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Effect of transcranial direct current stimulation on the Attention Network Task (ANT)

Michael Trumbo

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Mike Trumbo
_____
Candidate

Psychology
_____
Department

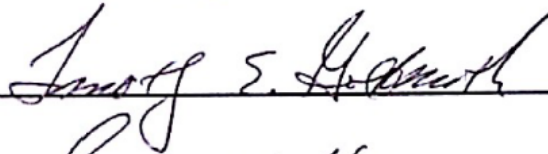This thesis is approved, and it is acceptable in quality and form for publication:

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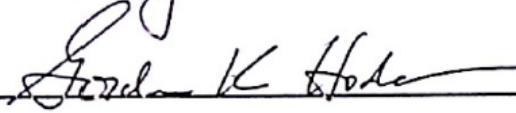_____, Chairperson

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Gordon Hodge
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EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON THE

ATTENTION NETWORK TASK (ANT)

by

Michael Trumbo

B.S., Psychology, The University of Wisconsin-Parkside, 2008

M.S., Psychology, The University of New Mexico, 2012

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ABSTRACT

This investigation studied the effects of transcranial direct current stimulation (tDCS) on the Attention Network Task (ANT) - a combination speeded response/flanker task, which elucidates activity of three attentional networks - alerting, orienting, and executive functioning. Anodal tDCS was applied over the right inferior frontal cortex at 0.1 mA or 2.0 mA for 30 minutes. Participants were tested prior to stimulation, roughly 30 minutes following cessation of stimulation, 70 minutes following cessation of stimulation, and 115 minutes following cessation of stimulation. Due to the areas being stimulated (RIFC), and results from previous studies that link the alerting network to frontal and parietal activation (Coull et al., 2001), and executive control function to the ACC and the lateral prefrontal cortex (Bush et al., 2000), it seemed reasonable that higher scores for these networks will be achieved by those in the active stimulation groups. However, the only network difference observed involved the alerting network, in an unexpected direction (higher scores for the sham group). The active group (2.0mA stimulation), while obtaining smaller differences in RT between conditions, responded

faster across all conditions. These results, however, were rendered non-significant due to group differences observed at the baseline measure. It is possible the RT scores related to levels of concentration, though a third variable could be the root of observed differences. Thus, results are inconclusive given the current set of data.

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GENERAL INTRODUCTION

A deeper understanding of the processes that define cognition has the potential to positively impact therapeutic interventions (those with the aim of correcting a particular defect or pathology) as well as enhancements in healthy individuals (those interventions with the aim of improving an already "healthy" cognitive system rather than targeting a specific defect). Cognition may be defined as the multitude of processes utilized by an organism to organize information, including perception (acquiring information), attention (selecting information from the environment), memory (retaining information), understanding (representing information), and learning (acquisition of knowledge or skills) (Bostrom & Sandberg, 2009).Therefore, a cognitive enhancement technique may target any of these core faculties.

The pursuit to enhance mental faculties is an old one, including such conventional methods as martial arts, meditation, yoga, and various pharmacological enhancements (nootropics), as well as school-based education and training. The modern study of nootropics began with the 1917 observation by Lashley that strychnine facilitates learning in rats (Lashley, 1917). Since then, memory enhancement has been studied using drugs such as stimulants (Lee & Ma, 1995; Soetens et al., 1993), cholinergic agonists (Iversen, 1998; Power et al., 2003; Freo et al., 2005), the piracetam family (Mondadori, 1996), ampakines, (Lynch, 1998; Ingvar et al., 1997), and consolidation enhancers (Lynch, 2002). In addition, researchers have investigated the role of nicotine in attention and memory (Warburton, 1992; Newhouse et al., 2004; Rusted et al., 2005), the effect of caffeine on arousal and learning (Erikson, 1985; Lieberman, 2001; Smith et al., 2003; Tieges et al., 2004), the possibility of cognitive enhancement via hormone therapy (Buchanan & Lovallo, 2001; Gulpinar & Yegen, 2004) or genetic alteration (Tang et al., 1999, Routtenberg et al., 2000), the use of dietary supplements to benefit cognitive performance (Rae

et al., 2003; McMorris et al., 2006), memory enhancement tied to emotional modulation (LaBar & Cabeza, 2006), and a variety of other drug treatments (Farah et al., 2004). These methods of enhancement offer a number of potential benefits in learning complicated tasks which normally require a great amount of time to master, and may also have clinical applications, such as enhancement of memory in dementia or other disorders of which a decrement in baseline cognitive functioning is common.

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a noninvasive method of neuromodulation in which a current generator delivers an electrical current via electrodes on the scalp, which alters behavior. The history of therapeutic electricity stretches back to antiquity, where torpedo fish were used to alleviate headache and gout (Dolhem, 2008). In the mid-1700's, when Dutch scientists in the South American colonies observed electric eels, the creatures current generation abilities were utilized to relieve headaches and treat neuralgia (Koehler & Boes, 2010). Around this time, some practitioners began using Leyden jars to treat neuralgia, contractions, and paralysis (Dolhem, 2008). Alessandro Volta, directly inspired by the electrical organs of the eel and torpedo fish, invented the Voltaic pile in 1800 (Kohler, Finger, & Piccolino, 2009). Combined with the studies of Luigi Galvani on "animal electricity" there emerged considerable interest in utilizing electrical current to treat a wide range of disorders (Dolhem, 2008). The first documented use of a procedure similar to modern tDCS was in 1868, where it was suggested as a potential therapeutic intervention for neuralgia, convulsions, and paralysis (Benedikt, 1868), whereas the first study to utilize the modern standard of current and electrode parameters was published just over a decade ago (Nitsche & Paulus, 2000).

In the ensuing 140 years there has been an expansion in ideas about the application of tDCS, and vast improvements in the understanding of the mechanisms which underlie the effects of, and methods for delivery of tDCS. Currently, tDCS is being examined as a potential treatment for multiple neurological and psychiatric disorders including addiction (Boggio et al., 2008a, 2009a), Alzheimer's disease (Boggio et al., 2009b), anorexia (Hecht, 2010), depression (Boggio et al., 2007, 2008b), epilepsy (Liebetanz et al., 2006), migraine (Chadaide et al., 2007), multiple sclerosis (Mori et al., 2010), pain management (Antal et al., 2008a), Parkinson's disease (Boggio et al., 2006a), rehabilitation after stroke (Ko et al., 2008), and traumatic spinal cord injury (Fregni et al., 2006).

