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Effects of Anodal tDCS on Neural Correlates of Cognitive Control in Mild-to-Moderate Traumatic Brain Injury

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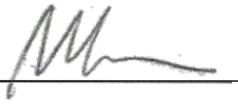

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EFFECTS OF ANODAL tDCS ON NEURAL CORRELATES OF COGNITIVE CONTROL IN MILD-TO-MODERATE TRAUMATIC BRAIN INJURY

BY

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EFFECTS OF ANODAL tDCS ON NEURAL CORRELATES OF COGNITIVE CONTROL IN MILD-TO-MODERATE TRAUMATIC BRAIN INJURY

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ABSTRACT

Traumatic brain injury is a worldwide epidemic and currently there is no successful treatment to combat the cognitive deficits sustained from a mmTBI. The goal of this analysis is to determine if active tDCS paired with cognitive training can aid in an individual's recovery on one specific consequence of mmTBI: cognitive control. To examine this novel treatment on cognitive control, EEG was recorded, and FM-theta activity collected from electrode FCz was analyzed. Three analyses were run to address the hypotheses of the present study: 1. A cluster analysis; 2. A series of repeated-measures ANOVAs; and 3. A series of multiple linear regressions. The results illustrate the heterogeneity of cognitive control in mmTBI. Moreover, the findings demonstrate the potential for near transfer of active tDCS on tasks that activate similar cognitive networks as those used on trained tasks. Finally, the results indicate EEG biomarkers can predict behavioral changes in mmTBI persons.

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INTRODUCTION

Traumatic brain injury (TBI) is a worldwide epidemic that has garnered considerable attention from several health organizations and governments. In the U.S. alone, TBI costs the nation an estimated 17 billion dollars each year in medical costs and lose of productivity (Gerberding & Binder, 2003). Moreover, the consequences of TBI regularly contribute to "premature death, disability, and adverse medical, social, and financial consequences for the injured persons, their families, and society" (Leibson et al., 2011, p. 837). Effective treatments for individuals that have experienced one or more TBIs are, therefore, needed to address the neurological consequences at the individual level. However, no such treatment currently exists.

The goal of this analysis is to determine if transcranial direct current stimulation (tDCS) paired with cognitive training can aid in an individual's recovery on one specific consequence of TBI: cognitive control. The following sections will cover several topics regarding the epidemiology and pathophysiology of TBI, how pathophysiology alterations result in functional dysfunction in cognitive control, and how tDCS can be used as a potential treatment for cognitive control deficits. The section will end with a brief overview of the hypotheses for the current analysis. The results of this analysis will help society better understand the nature of TBI, its impact on the individual, and how we can best treat those affected by it.

TBI in Today's World

Traumatic Brain Injury is a physiological disruption to normal cognitive function as a result of exposure to external forces (Blennow et al., 2016). The severity of TBIs is regularly categorized as mild, moderate, or severe as determined most commonly from a score on the Glasgow Coma Scale (GCS) ranging from 3 to 15, duration of loss of

consciousness, and duration of post-traumatic amnesia (see Table 1; Corrigan et al., 2014; McGuire, Ngwenya, & McCullumsmith, 2019). Mild TBIs (GCS score of 13-15) are the most common with an estimated 81.02% of all reported TBIs being categorized as such (Dewan et al., 2018). Moderate TBIs (GCS score of 9-12) make up approximately 11.04% of all reported cases, while the remain 7.94% are categorized as Severe TBIs (GCS ≤ 9; Dewan et al., 2018).

Table 1. Classification of TBI Severity

Criteria	Severity		
	Mild	Moderate	Severe
Glasgow Coma Scale	13 – 15	9 – 12	< 9
Loss of Consciousness (LOC)	0 – 30 min	> 30 min and < 24 h	> 24 h
Post-traumatic Amnesia	0 – 1 days	> 1 and < 7 days	> 7 days
Structural Neuroimaging	Normal	Normal or abnormal	Normal or abnormal

Duncan, Summers, Perla, Coburn, & Mirsky, 2011

Global reports published over the past decades have identified TBI as a "silent epidemic" with recent statistics on the number of individuals worldwide who have been hospitalized for one or more TBIs ranging from 57-69 million (Dewan et al., 2018; Langlois, Rutland-Brown, & Wald, 2006). Moreover, the World Health Organization (WHO) estimates that each year 10 million people are hospitalized or die due to a TBI (Hyder et al., 2007; Langlois, Rutland-Brown, & Wald, 2006). Importantly, it is projected that TBIs will become a leading cause of death in 2020, surpassing several other neurodegenerative diseases (Hyder et al., 2007).

The causes of TBI vary, but there are general trends that occur within the data. For instance, survey data shows that the majority of TBIs are sustained from falling, motor

vehicle accidents, being struck by or against an object, or some form of violence (Dewan et al., 2018; Hyder et al., 2007; Langlois, Rutland-Brown, & Wald, 2006; Taylor, Bell, Breiding, & Xu, 2017). Demographic characteristics show disparities by sex and age as well. Overall, males have a higher rate of TBI related emergency room visits caused by motor-vehicle accidents and being struck by or against objects, while females show higher prevalence of TBIs caused by falls (Dewan et al., 2018). Additionally, current statistics show that the majority of TBIs caused by falls occur in very young (0-4) and very old (65+) populations, TBIs due to being struck by or against an object occur most frequently in adolescents and young adults (5-24), and TBIs due to motor vehicle accidents most often occur in adulthood (15-44; Dewan et al., 2018). While these data are important, they only concentrate on the acute aspects of the epidemiology of TBI.

Regarding chronic aspects, current analyses estimate that globally between 3.17-5.3 million individuals are currently living with long-term disability caused by one or more TBIs (Langlois et al. 2006; Zaloshinja et al., 2008). Furthermore, a report examining health and social deficits at 5 years post-TBI found that an average of 20.6% of those surveyed had died either directly or indirectly from a TBI, 12.2% had been institutionalized, and 49.7% were re-hospitalized due to complications caused by a TBI (Corrigan et al. 2014). Even more troublesome, of those surveyed an average of 30.1% of individuals required assistance with motor tasks, 36.1% required assistance with cognitive tasks, and 28.8% reported that they were more dissatisfied with life. At 5 years post-injury 56.9% of individuals were unable to resume 50% of preinjury activities. What's more, the cited works acknowledge that the prevalence of TBIs reported are more than likely *underestimates* of the total rates of TBIs both domestically and internationally. These

inaccuracies and miscalculations can be caused by underreporting due to inadequate or incomplete data, lack of recognition of a TBI by individuals, and lack of access to sufficient treatment.

Biomechanisms and Outcomes of TBI

Traumatic brain injuries result from one or more distinct mechanical forces: rotational acceleration forces (the head rotating sideways), linear acceleration forces (the head move in the anterior-posterior direction), or deceleration forces (rapid, forceful deceleration of the head; Blennow et al., 2016). These mechanisms cause insult through physical deformations to brain structures in the local environment as well as diffuse trauma from "inertial effects due to rapid acceleration or increased pressure transients" (Hemphill, Dauth, Yu, Dabiri, & Parker, 2015, p. 1178). These physical deformations and inertial effects cause damage in the acute phase to the microenvironments and functions within the brain such as the cerebrovascular system, metabolism, and populations of neurons. These abrupt physiological alterations then result in diffuse axonal injury (DAI) and overall network dysfunction in the chronic stages of TBI. In the following paragraphs, the primary outcomes in the acute stage will be briefly examined followed by a discussion on DAI in the chronic stage of TBI.

Damage in the Acute Stage. TBI results in diminished cerebrovascular function; the network responsible for supplying blood to the brain. After a TBI weakened blood-brain barrier (BBB) integrity and reduced neurovascular unity (NVU) activation result in decreased elimination of neurotoxins such as amyloid beta, and increased neuroinflammation, which sum to decreased cerebral blood flow (CBF) and impaired neuronal metabolism (Ashley et al., 2018; Kenney et al., 2016). Decreased metabolic

function caused by TBI occurs in two stages. Initially, there is a high demand for adenosine triphosphate (ATP), a molecule identified as the brains primary source of energy (Stovell et al., 2017). Subsequently, as a result of ATP overproduction in sub-acute stages and decreased NVU function, there is a decreased energy supply to the brain even as demand remains high, creating an energy crisis within the brain (Glenn, Sutton, & Hovda 2018; Stovell et al., 2017).

Importantly, the inertia effects from acceleratory forces generate intracranial pressure that elicit shearing and strain forces, which then cause axons to stretch and tear (Blennow et al., 2016). When this damage is multifocal, effecting large numbers of white matter tracts within the brain, it is known as diffuse axonal injury (DAI; Blennow et al., 2016). During the acute stages, there is little to no physical evidence of DAI (Smith et al., 2003). Moreover, DAI in white matter bundles is rather heterogeneous anatomically due to factors such as genetics, age, sex, time since injury, injury severity, and access to treatment (Blennow et al., 2016; McGuire, Ngwenya, & McCullumsmith, 2019). Therefore, the consequences of DAI can only be observed at the microlevel. Current research reports that DAI is one of the most common outcomes of TBI occurring in approximately 40-50% of reported cases (Ashley et al., 2018; Mu et al., 2019; Smith, Meaney, & Shull, 2003; Taber & Hurley, 2007).

DAI results in is an efflux of K+ from neurons and an influx of Ca2+ into the extracellular environment (Glenn, Sutton, & Hovda, 2018). The efflux of K+ triggers a rapid neuronal depolarization and release of excitatory amino acids (EAA) such as glutamate (Glenn, Sutton, & Hovda, 2018). This rapid release of EAA coupled with the increased levels of K+ activate NMDA and AMPA receptors, which then triggers increased

consumption of glucose via ATP in an attempt to restore regular neuronal potentials (Glenn, Sutton, & Hovda, 2018). After this brief period of rapid neuronal depolarization, however, there is an extended period of hyperpolarization, which occurs in days following the initial TBI (Glenn, Sutton, & Hovda, 2018).

