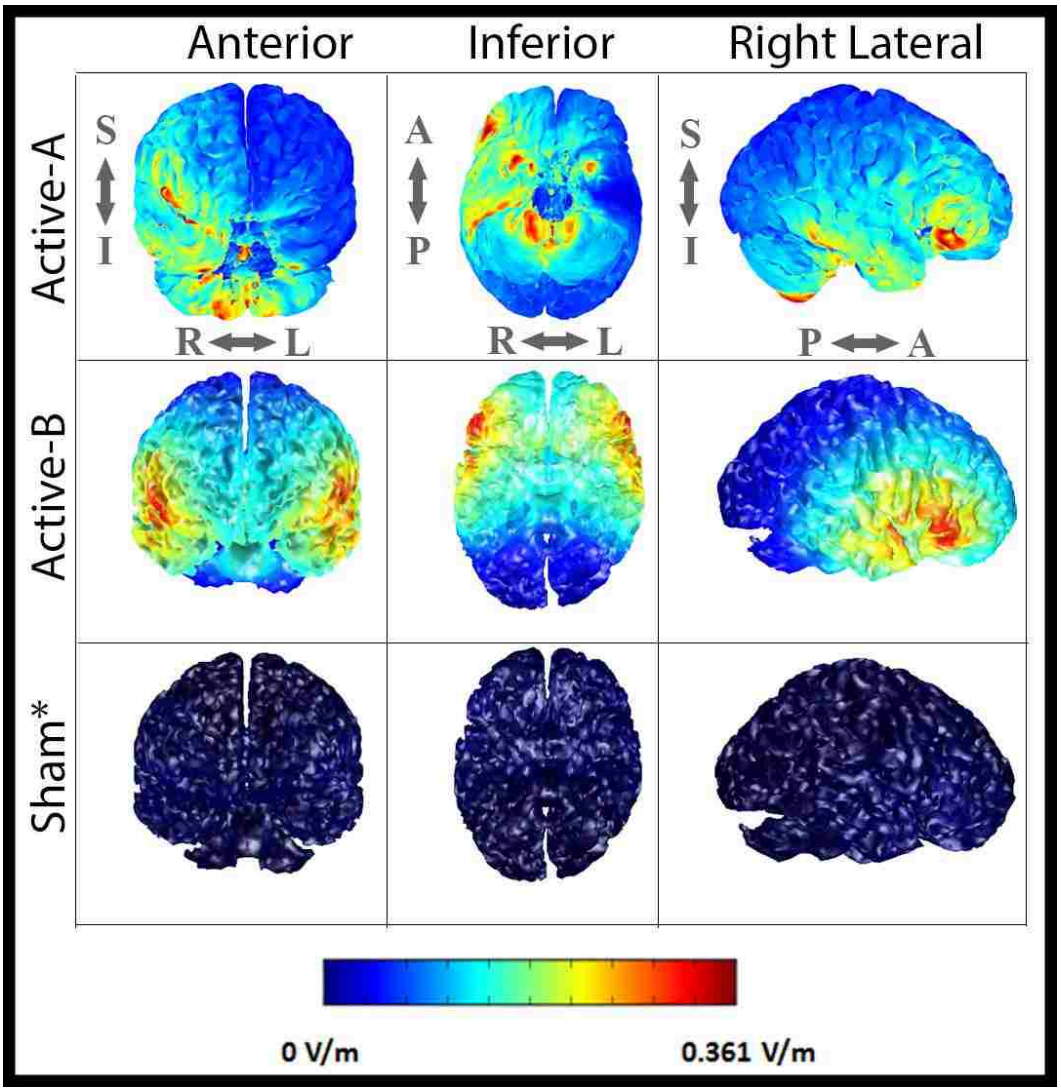
Transcranial Direct Current Stimulation

The effects of anodal tDCS over right VLPFC were examined using a randomized, double-blind, placebo-controlled experimental design, wherein participants were randomly assigned to one of two tDCS current strengths (0.1 mA or 2.0 mA) and one of two cathode placements (over left VLPFC or over the left bicep). This resulted in three experimental groups: two active tDCS groups, each with different cathode placement [Active-A (arm cathode) & Active-B (head cathode); 2.0 mA current], and one placebo group (Sham; 0.1 mA current), collapsed across cathode placement over either left VLPFC or the left bicep. See Table 2 for descriptive statistics. In each of the three groups, anodal tDCS was delivered for 30 minutes near

10-10 EEG location F10, over the right sphenoid bone and right VLPFC. The anode location was suggested from previous studies by our lab, demonstrating changes in attention and motor impulsiveness with tDCS anode placement over this region (Clark *et al.,* 2012; Coffman *et al.,* 2012a; Coffman *et al.,* 2012b). The cathode locations (over the left sphenoid bone and left VLPFC [F9] or over the lateral part of the left bicep muscle [Arm]) were suggested by our previous studies (Active-A; Clark *et al.,* 2012), and studies by Fecteau and colleagues (2007a; b) demonstrating changes in impulsive behavior (Active-B). TDCS was administered using the ActivaDose system through 3.3 cm x 3.3 cm saline-soaked sponge electrodes, which were secured to the scalp by the EEG cap, and to the upper arm using self-adherent bandage.

The only procedural difference between Active-A and Active-B groups was the placement of the cathode electrode; however, this led to complex differences in current distribution in the brain. Current distribution was modeled for the Active-A group using the Soterix HD-Explore method described by Datta et al. (2011), and for the Active-B group using the COMETS toolbox available in MATLAB (Jung *et al.,* 2013), to characterize the location and polarity of cortical areas affected by tDCS (Figure 1). In the Active-A group, left frontal cortex stimulation was minimal, and any effects of tDCS at left VLPFC are likely indirect. With this placement, tDCS current exerts the greatest influence over right VLPFC, right insula, right inferior temporal gyrus (ITG), right fusiform gyrus, bilateral temporal poles, and bilateral cerebellar tonsils/biventer lobules. In the Active-B group, however, a dipolar current is applied to the scalp with opposite current polarity applied to the left and right frontal cortex, and both frontal hemispheres are directly stimulated by tDCS. TDCS energy distribution with this placement is greatest at bilateral VLPFC and anterior temporal lobes. It should be mentioned that differences in implementation of finite element models between the two software platforms may

have accounted for some of the differences seen, as modeling of the extracephalic cathode using the COMETS software is not possible, and Soterix HD-Explore modeling results were only accessible for the Active-A group because this modeling was performed by a third party prior to modeling of the other placements using COMETS.



** Sham subjects were modeled using the F9 cathode placement*

Figure 1. Electric field intensity maps in Volts per Meter, showing distribution of electric fields at the cortex from three angles (columns) for the three tDCS groups (rows). Maps were generated for the Active-A group using the Soterix HD-Explore software (Datta *et al.*, 2011), while maps for Active-B and Sham were generated using the Comets MATLAB toolbox (Jung *et al.*, 2013). S = Superior; I = Inferior; R = Right; L = Left; A = Anterior; P = Posterior.

Experimenter blinding was accomplished using a coded switch box with inputs for positive and negative leads from two current generators (four electrodes) and outputs for only two electrode leads, 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. Three of the six positions were used here, with two supplying 2.0 mA current, and the third supplying 0.1 mA current. The inputs from the current generator not supplying current to the output leads were routed through a simple circuit loop to maintain the activity of the diverted current.

During tDCS, participants were asked to describe their physical sensations at approximately 1, 3, and 20 minutes after the start of tDCS (Figure 2) to monitor participant comfort. Participants were asked to report sensation on three 10-point Likert scales for itching, tingling, and heat/burning, where 1 represented no sensation, and 10 represented the most intense sensation imaginable (see Appendix C). TDCS was stopped if participants reported a 7 or higher on any scale (N=4). Electrodes were applied during EEG preparation and remained attached to the participant for the duration of the study. Electrodes were moistened prior to application and re-moistened immediately before the start of tDCS by applying a small amount of saline solution to the connection port on each electrode, which sits directly behind the sponge.

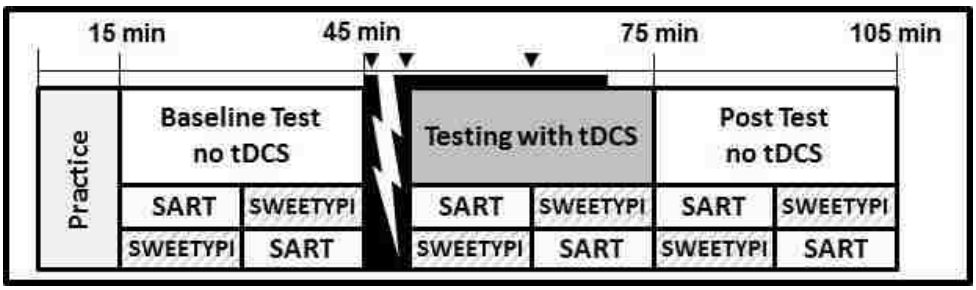


Figure 2. Graphical depiction of the study timeline. Participants were randomly assigned to one of two task orderings, as depicted by order of the SART and SWEETYPI. The lightning bolt represents the no-task tDCS acclimation period, and the black rectangle represents the duration of tDCS. Black triangles represent time points at which tDCS-related physical sensations were assessed.

Experimental Tasks and Study Design

Participants performed cognitive tasks during EEG before tDCS (baseline test phase), during tDCS (during-tDCS test phase), and following tDCS (post-tDCS test phase). Participants performed interleaved 15 minute blocks of the two tasks, with the order of the tasks counterbalanced across participants (see Figure 2). The Sustained Attention to Response Task (SART) was used to assess tDCS effects on attention. In this task, participants viewed single digits (numbers 1-9, duration = 150 ms; ISI = 1000 ms, 1.5º visual angle in height), and were instructed to press a button both as accurately and quickly as possible to each number, with the exception of the number 3. Participants were given a short practice run to become familiar with the task, in which feedback on accuracy and reaction time was displayed for 1000 ms after each trial. During this practice run, explicit instruction was given to avoid responses during the presentation of the stimulus to reduce anticipatory responses in the task and maximize accuracy, while maintaining the rhythmicity of the task. Importantly, this enforced 150 ms response delay is well within the 400 ms response delay window shown to be equivalent in performance by Seli

and colleagues (2012). The number 3 occurred on only ~11% of trials, which required that participants maintain attention to this repetitive task in order to withhold response to the target number 3 and maintain timing and accuracy to the non-targets (numbers other than 3). In one portion of the task, the Fixed SART (F-SART), the numbers were presented sequentially, enabling the participant to anticipate when the target stimulus is presented. In the Random SART (R-SART), numbers were presented randomly, though every number had an equal frequency of occurrence. Dependent variables in both versions of this task included accuracy [errors of omission (non-response to the non-targets), errors of commission (response to the target), impatient responses (responses made either during, or within the 100 ms prior to stimulus presentation), and *d*' (a measure of signal detection)], and response time (average, slope, variability, slope of the variability, and post-error slowing). Each version of the task (F-SART & R-SART) lasted just over 7.5 minutes, with 360 trials of standards and 45 trials of targets for each version, and the order of the F-SART & R-SART was counterbalanced across participants. Each testing phase for the SART (F-SART & R-SART combined) lasted a total of just over 15 minutes.

To measure decision making, an EEG-friendly task was developed based upon the Cambridge Gambling Task (CGT), which measures impulsive behavior control in a predictive wagering context (Rogers *et al.,* 1999). The Select, Wager, and Evaluate, Electroencephalography-Tailored, Yaw- and Pitch-Invariant (SWEETYPI) gambling task was developed to limit eye movement and touch-screen related limb movement, while maintaining the probability assessment, confidence determination, and outcome evaluation associated with the CGT. On each trial, participants were presented with circle subtending 8º visual angle, that was comprised of 10 wedge-shaped sections, each of which was colored either red or blue (see

Figure 3). Importantly, the ratio of red to blue colored wedges varied across trials, ranging from 9:1 to 1:9. Participants were asked to first predict which color concealed a yellow token (deliberation phase), then wager a proportion of his/her total points on this decision. The deliberation phase of the trial lasted until the participant made his/her response (mean deliberation time = 983 ms ± 311 ms SD). Participants were instructed to press a button beneath their left index finger to select red wedges, or beneath their right index finger to select blue wedges, which was in concordance with the arrangement of the stimuli on the screen (see Figure 3). Wagers were offered in ascending (5%, 25%, 50%, 75%, 95% of current points) or descending (95→5%) sequences, presented for 1500 ms each, and displayed at the center of the circle at 0.5º visual angle above the point of fixation. The participant's total points were displayed 0.5º visual angle below the point of fixation. The participant was instructed to press the button beneath his/her right thumb when the desired wager appeared. After selecting an amount to wager, a variable inter-stimulus-interval (ISI) of 500, 750, 1000, 1250, or 1500 ms was incorporated to minimize stimulus onset expectation effects, and the participant was then shown the correct answer when a yellow token appeared at one of the 10 wedges at 2º visual angle from the fixation point. At the same time, the wager amount was replaced by "Win" or "Lose" in red, and the wagered points were added to or subtracted from the total score. The duration of the feedback stimulus was 1500 ms. Each testing phase for the SWEETYPI gambling task lasted just over 15 minutes, where the final trial of both the ascending and descending wager portions of the task was restricted to begin less than 7.5 minutes after the beginning of that portion of the task. The presentation order of the ascending and descending wager portions of the task was counterbalanced across participants.

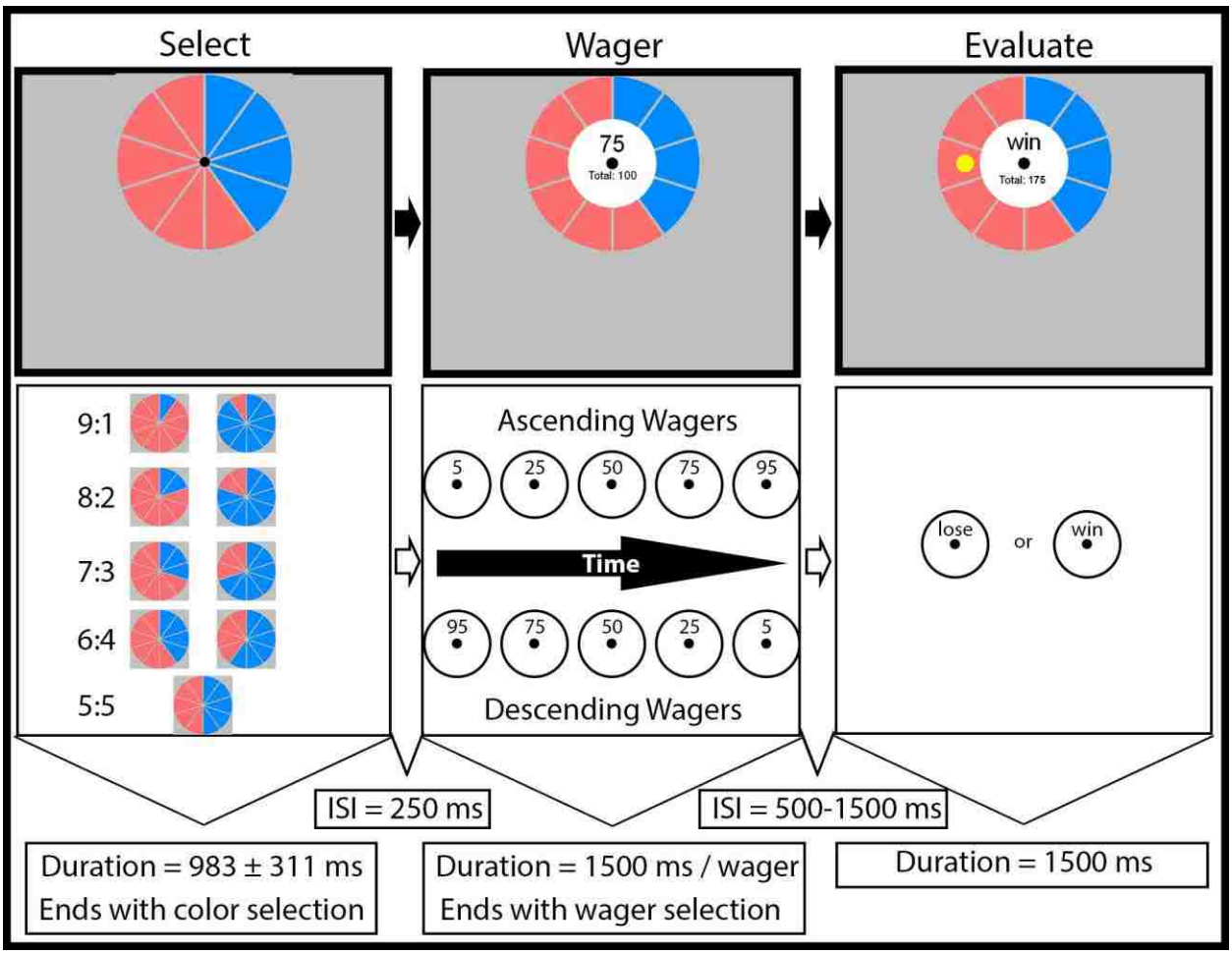


Figure 3. Graphical depiction of a single trial of the SWEETYPI gambling task. Upper panels show screenshots of example stimuli, while lower panels illustrate possible stimuli that could be shown to the participant at each of the three portions of the trial. Participants began each trial by selecting the color of the segment which they predicted would contain a yellow token at the end of a trial. Color proportions randomly varied from 9:1 to 1:9 from trial to trial. After selecting a color, the participant was required to wager on his/her decision by delaying response until presentation of the desired wager. In ascending wager trials, wagers started low (5%) and increased over time, while in descending trials the available wagers started high (95%) and decreased in increments shown in the lower central panel. After selecting a wager by button press, a variable inter-stimulus interval was presented, followed by the evaluate portion of the trial, where feedback was presented and points wagered were added to or subtracted from the total score. Participants focused on the black dot at the center of the circle. ISI = inter-stimulus interval.

To maintain participant motivation in the task, a two-stage incentive scheme was employed. Participants began with 100 points, an amount which is easily comprehendible and allows for meaningful wagering; however, once participants stray too far from this starting point in either direction, this may no longer be the case. For this reason, participants were given wins (green check-marks shown on the screen) for reaching 1000 points and strikes (red "X"s shown on the screen) for dropping to 10 points or less. Wins and strikes accumulated throughout each portion of the task (ascending or descending), and accumulated wins or strikes were overlaid on top of the other stimuli for 1500 ms when a win or strike was earned in the task, following feedback about wins or losses. Participants were instructed to acquire as few strikes and as many wins as possible in the task. Behavioral dependent variables in the SWEETYPI gambling task are similar to those in the CGT and include number of wins/strikes, number of trials in which the majority color was chosen (rational decisions), average deliberation time, average percentage wagered (higher bets indicate risk preference), impulsivity index (consistently early bets produce a high impulsivity index), and risk adjustment index (quantifies wagering preference across different probability ratios by weighting the percentage bet according to the probability ratio). Impulsivity index is calculated by subtracting average wager during the ascending wager sequences from the average wager during the descending wager sequences. Risk adjustment index is calculated with Equation 1 (Deakin *et al.*, 2004).

$$\text{Risk Adjustment} = \frac{[2\times(\%\text{ bet }9{:}1)]+(\%\text{ bet }8{:}2)-(\%\text{ bet }7{:}3)-[2\times(\%\text{ bet }6{:}4)]}{\text{average }\%\text{ bet}} \qquad (1)$$

Prior to EEG/tDCS preparation, and immediately after the consent process, basic demographic and personality trait information was collected using the Initial Questionnaire (see Appendix A). This electronic questionnaire contained questions about exclusion criteria,

demographic variables such as handedness, current medications, first-degree family mental health history, illicit drug use, general mental health history, and personality/trait measures. The Initial Questionnaire also included the trait version of the Positive and Negative Affect Schedule (PANAS; Watson, Clark, and Tellegen, 1988), the Behavioral Activation System & Behavioral Inhibition System (BAS/BIS; Carver & White, 1994) scales, the Barratt Impulsiveness Scale (BIS-11; Patton and Stanford., 1995), the Extroversion scale of the Neuroticism-Extroversion-Openness Five Factor Inventory (NEO-FFI; Costa and McCrae, 1992), and the Magical Ideation Scale (MIS; Eckblad & Chapman, 1983). State/mood was then assessed with the state version of the PANAS using a separate electronic questionnaire (see Appendix B). The state version of the PANAS was also administered at the end of the study to assess tDCS-related changes in mood. After completing the Initial and State/Mood Questionnaires, participants were prepared for EEG and tDCS as described above, and then moved to an electronically shielded room for task performance and EEG recording. Electrodes were checked for stable impedance within the normal range (less than 20 KΩ; with the exception of those EEG electrodes blocked by tDCS electrodes) and additional conductive gel was applied as needed. After the participant was comfortable, research assistants left the room and monitored the participant from the adjacent EEG control room using a camera and intercom system. Recorded instructions were given and a short practice run was presented for both tasks, which lasted approximately 15 minutes. EEG activity was recorded throughout baseline, during tDCS, and post-tDCS testing phases to assess changes in brain function related to tDCS. Participants were instructed to move as little as possible during the task and blink only after making a response to minimize blinking during analysis windows (epochs).

