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# Using Brain Stimulation to Enhance Working Memory: A Charged Topic

Michael Christopher Stefan Trumbo

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Michael C. S. Trumbo

*Candidate*

Department of Psychology

*Department*

*Dissertation Committee:*

Vincent P. Clark, PhD, Chairperson

Eric Ruthruff, PhD

Katie Witkiewitz, PhD

Robert Thoma, PhD

# USING BRAIN STIMULATION TO ENHANCE WORKING MEMORY: A CHARGED TOPIC

**by**

**MICHAEL C. S. TRUMBO**

B.S. Psychology, The University of Wisconsin-Parkside, 2008
M.S., Psychology, The University of New Mexico, 2012

DISSERTATION

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## ABSTRACT

Although working memory (WM) training programs consistently result in improvement on the trained task, benefit is typically short-lived and extends only to tasks very similar to the trained task. Pairing repeated performance of a WM task with brain stimulation may encourage plasticity in brain networks involved in WM task performance, thereby improving the training benefit. In the current study, transcranial direct current stimulation (tDCS) was paired with performance of a WM task. In Experiment 1, participants performed a spatial location-monitoring *n*-back during stimulation, while Experiment 2 used a verbal identity-monitoring *n*-back. In each experiment, participants received either active (2.0 mA) or sham (0.1 mA) stimulation with the anode placed over either the right or the left dorsolateral prefrontal cortex (DLPFC) and the cathode placed extracephalically. In Experiment 1, only participants receiving active stimulation with the anode placed over the right DLPFC showed marginal improvement on the trained spatial *n*-back, which did not extend to a near transfer (verbal *n*-back) or far transfer (fluid intelligence) task. In Experiment 2, both left and right anode placements led to improvement, and right DLPFC stimulation resulted in numerical (though not sham-adjusted) improvement on the near transfer (spatial *n*-back) and far transfer (fluid intelligence) task.

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# 1.0 INTRODUCTION

In the early 1980s, behavioral neuroscientist Dr. Edward Taub was employed at the Institute of Behavioral Research in Silver Spring, Maryland investigating the notion of learned non-use – a phenomenon in which individuals who had suffered brain damage ceased using limbs from which they no longer received sensory input. Taub believed limbs so affected were capable of movement, but were often abandoned to atrophy in the presence of another, more functional limb. To test his hypothesis, 17 macaque monkeys were subjected to a number of deafferentation conditions, including dorsal rhizotomy in which the afferent ganglia which convey sensory information from the arm to the brain are severed. Subsequently, monkeys were restrained such that only the deafferented limb was available for essential behaviors such as feeding. Under these conditions, it was found that a limb which did not provide sensory input could still be used to effectively perform motor functions (Taub et al., 1993).

Eventually, Taub would parlay this finding into the development of constraint-induced (CI) movement therapy, in which brain damaged individuals intensively train the use of a more-affected limb while restraining a less-affected limb. This approach has proven effective in enabling stroke survivors to regain the use of limbs thought to be paralyzed (Wolf et al., 2006), facilitating acquisition of motor skills by patients with cerebral palsy (Taub, Ramey, DeLuca, & Echols, 2004), treating focal hand dystonia (Candia et al., 1999), and alleviating phantom limb pain (Weiss, Miltner, Adler, Brückner, & Taub, 1999; for review see Taub, Uswatte, & Pidkiti, 1999). Prior to development of CI therapy, Taub would find himself embroiled in the first animal research case to reach the United States Supreme Court, the outcome of which would lead to an explanation for the broad efficacy of CI therapy, though it would cost the so-called Silver Spring monkeys their lives and nearly cost Taub his career.

While studying political science at George Washington University in 1980, longtime animal rights activist Alex Pacheco co-founded People for the Ethical Treatment of Animals (PETA) along with Ingrid Newkirk. In May of 1981, Alex volunteered to work in Taub's laboratory in order to gain firsthand experience regarding the conditions of an animal research facility (Pacheco & Francione, 1985). Over the next several months, Alex took photographs of laboratory conditions, and in September of 1981 reported Taub to the police under Maryland's animal cruelty laws, citing unsanitary conditions, malnourishment of animals, and improper wound care (Blum, 1994). Following the first police raid on an animal researcher in the U.S., Taub was charged with 17 counts of animal cruelty and failure to provide adequate veterinary care.

Though claiming he had been set up and Alex had staged many of the photographs, Taub was initially convicted on six counts. After a series of appeals, all convictions were overturned when the court concluded that (at the time) Maryland's animal cruelty laws did not apply to federally funded laboratories. The fight for custody of the monkeys would last nearly a decade, with the National Institute of Health (NIH) refusing to relinquish custody to PETA. In July of 1991, the Supreme Court denied PETA's application for custody, and several days later the remaining moneys were euthanized (Blum 1994). Dr. Timothy Pons of NIH and his colleagues (including Taub) agreed to the euthanasia, on the condition that they were able to first probe the somatosensory brain maps of the four macaques previously subjected to dorsal rhizotomy in order to determine if the procedure twelve years prior had resulted in any substantial change. The animals were anesthetized, their skulls cracked open, and recording electrodes implanted.

Prior experiments provided a glimpse at what the researchers would find. In the early 1980s, Dr. Michael Merzenich and colleagues amputated the fingers of adult owl and squirrel monkeys, waited 2-9 months, then took recordings from implanted electrodes in the somatosensory cortex regions previously associated with these fingers (Merzenich et al., 1983). Rather than quiescence reflecting lack of sensory input to these brain regions, researchers recorded substantial neural activity—when fingers adjacent to the amputated digit were stroked. This surprising result was attributed to remapping of neighboring impulses into the vacated regions, suggesting an unanticipated flexibility in the brain. The remapping occurred at a distance of 1-2 mm, within the range of the axon length for neurons in this brain regions, leading the authors to conclude that existing but previously inhibited axons existing in the region typically associated with the amputated finger were unmasked when sensory input ceased due to detachment of the extremity (Merzenich et al., 1983). Thus, cortical remapping was thought to be possible at the time Dr. Timothy Pons and colleagues investigated the Silver Spring macaques, who had received deafferentations many years before, but only in the context of preexisting hardwired circuits that may become active when competing impulses cease.

In light of this finding, Pons and colleagues expected to find a few millimeters of encroachment from sensory regions adjacent to the hand in the somatosensory cortex—those mapping to the face and the trunk—limited to the length of individual axons that may cross from one region to another. Instead, they found touching the face of each monkey resulted in activation in both the region typically associated with facial sensory input as well as activation in regions previously corresponding to the deafferentated limb (Pons et al., 1991). This was reorganization of over half an inch of cortex; too much real estate for a “preexisting axon” account to serve as a feasible explanation. These results have since been corroborated by neuroimaging studies involving human amputees (Karl, Birbaumer, Lutzenberger, Cohen, & Flor, 2001; MacIver, Lloyd, Kelly, Roberts, & Nurmikko, 2008; Pascual-Leone, Peris, Tormos, Pascual, & Catala, 1996), and such large scale cortical remapping has been suggested as a mechanism for phantom limb sensations (Ramachandran & Hirstein, 1998).

In this context, it makes sense that CI therapy could have wide-ranging effects, as sensory and motor regions otherwise dormant come back to life through remapping, similar to the phenomenon of collateral circulation in the circulatory system, by which blood vessels from an arterial tree adjacent to an obstructed artery provide compensatory perfusion (Faber, Chilian, Deindl, van Royen, & Simons, 2014). Indeed, functional magnetic resonance imaging (fMRI) has demonstrated that CI therapy engenders cortical reorganization in a fashion that allows for recovery of motor function in limbs previously deemed paralyzed (Levy, Nichols, Schmalbrock, Keller, & Chakeres, 2001). These findings spurred investigations into the ability of the human brain to adapt in response to environmental pressures, experiences, and physiological changes—referred to as plasticity. The resulting body of work would establish plasticity as a fundamental property of the human brain, overturning the long-held dogma that while the developing brain is a dynamic organ, the adult brain is largely hardwired with static structure and function (Burke & Barnes, 2006; Pascual-Leone, Amedi, Fregni, & Merabet, 2005).

A number of studies have underscored the relationship between plasticity and learning and memory. For instance, players of stringed instruments exhibit cortical reorganization reflecting greater representation for the fingering digits, correlated with time spent practicing (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995). Learning to read alters the way in which the brain processes language (Petersson, Reis, Askelof, Castro-Caldas, & Ingvar, 2000). Deaf and hearing subjects process American Sign Language differently, with evidence for practice-induced brain plasticity (Neville et al., 1998), and blind subjects who learn to read Braille activate the primary visual cortex when doing so (Sadato et al., 1996). Armed with the concept of plasticity, researchers have turned their attention to developing modulatory techniques that result in the desired behavioral outcome by altering brain function in a targeted fashion.

Brain modulation for the purpose of memory enhancement has been investigated using stimulants (Lee & Ma, 1995), cholinergic agonists (Freo et al., 2005), the piracetam family (Mondadori, 1996), ampakines (Ingvar et al., 1997), and consolidation enhancers (Lynch, 2002). In addition, researchers have investigated the role of nicotine in attention and memory (Newhouse et al., 2004; Rusted et al., 2005), the effect of caffeine on arousal and learning (Smith, Brice, Nash, Rich, & Nutt, 2003; Tieges et al., 2004), the possibility of cognitive enhancement via hormone therapy (Gulpinar & Yegen, 2004) or genetic alteration (Routtenberg et al., 2000), the use of dietary supplements to benefit cognitive performance (McMorris et al., 2006), memory enhancement tied to emotional modulation (LaBar & Cabeza, 2006), a variety of other drug treatments (Farah et al., 2004), and more traditional methods such as exercise (Hötting, K., & Röder, 2013) and meditation (van Vugt & Jha, 2011). One particular type of memory has proven a popular target for these interventions.

## 1.1 What is Working Memory?

Working memory (WM) is a psychological construct used to describe the storage and manipulation of transitory information necessary for complex tasks such as learning and reasoning (Baddeley, 1986; Becker & Morris, 1999; Cowan, 2001; Shah & Miyake, 1999). For instance, performing mental arithmetic (Ashcraft & Kirk, 2001) and reading comprehension (Daneman & Carpenter, 1980) both involve storage and manipulation of continuously updating information and therefore considered WM tasks. Initially coined by Miller, Galanter, and

Pribram, “working memory” was used in the context of describing the brain as analogous to a computer (Baddeley, 2003). Baddeley and colleagues later modeled working memory as a way to extend the concept of short-term memory to include manipulation of information. In this model, WM is compartmentalized into various slave systems responsible for maintenance of information in particular sensory domains (e.g., visual information is maintained in a sensory system deemed the visuospatial sketchpad while auditory information is maintained in the phonological loop), while the maintained information is manipulated by a central executive (Baddeley, 1986; Baddeley & Hitch, 1974). This model has been updated to incorporate an episodic buffer system that allows for binding of information across modalities and time (Baddeley, 2000).

While Baddeley’s model is still perhaps the most well-known and influential model of WM, there are several notable competitors. For instance, Cowan (1997, 2001, 2012) regards WM as a part of short-term memory that consists of representations in long-term memory that are brought into an active state via the focus of attention. A model proposed by Ericsson and Kintsch (1995) begins with the observation that many skilled memory tasks, such as reading, necessitate chunking of more than the standard 7 units supposed possible by other models in order to enable an understanding of the relationships between words (and sentences, paragraphs, pages, and chapters) in a text. Such an understanding is thought to be accomplished by storing pieces of information in long-term memory and linking them together through retrieval structures, such that items held in WM serve as cues to activate linked representations in long-term memory—a process referred to as long-term working memory.

WM may be distinguished from sensory memory and long-term memory by capacity limitation and time course. While sensory memory has a relatively high capacity, it is susceptible to disruption and lasts only several hundred milliseconds (Sperling, 1960). Long-term memory may persist over great durations and has a seemingly unlimited capacity (Von Neumann, 1958). WM is distinct with regard to capacity—limited to three or four items, in the visual domain—as well as with regard to time course, as it operates on the scale of seconds (Cowan, 2001; Luck & Vogel, 1997). Additionally, WM is attention-dependent and performance on WM tasks deteriorates substantially when attention is diverted (Awh & Jonides, 2001).

Thus, the critical extension from short-term memory to WM is the recognition that WM goes beyond a system that simply stores information, in that it involves manipulation of information—hence the "working" part of its moniker. The information that enters WM is thought to be guided by top-down processes related to goal maintenance, such that irrelevant information is filtered out via a gating mechanism (Hazy, Frank, & O'Reilly, 2006). The construct of WM thus encompasses encoding and maintenance of new information (i.e., updating) in a selective fashion via top-down biasing of processing, such that goal-relevant information enters WM for further manipulation while irrelevant information is suppressed (Baddeley, 1986; Engle, 2002; Fougnie & Marois, 2007; Hazy et al., 2006).

## 1.2 Improving Working Memory

Performance on WM measures predicts fluid intelligence (*r* = .55; Unsworth & Engle, 2007), language comprehension (*r* = .41-.52; Daneman & Merikle, 1996), attentional control (*r* = .32-.60 Shipstead, Harrison, & Engle, 2015;), mathematics proficiency (*r* = .22-.33; Miller & Bichsel, 2004), reading comprehension (*r* = .69; Daneman & Green, 1986), reasoning ability (*r* = .80-.90; Kyllonen & Christal, 1990), and scholastic achievement (*r* = .19 (science)-.62 (English); St. Clair-Thompson & Gathercole, 2006). Additionally, WM has been implicated in affective processing (Hoffmann, Schmeichel, & Baddeley, 2012) and WM deficits are apparent in a number of psychiatric disorders (Millan et al., 2012). For instance, depressed individuals may find it difficult to suppress intrusive negative thoughts from entering WM, leading to rumination (Joormann & Gotlib, 2008). Owing to its relevance for both healthy and clinical populations, interventions geared toward WM improvement have become popular (Rabipour & Raz, 2012). The goal of such training is to enhance the underlying construct of WM, thereby generalizing performance increases to additional tasks that rely on overlapping cognitive abilities or share neural systems (Dahlin, Neely, Larsson, Backman, & Nyberg, 2008; Owen et al., 2010). Notable attempts to improve WM function include the use of cognitive training programs, meditation, and exercise—all of which may encourage brain plasticity, thereby facilitating acquisition of knowledge and skills.

### *1.2.1 Cognitive Training Programs*

Fluid intelligence (G*f*) refers to aspects of intelligence involved in encoding and manipulation of novel information, thereby enabling adaptive reasoning and problem solving (Carpenter, Just, & Shell, 1990). G*f* may be contrasted with crystallized intelligence (G*c*), which refers to static knowledge such as vocabulary that accumulates over the lifespan (Carroll, 1993; Cattell, 1963). Typically, G*f* is characterized as a stable trait that may deteriorate due to aging, disease, or injury, but is otherwise resistant to intervention (Carroll, 1993; Jensen, 1998). This is partly due to the high heritability of G*f*, as 50-75% of its variance in healthy adults can be traced to genetic variation (Neisser et al., 1996), though heritability is not necessarily the same as immutability (Dickens & Flynn, 2001). In fact, a report demonstrating that G*f* could be enhanced via repeated performance of WM tasks has sparked a great deal of excitement and controversy.

In this landmark study, Jaeggi, Buschkuehl, Jonides, and Perrig (2008) reported that participants who practiced an adaptive dual *n*-back task designed to improve WM demonstrated significant control-adjusted gain in measures of G*f* following 18 training sessions. While additional research supports the notion that WM training is a promising way of increasing G*f* (e.g., Jaeggi, Buschkuehl, Shah, & Jonides, 2014; Klingberg, 2010; Perrig, Hollenstein, & Oelhafen, 2009; Sternberg, 2008), other research (e.g., Conway & Getz, 2010; Shipstead, Redick, & Engle, 2012; Sprenger et al., 2013; Chooi & Thompson, 2012; Redick et al., 2013; Thompson et al., 2013; Richmond, Wolk, Chein, & Olson, 2014) presents a more cautious view, concluding that WM training programs have limited efficacy regarding improvement of reasoning and general intelligence. Meta-analyses of cognitive training programs designed to enhance WM have also  advised caution, indicating that while WM training consistently produces improvement on tasks similar to the ones used during training, these effects tend to be short-lived and improvement fails to generalize to other domains (Melby-Lervåg & Hulme, 2013; Papp, Walsh, & Snyder, 2009; Valenzuela & Sachdev, 2009; cf. meta-analysis by Au et al., 2014, indicating a small but significant G*f* benefit as a result of *n*-back training). Such findings are congruent with a long research history demonstrating that although task-specific performance commonly increases with training, transfer remains rare (Chase & Ericsson, 1981; Detterman & Sternberg, 1982; Ericsson & Delaney, 1998; Healy, Wohldmann, Sutton, & Bourne, 2006; Owen et al., 2010; Singley & Anderson, 1989).

The controversy has done little to stem the proliferation and popularity of commercial cognitive training programs (e.g., AARP Staying Sharp, Brain Age, CogMed, Lumosity, Mindsparke Brain Fitness Pro, Posit Science Brain Fitness, Posit, WMPro) that are largely based on adaptive WM tasks (Melby-Lervåg & Hulme, 2013). In Norse mythology, Odin, the chief god of the Aesir, hung himself upside-down from the World Tree, Yggdrasil, for nine days of fasting and agony in order to attain wisdom. The modern equivalent suggested by cognitive training programs is to subject oneself to days or months of an adaptive *n*-back task in order to achieve sagacity. There is, however, little evidence that loading on a cognitive construct such as WM via repeated administration of adaptive tasks achieves a result analogous to strengthening a bicep through performing curls of increasing weight over time (Melby-Lervåg & Hulme, 2013); a burn without a benefit—a starving, pain-wracked Odin who has become none-the-wiser.

This is because improvement on a trained task may occur through avenues aside from a strengthening of the underlying neural architecture that subserves the task construct, including changes in motivation and strategy refinement (Hayes, Petrov, & Sederberg, 2015). During physical exercise, it is possible to consciously choose which muscle groups to work out by selecting a particular set of exercises. It is not clear, however, that we can choose which regions of the brain to use when accomplishing a task. Cognitive effort is metabolically intense (Fairclough & Houston, 2004; Kennedy & Scholey, 2000) and as such people typically attempt to use the minimum amount of cognitive effort necessary to perform a task or avoid cognitive demand when possible (Kool, McGuire, Rosen, & Botvinick, 2010; Westbrook & Braver, 2015).

Essentially, the brain has developed to accomplish tasks with the minimum amount of effort possible. In keeping with the physical exercise analogy, imagine approaching weight lifting simply as a task requiring a particular weight to be lifted up and down a particular number of times. While in the realm of physical exercise we can consciously choose to approach this task in a way that is demanding of our muscles, the brain solution is to implement a strategy akin to constructing a simple machine such as a pulley system attached to the weight that allows for task completion with a minimum of expended effort (Westbrook & Braver, 2015). While this accomplishes the task of lifting the weight repeatedly it does very little to enhance the intended muscle group, and indeed strategy mastery has been associated with decreases in brain activity (Klingberg, 2010).