Unlike the K+ and the EAAs described above, the influx of Ca2+ into the extracellular environment does not diminish in the chronic stages of injury (Glenn, Sutton, & Hovda, 2018). It is believed that the persistent presence of Ca2+ is a catalyst for neuronal cell death in TBI. Specifically, Ca2+ leads to breakdown of microtubules, neurofilament compaction, and axonal swelling/collapse, which results in excitotoxicity that leads to cell death in affected regions (Blennow et al. 2018; Glenn, Sutton, & Hovda, 2018; McGuire, Ngwenya, & McCullumsmith, 2019). Critically, Ca2+ presence within the axon has been linked to increased amyloid beta (Aβ) peptides and tau proteins around impacted axons (Blennow et al., 2018).

Studies have found Aβ plaques and tau proteins accumulation around axons damaged and have begun to use the presence of these peptides and proteins as early markers of DAI (Blennow et al., 2018; Bulut et al., 2006; Gabbita et al., 2005; Hemphill et al., 2015; Johnson, Stewart, & Smith, 2010; Tomita et al., 2019). When APP accrues around damage axons it is rapidly cleaved into Aβ plaques, which then continue to amass during the chronic stages of a TBI (Blennow et al., 2018). Tau proteins are associated with microtubules in the axons of neurons and it has been hypothesized that upregulation of tau following DAI is an attempt to stabilize the damaged microtubules (Blennow et al., 2018; Bulut et al., 2006). Interestingly, studies have found that decreased glymphatic system activity results in an insufficient clearly of Aβ plaques and tau proteins from the

extracellular axonal environment, which allows Aβ plaques and tau proteins to buildup (Iliff et al., 2014). As a result of Aβ plaques and tau protein aggregation, there is an increase in the upregulation of microglia (another biomarker of DAI in acute stages; Ashley et al., 2018; Mannix & Whalen, 2012). As these microglia shift from a passive to active state, they produce neuroinflammatory cytokine, which result in neuroinflammation, which is another early indicator of DAI (Ashley et al., 2018). Moreover, it has been hypothesized that the increase in cytokines also stimulate the genesis of Aβ plaques (Mannix & Whalen, 2012). Taken together, it is clear that the response to TBI in the acute phase of injury is multifocal, extensive, and complex.

Damage in the Chronic Stage. The damage to the microlevel environment in the acute stage of injury manifests in white matter dysfunction and network connectivity in higher order processes during the chronic phase of injury. In 2007, Kraus and colleagues conducted a diffuse tensor imaging (DTI) study comparing TBI individuals to controls on 13 white matter tracts previously correlated with measures of cognition such as executive function, attention, and memory using fractional anisotropy (FA). It was found that greater levels of white matter dysfunction (represented by lower FA values) were correlated with lower scores of executive, attention, and memory tasks (Kraus et al., 2007). Similarly, Kinnunen et al. (2011) found that disruptions in white matter tracts as a result of TBI were correlated with dysfunction in memory, executive function, and processing speed. Clearly, in the chronic stages of injury, disruptions to microlevel environments lead to population-level neuronal damage resulting in DAI. The extent of damage by DAI to cognitive processes can be investigated through network connectivity and dysfunction. One of the

most disabling consequences of the pathophysiology described about is deficits in cognitive control networks.

Cognitive Control in TBI

Cognitive control, broadly speaking, refers to the dynamic processes within the brain that allow for the pursuit of goal-oriented behavior such as attention, thought, motivation, and action (Cohen, 2017; Gu et al., 2015; Zelazo & Anderson, 2013). A more functional definition is the alteration of neuronal systems to enable a cognitive function to meet changing demands of a task (Gu et al., 2015). Cognitive control is comprised of three theoretical subprocesses (see Figure 1), namely cognitive flexibility, inhibitory control, and working memory (Zelazo & Anderson, 2013). Taken together, these elements of cognitive control acts as theoretical representations of the neuronal processes required to link vital networks for problem solving, selectively retrieve and attend to necessary information, and inhibit undesired responses to stimuli (Gu et al., 2015).

Recently, ample evidence in the field of neuroscience has begun to represent cognitive control through the connectivity of different brain regions to form what are known as brain networks. Utilization of graph theory brain regions are identified as nodes/hubs within a network and are connected via white matter tracts (Pandit et al., 2013). When different nodes spread across different cortical locations show strong "temporally correlated neuronal activity" they are likely to have similar functional properties and are described as intrinsic connectivity networks (ICNs; Sharp et al., 2014). Current trends have classified three networks that play a distinct role in cognitive control: the default mode network (DMN), the salience network (SN), and the cognitive control network (CCN; see Figure 2; Cole & Schneider, 2007; Sharp et al., 2014). The DMN is comprised of the

posterior cingulate cortex (PCC), precuneus, inferior parietal cortex (IPC), and the ventro-medial prefrontal cortex (VMPFC; Zhou et al., 2012). The SN encompasses anterior cingulate cortex (ACC), presupplementary motor area (pre-SMA), and the anterior insular cortex (AIC; Bonnelle et al., 2012). Studies have indicated the dorsolateral prefrontal cortex (DLPFC), and the ACC play major roles in the CCN (Cohen, Botvinick, & Carter, 2000). Additional research has shown that the posterior parietal cortex (PPC), AIC, pre-motor cortex (PMC), and pre-SMA are all also involved in the CCN (Cole, 2017). When functioning normally, the DMN is most active during rest and deactivates as a function of increased task difficulty (Sharp et al., 2014; Zhou et al., 2012). Meanwhile, the SN responds to salient stimuli in the external environment and when rapid changes in behavior

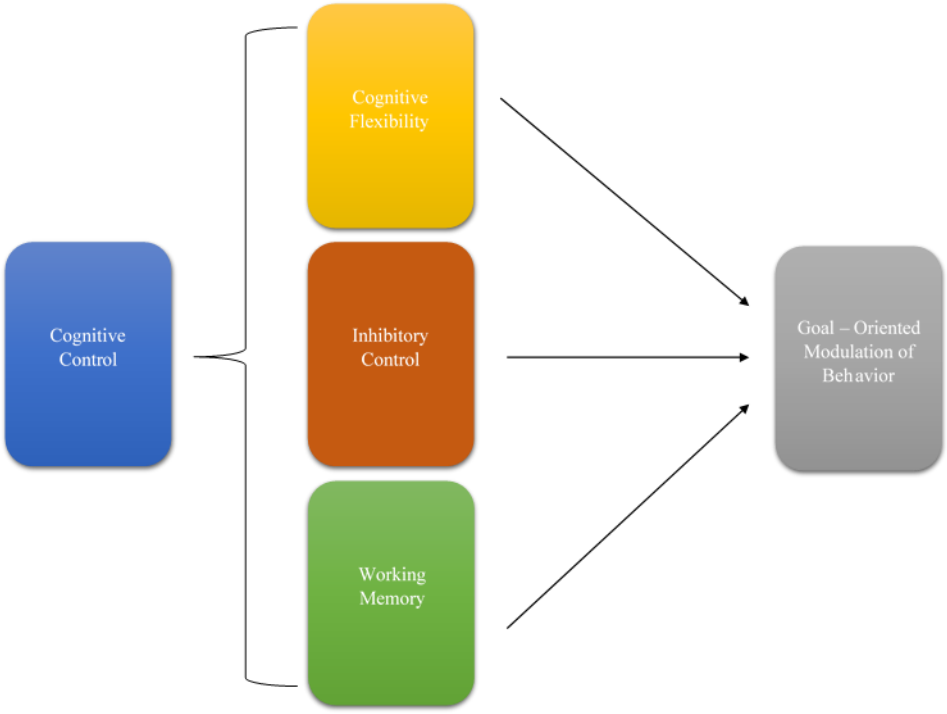

Figure 1. The subprocesses involved in cognitive control that allow for pursuit of goal-oriented behavior.

are required (Bonnelle et al., 2012; Sharp et al., 2014). Lastly, CCN, particularly the ACC and DLPFC, are involved in conflict monitoring/resolution processes and working memory

processes (Cole, 2017). The connectivity of structures within the CCN, DMN, and SN are vital networks whose normal functioning in tandem with one another is responsible for cognitive control.

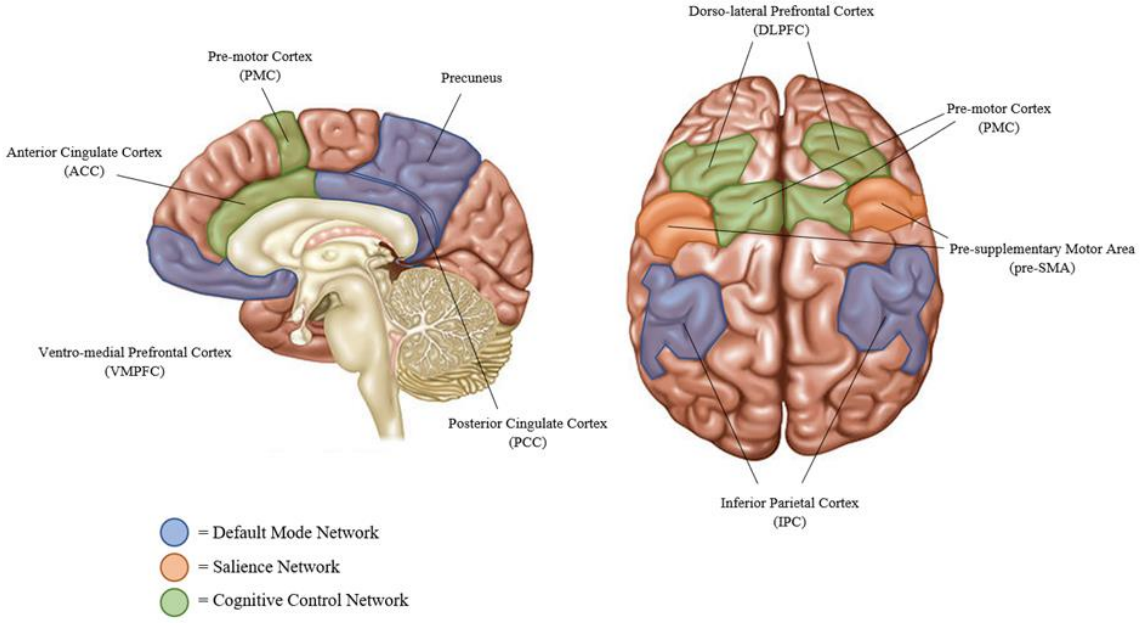

Figure 2. Anatomical regions associated with the Default Mode Network (DMN), Salience Network (SN), and Cognitive Control Network (CCN).