In recent years, transcranial direct current stimulation (tDCS) has garnered increasing interest for its application in cognitive enhancement in healthy subjects: tDCS has been shown to facilitate cognition (Fertonani et al., 2010), working memory (Fregni et al., 2006; Floel et al., 2008), motor learning (Antal et al., 2004; Reis et al., 2008; Reis et al., 2009; Galea & Celnik, 2009), motor function (Furubayashi et al., 2008), simple somatosensory and visual motion perception learning (Antal & Paulus, 2008b; Ragert et al., 2008), and memory for word lists (Marshall et al., 2004). A review of the literature yields more than 100 publications in which 2300 subjects and patients have participated in experiments utilizing tDCS over the past 5 years. Quantifying the effects of tDCS on brain function is essential to understand and implement treatment and experimentation in this vigorous, growing field.

The basic underlying mechanism of the short-term effects of tDCS is thought to be due to an alteration of the resting membrane potential in a polarity-specific manner, with anodal (positive electrode) stimulation increasing excitability through depolarization, and cathodal (negative electrode) stimulation decreasing excitability through hyperpolarization (Nitsche,

Liebetanz, Tergau, & Paulus, 2002; Sparing & Mottaghy, 2008). tDCS, in contrast to other stimulation techniques (e.g., transcranial magnetic stimulation, intracranial electrical cortical stimulation, electroconvulsive therapy), is not thought to induce neuronal firing (action potentials). Rather, by acting at the level of the membrane potential, tDCS modulates the spontaneous firing rate of neurons. These changes can lead to effects that persist beyond the end of stimulation for a period far outlasting stimulation duration (Sparing & Mottaghy, 2008). It is worth noting that while enhancement studies generally focus on the depolarization effects of anodal stimulation, the possibility of hyperpolarization has implications for unlearning phobias and addiction, as some pharmacological agents are used (Pitman et al., 2002; Hofmann et al., 2006) rather than enhancing learning and memory via increased neural activation. Typical current strengths are 1 - 2 milliamperes (mA) delivered for up to 30 minutes (Nitsche, 2008).

The mechanisms of the effects of tDCS in humans have been examined in simulations, as well as studies of electrophysiology, neurochemistry, and neuroanatomy. Modeling and simulation studies illustrate the current levels and distributions in the brain during the delivery of tDCS (Faria et al., 2009). The current distribution in the brain changes with the arrangement of the electrodes, such that specific areas of the brain can be targeted for delivery of anodal currents that increase the excitability of the underlying cortex, or cathodal stimulation that decreases excitability (Nitsche et al, 2008; Datta et al., 2009). While some models demonstrate that roughly 45% of applied current passes through the brain (Rush & Discroll, 1968; Dymond, Coger, & Serafeinides, 1975), others estimate (using 2.0mA of scalp stimulation, as in the current study) that only about 10 percent of the applied current reaches the cortex (Miranda et al., 2006). However, it is suggested that significant current density is only exhibited by areas relatively local to the stimulated cortex (Miranda et al., 2006; Wager et al., 2007). Animal studies show that DC

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

Some hemodynamic and neurochemical effects of tDCS have also been documented. Anodal stimulation resulted in an increase in the concentration of oxyhemoglobin in the cortex near the electrode (Merzagora et al., 2010). The concentrations of the neurotransmitters GABA and glutamate are also altered in the region of the electrodes as measured by magnetic resonance spectroscopy. Our lab has demonstrated increased glutamate activity in participants receiving tDCS using stimulation parameters similar to those in the present study (Clark et al., 2011). Stagg and colleagues (2009) showed that anodal stimulation reduces GABA activity, but not glutamate activity. This change in the ratio of glutamate to GABA activity is thought to relate, at least in part, to the increase in cortical excitability seen with anodal stimulation.

In fact, in neocortical slice preparations it has been shown that processes very similar to long-term potentiation (LTP; a mechanism for modulation of synaptic strength) can only be robustly induced via reduction of local GABAergic tone (Castro-Alamancos et al., 1995; Hess & Donoghue, 1996) and administration of a GABA agonist (lorazepam in this case) prior to stimulation of an intact rat cortex abolishes induction of LTP (Trepel & Racine, 2000). When it is considered that the process of LTP is critically dependent on changes within NMDA receptor-dependent glutamatergic interneurons (Castro-Alamancos et al., 1995; Hess & Donoghue, 1996). Taken together, the findings of GABA reduction in the 2009 Stagg et al. study, the findings from

our own lab of increased glutamate activity, the evidence for how LTP works, and the successful blocking of the aftereffects of anodal tDCS using dextromethorphane (an NMDA receptor antagonist) (Liebetanz et al., 2002), it seems a good bet that the aftereffects of anodal tDCS are dependent on both membrane depolarization and synaptic modulation. This has been seen in additional studies that provide mounting evidence that long-lasting effects are dependent upon these membrane potential changes as well as modulation of NMDA receptor efficacy (Nitsche et. al, 2004; Liebetanz, Nitsche, Tergau, & Paulus, 2002). The administration of drugs that alter neuronal sodium and calcium currents have also been observed to modulate the effects of tDCS (Nitsche et al., 2003a).

EXPERIMENT: EFFECT OF tDCS ON THE ATTENTION NETWORK TASK (ANT)

Introduction

It has been shown previously that learning to detect threats can be enhanced, in a dose-dependent manner, by the use of transcranial direct current stimulation (tDCS) (Clark et al., 2010). Subjects were trained to detect camouflaged threat cues (e.g., IEDs, trip wires, snipers) concealed within static images of a virtual environment designed to resemble the Middle East. Training lasted one hour, and tDCS was administered during the first thirty minutes of training at either 0.1mA (sham), or 2.0mA (active). Stimulation was administered using an Iomed Phoresor PM850 with 3.3cm x 3.3cm wet-sponge electrodes. The anode was placed near the right temple (close to F10 in the international 10-10 EEG system) and the cathode was placed on the upper left arm of the subject. The remainder of training took place immediately following cessation of tDCS.

One question arising from the previous study to be examined in this proposed study is: What is the cognitive mechanism behind the tDCS induced increase in learning rate? In the previous study, tDCS was administered over the right frontal and right parietal cortex; this stimulation led to increased learning suggests that a cognitive function shared by these two regions may be related to the learning effect. One well-established function that involves both regions is sustained attention or vigilance, as well as executive attention (Szczepanski 2010; Bolognini, Olgiati, Rossetti, & Maravita, 2010). To study the effects of tDCS on attentional processes the current study examined the effects of tDCS on three different forms of attention studied using the Attentional Networks Task (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002). This will show which forms of attention are most affected by tDCS using electrodes placed over the aforementioned areas. We hypothesize that tDCS over right frontal and parietal cortex produces an enhancement of attentional processing, which leads to increased learning in turn.