It is for this reason that WM training programs often utilize adaptive tasks which are designed to discourage strategy use by adjusting the difficulty of the task contingent on performance (Melby-Lervåg & Hulme, 2013). This presupposes, however, that a strategy formed during performance at one level of difficulty will not benefit performance at a higher level of difficulty. Additionally, during assessment it may be desirable to separate the influence of strategy use from WM capacity in order to obtain a pure measure of WM which has predictive ability (McNamara & Scott, 2001). When moving beyond assessment to performance of real world tasks, however, repeated stifling of strategy formation during training may hinder strategy use during job performance, resulting in suboptimal task execution (Matzen et al., 2015).

Despite these limitations, “brain-training” regimens have become a multi-billion dollar industry (“Brain Sells,” 2013), with programs such as Lumosity (http://www.lumosity.com) boasting upwards of 70 million registered users in over 180 countries. The scientific community has begun to respond to this industry built on early and contested findings. In fact, the common assertion by commercial programs that they have been designed by “leading neuroscientists” has prompted over 70 of the world’s leading cognitive psychologists and neuroscientists to release a statement describing the claims made by these programs as “exaggerated and misleading” (“A Consensus on the Brain Training Industry from the Scientific Community,” 2014). While cognitive training does not appear to harm cognitive abilities, it is important to consider engagement in these programs in terms of opportunity cost, with regard to both time and money. While playing “brain training” games likely benefits cognitive function when compared to watching reality television, if an individual is spending resources on an ineffective method of improvement they are forgoing the chance to engage in other activities that may enhance cognition, such as learning a language or how to play an instrument (Owen et al., 2010). In fact, there are several methods in addition to cognitive training that have shown some promise at improving cognitive functioning.

### *1.2.2 Meditation*

Mindfulness meditation comes from the Buddhist meditation approach found in Zen and Vipassana, and has been described as a complete, unbiased focus on the current moment (Kabat-Zinn, 1998). There are two major varieties of mindfulness meditation: focused attention and open monitoring (Travis & Shear, 2010). Focused attention meditation entails fixation on an object or process (e.g., a mantra, a visual stimulus, breath control); the meditator practices recognition of any distraction from this focus and subsequently attempts to re-engage with the chosen object or process. Open monitoring involves the practice of becoming aware of the present moment. This includes noting sensory experiences as they arise, as well as cognitions and emotions; simply observing without judging or reacting.

Practice of mindfulness meditation has been demonstrated to enhance a variety of cognitive processes, including sustained attention (Kozasa et al., 2012) and selective attention (Jha, Krompinger, & Baime, 2007), in addition to increasing awareness, relaxation, insight, emotional well-being (Hölzel et al., 2011), resistance to impulses and negative affect (Witkiewitz, Lustyk, & Bowen, 2012), reduction of pain (Zeidan et al., 2011) and improved self-control (Jenkins & Tapper, 2014). Given the emphasis of filtering out distraction, it is perhaps no surprise that mindfulness meditation has also been shown to improve WM (van Vugt & Jha, 2011).

Behavioral research supports the idea that even a brief amount of meditation may be beneficial. One study found that mindfulness meditation can improve attention and self-regulation in as little as five 20-minute sessions (Tang et al., 2007). Another demonstrated that in as little as four days of training, mindfulness meditation serves as an effective way to modulate the experience of pain (Zeidan et al., 2011). In a study investigating the effect of meditation on the anticipatory stress occurring prior to engaging in the stressful task, participants had no prior meditation experience yet still showed benefit – though in this case they were given guided meditation, led by an expert, prior to the task (Mohan, Sharma, & Bijlani, 2011). In fact, there are now a number of mindfulness training methods that are designed to improve cognitive functioning in as little as eight weeks (Hölzel et al., 2011; Kerr et al., 2011).

### *1.2.3 Exercise*

Alongside cognitive training programs and meditation, physical exertion is being explored as a method of improving cognitive abilities. For instance, Albert and colleagues (1995) demonstrated that for healthy 70 to 79 year-olds the best predictors of cognitive change (as measured by a battery of tasks assessing language, verbal memory, nonverbal memory, conceptualization, and visuospatial ability) over a 2 year period included history of strenuous activity and peak pulmonary expiratory flow rate (the force with which they are able to exhale). Other groups have found similar results in the elderly with follow-up periods ranging from two years (Etgen et al., 2010) to 31 years (Andel et al., 2008).

It is possible that the effect of physical activity on cognition is particularly pronounced for older individuals. The aging brain undergoes a number of changes, including deterioration of frontal lobe structures that relate to executive functioning, such as planning, organizing, managing time, and WM (West, 1996). Exercise is particularly suited to boosting these functions

(Colcombe & Kramer, 2003). Research directly comparing middle-aged adults (40-59 years of age) and older adults (60-82 years old) in order to examine what may be termed the "age-dependence hypothesis" of exercise benefit found that physical exercise did in fact provide a greater benefit to the older individuals (Hötting & Röder, 2013), supporting the idea that physical exercise has a greater effect on cognitive functions during life stages at which these functions are prone to decline.

On the other end of the age spectrum, associations between physical activity and cognitive functioning in children have found that cardiovascular fitness is a particularly strong predictor of performance on tasks that require a high amount of cognitive control, such as WM tasks that necessitate goal maintenance or filtering out irrelevant information (Chaddock et al., 2012). Academic achievement (Donnelly et al., 2009), creativity (Tuckman & Hinkle, 1986), and planning ability (Davis et al., 2011) have all been found to improve with physical exercise interventions in children. Executive functioning seems to be particularly open to benefit from physical exercise in children (Barenberg, Berse, & Dutke, 2011; Best, 2010), just as it is in elderly individuals – while elderly individuals are experiencing the decline of these brain areas and their associated functions, children have yet to develop them. As executive functioning depends critically on the development of frontal lobe structures that mature late in adolescence (Best & Miller, 2010), the nascent development of such circuitry may be more easily affected by physical exertion relative to more developed structures (Best, 2010).

None of this explains *why* exercise (or meditation) provides a boost to cognition. While it is true that cardiovascular fitness has an impact on the central nervous system via diffuse mechanisms such as a general enhancement of blood flow (Thomas et al., 2012), a more detailed examination of the impact of exercise and meditation on the brain is warranted.

### *1.2.4 Plasticity*

The cognitive benefits of exercise and meditation may be traced back to the concept of brain plasticity, which was demonstrated so forcefully by the work of Pons and colleagues (1991) when they dissected the Silver Spring monkeys. There is now a body of evidence indicating that physical exercise and meditation both influence brain activity. Exercise has been shown to result in an increased rate of neurogenesis (formation of new neurons) in the hippocampus of exercising animals (Brown et al., 2003; van Praag, Christie, Sejnowski, & Gage, 1999). Furthermore, physical exercise has been linked to increased gray matter (the dark tissue of the brain that consists of neuronal cell bodies and dendrites) in the hippocampus of humans (Erickson et al., 2011; Pajonk et al., 2010). In addition to the hippocampus, brain imaging research has established a link between physical activity during middle age and gray matter volume in frontal brain regions (thought to be important for executive functions) in later life (Rovio et al., 2010).

Additional neural changes related to physical activity include increases in dendritic spine density (Stranahan, Khalil, & Gould, 2007), enhanced long-term potentiation (a persistent increase in signaling strength between neurons that have been synchronously activated) (van Praag et al., 1999), increased levels of the neurotransmitters serotonin, norepinephrine, and acetylcholine (Lista & Sorrentino, 2010), increased dopamine receptor density (Fordyce & Farrar, 1991), and an augmented release of growth factors such as brain-derived neurotrophic factor (BDNF; Knaepen, Goekint, Heyman, & Meeusen, 2010) and insulin-link growth factor-1 (IGF-1; Rojas Vega, Knicker, Hollmann, Bloch, & Struder, 2010).

Neurotrophic factors are proteins that are responsible for the development and survival of nascent neurons, as well the maintenance of mature neurons and the connections between neurons, and may even facilitate the re-growth of damaged neurons (Deister & Schmidt, 2006). Increased BDNF has been found following acute bouts of aerobic exercise (Gold et al., 2003), and the amount released seems contingent on the intensity of the exercise, with greater intensity eliciting greater release (Ferris, Williams, & Shen, 2006). IGF-1, on the other hand, seems particularly associated with resistance training (Cassilhas et al., 2007). Thus, release of multiple neurotrophic factors may be achieved by combining exercise methods, perhaps explaining why combining regimens is particularly effective in producing cognitive benefits (Colcombe & Kramer, 2003).

Mindfulness meditation also impacts the brain in a variety of ways. Individuals trained in focused-attention mindfulness meditation are able to exert greater intentional influence over their brain alpha rhythms (Kerr et al., 2011), which may relate to the ability to screen out distractions. This finding is supported by fMRI research indicating that brain areas involved in voluntary control over attention (e.g., the rostral anterior cingulate cortex and the dorsal medial prefrontal cortex) tend to exhibit greater activity during mindfulness meditation (Hölzel et al., 2007). In addition, experienced meditators demonstrate greater cortical density in areas associated with attention, including the prefrontal cortex and the right anterior insula, which is positively associated with measures of cognitive performance (Lazar et al., 2005). The implications extend into the clinical realm, as alpha rhythm deregulation and deficits in attentional control are the hallmark of individuals with attention-deficit hyperactivity disorder (Koehler et al., 2009), offering a potential intervention that is not based on pharmaceuticals.

Long-term practitioners of meditation experience less brain shrinkage as they age (Luders, Clark, Narr, & Toga, 2011). The idea that meditation allows retention of gray matter is particularly critical given that gray matter has been found to be associated with sensory perception, emotional stability, and intelligence (Haier, Jung, Yeo, Head, & Alkire, 2004). Meditators also exhibit a greater degree of gyrification (Luders et al., 2012). Gyrification refers to the pattern and degree of folding of the cerebral cortex—this is evolution's way of cramming more surface area into a fixed space (the skull). Greater gyrification is associated with faster brain processing and better memory formation (Luders et al., 2012).

What makes these factors particularly important in the context of cognitive enhancement is the idea that in addition to resulting in brain changes, exercise and meditation may encourage neuroplasticity. Thus, the changes that occur in the brain are of a nature that results in a more pliable brain—a change that increases the ability to change, thereby making the brain more capable of acquiring new information. If this were true, it could be expected that combining exercise or meditation with a cognitive training regimen would result in gains that exceed those achieved by either intervention alone. Fabre, Chamari, Mucci, Masse-Biron, and Prefaut (2002) demonstrated that aerobic endurance training combined with a cognitive training battery designed to enhance a variety of cognitive functions (e.g., memory, attention, spatial skill) was more effective than either exercise or cognitive training alone, providing support for the idea that the brain changes induced by exercise benefit cognitive training programs.

As for the brain impact of cognitive training programs themselves, results are mixed. Increases and decreases in activity have both been demonstrated following cognitive training programs (Olesen, Westerberg, & Klingberg, 2004; Westerberg & Klingberg, 2007). Increased activity is thought to be a result of enhanced neural plasticity while decreases are thought to reflect strategy mastery (Klingberg, 2010). However, one would expect enhancement of neural substrates that subserve WM processes or strategy refinement to result in transfer to other WM tasks to the extent that the other tasks share neural real estate or are conceptually similar; given the lack of generalized performance gains (e.g., Dunning, Holmes, & Gathercole, 2013; Melby-Lervåg & Hulme 2013) it is not clear that fundamental changes in brain function are occurring as a result of cognitive training regimens alone. It may be necessary to combine cognitive training with other interventions that encourage plasticity in order to elicit a clear benefit; synergy may be a necessity. One option is to influence brain activity directly through electrical stimulation. Understanding the neural basis of WM is necessary in order to properly select stimulation parameters.

## 1.3 Neural Basis of Working Memory

While some of the major theoretical models of WM have been specifically evaluated by neurobiological methods (e.g., Buchsbaum & D'Esposito, 2008; Cowan et al., 2011; Guida, Gobet, Tardieu, & Nicolas, 2012; Nee & Jonides, 2013, Smith & Jonides, 1997) most research investigating the neural basis of WM has occurred independent of the main theoretical constructs (Marois, 2015). In fact, Baddeley's (1986) model of WM has been criticized on the grounds of biological implausibility (Hazy et al., 2006). Focusing on the neural basis of WM without attempting to shoehorn results into created without regard for the neural aspect of WM has revealed that WM is a distributed system in the brain. The first neurophysiological research focused on the prefrontal cortex (PFC) in the context of single-cell recordings in monkeys during performance of delayed response tasks in which monkeys were trained to make an eye movement toward a previously cued location (Fuster, 1992; Fuster & Alexander, 1971; Goldman-Rakic, 1987). Results indicate that lateral PFC cells exhibit sustained activity during the delay period, and moreover when this sustained activity did not occur there was likely to be a behavioral error following the delay interval (Fuster & Alexander, 1971; Goldman-Rakic, 1995). This sustained activity was interpreted as a neural correlate of maintenance of information in

WM. Cells in the inferotemporal cortex have shown similar delay activity (Fuster & Jervey, 1981), suggesting a role of other brain regions in WM processes.

With advances in neuroimaging technology, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have revealed robust prefrontal activity, along with parietal and occipital cortex involvement (for visual tasks) during WM task performance (D’Esposito et al., 1995; Fiez et al., 1996; Jonides et al., 1993; Petrides, Alivisatos, Meyer, & Evans, 1993). Imaging of human participant brains has allowed evaluation of neural activity during more complex WM tasks, such as the *n*-back task which requires participants to determine if a current stimulus replicates a previously presented stimulus. These tasks require more than simple maintenance of information, allowing an investigation into the neural basis of various WM components, allowing for dissociation of networks responsible for maintenance of information from those that subserve manipulation of information. This research indicates a consistent role of the PFC in executive processes (manipulation and gating of irrelevant information) often in conjunction with activity in the parietal cortex and sensory regions related to the sensory modality of the task (Courtney, Ungerleider, Keil, & Haxby, 1997; Nee et al., 2013).

This body of work has been incorporated into a proposed biologically based model of the cognitive architecture of the WM system referred to as the PFC, basal ganglia (BG) working memory model (PBWM; Hazy et al., 2006). This is a tripartite architecture in which three complementary brain systems perform various WM functions. The posterior cortex (PC) system performs sensory and motor processing thereby providing a substrate, upon which higher-level systems can act. The hippocampal system (HC) is specialized for rapid, potentially one-trial learning that is capable of binding arbitrary information for subsequent recall by memory systems, in contrast to the slow, integrative learning exhibited by the PC system. The PFC/BG system is responsible for active maintenance of information, with the PFC actively maintaining information and the BG providing a gating mechanism that learns when information should be passed into the PFC maintenance architecture via a dopamine-based reward system. In this model, WM is conceptualized as an emergent property of these distributed brain systems.

A particular region of the PFC, the dorsolateral region, is often given prominence in consideration of the neural correlates of WM. Evidence from single-cell, brain-imaging, and neuropsychological research has indicated a critical role of the dorsolateral PFC (DLPFC) in maintaining stimulus representations in accordance with task goals in interference-rich environments (Kane & Engle, 2002). Thus, the DLPFC has been suggested as a brain region that supports both the storage and processing components of WM (Courtney, 2004; Leung, Seelig, & Gore, 2004; Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002). This notion is supported by neuroimaging research indicating that the storage and manipulation of information often activate the same brain regions (Narayanan et al., 2005; Veltman, Rombouts, & Dolan, 2003; Zarahn, Rakitin, Abela, Flynn, & Stern, 2005) which is consistent with the idea that processing and memory functions are typically performed by the same neural substrates (Rumelhart et al., 1986). As such, the DLPFC has been strongly associated with general cognitive functioning (Goldman-Rakic, 1987).

Prior research has suggested an asymmetrical distribution of WM function in younger adults, such that verbal WM tasks are subserved by left frontoparietal regions while visuospatial WM tasks elicit relatively greater right frontoparietal activity (Reuter-Lorenz et al., 2000; Smith & Jonides, 1998; Smith & Jonides, 1999). With respect to the DLPFC, meta-analyses of normative neuroimaging data in the context of WM tasks have been inconclusive, suggesting roughly equal activity in the left and right DLPFC during processing of verbal and spatial stimuli (Nee et al., 2013; Owen et al., 2005). However, when examined at the level of identity vs. location, Owen and colleagues (2005) found relatively greater left-lateralized activity related to verbal as opposed to spatial identity-monitoring, while nonverbal location-monitoring (relative to nonverbal identity-monitoring) was associated with right DLPFC activation. Contrasting findings have been presented by Nystrom et al. (2000), who assessed brain regions activated by *n*-back tasks using 3 different types of stimuli (letter, abstract shapes, and locations) and found no activation patterns unique to stimuli modality.

## 1.4 Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a method of brain stimulation that uses a small electrical current injected through scalp electrodes to modulate neuronal activity (Nitsche & Paulus, 2000). Stimulation is thought to result in an acute modulation of cortical excitability (Nitsche & Paulus, 2000) followed by lasting effects that are NMDA-receptor dependent (Liebetanz, Nitsche, Tergau, & Paulus, 2002) and therefore similar to long-term potentiation (LTP) and long-term depression (LTD) processes posited to underlie learning and memory (Rioult-Pedotti, Friedman, Hess, & Donoghue, 1998). Amount of $Ca^{2+}$ influx is thought to be a critical factor in tDCS aftereffects, such that moderate and prolonged $Ca^{2+}$ release leads to LTD, a brief but intense burst of $Ca^{2+}$ facilitates LTP, and a moderate but brief release of $Ca^{2+}$ does not result in synaptic modulation (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche., 2013; Lisman, 2001; Nitsche et al., 2009). Animal research suggests that tDCS may modulate astrocyte $Ca^{2+}$ signaling, thereby extending the impact of stimulation to glial cells as well as neurons (Monai et al., 2016). Recent studies have shown that tDCS can improve cognitive performance in both clinical populations and healthy adults on tasks ranging from motor learning to decision making (for review see Coffman, Clark, & Parasuraman, 2014; Dayan, Censor, Buch, Sandrini, & Cohen, 2013; Manenti, Cotelli, Robertson, & Miniussi, 2012).

There are a number of models describing tDCS functions, including stimulation-dependent, zero-sum, excitation-inhibition balance, activity-selectivity, and stochastic resonance. Stimulation dependent, zero-sum, excitation-inhibition balance, and activity-selectivity models assume that anodal currents increase neural excitability while cathodal currents result in a decrease; stochastic resonance models make no such assumption (Bestmann, Berker, & Bonaiuto, 2015).