Network Dysfunction in TBI. Each of the networks (or the structures within them) have been implicated as systems disrupted by the chronic effects of DAI caused by TBI. A review by Sharp and colleagues (2014) found that damage to axons in the cingulum bundle, a major pathway for the nodes within the DMN and CCN, resulted in activation of the DMN network even when unexpected external stimuli are presented and change in attention is require. Additionally, Zhou et al. (2012) found decreased connectivity in the PCC and increased activation of the MLPFC in mild TBI individuals compared to controls. Importantly, the increase in activation by the MLPFC and cingulum bundle may reflect a "compensatory increase in cognitive control", meaning the brain is attempting to increase activation to compensate for a lack of cognitive control (Sharp et al., 2014). Bonnelle and

colleagues (2012) discovered similar patterns of increased activation in the DMN after a TBI. It was also found that damage to the SN results in failure to attend to unexpected external stimuli thereby resulting in failure to initiate cognitive control (Bonnelle et al., 2012). The lack of SN activation in tandem with increased DMN activation result in individuals with a TBI experiencing lapses in attention and an increased inability to orient and respond to external stimuli (Bonnelle et al., 2012; Sharp et al., 2014; Zhou et al., 2012). In other words, TBI individuals are lacking in the ability to update their behavior given changes in their environment.

Similar studies have found damage to integral structures and white matter tracts involved in the CCN also result in impairments to cognitive control. Mirroring the findings of Zhou and colleagues, Pandit et al. (2013) discovered a substantial reduction in PCC activation and increased activation in lateral frontal lobe locations. The authors showed that DAI in the corpus collosum and the superior longitudinal fasciculi significantly predicted the decreased network connectivity and efficiency of the network (Pandit et al., 2013). Scheibel et al. (2009) found that DAI in the corpus collosum resulted in increased activation of frontal-midline structures in the PFC during task-related cognitive function, offering support for Sharp and colleagues' theory of compensatory increases in function in the frontal lobe. A study by Turner and colleagues (2011) also found compensatory activation of the lateral PFC after TBI. Taken together, these findings reveal that DAI damage associated with the PFC has been implicated in working memory and planning deficits (Rabinowitz & Levin, 2014).

In summary, cognitive control processes and the networks underlying them are directly impacted by DAI. While there is clear evidence that multifocal damage to white

matter tracts and brain regions involved in cognitive control is a primary consequence of TBI, information regarding the link between physical damage and functional deficits is still lacking.

Utilizing EEG to Understand Cognitive Control in TBI

While ample fMRI and other structural imaging techniques exist and are implemented in the study of TBI, these tests are non-optimal with regard to precise temporal resolution of functional deficits. However, the use of electroencephalography (EEG) as a means for studying the effects of network connectivity during tasks that involve cognitive control networks has become a useful tool for understanding the effects of TBI in the temporal domain.

What is EEG Measuring? EEG, simply put, is measuring the electrochemical system that operates within the brain. At the neuronal level, the brain communicates through an electrochemical system whereby individual neurons experience changes in voltage from an exchange of neurotransmitters between the intracellular and extracellular space (Cohen, 2017; Kirschstein & Köhling, 2009). When this change in voltage manifests as an excitatory potential in postsynaptic extracellular space that is more negative than at other points in the neuron it generates what is known as a dipole (Jackson & Bolger, 2014). While one neuron generating a dipole is hard to detect, when several similarly oriented neurons fire in a synchronous fashion, the resulting dipoles generate a much more apparent signal (Jackson & Bolger, 2014). This signal is what EEG is recording. Specifically, EEG reflects the summed dipoles generated by "dendritic postsynaptic potentials" of pyramidal cells in parallel alignment firing in synchrony (Cohen, 2017; Jackson & Bolger, 2014).

The main benefits of using EEG in any study is the temporal accuracy and the direct

measurement of population-level neuronal activity (Cavanagh 2019; Cohen 2017). EEG records the changes in the summed electrical activity within the brain every one to two milliseconds (Jackson & Bolger, 2014). The temporal precision of EEG allows for its utilization in studies that attempt to answer questions concerning the coding, processing, and transmission of information within the brain (Cohen, 2011). Still, EEG is not without limitations. EEG can only measure population-level neuronal activity and relationships between EEG activity and neuronal mechanisms is at best "few-to-some" (Cohen 2017). In other words, the summed electrical activity observed at any particular electrode will be influenced not only by the neuronal activity on the cortical surface directly below that electrode, it will also be influenced by activity that is occurring with subcortically and from activity in other regions of the cortex (Jackson & Bolger, 2014). However, given these limitations, the literature linking EEG to cognitive processing is rapidly growing and methods of analyzing EEG data have been successful in finding certain correlations between changes in EEG and cognitive processes at the network level (Cohen 2017). In particular, event-related potentials (ERPs) and frontal-midline theta (FM-theta) activity are stable measures of cognitive control network processes. Both are discussed below.

ERPs and Cognitive Control. ERPs are fluctuations in voltage during an ongoing EEG that are time-locked to a stimulus (Kappenman and Luck, 2012). And while all components of an ERP are important, in this particular study, the N2 and P3 amplitude and latency elements of an average ERP waveform will be assessed. Briefly, the N2 is a negative deflection in the ERP waveform that occurs around 200 ms after stimulus onset (Sur & Sinha, 2009). The P3 component is a positive deflection in the ERP waveform that usually occurs 250-500 ms after stimulus onset (Linden, 2005; Sur & Sinha, 2009). The

N2 component, in terms of cognitive control, represents the early processes of conflict monitoring, specifically, response inhibition between competing responses (Rietdijk, Franken, & Thurik, 2014). The general interpretation of the P3 is as a representation of working memory apprising, with the latency component reflecting cognitive processing speed and the amplitude suggesting the amount of cognitive resource allocation or the salience of the stimuli (Hruby & Marsalek, 2003; Sur & Sinha, 2009). Importantly, the N2 and P3 components of the ERP waveform have been identified as reliable measures of cognitive control processes within the brain (Rietdijk, Franken, & Thurik, 2014). Studies have found that increased N2 and P3 amplitudes are correlated with higher task difficulty and complexity and reflect increased cognitive control (Megías et al., 2017; Swainson et al., 2003).

In TBI populations, researchers have found that the amplitudes of N2 and P3 are diminished and the latencies are longer compared to healthy populations (for review, see Duncan et al., 2011). These differences in the N2 and P3 components have been shown to correlate with deficits in cognitive control. Specifically, research has shown that changes in the N2 and P3 components reflect lack of inhibitory control and cognitive flexibility (for review, see Dockree & Robertson, 2011). Considering that N2 and P3 amplitudes increase with task difficulty, TBI individuals showing decreased amplitudes compared to healthy controls provides support for the examination of ERP components when addressing the functionality of cognitive control.

FM-theta Activity and Cognitive Control. One of the most prominent uses of EEG in cognitive control research is the examination of neuronal oscillations. The neuronal activity recorded by EEG is an amalgamation of several different oscillations driven by

rhythmic fluctuations in the excitability of neuronal populations (Cohen 2017). Depending on characteristics such as amplitude, timing, and frequency, oscillations are grouped into several different oscillatory bands (Cohen 2017). While the boundaries of each "distinct" oscillation is somewhat arbitrary, the five main categorizations of neuronal oscillations are the delta band (0.5 – 4 Hz), theta band (4 – 8 Hz), alpha band (8 – 12 Hz), beta band (12 – 30 Hz), and gamma band (> 30 Hz; Buzsáki, 2006). Each of these oscillation categories have been used to understand different cognitive processes occurring within the brain. Moreover, changes in frequencies can be quantified and graphically represented through time-frequency plots of different elements of the signal (see Figure 3). For the present study, the power spectrum and inter-trial phase clustering (ITPC) are interpreted. The power of a frequency signal typically measured in decibels (dB) is merely the amplitude of the signal squared and represents the general level of activation occurring at that frequency. The ITPC of a signal at a given electrode ranges from 0 to 1 and typically "reflects the temporal coordination of cortical processes" (Papenberg et al., 2013, p. 913). For higher order cognitive functions such as memory encoding and retrieval, working memory, and cognitive control, the theta band oscillations, particularly along the frontal mid-line, has been heavily implicated in recent years (Cavanagh and Frank, 2014).

Several studies on the associations between brain activity and cognitive control have supported the major role played by theta band activity in the frontal midline (Cavanagh & Frank, 2014; Gratton, 2018; Knyazev, 2007; Sauseng, Griesmayr, Freunberger, & Klimesch, 2010). And, although there is no definitive answer as to the source of this FM-theta activity, the ACC, mid-cingulate cortex (MCC), and the pre-SMA are some of the prominent structures that elicits FM-theta activity (Cavanagh & Frank,

2014; Onton, Delorme, & Makeig, 2005). These findings support the role of the cingulum bundle and other midline structures are vital for cognitive control. Moreover, within the context of FM-theta and cognitive control high ITPC may reflect the coordination of interactions between distinct brain areas (Papenberg et al., 2013). Still, the precise role of FM-theta in cognitive control is still not entirely clear. Nevertheless, current literature has implicated FM-theta in several cognitive control functions.