Additionally, the Eyelink 1000 eye-tracker system was used to ensure fixation during the tasks. The eye tracker settings were tailored for each participant by adjusting luminance thresholds and by optimizing the infrared light source location and camera position to obtain good-quality pupil representation and corneal reflection. This was followed by a five-point eye-tracker calibration sequence using stimuli of the same luminance and spatial extent as those used in the cognitive tasks. Calibration was repeated at the beginning and at each task alternation until average eye location error between calibration and validation tests was less than 1° and maximum location error was less than 2° across all positions. Though eye tracker data are not reported here, online monitoring of eye movements confirmed that participants were able to maintain fixation in both the SWEETTYPI and SART tasks.

EEG Data Acquisition

EEG data were acquired using a 128-channel ActiveTwo system (Biosemi). An active electrode (CMS) and a passive electrode (DRL) were applied to form a feedback loop, which drives the average electrical potential at the scalp (the Common Mode voltage) as close as possible to the analog-to-digital (AD) converter reference voltage in the AD-box (www.biosemi.com/faq/cms&drl.htm). Bipolar electro-oculogram (EOG) recordings were acquired with electrodes placed above the left eye and at the outer canthus of the right eye. Bipolar electrocardiogram (ECG) recordings were acquired with electrodes placed symmetrically approximately 1 cm lateral and inferior to the clavicle bone. All signals were recorded using ActiView software and digitized at 1,024 Hz with 24-bit AD conversion. 3D-digitization of electrode locations was completed using the Polhemous FastTrak system.

EEG Preprocessing

EEG data were pre-processed through an automated Linux C-Shell pipeline utilizing the MATLAB toolboxes EEGLAB (http://sccn.ucsd.edu/eeglab/) and ERPLAB (http://erpinfo.org/erplab). Data from each channel were first high-pass filtered at 0.01 Hz and DC offset was removed to eliminate scalp potentials, DC voltage offset associated with tDCS, and other slow drifts in the data. Channel locations acquired at EEG preparation were then applied to each participant's dataset. Bad channels (including, in all cases, the EEG channels blocked by the tDCS electrodes) were visually detected and removed from each dataset, and Independent Components Analysis (ICA) was used to remove artifacts from the data. Artifacts removed with ICA included blinks, cardiac signal, tDCS-related voltage deflections, and 60 Hz line noise. Six different ICA algorithms were tested for their ability to isolate maximally independent components from test data during tDCS (datasets containing voltage deflection artifacts associated with tDCS) in order to select the appropriate algorithm for use in this study. Four separate measures were examined, assessing general and tDCS-artifact-specific independence of components (for details see Appendix D). Results from this comparison demonstrated a clear advantage for the AMICA (Adaptive Mixture of ICA models) algorithm (Palmer *et al.*, 2007) compared to other algorithms tested, so AMICA was used to process and remove artifacts in all datasets. Following data decomposition using AMICA, components clearly representing eye blinks, cardiac signal, and 60 Hz line-noise were selected visually, and components reflecting tDCS-related voltage deflections were selected according to the following criteria: (1) 90^{th} percentile in percent of data variance explained (compared to other components); (2) power timecourse that was temporally correlated with tDCS duration; and (3) scalp map distribution that was spatially correlated with tDCS electrode placement. Example

component activation timecourses, power timecourses, and scalp maps for each type of component can be found in Figure 4. Following artifact component selection/removal and data back-reconstruction, channels were referenced to the average and electrodes that had been removed prior to ICA were interpolated to recover the complete sensor array. Preprocessed continuous EEG data were epoched from 200 ms prior to 800 ms following stimulus onset for all analyses. Epochs were baseline-corrected using the entire pre-stimulus interval [-200 0], and epochs were rejected in which the voltage in any channel exceeded 300 μV. Epochs surviving this rejection criterion were then averaged, a low-pass filter of 30 Hz was applied, and linear detrending was applied over the entire ERP.

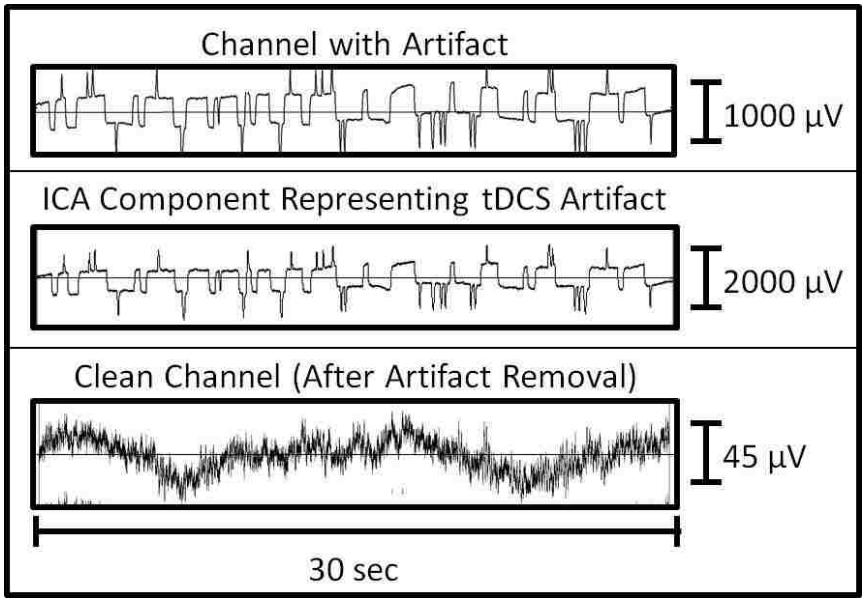


Figure 4. Example of a typical tDCS artifact removal result for 30 seconds of data. The upper panel shows an EEG channel containing the tDCS artifact, the middle panel shows an example ICA component representing the artifact and the lower panel shows the same channel depicted above after removing tDCS and other artifacts using ICA and back-reconstruction. Scales shown are in microvolts.

For the F-SART, numbers 1, 2, 3, 4, and 9 were epoched, and ERP amplitude was characterized in the time window of the N2 response (200-350 ms after stimulus onset), as

suggested by previous research on temporal cuing (see review in Chapter 1). These stimuli were chosen because they show the greatest task-relatedness in previous ERP research (Dockree *et al.,* 2005). For the R-SART, ERP amplitude was characterized for the time window of the P3 response (300-500 ms after stimulus onset) for "No-Go" trials (number 3) and "Go" trials (numbers other than 3). For the SWEETYPI gambling task, each feedback stimulus (losses and wins) was epoched separately. Difference waves were then calculated representing the medial frontal negativity (MFN) response by subtracting the response to wins from response to losses across wager levels. The MFN, as well as separate responses to losses and wins, was compared in the time range of the N2 response, as is typical for this type of task.

Data Analysis

Data Screening

All form/survey data were collected using electronic forms which required no additional data entry, with the exception of the tDCS sensation questionnaire which was recoded on paper. Manual data entry for this form was verified by double entry. Behavioral data entry and pre-processing programs were written in Excel Visual Basic, Linux C-Shell, and MATLAB and programing and data were checked for accuracy both prior to and following all analyses. Although the assumption of normality is not relevant to the multivariate statistics used here, dependent variables were assessed for normality for follow-up univariate tests performed on individual measures. Where appropriate, transformations were used to normalize dependent variables. To limit the contribution of ERPs with low signal-to-noise ratio, number of trials surviving rejection criteria was assessed and mean ERP amplitude values for averages containing too many rejected trials (>50%) for a given trial type were removed from the data. Missing

values were replaced using linear interpolation with the linear trend at that point, within group, with data sorted by the baseline measure for that run. Linear interpolation, a longitudinal imputation method, was used in this design because it has proven preferable to mean replacement and other imputation methods (Twisk and de Vente, 2002). If data for the baseline measure for a given value were missing, the data were sorted by the measure taken at the post-tDCS test phase before interpolating the missing value.

Behavioral Performance

Differences in behavioral performance between groups were assessed using the general linear model. Dependent variables were compared using two split-plot multivariate ANOVAs (SP-MANOVA, also known as Doubly MANOVA), with group (Active-A, Active-B, or Sham) entered as a between subjects variable and testing period (baseline, during-tDCS, or post-tDCS) entered as a within subjects variable. When significant main or interaction effects were found in the overall SP-MANOVA, these were followed by univariate tests of simple effects and/or pairwise comparisons that were corrected for multiple comparisons using least significant difference (LSD) corrections of alpha and Greenhouse-Geisser corrections of degrees of freedom. All analyses were performed using IBM SPSS 21.

The first SP-MANOVA compared the effects of tDCS condition on *attention* as a function of testing phase by assessment of six measures: Slope of the variability in response time observed across segments of the F-SART (1) and R-SART (2), variance of the variability in response time observed across segments of the F-SART (3) and R-SART (4), and signal detection (*d'*) observed in the F-SART (5) and R-SART (6). Other measures were considered as candidates for this test, including mean reaction time, slope of reaction time, and post-error

slowing; however, upon examination of correlation matrices of all twelve measures across groups, these measures were found to be uncorrelated with other candidate variables for the model. Measures 1-4 were calculated by segmenting each testing phase into blocks of 20 trials, then calculating standard deviation of response time within each of the segments. Slope and variance were then calculated across these segments. These measures represent the change in variability of responses over time. The second SP-MANOVA compared the effects of tDCS condition on *impulsiveness* as a function of testing phase by assessment of six measures: (1) rational choices; (2) risk adjustment index; (3) average wager; (4) impulsivity index (measures 1-4 from the SWEETYPI gambling task); (5) number of impatient responses; and (6) proportion of false alarms (measures 5 & 6 from the R-SART).

Pearson correlation was then performed to determine relationships between the effects of tDCS and state/trait variables assessed with the BIS/BAS and Barratt Impulsiveness Scale. Two sets of correlations were made assessing: (1) relationships between attention-related task measures and attention-related survey measures (i.e. BIS/BAS behavioral inhibition subscale, Barratt attention subscale); and (2) relationships between impulsiveness-related task measures and impulsiveness-related survey measures (i.e. BIS/BAS reward responsiveness and fun seeking subscales, Barratt self-control subscale).

Event-Related Potentials: Fixed SART

ERP mean amplitudes were computed for the time window of 200 – 350 ms following stimulus onset for the N2 response. To limit the complexity of the statistical design, difference scores were calculated for N2 responses by subtracting mean amplitudes at baseline from mean amplitudes during-tDCS and post-tDCS tests. These difference scores were then compared using

two separate SP-MANOVAs examining tDCS effects on N2 amplitude during- and post- tDCS. These 4-way SP-MANOVAs compared group (Sham, Active-A, or Active-S), stimulus (number 1, 2, 3, 4, or 9), and spatial distribution of the response, which was characterized by two separate factors, representing the anterior-posterior direction (anterior frontal, frontal, central, or parietal)[1] and left-right direction (left, mid-line, or right)[2]. When significant multivariate effects were found, these were followed by univariate tests of simple effects, corrected for multiple comparisons using least significant difference (LSD) corrections of alpha. Univariate ANOVA results were assessed using Greenhouse-Geisser corrections of degrees of freedom. Four-way interactions were examined using planned three-way ANOVAs comparing either simple effects of spatial distribution and tDCS group within stimulus types, or simple effects of stimulus types and tDCS group within spatial regions. The relationship between behavioral performance and N2 amplitude in regions of significant group differences was assessed using Pearson correlation.

Event-Related Potentials: Random SART

Mean amplitudes were computed across the 300 – 500 ms time window (P3 response). As with the F-SART analyses, difference scores were calculated by subtracting mean P3 amplitudes at baseline from mean amplitudes during-tDCS and post-tDCS testing phases. These difference scores were then compared using two separate SP-MANOVAs examining tDCS effects on P3 amplitude during and after tDCS. These 4-way SP-MANOVAs compared tDCS group (Sham, Active-A, or Active-S), stimulus type ("Go" trials or "No-Go" trials), and spatial distribution of the response, which was characterized by two separate factors, representing the

[1] Anterior frontal electrodes included AF7, FpZ, and AF8; frontal electrodes included F3, FZ, & F4; Central electrodes included C3, CZ, and C4; parietal electrodes included electrodes P3, PZ, and P4.

[2] Left electrodes included AF7, F3, C3, and P3; mid-line electrodes included FpZ, FZ, CZ, and PZ; right electrodes included AF8, F4, C4, and P4.

anterior-posterior direction and left-right direction. As with the analysis described above, the relationship between behavioral performance and P3 amplitude in regions of significant group differences was assessed using Pearson correlation.

Event-Related Potentials: SWEETYPI Gambling Task

ERP mean amplitudes were computed for the 200– 350 ms time window for the loss minus win difference waves representing the MFN response, as well as the response to wins and losses, independently. Mean MFN was compared using an analysis strategy similar to ERP analyses listed above, only three-way SP-MANOVA was performed, since stimulus type was not a factor in this analysis. As with the analysis described above, the relationship between behavioral performance and MFN amplitude in regions of significant group differences was assessed using Pearson correlation.

CHAPTER 3: RESULTS

Effects of tDCS on Attention

Before performing statistical tests, dependent variables were checked for missing values and the agreement with the assumptions of statistical tests was examined. One participant in the sham group was missing data for the baseline assessment of the R-SART, and this data was replaced using linear interpolation. No univariate or bivariate outliers were detected in these data and no multivariate outliers were found to exist using Mahalanobis distance with $p < 0.001$. Six variables were found to be significantly positively skewed (range = 1.53 – 4.34; SE = 0.44), but this was restricted to only two measures (variance of the variability in response time for both tasks) across all 3 test conditions. These variables were log-transformed before any group comparisons (post-transformation skewness = -0.19 – 0.72; SE = 0.44).

MANOVA results indicated a significant interaction between tDCS group and testing phase on the combined dependent variable assessing attention, with a medium effect size [Wilks' Λ =0.14, $F(24,30) = 2.14$, $p < 0.05$, $\eta^2 = 0.632$]. In general, a similar pattern can be seen in each measure, where Active groups outperform Sham, and effects of tDCS were greater in measures obtained from R-SART than F-SART (Figure 5). Univariate ANOVA confirmed this qualitative assessment of the multivariate results. Significant tDCS group x testing phase interactions were found for *d*' [$F(4,52) = 2.96$; $p = 0.029$; $\eta^2 = 0.186$] and variance of response time variability [$F(4,52) = 3.51$; $p = 0.013$; $\eta^2=0.213$], only during the R-SART. Significant simple effects of group were found during tDCS [*d*': $F(2,26) = 7.88$; $p = 0.002$; $\eta^2=0.377$; RT variance: $F(2,26) = 3.49$; $p = 0.045$; $\eta^2 = 0.212$], but not baseline or post, and pairwise comparisons revealed that these effects were driven by differences between Active-A [*d*': (Mean ± SE) = 3.02 ± 0.23; 95%

CI = (2.54 – 3.49); RT variance: 68.8 ± 23.6 ms; 95% CI = (20.1 ms – 117.3 ms)] and Sham [*d*': Mean = 1.78 ± 0.22 SE; 95% CI = (1.30 – 2.21); $p < 0.001$); RT variance: 144.8 ± 22.6 ms; 95% CI = (98.3 ms – 191.3 ms); $p = 0.028$]. Mean reaction times in the R-SART and F-SART are shown in Table 3 & 4, respectively.

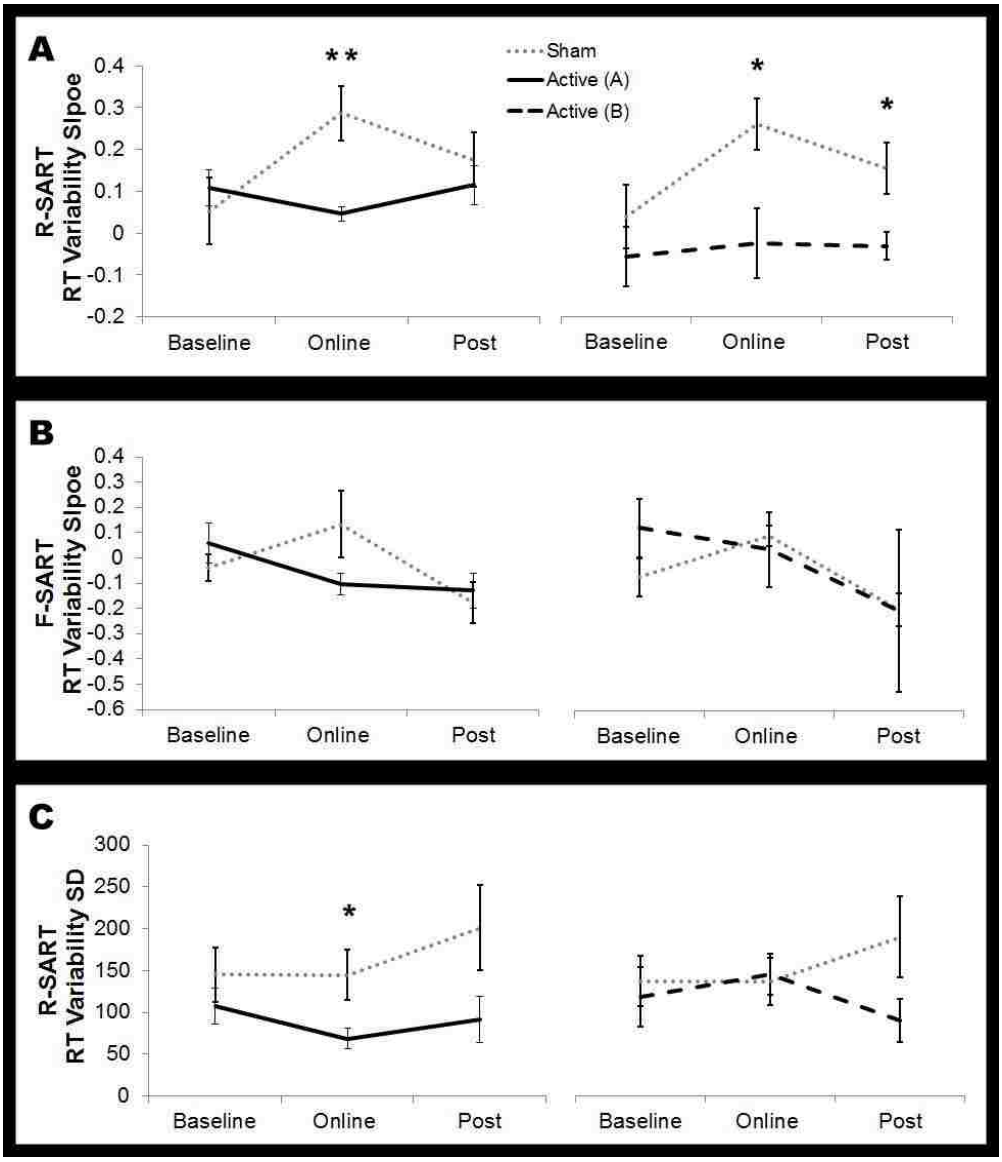
	Sham M ± SEM (ms)	Active (A) M ± SEM (ms)	Active (B) M ± SEM (ms)
Baseline			
"Go"	197 ± 9	223 ± 11	218 ± 28
"No-go"	157 ± 6	159 ± 7	162 ± 16
During-tDCS			
"Go"	203 ± 15	211 ± 13	200 ± 32
"No-go"	156 ± 7	166 ± 6	158 ± 20
Post-tDCS			
"Go"	204 ± 13	204 ± 17	158 ± 20
"No-go"	168 ± 12	157 ± 6	180 ± 17

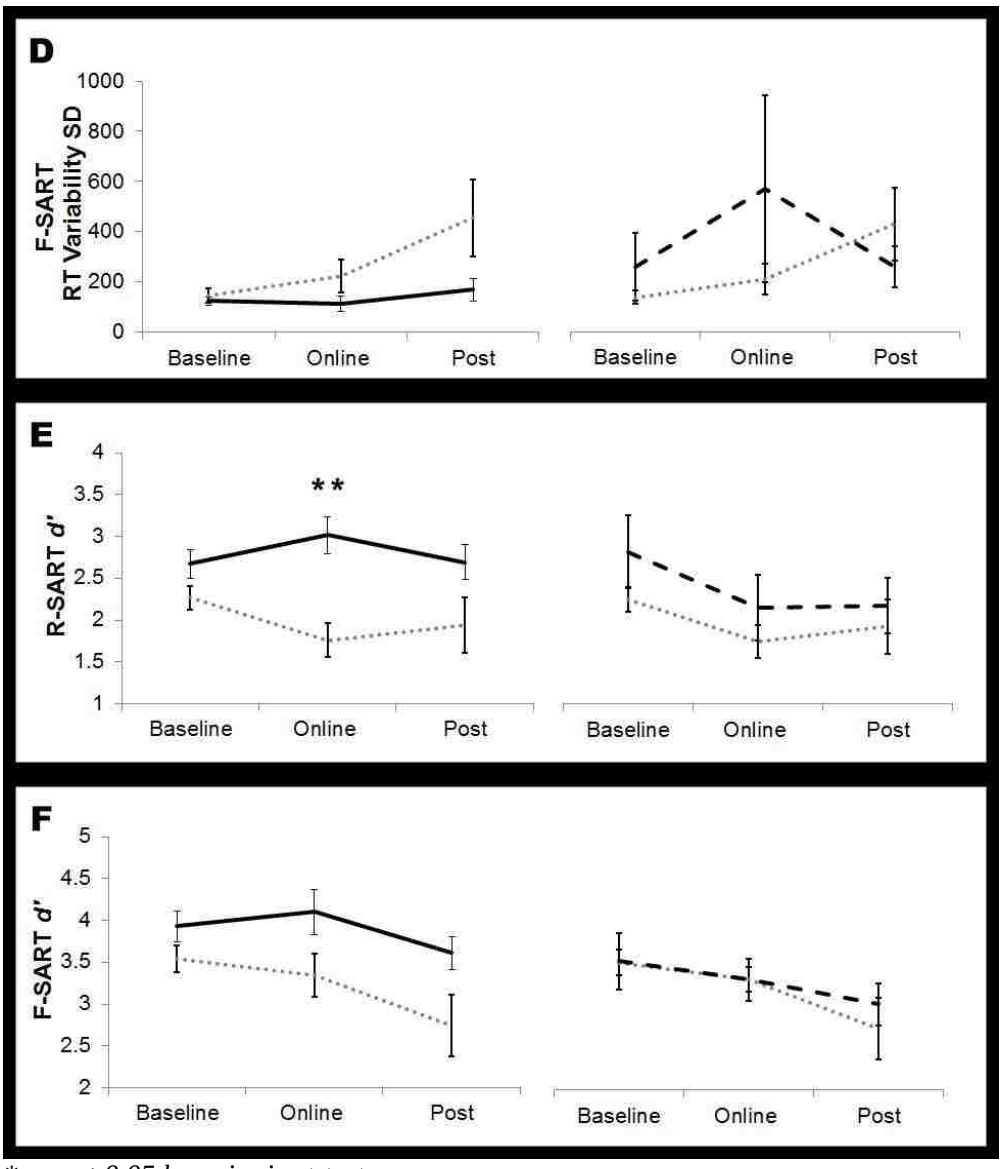
Table 3. Mean reaction times (in ms) for R-SART trials for each group and each testing phase.