### *1.4.1 Stimulation Dependent Model of tDCS*

The first proposed mechanism of tDCS functioning was the anodal excitation/cathodal inhibition (AeCi) hypothesis, in which the brain is essentially treated as a passive organ that is driven by the characteristics of stimulation (Fertonani & Miniussi, 2016). In this model, anodal stimulation leads to depolarization of the membrane potential, resulting in enhanced neural excitability and behavioral improvement. Conversely, cathodal stimulation hyperpolarizes and impairs behavioral performance. This model has since been criticized on the grounds that it is overly simplistic, and fails to account for the baseline level of brain activity at the time of stimulation, the dynamic nature of the brain which may react to external injection of energy, and the cerebral cytoarchitecture of the areas affected by current (Bestmann et al., 2015; Fertonani & Miniussi, 2016). For instance, according to the AeCi model anodal stimulation increases excitability of affected neurons, but if excitability of inhibitory interneurons is increased the net result may be network-level inhibition. Additionally, increasing the excitability of neurons that do not provide a signal that benefits task performance may result in behavioral impairment in the context of increased network excitability. With regard to consideration of the brain as a passive organ, Fricke and colleagues (2011) demonstrated that while a single 5-minute session of anodal or cathodal stimulation over primary motor cortex supported the AeCi model (i.e., anodal stimulation increased excitability and cathodal decreased excitability), following this stimulation session with another of the same polarity resulted in a reversal of excitability (i.e., anodal stimulation resulted in inhibition while cathodal was excitatory) when a 3-minute break between sessions was used, but not when a 30-minute break was implemented. This finding underscores the oversimplifications inherent in the AeCi model; it is necessary to consider the brain a dynamic, reactive organ in the context of brain stimulation.

### *1.4.2 Zero-Sum Model of tDCS*

The zero-sum model of tDCS function considers stimulation in the context of brain homeostasis, positing that any gain in cognitive function is necessarily balanced by a loss (Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014). This is consistent with cognitive models of brain function that posit limited resources in the brain (e.g., Anderson, 2005). One study to date has demonstrated zero-sum functioning of tDCS (Iuculano & Kadosh, 2013). Participants in this study learned an artificial numerical system that was then used in a numerical Stroop task in which participants were asked to compare the physical size and numerical notation of two stimuli presented side by side, and indicate whether the trial was congruent (the physically larger stimulus corresponded to the numerically larger number) or incongruent (a mismatch between the relative physical size and numerical value of the two stimuli). Stimulation was delivered daily for six days of task training over the posterior parietal cortex (PPC) or the DLPFC. Active stimulation over the PPC benefitted learning of the pairings between artificial and standard numerical symbols while impairing automaticity of learned material as measured by the numerical Stroop task, while stimulation over the DLPFC resulted in the opposite. Therefore, stimulation-induced benefit to one system may impair function of a competing system. It is important to note, however, that support for zero-sum functioning of tDCS is limited to date to a single study (Iuculano & Kadosh, 2013), perhaps because it is practically difficult to measure a vast array of cognitive functions within a single experimental session.

### *1.4.3 Excitation-Inhibition Balance Model of tDCS*

The excitation-inhibition balance model posits that optimal brain function results from achieving the appropriate balance of excitation and inhibition in the neocortex (Okun & Lampl, 2008). This notion was introduced to the field of brain stimulation by Krause and colleagues (2013), who argued that stimulation shifts the excitation-inhibition balance, and the resulting change in behavioral performance is determined by whether or not this shift enhances or worsens the balance. This model has particular appeal in the realm of applying brain stimulation to the clinical realm, in which an out-of-balance network may be normalized by application of appropriate stimulation parameters (Priori, 2003). Magnetic resonance spectroscopy studies provide support for this model by demonstrating brain stimulation affects the concentrations of excitatory and inhibitory neurotransmitters (Clark, Coffman, Trumbo, & Gasparovic, 2011; Stagg & Johansen-Berg, 2013). This model has, however, been criticized in similar fashion to the AeCi model, in that anodal and cathodal are simply replaced with glutamate and GABA, respectively, and on the grounds that there is little information describing the relationship between stimulation parameters, network excitation-inhibition balance, and behavior (Ferotonani & Miniussi, 2016).

### *1.4.4 Activity-Selectivity Model of tDCS*

In the activity-selectivity model, the impact of stimulation depends on both the stimulation parameters and the activity of the brain. As tDCS is thought to affect neurons close to the discharge threshold rather than inducing action potentials in otherwise inactive neurons (Siebner et al., 2009), the activity-selectivity model proposes that tDCS is a neuromodulatory technique, and therefore exerts particular influence on neurons that are engaged at least to some degree in task performance (Bikson & Rahman, 2013; Dayan et al., 2013). Furthermore, neural networks on the whole are thought to be more susceptible to modulation than the average individual neuron (Francis, Gluckman, & Schiff, 2003). Therefore, the activity-selectivity model predicts that when neural networks exhibit anatomical overlap, the network most involved in task demands will benefit from stimulation as a result of winner-take-all principles of neural network function (Maass, 2000), providing a potential explanation for specific cognitive effects in the context of spatially diffuse stimulation (Fertonani & Miniussi, 2016). Bortoletto, Pellicciari, Rodella, and Miniussi (2015) demonstrated the interaction between stimulation and task-induced neural activity by showing that motor task learning was impaired when participants practiced one version of a task but improved when they practiced another version of the task, even though stimulation parameters were identical for both practice conditions. A number of additional experiments support the network level activity-selectivity model of tDCS function by demonstrating modulation of behavior contingent on neural activity induced by task demands (Antal et al., 2004; Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Furuya, Klaus, Nitsche, Paulus, & Altenmuller, 2014; Gill, Shah-Basak, & Hamilton, 2015).

### *1.4.5 Stochastic Resonance Model of tDCS*

The concept of stochastic resonance may be understood by defining its constituent terms. Stochastic refers to the involvement of chance or probability, while resonance in this this context refers to the intensification or enrichment of a signal via supplementation. Therefore, stochastic resonance refers to the phenomenon by which the detectability of a weak signal is improved via the addition of noise to that signal; resonance of signal with noise boosts the signal (McDonnell & Ward, 2011). In the context of tDCS, the externally delivered electrical current may be thought of as the “noise” being injected into the brain, thereby boosting the “weak” signal of neurons that would reach near – but not otherwise achieve – their discharge threshold by providing the additional energy needed to reach that threshold. In this model, tDCS therefore is thought to primarily affect neurons on the edge of firing (Miniussi, Harris, & Ruzzoli., 2013), and may improve or impair performance contingent on the level of noise introduced and state of the system into which the noise is injected. If the amount of noise increases propagation of signal relevant to task performance without increasing propagation of irrelevant signal, performance will improve; otherwise, noise may decrease performance (Gammaitoni, Hänggi, Jung, & Marchesoni, 1998; Kitajo, Nozaki, Ward, & Yamamoto, 2003). This framework may help explain inconsistency of participant response to stimulation (Edwards et al., 2013).

## 1.5 DLPFC Stimulation for WM Enhancement

Many brain stimulation studies have focused on working memory (Fregni et al., 2005; Ohn et al., 2008) or episodic memory (e.g., Chi, Fregni, & Snyder, 2010; Javadi & Walsh, 2012), and the majority of this work suggests that tDCS can improve performance. However, other studies found little or no benefit from tDCS (e.g., Elmer, Burkard, Renz, Meyer, & Jancke, 2009), suggesting that conditions under which memory might improve are not yet fully understood. It is important to note that tDCS alone during rest does not seem to affect performance on WM tasks (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011). Additionally, the nature of the task performed during tDCS may influence the effectiveness of training; for instance, cognitive demands may need to reach a certain threshold in order for stimulation to benefit performance (Gill et al., 2015).

In order to capitalize on the plasticity engendered by stimulation (Ridding & Ziemann, 2010) a task must be administered at a time conducive to learning, typically during or immediately following stimulation within the temporal window of altered cortical excitability (Coffman et al., 2014). Additionally, the location of the stimulating electrodes must be such that brain areas involved in task performance are targeted – a method that has yielded a strong benefit to learning in the past (Clark et al., 2012). Thus, the principle of being in the right place at the right time applies to the synergy between brain stimulation and cognitive training.

Due to its involvement in WM, the DLPFC has proven a popular target for research investigating the impact of tDCS on WM task performance, often utilizing the *n*-back task (e.g., Andrews et al., 2011; Berryhill & Jones, 2012; Fregni et al., 2005; Gill et al., 2015; Mylius et al., 2012; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Lally, Nord, Walsh, & Roiser, 2013; Ohn et al., 2008; Teo, Hoy, Daskalakis, & Fitzgerald, 2011; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011; see Berryhill, Peterson, Jones, & Stephens, 2014; Brunoni & Vanderhasselt, 2014 for reviews). As the *n*-back predicts individual differences in G*f* and is accepted as a WM task (Gray, Chabris, & Braver, 2003; Jaeggi et al., 2010; Kane, Conway, Miura, & Colflesh, 2007; Schmiedek, Hildebrandt, Lövdén, Lindenberger, & Wilhelm, 2009) it makes a likely task candidate for investigating the influence of tDCS on WM.

Studies using tDCS to stimulate DLPFC during *n*-back performance have not been comprehensive, as typically only the left, not the right DLPFC is stimulated (e.g., Andrews et al., 2011; Fregni et al., 2005; Gill et al., 2015; Lally et al., 2013; Ohn et al., 2008; Teo et al., 2011; Zaehle et al., 2011). While all of the cited works found a benefit of stimulation on *n*-back performance, it is worth noting that effect sizes in tDCS WM studies tend to be smaller than studies evaluating the effect of tDCS on attention or visual perception (Coffman et al., 2014). In one evaluation of hemispheric asymmetry of function, Berryhill and Jones (2012) stimulated either the left or right DLPFC during performance of verbal and visual 2-back tasks, and found both left and right stimulation to be uniformly beneficial to task performance. However, participants were older adults for whom bilateral as opposed to asymmetrical DLPFC activity is typical during WM task performance (Reuter-Lorenz et al., 2000), and only those with relatively high levels of education benefitted from stimulation. It is unknown whether a similar effect would be found in college-age participants.

## 1.6 Transfer

One issue common to all methods of cognitive enhancement is how exactly to determine when cognition has been changed. The typically desired result of a training program is generalization to other domains (Dahlin et al., 2008). For instance, although an individual may jog along the same route at the same time each day, the expectation is attainment of general cardiovascular improvement that allows for behavioral advantages in contexts aside from jogging. Likewise, in WM training, the goal is not to become better at an *n*-back task, but to enhance the underlying construct of WM such that performance is improved for the vast number of tasks that involve WM. Generalizability of performance gains may be divided into near transfer ( to a similar context) and far transfer (i.e., to a dissimilar context; Barnett & Cerci, 2002).

The idea of task transfer dates back to a debate in the early 1900s concerning the work of Charles Judd and the contrasting findings of Edward Thorndike. Research by Judd (1908) indicating that students provided with a theoretical explanation of optical refraction performed better on a task that involved hitting an underwater target with a dart. This finding fueled the belief that teaching broad principles would allow for generalization to a variety of contexts, thereby providing benefit across various domains. As a result, the doctrine of formal discipline was born, with some scholars advocating training pupils in basic processing that would strengthen the core faculties of the mind – teaching people how to learn rather than teaching them specific facts (Binet, 1908, cited in Gould, 1981, p. 154).

Thorndike, on the other hand, had failed to find much evidence that transfer would occur across superficially disparate tasks even when those tasks entailed similar underlying operations. For instance, following instructions on how to estimate the area of geometric shapes, participants often failed to transfer this concept to word problems concerning real-world problem solving in which geometric area estimation would resolve the problem (Thorndike & Woodworth, 1901). This began a debate over the nature, prevalence, and contexts of transfer that continues today (e.g., Brown, Kane, & Long, 1989; Detterman, 1993; Halpern, 1998). The idea that transfer occurs to a greater degree when the testing context matches the learning context is implicit in cognitive psychology, as evidenced by concepts such as encoding specificity and state-dependent learning (Tulving & Thomson, 1973). Thus, the controversy that erupted following the reported far transfer gains in G*f* as a result of WM training (Jaeggi et al., 2008) represents a microcosm of a larger debate that has been waged for over a century.

## 2.0 STUDY DESIGN

The current study was designed in light of these conflicting findings regarding hemispheric asymmetrical functioning of DLPFC and in the context of controversy surrounding transfer effects in WM training. As tDCS-WM paradigms often use the same task to train and evaluate WM function (e.g., Fregni et al., 2005; Ohn et al., 2008; Zaehle et al., 2011), thereby conflating task-specific practice effects with enhanced WM, the current study incorporated a verbal 3-back task, a spatial 3-back task, and a G*f* task. Furthermore, both spatial and verbal tasks were trained in different groups, and both spatial and verbal WM tasks were tested within groups, to compare transfer in both directions between verbal and spatial WM.

In Experiment 1, the impact of tDCS on a trained spatial location-monitoring 3-back was evaluated; an untrained verbal identity-monitoring 3-back and an untrained G*f* task were used to assess near transfer and far transfer, respectively. Prior research has indicated that WM and G*f* share between 50% (Kane, Hambrick, & Conway, 2005) and 60% of their variance (Gignac, 2014). As G*f* relates to academic achievement (Rohde & Thompson, 2007), it represents a theoretically and practically relevant task by which to examine the effectiveness of WM training. It was hypothesized that (1) right DLPFC active stimulation during training on a spatial WM task would result in task improvement relative to participants who received sham stimulation that would transfer to an untrained verbal WM task and a G*f* task, and (2) left DLPFC stimulation during training on a spatial WM task would not result in task improvement, providing support for the lateralized asymmetry of DLPFC contribution to WM.

In Experiment 2, the impact of tDCS on a trained verbal identity-monitoring 3-back was evaluated; an untrained spatial location-monitoring 3-back and G*f* task were used to assess transfer. In both experiments, participants received stimulation with the anode placed over the left (F3) or right (F4) DLPFC. It was hypothesized that (1) right DLPFC stimulation during training on a verbal WM task would not result in task improvement, and (2) left DLPFC stimulation during training on a verbal WM task would result in task improvement that would transfer to an untrained spatial WM task and G*f* task, providing support for left DLPFC involvement in verbal WM.

All tasks maintained a static difficulty level rather than implementing an adaptive performance-based difficulty. As the design of both experiments was between rather than within-subjects in nature, non-adaptive tasks allow a comparison between participants that is not confounded with group differences in average task difficulty. This approach has been effectively implemented in the past for between-subject tDCS-WM paradigms (Jones, Stephens, Alam, Bikson, & Berryhill, 2015). Additionally, a recent meta-analysis suggests no difference in performance benefit elicited by adaptive and non-adaptive WM training programs (Karbach & Verhaeghen, 2014).

## 2.1 Experiment 1 – Spatial WM Training

### Method

***Participants.*** Thirty-seven participants gave informed consent. One participant was excluded for high scalp impedance. Therefore, 36 participants completed the study. All participants were right-handed, as measured by the Edinburgh handedness inventory (Oldfield, 1971), native English speakers with no history of neurological or psychiatric disorders, head injuries, or vision or hearing problems. None of the participants had surgical or other metal implants in their head, neck, shoulders, or arms, and none reported taking any psychoactive medications at the time of the study. In order to control for stimulation naiveté, participants were excluded if they had previously experienced tDCS. Participants were also excluded for bilingualism which is associated with increased performance on measures of WM (Kroll & Bialystok, 2013; van den Noort, Bosch, & Hugdahl, 2006).

Participants were randomly assigned to stimulation conditions such that 12 received left frontal active stimulation, 12 received right frontal active stimulation, and 12 received sham stimulation. Participants receiving sham stimulation were balanced such that 6 received sham stimulation at site F3 and 6 at site F4. There were no significance differences on any metrics of interest between these two groups, so for analysis purposes the two sham placements were merged to form one sham group consisting of 12 participants. Great effort was made to balance age, gender, handedness, and years of education between groups, and no significant differences were found as determined by individual independent-samples t-tests with α = 0.05 (see Table 1). Immediately prior to stimulation, impedance was measured for each participant (average impedance 43.45 kOhms, SD = 23.56, range 10-79). There was not a significant difference in pre-stimulation impedance between any pair of groups, as determined by individual independent-samples t-tests with α = 0.05.

**Table 1:** Participant demographics for Experiments 1 and 2

| | | N | # Males | Age Mean ± SD | Education Mean ± SD | Handedness* Mean ± SD |
|---|---|---|---|---|---|---|
| Experiment 1 – Spatial WM Training | Left Frontal tDCS | 12 | 6 | 18.75 ± 0.87 | 13.17 ± 0.52 | 76.78 ± 25.71 |
| | Right Frontal tDCS | 12 | 6 | 21.42 ± 5.33 | 14.04 ± 0.52 | 85.05 ± 17.41 |
| | Sham tDCS | 12 | 6 | 20.00 ± 2.09 | 13.63 ± 0.52 | 84.63 ± 18.23 |
| | Total | 36 | 18 | 20.06 ± 3.43 | 13.61 ± 0.51 | 82.15 ± 20.55 |
| Experiment 2 – Verbal WM Training | Left Frontal tDCS | 12 | 6 | 22.25 ± 5.76 | 13.54 ± 0.51 | 77.35 ± 28.37 |
| | Right Frontal tDCS | 12 | 6 | 18.92 ± 0.67 | 12.88 ± 0.52 | 68.41 ± 24.49 |
| | Sham tDCS | 12 | 6 | 21.50 ± 6.40 | 14.17 ± 0.52 | 70.31 ± 30.16 |
| | Total | 36 | 18 | 20.89 ± 5.08 | 13.53 ± 0.51 | 72.02 ± 27.25 |

*Handedness quotient: 100 = right hand dominant, -100 = left hand dominant, 0 = ambidextrous.

***Tasks/Materials.*** Experimental tasks consisted of a spatial location-monitoring *n*-back task, a verbal identity-monitoring *n*-back task, and an analogical reasoning task based on the Raven's Progressive Matrices task (the Sandia Matrices, Matzen et al., 2010).

In the *n*-back tasks, participants were asked to determine if a stimulus replicated a previously presented stimulus, with a particular lag (in this case, the stimulus that was presented 3 items prior to the current stimulus, setting the value of *n* at 3). An *n* of 3 was selected because prior tDCS studies have found ceiling effects for 1-and 2-back tasks, making the results difficult to interpret (Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Mylius et al., 2012). Stimuli were presented in 24-point Courier New font.

The verbal 3-back task used eight letters as stimuli (B, F, H, K, M, Q, R, and X), which appeared in either upper or lower case on a given trial. This was done to encourage verbal encoding of letter identity as opposed to a visual perceptual mapping between the shapes. Each block consisted of 100 trials: 45 fillers (did not match any of the four previous trials), 35 targets (matched the letter presented 3 trials previously), 10 *n*+1 lures (matched the letter presented four trials previously), and 10 *n*-1 lures (matched the letter presented two trials previously). Each trial was initiated by a 500 ms duration fixation cross, followed by a 500 ms period during which the stimulus appeared directly above the fixation point, and ended with a 1500 ms duration blank screen. Participants were asked to respond as quickly and accurately as possible, and were given up to two seconds (stimulus presentation duration + blank screen duration) to respond to each stimulus by pressing keyboard keys that corresponded to “yes” (target) and “no” (non-target).