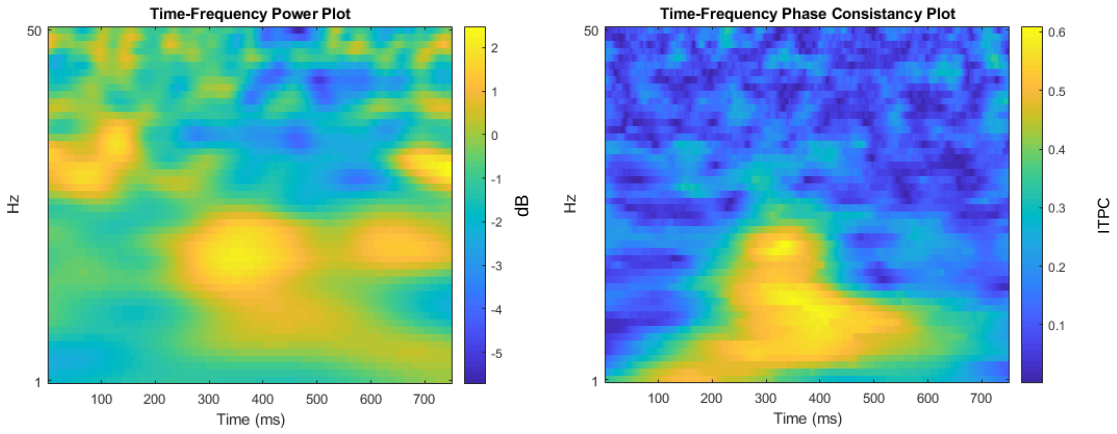

Figure 3. Time-Frequency plots of Power and Inter-trial Phase Consistency for participant 43985.

Jensen and Tesche (2002) found that FM-theta increased as task difficulty increased in a working memory task. Specifically, the authors found that FM-theta plays a prominent role in memory maintenance, which has been implicated as an important component of cognitive control (Jenson & Tesche, 2002). Onton and colleagues (2005) also showed an increase in FM-theta activity as a result of increased cognitive effort needed during a working memory task. Later, Cavanagh and Frank (2014) posited that FM-theta activity reflects activation within the prefrontal cortex (PFC) in response to novel stimuli, working memory, memory encoding and retrieval, and top-bottom realization of cognitive control. They suggest that FM-theta activity occurs as a means of regulating communication between networks when higher cognitive processing is required (Cavanagh & Frank,

2014). Berger et al. (2019) tested this hypothesis and concluded that high frequency oscillations in the parietal lobes spiked at different phases of FM-theta depending on the complexity of the task. Specifically, as the need for cognitive control arose due to greater task complexity, parietal activity shifted from the peak to the trough of the FM-theta wave (Berger et al., 2019). Cohen and Donner (2013) also found that FM-theta activity was strongly correlated with conflict detection and resolution processes when selecting one response over another. Taken together, FM-theta activity has been correlated with several cognitive processes involved in cognitive control, thus, supporting its role as a biomarker.

Interestingly, research into several neurological disorders and TBI has found deficits in cognitive control represented by alterations to EEG, specifically FM-theta activity. Ryman and colleagues (2018) found severely impaired FM-theta activity in patients with schizophrenia compared to controls in a task requiring cognitive control. A similar decrease in FM-theta activity during cognitive control was found in Parkinson patients (Singh, Richardson, Narayanan, & Cavanagh, 2018). Within TBI, research suggests that alterations in FM-theta band synchrony, while variable, are able to predict treatment outcomes for individuals (Cavanagh et al., 2019).

In summary, EEG is useful for effective identification of cognitive control deficits in TBI. Studies have shown a clear link between white matter tracts implicated in cognitive control networks and EEG data, specifically the N2 and P3 components of ERPs, and FM-theta activity. Furthermore, changes in ERPs and FM-theta activity as a result of neurological, neuropsychiatric disorders, and TBI are shown to correlate with cognitive deficits in control processes. Within TBI, examination of ERP components and FM-theta activity as it relates to cognitive control can provide substantial information in attempting

to stem the damage caused by an insult to the brain. And still, to truly combat the consequences of TBI on cognitive control, a safe and effective treatment is needed.

tDCS as a Treatment for Cognitive Control Deficits in TBI

The heterogeneity of TBI has hindered the development of effective treatments in the acute and chronic stages (Blennow et al., 2016). Nevertheless, the use of noninvasive brain stimulation (NIBS) techniques have been seen as a possible treatment for deficits in cognitive control (Sharp et al., 2014).While many forms of noninvasive transcranial stimulation are utilized, transcranial direct current stimulation (tDCS) is one of the most prominent techniques used. In this section, the general methodology of tDCS as well as the advantages and limitations of use will be discussed. Then, a brief overview of the use of tDCS in multiple areas of research concerning general cognitive function and in clinical studies will be provided. Finally, the utilization of tDCS to augment cognitive control in healthy and TBI populations will be examined in detail.

What is tDCS and what does it do? Transcranial direct current stimulation applies a low electrical current of 0.5-2 mA to the scalp that passes through the cortex via two electrodes to modulate neuronal firing (Chase, Boudewyn, Carter, & Phillips, 2019; Imburgio & Orr, 2018). The direction of the tDCS current flow determines whether brain activity is excited or inhibited (Imburgio & Orr, 2018). Specifically, anodal tDCS has been shown to have an excitatory effect on neurons while cathodal tDCS has been shown to have an inhibitory effect (Imburgio & Orr, 2018). While simple in design, the means by which tDCS affects the cognitive processes occurring within the brain is still ambiguous (Chase, Boudewyn, Carter, & Phillips, 2019). Nevertheless, in recent years, researchers have attempted to determine the mechanism of action behind tDCS.

Unlike other forms of NIBS, such as transcranial magnetic stimulation (TMS) that "induce neuronal firing by suprathreshold neuronal membrane depolarization", tDCS modulates the cortical excitability of populations of neurons (Brunoni et al., 2012, p. 177). Instead of directly causing neurons to fire, tDCS has been shown to affect the neuronal oscillatory activity within brain networks (Chase, Boudewyn, Carter, & Phillips, 2019; Liu et al., 2018). As discussed by Dayan and colleagues (2013) the brain is comprised of complex, intertwined networks that communicate "through transient or long-lasting synchronization of oscillatory activity" (Dayan et al., 2013, p. 843). tDCS is able to augment and modulate these neuronal oscillations and cause changes in network level cognitive processes (Chase, Boudewyn, Carter, & Phillips, 2019; Dayan et al., 2013).

There are several advantages to using tDCS as opposed to other forms of NIBS. For instance, tDCS systems are relatively inexpensive, easily portable, and safe to use compared to other stimulation devices (Chase, Boudewyn, Carter, & Phillips, 2019). Additionally, the side effects of tDCS, namely itching, tingling, a slight burning sensation, and headache or dizziness are relatively mild and do not last for a prolonged period of time (Berryhill & Martin, 2018; Chase, Boudewyn, Carter, & Phillips, 2019). These mild sensations allow tDCS to be used simultaneously with cognitive training (Miniussi et al., 2008). Moreover, tDCS by design can cause differing effects depending on the direction of the current flow (Miniussi et al., 2008). Finally, and most importantly, because the mechanism of action of tDCS appears to be modulation of neuronal oscillations, paradigms in which tDCS is paired with EEG allow for the neuronal correlates of behavior outcomes to be isolated (Berryhill & Martin, 2018). Taken together, the low risk involved with using tDCS to augment brain activity has become a focal argument for its popularity among

scientists, the media, and the general public. Still, tDCS does have some disadvantages.

tDCS is not as focal, meaning that the it is difficult to target localized brain regions (Miniussi et al., 2008). Furthermore, the amount of current that makes it through the skin and skull to modulate activity within the brain may be only a fraction of the 2mA applied at the scalp (Vöröslakos et al., 2018). This may be one reason why recent meta-analyses have found that tDCS may not be as effective as once thought (Medina & Cason, 2017; Horvath et al., 2015). Yet, given these limitations, dependable support for tDCS as a modulator of brain activity still exist.

Berryhill and Martin (2018) discovered that the most reliable findings for tDCS as a potential modulator of brain activity were found in studies paradigms that paired multiple sessions of tDCS with cognitive training. Specifically, the authors report that several studies have found improvements in visual and verbal working memory, multitasking, attention, and decision making as a result of cognitive training paired with multiple sessions of tDCS in healthy populations (Berryhill & Martin, 2018). Furthermore, Brunoni and colleagues (2012) indicated that the magnitude and duration of the effects of tDCS in healthy populations increases when the length of stimulation time and the number of sessions also increases. These findings suggest that studies involving multiple sessions of tDCS can result in significant changes to brain activity in healthy populations. As for clinical populations, there remains a lack of abundant research for any single clinical group (Berryhill & Martin, 2018). Nevertheless, within recent decades several studies have been published on the effects of tDCS on an array of cognitive processes in both healthy and clinical populations. One particular example is the use of tDCS for enhancing cognitive control in healthy and TBI populations.

Using tDCS to Augment Cognitive Control. Studies examining the effects of 1-2 mA of anodal active tDCS on elements of cognitive control have found significant behavioral results such as increased accuracy (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Gill, Shah-Basak, & Hamilton, 2015; Javadi & Walsh, 2012; Wiegand, Sommer, Nieratschker, & Plewnia, 2019), decreased decision-making speed and reaction time (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Filmer, Varghese, Hawkins, Mattingley, & Dux, 2016; Gill, Shah-Basak, & Hamilton, 2015; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011), increased proactive control and response inhibition (Boudewyn, Roberts, Mizrak, Ranganath, & Carter, 2019; Hogeveen et al., 2016), and greater ability to update behavior based on shifts in the task (Imburgio & Orr, 2018; Metuki, Sela, & Lavidor, 2012). Importantly, several of these studies found that the effects of tDCS were moderated by the complexity/difficulty of the task participants were trained on during the stimulation (Gill, Shah-Basak, & Hamilton, 2015; Metuki, Sela, & Lavidor, 2012; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Wiegand, Sommer, Nieratschker, & Plewnia, 2019). Clearly, tDCS applied to the DLPFC results in numerous observable changes in cognitive control. But it still remains vital to determine how cognitive control networks are directly impacted by tDCS over the DLPFC through examination of task-related EEG.