Methods

Inclusion/Exclusion Criteria

All participants met the following criteria: English as a first language, no history of head injuries or concussions resulting in loss of consciousness or hospitalization, right-handedness according to the Edinburgh Handedness Inventory (Oldfield, 1971), no history of psychiatric or neurological disorders, alcohol or drug abuse, or current medication affecting the CNS, and good or corrected vision and hearing. Additionally, all participants were naive to tDCS (i.e., had not previously participated in a study involving tDCS). These criteria were assessed via a

questionnaire participants were asked to fill out immediately following consent. This initial questionnaire is also designed to collect demographic information.

Participants

Participants were recruited through the psychology research website at the University of New Mexico, and received course credit for their participation in the study. A total of 27 participants gave informed consent and participated in this study. Three participants with accuracy scores during the immediate test greater than two standard deviations below the mean were excluded from analysis. Therefore, the results from 24 participants (17 female, average age = 21.6 yrs, 6.8 yrs SD) are included in this study. Of these 24 participants, 12 received 2.0mA tDCS, while the other 12 received 0.1mA.

Administration of tDCS

Stimulation was similar to the previous study, but with some modifications. In order to create a double blind condition, a pair of Activatek stimulation units were used to deliver the current (0.1mA for sham condition and 2.0mA for the active condition). Both participants and experimenters were kept blind to the treatment condition (2.0mA or 0.1mA) by the use of a custom-made blinding apparatus which consists of multiple coded switch boxes. These boxes consist of two sets of inputs (A and B, with each letter corresponding to one of the stimulation units), a 6-way switch, and one set of output terminals. The 6-way switch is coded, such that three of the positions on the switch allow input A to pass through to the output, while the other three allow input B to pass through to the output terminals. The switch positions which code for

inputs A and B are different on each of the 3 switch boxes, and only the principal investigator of the study has access to the codes until the study is completed.

Electrodes consisted of a pair of 3.3cm x 3.3cm wet sponge electrodes soaked in saline solution. The anode location, over the sphenoid bone (right temple, nearby site F10 in the international 10-10 system), was suggested from functional magnetic resonance imaging (fMRI) studies of changes in brain networks associated with the acquisition of expertise (Clark et al., 2010). The cathode was placed on the subject's left upper arm. Electrodes were secured to the scalp and upper arm using Coban self-adherent wrap. Stimulation lasted a total of thirty minutes.

The Attention Network Task (ANT).

In recent years three attentional networks have been defined in both functional and anatomical terms. These networks are an alerting network, an orienting network, and an executive network. The alerting network has been functionally defined as a network that facilitates achievement and maintenance of an alert state; the orienting network is responsible for allowing attending to sensory events through movement of attention through space; and the executive control network has been defined as a network that resolves conflict between expectation, stimulus, and response (Fan et al., 2002). The efficiencies of these networks have been shown to lack significant correlation, and have been deemed functionally orthogonal constructs (Fan, et al., 2002). Jin Fan, Michael Posner, and colleagues have developed an Attention Network Task (ANT) which examines the efficiency of each of these three networks. The ANT consists of a combination of the cued reaction time (RT) task (Posner, 1980) and the flanker task (Eriksen & Eriksen, 1974), and it requires participants to indicate whether a central arrow points to the left or to the right. Efficiency of the three networks is then assessed by

measuring how response times are influenced by alerting cues (used to assess the alerting network), spatial cues (orienting network), and flankers (executive network).

Neuroimaging studies using the ANT have been able to link the orienting network to activation of the parietal lobe and frontal eye fields (Fan et al., 2005), while the alerting network has been associated with frontal and parietal activation (Coull, Nobre, & Frith, 2001). The executive control function has been found to be associated with activity in the anterior cingulate cortex (ACC) and the lateral prefrontal cortex (Bush, Luu, & Posner, 2000). Given that the alerting and orienting networks utilize the parietal cortex and the executive control network uses the lateral frontal network, it seems conceivable that all three networks may respond to the method of tDCS administration used in the study by Clark et al., resulting in a learning enhancement (2010).

Previously the ANT has been used to provide a description of the attention hindrances associated with disorders such as Borderline Personality Disorder (Rogosch & Cicchetti, 2005), dyslexia (Bednarek et al., 2004), schizophrenia (Wang et al., 2005), attention-deficit hyperactivity disorder (Adolfsdottir, Sorensen, & Lundervold, 2008), and depression (Murphy & Alexopoulos, 2006), as well as genetic disorders such as 22q11 deletion syndrome (Fan & Posner, 2004). Furthermore, a multitude of studies have been conducted using that ANT that point to a specific attentional deficit rather than a general deficiency of attention. For example, specific deficits in the alerting network have been discovered for elderly individuals relative to a younger population (Jennings, Dagenback, Engle, & Funk), and alerting network scores have been utilized to differentiate subtypes of ADHD (Booth, Carlson, & Tucker, 2007). Orienting network deficits have been reported in individuals who have experienced a concussion (van Donkelaar et al., 2005). Executive control network have been found in individuals with morbid

obesity (Beutel et al., 2006), posttraumatic stress disorder (Leskin & White, 2007), borderline personality disorder (Posner et al., 2002), dyslexia (Bednarek et al., 2004) and 22q11 deletion syndrome (Bish et al., 2005). If tDCS is discovered to increase the functioning of the attentional networks that have deteriorated in these disorders, it may potentially serve as a treatment option to mitigate the attentional deficits experienced by those afflicted with these maladies. The ANT has been widely used, appearing in at least 65 original research papers since 2001 (MacLeod, et al., 2010).

Stimuli for the ANT consist of visually presented horizontal black lines, which have arrowheads pointing either to the left or to the right. The target consists of the arrowhead horizontally centered with a visible cross target (+) that remains continuously at the center of the screen. The target is flanked on either side by two arrows facing the same direction as the target (the congruent condition), two arrows facing a different direction than the target (the incongruent condition), or by dashes on both sides (the neutral condition). The task of the participant is to press a key corresponding to the direction of the target arrow (e.g., press the "left" arrow on a keyboard for an arrow pointing left, or press the "right" arrow on a keyboard for an arrow pointing to the right). A single trial consists of five events, beginning with a fixation period for a random variable duration (ranging from 400 – 1600 ms). Next, a warning cue is presented for 100 ms, followed by a 400 ms fixation period, after which the target and flankers (if appropriate) appear simultaneously. Following the presentation of the target, the participant is given up to 1700 ms to respond. Immediately after the participant responds the target and flanker disappear and there is a post-target fixation period which lasts a variable duration based on the duration of the initial fixation and the RT of the participant (3500 ms minus the duration of the first fixation period minus the RT of the participant). The arrow(s) appear either 1.06^{o} above or below the

fixation cross, with location always uncertain in a given trial except when a spatial cue is presented.