	Sham M ± SEM (ms)	Active (A) M ± SEM (ms)	Active (B) M ± SEM (ms)
Baseline			
#1	187 ± 10	198 ± 12	190 ± 40
#2	156 ± 12	172 ± 15	175 ± 43
#3 *("No-Go")*	185 ± 18	188 ± 5	280 ± 41
#4	157 ± 12	170 ± 14	153 ± 24
#5	157 ± 13	179 ± 15	174 ± 39
#6	147 ± 12	170 ± 16	178 ± 45
#7	149 ± 12	158 ± 16	179 ± 46
#8	147 ± 11	154 ± 13	161 ± 42
#9	146 ± 10	153 ± 13	168 ± 42
During-tDCS			
#1	172 ± 13	159 ± 8	255 ± 90
#2	152 ± 14	140 ± 11	163 ± 29
#3 *("No-Go")*	171 ± 16	166 ± 24	181 ± 29
#4	152 ± 13	152 ± 9	140 ± 22
#5	148 ± 15	142 ± 9	135 ± 16
#6	149 ± 16	137 ± 13	135 ± 13
#7	156 ± 15	146 ± 21	148 ± 14
#8	151 ± 15	136 ± 11	128 ± 16
#9	146 ± 15	135 ± 10	183 ± 44
Post-tDCS			
#1	181 ± 15	*138 ± 7	189 ± 30
#2	164 ± 15	*123 ± 5	150 ± 24
#3 *("No-Go")*	192 ± 22	181 ± 8	163 ± 25
#4	166 ± 16	142 ± 9	137 ± 22
#5	164 ± 14	*118 ± 10	144 ± 23
#6	158 ± 13	*121 ± 8	142 ± 18
#7	166 ± 19	*119 ± 6	134 ± 25
#8	155 ± 17	*113 ± 7	139 ± 22
#9	162 ± 17	*119 ± 5	143 ± 24

* $p < 0.05$ (compared to Sham values for the same measure)

Table 4. Mean reaction times (in ms) for F-SART trials for each group and each testing phase.





* $p < 0.05$ by pairwise t-test
** $p < 0.01$ by pairwise t-test

Figure 5. Behavioral data for variables assessing attention in Sham (dotted), Active-A (solid), and Active-B (dashed) groups are shown in separate line charts. The twelve charts shown represent data from (top to bottom) R-SART and F-SART, respectively, for (A & B) slope of RT variability, (C & D) variance of RT variability, and (E & F) *d'*. The x-axis for all graphs represents baseline, during-tDCS, and post-tDCS test. Error bars denote SEM.

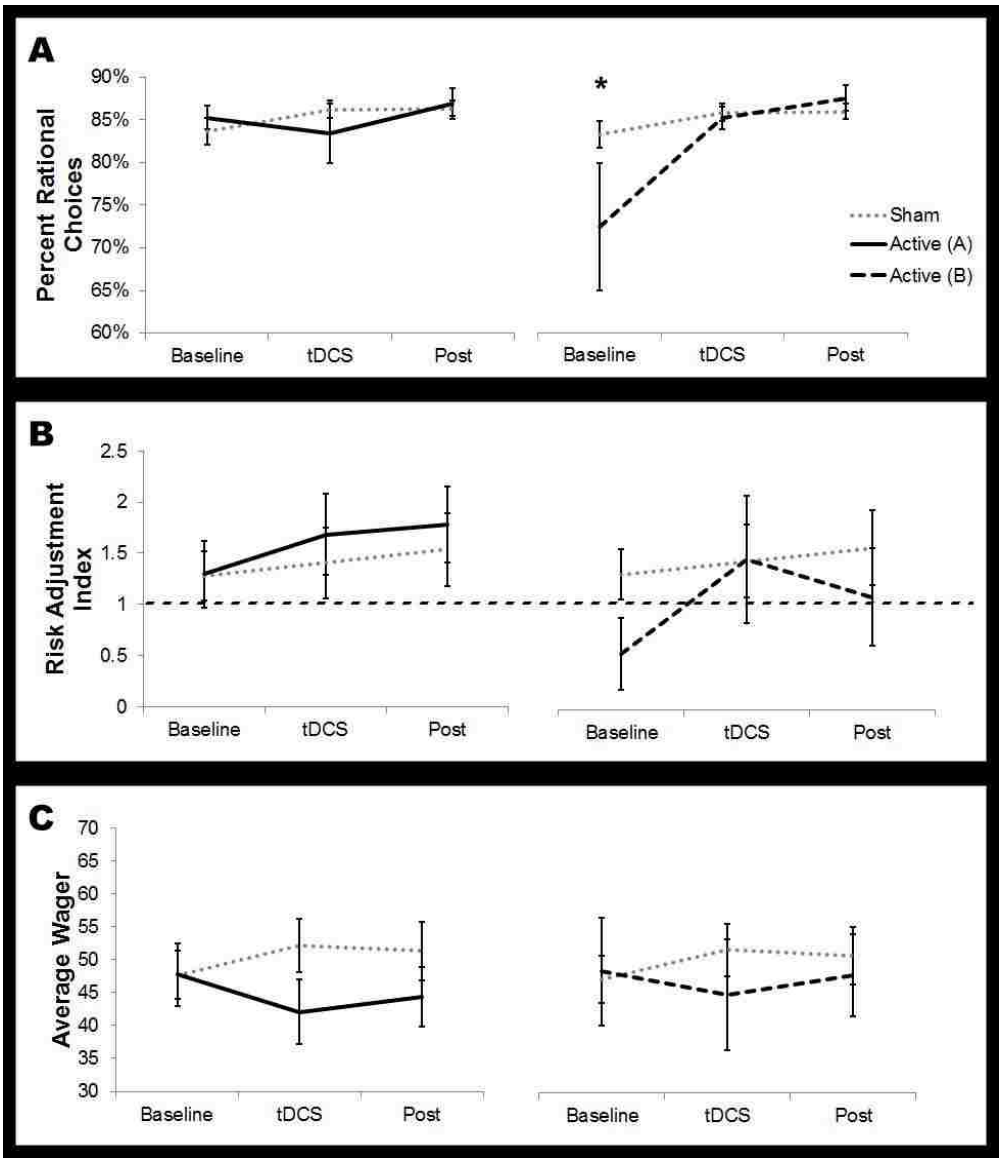
In an attempt to limit Type 1 error due to a large number of comparisons, correlation analysis was limited to the Active-A and Sham groups and to the measures which differentiated groups (i.e. *d*' and RT variance, for R-SART). Correlations were found only in the Active A group, between the behavioral inhibition scale (greater scores = less impulsive) of the BIS/BAS and variance RT variability in the R-SART at baseline (r = -0.71; p = 0.014) and post-tDCS tests (r = -0.68; p = 0.019). A lesser, non-significant correlation was found during-tDCS (r = -0.52; p > 0.1). This should be interpreted with caution, however, as the range of the behavioral inhibition measure was restricted for the Active-A group (range = 18-24).

Effects of tDCS on Impulsive Behavior

Before beginning our analysis of these data, dependent variables were checked for missing values and agreement with assumptions of MANOVA was examined. No univariate or bivariate outliers were detected in these data and no multivariate outliers were found to exist using Mahalanobis distance with $p < 0.001$. Three variables (percent rational choices in the SWEETYPI gambling task, all three test conditions) were significantly negatively skewed (range = -2.04 – -3.59; SE = 0.43), and three variables (R-SART impatience trials, all three test conditions) were significantly positively skewed (range = 1.46 – 2.52; SE = 0.43); however, no transformations could achieve normal distribution for these variables, so the original values were used in all statistical comparisons.

MANOVA results indicated significant group differences on the combined dependent variable assessing impulsivity with a medium effect size [Wilks' Λ =0.12, $F(24,30) = 2.30$, p = 0.016 $\eta^2 = 0.608$]. In general, a similar pattern can be seen in each measure, where Active groups outperform Sham (Figure 6); however, univariate ANOVA results were unconvincing.

Significant group-by-time interactions were found only for rational choices in the SWEETYPI gambling task [$F(4,52) = 3.25$; $p = 0.045$; $\eta^2 = 0.20$]. Simple effects analysis revealed that this interaction was driven by group differences at baseline.



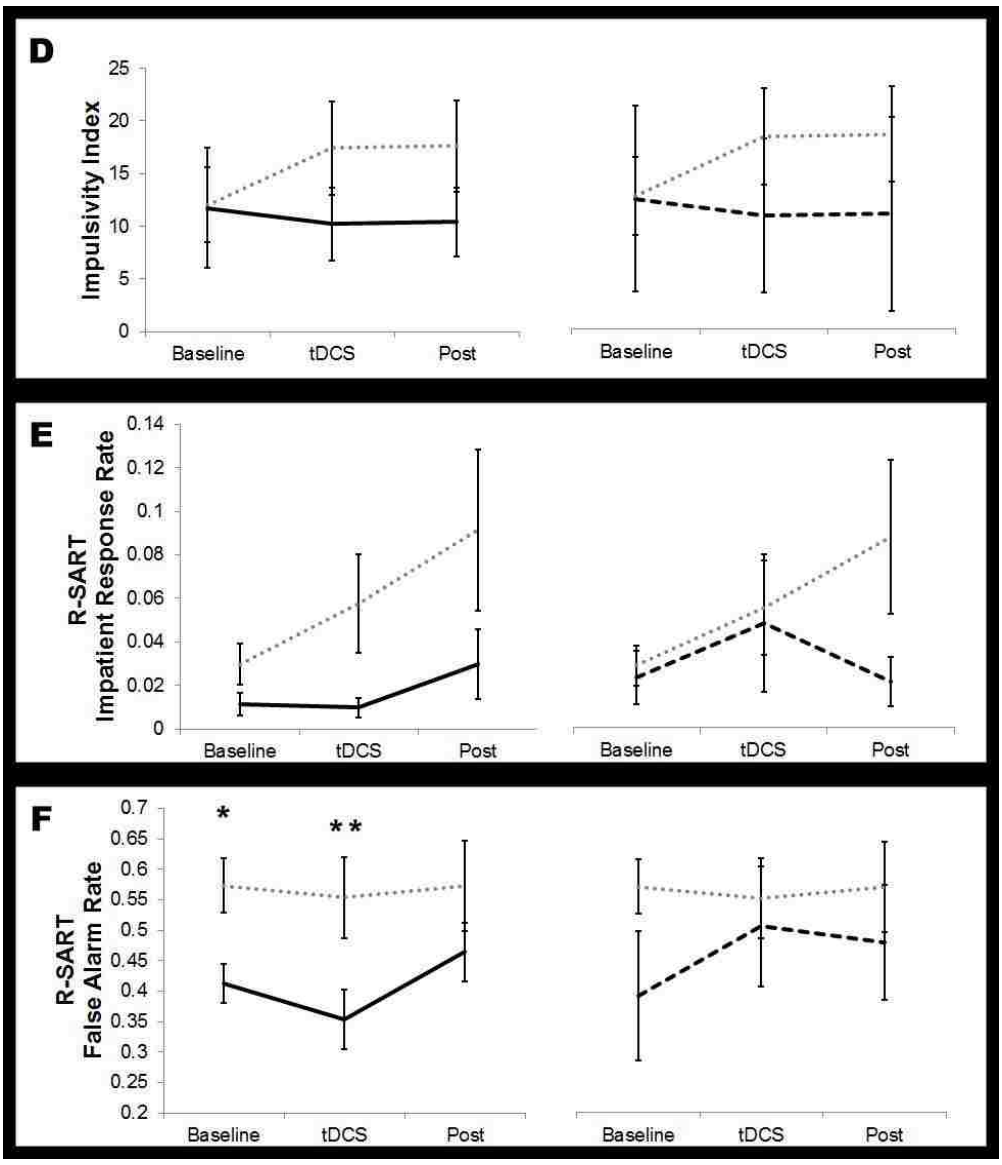


Figure 6. Behavioral data for variables assessing impulsive behavior in Sham (dotted), Active-A (solid), and Active-B (dashed) groups are shown. The twelve plots shown represent data from (A) Percent rational choices (B) risk adjustment index, (C) average wager, and (D) impulsivity index in the SWEETYPI gambling task, and (E) impatient responses and (F) false alarm rate in the R-SART. The x-axis for all graphs represents baseline, during-tDCS, and post-tDCS test. Error bars denote SEM. The dotted line in B represents the point at which wagering strategy becomes counterproductive.

To limit Type 1 errors due to a large number of multiple comparisons, correlation analysis was limited to the Active-A and Sham groups and to the measures which differentiated groups during-tDCS and post-tDCS testing phases. As no behavioral variables significantly differentiated groups in these tests, those with the greatest difference in slope of the mean across tests between Active and Sham groups were assessed (i.e. impulsivity index in the SWEETYPI gambling task and R-SART impatience trials). No significant correlations were found.

Event-Related Potentials: P3 Amplitude in Random SART

Before beginning our analysis of these data, dependent variables were checked for missing values and the agreement with the assumptions of statistical tests was examined. One participant in the Sham group and one participant in the Active-A group was found to have greater than 50% of trials rejected for either the post-tDCS or baseline assessment of the R-SART, and post-tDCS P3 difference scores were replaced for these participants using linear interpolation. Two participants in the sham group, five from the active-A group, and two from the Active-B group were found to have more than 50% of trials excluded either for the baseline assessment or during tDCS for the R-SART and P3 difference scores during tDCS were replaced for these participants using linear interpolation. No univariate or bivariate outliers were detected in these data and no multivariate outliers were found to exist using Mahalanobis distance with $p < 0.001$. Very few variables violated the assumptions of normality: no variable exceeded skewness of ± 2, and 3/48 dependent variables tested exhibited kurtosis greater than 7; however this seemed to be due to a bimodal distribution of means in many cases, and transformations were not successful in reducing kurtosis overall.

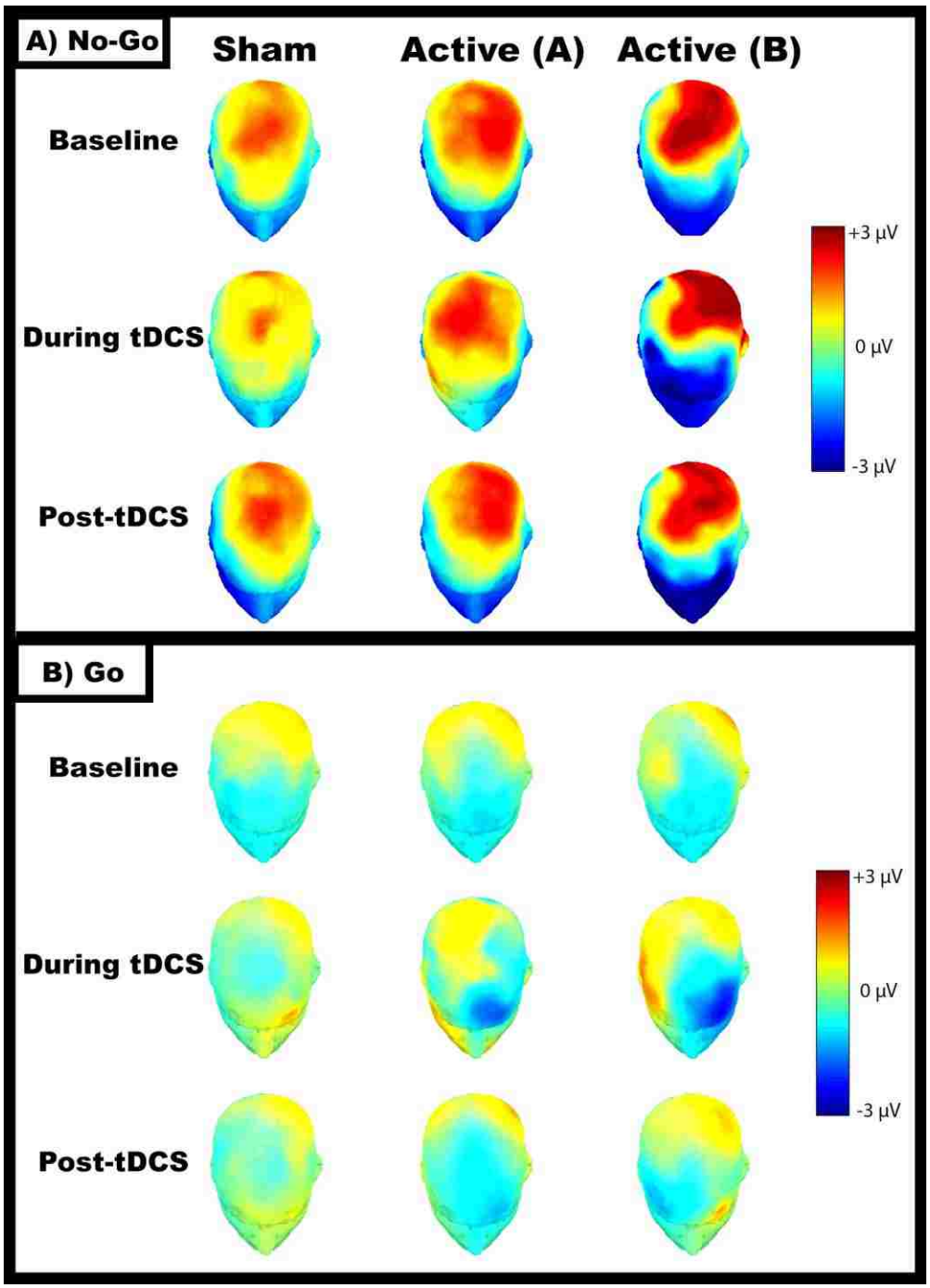


Figure 7. Scalp maps showing spatial distribution of the P3 response by tDCS condition and testing phase for (A) No-Go, and (B) Go stimuli in the R-SART. Color values represent mean amplitude across the interval of 300 to 500 ms after stimulus onset. Cold colors indicate negative mean amplitude, while warm colors indicate positive mean amplitude.