Boudewyn and colleagues (2019) found a significant within-subjects change in high-frequency gamma-band activity in the frontal lobe during a dot pattern expectancy (DPX) task when comparing active versus sham tDCS over the left DLPFC. In another study conducted by Miller et al. (2015) increases in FM-theta oscillatory activity, as well as increases in delta and alpha activity, was found in resting state EEG after a single 15-

minute session of 1mA of anodal-tDCS over the left DLPFC. Furthermore, a study by Zaehle and colleagues (2011) also found increases in FM-theta activity in a 2-back task after a single 15-minute session of 1.0mA of anodal-tDCS. Taken together, these studies lend support to the theory that the mechanism of action for tDCS is modulating oscillatory activity within the brain. Particularly, active tDCS stimulation to the DLPFC appears to augment oscillatory activity in cognitive control networks within the frontal lobe.

Using tDCS to Improve Cognitive Control After TBI. tDCS has also been tested as a potential treatment in several clinical populations. Currently, studies have found active tDCS reduces depression and anxiety symptoms in major depression disorder (Kalu, Sexton, Loo, & Ebmeier, 2012), reduces chronic pain and tinnitus, and aids in the recovery from substance abuse (for review see Kuo, Paulus, & Nitsche, 2014). tDCS has also been employed in studies of neurodegenerative disorders such as dementia, Alzheimer's disease, mild cognitive impairment, and aphasia (Pellicciari & Miniussi, 2018). tDCS has also shown to be effective in the regulation of emotion and improved cognitive functioning in patients with schizophrenia (Reinhart, Zhu, Park, & Woodman, 2015).

In recent years, the use of tDCS stimulation has been tested in TBI populations. Kang and colleagues (2012) found immediate but no lasting improvements in attention after a single session of 2mA anodal-tDCS over the left DLPFC. However, Lesniak et al. (2014) found no significant changes in attention or memory after 10 sessions of 1mA anodal-tDCS over the left DLPFC. Additionally, Ulam and colleagues (2015) found increased alpha activity and decreased delta power, which were correlated with improvements in attention and working memory, after 10 sessions of 1mA anodal-tDCS. O'Neil-Pirozzi and colleagues (2017) found that after 2mA of active tDCS P3 amplitudes

increased compared to the sham condition. Clearly, the current literature utilizing tDCS for TBI is somewhat limited. In order to truly comprehend the effects of tDCS in a TBI population more research is necessary. Specifically, there remains a critical need to further understand the effects of tDCS on cognitive control in a chronic TBI population. The pieces of the cognitive puzzle are all there, someone just needs to put them together.

Taken together, this review of literature suggests several key understandings of cognitive control and how it is affected by TBI:

1. TBI is a global epidemic that affects millions of people each year.
2. The cognitive deficits and other consequences of TBI are persist years beyond the initial injury.
3. Damage due to the brain in the acute phase of TBI results in DAI in chronic stages.
4. DAI causes dysfunction in ICNs within the brain leading to decreased cognitive control in TBI individuals.
5. The P3 component of an ERP and FM-theta activity reflects cognitive control processes in the brain and TBI alters ERPs and diminishes FM-theta activity.
6. tDCS as a modulator of cognitive control via neuronal oscillations in healthy populations and its use in clinical populations like TBI has gained sizeable attention in recent decades.

Current Study Hypotheses

Hypothesis 1: Differences in EEG Biomarkers between Controls and mmTBI Individuals. Given the information provided above, it is believed that individuals that have experienced one or more TBI will demonstrate decreased cognitive control ability compared to normal, healthy controls. To test whether or not these differences in cognitive

control ability can be viewed in EEG, the current analysis will begin with determining whether an mmTBI group show significant differences in EEG biomarkers compared to healthy controls. Specifically, the current analysis will examine the N2 and P3 components of ERP waveforms and FM-theta activity.

Examining the differences in the P3 component of an ERP waveform and the FM-theta activity, which have been identified as robust indicators of cognitive control, between a control group and an mmTBI group is critically relevant to determining if tDCS works as a treatment. Consequently, the first hypothesis of the study is that when compared to normal healthy controls, mmTBI individuals will show decreased P3 amplitude, longer P3 latencies, and diminished FM-theta activity.

Hypotheses 2 and 3: Differences in EEG Biomarkers as a Result of Active tDCS. Furthermore, the reviewed literature posits that active tDCS will lead to improvements in cognitive control in a mild-to-moderate TBI (mmTBI) population. Applying anodal-tDCS to the left DLPFC paired with cognitive training in a chronic TBI population may result in increased functional connectivity in cognitive control networks resulting in restored cognitive control. Specifically, it is postulated that application of active tDCS will result in changes to neurophysiological biomarkers of cognitive control present in EEG. In the context of the present study, it is posited that longer P3 latency and diminished P3 amplitudes reflect deficits in cognitive control in an mmTBI sample while completing relevant tasks. Therefore, the second hypothesis is that those individuals that receive active tDCS stimulation will have decreased P3 latencies and increased P3 amplitude compared to baseline measures and those that individuals that received sham tDCS.

Another prospective change due to active tDCS in a biomarker of cognitive control

is FM-theta activity. FM-theta oscillations have already been deemed as an marker of cognitive control in the frontal lobes and diminished FM-theta activity in a number of clinical populations correlates with reduced cognitive control. Thus, the third hypothesis is that active tDCS stimulation will result in increased FM-theta activity compared to baseline and those that received sham tDCS.

Hypothesis 4: EEG Biomarkers as Predictors of Treatment Outcomes. In addition to examining changes in EEG biomarkers, the current analysis is concerned with the potential of these biomarkers to establish a means for predicting treatment outcomes in mmTBI populations. Individual differences in brain activity have come to be recognized as a resilient limitation of TBI treatments (Blennow et al., 2016). For instance, a person with adequate P3 amplitudes and FM-theta activity may not respond to active tDCS whereas a person will low P3 amplitudes and FM-theta activity may respond very well. Without taking the heterogeneous nature of individuals, especially those that have endured a TBI, a robust treatment protocol may not be developed. Therefore, the final hypothesis of the study is that individual differences in EEG biomarkers (i.e. N2, P3, and FM-theta) will result in different treatment outcomes. Specifically, those individuals with relatively normal N2 and P3 components as well as adequate FM-theta activity will see little to no benefit of active tDCS and cognitive training. Meanwhile, individuals with relatively abnormal/diminished N2 and P3 components and reduced FM-theta activity will see greater positive effects of active tDCS and cognitive training.

METHODS

Participants

Thirty-nine participants with mmTBI were recruited through contacts with local brain injury organizations, flyers, and searches of the University of New Mexico medical records. Six participants either withdrew from the study or were excluded before completion of the protocol. Data from thirty-three participants will be analyzed. Table 2 provides a summary of the demographics of the participants. The average age of the participants was 33.6 (SD = 12.5). The average years of education was 15.0 (SD = 2.65). Twenty-three individuals were classified as having mild TBI and ten were classified as having moderate TBI. The average time since injury was 5.45 (SD = 3.71) years.

Additionally, a control group consisting of thirty-two individuals collected from a study utilizing a subset of tasks completed by the TBI group was included for the first analysis of the present study. The control and TBI groups were relatively matched on age and years of education (see Table 2).

Table 2. Descriptive Statistics for Demographic Variables for Control and TBI samples

	TBI			Control		
	N	*Mean*	*Std. Dev.*	N	*Mean*	*Std. Dev.*
Age	33	33.6	12.5	32	29.6	10.6
Years of Education	33	15.0	2.65	32	14.8	2.70
Time Since Injury	33	5.45	3.71	-	-	-

Inclusion/Exclusion Criteria

Participants were all between 18 and 55 years of age, fluent in English, and had sustained a TBI within 3 months to 15 years prior to their enrollment in the study. Participants were classified as mild TBI had a Glasgow Coma Scale (GCS) score between

13 and 15, experienced a loss of consciousness less than 30 minutes, and less than 24 hours of post-traumatic amnesia. Participants were classified as moderate TBI had a GCS score of 9 to 12, experienced a loss of consciousness between 30 minutes and 24 hours, and had post-traumatic amnesia lasting between 24 hours and 7 days. All participants were recognized to have at least 1 cognitive symptom on the Neurobehavioral Symptom Inventory. Participants were excluded from participating for any history of seizures, psychosis, neurological disease, or substance/alcohol dependence. Additionally, participants were also excluded for recent medical instability, recent changes in psychotropic medications, pregnancy, presence of implanted electrical devices, and discontinuity in skull conductivity.

Study Procedure

Participants were initially screened over the phone to determine their eligibility for the study. Participants deemed eligible participants were recruited for a 14-day protocol (see Figure 4). Participants completed two days of pre-treatment neuropsychological testing (described below) followed by ten days of either active or sham tDCS coupled with cognitive training. Finally, participants completed the same neuropsychological testing post-treatment.

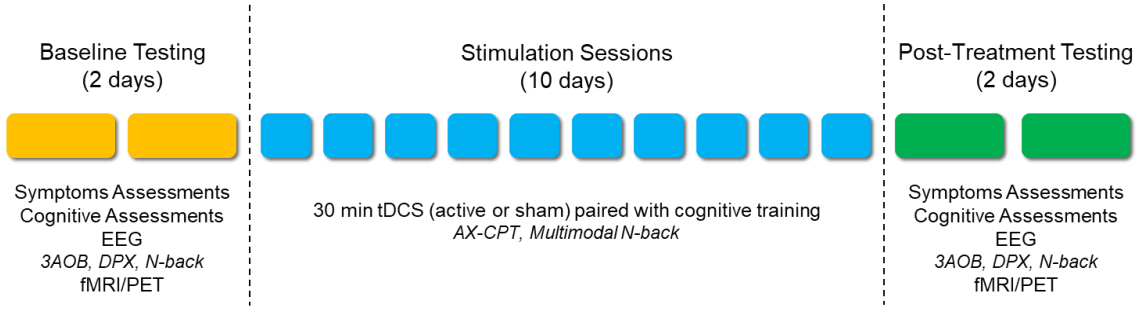

Figure 4. Study timeline for mmTBI participants.