In order to measure alerting and/or orienting efficiency, there are four warning conditions, with a cue consisting of an asterisk (*). These consist of a no-cue condition, in which participants see only the fixation cross before stimuli presentation; a center-cue condition, in which an asterisk is placed on top of the center fixation point for 100 ms (this alerts the participant to impending stimulus presentation); a double-cue condition in which an asterisk is presented both above and below the center fixation point for 100ms, corresponding to the two possible target positions (it is hypothesized that alerting is involved, but the attentional field is larger under this condition than under the central-cue condition); and a spatial-cue condition consisting of a single asterisk either above or below the center fixation point, indicating the impending target position (spatial-cues are always valid).

The alerting effect is calculated by subtraction of the mean RT of the double-cue condition from the mean RT of the no-cue condition, as neither of those conditions provide information concerning whether the target would appear above or below the fixation point. Without a warning cue (the no-cue condition), attention tends to remain diffused across the upper and lower possible target locations; the double-cue condition diffuses attention in the same way, except it alerts the participant to the imminent appearance of the target. The orienting effect is calculated by subtraction of the mean RT of the spatial-cue condition from the mean RT of the center-cue condition. Both of these conditions provide information concerning the impending presentation of a target, but the spatial-cue carries the additional information of target location, allowing subjects to orient attention to the appropriate location prior to target presentation. The executive control effect (conflict resolution) is calculated by subtracting the mean RT of the

congruent flanking conditions (all five arrows pointing the same direction) from the mean RT of the incongruent flanking conditions (the target arrow pointing the opposite direction of the flanking arrows).

Estimates of efficiency for each of the three networks as well as for the overall RT has produced significant test-retest reliability, with executive control network estimations being the most reliable (.77) followed by orienting network estimations (.61) and alerting network estimations (.52) (Fan et al., 2002). It has been recommended that to reduce power differences in detection of network efficiencies that the ANT be administered repeatedly (MacLeod et al., 2010). That advice was followed in this study by administering the ANT to each subject four times. Administration of the ANT to a single subject takes roughly twenty minutes the first time, and eighteen minutes on subsequent administrations. The additional time allotted during initial administration is due to instructions being given as well as a brief practice round that is eliminated after the first administration. The ANT was administered a total of four times during this study; once prior to stimulation in order to obtain a baseline measure, once immediately following stimulation, once a short delay after stimulation, and once after a long delay interval. The ANT was administered via a windows based PC using the E-Prime software platform.

Facilities

This study, in its entirety, was performed in Logan Hall. Participants completed the ANT as well as mood and initial questionnaires designed to collect demographics information and screen for exclusionary criteria at a windows-based PC housed in a testing room. This PC is equipped with the software platform E-Prime, which was used to display the ANT. Participants entered responses to stimuli via a response pad with labeled keys.

Risks

In order to minimize potential risks during experimentation, a researcher was present during the entire study and participants were able to communicate with the investigator at all times. Participants' mood and physical sensation were monitored to ensure participant safety. There is evidence that tDCS can result in affective changes, although no studies have found these effects to be negative. Studies designed to investigate the safety aspects of tDCS, however, have reported no significant changes in mood (Poreisz, 2007; Nitsche, 2008). Therefore, we did not anticipate any changes in mood or affect resulting from our study. To further ensure that participants were not experiencing potentially debilitating alterations in mood or mental state we administered a subjective mood questionnaire before and following experimentation. The mood questionnaire is a 10 item, self-report measure that assesses ten domains, on a scale ranging from zero to five with zero corresponding to the extreme low end and five to the extreme high end. Participants are asked to mark how strongly they identify with such statements as "I am tired or fatigued" and "I feel nervous." Any significant changes in answers provided following the experiment resulted in further assessment every 15 minutes until participants return to near the baseline state obtained at the beginning of the study.

Nitsche et al. (2003b) suggest that there may be a slight risk of skin damage when using tDCS. With the exception of Iyer et al. (2005), who reported transient redness at the stimulating electrode site in two men who had recently shaved their heads, we have encountered no reports of skin damage or irritation in any of the tDCS literature. In the previous studies by Clark et al., it was found that tap-water soaked electrodes were related to higher sensations than those soaked in saline solution. We therefore soaked our electrodes in saline solution in this study.

Outside of our lab, over 100 studies have been performed using tDCS in both healthy controls and in patient populations, and no serious side effects have been reported (Nitsche et al., 2008). Though tissue damage has been detected at charges of 216 C/cm^2 in a study involving direct cortical stimulation (Yuen et al., 1981), typical tDCS (2mA for 20 minutes) results in a total charge of only .09 C/cm^2. Additionally, a study performed on rats using an epicranial electrode montage similar to that used in standard tDCS found that brain lesions occurred at current densities exceeding 1429 mA/cm^2 when duration of stimulation was greater than 10 minutes (Liebetanz et al., 2009). This may be contrasted with standard tDCS human-study protocols, in which a current density of approximately 0.05 mA/cm^2 is produced (Stagg & Nitsche, 2011).

Participants were encouraged at the beginning of the tDCS procedure to report any pain or discomfort that they may encounter throughout the procedure. During tDCS participants were asked to describe sensations that they experience at three intervals: 1 minute, 5 minutes, and 12 minutes after the start of tDCS. Sensation data were recorded using three, 10-point Likert scales measuring subjective itchiness, heat/burning, and tingling at the electrode sites. There is a section at the end of each sensation block that allows participants to indicate any sensations aside from the three explicitly addressed in the questionnaire that they are feeling. This questionnaire exists both because it may turn out that feeling a particular amount of sensation is tied to the effect tDCS has on an individual (though in the previous study by Clark et al. it was found performance facilitation was not related to tDCS induced sensation), and because it constitutes an important safety measure. Any report of significant pain or if the participant reports a 7 or higher on any of the three measures of physical sensation at the electrode sites resulted in the immediate termination of stimulation and the subjects' further participation in the study, as the experience

is deemed intense enough that it may be uncomfortable for the participant (this type of exclusion did not occur for any participants in this study).

The electrodes used are rather large (3.3cm x 3.3cm). Although the somewhat expansive surface area of these sponges limits focality of stimulation, this surface area constitutes an important safety parameter in that it keeps the current density participants are exposed to at a low level. All participants who pass the initial screening were given full credit for their participation.