The results of MANOVA comparing effects of tDCS (during-tDCS minus baseline) indicated differences in spatial distribution of P3 amplitude change by a four-way interaction between tDCS group, stimulus type, anterior-posterior, and left-right spatial distribution [Wilks' $\Lambda = 0.37$, $F(12,42) = 2.61$, $p = 0.026$, $\eta^2 = 0.392$]. This interaction is driven by three separate effects:

(1) A trend-level simple two-way interaction between tDCS group and left-right distribution was found for "Go" trials within anterior frontal channels [$F(4,52) = 2.66$, $p = 0.053$, $\eta^2 = 0.169$], where significant group differences were present only for the AF7 (left) electrode [$F(2,26) = 4.35$, $p = 0.024$, $\eta^2 = 0.251$], driven by decreased amplitude in Active-B participants [-1.88 ± 0.69 μV; 95% CI = (-3.30 μV – -0.46 μV)] compared to Sham [0.58 ± 0.48 μV; 95% CI = (-0.42 μV – 1.59 μV); $p_{(BvS)} = 0.007$]. This effect can be seen as a negativity in the left frontal area in both active groups in Figure 7, panel B, and is best represented in Figure 8 (lower panels), where the effect is shown to exist primarily in the early portion of the analysis window, in the N2 range.

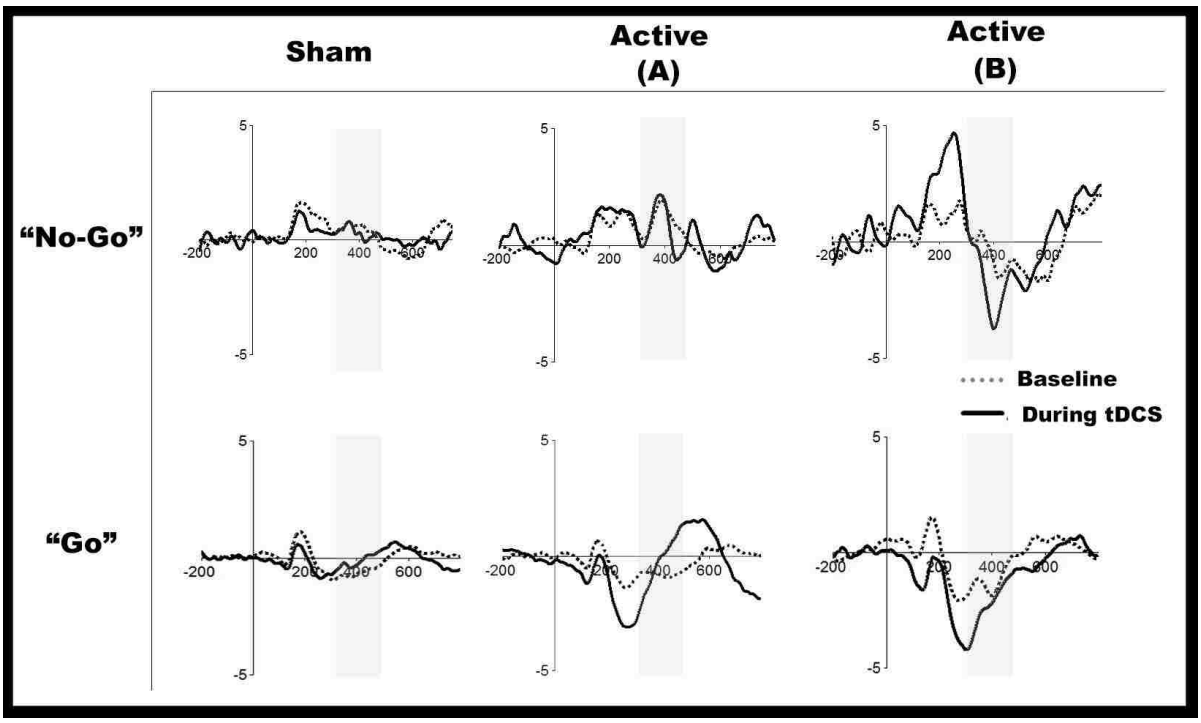


Figure 8. ERP traces for "No-Go" and "Go" trials in the R-SART at baseline (solid) and during-tDCS (dotted) testing phases. The upper three plots show data for responses to "No-Go" stimuli from channel AF7 (left anterior frontal), while the lower three show data for responses to "Go" stimuli from channel F3 (left frontal). The columns represent group averaged ERPs for (left to right) Sham, Active-A, and Active-B participants. The y-axes range from -5 to +5 μV and cross the x-axes at stimulus onset. The x-axes range from 200 ms before to 800 ms after stimulus onset. The six vertical grey rectangles represent the window of P3 analysis, from 300 to 500 ms after stimulus onset.

(2) A simple two-way interaction between tDCS group and stimulus type was found within frontal channels [$F(2,52) = 6.02$, $p = 0.007$, η^2=0.316], where significant group differences were present only for "No-Go" trials [$F(2,26) = 3.38$, $p = 0.039$, $\eta^2 = 0.221$], and

were driven by decreased amplitude in Active-B [-1.38 ± 0.52 μV; 95% CI = (-2.39 μV – -0.26 μV)] compared to Sham [0.35 ± 0.38 μV; 95% CI = (-0.37 μV – 1.15 μV); $p_{(BvS)}$= 0.012]. Trend-level differences in frontal channel amplitude change were present between Active-B and Active-A [Active-A = -0.07 ± 0.38 μV; 95% CI = (-0.86 μV – 0.71 μV); $p_{(BvA)}$ = 0.063]. This large, general frontal decrease for the Active-B group is also characterized by a trend-level simple three-way interaction between tDCS group, left-right, and anterior-posterior spatial distribution within "No-Go" trials [$F(12,156) = 2.043$, $p = 0.056$, $\eta^2 = 0.136$], containing a simple-simple main effect of group within frontal channels.

(3) A second simple-simple two-way interaction within this model illustrates the group differences present in left frontal channels for "No-Go" trials, shown as an increase for Sham and a decrease for Active-A and Active-B groups in Figure 7, panel A. Within the framework of the simple three-way interaction described above (group by spatial distribution within "No-Go" stimuli), a simple-simple interaction between group and anterior-posterior spatial distribution was present within left channels [$F(6,78) = 3.79$, $p = 0.010$, $\eta^2 = 0.226$], with a simple[3] (simple-simple-simple) main effect of group in left frontal areas [channel F3; $F(2,26) = 6.28$, $p = 0.006$, $\eta^2 = 0.326$], and pair-wise group differences revealed effects of tDCS for both Active groups, compared to Sham (p's < 0.005). Timing of this effect is shown in Figure 8 (upper panels), where the differences are evident within a negative peak occurring at ~400 ms for all groups. See Table 5 for descriptive and inferential statistics.

Interestingly, F3 amplitude change was negatively correlated with scores on the behavioral inhibition scale of the BIS/BAS ($r = -0.79$; $p = 0.004$) in the Active A group, indicating greater impulsivity is associated with lower amplitude in this group; however, as with

other correlations found with this variable, this should be interpreted with caution, as the range of this variable was restricted for this group (range = 18-24).

	$F(2,26)$	p	η^2	Sham M ± SEM (μV) [95% CI]	Active (A) M ± SEM (μV) [95% CI]	Active (B) M ± SEM (μV) [95% CI]
During				0.81 ± 0.42	-0.99 ± 0.44	-1.32 ± 0.59
F3	6.28	0.006	0.326	[-0.05 – 1.66]	[-1.89 – -0.09]	[-2.53 – -0.12]
Post				0.57 ± 0.29	-0.14 ± 0.31	-0.68 ± 0.41
Left	3.36	0.050	0.206	[-0.03 – 1.17]	[-0.77 – 0.49]	[-1.53 – 0.17]
				-0.48 ± 0.31	-0.60 ± 0.32	0.87 ± 0.44
Right	3.196	0.057	0.197	[-1.11 – 0.16]	[-1.72 – 0.60]	[-0.03 – 1.77]

Table 5. One-way simple main effects of tDCS group on P3 amplitude change scores for "No-Go" trials in the Random SART during- and post-tDCS

MANOVA results comparing lasting effects of tDCS (post-tDCS minus baseline) indicated differences in spatial distribution in the left-right axis between tDCS groups by a three-way interaction between tDCS group, stimulus type, and left-right distribution [Wilks' $\Lambda = 0.56$, $F(4,50) = 4.28$, $p = 0.005$, $\eta^2 = 0.255$]. This interaction can be best described as a left-right bias in amplitude change (left increase, right decrease) in "No-Go" trials that is not present in active groups [$F(4,52) = 3.56$, $p = 0.019$, $\eta^2 = 0.217$], though the effect size is small, and is not easily apparent in Figure 7. The interaction was driven primarily by opposing differences between Sham and Active-B at left channels (p's < 0.05). See Table 5 for descriptive and inferential statistics.

Post-tDCS change in P3 response amplitude relative to baseline during "No-Go" trials in left channels was significantly correlated with the attention scale of the Barratt ($r = 0.70$; $p = 0.017$), while amplitude change in right channels significantly correlated with impulsivity index

during-tDCS (r = 0.76; p = 0.007) and at post-tDCS assessment (r = 0.70; p = 0.017), but not baseline (r = 0.40; p = 0.221) in Active-A subjects only. Finally, post-tDCS change in P3 response amplitude in left channels was positively correlated with change in left frontal areas during-tDCS, only for Sham participants (r = 0.72; p = 0.009).

Event-Related Potentials: N2 Amplitude in the Fixed SART

Before beginning our analysis of these data, dependent variables were checked for missing values, and the agreement with the assumptions of statistical tests was examined. No participants had greater than 50% of trials excluded for post-tDCS or baseline assessments of the F-SART; however, two participants in the Sham group and three in the Active-A group had more than 50% of trials excluded for the assessment of the F-SART during-tDCS, and N2 difference scores during-tDCS were replaced for these participants using linear interpolation. No univariate or bivariate outliers were detected in these data and no multivariate outliers were found to exist using Mahalanobis distance with $p < 0.001$. Very few variables violated the assumptions of normality: no variable exceeded skewness of ± 2, and 13/96 dependent variables tested exhibited kurtosis greater than 7; however this seemed to be due to a bimodal distribution of means in many cases, and transformations were not successful in reducing kurtosis overall.

Results of MANOVA comparing effects during tDCS (during-tDCS minus baseline) indicated group differences in spatial distribution of N2 amplitude change by a four-way interaction between tDCS group, stimulus type (1,2,3,4, or 9), anterior-posterior, and left-right spatial distribution, with a large effect size [Wilks' $\Lambda = 0.01$, $F(40,14) = 3.43$, $p = 0.008$, $\eta^2 = 0.908$]. Significant simple effects were found when comparing spatial distribution of change in N2 amplitude by group for numbers 1, 2, and 3, but not 4 & 9.

For number 1 (the first number in the sequence), a three-way simple interaction was present between tDCS group, left-right, and anterior-posterior distribution [$F(12,42) = 2.22$, $p = 0.029$, $\eta^2=0.388$], which is represented by simple-simple interactions representing tDCS group differences in the left/right direction in central channels [$F(4,52) = 2.92$, $p = 0.057$, $\eta^2=0.184$] and parietal channels [$F(4,52) = 2.86$, $p = 0.004$, $\eta^2=0.272$], and in the anterior-posterior direction at the mid-line [$F(6,78) = 2.37$, $p = 0.042$, $\eta^2=0.154$]. These three effects can be boiled down to four simple[3] main effects of tDCS group, existing within channels AF8, FpZ, CZ, and P3. At left and mid-line anterior frontal areas (channels AF8 and FpZ), a greater decrease in N2 amplitude was found for Active-B than Sham. This can be seen as a large decrease in amplitude from baseline to during tDCS in the anterior frontal areas in Active-B in the top panels of Figure 9 (p's < 0.01). At central midline electrode CZ, a difference in N2 amplitude was found for both Active groups compared to Sham, representing the *increased* amplitude in Sham, and *decreased* amplitude for Active groups at this channel (p's < 0.01). This effect is evident in both panels of Figure 9, but is most apparent in the top panels, and can be seen as more negative response at the top of the head during tDCS in active groups. At left parietal electrode P3, an opposing difference in N2 amplitude was found for both Active groups compared to Sham, representing the *decreased* amplitude in Sham, and *increased* amplitude for Active groups at this channel (p's < 0.05). This effect is seen as an increasing positivity on the left in active groups in the lower panel of Figure 9. See Table 6 for descriptive and inferential statistics.

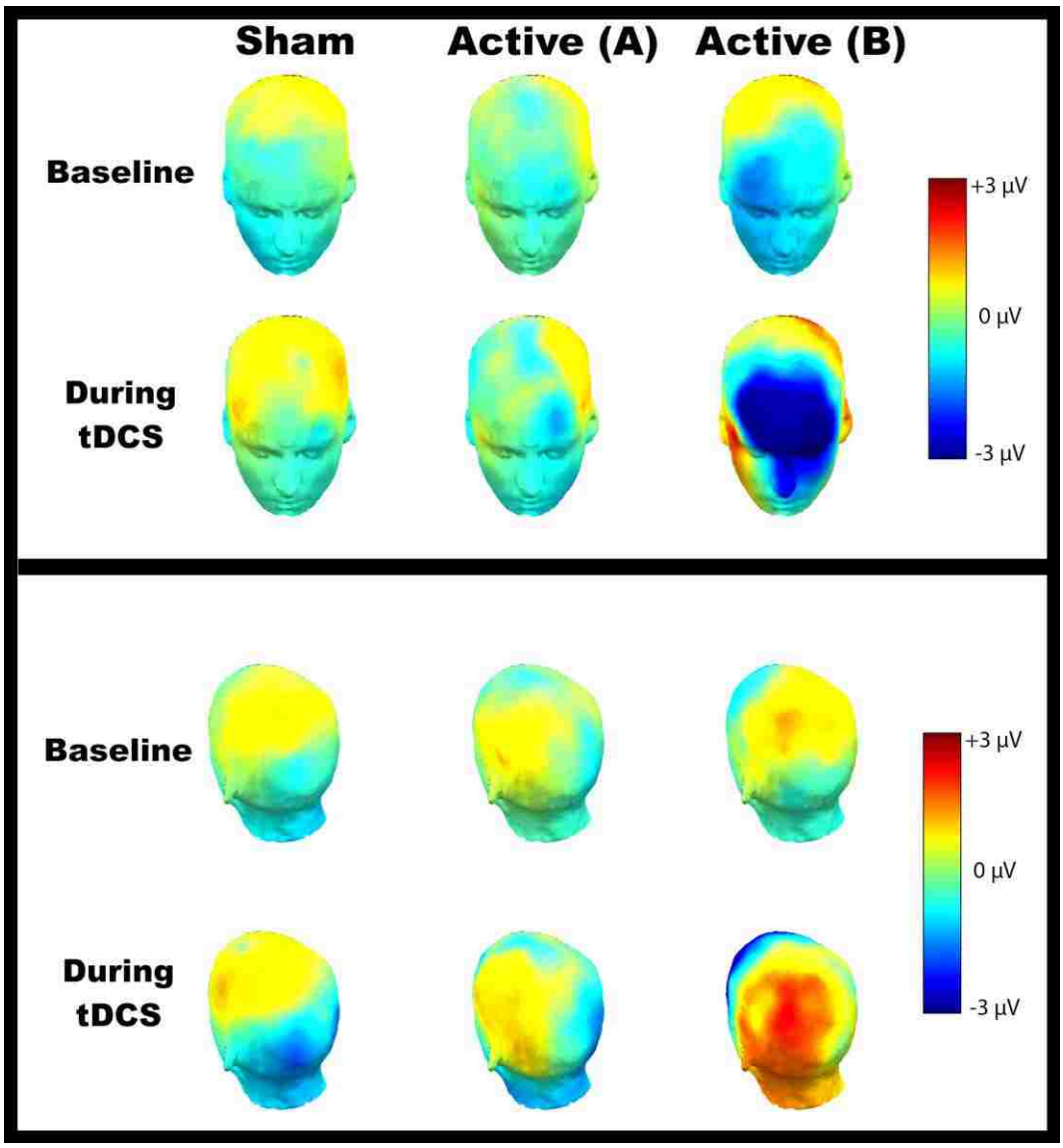


Figure 9. Scalp maps showing spatial distribution of mean N2 amplitude (average response 200-350 ms after stimulus onset) in response to the number 1 in the F-SART. Upper and lower panels show the same response, only from different angles. Within each panel, N2 spatial distribution is plotted by tDCS condition (left to right) for baseline (upper row) and during-tDCS (lower row) testing phases. Cold colors indicate positive amplitude, while warm colors indicate negative amplitude.

Change in N2 response amplitude during-tDCS at right anterior frontal channel AF8 was positively correlated with extroversion ($r = 0.62$; $p = 0.042$), and change at central mid-line channel CZ was positively correlated with Magical Ideation ($r = 0.61$; $p = 0.025$) in Active subjects, while change at CZ was negatively correlated with extroversion in Sham participants ($r = -0.65$; $p = 0.021$). Within Sham participants, amplitude change in channels AF8, FpZ, and P3 (but not CZ) were highly inter-correlated (p 's < 0.05). Within Active participants AF8, CZ, and P3 (but not FpZ) were highly inter-correlated (p's < 0.05).

For N2 response to the number 2 during tDCS (the number preceding the "No-Go" trial), another three-way simple interaction was present between tDCS group, left-right, and anterior-posterior distribution [$F(12,42) = 2.77$, $p = 0.007$, $\eta^2=0.442$]. This effect is driven by a single significant simple-simple 2-way interaction between tDCS group and anterior-posterior direction in right channels [$F(6,78) = 2.77$, $p = 0.027$, $\eta^2=0.176$]. Trend-level significant differences further characterizing this effect were found at right parietal electrode site P4, with significantly greater decrease in N2 amplitude in Active-B compared to Active-A and Sham (p's < 0.01). This effect is seen as a shift from left to right lateralization of posterior positivity in Active-A, and a shift from right to left lateralization of posterior positivity in Active-B in Figure 10. See Table 6 for descriptive and inferential statistics.

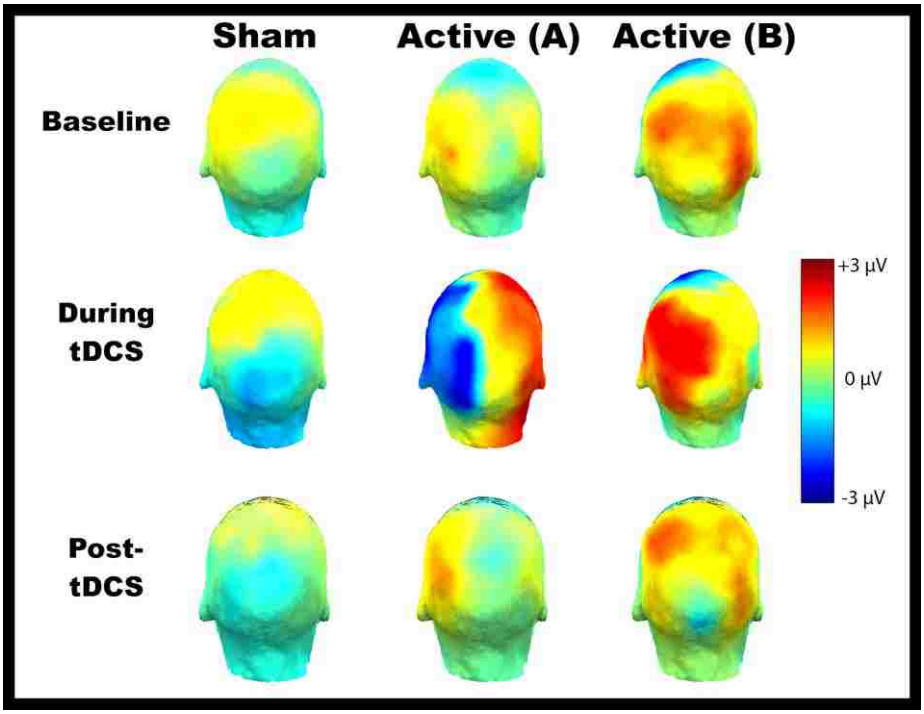


Figure 10. Scalp maps showing spatial distribution of mean N2 amplitude in response to the number 2 in the F-SART (average response 200-350 ms after stimulus onset). N2 spatial distribution is plotted by tDCS condition (left to right) for baseline (upper row), during-tDCS (center row), and post-tDCS (lower row) testing phases. Cold colors indicate positive mean amplitude, while warm colors indicate negative mean amplitude.

Right parietal change in mean amplitude of N2 response to number 2 during tDCS was positively correlated with many variables in Sham and Active groups. For Sham, N2 amplitude change was correlated with R-SART *d'* scores at the post-tDCS test phase (r = -0.74; p = 0.006), RT variability at all three assessments (r = 0.70 – 0.72; p*'s* < 0.05), and number of impatient responses in during-tDCS and post-tDCS assessments in the R-SART (r = 0.58 – 0.68; p*'s* < 0.05). For Active, change in N2 response to number 2 was positively correlated with response to

number 1 at midline anterior frontal channel FpZ ($r = 0.87$; $p < 0.001$), number of impatient responses during-tDCS and post-tDCS assessments in the R-SART ($r = 0.67 – 0.77$; p *'s*<0.05), and baseline impulsivity index ($r = -0.64$; $p = 0.033$). No correlations were present with behavioral variables in the F-SART.