Baseline and Post-Treatment Testing. After providing written consent to participate, subjects completed a series of symptoms assessments including the Neurobehavioral Symptom Inventory (NSI; King et al., 2012); the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960); the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996); the Posttraumatic Stress Disorder Checklist-Civilian version (PCL-C; Weathers et al., 2013); the Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29; Cella et al., 2010); the Glasgow Outcome Scale-Extended (GOS-E; Jennett, Snoek, Bond, & Brooks, 1981); and the Frontal Systems Behavior Scale (FrSBe; Grace, 2011). Furthermore, participants also completed several cognitive assessments including the NIH Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER) battery (Kramer et al., 2014), and a neuropsychological battery that included the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV): Digit Span and Coding subtests (Wechsler, 2008) and the Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt & Benedict, 2001). Participants also completed the Test of Memory Malingering (TOMM; Tombaugh, 1996) and the Test of Premorbid Functioning (PsychCorp, 2009) at the pre-treatment testing only.

EEG and Cognitive Control Assessment. In addition to the assessments described above, participants also completed three tasks used to measure cognitive control while EEG was recorded concurrently. EEG was recorded continuously on a 64 channel Brain Vision system from sintered Ag/AgCl electrodes across .1 to 100 Hz with a sampling rate of 500 Hz, an online CPz reference, and a ground at AFz. The vertical electrooculogram (VEOG) was recorded from bipolar auxiliary inputs. Participants completed an auditory oddball task, a variant of the AX Continuous Performance Task (AX-CPT; see McDonald,

Flashman, and Saykin 2002) known as the dot pattern expectancy (DPX) task, and an n-back task.

In the 3-auditory oddball task, three different types of sounds were presented over stereo speakers. Participants were instructed to attend to and count the number of "targets" (i.e. high-toned sounds) while ignoring "standards" (i.e. low-toned sounds). Moreover, participants also had to ignore "novels", which were random sounds such as a dog barking or people laughing. Participants completed two blocks of 100 trials. The targets and novel stimuli each occur in 15 of all trials completed while the standard sounds occur in the remaining 70 of the trials. Each stimulus was presented for 50 ms followed by a randomized inter-stimulus interval between 100 to 150 ms. The order of stimulus presentation was randomly generated for each block of the task. This task was administered using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997; Kleiner et al, 2007) extension in MATLAB (R2015b).

In the DPX task participants are presented with a cue stimulus (a combination of dots in either an "A" or "B" format) followed by a brief delay and probe stimulation (a combination of dots in either an "X" or "Y" format; see Figure 5).

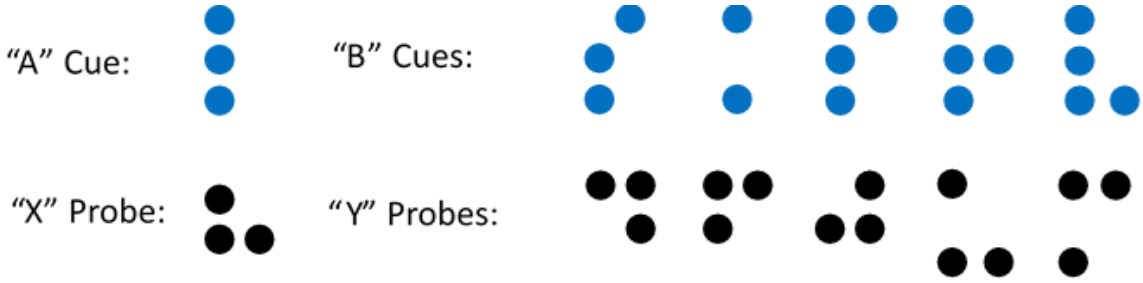

Figure 5. Dot patterns associated with letter assignments in the DPX task.

Each of the cue-probe pairs had a unique probability of occurrence and required participant to response in different ways depending on the pair. The A-X combination occurred for 70% of the trials and required a left button press followed by a right button press. The A-Y combination occurred in 12.5% of the trials and required a left button press followed by another left button press. These two combinations create a habituation to responding (the A-X combination) and a reactive cognitive control to force a change to the formed habit (the A-Y combination). The B-X combination also occurred in 12.5% of the trials and required the same combination of presses for the A-Y combination: a left button press followed by another left button press. Lastly, the B-Y combination occurred in 5% of the trials and required the same response sequence as the B-X condition. These two combinations are meant to represent a proactive cognitive control since a left button press is required for all probes following the B cues. Participant's completed five blocks of 50 trials within each block (see Cavanagh et al. 2019 for a full description of the task). This task was administered using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997; Kleiner et al, 2007) extension in MATLAB (R2015b).

In the n-back task participants were presented a series of letters one at a time on a screen. Participants were asked to match the letter being shown on screen to the letter shown *n* letters before it (see Figure 6). This task consisted of three blocks, each with increasing working memory load. In the 1-back variant of the task participants are instructed to indicate via a button press when the current letter on the screen matched the letter presented immediately before it. In the 2-back and 3-back conditions participants were told to indicate when the letter currently on the screen matched the letter presented 2 and 3 instances, respectively, prior to it. Participant's completed one block of 190 total

trials for each n-back condition. Of the 190 trials per block, 50 trials are targets, wherein the participant should respond with a button press, and 140 are distractors and should be ignored by the participant. Each letter in the sequence was presented for 500 ms followed by a 1400 ms inter-stimulus interval. This task was administered using Presentation® software (Version 14.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

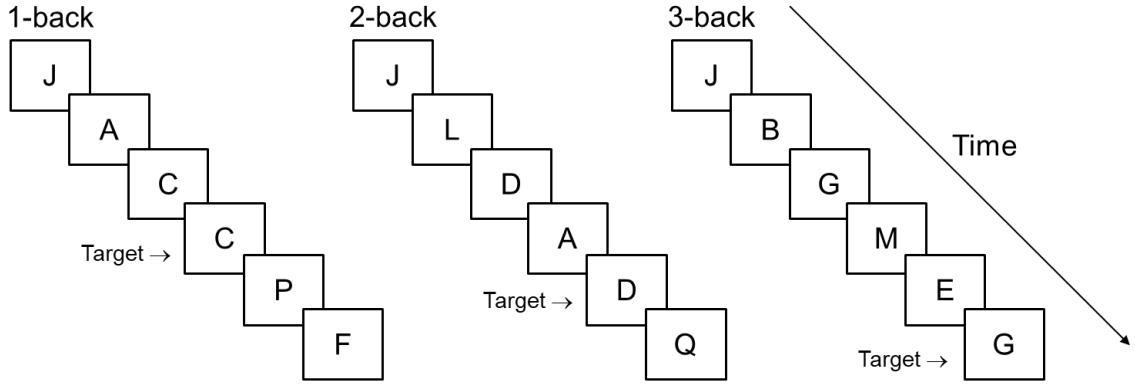

Figure 6. The n-back task. Target letters are those that are the same as the letter that appeared *n* instances before it, where *n* is the number associated with the condition.

tDCS Protocol. Participants were randomly placed into either active (n = 16) or sham (n = 17) tDCS groups. tDCS sessions consisted of 30 minutes of stimulation paired with cognitive training for 10 consecutive weekdays. A NeuroConn tDCS device (neuroCare Group GmbH, Munich, Germany) was used to administer tDCS. The anodal electrode was placed on the left dorsolateral prefrontal cortex (DLPFC; F3 position, International 10-20 system) and the cathode was placed extracranially on the right upper arm. Current for the active condition was applied at 2.0 mA for a total delivered charge of 60 mA-min and a current density of 0.08 mA/cm^2. Stimulation current was ramped up over 1 minute at initiation, maintained for 30 minutes, and ramped down over 1 minute at termination. Sham stimulation was delivered with an initial ramping up of current to 2.0

mA for 1 min, then ramping down and remaining at 0.02 mA for the duration of the session.

All participants completed 10 minutes of the AX-CPT and 20 minutes of a multimodal (visual and auditory) n-back task while receiving either active or sham stimulation. In the dual n-back task participants were presented with sequences of visual (squares appearing in different places on a grid) and auditory (spoken numbers) stimuli simultaneously. In the 1-back condition, participants were instructed to respond with a button press when either one of the stimuli matched the stimuli presented one immediately before it or when both stimuli matched the stimuli presented one immediately before it. Task difficulty increased in the 2-back condition when participants had to determine whether stimuli matched the ones that came two instances before it.

Data Analysis

EEG Processing. The EEG data was first preprocessed in MATLAB (R2018b) using EEGlab (Version 14_1_2b; Delorme and Makeig, 2004). Data for each task were high-pass filtered at 0.1 Hz and epoched around stimulus onset. Activity at the reference electrode, CPz, was re-created via referencing. Temporal sites, VEOG, and EKG channels were removed, leaving 60 electrode sites. Bad channels and bad epochs were identified, interpolated and rejected using the FASTER algorithm (Nolan, Whelan, and Reilly, 2010) and the pop_rejchan function from EEGlab (Delorme and Makeig, 2004). Data was then re-referenced, and an independent components analysis was run in EEGlab to remove the eye blinks from the data.

ERPs were collected by taking the epoched EEG data and applying a low-pass filter at 20 Hz and a high-pass filter at 0.1 Hz. The data was then baseline corrected for normalization and the averaged across similar trials to construct an average ERP for each

session of each participant. For the purposes of the analysis, scalar values for the P3 and N2 amplitudes and latencies were determined by finding the position of the maximum positive value of the ERP between 300 and 500 ms and the position of the maximum negative value of the ERP between 150 and 300 ms, respectively. These time windows were determined from previous literature and visual examination of the averaged ERPs for all subjects.

Time-frequency components were obtained by computing the fast Fourier transformed (FFT) power spectrum of each individual EEG trial and multiplying it by the FFT power spectrum of a set of 50 complex Morlet wavelets (defined as a Gaussian-windowed complex sine wave). The frequencies of the Morlet wavelets increased logarithmically between 1 and 50 Hz and the width of each frequency increased from $3/(2\pi f)$ to $10/(2\pi f)$ with every increase in frequency. Time series was then recovered by taking the inverse FFT of the signal generated by multiplying the original signal by the Morlet wavelets; this process is identical to time-domain wavelet convolution. Estimates of the instantaneous power of the signal as well as the phase angle of the signal were obtained. Averaged power was normalized by conversion to a decibel scale from a common averaged baseline of -300 to -200 ms prior to stimulus onset. Inter-trial phase clustering (ITPC) was quantified as the length of the average of all unit-length vectors distributed along a unit circle according to differences in the phase angle of the signal for each individual trial for a specific condition (see Cavanagh et al. 2019 for a full description of the process). Only time-frequency data from theta-band activity of the signal in electrode FCz will be used in the current analyses. Scalar values for the FM-theta activity were obtained by averaging the power and ITPC values between 4-8 Hz between 300-500 ms.