It is worth considering that although the concept of a technique that alters brain activity may seems threatening to some, even traditional methods of cognitive enhancement have been shown to induce changes in brain activity. For example, learning to read alters the way that language is processed in the brain (Petersson et al., 2000), and environments rich in stimulation possibilities have been found to increase dendritic arborisation as well as lead to synaptic changes, neurogenesis, and improved cognition in animal studies (Walsh et al., 1969, Nilsson et al., 1999). In fact, several studies have determined that the study of economics leads to students becoming more selfish than they were prior to study (Frank et al., 1993), so even something so seemingly benign and so common as education may carry with it risks . It is important to keep in mind that these risks are generally seen as acceptable when weighed against the enhancement of cognitive skills and capacities provided by education; such a risk-benefit analysis may prove valuable to other cognitive enhancement methods, as well.

Procedure

Following informed consent, demographics questionnaire, and entrance mood questionnaire, participants were given instructions on how to complete the ANT, and proceeded to take the baseline form of the ANT (which includes a practice run). Upon completion of the

baseline ANT, the tDCS procedure was explained once more to participants, after which electrodes were applied and stimulation began. Immediately following initiation of stimulation, participants were asked to fill out the first block of the sensation questionnaire. The second block was filled out at the five minute mark, and the third block was filled out at the fifteen minute mark. Stimulation lasted a total of thirty minutes. Following cessation of stimulation and removal of electrodes, participants completed the ANT again (referred to subsequently as the "immediate test", which took place roughly 30 minutes following cessation of stimulation), this time with no practice run. Following this, participants were given a fifteen minute break, after which they completed the ANT again (referred to hereafter as the "short delay test", beginning roughly 70 minutes after cessation of stimulation). After another fifteen break, participants completed the final run of the ANT (the "long delay test", which began roughly 115 minutes after cessation of stimulation). After this last test run, participants filled out the exit mood questionnaire, were given an opportunity to ask questions, and were given course credit for their time.

Data Analysis

First, network scores were computed via the methods described above - that is, the alerting effect was calculated by subtraction of the mean RT of the double-cue condition from the mean RT of the no-cue condition, the orienting effect was calculated by subtraction of the mean RT of the spatial-cue condition from the mean RT of the center-cue condition, and the executive control effect (conflict resolution) was calculated by subtracting the mean RT of the congruent flanking conditions (all five arrows pointing the same direction) from the mean RT of the incongruent flanking conditions (the target arrow pointing the opposite direction of the

flanking arrows). These scores were calculated for each of the test points (baseline, immediate, short delay, and long delay).

We then examined attentional network scores via a 2 x 3 repeated measures ANOVA comparing tDCS current (0.1mA and 2.0mA) with network score (repeated measure; immediate test, short delay test, and long delay test). This was done for each of the three network scores (alerting, orienting, and executive functioning), for a total of 3 repeated measures ANOVAs.

Based on results obtained from those ANOVAs, we proceeded to evaluate the overall accuracy of each test run using a 2 x 3 repeated measures ANCOVA, comparing tDCS current (0.1mA and 2.0mA) and test (repeated measure; immediate test, short delay test, and long delay test) with the baseline performance used as a covariate. The overall proportion of correct responses was used as a measure of accuracy for this analysis. A second 2 x 3 repeated measure ANCOVA was performed comparing tDCS current (0.1mA and 2.0mA) and test (repeated measure; immediate test, short delay test, and long delay test), this time evaluating the mean response time (RT) per test run, again using the baseline measure as a covariate.

The impact of sensation and demographics variables on performance (mean accuracy and mean response time) was examined using a correlation matrix. Sensation ratings from all three measures (itching, heat, and tingling) were evaluated separately, per time point (immediately after stimulation, at the five minute mark, and at the fifteen minute mark). In addition, a series of t-tests were performed on mood questionnaire data in order to determine if any significant differences existed between groups at either the baseline or at the end of the study. As a result of that analysis, follow-up measures were performed that consisted of an ANOVA in order to determine if there were significant changes in mood, and a correlation matrix was computed in

order to examine if mood differences in mood significantly were related to performance measures.

<div align="center">Results</div>

There was a significant main effect of group (0.1mA condition vs 2.0mA) on alerting network scores; $F(1, 22)=4.736, p=0.041$, such that the sham group exhibited higher alerting network scores, while there was not a significant main effect of test point (immediate vs. short delay vs. long delay); $F(2,44)=1.839, p=0.171$, and no significant interaction; $F(2,44)=.500, p=0.610$. There was not a significant main effect of group on orienting score; $F(1,22)=0.885, p=0.357$, nor a significant main effect of test point; $F(2,44)=0.034, p=0.967$, and no significant interaction; $F(2,44)=1.115, p=0.337$. There was no significant main effect of group on executive functioning score; $F(1,22)=.521, p=0.478$, no significant main effect of test point; $F(2,44)=.532, p=0.591$, and no significant interaction; $F(2,44)=2.206, p=0.122$. These results can be respectively seen in Figs. 1-3, which include baseline measures.
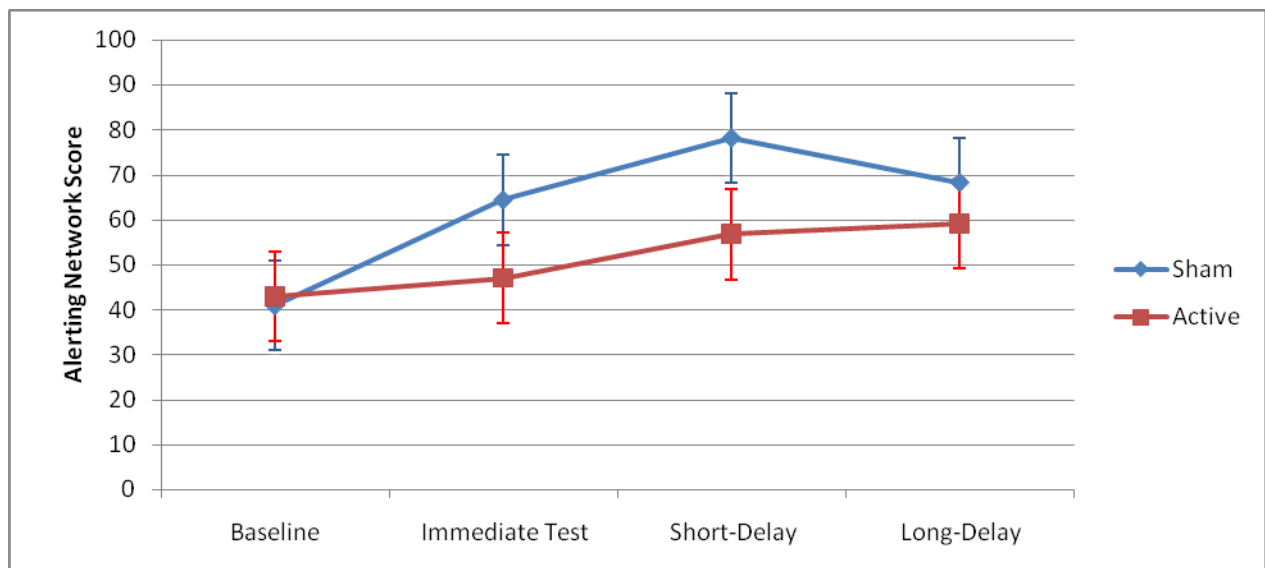