The structure of the spatial location-monitoring 3-back task was identical to that of the verbal identity-monitoring 3-back with regard to timing and number/distribution of trial types, though the nature of the stimuli differed. An array of eight box outlines (white outline on a black background) was presented around the fixation point. The boxes were arranged in a square shape with two boxes on each side of the fixation point (above, below, left and right). Participants viewed the array of boxes for 500 ms, after which one box was filled in white for 500 ms. Participants were asked to indicate if the location of the filled box matched the location of the filled box from three trials previously. Each WM task block contained the same distribution of stimuli type (i.e., number of targets, fillers, and lures) but stimuli were presented in a different order for each block.

The Sandia Matrices task is based on Raven's Progressive Matrices (RPM), a measure of Gf in which participants are asked to identify a missing element that completes a pattern (Raven, Court, & Raven, 1998). The Sandia Matrices task expands upon RPM by using similar problem structures to generate a much larger set of matrix problems. These problems have been normed against the Raven's problems and are of equivalent difficulty (Matzen et al., 2010), and have previously been used to evaluate the impact of brain stimulation on Gf (Santarnecchi et al., 2013). Two sets of matrices were created, containing nine problems each. The matrices in each set had equivalent structures, making the two sets equally difficult. The order in which participants completed the two sets was counterbalanced within each group. For each trial, participants were presented with a 3x3 matrix problem. Participants were given 8 potential solutions to the problem, presented at the bottom of the screen concurrent with the matrix problem, and were asked to select the most appropriate solution by pressing the keyboard number that corresponded to the solution number (1-8). Participants were given up to 45 seconds to respond to each matrix. Following either a response or expiration of the time limit, the task progressed to the next matrix problem. All tasks were programmed using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

A sensation questionnaire was used to assess the physical sensations experienced by participants during stimulation. Participants were asked to use an 11-point Likert scale that ranged from 0 ("none") to 10 ("excessive") to report their perception with regard to the sensations of tingling, itching, and heat/burning, as in previous tDCS research (Coffman, Trumbo, & Clark, 2012). This questionnaire was administered at three points during stimulation:

first at one minute following initiation of stimulation, then again at the five minute mark, and again at the ten minute mark. Stimulation was stopped if participants reported a 6 or higher on any scale.

In order to determine if stimulation impacted participant mood, participants were given a mood questionnaire both before and after stimulation. Participants were asked to indicate their level of agreement with nine statements, including “I feel nervous or excited”, “I feel tired or fatigued”, “I feel confused or disoriented”, “I feel sad or down”, “I feel tense or frustrated”, “I feel dizzy or light-headed”, “I feel nauseous”, “I feel physical pain or discomfort”, and “I feel unable to concentrate or pay attention” on a 6-point Likert scale ranging from 0 (“not at all”) to 5 (“very much”). Prior research indicates that tDCS may impact mood and affect (Barrett et al., 2004). While the stimulation parameters used in the current study are somewhat different (e.g., along the dimensions of current strength, stimulation duration, and electrode size), mood data was collected both as a safety precaution and as a potential metric of interest in the event of post-stimulation changes.

***tDCS.*** Stimulation was delivered using an ActivaTEk ActivaDose II system. In order to avoid bias arising from cephalic placement of electrodes with opposite polarity, an extracephalic placement was used for the reference electrode. The anode was placed either near location F3 or location F4 on the international 10-20 EEG system, above either the left (F3) or right (F4) DLPFC, while the cathode was placed on a fleshy area near the bicep between the elbow and shoulder, on the arm contralateral to the anode placement. Anode placement was determined using the Beam F3 system of electrode placement (Beam, Borckardt, Reeves, & George, 2009), which has been demonstrated to provide a reasonable approximation to MRI-guided targeting of DLPFC (Mir-Moghtadaei et al., 2015).

Current was delivered for thirty minutes at either 0.1 mA (sham) or 2.0 mA (active) via Amrex A102 square sponge electrodes which have a sponge length of 3.3 cm (11 $cm^2$) and an outer length of 5 cm (25 $cm^2$). Sponges were saturated with saline (6.25 mL of 150 mM NaCl solution per sponge) and secured to the participant using Coban self-adhering wrap. A current strength of 0.1 mA was chosen as the sham stimulation condition in order to induce physical sensations typically associated with tDCS without stimulating the cortical area beneath the anode. A study modeling electrical current indicates a current strength of less than 0.5 mA at the electrode size used in this experiment has no impact on brain activity in neural tissue 12 mm beneath the surface of the skin (Miranda, Faria, & Hallett, 2009). Participants in our sham group received 20% of this current strength, making it unlikely that the 0.1 mA administered in our sham condition had a meaningful impact on brain function. A current strength of 2.0 mA was chosen as the active stimulation current strength as prior research shows that 1.0 mA may be an insufficient current strength to benefit WM task performance (Boggio et al., 2006).

A constant-current sham procedure was used because the traditional method of ramping up the current at the initiation of stimulation then ramping it back down (typically after 30 s) may not be an efficacious blinding method as sensations associated with active stimulation persist beyond this 30 s window (Dundas, Thickbroom, & Mastaglia, 2007; Poreisz, Boros, Antal, & Paulus, 2007).

Double-blinding was accomplished via use of a switch box that contained inputs for both positive and negative leads from two current generators, but outputs for only two electrodes. One current generator was configured to deliver the sham current strength of 0.1 mA, and the other to deliver the active current strength of 2.0 mA. A six-way switch coded by a third party not involved in data collection dictated whether current from the sham or the active generator was allowed to pass to the output electrodes. Three settings supplied current to the output electrodes from the sham configured generator, and the remaining three supplied the current from the active current generator. The inputs that were not actively supplying current to the electrodes were routed through a circuit loop to maintain the activity of the inactive current generator. The blinding and sham methodology used in the current study are identical to methods used effectively in several prior tDCS studies with similar stimulation parameters (Coffman et al., 2012; Falcone, Coffman, Clark, & Parasuraman, 2012). Coding was released to the experimenters upon completion of data collection.

### ***Procedure***

Before starting the experiment, participants gave informed consent, were screened for inclusion and exclusion criteria, and provided demographic and handedness information. Participants then completed a mood questionnaire to serve as a pre-stimulation baseline assessment of emotional state and began the experimental tasks, beginning with the far transfer (G*f*) baseline task, near transfer (NT) WM task baseline, and trained (TR) WM task baseline (see Figure 1 for structure of the experiment).

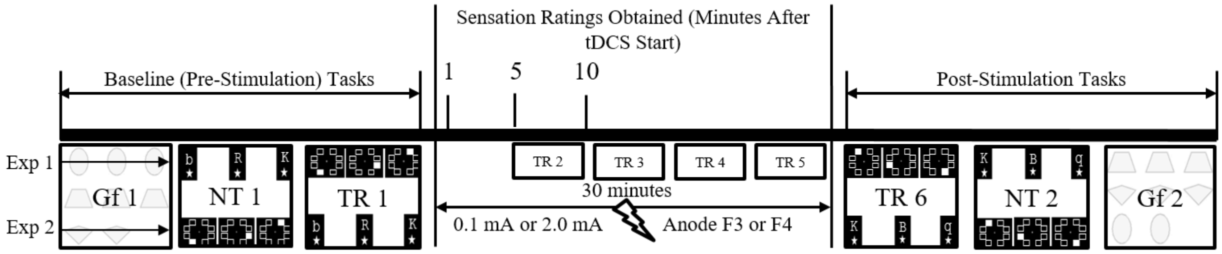

Figure 1 – Timeline of experiments. G*f* refers to the fluid intelligence task (Sandia Matrices), NT refers to near transfer task (verbal 3-back in Experiment 1, spatial 3-back in Experiment 2), and TR refers to the trained WM task (spatial 3-back in Experiment 1, verbal 3-back in Experiment 2). Run 1 for each task (G*f*, NT, TR) was treated as a pre-stimulation baseline.

First, participants completed one block of the Sandia Matrices (G*f*) task, followed by one block of the verbal 3-back and one block of the spatial 3-back. Included in each baseline block was a brief practice session (1 example matrix problem, 10 practice trials for each *n*-back) in which participants received task instructions. Following completion of these baseline tasks, stimulation was initiated. During stimulation, participants periodically reported physical sensations in tandem with completing four blocks of the trained WM task (spatial 3-back). Following cessation of stimulation, participants completed, in order, one block of the trained WM task (spatial 3-back), one block of the near transfer task (verbal 3-back), and one block of the far transfer (G*f*). Participants were instructed to respond to stimuli using the hand ipsilateral to the anode (i.e., for anode position F3, participants responded with the left hand; for anode position F4, participants responded with the right hand). This was done to limit the potential for spread of cortical excitability to the motor cortex in the stimulated hemisphere contributing to reaction time (RT) effects, a technique previously implemented in tDCS-WM research targeting the DLPFC (Ohn et al., 2008). This is a particularly salient issue given the findings of a recent meta-analysis indicating that tDCS over the DLPFC reliably improves RTs but not accuracy for *n*-back tasks (Brunoni & Vanderhasselt, 2014).

## 2.2 Experiment 2 – Verbal WM Training

### Method

Following completion of Experiment 1, a similar experiment was conducted in order to determine if switching the task performed during stimulation from a spatial location monitoring WM task to a verbal identity monitoring WM task would affect results. Tasks, task structures, tDCS parameters, and experimental procedure were identical to those used in Experiment 1 with a single difference—the verbal 3-back became the trained task performed during stimulation while the spatial 3-back was used as the near transfer task (see Figure 1). New participants were recruited for the purposes of data analysis.

***Participants.*** Thirty-seven participants gave informed consent. One participant was excluded due to perception of high sensations (tingling > 6) during stimulation. Therefore, 36 participants completed the study. Inclusion and exclusion criteria and group assignment process were identical to those in Experiment 1. No significant differences in age, gender, handedness, or years of education were present between groups, as determined by individual independent-samples t-tests with $\alpha = 0.05$ (Table 1). Following informed consent, participants completed the study in accordance with the procedure described in Experiment 1, with the order of WM task performance reversed. There was not a significant difference in pre-stimulation impedance between any groups, as determined by individual independent-samples t-tests with $\alpha = 0.05$ (average impedance 57.81 kOhms, SD = 19.54, range 18-82).

# 3.0 DATA ANALYSIS AND RESULTS

## 3.1 Data Analysis

Effects of tDCS on measures of accuracy, signal detection (*d*'), and RT were compared between cognitive tasks separately for each experiment (spatial training and verbal training) and each stimulation target (left or right DLPFC) using split-plot multivariate analysis of covariance (MANCOVA). Standardized change scores were first computed for each subject by dividing the difference from baseline (run 1) by the baseline standard deviation for each of the three cognitive tasks, separately for each group. In order to assess task-specific performance changes within the trained WM task (spatial memory in Experiment 1, verbal in Experiment 2), a 2 (active and sham) x 5 (TR run 2-6) MANCOVA was used, where the five TR scores were entered into the model as the within-subjects factor and group designation as the between-subjects factor. To assess task-general performance changes, a second set of MANCOVAs were used, where independent variables comprised tDCS condition (active and sham) and cognitive assessment type (TR, NT, and Gf). Signal detection measures were not assessed in the analysis of task-general effects because this measure cannot be calculated for the Sandia Matrices task. Gender and handedness were included as covariates in both analyses as: (1) Gender is a known factor in WM experiments (Speck et al., 2000); (2) Handedness is a known factor in cortical lateralization of WM function (Burbaud et al., 1995) and handedness laterality quotient is linearly related to laterality of language dominance (Knecht et al., 2000), which itself overlaps with verbal WM function (Gruber & Goschke, 2004); (3) Both gender and handedness were correlated with WM training performance in this study. Follow-up univariate tests were used to further examine significant effects, as appropriate.

To assess the degree to which effects reported here were related to physical sensation or mood associated with tDCS, mean sensation levels (three measures: itching, heat, and tingling), initial mood rating, (nine measures: nervousness, tiredness, confusion, sadness, tenseness, dizziness, nausea, pain, and concentration), and change in mood rating (post minus baseline) were compared between tDCS groups for each experiment and stimulation target using individual independent-samples t-tests. Additionally, relationships between sensations and demographic variables were examined using Pearson correlation in an attempt to characterize parameters that led to physical sensation of tDCS current. These variables included measures of head size (width, length, and circumference), gender, age, handedness, and the ratio of amount of sleep on the previous night to the amount of sleep on a normal night, as sleep deprivation may lead to changes in pain perception (Lautenbacher et al., 2006). Pearson correlation was performed separately for participants receiving active and sham tDCS.

Prior to inferential statistical analysis, the data were checked for outliers and assumptions of univariate analyses were tested. Two outliers existed due to lapse in performance for only one post-tDCS testing data point, with accuracy values of 25% and 2%. These two data points were removed and then interpolated based on baseline performance and participant group. Strong correlation between baseline and post-tDCS scores was confirmed prior to interpolation ($r > 0.8$ in all cases). Data were additionally analyzed with and without these two participants, and no substantive differences were found in results of the two analyses. All variables tested met assumptions of normality (using The Shapiro–Wilk test, $p>0.01$) and multicolinearity, and pairwise linearity between groups was confirmed by visual assessment of scatterplots. All analyses were performed using IBM SPSS Statistics 21 (IBM, Armonk, NY, US).

## 3.2 Results

### *3.2.1 Experiment 1: Spatial Working Memory Training*

Accuracy for each stimulation group is displayed in Figure 2, and standardized change scores are listed in Table 2 and Table 3. Although there were no main effects or interactions within the omnibus MANCOVA of task-specific effects for either stimulation group, there was an interaction between the effects of tDCS and trained, on-stimulation task (TR) run on d' for right DLPFC stimulation [Wilks' $\Lambda$ =0.55, $F(4,17) = 3.12$, $p < 0.05$, $\eta_p^2=0.42$]. Although there were no significant simple effects (*p*s > 0.1), this interaction was driven by greater group differences in d' change scores at TR3 and TR5. Similar TR-run-dependent group differences were observed for accuracy, but these differences also did not achieve statistical significance (Table 3).

There were no significant main effects or interactions within the MANCOVA of task-general effects for Experiment 1 (all *p*s > 0.1), indicating no effects of tDCS, and no significant difference in effects of spatial WM training on performance across the three cognitive tests examined here (Table 2). To investigate whether null effects of cognitive assessment type in the analysis of task-general behavioral effects were due to null effects of spatial WM training, in general, or whether performance for all cognitive assessment types changed similarly over time, one-sample t-tests were used to assess change from baseline in each of the three cognitive assessment types, collapsing across tDCS groups (N=36). Interestingly, significant change from baseline was found only for verbal WM difference scores ($t(35) = 6.02$, $d = 2.03$; $p < 0.001$), suggesting a practice effect for *verbal* WM, even in the context of *spatial* WM training, regardless of stimulation.

**Table 2:** Comparisons of standardized change scores between Left Frontal tDCS and sham groups in Experiment 1. TR refers to the trained, on-stimulation task (spatial 3-back), NT refers to the near transfer task (verbal 3-back) and G*f* refers to the far transfer matrix reasoning task

| | **Change Scores** | | **Standardized Change Scores** | | |
|---|---|---|---|---|---|
| | Sham | Active | Sham | Active | Stats |
| **RT (ms)** | | | | | |
| TR2 – TR1 | -25 ± 18 | -59 ± 18 | -0.14 ± 0.1 | -0.34 ± 0.1 | $F(1,20)=1.90; p>0.1$ |
| TR3 – TR1 | -84 ± 32 | -80 ± 32 | -0.48 ± 0.18 | -0.46 ± 0.18 | $F(1,20)=0.01; p>0.1$ |
| TR4 – TR1 | -161 ± 34 | -132 ± 34 | -0.92 ± 0.19 | -0.76 ± 0.19 | $F(1,20)=0.37; p>0.1$ |
| TR5 – TR1 | -229 ± 42 | -129 ± 42 | -1.31 ± 0.24 | -0.74 ± 0.24 | $F(1,20)=2.85; p>0.1$ |
| TR6 – TR1 | -215 ± 33 | -197 ± 33 | -1.23 ± 0.19 | -1.13 ± 0.19 | $F(1,20)=0.14; p>0.1$ |
| **d’** | | | | | |
| TR2 – TR1 | 0.15 ± 0.17 | 0.25 ± 0.17 | 0.17 ± 0.19 | 0.28 ± 0.19 | $F(1,20)=0.16; p>0.1$ |
| TR3 – TR1 | 0.08 ± 0.19 | 0.13 ± 0.19 | 0.09 ± 0.22 | 0.14 ± 0.22 | $F(1,20)=0.03; p>0.1$ |
| TR4 – TR1 | 0.12 ± 0.24 | -0.02 ± 0.24 | 0.13 ± 0.26 | -0.02 ± 0.26 | $F(1,20)=0.16; p>0.1$ |
| TR5 – TR1 | 0.06 ± 0.24 | -0.14 ± 0.24 | 0.07 ± 0.27 | -0.16 ± 0.27 | $F(1,20)=0.36; p>0.1$ |
| TR6 – TR1 | 0.31 ± 0.26 | -0.02 ± 0.26 | 0.34 ± 0.29 | -0.02 ± 0.29 | $F(1,20)=0.75; p>0.1$ |
| **Accuracy** | | | | | |
| TR2 – TR1 | 1% ± 2% | 2% ± 2% | 0.11 ± 0.16 | 0.16 ± 0.16 | $F(1,20)=0.06; p>0.1$ |
| TR3 – TR1 | 0% ± 2% | 2% ± 2% | 0.04 ± 0.19 | 0.19 ± 0.19 | $F(1,20)=0.34; p>0.1$ |
| TR4 – TR1 | 0% ± 3% | 1% ± 3% | -0.03 ± 0.23 | 0.05 ± 0.23 | $F(1,20)=0.05; p>0.1$ |
| TR5 – TR1 | -1% ± 3% | -1% ± 3% | -0.07 ± 0.23 | -0.05 ± 0.23 | $F(1,20)=0.01; p>0.1$ |
| TR6 – TR1 | 2% ± 3% | 1% ± 3% | 0.18 ± 0.24 | 0.08 ± 0.24 | $F(1,20)=0.09; p>0.1$ |
| NT2 – NT1 | 12% ± 2% | 5% ± 2% | 1.1 ± 0.21 | 0.48 ± 0.21 | $F(1,20)=4.36; p<0.05$ |
| Gf2 – Gf1 | 4% ± 5% | 5% ± 5% | 0.24 ± 0.3 | 0.32 ± 0.3 | $F(1,20)=0.04; p>0.1$ |