Analysis. Data was managed and manipulated in R version 3.6.2 (R Core Team, 2019). Analyses were conducted in R version 3.6.2 (R Core Team, 2019) and Jamovi version 1.1.9.0 (The Jamovi project, 2020). To begin, an unsupervised k-means cluster analysis was run on a set of EEG data containing control participants from another study and mmTBI subjects from the present. In general, the unsupervised approach of data analysis attempts to find an underlying structure of the given data (James, Witten, Hastie, & Tibshirani, 2013). Within cluster analysis, the differences between groups should be quite distinct while differences within groups should be relatively small (James, Witten, Hastie, & Tibshirani, 2013). The goal of this analysis in the context of the present study is to identify groups whose cognitive control features show similar patterns. It is anticipated that these groups will classify controls and mmTBI individuals into two distinct groups based on their EEG characteristics. Thus, this component of the analysis addresses the first hypothesis that differences in EEG biomarkers exist between controls and mmTBI persons.

To ease the interpretation and reduce the possibility of overfitting with a small sample size, the cluster analysis will be run on a limited set of twelve variables associated with cognitive control. These twelve measures include the average theta power, average ITPC, and the four elements of the averaged ERP components (P3 amplitude, P3 latency, N2 amplitude, and N2 latency) for the "A" and "B" cues from the DPX task. Variables were standardized o adjust for magnitude differences. Normalized Euclidean distances were used to calculate interindividual similarities to allow clusters to reflect grouping based on similar patterns in activation. K-means clustering was conducted using the kmeans function and the factoextra package (Kassambara and Mundt, 2020) in R. Centroids for initial clusters were randomly generated 100 times and redefined with each iteration. The

number of clusters was determined a priori to theoretically represent the two distinct groups of data: the control group and the mmTBI group. Furthermore, cluster validation was determined using Silhouette width, Hopkins statistic, and the Dunn index.

Next, a series of repeated-measures ANOVA were used to determine if EEG components were significantly different from baseline to post-treatment testing and whether receiving active tDCS resulted in significant differences compared to sham tDCS. The within-subjects factor was Session (i.e. Pre-Treatment v. Post-Treatment) and the between-subjects factor was Condition (i.e. Active v. Sham). Additionally, for the n-back task another within-subjects factor of n-back level (i.e. 1-back v. 2-back v. 3-back) was also included. Complex planned contrasts between the levels of the n-back will also be included to account for the changes in task difficulty. ANOVA assumptions for homogeneity of variance and sphericity were tested.

Each of the following EEG components was tested for the 3AOB, DPX, and n-back tasks: average FM-Theta power, average FM-Theta ITPC, P3 amplitude, P3 latency, N2 amplitude, and N2 latency. All analyses for the 3AOB and n-back tasks were limited to correct response trials. In other words, the 3AOB analysis will examine changes in the EEG components for trials identified by the target stimulus. The n-back analysis will examine the changes in EEG components for the trials identified by a hit response to a target stimulus. Furthermore, the DPX analysis will only examine changes in the changes in EEG components for trials identified by either an A or B cue stimulus. This is due to a lack of data for the probe conditions; roughly 80% of participant data was missing for the probe conditions. Only results with significant main effects of Condition and Session or interactions between Condition and Session are discussed.

Finally, using a multiple linear regression framework, neurophysiological biomarkers in EEG, specifically the FM-theta oscillatory activity (power and ITPC) were used as predictors in determining response to treatment, which will be represented by changes in accuracy (computed by taking the total number of accurate responses and dividing by the total number of events where accurate responses could occur) for the n-back task and changes in the reaction time on the n-back and DPX tasks. Tests were not run on the 3AOB as behavioral measures were not actively recorded during testing. To begin, repeated-measures ANOVAs were run to determine if there was a significant change in the behavioral measures between baseline and post-treatment testing, and whether there was significant difference between active and sham tDCS groups. Next, in a series of sequential regressions, nested models were fit to the data. The first model contained control variables such as Age, Years of Education, and Time Since Injury. The second model added the EEG biomarkers, namely Average FM-theta Power (dB) and Average FM-theta ITPC, as additional predictors. For these EEG biomarkers, an average of each measure was computed for baseline testing and then mean-centered to reduce possible collinearity in the final analysis. Assumptions of homogeneity of variance, linearity, independence, and normality were tested. Finally, the best model that fits the data was determined using the Akaike Information Criteria (AIC). AIC is a measure of model fit by computing the loglikelihood of the overall model fit while introducing a penalty for the number of parameters in the model. A lower AIC value indicates a better fitting model.

As a final note, it must be observed that the sample size for the current study is relatively small ($n = 33$) and there are participant's with missing data for certain variables used in the analysis. As such, this may affect the current analyses in some ways. For

instance, with a relatively small sample size comes decreased power. Additionally, small changes between groups may not exceed the critical value required for statistically significant results. However, this does not necessarily indicate whether there is a true significant result. As such, the current study will also focus on measures of effect size to enhance the overall conversation on the analyses taking place.

RESULTS

Cluster Analysis to Distinguish mmTBI from Control

All fit measures indicated that a two-cluster solution fit best to the data (see Figure 7). The clustering solution defined two distinct groups, one with 17 members and another with 50 members. Table 3 presents the cluster means of the variables used to define the cluster solution. Although standardized values were used for the calculation of the cluster analysis, the means shown in Table 3 reflect the unstandardized means for the groups. Examination of the differences in group means led to the assignment of labels for each group. Group 1 is described as the "High Activation" group while Group 2 represents the "Low Activation" group. Importantly, however, the groups defined by the cluster analysis do not partition the overall sample into groups that align with membership in a control or mmTBI group. Table 4 shows which members of the control and mmTBI groups were classified in high activation group and the low activation group.

Repeated-Measures ANOVA of EEG Biomarkers

Table 5 shows the changes in EEG components from baseline to post-treatment, and the differences between active and sham tDCS conditions. Assumptions of homogeneity of variance and sphericity were not violated for all models. There was a significant main effect of Session for the Average FM-Theta Power ($F(1,28) = 4.88, p = 0.036, \eta_p^2 = 0.148$) and P3 Amplitude ($F(1,28) = 6.79, p = 0.014, \eta_p^2 = 0.195$) in the 3AOB task. Post-hoc t-test with Bonferroni's correction for multiple comparisons revealed that compared to baseline testing, the mean of participant's average FM-theta power decreased by 0.533 decibels (dB; $t(28) = 2.21, p_{bonferroni} = 0.036$). A similar trend was seen with changes in P3 amplitude; compared to baseline testing, the mean of participant's

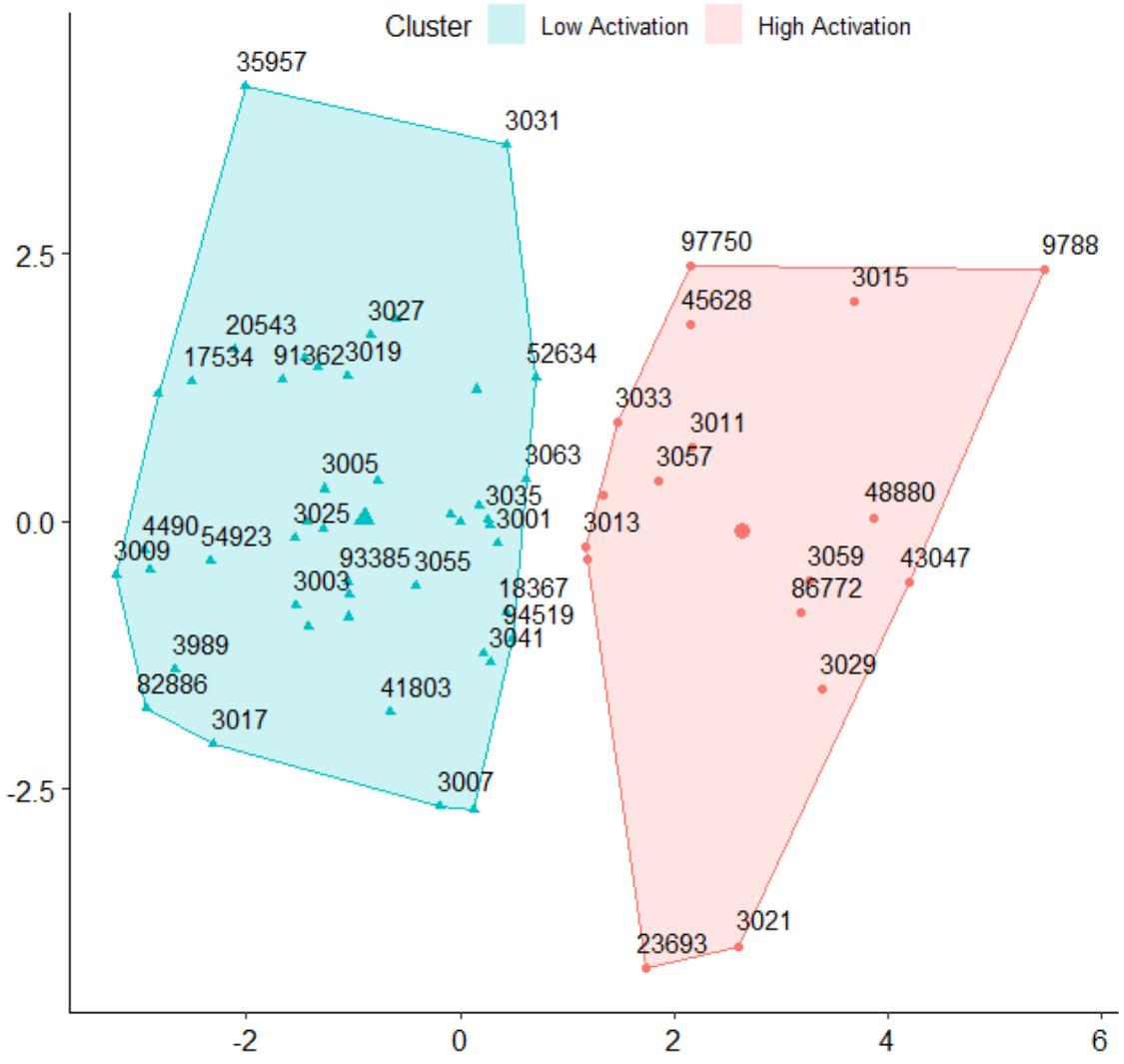

Figure 7. Graph of clusters for a k-means two-cluster solution.