For number 3 (the "No-Go" trial), two separate two-way simple interactions were present representing differences between tDCS groups in the left-right [$F(4,50) = 6.15$, $p < 0.001$, $\eta^2 = 0.330$] and anterior-posterior directions [$F(6,48) = 2.58$, $p = 0.030$, $\eta^2 = 0.244$]. These effects represent the large left/mid-line frontal decrease seen in Active-B and (to a lesser extent) Active-A groups in Figure 11, and is illustrated in simple-simple main effects of tDCS group at both mid-line channels and anterior frontal channels (p's < 0.01). See Table 6 for descriptive and inferential statistics. Change in N2 response amplitude to number 3 at anterior frontal channels during-tDCS was positively correlated with change in tDCS-related voltage in Active participants ($r = -0.69$; $p = 0.027$). No correlations were found with anterior frontal or mid-line N2 amplitude changes for Sham participants.

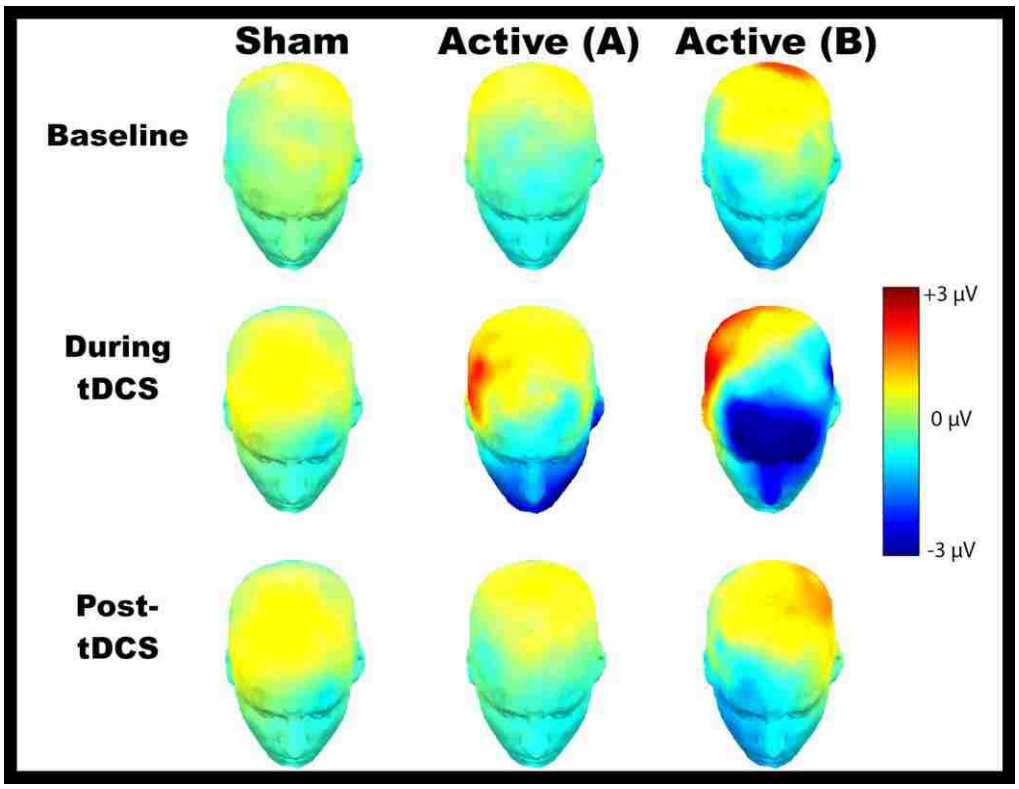


Figure 11. Scalp maps showing spatial distribution of mean N2 amplitude in response to the number 3 in the F-SART (average response 200-350 ms after stimulus onset). N2 spatial distribution is plotted by tDCS condition (left to right) for baseline (upper row), during-tDCS (center row), and post-tDCS (lower row) testing phases. Cold colors indicate positive mean amplitude, while warm colors indicate negative mean amplitude.

		$F(2,26)$	p	η^2	Sham M ± SEM (μV) [95% CI]	Active (A) M ± SEM (μV) [95% CI]	Active (B) M ± SEM (μV) [95% CI]
#1	AF8	4.00	0.031	0.235	1.06 ± 0.73 [-0.45 – 2.56]	-0.79 ± 0.77 [-2.36 – 0.79]	-2.42 ± 1.04 [-4.55 – -0.29]
	FpZ	8.83	0.001	0.404	0.12 ± 0.30 [-0.50 – 0.74]	-.54 ± 0.312 [-1.12 – 0.10]	-2.08 ± 0.43 [-2.95 – -1.20]
	CZ	6.41	0.005	0.330	0.65 ± 0.23 [0.17 – 1.13]	-0.39 ± 0.24 [-0.89 – 0.11]	-0.52 ± 0.32 [-1.20 – 0.15]
	P3	6.07	0.007	0.318	-1.04 ± 0.54 [-2.15 – 0.08]	0.63 ± 0.56 [-0.53 – 1.79]	2.13 ± 0.76 [0.56 – 3.70]
#2	P4	3.13	0.060	0.194	0.02 ± 0.84 [-1.71 – 1.75]	0.22 ± 0.88 [-1.59 – 2.02]	-3.22 ± 1.18 [-5.66 – -0.78]
#3	Midline	20.67	<0.001	0.614	0.38 ± 0.15 [0.07 – 0.69]	-0.36 ± 0.16 [-0.68 – -0.04]	-1.26 ± 0.21 [-1.69 – -0.83]
	A. Frontal	10.24	0.001	0.441	0.65 ± 0.30 [0.04 – 1.27]	-0.47 ± 0.31 [-1.11 – 0.17]	-1.63 ± 0.42 [-2.50 – 0.76]

Table 6. One-way simple main effects of tDCS group on N2 amplitude change scores during tDCS (during-tDCS minus baseline test phase) in the F-SART. #'s indicate the stimulus type in the F-SART.

MANOVA results comparing lasting effects of tDCS (post - baseline) indicated differences in spatial distribution change in the left-right axis between tDCS groups by a three-way interaction between tDCS group, stimulus type, and left-right distribution [Wilks' Λ =0.23, $F(16,38) = 2.58$, $p = 0.008$, η^2=0.521]. Simple interaction effects were found only within number 3 ("No-Go") trials [$F(4,52) = 3.24$, $p = 0.024$, η^2=0.200], where simple-simple main effects of tDCS group existed in left channels [$F(2,26) = 3.46$, $p = 0.046$, η^2=0.210], driven by a significant increase in N2 amplitude in the Active-B group compared to Sham [Sham = -0.37 ± 0.20 μV;

95% CI = (-0.77 μV – 0.05 μV); Active-B = 0.48 ± 0.42 μV; 95% CI = (-1.28 μV – 0.45 μV); $p_{(AvS)} = 0.022$].

Event-Related Potentials: Medial Frontal Negativity in the SWEETYPI Gambling Task

Prior to statistical comparison, number of trials surviving rejection criteria was assessed for rejection of noisy ERPs, and agreement with assumptions of MANOVA was examined. One participant in the Active-B group had greater than 50% of trials excluded for post-tDCS assessments, while two participants each from the sham group and the Active-A group had more than 50% of trials excluded for the during-tDCS or baseline assessment of MFN in the SWEETYPI gambling task, and during-tDCS MFN difference scores were replaced for these participants using linear interpolation. No univariate or bivariate outliers were detected in these data and no multivariate outliers were found to exist using Mahalanobis distance with $p < 0.001$. Very few variables violated the assumptions of normality: no variable exceeded skewness of ±2, and 2/12 dependent variables tested exhibited kurtosis greater than 7; however this seemed to be due to a bimodal distribution of means in many cases, and transformations were not successful in reducing kurtosis overall.

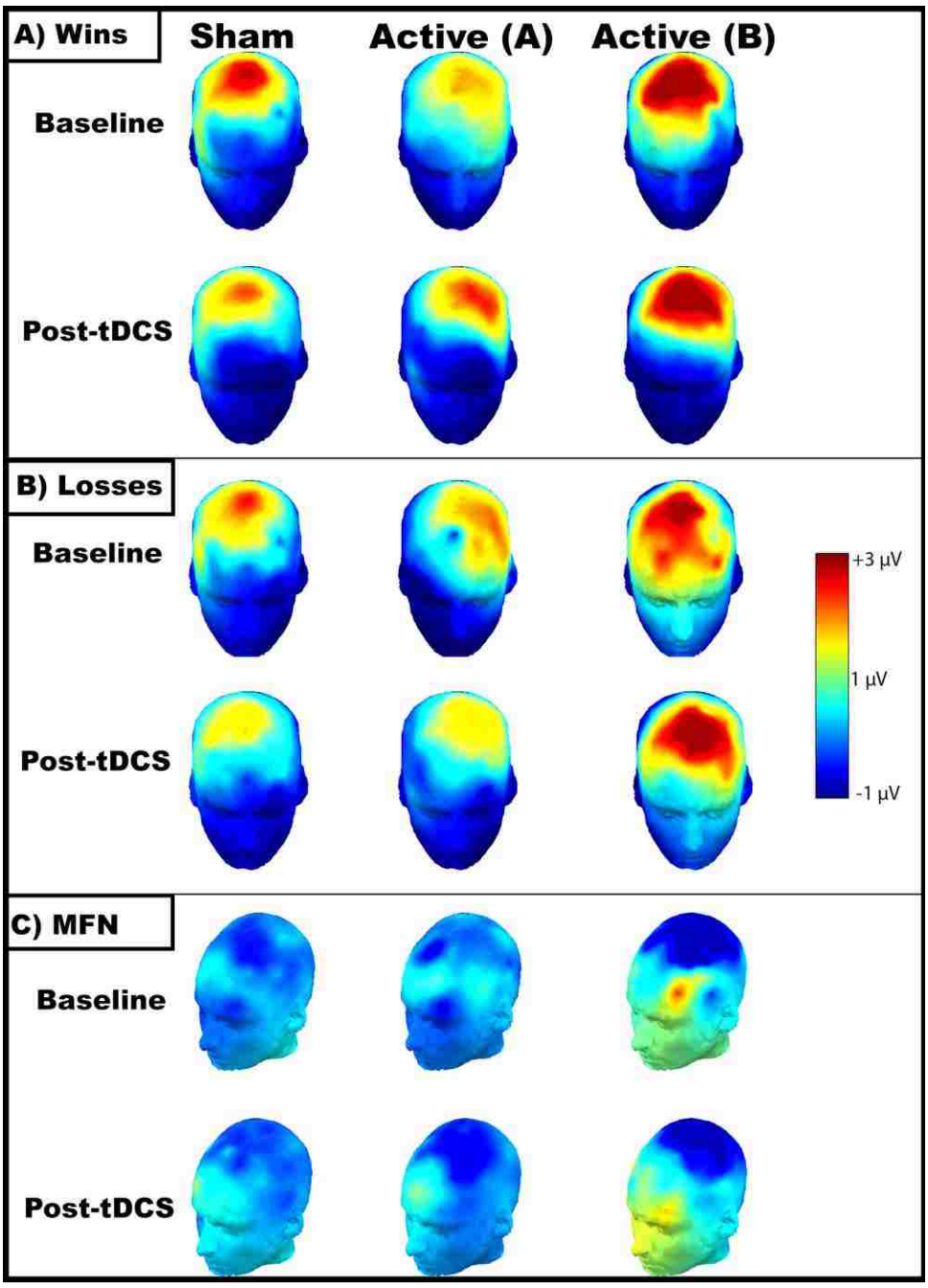


Figure 12. Scalp maps showing spatial distribution of mean amplitude of the response to feedback in the SWEETYPI gambling task in the window from 200 – 350 ms after stimulus onset for (A) wins, (B) losses, and (C) medial frontal negativity difference waves (loss minus win). Scalp maps are plotted for each response by tDCS condition (left to right) for baseline (upper row) and post-tDCS (lower row) test phases. Cold colors indicate positive mean response amplitude, while warm colors indicate negative mean response amplitude.

No effects of tDCS on MFN amplitude were found during tDCS; however, MANOVA results comparing lasting effects of tDCS (post-tDCS minus baseline) indicated trend-level differences in spatial distribution change between tDCS groups by a three-way interaction between tDCS group, left-right, and anterior-posterior distribution with a medium effect size [Wilks' Λ =0.41, $F(12,42) = 1.98$, $p = 0.050$, $\eta^2 = 0.362$]. This interaction is best characterized by a simple two-way interaction between left-right lateralization and tDCS group in frontal channels [$F(4,50) = 2.91$; $p = 0.031$; $\eta^2 = 0.189$], which was driven by differences in the left frontal region, at electrode F3, where a significantly greater decrease in MFN amplitude (increased negativity) was present for Active groups compared to Sham (p's < 0.05, see Figure 12, panel C). Closer examination of these differences revealed that mean amplitude increased for wins in the 200 – 350 ms time window in Active groups, rather than a decreased response to losses (Figure 13). A 2 x 3 ANOVA assessing differences in response amplitude change for wins and losses between tDCS groups confirmed this assessment of the data [$F(2,26) = 5.15$; $p = 0.044$; $\eta^2 = 0.214$]. Though differences in response amplitude are apparent for both wins and losses, responses to wins reached significance in the one-way ANOVA, with significant differences between Active-B and Sham ($p < 0.005$) and trend-level differences between Active-A and Sham ($p = 0.079$). Trend-level differences were also present for change in response amplitude for losses between Active-A and Sham participants, in the opposite direction ($p = 0.064$). See Table 7 for descriptive and inferential statistics. See Figure 12 for scalp maps of responses to wins, losses, and MFN difference waves. Post-tDCS change in response amplitude to losses at F3 was correlated with the attention scale of the Barratt ($r = -0.77$; $p = 0.005$) and post-tDCS change in P3 response amplitude to "No-Go" trials in the R-SART ($r = 0.67$; $p = 0.026$) in Active participants. No correlations were present for Sham participants.

	$F(2,26)$	p	η^2	Sham M ± SEM (μV) [95% CI]	Active (A) M ± SEM (μV) [95% CI]	Active (B) M ± SEM (μV) [95% CI]
MFN	10.29	0.044	0.214	0.58 ± 0.49 [-0.44 – 1.59]	-1.07 ± 0.51 [-2.12 – -0.01]	-1.25 ± 0.70 [-2.68 – 0.19]
Wins	5.25	0.012	0.287	-0.45 ± 0.31 [-1.10 – 0.19]	0.29 ± 0.33 [-0.39 – 0.96]	1.29 ± 0.44 [0.38 – 2.20]
Losses	2.10	0.123	0.139	0.13 ± 0.32 [-0.54 – 0.79]	-0.77 ± 0.34 [-1.47 – -0.08]	0.05 ± 0.46 [-0.89 – 0.99]

Table 7. One-way simple main effects of tDCS group on post-tDCS mean amplitude change scores (post-tDCS minus baseline testing phase) for medial frontal negativity (MFN), wins, and losses at left frontal electrode F3 in the SWEETYPI gambling task.

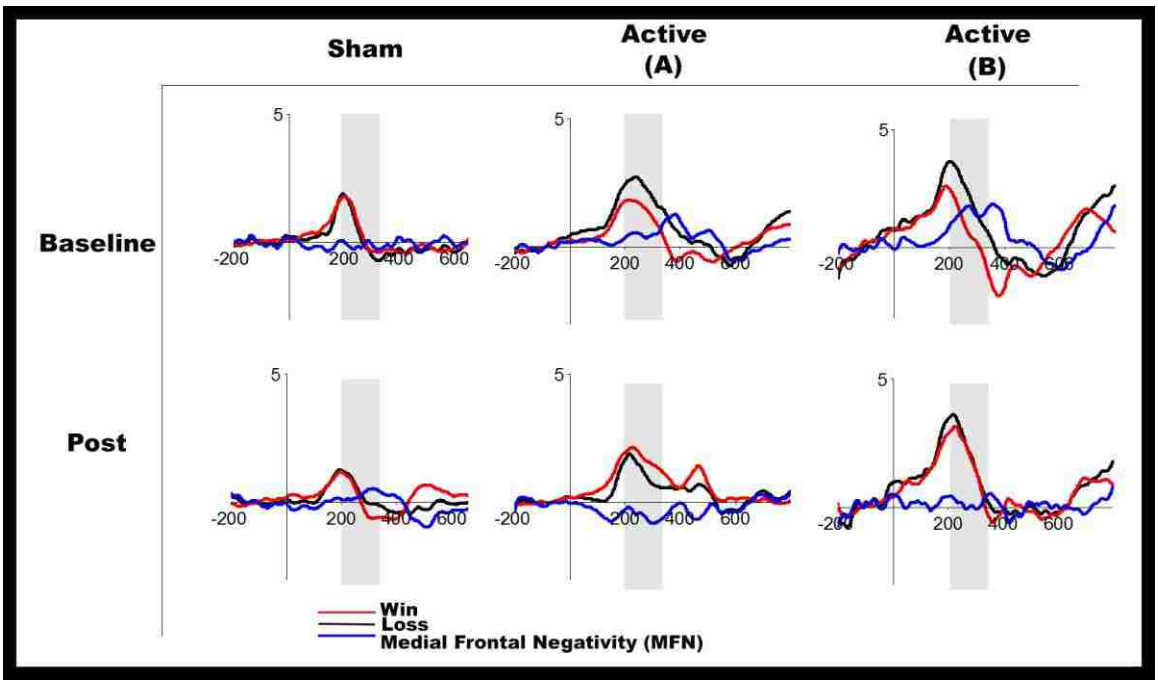


Figure 13. ERP traces at electrode site F3 for wins (red), losses (black), and MFN difference waves (blue) obtained during the SWEETYPI gambling task. The six plots shown represent data from (left to right) Sham, Active-A, and Active-B tDCS groups, for (top to bottom) baseline and post-tDCS test phases. The y-axes range from -3 to 5 μV and cross the x-axes at feedback stimulus onset. The x-axes range from 200 ms before to 800 ms after stimulus onset. The six vertical grey rectangles represent the window of analysis, from 200 to 350 ms after stimulus onset.

Assessment of Possible Confounds

None of the reported effects were associated with task order, as assessed by multiple individual univariate ANOVAs comparing each of the variables at which group differences were observed (all p's > 0.1, all η^2's < 0.1). There was a significant difference in retrospective ability to detect tDCS condition between groups, as indicated by assessment via the Mood

Questionnaire given after tDCS (*p's* < 0.01 for retrospective sensation rating and ability to detect tDCS condition by χ^2 test; see Appendix B), where approximately 1/3 (10/29) of participants were able to correctly guess tDCS condition, and the ability to detect tDCS condition did not differ by group ($p > 0.1$, $\chi^2 = 0.03$). Also, sensation ratings taken during tDCS were not significantly different by group (all *p's* > 0.1), and there was no difference in behavioral or ERP amplitude between those who indicated that they could or could not detect tDCS condition, as assessed by multiple individual univariate ANOVAs comparing each of the variables at which group differences were observed (all *p*'s > 0.1, all η^2's < 0.1).

CHAPTER 4: DISCUSSION

In this study of tDCS effects on the behavioral and electrophysiological correlates of cognitive control of attention and decision making, results have generally confirmed the hypotheses which initiated this research. Behavioral effects in this study were greatest in the Active-A group and were most pronounced for attention-related assessments of cognitive control. In fact, Active-A outperformed Sham for all measures tested during tDCS and most post-tDCS measures. This was not true for Active-B, although large effects were seen in some cases, such as effects on slope of RT variability in the R-SART during- and post-tDCS testing phases. Although these multivariate differences are visually apparent when comparing means/variability and pairwise t-tests, as shown in Figure 5, only two measures achieved significance by univariate simple effect testing, and resulting pairwise comparisons within those effects indicate that the strongest effects occurred during tDCS.

Significant effects of tDCS on impulsiveness were present in the overall MANOVA, although these differences were not evident in individual univariate tests. No univariate test or pairwise comparison of simple effects demonstrated meaningful significant results. The only significant pairwise comparisons were driven by baseline differences among the groups (Figure 6, percent rational choices and proportion of false alarms). As with the attention-related effects of tDCS on cognitive control, visual comparison of group means/variances plotted in Figure 6 points to stronger behavioral effects for the Active-A condition than for Active-B. Comparisons of group mean differences by test phase were most dramatic for measures of impatience (impulsivity index, average wager, and proportion of impatience trials), with little difference in measures of non-planning impulsiveness (percent rational choices and risk adjustment index) and motor impulsiveness (false alarms). This assessment of the results of individual measures should

be accepted with caution, however, as statistical significance was found only for the omnibus multivariate test of the combined dependent variable representing cognitive control of impulsiveness.