Figure 1 - Alerting Network Scores at Each Test Point
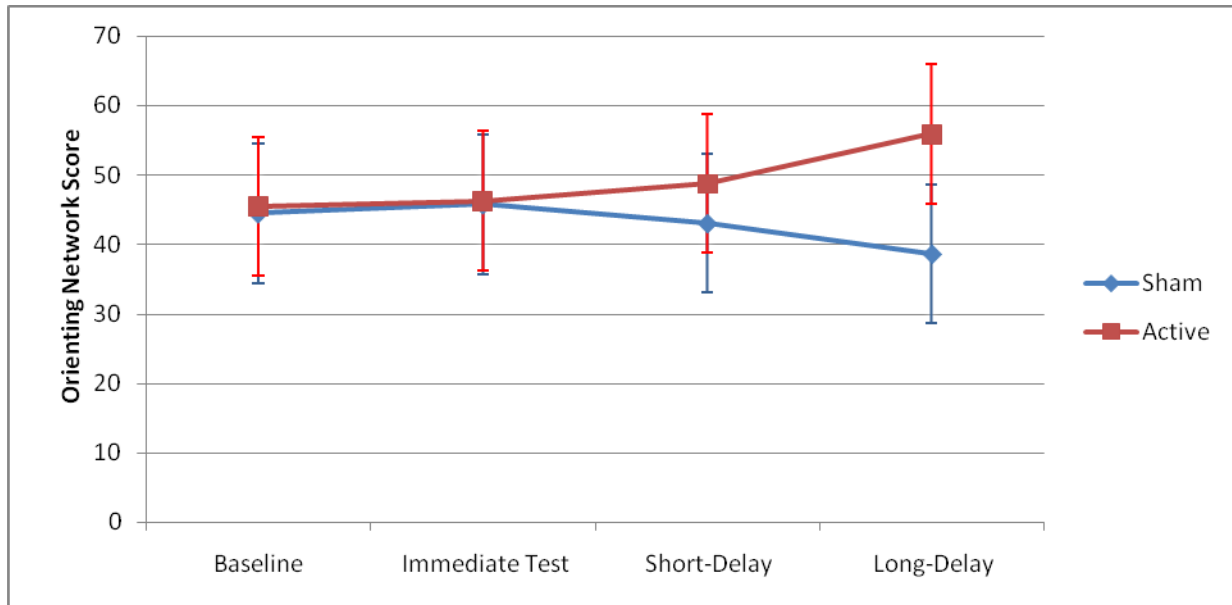
Figure 2 - Orienting Network Scores at Each Test Point
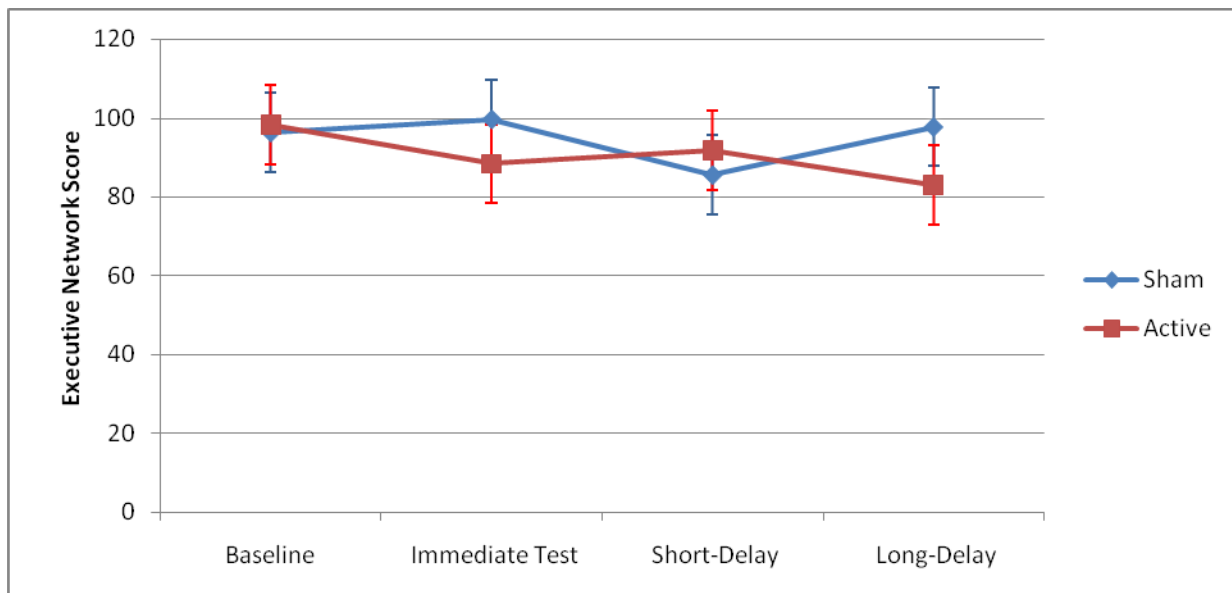

Figure 3 - Executive Network Scores at Each Test Point

As these results (a significant difference between groups in alerting network scores such that the sham group achieved higher scores than the active group) seemed counterintuitive based

on the results of the 2012 Clark et al. study, this necessitated a closer look at the data, specifically the overall RT and accuracy measures, between groups. As there appeared to be differences between groups on both RT and accuracy, two independent samples t-tests were performed to examine possible significance of these baseline difference. The t-test on mean RT at baseline revealed no significant difference between active and sham groups; $t(22)=1.590, p=0.126$, nor did the t-test on accuracy; $t(22)=-.1348, p=0.191$. Though these differences were not significant, they may still have an impact on later results, and were thus included as covariates in an ANCOVA analysis.