**Table 3:** Comparisons of standardized change scores between Right Frontal tDCS and sham groups in Experiment 1. TR refers to the trained, on-stimulation task (spatial 3-back), NT refers to the near transfer task (verbal 3-back) and G*f* refers to the far transfer matrix reasoning task

| | **Change Scores** | | **Standardized Change Scores** | | |
|---|---|---|---|---|---|
| | Sham | Active | Sham | Active | Stats |
| **RT (ms)** | | | | | |
| TR2 – TR1 | -20 ± 21 | -76 ± 21 | -0.11 ± 0.12 | -0.43 ± 0.12 | *F*(1,20)=3.67; *p*=0.07 |
| TR3 – TR1 | -85 ± 24 | -124 ± 24 | -0.49 ± 0.14 | -0.71 ± 0.14 | *F*(1,20)=1.26; *p*>0.1 |
| TR4 – TR1 | -159 ± 34 | -181 ± 34 | -0.91 ± 0.19 | -1.04 ± 0.19 | *F*(1,20)=0.21; *p*>0.1 |
| TR5 – TR1 | -232 ± 32 | -208 ± 32 | -1.33 ± 0.19 | -1.19 ± 0.19 | *F*(1,20)=0.29; *p*>0.1 |
| TR6 – TR1 | -214 ± 35 | -196 ± 35 | -1.22 ± 0.2 | -1.12 ± 0.2 | *F*(1,20)=0.14; *p*>0.1 |
| **d’** | | | | | |
| TR2 – TR1 | 0.15 ± 0.15 | 0.24 ± 0.15 | 0.16 ± 0.17 | 0.27 ± 0.17 | *F*(1,20)=0.20; *p*>0.1 |
| TR3 – TR1 | 0.1 ± 0.17 | 0.5 ± 0.17 | 0.11 ± 0.19 | 0.55 ± 0.19 | *F*(1,20)=2.64; *p*>0.1 |
| TR4 – TR1 | 0.13 ± 0.24 | 0.31 ± 0.24 | 0.14 ± 0.27 | 0.34 ± 0.27 | *F*(1,20)=0.27; *p*>0.1 |
| TR5 – TR1 | 0.07 ± 0.26 | 0.68 ± 0.26 | 0.08 ± 0.29 | 0.75 ± 0.29 | *F*(1,20)=2.76; *p*>0.1 |
| TR6 – TR1 | 0.35 ± 0.26 | 0.27 ± 0.26 | 0.39 ± 0.29 | 0.3 ± 0.29 | *F*(1,20)=0.05; *p*>0.1 |
| **Accuracy** | | | | | |
| TR2 – TR1 | 1% ± 2% | 5% ± 2% | 0.11 ± 0.19 | 0.41 ± 0.19 | *F*(1,20)=1.34; *p*>0.1 |
| TR3 – TR1 | 1% ± 3% | 8% ± 3% | 0.07 ± 0.22 | 0.67 ± 0.22 | *F*(1,20)=3.83; *p*=0.06 |
| TR4 – TR1 | 0% ± 3% | 5% ± 3% | -0.01 ± 0.25 | 0.45 ± 0.25 | *F*(1,20)=1.74; *p*>0.1 |
| TR5 – TR1 | 0% ± 3% | 8% ± 3% | -0.04 ± 0.28 | 0.7 ± 0.28 | *F*(1,20)=3.36; *p*=0.08 |
| TR6 – TR1 | 3% ± 3% | 5% ± 3% | 0.22 ± 0.26 | 0.45 ± 0.26 | *F*(1,20)=0.36; *p*>0.1 |
| NT2 – NT1 | 12% ± 2% | 8% ± 2% | 1.11 ± 0.21 | 0.71 ± 0.21 | *F*(1,20)=1.76; *p*>0.1 |
| Gf2 – Gf1 | 4% ± 5% | 7% ± 5% | 0.23 ± 0.31 | 0.45 ± 0.31 | *F*(1,20)=0.27; *p*>0.1 |

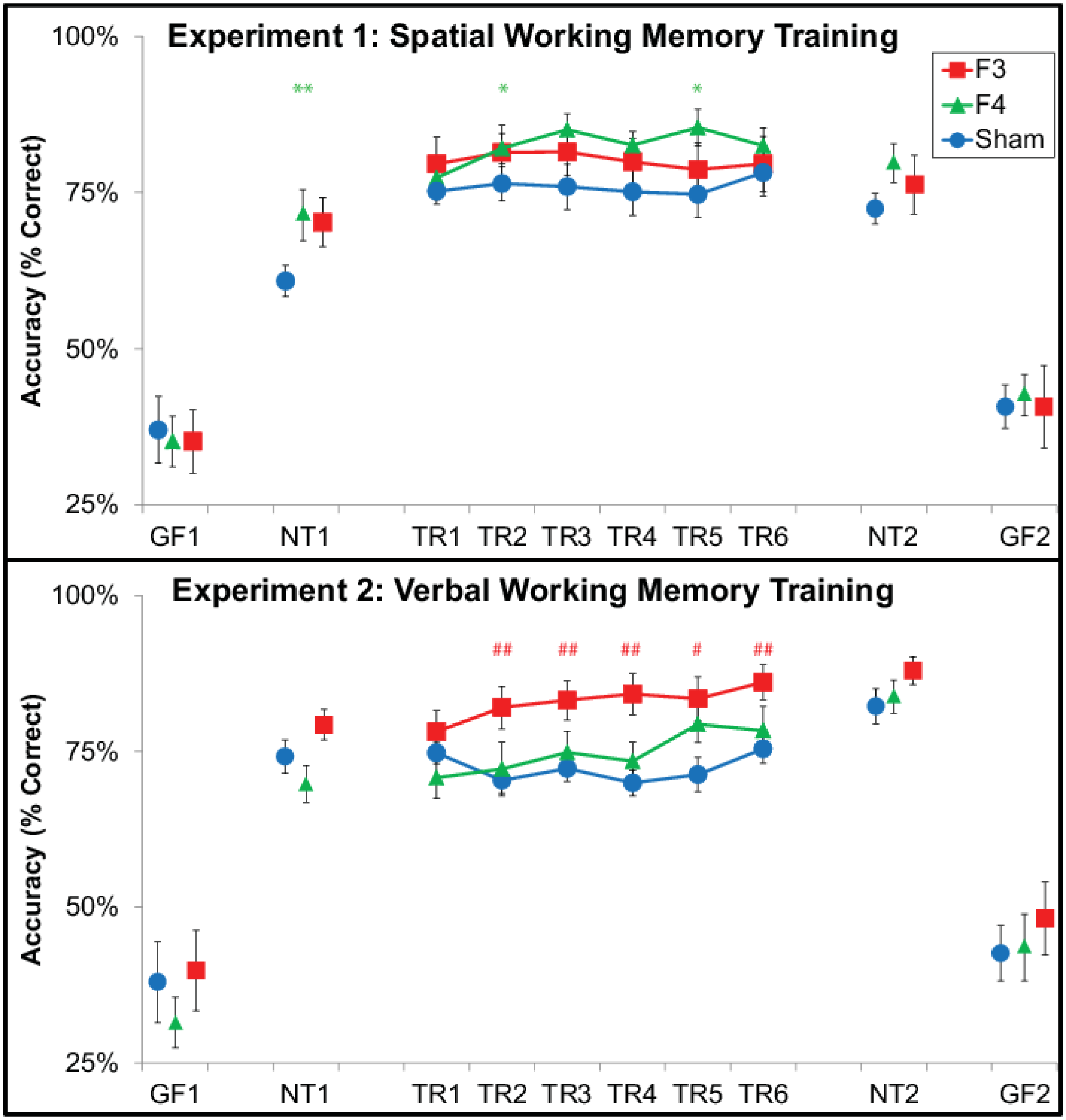

**Figure 2:** Mean accuracy for all tasks, groups, and experiments. Results from Experiment 1 are shown in the upper panel, while results from Experiment 2 are shown in the lower panel. Mean accuracy for sham tDCS groups are depicted by blue circles, F3 stimulation groups are depicted by red squares, and F4 stimulation groups are depicted by green triangles. Error bars denote SEM. * $p$<0.05 (F4 vs Sham). ** $p$<0.01 (F4 vs sham). $^{\#}$ $p$<0.05 (F3 vs. sham). $^{\#\#}$ $p$<0.01 (F3 vs. sham)

### *3.2.2 Experiment 2: Verbal Working Memory Training*

#### *Effects of Left Frontal (F3) tDCS*

Accuracy for each stimulation group is displayed in Figure 2, and change scores are listed in Table 4. A significant effect of tDCS was found within the omnibus MANCOVA of task-specific effects for left frontal tDCS vs. sham [Wilks' $\Lambda$ =0.57, $F(3,18) = 4.51$, $p < 0.05$, $\eta_p^2$=0.43], where tDCS differed from sham in standardized accuracy and d' change scores, but not RT change scores, across all TR runs [Accuracy: $F(1,20) = 14.28$, $p < 0.001$, $\eta_p^2$=0.42; d': $F(1,20) = 12.82$, $p < 0.01$, $\eta_p^2$=0.39] (Table 4).

In the analysis of task-general effects, a significant interaction was found between tDCS condition and cognitive assessment type [Wilks' $\Lambda$ =0.73, $F(2,19) = 3.52$, $p < 0.05$, $\eta_p^2$=0.28] indicating significantly different effects of tDCS during verbal WM training for each of the three cognitive assessment types (Table 4). Further investigation of these effects revealed significant differences between active and sham tDCS groups only for the verbal WM assessment type ($F(1,20) = 6.60$, $p < 0.05$), and not spatial WM or G*f*, indicating enhancement of verbal WM training with left frontal tDCS, which did not transfer to other assessment types. Interestingly, verbal WM scores increased in the active tDCS condition ($t(11) = 4.69$, $\underline{d} = 2.83$, $p < 0.001$), and not sham ($p > 0.1$), indicating that verbal WM training resulted in enhanced performance with active current, and not without. Collapsing across sham and active tDCS groups, spatial WM scores were significantly increased ($t(23)= 3.70$, $\underline{d} = 1.54$, $p < 0.01$), but G*f* scores were not ($p > 0.1$) .

**Table 4:** Comparisons of standardized change scores between Left Frontal tDCS and sham groups in Experiment 2. TR refers to the trained, on-stimulation task (verbal 3-back), NT refers to the near transfer task (spatial 3-back) and G*f* refers to the far transfer matrix reasoning task

| | **Change Scores** | | **Standardized Change Scores** | | |
|---|---|---|---|---|---|
| | Sham | Active | Sham | Active | Stats |
| **RT (ms)** | | | | | |
| TR2 – TR1 | -16 ± 23 | -15 ± 23 | -0.09 ± 0.13 | -0.08 ± 0.13 | $F(1,20)=0.00$; $p>0.1$ |
| TR3 – TR1 | -68 ± 33 | -75 ± 33 | -0.38 ± 0.19 | -0.42 ± 0.19 | $F(1,20)=0.02$; $p>0.1$ |
| TR4 – TR1 | -123 ± 38 | -78 ± 38 | -0.68 ± 0.21 | -0.43 ± 0.21 | $F(1,20)=0.70$; $p>0.1$ |
| TR5 – TR1 | -93 ± 43 | -112 ± 43 | -0.52 ± 0.24 | -0.63 ± 0.24 | $F(1,20)=0.10$; $p>0.1$ |
| TR6 – TR1 | -131 ± 37 | -95 ± 37 | -0.73 ± 0.21 | -0.53 ± 0.21 | $F(1,20)=0.48$; $p>0.1$ |
| **d’** | | | | | |
| TR2 – TR1 | -0.32 ± 0.16 | 0.44 ± 0.16 | -0.45 ± 0.22 | 0.62 ± 0.22 | $F(1,20)=11.59$; $p<0.01$ |
| TR3 – TR1 | -0.21 ± 0.17 | 0.38 ± 0.17 | -0.29 ± 0.24 | 0.54 ± 0.24 | $F(1,20)=5.72$; $p<0.05$ |
| TR4 – TR1 | -0.33 ± 0.2 | 0.5 ± 0.2 | -0.46 ± 0.28 | 0.71 ± 0.28 | $F(1,20)=8.64$; $p<0.01$ |
| TR5 – TR1 | -0.25 ± 0.22 | 0.54 ± 0.22 | -0.36 ± 0.31 | 0.76 ± 0.31 | $F(1,20)=6.52$; $p<0.05$ |
| TR6 – TR1 | -0.15 ± 0.23 | 0.75 ± 0.23 | -0.22 ± 0.32 | 1.06 ± 0.32 | $F(1,20)=7.72$; $p<0.05$ |
| **Accuracy** | | | | | |
| TR2 – TR1 | -4% ± 2% | 4% ± 2% | -0.44 ± 0.15 | 0.38 ± 0.15 | $F(1,20)=13.66$; $p<0.001$ |
| TR3 – TR1 | -2% ± 2% | 5% ± 2% | -0.22 ± 0.21 | 0.46 ± 0.21 | $F(1,20)=5.04$; $p<0.05$ |
| TR4 – TR1 | -4% ± 2% | 6% ± 2% | -0.44 ± 0.24 | 0.55 ± 0.24 | $F(1,20)=8.37$; $p<0.01$ |
| TR5 – TR1 | -3% ± 3% | 5% ± 3% | -0.34 ± 0.24 | 0.51 ± 0.24 | $F(1,20)=5.90$; $p<0.05$ |
| TR6 – TR1 | 1% ± 2% | 8% ± 2% | 0.14 ± 0.17 | 0.74 ± 0.17 | $F(1,20)=6.24$; $p<0.05$ |
| NT2 – NT1 | 8% ± 2% | 9% ± 2% | 0.85 ± 0.23 | 0.88 ± 0.23 | $F(1,20)=0.01$; $p>0.1$ |
| Gf2 – Gf1 | 5% ± 5% | 8% ± 5% | 0.28 ± 0.25 | 0.38 ± 0.25 | $F(1,20)=0.09$; $p>0.1$ |

### *Effects of Right Frontal (F4) tDCS*

Accuracy for each stimulation group is displayed in Figure 2, and change scores are listed in Table 5. A significant effect of tDCS was found within the omnibus MANCOVA of task-specific effects for right frontal tDCS vs. sham [Wilks’ $\Lambda$ =0.56, $F(3,18) = 4.65$, $p < 0.05$, $\eta_p^2$=0.44], where active current differed from sham in standardized accuracy and d' change scores, but not RT change scores, across all TR runs [Accuracy: $F(1,20) = 9.26$, $p < 0.01$, $\eta_p^2=0.32$; d': $F(1,20) = 13.83$, $p < 0.001$, $\eta_p^2=0.41$] (Table 5).

A significant main effect of tDCS condition was found [$F(1,20) = 4.44$, $p < 0.05$, $\eta_p^2=0.18$] indicating similar effects of tDCS during verbal WM training for each of the three cognitive assessment types (Table 5). Although no significant differences were present when comparing Active vs. Sham accuracy at individual tests (Table 5), scores were significantly increased from baseline for active tDCS participants for all cognitive assessment types (verbal: $t(11) = 2.79$; $\underline{d} = 1.68$, $p < 0.01$; spatial: $t(11) = 5.61$; $\underline{d} = 3.38$, $p < 0.01$; Gf: $t(11) = 2.78$; $\underline{d} = 1.68$, $p < 0.01$), while only spatial WM was significantly increased in sham tDCS participants ($t(11) = 3.27$, $\underline{d} = 1.97$, $p < 0.01$). No effects were found for RT measures ($p$s > 0.1).

**Table 5:** Comparisons of standardized change scores between Right Frontal tDCS and sham groups in Experiment 2. TR refers to the trained, on-stimulation task (spatial 3-back), NT refers to the near transfer task (verbal 3-back) and G*f* refers to the far transfer matrix reasoning task

| | **Change Scores** | | **Standardized Change Scores** | | |
|---|---|---|---|---|---|
| | Sham | Active | Sham | Active | Stats |
| **RT (ms)** | | | | | |
| TR2 – TR1 | -14 ± 30 | -1 ± 30 | -0.08 ± 0.17 | -0.01 ± 0.17 | *F*(1,20)=0.09; *p*>0.1 |
| TR3 – TR1 | -71 ± 36 | -60 ± 36 | -0.4 ± 0.2 | -0.34 ± 0.2 | *F*(1,20)=0.05; *p*>0.1 |
| TR4 – TR1 | -127 ± 49 | -122 ± 49 | -0.71 ± 0.27 | -0.68 ± 0.27 | *F*(1,20)=0.01; *p*>0.1 |
| TR5 – TR1 | -91 ± 47 | -136 ± 47 | -0.51 ± 0.26 | -0.76 ± 0.26 | *F*(1,20)=0.45; *p*>0.1 |
| TR6 – TR1 | -127 ± 38 | -167 ± 38 | -0.71 ± 0.21 | -0.93 ± 0.21 | *F*(1,20)=0.57; *p*>0.1 |
| **d’** | | | | | |
| TR2 – TR1 | -0.32 ± 0.12 | 0.16 ± 0.12 | -0.45 ± 0.17 | 0.22 ± 0.17 | *F*(1,20)=7.95; *p*<0.05 |
| TR3 – TR1 | -0.23 ± 0.15 | 0.36 ± 0.15 | -0.33 ± 0.21 | 0.51 ± 0.21 | *F*(1,20)=7.78; *p*<0.05 |
| TR4 – TR1 | -0.36 ± 0.17 | 0.19 ± 0.17 | -0.5 ± 0.24 | 0.27 ± 0.24 | *F*(1,20)=5.19; *p*<0.05 |
| TR5 – TR1 | -0.26 ± 0.2 | 0.58 ± 0.2 | -0.36 ± 0.28 | 0.83 ± 0.28 | F(1,20)=9.11; *p*<0.01 |
| TR6 – TR1 | -0.15 ± 0.22 | 0.58 ± 0.22 | -0.22 ± 0.31 | 0.82 ± 0.31 | F(1,20)=5.56; *p*<0.05 |
| **Accuracy** | | | | | |
| TR2 – TR1 | -4% ± 2% | 1% ± 2% | -0.43 ± 0.19 | 0.14 ± 0.19 | *F*(1,20)=4.33; *p*<0.05 |
| TR3 – TR1 | -3% ± 2% | 4% ± 2% | -0.25 ± 0.2 | 0.41 ± 0.2 | *F*(1,20)=5.24; *p*<0.05 |
| TR4 – TR1 | -5% ± 3% | 3% ± 3% | -0.48 ± 0.27 | 0.27 ± 0.27 | *F*(1,20)=3.94; *p*=0.06 |
| TR5 – TR1 | -4% ± 3% | 9% ± 3% | -0.35 ± 0.28 | 0.85 ± 0.28 | *F*(1,20)=9.30; *p*<0.01 |
| TR6 – TR1 | 1% ± 3% | 8% ± 3% | 0.12 ± 0.28 | 0.75 ± 0.28 | *F*(1,20)=2.56; *p*>0.1 |
| NT2 – NT1 | 9% ± 2% | 14% ± 2% | 0.89 ± 0.25 | 1.4 ± 0.25 | *F*(1,20)=2.19; *p*>0.1 |
| Gf2 – Gf1 | 4% ± 4% | 12% ± 4% | 0.23 ± 0.22 | 0.62 ± 0.22 | *F*(1,20)=1.55; *p*>0.1 |

### *Physical Sensation and Mood*

Physical sensations, initial mood ratings, and change in mood ratings did not differ significantly between tDCS groups in Experiment 1 or Experiment 2, for either stimulation condition, and physical sensations did not significantly correlate with any performance outcome measures (*p*s > 0.05). This suggests that performance differences between active and sham groups are indicative of neural modulation rather than due to nonspecific arousal effects caused by physical sensations. Sensation during sham tDCS was significantly correlated with handedness and head size measures. These correlation statistics can be found in Table 6.