Effects of tDCS on ERP components examined in this study help to elucidate the effects on cognitive control and decision making; however, the interpretation of some of these ERP effects is somewhat different from the anticipated findings. It was predicted that amplitude of the P3 response to "No-Go" stimuli recorded at parietal channels would be *increased* by tDCS in the R-SART, based on the known relationship between this response and measures of attention in previous studies. Significant differences were found to exist in the time window of the P3 response here; however, contrary to this prediction, effects of tDCS on ERP amplitude in the 300 – 500 ms time window were generally related to a *decrease* in amplitude during tDCS at left frontal channels, with this decrease occurring at a more anterior distribution for "Go" trials compared to "No-Go" trials.

Closer examination of the ERP waveforms for responses to "No-Go" stimuli revealed a somewhat different effect than had been predicted, in which the so-called N3/Frontal P4 response was enhanced in left frontal areas. The N3 response is less well-known than the P3. It is reported in EEG studies of stimulus salience, where amplitude of the N3 changes as a function of conscious cognitive control of spatially-directed attention (e.g., Proverbio, Riva, & Zani, 2009), and may reflect greater cognitive control over attention toward the location of stimuli in the SART task. Interestingly, this left N3 effect persisted somewhat into the post-tDCS test phase, suggesting effects of tDCS were not only restricted to the period when stimulation was being delivered. These effects were most pronounced for the Active-B group, although these results should be interpreted with caution due to the small sample size of this group. Post-tDCS change

in amplitude of the N3 response was correlated with change during tDCS only for Sham participants, which likely demonstrates the progression of fatigue in these participants over time (i.e. decreased N3 response at both testing phases). In the Active-A group, post-tDCS change in amplitude of this response correlated with impulsivity index during and post-tDCS, but not at baseline, suggesting a link between the effects of tDCS on these phenomena.

A separate effect was present for "Go" trials within this time range, in which enhanced negativity of the N2 response was related to the frontal negativity seen in both Active-A and Active-B during tDCS. The N2, as described in detail in Chapter 1, has been linked to cognitive control of attention in a variety of studies. Interestingly, the N2 response is most often cited as a response to conflict arising from competition between execution and inhibition of a response, where greater N2 response is present for stimuli with low frequency of occurrence, irrespective of response (Nieuwenhuis *et al.*, 2003). In the R-SART, all stimuli have equal probability of occurrence; therefore, this enhancement of the N2 response to "Go" stimuli may reflect greater assessment of defining stimulus characteristics in the task.

The effects of tDCS on the N2 response were examined more explicitly in the F-SART, where complex differences were found during and post-tDCS. Significant effects in this task were limited to the responses to stimuli with the most attentional salience, as predicted. During tDCS, amplitude of the N2 response to the first stimulus in the sequence (number 1) was altered in (mostly left) frontal and parietal regions. Decreases in amplitude at left frontal regions were very similar in nature to differences found in the analysis of responses to "Go" stimuli in the R-SART during tDCS. These effects were so similar, in fact, that they might be considered indicative of the same phenomenon. Responses to the "No-Go" stimulus (number 3) in the F-SART further demonstrated N2 alterations related to tDCS, similar to the ERP effects for

responses to the number 1 stimuli in the F-SART, or the "Go" stimuli in the R-SART. This frontal negativity is most pronounced in the Active-B group, though it can be seen in the Active-A group as well, and the effect is confirmed by statistical significance of differences at midline and frontal electrodes.

The parietal increase in N2 amplitude in response to the first number in the sequence (number 1) in the F-SART is somewhat different. This difference is quite interesting as the distribution of the effect is distant from the stimulating electrode and positivity in this spatial area and time range has been linked to attentional demands of the task at hand, particularly within the F-SART (Manly *et al.*, 2003). This change in amplitude in parietal channels may be in some way related to the greater N3 negativity present in "No-Go" trials in the R-SART, although no correlations were present between these responses in either group. A similar change was seen in parietal channels in response to the stimulus preceding the "No-Go" stimulus in the F-SART (number 2), though statistical results of simple effects do not validate the group differences seen here. Increased amplitude is seen in parietal channels for both Active tDCS groups during stimulation, with a highly-lateralized polarity of the response. Interestingly, the right-positive/left-negative orientation seen in the Active-A group matches the bias seen in energy distribution modeling presented in Figure 3. Although not statistically significant, the effect of tDCS on N2 response amplitude at parietal channels seems to persist somewhat into the post-tDCS test phase. Right parietal change in mean amplitude of N2 response to number 2 during tDCS was positively correlated with many variables in Sham and Active groups, however similar correlations were found for many of these variables in both groups. The only correlations with N2 response which differentiated active and sham groups were with post-tDCS *d*' in the R-SART, and baseline impulsivity in the SWEETYPI gambling task and the direction of these

correlations was unexpected and difficult to interpret. Further assessment of the N2 response effect in relation to behavioral changes associated with tDCS is warranted.

The amplification of the N2/N3 responses by tDCS in this study is interpreted here as an effect on cognitive control over attention to the task, regardless of the specific spatial or temporal nature of the effect. Previous research examining effects of tDCS over right VLPFC suggests an effect on alertness to temporal cues (Coffman *et al.,* 2012a). As N2 responses were enhanced to some degree over parietal areas in this study, and N3 responses that were seen here have been linked to cognitive control over spatial attention in previous work (Proverbio *et al.,* 2009), the results here seem to suggest a relationship with direction of spatial attention as well, although no behavioral data is available to inform this distinction, as spatial attention was not measured in this study. In any case, the frontal N2 response is thought to be indicative of the degree to which cognitive control is devoted to the task (Nieuwenhuis *et al.,* 2003). This has been shown through variation of task difficulty (Polich, 1987), dual-task interference (Braver, Reynolds, & Donaldson, 2003), and pharmacological manipulations of alertness (Sunohara *et al.,* 1999). Also, this response is deficient in clinical populations where cognitive control is a key defining factor, such as ADHD (Schmajuk *et al.,* 2005) and individual differences in related components such as the MFN response to positive versus negative feedback have been linked to clinical issues related to impulsive decision making, such as substance use disorders and addiction (Dong, Zhou, & Zhao, 2011).

Though effects were present between tDCS groups in the amplitude of the MFN difference wave, which is related to the N2 response in many ways, closer examination of these effects suggested an alteration of deferential response to wins and losses across the entire frontal P2-N2-P3 complex. Significant differences were found in the change in responses to positive

feedback, where increased evoked response to wins was found for Active groups compared to sham at the post-tDCS test phase. Post-tDCS change in response amplitude to losses at left frontal channels was also correlated with post-tDCS change in N3 response amplitude to "No-Go" trials in the R-SART in Active participants, linking effects on cognitive control of motor inhibition to effects on reward responsiveness in this study. This finding is particularly relevant in light of research showing differential responses to reward and punishment in stimulating versus instrumental risk takers, where stimulating risk takers are more responsive to losses and instrumental risk takers are more responsive to wins. Increased response to wins and decreased response to losses in this case may be indicative of increased instrumental risk assessment in the active tDCS groups. Increased risk adjustment index from baseline with Active tDCS alludes to this as well, although these effects did not achieve statistical significance here.

Along these lines, post-tDCS change in left frontal response amplitude to losses was correlated with the attention scale of the Barratt in Active participants, where higher trait-level cognitive control of attention was related to greater change in response to losses from baseline. Post-tDCS change in N3 response to "No-Go" trials in the R-SART was also significantly correlated with the attention scale of the Barratt in Active subjects and, as stated previously, these responses were inter-correlated. Furthermore, change in this response during tDCS was correlated with cognitive control of impulsive behavior, as measured by the behavioral inhibition scale of the BIS/BAS. These correlational results suggest that tDCS may increase cognitive control in those predisposed to utilize cognitive control on an everyday basis. Correlations were also present between N2 response to the number 1 stimulus in the F-SART during tDCS and extroversion/magical ideation personality measures, where opposing direction of correlations was found for extroversion in Active and Sham tDCS groups. This is interesting, given previous

tDCS research suggesting relationships between tDCS effectiveness and the extroversion personality trait (Peña-Gómez *et al.*, 2011); however, no other correlations with personality trait variables were found in this study, and so no attempt was made to further interpret these results.

These results support the involvement of right VLPFC in cognitive control, though the specific role of this region remains uncertain. Anodal tDCS of the right VLPFC in this study enhanced behavioral measures of cognitive control of attention and, to a lesser extent, impulsive decision making. Additionally, left frontal ERP responses near DLPFC were altered in ways which support the role of right VLPFC in coordination and direction of response selection mechanisms in DLPFC, leading to greater attention in the task. Enhancement of parietal ERPs are also in concordance with this hypothesis, as this indicates even further downstream effects of tDCS via attentional control. Polarity and location of the effects of tDCS on response amplitude to the number 2 stimulus in the F-SART in relation to modeled tDCS energy distribution is striking, and this alteration in the whole-scalp recording may be important with regard to the effect of tDCS on cognitive control in this study.

These results are particularly relevant to clinical populations with cognitive control deficits, such as individuals with ADHD, FASD, schizophrenia, and addictions (Barkley, 2005; Fryer *et al.*, 2007, Cohen, Braver, & O'Riley, 1996; Dong, Zhou, & Zhao, 2011). Current treatment strategies for deficits in cognitive control are less than ideal for multiple reasons. Medications such as amphetamines have many unwanted side effects, such as irritability, dizziness, and high blood pressure (Barkley *et al.*, 1990). Cognitive/behavioral therapies, while safe and effective, can be time-intensive, leading to problems with compliance (Helbig & Fehm, 2004). The development of tDCS as a treatment for problems with cognitive control could circumvent these issues: tDCS is easy to administer, inexpensive, and fast-acting. Future studies

might compare the effectiveness of these methods directly, or study the effects of combining different treatment methods. Indeed, Nitsche and colleagues (2004) have reported enhancement of the duration of the effects of anodal tDCS using amphetamines in a study of pharmacological manipulation of the tDCS effects on motor cortex stimulation, and similar effects should be expected with stimulation of systems more closely related to the endogenous mesolimbic dopamine system, such as VLPFC and other cognitive control areas (Oades & Halliday, 1987).

Limitations of this research were primarily related to the participant sample. Sample size was small for all groups, but particularly within the Active-B group, where a disproportionate number of participants were discontinued for high sensation ratings related to tDCS. Interestingly, there was no difference in average sensation between groups when restricting the analysis to subjects making it through the entire study. Future studies should examine differences in sensation between extracephalic versus cephalic cathode placements for this reason. The external validity of the study was also somewhat limited by the psychology undergraduate student population from which participants were sampled. This population may not be representative of the population at large for multiple reasons, including motivation issues associated with course-credit-based compensation, representativeness of social economic status of college students, and gender bias. The strong bias in female over male enrollment in Psychology courses likely contributed to the low number of male participants in this study. Also, inclusion of intelligence measures, such as IQ, may have enabled further characterization of baseline differences between groups, leading to greater power to detect effects of tDCS. Finally, this was the first research study performed at the new Psychology Clinical Neuroscience Center at the University of New Mexico, and technical difficulties associated with the use of new

equipment resulted in the exclusion of a greater number of participants than would normally be seen for a study of this size.

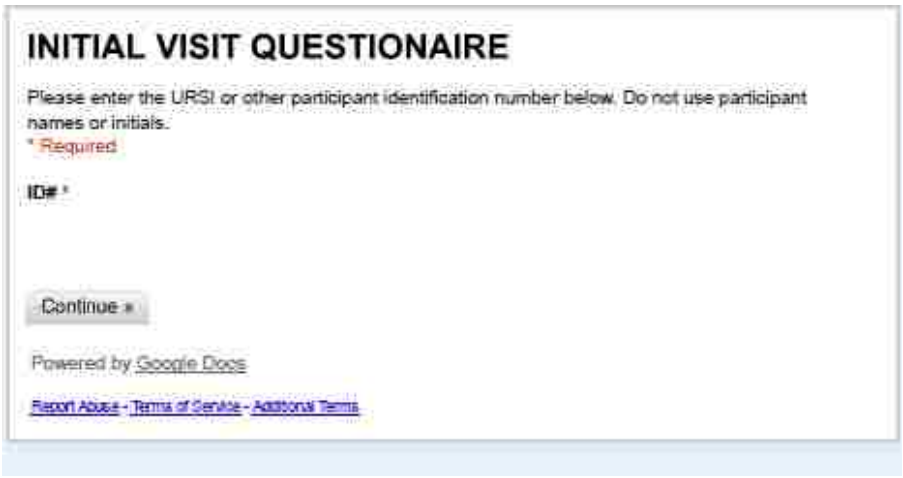
These results are being further examined in clinical and healthy normal populations using these and other tasks of cognitive control over attention and decision making. Future manuscripts will focus on application of this research to FASD using this protocol, as deficits in cognitive control are a hallmark of this disorder. It is hoped that tDCS will prove effective in normalizing deficiency in cognitive control in FASD in these studies, furthering the development of tDCS as a clinical tool. Additionally, the correlation between change in N2 response amplitude for number 3 stimuli in the F-SART and change in tDCS-related voltage in Active participants suggests that specific individual differences in the voltage associated with tDCS current may be important to its effects. Future studies will examine this phenomenon in more detail.

CHAPTER 5: CONCLUSIONS

This research was initiated with specific hypotheses related to the enhancement of cognitive control with tDCS. It was hypothesized that anodal tDCS of the right VLPFC would enhance cognitive control of attention and impulsiveness, that tDCS would enhance ERP responses related to cognitive control, and that both tDCS conditions would exhibit effects in these domains. Each of these hypotheses was supported by the results of this study, though there are caveats to the interpretation of these findings, and further research is warranted. Notwithstanding these limitations, basic scientific and clinical implications of the aforementioned experiments are significant. This study lends further support to the role of right VLPFC in cognitive control, demonstrates the effectiveness of tDCS for modulation of cognitive control, and suggests an effect of tDCS on impulsive decision making that may be related to the effects on cognitive control of attention. Although behavioral effects on impulsive decision making and cognitive control of attention were not inter-correlated, specific alterations in EEG measures of cognitive control were correlated with behavioral effects obtained in other measures, suggesting a common factor of cognitive control over alteration in these behavioral affects. Of note is the alteration of N3 amplitude to "No-Go" trials in the R-SART, which was correlated with change in response to feedback in the SWEETYPI gambling task, and effects on impulsivity during and post-tDCS. Replication and further examination of these effects are needed here; however, researchers studying the effects of anodal tDCS of the right frontal cortex on decision making should consider the potential impact of cognitive control when generating new hypotheses.

APPENDICES

APPENDIX A: INITIAL QUESTIONNAIRE FORM



INITIAL VISIT QUESTIONAIRE

Please enter the URSI or other participant identification number below. Do not use participant names or initials.

* Required

ID# *

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For the following questions, please respond yes or no.

Have you ever experienced a learning difficulty or been enrolled in special education classes? *

- Yes
- No

If yes, please explain:

Have you ever been diagnosed with or thought you might have an attention deficit? *

- Yes
- No

If yes, please explain:

Have you ever had a head injury? *

- Yes

- No

If yes, was there loss of consciousness?

- Yes
- No

If so, how long?

Have you ever had seizures, fainting spells, or migraines? *

- Yes
- No

If yes, please explain:

Have you been hospitalized for a possible psychological disorder in the last 6 months? *

- Yes
- No

Have you ever been treated (or thought you needed treatment) for alcohol or drug abuse? *

- Yes
- No

If yes, please explain:

Are you currently taking any medications? *

- Yes
- No

If yes, please list what and how much, including prescription or over-the-counter medicines, pain relievers, oral contraceptives, herbal supplements, etc.

Do you wear glasses or contacts? *

- Glasses
- Contacts
- Both
- Neither

If yes, are you:

- Nearsighted

- Farsighted
- Both

Do you have any visual problems not correctable by lenses, such as color blindness or astigmatism? *

- Yes
- No

Do you have any hearing loss that you are aware of? *

- Yes
- No

If yes, please explain:

Have you had any major surgeries or received long-term treatment for any illness? *

- Yes
- No

If yes, please explain:

INITIAL VISIT QUESTIONAIRE

* Required

For the following questions, please respond yes or no:

How many hours did you sleep last night? *

What is your average amount of sleep per night? *

Do you drink caffeine? *

- Yes
- No

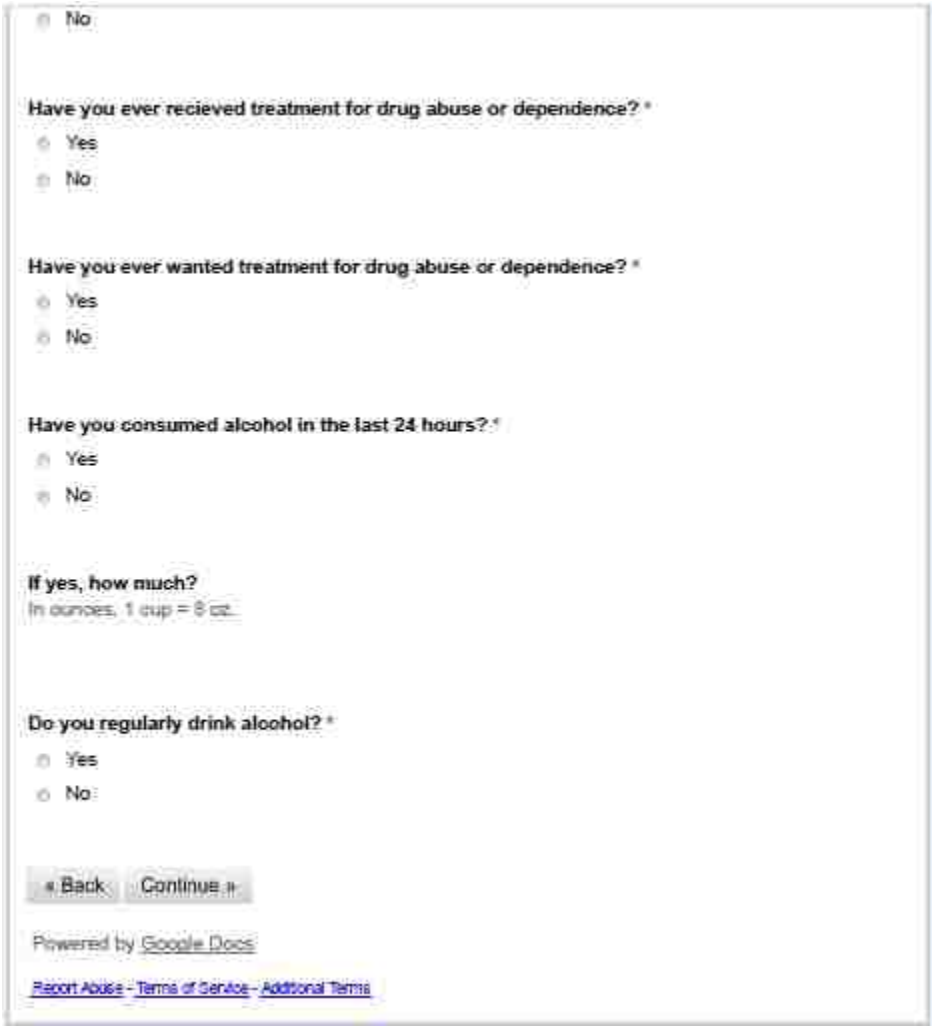
If yes, when was your last caffeinated beverage?

How much?
In ounces: 1 cup = 8 oz.

How many drinks (ounces of coffee/soda) per day on average?
1 cup = 8 oz.

Have you used any illicit drugs (e.g. stimulants, opiates, hallucinogens) in last 24 hours? *

- Yes



No

Have you ever recieved treatment for drug abuse or dependence? *

Yes

No

Have you ever wanted treatment for drug abuse or dependence? *

Yes

No

Have you consumed alcohol in the last 24 hours? *

Yes

No

If yes, how much?

In ounces, 1 cup = 8 oz.