The ANCOVA performed on RT results, with baseline meat RT as a covariate, revealed no significant main effect of group; $F(1,21)=3.781, p=0.061$, no significant main effect of test point; $F(2,42)=0.521, p=0.598$, and no significant interaction; $F(2,42)=1.460, p=0.244$. Likewise, the ANCOVA performed an accuracy results, with baseline measure as a covariate, did not result in a significant main effect of group; $F(1,21)=2.156, p=0.157$. Additionally, there was no significant interaction; $F(2,42)=1.397, p=0.259$. There was, however, a significant main effect of test point on accuracy; $F(2,42)=8.945, p=0.001$. The changes in RT and accuracy are depicted in Figs. 4 and 5.
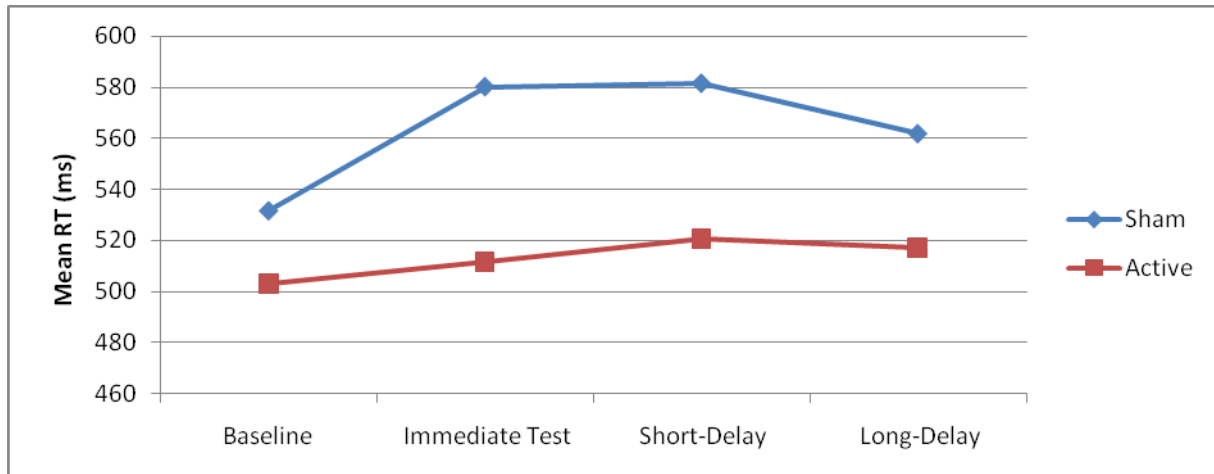
Figure 4 - Mean RTs at Each Test Point
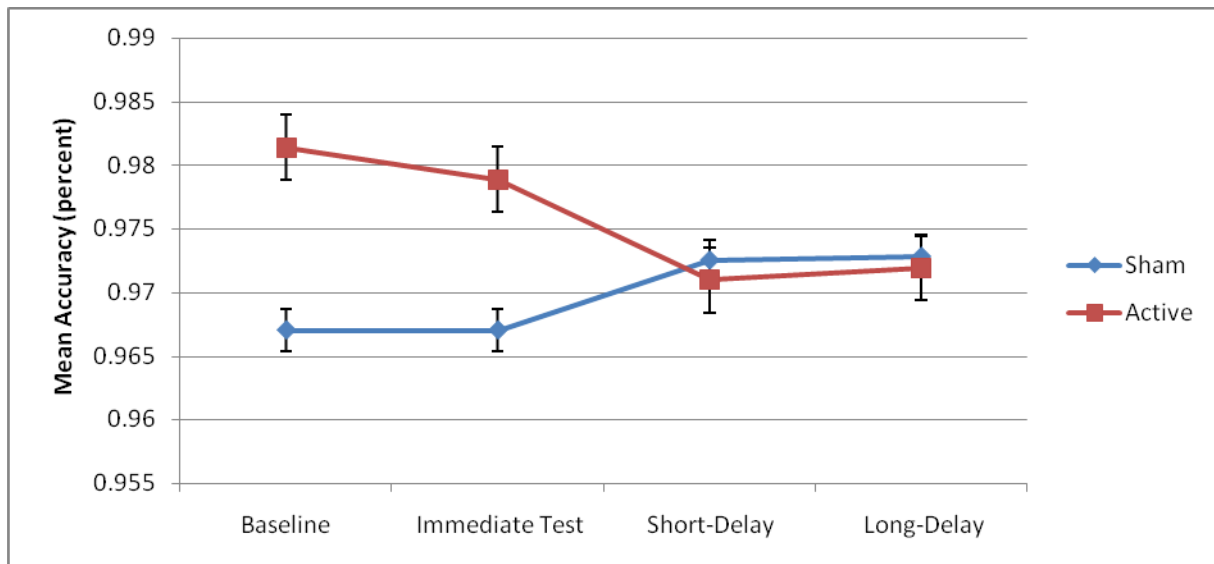
Figure 5 - Mean Accuracy at Each Test Point

The influence of sensation on accuracy and RT was examined using a correlation matrix. Sensation ratings from all three measures (itching, heat and tingling, taken at three points during stimulation, for a total of nine sensation-related measures per participant) at each of the post-stimulation test points (immediate, short delay, and long delay) were included in the matrix. None of the sensation measures correlated significantly with performance measures. Additionally, when sensation was reported as a binary variable (present or absent), no significant effect of sensation was found on RT or accuracy measures.

In order to evaluate the potential impact of tDCS on mood, a series of T-Tests were computed, examining the possibility of differences between groups on mood scores at the start of the study and at the end of the study. The groups did not significantly differ on any mood measures at the pre-tDCS point, though at the end of the study a difference was found for the item reading "I feel unable to concentrate or pay attention", with those in the sham group tending to agree significantly more with this statement than those in the active stimulation group; $T(22)=2.037, p=0.036$. As a follow-up to this, a 2 x 2 ANOVA was performed, investigating possible changes in the concentration measure between groups (active vs. sham) throughout the course of the study (repeated measure; start of study and end of study). Though there was no significant main effect of group on concentration; $F(1,22)=4.166, p=0.056$, there was a significant main effect of time point; $F(1,22)=9.164, p=0.006$, and a significant interaction; $F(1,22)=5.006, p=0.036$. In order to determine if ability to concentrate had an impact on performance measures, the correlations of agreement with the statement "I feel unable to concentrate or pay attention" with RT and accuracy measures at all test points were investigated. Though concentration failed to correlate significantly with any accuracy measures, inability to concentrate positively correlated with baseline mean RT; $r(22)=.503, p=0.012$, with immediate test mean RT; $r(22)=.457, p=0.025$, with short-delay mean RT; $r(22)=.465, p=0.022$, and with long-delay mean RT; $r(22)=.444, p=0.030$ (that is, inability to concentrate correlated positively