**Table 6:** Pearson correlation statistics comparing tDCS sensation and participant demographics for sham tDCS participants. *p < 0.05, ** p < 0.01

| | Itching | Heat | Tingling |
|---|---|---|---|
| Itching | 1 | .144 | .546** |
| Heat | .144 | 1 | .634** |
| Tingling | .546** | .634** | 1 |
| Handedness | -.612** | -.226 | -.681** |
| Sleep Ratio | -.003 | -.133 | -.281 |
| Extraversion | -.244 | -.005 | -.192 |
| Head Width | -.582** | -.329 | -.425* |
| Head Length | -.401 | -.410* | -.519** |
| Head Circumference | -.527** | -.307 | -.539** |
| Gender | -.390 | -.185 | -.315 |

At the conclusion of the session, participants were asked to indicate which level of stimulation they thought they had received. Options read “0.1 mA (sham),” “2.0 mA (active),” and “I was unable to tell.” In Experiment 1, 18 of 36 participants (11/24 in the active condition, 7/12 in the sham condition) correctly indicated their stimulation condition; accuracy did not differ between groups ($\chi^2(2) = 0.63$, $p > 0.1$). In Experiment 2, 15 of 36 participants (13/24 in the active condition, 2/12 in the sham condition) correctly indicated their stimulation condition and this significantly differed between groups ($\chi^2(2) = 6.88$, $p < 0.05$). Overall, 33/72 participants correctly indicated their stimulation condition. In addition, in order to determine if any groups responded more accurately than chance would predict, chi-square tests comparing each group against a hypothesized null distribution (evenly distributed responses) were conducted. Similar to between-group comparisons, the only group to respond significantly different than chance was the Experiment 2 sham group ($\chi^2(2) = 7.24$, $p < 0.05$), driven by 10 out of 12 participants responding “I was unable to tell.”

# 4.0 DISCUSSION

Experiment 1 results suggest improvement in performance of spatial location-monitoring 3-back task for participants who received active relative to sham stimulation with the anode placed over the right DLPFC (hereafter referred to as the F4/spatial group) during training. These findings did not reach statistical significance, but consistent superior performance of the active group relative to the sham group with regard to training increases across training blocks and marginal significance at training blocks 3 and 5 support the notion that right DLPFC is involved in spatial location-monitoring WM (Owen et al., 2005) and that tDCS can improve performance on a visuospatial WM task (Jeon & Han, 2012).

In Experiment 2, results indicate a selective improvement of verbal identity-monitoring WM for participants who received active relative to sham stimulation when the anode was placed over left DLPFC, during verbal 3-back performance (hereafter referred to as the F3/verbal group). This supports findings demonstrating left DLPFC is involved in verbal WM (Owen et al., 2005) and that tDCS can improve performance on a verbal WM task when the anode is placed at F3 (Andrews et al., 2011; Fregni et al., 2005; Lally et al., 2013; Ohn et al., 2008; Teo et al., 2011; Zaehle et al., 2011). When the anode was placed at position F4 during verbal 3-back training (hereafter referred to as the F4/verbal group), participants in the active stimulation group outperformed those in the sham stimulation group not only on the trained task, but also significantly improved on a near transfer task (spatial 3-back), and a far transfer task (matrix reasoning).

Interestingly, there was a practice effect evident during both Experiment 1 and Experiment 2 for the near transfer tasks only (verbal 3-back in Experiment 1, spatial 3-back in Experiment 2). In other words, repetition improved verbal 3-back task performance only when this task was performed twice, in the absence of active stimulation; the same is true of spatial 3-back performance. Therefore, the performance increase exhibited on the trained task by participants in the F4/spatial group in Experiment 1 and the F3/verbal and F4/verbal occurred in the absence of a practice effect by participants receiving sham stimulation, allowing for performance gains significantly superior (or marginally so) to the performance of the sham groups. For the near transfer tasks, however, there was a practice effect evident for both Experiment 1 and Experiment 2, such that the significant gains exhibited by active participants on these near transfer tasks were not significantly superior to the gains demonstrated by the participants receiving sham stimulation.

This pattern suggests behavioral fatigue for repeatedly administered, non-adaptive n-back tasks, which is not evident during active stimulation using particular electrode placements. It is worth noting that active and sham groups did not differ with regard to intensity of physical sensations experienced during stimulation, and sensations did not correlate significantly with performance, suggesting that an explanation of arousal due to physical sensations is not responsible for mitigation of behavioral fatigue in the active groups. Additionally, the F3 placement in Experiment 1 (spatial training) did not significantly improve performance, and the F4 placement only marginally so, arguing against a non-specific arousal effect of active stimulation. These results confirm that effects are specific to electrode placement (Boggio et al., 2006; Fregni et al., 2005) and likely due to neuromodulatory effects.

This may occur through a strengthening of neuronal connections subserving WM performance. Previous work indicates tDCS induces LTP-like changes which result in the altering of neuronal connections (Liebetanz et al., 2002). It is possible that tDCS promoted cortical connections supporting WM performance in the active stimulation group. This is consistent with prior evidence demonstrating that a single session of tDCS is sufficient to change connectivity between cortical regions (Hunter et al., 2015), and DLPFC stimulation increases connectivity in bilateral fronto-parietal networks (Keeser et al., 2011). Additionally, frontostriatal connections may have strengthened as a result of training and stimulation (Kühn et al., 2011; Bäckman et al., 2011), leading to enhancement of striatal dopaminergic activity which has been implicated in WM updating (Bäckman & Nyberg, 2013).It is worth noting that the F4/verbal group is the only group to demonstrate significantly improved performance from baseline to post-stimulation on the G*f* task. There are a number of potential explanations for improvement on a G*f* measure, including practice effect, actual increase in Gf, improvement in abilities related to task proficiency (e.g., visuospaitial abilitiy), test-taking strategy, and participant motivation.

With regard to motivation, one hypothesis is that improvement on a trained task will motivate participants to perform well on tasks completed following training, resulting in a performance boost in the absence of WM or G*f* enhancement, per se (Hayes et al., 2015). Prior research has indicated that when control groups practice tasks that instill motivation equitable to treatment groups, test scores may improve comparably (Melby-Lervåg & Hulme, 2013; Redick et al., 2013). Thus, motivation transfer may be conflated with transfer due to construct enhancement. Research controlling for motivational factors, however, suggests that in the context of WM transfer to G*f* task performance motivation is unlikely to solely account for G*f* task improvement (Jaeggi et al., 2014). In the current work, three electrode placement/training combinations (F4/spatial, F3/verbal, F4/verbal) resulted in improvement on the trained task, yet in only one instance G*f* task improvement occurred (F4/verbal). If improvement on a trained task were sufficient to increase participant motivation which then transfers to improvement on untrained tasks in the absence of WM or G*f* enhancement, per se (Hayes et al., 2015), we would expect to see task transfer in each instance in which stimulation resulted in improvement on a trained task.

Another potential explanation is improvement of visuospatial ability. Prior research using a battery of G*f* tasks before and after WM training suggests that visuospatial ability rather than G*f* is improved by the WM training implemented in these studies (Colom et al., 2013; Jaeggi et al., 2014). In the current study, the F4/verbal group demonstrated task improvement for tasks that involve a strong visuospatial component – a spatial location-monitoring 3-back and a visual matrix reasoning task – following right DLPFC stimulation, which is associated with improvement in spatial WM (Jeon & Han, 2012).

In Experiment 1, however, F4/spatial training resulted in marginal improvement for the active relative to the sham group on the trained task, but this did not transfer to significant improvement on the matrix reasoning task. If stimulation with the anode over F4 enhanced general visuospatial ability, there should have been an improvement in performance on the matrix reasoning task, to the extent that G*f* task performance relies on visuospatial ability. As matrix performance did not increase with the anode at F4 in Experiment 1, it is unlikely that enhanced visuospatial ability is responsible for the transfer observed with the anode over F4 in Experiment 2.

Another candidate for an explanation of transfer is task strategy. Even in the absence of direct strategy instruction (consistent with the current study) repeated performance of WM tasks is typified by development of strategy use (Holmes, Gathercole, & Dunning, 2009; McNamara & Scott, 2001), and a variety of strategies have been found to improve performance on WM measures (Bengson & Luck, 2015; Turley-Ames & Whitfield, 2003). Therefore, improvement on

WM tasks may reflect optimization of existing capacity rather than capacity increase, as repeated task completion promotes development of compensatory strategies, either to overcome an area of weakness or exploit an existing strength (Holmes et al., 2009). Similarly, strategy refinement has been found to account for one-third of the variance of score gains on matrix reasoning problems (Hayes et al., 2015) as indicated by eye-tracking data demonstrating development of more systematic row-wise scanning is associated with performance increase. Transfer of strategy use is thought to occur when tasks share features, thereby enabling an effective strategy developed during performance of one task to enable performance increase on another (Dunning & Holmes, 2014). Some aspects of task performance are similar between WM and matrix reasoning tasks – determining if the identity of one stimulus matches the identity of another, storing multiple items concurrently in memory – which may explain the shared variance between WM and G*f* tasks (Gignac, 2014). Thus, transfer of WM training to matrix reasoning tasks may occur in part due to strategy refinement rather than G*f* improvement. Research demonstrating that strategies developed during performance of one WM task transfer to untrained WM tasks (Dunning & Holmes, 2014) supports this idea by demonstrating that tasks that share performance aspects, such as Gf and WM tasks (Gignac, 2014), may be amenable to strategy transfer.

Notably, fMRI data collected during 3-back performance indicates brain activity in bilateral DLPFC during high-interference trials (lures) is predictive of G*f* and WM span, suggesting that interference control is a task component common to WM and G*f* tasks, and involves bilateral DLPFC (Burgess, Gray, Conway, & Braver, 2011). The right DLPFC in particular is associated with development of compensatory strategies during WM task performance, and is posited as one reason older adults exhibit bilateral DLFPC activation during performance of a verbal WM task (Reuter-Lorenz et al., 2000). Additionally, males demonstrate bilateral or right-side DLPFC dominance during verbal WM task performance, which may relate to strategy use to compensate for otherwise weaker verbal WM ability (Speck et al., 2000). A study utilizing repetitive transcranial magnetic stimulation over left or right DLPFC found that memory retrieval was selectively disrupted when applied over the right DLPFC only for participants who reported using a strategy, suggesting right DLPFC involvement in cognitive control processes engaged by strategy use (Manenti et al., 2010). While transfer in the current study did not occur when right DLPFC stimulation was paired with spatial WM training, this may be due to task-dependent effects of stimulation such that stimulation during verbal 3-back performance has a different impact than stimulation during spatial 3-back performance. In prior tDCS research targeting left DLPFC, near transfer only occurred when stimulation was applied during performance of a more difficult 3-back task, not when applied during 1-back performance (Gill et al., 2015) demonstrating that task demands during stimulation impact transfer. It is possible that F4/spatial training did not result in transfer because development of a task strategy did not occur, whereas F4/verbal training facilitated activity related to strategy development.

An increase in G*f* and strategy refinement are not mutually exclusive explanations. In fact, it has been argued that the ability to both learn and effectively deploy cognitive strategies may be part of G*f* (Hayes et al. 2015). The situation is further complicated by research suggesting that higher WM capacity affords the opportunity for strategy development during task performance, particularly when a task or strategy is demanding such that maintaining task performance during concurrent strategy development and evaluation would require a high WM capacity (Dunlosky & Kane, 2007; Dunlosky & Thiede, 2004; Turley-Ames & Whitfield, 2003). Therefore an increase in WM capacity and strategy refinement may overlap. Given the results from Experiment 1 indicating a selective improvement of spatial WM performance with F4 anode placement, it is also possible that F4 stimulation improves spatial WM independently, such that Experiment 2 results reflect multiple enhancments – strategy refinement associated with verbal WM performance during stimulation, spatial WM near transfer due to carryover effects from recent stimulation over right DLPFC, and G*f* improvement due to strategy refinement that occurred during verbal WM performance. Future work should control for strategy use in order to disentangle the potential contributions of increased WM capacity and strategy use.

In all instances of improved performance, improvement was evident with regard to accuracy and d' rather than RT reduction. This finding is in accordance with prior tDCS WM research (e.g., Fregni et al., 2005; Ohn et al., 2008) but stands in contrast to other findings (Mulquiney et al., 2011), including a recent meta-analysis indicating that tDCS results in reliable improvement of RTs but not accuracy with regard to *n*-back performance (Brunoni & Vanderhasselt, 2014). This may be the result of requiring participants to use the hand ipsilateral to the cephalic electrode, thereby reducing the possibility of spreading activation to the motor cortex associated with the response hand impacting RTs, a practice implemented in prior tDCS WM research that has found accuracy rather than RT improvement (Ohn et al., 2008). Another possibility is that the stimulation parameters, particularly current density (i.e., current strength/electrode surface area; 0.182 mA/cm$^2$ in the current study) and density charge (i.e., (current density)*(stimulation duration); 5.46 C/cm$^2$ in the current study) may have been high enough to affect brain activity differently than studies using less intense stimulation parameters. A recent meta-analysis examining the relationship between stimulation parameters and behavioral effects of tDCS found that both higher current density and higher density charge were associated with stronger effects of anodal tDCS on performance accuracy for healthy participants when the anode was placed to target DLPFC, reporting a mean current density of 0.04 mA/cm$^{2,}$ and a mean density charge of 0.05 C/cm$^2$ for surveyed studies (Dedoncker, Brunoni, Baeken, & Vaderhasselt, 2016). This supports a similar finding from a previous meta-analysis that exclusively examined WM tasks, but pooled healthy and clinical participants (Hill, Fitzgerald, & Hoy, 2014).

Results suggest that research utilizing a single WM task (e.g., Fregni et al., 2005; Ohn et al., 2008; Zaehle et al., 2011) should be interpreted with caution, as enhancement of WM task performance via tDCS does not guarantee generalization of improvement. The possibility that tDCS-enhanced performance on a WM measure may be task specific undermines the argument that the construct of WM is improved by stimulation when only a single task is administered (e.g., Fregni et al., 2005; Ohn et al., 2008; Zaehle et al., 2011). Performance benefit should occur on other tasks that utilize the same neural substrate (Dahlin et al., 2008), but as the current work demonstrates this generalized improvement is not a guarantee, at the very least it may be necessary to qualify improvement as specific to particular aspects or types of WM (e.g., visuospatial WM) for instances lacking demonstration of transfer.

## 4.1 Limitations

There are a number of important limitations to the current work that should be addressed in future research. Broadly speaking, these limitations may be divided into characteristics of the tasks, characteristics of stimulation, and characteristics of the participants. Each of these categories will be described in turn. It is worth mention that there are many gaps in our current understanding of the mechanisms by which tDCS alters behavior (Bestmann et al., 2015; Fertonani & Miniussi, 2016) such that a mechanistic explanation of the current results is highly speculative. Indeed, as noted by de Berker, Bikson, and Bestmann (2013), "…there is no theoretical or mechanistic explanation for why depolarizing cells would improve such complex behaviors as perceptual decision-making, mathematical ability, or motor learning."

### *4.1.2 Task Characteristics*

G*f* is typically considered the latent variable that explains interrcorrleated performance on a variety of tasks, such as analogy making, reasoning, and novel problem solving (Engle, Tuholski, Laughlin, & Conway, 1999). It has previously been recommended that construct assessment should occur via a battery of multiple tests, which allows for creation of latent variables which avoid task idiosyncrasies driving results (Shipstead et al., 2012). Multiple tests would enable creation of a latent difference score model that uses factor-analysis techniques in order to assess gains at the latent level (Schmiedek et al., 2010). By only using a single measure each of G*f*, spatial WM, and verbal WM, we were unable to take a latent variable approach for these constructs. As far transfer has been demonstrated to be dissociable and limited to the visual modality in previous cognitive training studies (Colom et al., 2013; Harrison et al., 2013; Jaeggi et al., 2014; Stephenson & Halpern, 2013), a battery of tasks would offer the additional benefit of allowing for transfer effects to be examined along the dimension of stimulus modality.

In a similar vein, it is suggested that WM is dissociable along the dimensions of capacity (i.e., the number of representations maintained) and resolution (i.e., the level of detail for each representation) and it is capacity rather than resolution that mediates the relationship between WM and G*f* (Fukuda, Vogel, Mayr, & Awh, 2010). Therefore, future work examining these particular aspects of WM may elucidate the nature of WM enhancement that occurs under stimulation. A clear hypothesis is that capacity rather than resolution is enhanced when far transfer occurs, given the relationship between WM capacity and G*f*.

In the current study, all tasks maintained a static difficulty level rather than implementing an adaptive performance-based difficulty. As the design of both experiments was between rather than within-subjects in nature, non-adaptive tasks allow a comparison between participants that is not confounded with task difficulty (Jones et al., 2015). Additionally, a recent meta-analysis suggests no difference in performance benefit elicited by adaptive and non-adaptive WM training programs (Karbach & Verhaeghen, 2014).

### *4.1.3 Stimulation Characteristics*

A number of stimulation characteristics may influence current distribution in the brain and resulting behavioral outcome. These include electrode size, shape, number, position, and composition, the current intensity and duration, number of stimulation sessions, and the conductive medium (Guleyupoglu, Schestatsky, Edwards, Fregni, & Bikson, 2013; Peterchev et al., 2012). While these factors were held constant between participants in the current study, it is likely that adjusting stimulation along these dimensions would influence the behavioral results.