Do you regularly drink alcohol? *

Yes

No

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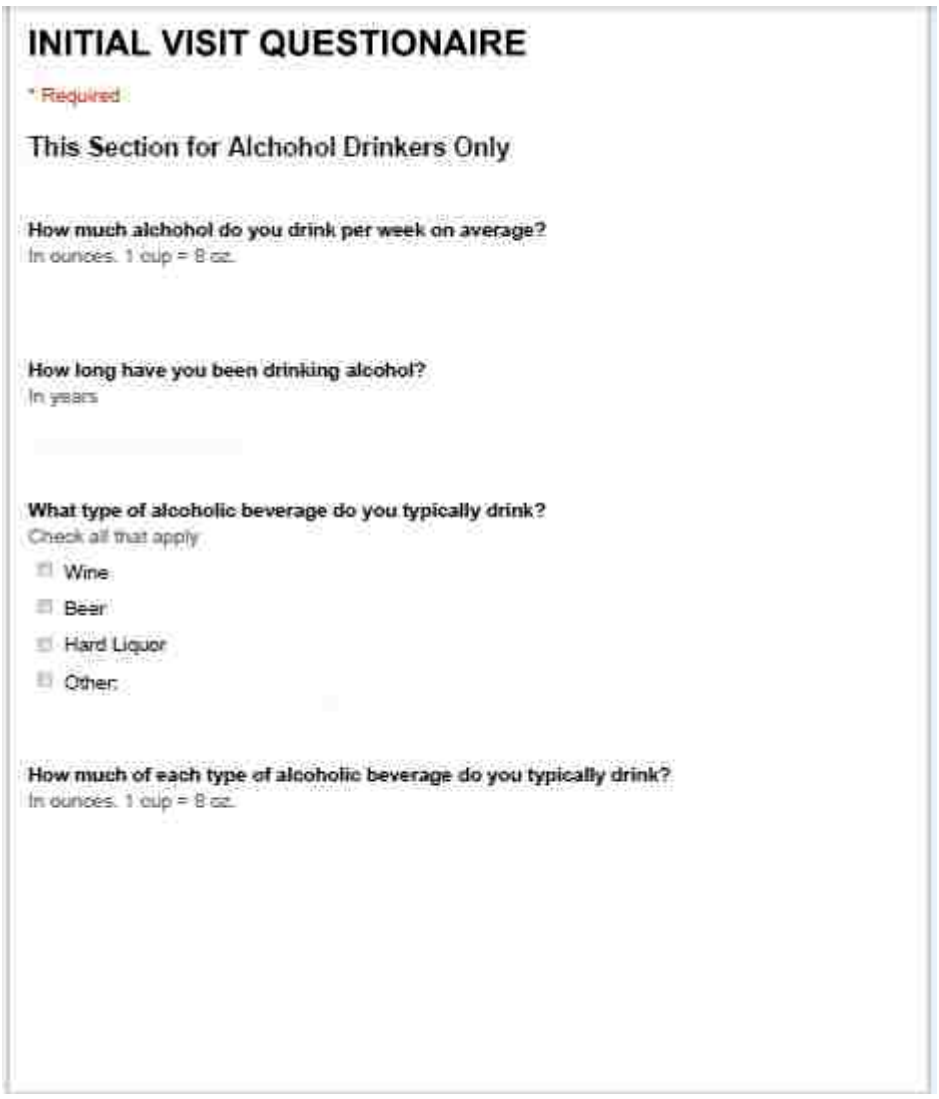

INITIAL VISIT QUESTIONAIRE

* Required

This Section for Alchohol Drinkers Only

How much alchohol do you drink per week on average?
In ounces. 1 cup = 8 oz.

How long have you been drinking alcohol?
In years

What type of alcoholic beverage do you typically drink?
Check all that apply

- [ ] Wine
- [ ] Bear
- [ ] Hard Liquor
- [ ] Other:

How much of each type of alcoholic beverage do you typically drink?
In ounces. 1 cup = 8 oz.

Have you ever recieved treatment for alcohol abuse or dependence? *

- ( ) Yes
- ( ) No

Have you ever wanted treatment for alcohol abuse or dependence? *

- ( ) Yes
- ( ) No

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INITIAL VISIT QUESTIONAIRE

* Required

For the following questions, please respond yes or no:

Of what ethnic/racial group or groups do you consider yourself a member? *
Check all that apply

- Asian
- African American
- Hispanic
- Native American
- White
- Other:

How many years of education have you had? *
HS Graduate = 12 yrs

Any degrees held:

How many years of education did your mother complete? *
If unknown, write UNK

How many years of education did your father complete? *
If unknown, write UNK

What is your current occupation? *

What is your father's occupation? *

What is your mother's occupation? *

What is your primary language? *

Were other languages used by your family? *

- Yes
- No

List any other languages you speak fluently:

List any other languages you speak, but not fluently:

Do you play video games? *

- Yes
- No

What is your dominant hand? *

- Left
- Right
- No Preference

What is your mother's dominant hand? *

- Left
- Right
- No Preference
- Unknown

What is your father's dominant hand? *

- Left
- Right
- No Preference
- Unknown

How many of your brothers and sisters are LEFT handed? *

How many of your brothers and sisters are RIGHT handed? *

How many of your children are LEFT handed? *

How many of your children are RIGHT handed? *

For the following activities, please indicate your hand preference by marking the most appropriate space. Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets. The phrases "Never right" and "Never left" mean you would only use that hand if forced to.

Writing *

- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred
- Only Right , Never Left

Drawing *

- Only Left, Never Right
- Left Preferred

- No Preference
- Right Preferred
- Only Right , Never Left

Throwing *
- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred
- Only Right , Never Left

Scissors *
- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred
- Only Right , Never Left

Toothbrush *
- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred
- Only Right , Never Left

Knife (without fork) *
- Only Left, Never Right
- Left Preferred
- No Preference

- Right Preferred
- Only Right , Never Left

Spoon *

- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred
- Only Right , Never Left

Broom (Upper hand) *

- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred
- Only Right , Never Left

Striking Match (Match) *

- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred
- Only Right , Never Left

Opening box (lid) *

- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred

- Only Right , Never Left

Foot used for kicking *

- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred
- Only Right , Never Left

Preferred eye when using only one (e.g. looking in a camera or telescope) *

- Only Left, Never Right
- Left Preferred
- No Preference
- Right Preferred
- Only Right , Never Left

The words listed below describe different feelings and emotions. Read each item and indicate the extent to which you generaly feel that way, that is, how you feel on the average.

interested *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

distressed *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

excited *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

upset *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

strong *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

guilty *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

scared *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

hostile *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

enthusiastic *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

proud *

- very slightly or not at all

- a little
- moderately
- quite a bit
- extreemly

irritable *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

alert *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

ashamed *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

inspired *
- very slightly or not at all
- a little

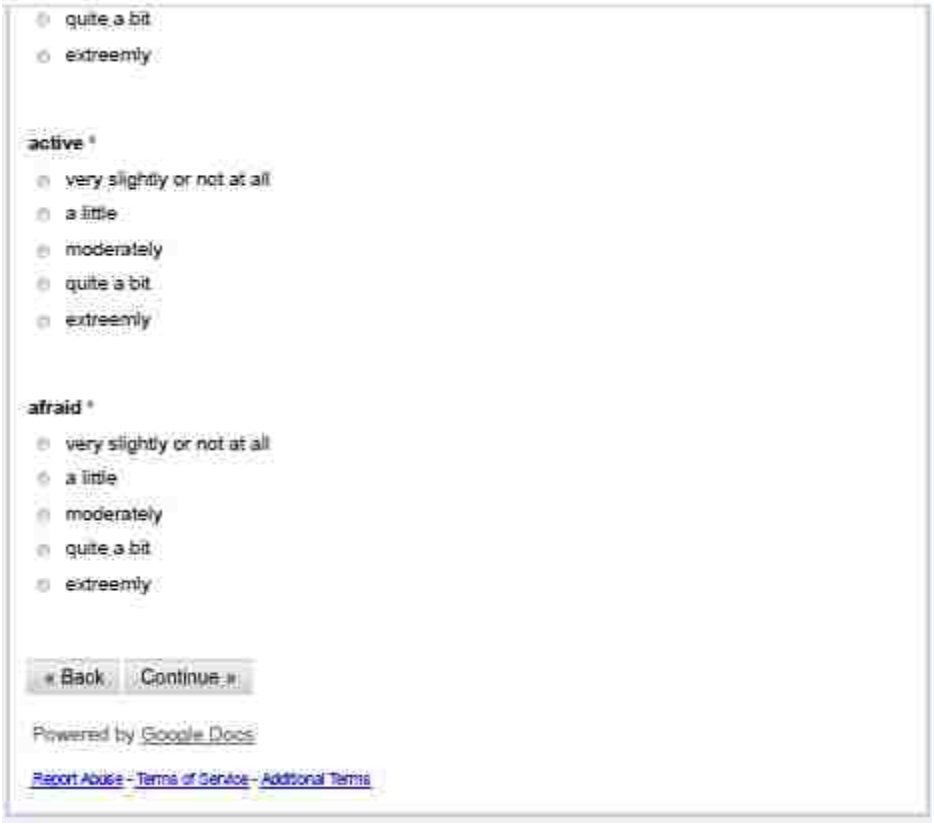
- moderately
- quite a bit
- extreemly

nervous *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

determined *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

attentive *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extreemly

jittery *
- very slightly or not at all
- a little
- moderately



quite a bit
extreemly

active *
very slightly or not at all
a little
moderately
quite a bit
extreemly

afraid *
very slightly or not at all
a little
moderately
quite a bit
extreemly

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INITIAL VISIT QUESTIONAIRE

* Required

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses.

1. A person's family is the most important thing in life *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

2. Even if something bad is about to happen to me, I rarely experience fear or nervousness. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

3. I go out of my way to get things I want. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

4. When I'm doing well at something I love to keep at it. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

5. I'm always willing to try something new if I think it will be fun. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

6. How I dress is important to me. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

7. When I get something I want, I feel excited and energized. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

8. Criticism or scolding hurts me quite a bit. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

9. When I want something I usually go all-out to get it. *
- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

10. I will often do things for no other reason than that they might be fun. *
- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

11. It's hard for me to find the time to do things such as get a haircut. *
- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

12. If i see a chance to get something I want I move on it right away. *
- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

13. I feel pretty worried or upset when I think or know somebody is angry at me. *
- very true for me
- somewhat true for me
- somewhat false for me

- very false for me

14. When I see an opportunity for something I like I get excited right away. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

15. I often act on the spur of the moment. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

16. If I think something unpleasant is going to happen I usually get pretty "worked up." *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

17. I often wonder why people act the way they do. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

18. When good things happen to me, it affects me strongly. *

- very true for me

- somewhat true for me
- somewhat false for me
- very false for me

19. I feel worried when I think I have done poorly at something important. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

20. I crave excitement and new sensations. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

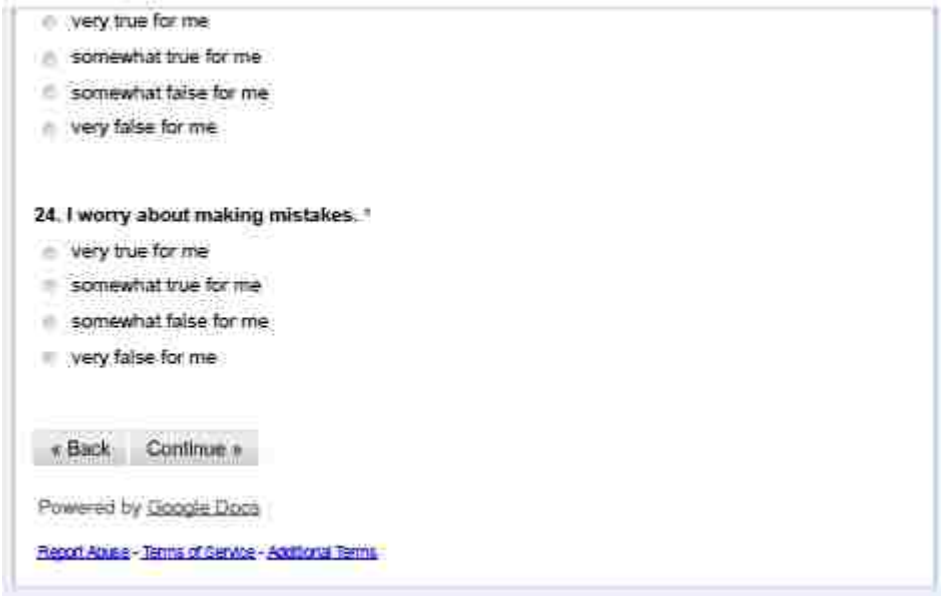
21. When I go after something I use a "no holds barred" approach. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

22. I have very few fears compared to my friends. *

- very true for me
- somewhat true for me
- somewhat false for me
- very false for me

23. It would excite me to win a contest. *



very true for me
somewhat true for me
somewhat false for me
very false for me

24. I worry about making mistakes. *

very true for me
somewhat true for me
somewhat false for me
very false for me

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INITIAL VISIT QUESTIONAIRE

* Required

People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and mark the appropriate answer . Do not spend too much time on any statement. Answer quickly and honestly

I plan tasks carefully. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I do things without thinking. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I make-up my mind quickly. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I am happy-go-lucky. *

- Rarely/Never

- Occasionally
- Often
- Almost Always/Always

I don't "pay attention." *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I have "racing" thoughts *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I plan trips well ahead of time. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I am self controlled. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I concentrate easily. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I save regularly. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I "squirm" at plays or lectures. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I am a careful thinker. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I plan for job security. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I say things without thinking. *
- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I like to think about complex problems. *
- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I change jobs. *
- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I act "on impulse." *
- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I get easily bored when solving thought problems. *
- Rarely/Never
- Occasionally
- Often

- Almost Always/Always

I act on the spur of the moment. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I am a steady thinker. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I change residences. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I buy things on impulse. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I can only think about one thing at a time. *

- Rarely/Never

- Occasionally
- Often
- Almost Always/Always

I change hobbies. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I spend or charge more than I earn. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I often have extraneous thoughts when thinking. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I am more interested in the present than the future. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I am restless at the theater or lectures. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I like puzzles. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

I am future oriented. *

- Rarely/Never
- Occasionally
- Often
- Almost Always/Always

This questionnaire consists of 12 statements In relation to your personality. Please read each sentence carefully. There are no right or wrong answers. Answer the questions sincerely and express your opinions as to the best of your ability. There is not a time limit, but try finish as quickly as possible.

I am a very cheerful and lively person. *

- Strongly Disagree
- Disagree
- Neutral

- Agree
- Strongly Agree

I enjoy talking with people. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

I have fun at large parties. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

I don't consider myself to be especially happy. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

I like to have a lot of people around me. *

- Strongly Disagree
- Disagree
- Neutral
- Agree

- Strongly Agree

A am not as vivid or so animated as others. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

I'm a very active person. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

In general, I prefer other people to talk at meetings. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

I tend to avoid large crowds. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

Sometimes I have moment of extreme happiness. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

I like to be wherever the action is. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

I do not like to make small talk with people. *

- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree

People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and mark the appropriate answer. Do not spend too much time on any statement. Answer quickly and honestly.

I have occasionally had the silly feeling that a TV or radio broadcaster knew I was listening to

him. *

- True
- False

I have felt that there were messages for me in the way things were arranged, like in a store window. *

- True
- False

Things sometimes seem to be in different places when I get home, even though no one has been there. *

- True
- False

I have never doubted that my dreams are the products of my own mind. *

- True
- False

I have noticed sounds in songs that are not there at other times. *

- True
- False

I have had the the momentary feeling that cetain thoughts of mine really belonged to someone else. *

- True
- False

I have wondered whether the spirits of the dead can influence the living. *

- True

- False

At times I perform certain little rituals to ward off negative influences. *
- True
- False

I have felt that I might cause something to happen just by thinking too much about it, *
- True
- False

At times, I have felt that a Professor's lecture was meant especially for me. *
- True
- False

I have sometimes felt that strangers were reading my mind. *
- True
- False

If reincarnation were true, it would explain some unusual experiences I have had. *
- True
- False

I sometimes have a feeling of gaining or losing energy when certain people look at me or touch me. *
- True
- False

It is not possible to harm others merely by thinking bad thoughts about them. *

- True
- False

I have oftern senesed an evil presence around me, although I could not see it. *

- True
- False

People often behave so strangely that one often wonders if they are part of an experiment. *

- True
- False

The government refuses to tell us the truth about flying saucers. *

- True
- False

I almost never dream about things before they happen. *

- True
- False

I have sometimes had the passing thought that strangers are in love with me. *

- True
- False

The hand motions that strangers make seem to influence me at times. *

- True
- False

Good luck charms don't work. *

- True
- False

I have sometimes been fearful of stepping on sidewalk cracks. *

- True
- False

Numbers like 13 amd 7 have no special powers. *

- True
- False

I have had the momentary feeling that I may not be human. *

- True
- False

I think I could learn to read others' minds if I wanted to. *

- True
- False

Horoscopes are right too often for it to be a coincidence. *

- True
- False

Some people can make me aware of them just by thinking about me. *

- True
- False

I have worried that people on other planets may be influencing what happens on earth. *

- True
- False

When introduced to strangers, I rarely wonder whether I have known them before. *

- True
- False

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APPENDIX B: MOOD QUESTIONNAIRE FORM

Positive and Negative Affect Scale

* Required

ID# *

Survey # *

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Positive and Negative Affect Scale

* Required

The words listed below describe different feelings and emotions. Read each item and then, in the space next to that word, indicate the extent to which you feel that way at the moment, that is, how you feel right now.

interested *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

distressed *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

excited *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

upset *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

strong *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

guilty *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

scared *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

hostile *

- very slightly or not at all
- a little
- moderately

- quite a bit
- extremely

enthusiastic *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

proud *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

irritable *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

alert *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

ashamed *

- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

inspired *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

nervous *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

determined *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

attentive *
- very slightly or not at all
- a little
- moderately

- quite a bit
- extremely

jittery *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

active *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

afraid *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

tired/fatigued *
- very slightly or not at all
- a little
- moderately
- quite a bit
- extremely

The following questions are to be completed AT THE END OF THE STUDY.

Did you notice or feel any sensation during the tDCS application?

- yes
- no

If yes, please describe:

Which stimulation condition do you think you received?

- 2.0 mA (Active)
- 0.1 mA (Sham)
- Couldn't tell

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APPENDIX C: SENSATION QUESTIONNAIRE FORM

URSI____________________ Date____________ RA_______________

tDCS Sensation Questionnaire

Circle the number which best describes what you are feeling for the following descriptors:

Itching

1 2 3 4 5 6 7 8 9 10

Heat/Burning

1 2 3 4 5 6 7 8 9 10

Tingling

1 2 3 4 5 6 7 8 9 10

Other Sensations you are feeling:

____

____

Time Point____ Time_____________

Circle the number which best describes what you are feeling for the following descriptors:

Itching

1 2 3 4 5 6 7 8 9 10

Heat/Burning

1 2 3 4 5 6 7 8 9 10

Tingling

1 2 3 4 5 6 7 8 9 10

Other Sensations you are feeling:

____

____

Time Point____ Time_____________

Circle the number which best describes what you are feeling for the following descriptors:

Itching

1 2 3 4 5 6 7 8 9 10

Heat/Burning

1 2 3 4 5 6 7 8 9 10

Tingling

1 2 3 4 5 6 7 8 9 10

Other Sensations you are feeling:

____

____

Time Point____ Time_____________

APPENDIX D: USING ICA TO REMOVE tDCS ARTIFACTS IN EEG

Introduction and Rationale

Transcranial direct current stimulation (tDCS) is becoming increasingly popular for the augmentation of cognition and therapeutic intervention for cognitive dysfunction. In particular, tDCS has shown promise for the enhancement of working memory and attention across a wide range of studies (for a review, see Coffman, Clark, & Parasuraman 2014). Electroencephalography (EEG) data are often examined in attention and working memory studies to identify and assess the electrophysiological correlates of these processes. Unfortunately, the combined use of tDCS to enhance cognition and EEG to examine the underlying neurophysiology of cognition leads to a significant issue, as voltage fluctuation at the scalp associated with maintenance of constant current by tDCS can result in a large, often global artifact in the EEG signal. This non-physiological artifact can be simultaneously monitored and removed online during EEG recording (Schestatsky, Morales-Quezada, & Fregni, 2012), though this requires special equipment which may be cost-prohibitive in many labs. An alternative option is the use of blind-source separation (BSS) methods such as independent components analysis (ICA) to isolate and remove this artifact.

Throughout the last fifteen years, popularity of the use of BSS for removal of physiological artifacts such as eye blinks and involuntary eye movements has increased. For removal of spatially stereotyped artifacts (artifacts where spatial distribution of the voltage changes little over time), the use of BSS methods has almost completely replaced epoch-rejection methods, in which simple voltage thresholds are used to remove entire epochs in which these artifacts have occurred. BSS methods allow researchers to maintain data that would not

otherwise be available using voltage-threshold-based artifact rejection techniques, particularly in cases where usable data may be limited for other reasons, such as with patient populations or boring tasks, where eye-blink artifacts are more common.