with RT at every test point). Fig. 6 depicts concentration levels between groups over time.
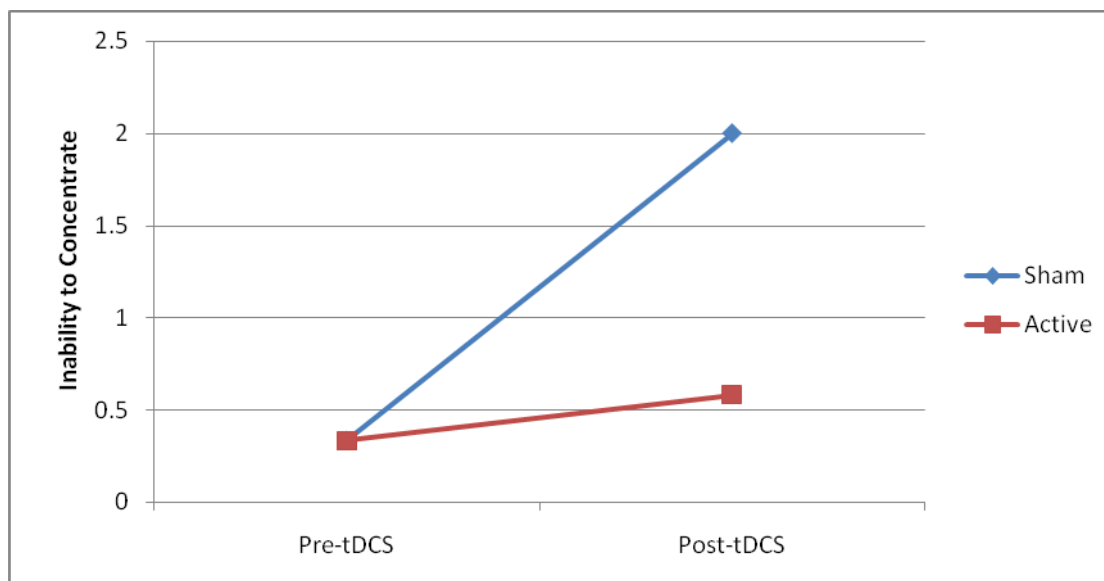

Figure 6 - Average agreement with the statement "I feel unable to concentrate or pay attention" between groups, with larger number indicating stronger agreement with the statement.

In order to determine if demographic variables played a role in the pre-existing group differences, a correlation matrix was computed to examine if any demographic measures resulted in significant correlation with performance measures (mean RT, mean accuracy). Although it was determined that average caffeine consumption was significantly correlated with baseline RT; $r(22)=.692, p<.001$, and age was significantly correlated with baseline accuracy; $r(22)=.584, p=0.003$, the groups did not significantly differ on these measures (for the sham group, avg. age = 21.33 yrs, SD = 5.24; for the active group, avg. age = 21.83 yrs, SD = 8.33 yrs; for the sham group, avg. caffeine consumption = 15.67 oz/day, SD = 14.91; for the active group, avg. caffeine consumption = 9.50 oz/day, SD = 10.55 Oz). Furthermore, these measures were only predictive of baseline values - they did not significantly predict subsequent performance measures.

Discussion

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

Enhancing the excitability of the right frontal cortex could facilitate image detection performance for several reasons: Lateral frontal cortex has been suggested by Posner and Peterson (1990) to be a key component of the fronto-parietal attention network, a brain network active in attention requisition during target detection. Greater attention requisition during visual search may lead to a greater probability of noticing objects in the images, enhanced encoding of the image and, therefore, greater accuracy. In order to determine the involvement of attention in the previous findings, the current study examined the effect of tDCS (applied using the same parameters as the 2012 Clark et al. study) on three different attentional networks (alerting, orienting, and executive functioning).

The analysis of attentional networks revealed only one significant difference between groups, with the sham group exhibiting significantly higher alerting scores. As the alerting network is defined as a network that facilitates achievement and maintenance of an alert state, greater activation of this network in the sham group does not provide an explanation for the increased performance exhibited by the active stimulation in the previous study by Clark et al. (2012). Since this score is essentially a RT difference score, the mean

RTs were investigated for both the sham and active conditions at each of the four test points. From this analysis, it was determined that though the difference scores (and therefore network scores) for the alerting network were smaller for the active group, they responded faster on average across stimuli conditions (though this difference was present prior to tDCS administration, and when the baseline measure was used as a covariate, subsequent differences in RT failed to achieve significance).

It is interesting to note that these faster RTs, while not quite significant, did not occur at the cost of accuracy, as there were no significant between-group differences in accuracy. There was however a significant effect of test point on accuracy. This situation is difficult to interpret in the context of RT changes, as over time the sham group exhibited increased RTs and increased accuracy (which may make sense in that taking longer to respond resulted in greater accuracy), whereas the active group, while also experiencing elevated RTs showed a decrement in accuracy over time. It is possible that these results relate to fatigue, which is perhaps offset somewhat by a practice effect. Of course, the RT changes did not reach significance, and there was no main effect of group on accuracy, so these results need to be interpreted with caution as they do not definitively point to any particular explanation. The above potential explanations are merely speculation.

One possible explanation for the while not significant, consistently present difference in RTs. Self-reported measures of ability to concentrate reveal that although at the start of the study, both active and sham groups reported near identical lack of concentration, at the end there was a significant difference between groups such that the sham group reported having a greater inability to concentrate than the active stimulation group. Moreover, the exit measure of inability to concentrate correlated positively at significant levels with RT measures at all four test points, such that higher reported inability to concentrate resulted in longer RTs.

Given that the active stimulation group responded faster and more accurately to stimuli at the baseline level, these results are not conclusive. In an attempt to determine if there was a "third variable" leading to these pre-existing group differences, a correlation matrix was computed to examine if any demographic measures resulted in significant correlation with performance measures (mean RT, mean accuracy, alerting, orienting, or executive function scores). Though average caffeine use and age correlated positively with baseline measures at a significant level, they failed to significantly correlate with post-stimulation performance measures. Thus, if a third variable is at the root of the group differences, it is not a variable measured in this study.

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

CONCLUSION

In summary, due to the areas being stimulated (RIFC), and the previously mentioned neuroimaging studies that link the alerting network to frontal and parietal activation (Coull et al., 2001), and executive control function to the ACC and the lateral prefrontal cortex (Bush et al., 2000), it seemed reasonable that higher scores for these networks will be achieved by those in the active stimulation groups. However, the only network difference observed involved the alerting network, in an unexpected direction (higher scores for the sham group). As it turned out, the active group, while obtaining smaller differences in RT between conditions, responded faster across all conditions. These results, however, were rendered non-significant due to group differences observed at the baseline measure. It is possible the RT scores related to levels of concentration, though a third variable could be the root of observed differences. Thus, results are inconclusive given the current set of data.

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