One limitation common to standard tDCS research is the lack of focality regarding stimulated brain regions (Zheng, Alsop, & Schlaug, 2011). Frontal areas aside from the DLPFC were likely impacted by stimulation. These additional regions include frontal regions implicated in operations such as inhibition (Ditye, Jacobson, Walsh, & Lavidor, 2012), planning (Dockery, Hueckel-Weng, Birbaumr, & Plewnia, 2009) and risk-taking (Fecteau et al., 2007), as well as cerebellar and brain stem structures (Bikson, Rahman, & Datta, 2012). The cerebellum has previously been targeted directly in tDCS WM paradigms, with both anodal and cathodal stimulation either impairing task performance (Boehringer, Macher, Dukart, Villringer, & Pleger, 2012; Ferrucci et al., 2008) or having no effect (van Wessel, Verhage, Holland, Frens, & van der Geest, 2015). In the current work, participants typically benefitted from tDCS; in the one instance in which they did not (F3/spatial training) it was hypothesized that no benefit of tDCS would occur based on PFC asymmetry of function. Therefore, we do not believe cerebellar stimulation played a significant role in the results of the current work. In order to determine the specific portion of the frontal cortex involved in enhancement of WM training, it may be necessary to utilize additional stimulation methods with superior spatial resolution, such as transcranial magnetic stimulation (TMS) (Roth, Amir, Levkovitz, & Zangen, 2007), high-density (HD) tDCS (Kuo et al., 2014), transcranial pulsed ultrasound (Tufail et. al., 2010), or additional targeting systems such as the OLE-system (Seibt, Brunoni, Huang, & Bikson, 2015).

A meta-analysis suggests that single-session tDCS does not reliably benefit any cognitive domain, including WM (Horvath, Forte, & Carter, 2015). While assessment of task transfer is inconclusive in the current work, we did find clear evidence of single-session tDCS task improvement on a WM task performed during stimulation. Overall results are consistent with multi-session tDCS research indicating enhancement of verbal WM performance during training, with near transfer effects evident only when comparing active stimulation to a no-contact control group (Richmond et al., 2014). Similar research has found task transfer effects present only at a 1-month follow-up rather than directly after training (Jones et al., 2015; Martin et al., 2013). Future research should implement a follow-up in order to determine the duration of task improvements as well as evaluate potential sleeper effects. Thus, tDCS may have an additive effect beyond training alone, or extend the duration of training benefit, but training may serve as the key component.

#### 4.1.3.1 Blinding

One aspect of participant blinding that receives a great deal of attention in tDCS literature is the sensation ratings reported by participants. It is possible for aggregate physical sensations to differ between participants receiving active and sham stimulation without participants guessing their stimulation condition at levels that exceed chance in between-subject studies (e.g., Matzen et al., 2015). In addition, even in the context of aggregate differences in sensation, sensations themselves may not be significantly correlated with outcome measures (Clark et al., 2012; Kessler, Turkeltaub, Benson, & Hamilton, 2012; Matzen et al., 2015). However, within-subject studies in which participants will have the opportunity to compare their sensations across stimulation sessions are more common than between-subject studies in which participants will not have a frame of reference for their stimulation experience (Woods et al., 2016). Therefore, participant sensorial experience is often considered a critical component of blinding.

In the first study to directly compare discomfort ratings in healthy adults (n=24), in which some participants received more than one stimulation condition and some did not, there was no difference in sensation ratings between anodal, cathodal, and sham tDCS (Gandiga, Hummel, & Cohen, 2006). In contrast, Kessler and colleagues (2012) found that active stimulation resulted in more intense tingling, itching, burning, and pain relative to sham; again with some participants receiving only one session (n=41) and some receiving multiple sessions (n=90). Additional findings support those of Matzen et al. (2015), by collecting data from 149 participants over 195 stimulation sessions and finding that participants experienced greater sensations when receiving active relative to sham stimulation, yet were unable to reliably indicate whether they had received active or sham stimulation (Russo, Wallace, Fitzgerald, & Cooper, 2013). Notably, the results reported by Russo and colleagues (2013) were under stimulation conditions of 2.0 mA for 30 minutes, as in prior work with equitable results (Matzen et al., 2015) and as in the current study. In contrast, however, O’Connell et al. (2012) collected data from 100 participants in a purely within-subjects design and found that at 2.0 mA participants were able to judge whether they received active or sham stimulation at levels significantly greater than chance.

In the largest published analysis to date on sensations associated with stimulation, including 434 tDCS sessions (184 anodal, 131 cathodal, and 119 sham), it was found that anodal (but not cathodal) tDCS produced an average discomfort rating roughly 25% higher than sham stimulation, though this value did not quite reach significance ($p = 0.056$) (Fertonani, Ferrari, & Miniussi, 2015). These data were collected from various experiments, and therefore represent a mixture of within- and between-subject designs as well as varying stimulation parameters along dimensions such as current intensity and density, electrode size, and electrode montage. Additional analyses revealed that larger electrodes and greater current intensities were associated with higher discomfort ratings. These findings are consistent with prior research that suggests larger electrodes result in greater discomfort due to a greater number of cutaneous receptors being stimulated relative to smaller electrode use (Turi, Ambrus, Ho, Sengupta, Paulus, & Antal, 2014).

Rather than using participants who are naïve to stimulation at the outset, one study first familiarized participants with anodal, cathodal, and sham stimulation at both 1.0 and 2.0 mA, after which participants were exposed to the different stimulation types and asked to identify their stimulation condition (Tang, Hammond, & Badcock, 2016). While participants were able to correctly identify their stimulation intensity at better than chance levels, they were unable to determine the type of stimulation (anodal or cathodal) they were receiving. This finding suggests that participants in repeated measures conditions may, with practice, be able to determine when they are receiving active stimulation rather than sham, but may not be able to determine if they are receiving anodal or cathodal stimulation.

Overall, these results suggest that creating a sham protocol that effectively blinds between stimulation conditions may prove challenging, particularly at higher current intensities and for repeated measures conditions. One potential solution is to use topical anesthetics in order to attenuate sensations (Guleyupoglu, Febles, Minhas, Hahn, & Bikson, 2014). Skin damage is not reliably associated with skin sensations (Palm et al., 2008), so elimination of skin sensations should not put participants at risk as long as safety guidelines are followed carefully. Another option is the inclusion of an active control condition, in which active stimulation is applied over an area thought to be irrelevant for task performance.

Often absent from discussion of blinding is experimenter blinding. Experimenter blinding is typically assumed by concealing participant condition from the person collecting data from participants. However, the experimenter can still make guesses as to participant condition based on observations of sensations and erythema following stimulation. In one study that has tracked experimenter blinding, it was found that at 2.0 mA experimenter accuracy in determining participant stimulation condition is greater than chance, based largely on the presence of skin erythema (O'Connell et al., 2012). Again, one potential solution is drug based; a dose of acetylsalicylate or topical application of ketoprofen may reduce erythema (Durand, Fromy, Bouyé, Saumet, & Abraham, 2002; Guarienti et al., 2014). Another potential solution is to leave electrodes on following stimulation until study completion, or to have the electrodes removed and skin covered by another experimenter who is not otherwise involved in data collection.

In the current study, although blinding was apparently successful based on lack of sensation differences between stimulation conditions and on inability of participants to correctly identify stimulation condition (see Section 3.2). This latter result was, however, driven largely by participants selecting "I was unable to tell" with regard to indicating their stimulation condition.

It is possible that a forced-choice follow-up question for these individuals would reveal a greater degree of accuracy. In addition, participants were not queried as to why they selected a particular stimulation condition – responses may be driven by sensations felt during stimulation, but it is possible that participants based their responses on whether or not they felt a cognitive change (e.g., more or less focused) during stimulation. Furthermore, experimenter blinding was not assessed, and the same experimenter who collected data was also responsible for electrode removal, which occurred shortly following cessation of stimulation such that participants completed post-stimulation tasks under the supervision of a conceivably unblinded experimenter. Future research should address these issues by adjusting questionnaire structure and implementing more stringent blinding procedures.

### *4.1.4 Participant Characteristics*

As tDCS is considered a neuromodulatory technique in that it influences ongoing brain activity (Woods et al., 2016), it is important to consider individual factors that may influence brain state at the time of stimulation. Individual variability with regard to the following factors that influence brain state may help explain inconsistent results between individuals or within the same individual across stimulation sessions.

#### 4.1.4.1 Sex Differences

Sex differences relevant to brain stimulation protocols include any systematic differences in brain state between sexes, which may interact with stimulation. One such source of variability is hormonal levels, which fluctuate to a greater degree in females relative to males. While some researchers have taken to excluding females entirely from stimulation protocols in order to reduce noise (e.g., Alonzo, Brassil, Taylor, Martin, & Loo, 2012), a meta-analysis focusing on DLPFC stimulation suggests that stronger effect sizes are associated with a higher percentage of female participants (Dedoncker et al., 2016). This may be due to anatomical differences in DLPFC location – the DLPFC tends be located more medial in females relative to males (Mylius et al., 2013) – or to task approach differences, as females are more likely to adopt a top-down cognitive strategy than males, (Butler et al., 2007). The meta-analysis authors, however, offer up hormonal differences which impact cortical excitability, thereby interacting with stimulation outcome, as the most plausible explanation (Dedoncker et al., 2016).

Prior research indicates that cortical inhibition may be relatively high and excitability relatively low when levels of progesterone are elevated, as during the luteal phase of the menstrual cycle (Smith et al., 1999). During the first half of the follicular phase, characterized by both low progesterone and low estradiol, cortical excitation tends to be low, but during the second half of the follicular phase, characterized by low progesterone but now elevated levels of estradiol, excitation is high (Smith, Adams, Schmidt, Rubinow, & Wasserman, 2002). Thus, progesterone levels seem to be associated with cortical inhibition, while estradiol levels are tied to excitation. It may be necessary, however, to consider brain regions individually. Harada, Kubo, Nose, Nishitani, and Matsuda (2011) used MRS to track GABA levels in three brain regions, and found that in the lentiform nuclei and left frontal cortex GABA levels were decreased during the luteal phase, but the same was not true of the anterior cingulate cortex.

In the current study, groups were female/male balanced, and gender was used as a covariate in data analysis. Group sizes, however, were too small to be meaningfully split along the dimension of gender in order to say conclusively whether there were gender differences under the stimulation protocol used in the current study. Future work could benefit from inclusion of enough participants to determine the direction and magnitude of sex differences, should they exist.

#### 4.1.4.2 Age Differences

Given the importance of WM to activities of daily living, WM decline with age and associated neural changes (Wang et al., 2011) are particularly relevant to the current study. There are a number of brain changes associated with aging that may influence stimulation outcome. Neurotrophic factors are proteins that are responsible for the development and survival of nascent neurons, as well as the maintenance of mature neurons and the connections between neurons (Deister and Schmidt, 2006). Brain-derived neurotrophic factor (BDNF) is thought to play a role in LTP- and LTD-like stimulation after-effects via protein synthesis regulation at the synapse (Chaieb, Antal, Ambrus, & Paulus, 2014). However, older adults typically exhibit decreased levels of BDNF secretion relative to their younger counterparts (Li et al., 2008). Additionally, GABA mediated inhibitory processes may be impaired in older adults (Levin, Fujiyama, Boisgontier, Swinnen, & Summers, 2014). Aging has also been tied to degeneration of dopamine neurons (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006) which may relate to memory decline in elderly individuals (Chowdhury, Guitart-Masip, Bunzeck, Dolan, & Dunzel, 2012). As D2 dopamine receptors are thought to play an important role in cortical neuroplasticity (Nitsche et al., 2012), and the after-effects of tDCS are modulated by several neurotransmitter systems, including dopamine (Medeiros et al., 2012), dopamine degeneration associated with aging may make it more difficult to achieve LTP-like after-effects of tDCS for older adults (Summers, Kang, & Cauraugh, 2016).

It is often suggested that tDCS may particularly benefit individuals who are at a lower baseline level of functioning, thereby providing particular benefit with regard to correction of age-related cognitive decline. Brain stimulation protocols have been specifically designed to mitigate cognitive decline associated with aging. Experimental results, however, are mixed.

Reasons for optimism include research in which anodal tDCS has been applied to the motor cortex of mice, resulting in enhanced BDNF secretion (Fritsch et al., 2010), suggesting that tDCS may be able to correct for decreased BDNF secretion associated with aging in humans. Additionally, tDCS has been found to benefit learning of a complex motor task for older adults who initially exhibited relatively poor task performance, but did not benefit younger adults for whom baseline performance was relatively high (Zimerman et al., 2013). Anodal tDCS has also been used in an attempt to increase activity of GABAergic interneurons in the aging brain (Heise et al., 2014), thereby correcting the cognitive and motor impairments associated with reduced ability to modulate GABAergic tone (Gleichmann, Chow, & Mattson, 2011). It is worth noting, however, that those older adults with preserved modulatory capacity were more likely to benefit from stimulation (Heise et al., 2014), suggesting a certain baseline level of functioning may be necessary in order to benefit from stimulation.

In support of this *necessary baseline* hypothesis, Berryhill and Jones (2012) found that stimulation improved WM task performance in older adults, but only for those individuals with a relatively high amount of education. In contrast to selective improvement for high functioning adults as a result of stimulation, research using a spatial attention task has found that poor baseline performers – both young and old – were impaired by left PPC stimulation, while stimulation did not affect high performers (Learmonth, Thut, Benwell, & Harvey, 2015). Likewise, in a face-name associative memory paradigm, stimulation improved performance for younger adults (Matzen et al., 2015) but impaired performance for older adults (Leach, McCurdy, Trumbo, Matzen, & Leshikar, 2016), who typically find this task more difficult than younger adults (Naveh-Benjamin, Guez, Kilb, & Reedy, 2004). Taken together, these results suggest that tDCS may fail to improve, or even hinder performance, under conditions in which performance is already poor.

It is difficult, however, to directly compare young and old adults in the context of brain stimulation experiments. The brain often exhibits different patterns of task-related activity in old age, perhaps reflecting use of different strategic approaches to tasks between younger and older adults (Reuter-Lorenz et al., 2000). In addition, anatomy may change with age in ways that impact current distribution in the brain. For instance, the distance between the skull and the brain tends be greater in older versus younger adults, such that older adults may have a thicker layer of conductive cerebrospinal fluid (CSF) which attenuates electric field strength on the cortex via increased shunting of current (Laakso, Tanaka, Koyama, Santis, & Hirata, 2015). Therefore, stimulation parameters that facilitate performance in one age group may not do so in another due to differences in baseline brain state or anatomy.

In one study, stimulation with the anode placed over the right anterior temporal lobe (ATL) improved proper name recall for younger adults, while left ATL stimulation did not (Ross, McCoy, Wolk, Coslett, & Olson, 2010). Conversely, a follow-up study demonstrated that right ATL stimulation did not affect proper name recall for older adults, while placing the anode over the left ATL benefitted performance (Ross, McCoy, Coslett, Olson, & Wolk, 2011). In a similar vein, Fecteau and colleagues (2007) demonstrated that DLPFC stimulation decreased risk-taking in young adults, while Boggio and colleagues (2011), using identical methodology, found an increase in risk-taking behavior for older adults, suggesting that stimulation may affect young and old age groups in opposite directions. Therefore, a low baseline level of performance may or may not equate to a greater opportunity to benefit from stimulation; performance differences between age groups may be associated with brain differences, such that different stimulation parameters may be necessary to elicit benefit, or stimulation may be ineffective in situations in which neural architecture lacks the necessary structure to support plasticity.

In the current study, participants were younger adults enrolled in an entry level psychology course. It is therefore unclear if similar results would be obtained for older participants for whom WM decline and associated neural changes are likely (Wang et al., 2011). Future work may benefit from the inclusion of participants who may respond differently to stimulation-enhanced cognitive training programs, such as older adults who may be particularly impacted by WM loss as a result of cognitive decline associated with aging (Gutchess, 2014).

#### 4.1.4.3 Genetics

Genetic polymorphisms which encode neuromodulatory proteins such as BDNF and catechol-*O*-methyltransferase (COMT) have been shown to contribute to individual differences in cognitive performance (Egan et al., 2001; Chen et al., 2006). These polymorphisms may affect the outcome of brain stimulation protocols by modulating the susceptibility of synapses to LTP- and LTD-like changes (Mizundo, Yamada, Olariu, Nawa, & Nabeshima, 2000; Poo, 2001). One particular polymorphism has been the subject of brain stimulation research; a single-nucleotide polymorphism in the BDNF gene is implicated in level of BDNF secretion based on valine-to-methionine substitution at codon 66 (Val66Met). Carriers of the Met allele secrete reduced levels of BDNF, which is thought to reduce potential for synaptic plasticity relative to Val/Val homozygote carriers (Egan et al., 2003).

In one series of studies, it was demonstrated that Val/Val homozygote carriers generally exhibit an enhanced level of plastic changes relative to carriers of the Met allele, as measured by protocols designed to induce LTP or LTD-like effects over motor cortex and verified by TMS motor-evoked potentials (MEPs) (Cheeran et al., 2008). While some similar work supports the idea that Val/Val homozygotes demonstrate higher plasticity induction (Kleim et al., 2006; McHughen et al., 2010) other research has failed to find a difference between Val/Val and Val/Met carriers (Di Lazzaro et al., 2012; Voti et al., 2011), or has found that Met carriers demonstrate a greater degree of post-intervention changes in cortical excitability, suggesting that stimulation may correct for reduced BDNF secretion exhibited by Met carriers (Antal et al., 2010; Puri et al., 2015; Teo et al., 2014).

While these inconsistent results may reflect differences in stimulation protocols or study populations, another source of variability may be additional genetic polymorphisms which interact with BDNF polymorphisms. Witte and colleagues (2012) found that in the context of a TMS protocol designed to enhance cortical excitability, BDNF carrier status alone was not enough to predict cortical response. When considering BDNF polymorphisms in conjunction with COMT polymorphisms, however, it was revealed that higher plasticity following stimulation was exhibited for BDNF Val/Val carriers relative to Met carriers, but only for COMT Met homozygotes. Therefore, it may be necessary to consider interactions between genetic polymorphisms in order to achieve a comprehensive understanding of genetic influence on stimulation outcome.

An important caveat to the above findings is that all of the cited work examining the relationship between genetics and stimulation outcome has focused on stimulation of the primary motor cortex. This may be because these protocols allow cortical excitability to be readily measured before and after stimulation using TMS pulses and recording resulting activity in the muscle corresponding to the targeted location (i.e., motor-evoked potentials, or MEPs). In contrast, confirmation of shift in cortical excitability in non-sensorimotor areas typically relies on measuring behavioral rather than physiological changes, which introduces complications in interpretation as behavioral performance may be subject to a variety of factors (e.g., participant motivation and task strategy) that are not relevant to MEP measurement (Summers et al., 2016). In one of the few instances in which the effect of tDCS on higher-order cognitive functioning has been assessed in conjunction with genotype, left DLPFC anodal stimulation during Go/No-Go task performance led to impaired set-shifting ability for COMT Met/Met carriers only (Plewnia et al., 2013). In a follow-up study with identical methodology but using cathodal stimulation instead, it was found that response inhibition ability was decreased selectively for participants expressing Val/Val homozygous COMT polymorphism (Nieratschker, Kiefer, Giel, Krüger, & Plewnia, 2015). The authors discuss the results of these two studies in terms of the "inverted-U" theory of frontal dopamine levels. This theory posits that there is an optimal level of frontal dopamine, such that going above or below the optimal level leads to impaired cognitive functioning (Cools & D'Esposito, 2012). Therefore, anodal stimulation over left DLPFC impairs Go/No-Go performance selectively for Met/Met COMT carriers who typically already have a high level of frontal dopamine by pushing dopamine levels above the optimal threshold (Plewnia et al., 2013). Conversely, cathodal stimulation impairs performance for Val/Val homozygotes with typically low levels of frontal dopamine by decreasing dopamine levels below the optimal threshold (Nieratschker et al., 2015).