ICA is the favored BSS method for artifact rejection, though other BSS options are available (Jung *et al.*, 2000). The goal of the BSS in EEG is to recover source signals, given sensor-level observations. These decompositions are reliant on assumptions of orthogonality and linearity. Orthogonality is achieved by a preprocessing step called whitening, which is included in all algorithms tested here. The most fundamental assumption to BSS is that data measured at sensors (x, a matrix of sensors by time points) are the simultaneous linear mixing of sources (S, a matrix of sources by time points) weighted by a mixing matrix (M, a matrix of sources by channels), plus noise (N, an additive matrix):

$$x = MS + N \tag{D1}$$

Based on this principle, BSS algorithms estimate the noisy component matrix (y), where:

$$y = Wx \tag{D2}$$

Methods for calculation of the unmixing matrix (W, equal to the inverted mixing matrix M^{-1}) differ between BSS methods. Even within ICA there are several algorithms available, which implement different approaches to maximizing independence. There are subtle differences between the algorithms tested here, but they can be roughly grouped into three different types: (1) Natural Gradient Descent (NGD) ICA algorithms, including Infomax, Extended Infomax, and AMICA; (2) Cumulant Diagonalization (CD) ICA algorithms, which includes only Joint Approximate Diagonalization of Eigenmatrices (JADE); and (3) time-Dependent (TD) BSS

algorithms, including Second Order Blind Identification (SOBI) and SOBI with Robust Orthogonalization (SOBI-RO).

NGD algorithms are iterative procedures where maximum entropy (or information content) of the output vectors $h(y)$ is achieved by minimizing the mutual information $I(y)$ shared between them. Entropy within a vector of random data (such as data from an EEG sensor) is given by the equation:

$$h(x) = E\{-log\, p(x)\} \tag{D3}$$

where entropy *h* of the vector *x* is the expected value of the log transformed probability density function (PDF) for the vector/sensor *p(x)*, which ranges from 0 to 1. In essence, entropy can be described as the area under the curve of the PDF. For a linear transformation Y=BX, entropy of the vector Y can be calculated with the sum of the entropy of vector X and the log determinant of weighting vector B using the formula:

$$h(Y) = log\, |det\, B| + h(X) \tag{D4}$$

Because sensor *x* and component *y* have a linear relationship by the factor *W*, as in (D2), the entropy of component *y* can be calculated by:

$$h(y) = log\, |det\, W| + h(x) \tag{D5}$$

Pairwise mutual information (I) between two vectors X_1 and X_2 (which could be two EEG sensors or two ICA components) can be defined as:

$$I(X_{1,2}) = h(X_1) + h(X_2) - h\left(X_{1,2}\right) \tag{D6}$$

where $h(X_{1,2})$ is the joint entropy across the two vectors. Similarly, mutual information *I* among *N* components *Y* derived from a vector/sensor can be defined as:

$$I(Y) = h(Y_1) + \ ... \ + \ h(Y_N) - h(Y) \tag{D7}$$

Therefore, by equation D5, mutual information between component timecourses $y_{1...n}$ can be defined as

$$I(y) = h(y_1) + \ ... \ + \ h(y_n) - \ log\ |det\ W| - h(x) \tag{D8}$$

All of the BSS methods tested here effectively work by minimization of $I(y)$, though the specific methods achieve this in different ways. The Infomax ICA algorithm achieves minimization of $I(y)$ based on the information maximization principle (Bell & Sejnowski, 1995). Extended Infomax is similar to Infomax, with the additional ability to separate mixed non-Gaussian signal distributions. This is done by a learning rule which adaptively changes the sign of the 4th-order moment of the PDF to fit sub- and super-Gaussian distributions. Adaptive Mixture ICA (AMICA) goes a step farther and models adaptive mixtures of Gaussian PDFs fit to individual component timecourses and spatial projections in entropy maximization, rather than a selecting single Gaussian or non-Gaussian PDFs.

The JADE algorithm performs mutual information reduction on data transformed to the cumulant of the PDF. In particular, JADE minimizes $I(y)$ by rotation and diagonalization of the 4th-order cumulant, which is related mathematically and conceptually to the 4th-order moment (kurtosis). Using the Jacobi technique, JADE reduces mutual information contained in the matrices of the component PDFs by rotating the weighting matrix *W* until cumulant matrices are maximally diagonal (Cardoso & Donoho, 1999).

The SOBI algorithm takes advantage of the temporal structure in the observed data by comparing time-lagged versions of the PDF. In short, correlations between individual components are expected to exist in time, though instantaneous mutual information content is minimized like the other methods described. SOBI, like JADE, uses the Jacobi technique to achieve diagonalization, though SOBI achieves diagonalization of the *correlation matrix* of the component PDFs. SOBI-RO is similar to SOBI, but was specifically designed to handle noisy signals by incorporating a robust whitening step (Belouchrani & Cichocki, 2000).

Because perfect independence cannot normally be reached in real datasets, different algorithms return somewhat different results when applied to EEG data. The artifact associated with tDCS, though extraphysiologic in nature, is spatially stereotypic; therefore, ICA was expected to be successful in removing this artifact, and no specific hypotheses were made with regard to the relative success of each algorithm. Here each of the six popular BSS algorithms described above are compared in their ability to remove tDCS artifact pre-processed 128-channel EEG datasets (BioSemi) acquired during tDCS delivered with two different tDCS electrode placements and two different tDCS amperages.

Methods

Participants in this study were the same as those included in the main study, and the same exclusions applied here. Participants were grouped by cathode location [Arm (A) or near EEG location F9 (B)] and tDCS amperage [0.1 mA (lo) or 2.0 mA (hi)], resulting in four groups (A-lo, A-hi, B-lo, and B-hi). The anode was positioned near EEG 10-10 location F10 for all participants. Pertinent descriptive statistics not reported in the main manuscript, including head measurements and group sample sizes are reported in Table D1.

	N	Circumference ($\bar{X}$ ± SD)	Width * ($\bar{X}$ ± SD)	Length † ($\bar{X}$ ± SD)
A-lo	7	54.9 ± 1.9	32.1 ± 3.1	32.0 ± 1.8
A-hi	11	55.8 ± 1.9	33.2 ± 2.6	34.0 ± 1.4
B-lo	5	55.1 ± 1.8	32.3 ± 1.9	33.1 ± 2.9
B-hi	6	54.8 ± 2.7	33.3 ± 3.8	34.3 ± 3.7

* Width was measured as the distance from the left to right pre-auricular points
† Length was measured as the distance from the nasion to inion

Table D1. Participant sample size and head size by tDCS group

Prior to ICA decomposition, EEG data were pre-processed through an automated Linux C-Shell pipeline utilizing the MATLAB toolboxes EEGLAB (http://sccn.ucsd.edu/eeglab/) and ERPLAB (http://erpinfo.org/erplab). Data from each channel were first high-pass filtered at 0.01 Hz and DC offset was removed to eliminate scalp potentials, DC voltage offset associated with tDCS, and other slow drifts in the data. Channel locations acquired at EEG preparation were then applied to each participant's dataset, bad channels (including, in all cases, the EEG channels blocked by the tDCS electrodes) were visually detected and removed from each dataset, and reregistration was performed for dipole fitting purposes. AMICA, Infomax, Extended Infomax, JADE, SOBI, and SOBI-RO algorithms were applied to each dataset, after which single dipoles were fit to each of the components using the EEGLAB DIPfit plugin (http://sccn.ucsd.edu/wiki/A08:_DIPFIT).

The first two measures used to assess these data, Mutual Information Reduction (MIR) between the component timecourses and the original data, and mean Remaining Pairwise Mutual information (PMI) among components, assess success of the primary goal of ICA algorithms in

general: reduction of component interdependence. MIR is calculated as the difference in mutual information contained in the ICA components compared to the EEG sensor data:

$$MIR = I(x) - I(y) \tag{D9}$$

PMI is calculated as the average across all pairwise assessments of mutual information for *n* components, and is given by the equation:

$$PMI = \left[\sum_{i=1}^{n-1} I(y_i, y_{i+1}) + I(y_n, y_1) \right] \Big/ n \tag{D10}$$

The two other measures examined here, Remaining Variance (RV) within tDCS artifact components after dipole fitting and mean Euclidian distance between the tDCS artifact component dipole and non-tDCS component dipoles, or Mean Dipole Distance (MDD), assess the extraction quality of the tDCS artifact and independence of non-artifact components, respectively. RV is based on the assumption that independent components are dipolar (Delorme *et al.*, 2012), and is a measure of tDCS artifact component independence. MDD measures the independence of the tDCS artifact dipole locations from the rest of the components. ICA algorithms were compared by cathode location and tDCS amperage with a three-way multivariate split-plot ANOVA (SP-MANOVA), also referred to as a Doubly MANOVA, with four measures: MIR, PMI, RV, and MDD. As no interactions were found with between-subject variables included in the model, main effects of ICA algorithm were followed by univariate one-way repeated measures ANOVAs within each of the four measures and pairwise comparisons between individual algorithms using paired *t*-tests.

Results and Conclusions

Artifact removal was best accomplished by the AMICA algorithm. Significant main effects of ICA algorithm were found with a large effect size [Wilks' $\Lambda = 0.17$, $F(20,6) = 17.06$, $p = 0.001$, $\eta^2 = 0.983$] and no interactions were found with the tDCS characteristics tested here. Significant differences were present between ICA algorithms for each of the four measures tested (p's < 0.05) and, although mean differences did not always favor AMICA, significant pairwise mean differences favored AMICA for all but one measure (i.e., PMI). Additional visual inspection of ICA component spatial differences confirms this statistical comparison; scalp maps for components extracted using the AMICA algorithm were strikingly more dissimilar compared to those from other algorithms. Examples of scalp maps from each algorithm except Infomax Extended (where ICA components were nearly identical to those extracted using Infomax) can be seen for a subject from each tDCS condition in Figure D1. Mean comparisons for dependent measures are displayed in Figure D2 and inferential and descriptive statistics can be found in Table D2.

Based on the results from this comparison, it was concluded that AMICA is the most appropriate BSS method for removal of artifacts associated with tDCS of the right VLPFC, regardless of amperage or cathode placement. Head size and number of males (reported in the main manuscript) was similar between groups, so it is unlikely that these factors confounded these results. It is possible that this study was underpowered in detecting some pairwise differences between algorithms; however, this would not have changed the conclusions based on these results. AMICA did perform significantly worse than Infomax algorithms with regard to remaining mean pairwise mutual information (PMI); however, the opposite effect was found for mean dipole distances and visual inspection of component scalp maps favored AMICA, which

was considered to be more relevant to these comparisons of tDCS artifact removal quality. AMICA was therefore used to remove tDCS artifacts during EEG preprocessing in the main study.

	F(2,26)	*p*	η^2	Mean	SEM	95% CI
MIR	17.76	<0.001	0.415			
AMICA				403.95	17.87	367.15 – 440.74
Infomax				399.08	18.95	360.05 – 438.10
Infomax Ext.				397.96*	18.96	358.92 – 437.01
JADE				394.72*	18.94	355.71 – 433.72
SOBI				391.54**	19.01	352.39 – 430.70
SOBI-RO				388.77**	18.96	349.71 – 427.83
PMI	93.52	<0.001	0.789			
AMICA				28.53	2.12	24.16 – 32.89
Infomax				26.58*	1.82	22.83 – 30.33
Infomax Ext.				26.69*	1.62	23.34 – 30.03
JADE				26.82	1.66	23.40 – 30.24
SOBI				46.46**	3.57	39.10 – 53.82
SOBI-RO				46.32**	3.49	39.13 – 53.51
RV	5.24	0.019	0.173			
AMICA				0.26	0.03	0.21 – 0.31
Infomax				0.29	0.03	0.22 – 0.35
Infomax Ext.				0.28	0.03	0.22 – 0.34
JADE				0.29	0.03	0.22 – 0.35
SOBI				0.29*	0.03	0.22 – 0.36
SOBI-RO				0.39	0.04	0.32 – 0.47
MDD	13.13	<0.001	0.344			
AMICA				55.91	3.56	48.57 – 63.25
Infomax				36.36**	3.69	28.75 – 43.97
Infomax Ext.				36.52**	3.94	28.40 – 44.64
JADE				30.38**	3.07	24.06 – 36.69
SOBI				56.95	3.10	50.56 – 63.35
SOBI-RO				50.76	5.51	39.42 – 62.11

$^{*}p<0.05$ (compared to AMICA) *$^{**}p<0.01$ (compared to AMICA)*

Table D2. One-way simple main effects of ICA algorithm on the four measures tested. MIR = Mutual Information Reduction. PMI = Pairwise Mutual Information, averaged across components. RV = Remaining Variance after dipole fit. MDD = Mean Dipole Distance from the tDCS artifact dipole, for dipoles fit to components not representing tDCS artifact.

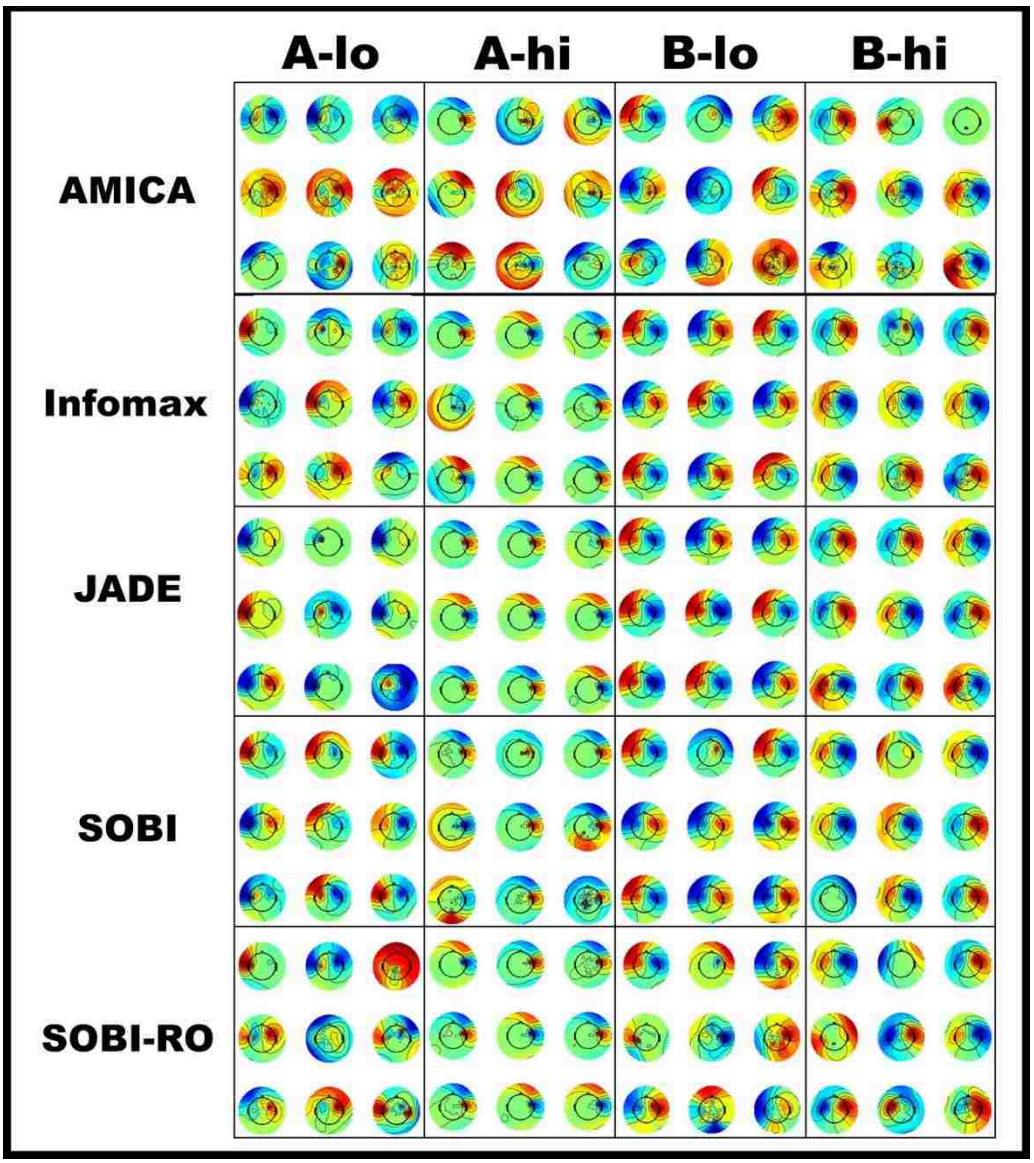

Figure D1. Scalp maps showing spatial similarity of ICA components for one subject from each tDCS groups (major columns). For each subject, a set of nine scalp maps is shown from each algorithm (except Infomax Extended, where component scalp maps were nearly identical to those extracted by Infomax). The nine scalp maps within each cell represent a stratified sample of the complete set of components, and, (from left to right and top to bottom) components 1, 11, 21, 31, 41, 51, 61, 71, 81, & 91 are depicted for each subject/algorithm. Cold colors and warm colors indicate opposing polarity of components and are proportional to μV; however, the component activations have no unit of measure. Note the dissimilarity between components within AMICA results, compared to similarity between components in the others.

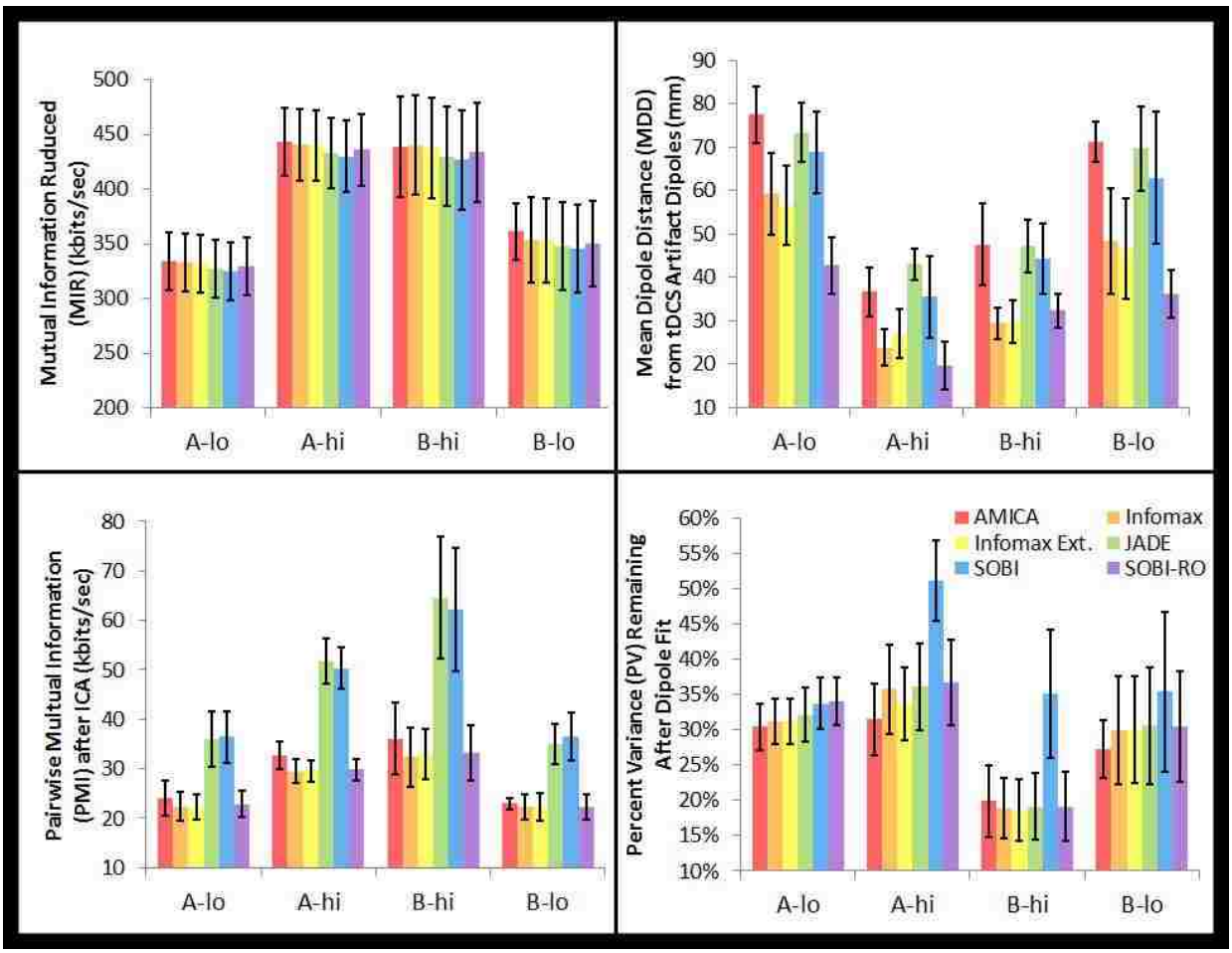

Figure D2. Histograms showing mean values for (from left to right and top to bottom), mutual information reduction, mean dipole distance from the tDCS artifact dipole, pairwise mutual information across components, and remaining variance in tDCS artifact components after dipole fit. tDCS group is represented on the x-axis of each graph, and ICA algorithms are represented by bar color. Error bars denote SEM.

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