Thus, although little is known about the interaction between genotype and stimulation outcome, it appears that various genetic polymorphisms result in neurophysiology that varies enough between individuals to have a significant impact on stimulation efficacy. Although the current study did not incorporate genotyping, future work could benefit from inclusion of genetic assays in order to facilitate understanding of the relationship between genotype, stimulation, and cognitive functioning in realms such as WM.

#### 4.1.4.4 Anatomy

Individual variability in anatomy may influence distribution of current flow through the brain, perhaps explaining why stimulation outcomes are not always consistent between participants when using identical stimulation parameters. Finite element modeling (FEM) may be used in order to determine the anatomic distribution of the electric fields produced by a given electrode montage (for review, see Bikson et al., 2012), and is therefore a relevant tool in experiments geared toward determining the impact of anatomy on current distribution. One experiment had participants perform a verbal 3-back task while receiving anodal stimulation over the left DLPFC (Kim, Kim, Chang, Kim, & Im, 2013). In addition, structural MRI of each participant was used in conjunction with FEM to simulate the current density values at the DLPFC on an individual basis. Results indicate that participants who exhibited increased task performance were also projected to have a significantly greater current density at the targeted DLPFC relative to participants who did not demonstrate task improvement, supporting the notion that individual anatomy can influence current path through the brain which in turn can have a significant impact on behavioral outcome of stimulation. A number of anatomical characteristics have been identified that may be important in determining the current distribution in the brain, as follows.

Thickness of the CSF layer has been found to explain a significant amount of variability in cortical field strength during stimulation. As the medium with the highest conductivity in the brain, a thick layer of CSF can lead to increased shunting of current prior to reaching the cortex thereby attenuating cortical current density; conversely, a thin CSF layer can lead to stimulation hotspots at the cortex (Opitz, Paulus, Will, Antunes, & Thielscher, 2015). Increased CSF thickness is associated with a variety of patient populations for which brain atrophy is typical

(Opitz et al., 2015), as well as in older adults for whom neural degeneration associated with aging may lead to greater distance between the skull and the brain occupied by shunting CSF (Laakso et al., 2015). For these populations, it may be necessary to adjust stimulation parameters in order to deliver cortical current density equitable to effective doses in young, healthy adults.

In addition to the thickness of the CSF layer, skull thickness and composition have been found to be significant predictors of the amount of current that penetrates into the brain. In contrast to the highly conductive CSF layer, the skull is the least conductive medium in the human head and is therefore generally resistive to current penetration (Opitz et al., 2015). Anatomically realistic FEM modeling research, however, presents a more complicated picture than a simple negative linear relationship between skull thickness and current penetration. Spongy bone, which is relatively conductive, is found mainly in the thicker regions of the skull, balancing to some degree increased skull thickness with increased conductivity and sharply reducing the relationship between skull thickness and current penetration to a weak correlation (Opitz et al., 2015). In a similar vein, skull openings and sutures allow for greater penetration of electrical current (Datta, Bikson, & Fregni, 2010; Mekonnen, Salvador, Ruffini, & Miranda, 2012).

This may explain in part why stimulation delivered over certain areas of the skull seems to be particularly effective. For example, the pterion refers to a particularly thin region of the skull at which the frontal, parietal, temporal, and sphenoid bones join together, and as such is the location of three cranial sutures: the sphenoparietal suture joining the sphenoid and parietal bones, the coronal suture joining the frontal bone to the sphenoid and parietal bones, and the squamous suture which joins the temporal, sphenoid, and parietal bones (Kumar, Anurag, Chauhan, Chaudhary, & Jain, 2013). The thin nature of this skull location combined with the presence of three cranial sutures may allow for relatively high current penetration when stimulation is delivered near this area, leading to large behavioral effects (e.g., Clark et al., 2012).

Variability in gyri and sulci patterns between individuals tends to be high (Ono, Kubick, & Abernathy, 1990) which likely contributes to high interindividual response to stimulation (Rademacher, Caviness, Steinmetz, & Galaburda, 1993). This may be due to a variety of factors, including gyral depth, such that less depth is associated with greater current density (Opitz et al., 2015), and neural orientation relative to current direction, such that radial flow of current is thought to particularly impact the soma while tangential current flow appears to predominantly result in polarization at the axon terminal, with tangential current flow dominating in the cortex (Bikson et al., 2004; Rahman et al., 2013). Variability in white matter integrity may also play a role in current distribution. Rosso and colleagues (2014) applied cathodal tDCS over the right inferior frontal gyrus (rIFG) in a bid to increase performance on a picture naming task following stroke. Results indicate performance increase was correlated with white matter tract size and degree of functional connectivity between the right supplementary motor area and the rIFG. This is consistent with FEM research indicating a significant role of white matter integrity in current distribution, though the effect is highly dependent on the electrode montage (Shahid, Wen, & Ahfock, 2014). The role of white matter integrity in current distribution may be particularly critical when stimulation is applied to clinical populations for which white matter integrity is typically compromised, such as participants with schizophrenia (Kubicki et al., 2005) or multiple sclerosis (Kutzelnigg et al., 2005)

Other anatomical characteristics may also play a minor role. For example, relatively resistive subcutaneous head fat may contribute roughly 10 percent of the variability in cortical current density (Truong, Magerowski, Blackburn, Bikson, & Alonso-Alonso, 2013), which is a relatively weak contributor to variance compared to the 1.5- to 3-fold cortical current density variability that exists on the whole for healthy adults (Datta, Truong, Minhas, Parra, & Bikson, 2012). Likewise, scalp temperature may affect shunting of current, such that higher temperatures increase shunting while lower temperatures allow for greater current penetration to the brain (Gholami-Boroujeny, Mekonnen, Batkin, & Bolic, 2015).

In the current study, tracking of anatomical differences was limited to gross metrics such as head size and circumference; characteristics such as skull thickness, CSF density, and topography of the cortical surface were not measured making it impossible to determine to what extent these anatomical factors played a role in stimulation outcome. Future research should attempt to collect these metrics in order to enhance understanding of what particular characteristics are important in obtaining the desired behavioral outcome, and how stimulation may be adjusted in order to account for these individual differences while maintaining the desired result.

#### 4.1.4.5 Task Approach and Practice Effects

Individual differences in neurophysiological activity during task performance can interact with stimulation parameters and produce variability in stimulation outcome (Antal, Terney, Poreisez, & Paulus, 2007). As a result of task practice and experience, the brain may reorganize at a number of levels, ranging from synaptic changes to large-scale neural network alterations (Buonomano & Merzenich, 1998). This reorganization may occur due to increased mastery over time using a previously developed strategy or due to the development of a novel strategy (Jonides, 2004). The most common result of brain activity as a result of practice is a decrease in overall activation, which is thought to be the consequence of enhanced neural efficiency (Kelly

& Garavan, 2005). This increased efficiency may manifest due to winner-take-all network dynamics such that once task mastery is achieved less neurons are active during task performance but due to their increased dominance with regard to inhibiting competing neurons they exhibit a greater signal-to-noise ratio than was present prior to practice (Poldrack & Gabrieli, 2001). Depending on the task and strategy used, however, increased activation may also be associated with mastery, either through expansion of cortical representations (i.e., an increased number of neurons firing during task performance) or an increase in activation strength (i.e., the same number of neurons fire, but at an increased rate relative to novice performance) (Poldrack & Gabrieli, 2001).

Reorganization of functional brain anatomy may be characterized as redistribution or as true reorganization. Redistribution refers to a quantitative increase or decrease in activation within particular brain regions, such that the same regions that were active at the novice level remain active during expert performance, but to a greater or lesser degree. This is thought to be the result of a scaffolding-storage process, in which practice leads to increased automaticity and resultant decreased activity in brain regions associated with generic processes such as attention and cognitive control (the scaffolding falls away), coupled with increased activation in brain regions related to task-specific storage and processing (Petersen, van Mier, Fiez, & Raichle, 1998). Saki and colleagues (1998) have provided experimental support for the concept of redistribution. Participants were asked to learn the correct sequence of button presses in response to 10 target pairs; as task automaticity increased participants exhibited decreased activation in the left DLPFC and presupplementary motor area, as well as increased activity in the precuneus and intraparietal sulcus. The authors interpreted this shift in activity as a transition from declarative processes that require focused attention to automatic procedural processes, a pattern indicative of practice-induced de-emphasis on generic attention and cognitive control coupled with increased activity in brain areas related to task-specific performance. It is worth noting that participants who mastered the task relatively quickly also exhibited a more rapid decline in prefrontal activity relative to slow learners, indicating that greater time to mastery was associated with prolonged use of attentional scaffolding.

True organization, as opposed to redistribution, refers to a change in the brain regions involved in task performance, rather than an adjustment of activity levels within given regions. While redistribution is associated with mastery over a strategy, true reorganization is indicative of a shift in the strategy being used (Bernstein, Scheffers, & Coles, 2002; Glabus et al., 2003). Therefore, in circumstances in which true reorganization occurs, novice task performance is both neurobiologically and cognitively different from expert task performance. Experimental evidence for true reorganization has been provided by research in which participants performed a mirror reading task while undergoing fMRI (Poldrack & Gabrieli, 2001). In between baseline and post-training fMRI sessions, participants practiced the task for two weeks. As a result of practice, brain activation shifted from the dorsal visual stream, involved in visuospatial information and object interaction, to the ventral visual stream, involved in object identification and recognition. This reorganization occurred selectively for participants who ceased mentally transforming mirror-oriented words and began to automatically recognize them (sight-reading), consistent with the idea that reorganization is associated with a shift in strategy rather than mastery over a strategy. It is important to note, however, that there may not be a clear line of demarcation between strategy shift and strategy mastery, as strategy practice begins immediately with the selection of a strategy such that reorganization may be swiftly followed by redistribution as a newly implemented strategy is practiced. Additional factors, such as task domain and complexity, may impact the types of brain changes that occur as a result of practice (Schiltz et al., 2001). For instance, PFC neurons may increase dendritic spine density as a result of practice, while neurons in the parietal and occipital lobes may alter the length of their dendrites instead (Kolb & Gibb, 2002).

As practice and strategy development may result in recruitment of different brain regions, these factors may contribute to variability of response to stimulation. In fact, Jones and Berryhill (2012) have provided evidence for this possibility by demonstrating that stimulation of the right parietal cortex improved task performance, but only for difficult levels of the task and only for individuals with high task performance. The authors suggest that different task strategies and resulting recruitment of brain regions interacted with stimulation characteristics to result in selective improvement. The potential for reorganization or redistribution of brain activity as a result of practice is a particularly salient concern for stimulation protocols that combine stimulation with multiple cognitive training sessions, as stimulation parameters typically remain static throughout training sessions, but brain activity (and therefore interaction with stimulation) may shift (e.g., Jones et al., 2015; Martin et al., 2013). One method that has been effectively utilized in the past is to determine brain activation patterns associated with task mastery, then use stimulation to encourage activity in these regions during training (Clark et al., 2012). Overall, these findings suggest that optimal stimulation outcomes may require knowledge of how brain activation patterns typically shift during the process of task mastery.

In the current study, strategy use was not tracked. As task strategy offers a potential explanation for the improved G*f* task performance observed in the current study by the F4/verbal group, future research should track participant strategy, through strategy use interviews tailored to WM tasks (Dunning & Holmes, 2014), independent physiological measures of strategy, such as eye-tracking (Hayes et al., 2015), and use of tasks that encourage or discourage strategy use by manipulating aspects of the task such as presentation rate or semantic links between stimuli (Dunning & Holmes, 2014).

### 4.1.4.6 Circadian Rhythm

Circadian influences may also play a role in stimulation outcome by influencing cortical excitability. Intracortical inhibition is thought to decrease throughout the day (Lang et al., 2011), while increasing time awake is associated with gradually increasing cortical excitability increases (Huber et al., 2013). These patterns may relate back to hormonal fluctuations. Plasma cortisol concentration is typically highest in the morning, but declines throughout the day, hitting a low point roughly 14 hours after waking and remaining diminished throughout sleep (Ranjit, Young, Raghunathan, & Kaplan, 2005). Elevated levels of cortisol have been found to inhibit neuroplasticity induction in the motor cortex (Sale, Ridding, & Nordstrom, 2008). Conversely, tDCS targeting frontal cortex has been demonstrated to improve declarative memory when administered during sleep, when cortisol levels are typically low, but not when administered during wakefulness (Marshall, Mölle, Hallschmid, & Born, 2004).

It has been suggested that tDCS protocols mimic TMS studies that have historically made efforts to test participants at similar times of day (Li, Uehara, & Hanakawa, 2015). This may be a difficult practice to put into effect for populations such as undergraduate students and clinical populations for whom deficient sleep patterns or abnormal circadian rhythms are common (Anderson et al., 2003; Carney, Edinger, Meyer, Lindman, & Istre, 2006; Ohayon, 1997). In addition, cortisol levels may influenced by factors other than time since waking, such as stressful events (McEwen & Sapolsky, 1995).

It is worth noting that active stimulation alone is not likely to constitute a stressful event. In a study using a frontal anode placement in conjunction with an extracephalic reference electrode, active stimulation did not result in differential arousal relative to sham stimulation as measured by heart rate variability, respiratory rate, blood pressure, and sympatho-vagal balance – at least at a current strength of 1.0 mA (Vandermeeren, Jamart, & Ossemann, 2010). However, bilateral tDCS with the anode over the left PFC has been found to decrease cortisol levels, possibly through top-down modulation of the hypothalamic-pituitary-adrenal axis system (Brunoni et al., 2013). This effect was particularly pronounced when stimulation was paired with viewing images of a negative (as opposed to neutral) valence, suggesting that task conditions may influence cortisol release, which in turn may affect stimulation. Therefore, analysis of cortisol levels prior to and following stimulation may be necessary for an accurate depiction of cortisol circulation, and this may be a particularly relevant metric for studies incorporating tasks that participants may find stressful, such as those utilizing emotional stimuli.

In the current study, participants were college undergraduates run at either a late morning or early afternoon time slot. While this limits the time of day variability with regard to stimulation session, it may be that time since waking rather than time of day is the critical component, given the typical patterns of cortisol fluctuation throughout the day are based on time since waking rather than time of day (Ranjit et al., 2005). For a participant population with well regulated sleep habits, time of day consistency may roughly equate to time since waking since most participants will be on similar sleep schedules. For a participant population with highly variable sleep patterns such as college undergraduates (Carney et al., 2006), however, it may be beneficial to communicate with participants to schedule stimulation sessions that keep time since waking consistent between participants. In the current study, amount of sleep the night preceding stimulation was collected, but it is impossible to tell based on the collected data how long participants had been awake at the time of the stimulation session. Additionally, amount but not quality of sleep was tracked. Future research may therefore benefit by collecting sleep quality data via questionnaires such as the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and by tracking time since waking at the initiation of stimulation.

### *4.1.5 Interactions and Additional Sources of Variability*

There are a number of ways in which the characteristics of stimulation, participants, and tasks may interact – likely many as of yet are undiscovered. For instance, skull thickness and composition may differ by age (Wolf et al., 2003), ethnicity (Adeloye, Kattan, & Silverman, 1975), and gender (Wijnhoud, Franckena, Van Der Lugt, & Koudstaal, 2008). Females may approach tasks with different strategies than males (Reuter-Lorenz et al., 2000), and older adults may use different strategies than younger adults (Speck et al., 2000) resulting in recruitment of different brain regions which may interact with electrode montage. Hormonal influence on cortical excitability may interact with participant lifestyle, as GABA has been found to be higher during the follicular phase relative to the luteal phase of the menstrual cycle, but only in nonsmoking women (Epperson et al., 2005). Additionally, interaction may involve multiple modifiers. For instance, tDCS administered during rest prior to task performance is thought to reduce the efficacy of stimulation (Andrews et al., 2011; Galea & Celnik, 2009). For older adults, however, a meta-analysis suggests a greater benefit of offline stimulation (Summers et al., 2016). This was only true for cognitive tasks – motor tasks still benefitted more from online stimulation. Thus, stimulation timing may interact with both age and task type.

There are a number of potential sources of variability in stimulation outcome that have not been discussed above, either because these sources are not well characterized or because they are not as relevant to the current study. Participant diet is likely to interact with stimulation outcome, as diet may alter cortical excitability in a fashion that interacts with disease state (Bella et al., 2015), sex (Yang et al., 2016), and brain region (Underwood & Thompson, 2016). Participant need for cognition and implicit theories regarding intelligence may influence training and transfer outcomes (Jaeggi et al., 2014). For a host of additional individual differences which may contribute variability, including brain injury, disease state, psychological state, level of attention, task habituation, and more, see Li et al. (2015) as well as Krause and Cohen Kadosh (2014).

The panoply of individual differences that seem to matter in the context of brain stimulation research may explain why, when examined at the individual level, participants seem to be able to be divided into responders and non-responders (López-Alonso, Cheeran, Río-Rodríguez, & Fernández-del-Olmo. 2014; Wiethoff, Hamada, & Rothwell, 2014). In a number of ways, the issues of between- and within-participant variability in the context of brain stimulation research parallel those in the field of cognitive state assessment using physiological sensors. Differences between individuals or within individuals over time may necessitate individualized and repeated calibration of instruments (see Trumbo et al., 2016 for review). Likewise, in order to account for the multitude of modifiers that seem to exist in the realm of brain stimulation it may necessary to collect individual data and tailor a stimulation program on an individual basis in order to achieve precise, desired results.

# 5.0 CONCLUSION

The strong heritability of G*f* (Neisser et al., 1996) has led to its conceptualization as a stable trait resistant to adulthood interventions (Carroll, 1993; Jensen, 1998). Though heritability does not preclude malleability (Dickens & Flynn, 2001), any interventions suggesting alteration of a typically stable construct should be approached skeptically and demand replication and methodological refinement addressing limitations. Prior work pairing 10 stimulation and cognitive training sessions has failed to detect far transfer effects (Jones et al., 2015; Martin et al., 2013; Richmond et al., 2014), making the single-session improvement on a G*f* task in the current study somewhat surprising. Type of training, however, may be more important than the training duration (Karbach & Verhaeghen, 2014). If the particular paradigm here is verified as an effective means of improving WM, the shorter duration of training to achieve benefit, the better – in terms of cost, time investment, and participant attrition (Thompson & Foth, 2005). Therefore, while the current study suggests that tDCS paired with WM task performance may improve both WM and G*f* under particular circumstances, it is necessary that future work addresses the above limitations in order to assess the veridicality of the current findings.

## 6.0 REFERENCES

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