P3 amplitude decreased by 0.949 millivolts (μV; $t(28) = 2.61, p_{bonferroni} = 0.014$). However, upon further examination of the marginal means it appears that this particular result is driven by a significant difference in P3 amplitudes among the active and sham tDCS groups at baseline followed by a minimal difference between the groups at post-testing (see Figure 8a). Therefore, the P3 amplitude result will not be discussed further.

Table 3. Cluster Differences on EEG Cognitive Control Components

	Cluster Means (raw scores)	
	Group 1 ($n = 17$)	Group 2 ($n = 50$)
DPX "A" Cue		
Average FM-Theta Power	2.54	0.73
Average FM-Theta ITPC	0.46	0.27
P3 Amplitude	4.67	3.35
P3 Latency	350.24	363.32
N2 Amplitude	-1.83	-1.38
N2 Latency	270.41	235.48
DPX "B" Cue		
Average FM-Theta Power	3.17	1.10
Average FM-Theta ITPC	0.47	0.29
P3 Amplitude	6.04	3.69
P3 Latency	378.65	380.39
N2 Amplitude	-1.32	-1.51
N2 Latency	267.29	224.32

Table 4. Classification of Control and mmTBI into Clusters

	Group 1	Group 2
Control	9	22
mmTBI	8	27
Total	17	50

Moreover, there was a significant Session by Condition interaction for the N2 amplitude ($F(1,28) = 4.24, p = 0.049, \eta_p^2 = 0.131$) in the 3AOB task. Post-hoc t-tests using Bonferroni's correction for multiple comparisons, however, revealed no significant

differences present between any groups and any timepoints. Upon closer investigation of the marginal means it is clear that the same baseline group differences followed by minimal difference between groups in pos-testing were responsible for the significant interaction within this analysis (see Figure 8a). Thus, this result as well will not be discussed further.

There was a significant Session by Condition interaction for the P3 amplitude ($F(1,28) = 9.87, p = 0.004, \eta_p^2 = 0.261$) and N2 latency ($F(1,28) = 4.67, p = 0.039, \eta_p^2 = 0.143$) for the "A" Probe in the DPX task. Post-hoc t-tests using Bonferroni's correction found that for the significant interaction seen in the P3 amplitude there was a significant increase in the active tDCS group after treatment ($t(28) = 3.803, p_{bonferroni} = 0.004$). Additionally, the active tDCS group showed significantly higher P3 amplitudes compared to the sham group at post-treatment ($t(28) = 2.840, p_{bonferroni} = 0.045$). Post-hoc t-test with Bonferroni's correction revealed that for the significant interaction seen in the N2 latency, the effect was driven by a significant decrease in N2 latency for the active tDCS group at post-treatment when compared to baseline ($t(28) = 3.810, p_{bonferroni} = 0.004$).

In addition to the results above, there was a main significant effect of Condition on the P3 latency ($F(1,28) = 5.03, p = 0.033, \eta_p^2 = 0.152$) in the DPX "B" Cue condition. Post-hoc t-test with Bonferroni's correction for multiple comparisons shows that the sham tDCS had a less delayed P3 latency compared to the active tDCS group ($t(28) = -2.24, p_{bonferroni} = 0.033$). However, further examination of the marginal means revealed that the differences in P3 latency were present at baseline and remained present at post-treatment, calling the true significance of this result into question (see Figure 8c). With this consideration in mind, this result will not be discussed further.

Table 5. Statistical values for repeated-measures ANOVAs of EEG components of Cognitive Control

	Main Effect of Session	Main Effect of Condition	Session * Condition Interaction
3AOB			
Average FM-Theta Power	$\boldsymbol{F(1,28) = 4.88, p = 0.036, \eta_p^2 = 0.148}$	$F(1,28) = 0.13, p = 0.726, \eta_p^2 = 0.004$	$F(1,28) = 1.45, p = 0.239, \eta_p^2 = 0.049$
Average FM-Theta ITPC	$F(1,28) = 0.16, p = 0.691, \eta_p^2 = 0.006$	$F(1,28) = 0.78, p = 0.383, \eta_p^2 = 0.027$	$F(1,28) = 2.11, p = 0.158, \eta_p^2 = 0.070$
P3 Amplitude	$\boldsymbol{F(1,28) = 6.79, p = 0.014, \eta_p^2 = 0.195}$	$F(1,28) = 0.935, p = 0.342, \eta_p^2 = 0.032$	$F(1,28) = 2.28, p = 0.142, \eta_p^2 = 0.075$
P3 Latency	$F(1,28) = 0.49, p = 0.490, \eta_p^2 = 0.017$	$F(1,28) = 0.80, p = 0.377, \eta_p^2 = 0.028$	$F(1,28) = 0.41, p = 0.529, \eta_p^2 = 0.014$
N2 Amplitude	$F(1,28) = 1.94, p = 0.174, \eta_p^2 = 0.065$	$F(1,28) = 0.24, p = 0.626, \eta_p^2 = 0.009$	$\boldsymbol{F(1,28) = 4.24, p = 0.049, \eta_p^2 = 0.131}$
N2 Latency	$F(1,28) = 0.05, p = 0.821, \eta_p^2 = 0.002$	$F(1,28) = 0.23, p = 0.635, \eta_p^2 = 0.008$	$F(1,28) = 1.12, p = 0.298, \eta_p^2 = 0.039$
DPX "A" Probe			
Average FM-Theta Power	$F(1,28) = 2.16, p = 0.153, \eta_p^2 = 0.072$	$F(1,28) = 0.373, p = 0.546, \eta_p^2 = 0.013$	$F(1,28) = 0.07, p = 0.798, \eta_p^2 = 0.002$
Average FM-Theta ITPC	$F(1,28) = 0.468, p = 0.500, \eta_p^2 = 0.016$	$F(1,28) = 0.16, p = 0.693, \eta_p^2 = 0.006$	$F(1,28) = 0.63, p = 0.434, \eta_p^2 = 0.022$
P3 Amplitude	$\boldsymbol{F(1,28) = 5.01, p = 0.033, \eta_p^2 = 0.152}$	$F(1,28) = 3.84, p = 0.060, \eta_p^2 = 0.121$	$\boldsymbol{F(1,28) = 9.87, p = 0.004, \eta_p^2 = 0.261}$
P3 Latency	$F(1,28) = 0.20, p = 0.656, \eta_p^2 = 0.007$	$F(1,28) = 1.00, p = 0.325, \eta_p^2 = 0.035$	$F(1,28) = 0.80, p = 0.378, \eta_p^2 = 0.028$
N2 Amplitude	$F(1,28) = 0.85, p = 0.366, \eta_p^2 = 0.029$	$F(1,28) = 0.14, p = 0.710, \eta_p^2 = 0.005$	$F(1,28) = 0.00, p = 0.952, \eta_p^2 = 0.000$
N2 Latency	$\boldsymbol{F(1,28) = 10.42, p = 0.003, \eta_p^2 = 0.271}$	$F(1,28) = 0.10, p = 0.758, \eta_p^2 = 0.003$	$\boldsymbol{F(1,28) = 4.67, p = 0.039, \eta_p^2 = 0.143}$

Note. Type 3 Sums of Squares.

Table 5 continued. Statistical values for repeated-measures ANOVAs of EEG components of Cognitive Control

	Main Effect of Session	Main Effect of Condition	Session * Condition Interaction
DPX "B" Probe			
Average FM-Theta Power	$F(1,28) = 0.04, p = 0.835, \eta_p^2 = 0.002$	$F(1,28) = 0.95, p = 0.338, \eta_p^2 = 0.033$	$F(1,28) = 0.75, p = 0.393, \eta_p^2 = 0.026$
Average FM-Theta ITPC	$F(1,28) = 0.75, p = 0.393, \eta_p^2 = 0.026$	$F(1,28) = 0.25, p = 0.621, \eta_p^2 = 0.009$	$F(1,28) = 0.76, p = 0.392, \eta_p^2 = 0.026$
P3 Amplitude	$F(1,28) = 0.01, p = 0.915, \eta_p^2 = 0.000$	$F(1,28) = 2.53, p = 0.123, \eta_p^2 = 0.083$	$F(1,28) = 0.15, p = 0.704, \eta_p^2 = 0.005$
P3 Latency	$F(1,28) = 0.09, p = 0.772, \eta_p^2 = 0.003$	$\boldsymbol{F(1,28) = 5.03, p = 0.033, \eta_p^2 = 0.152}$	$F(1,28) = 0.10, p = 0.754, \eta_p^2 = 0.004$
N2 Amplitude	$F(1,28) = 0.02, p = 0.900, \eta_p^2 = 0.001$	$F(1,28) = 1.16, p = 0.290, \eta_p^2 = 0.040$	$F(1,28) = 0.23, p = 0.637, \eta_p^2 = 0.008$
N2 Latency	$F(1,28) = 0.47, p = 0.500, \eta_p^2 = 0.016$	$F(1,28) = 0.03, p = 0.871, \eta_p^2 = 0.001$	$F(1,28) = 1.93, p = 0.176, \eta_p^2 = 0.064$
N-back			
Average FM-Theta Power	$F(1,27) = 7.88^{-7}, p = 0.999, \eta_p^2 = 0.000$	$F(1,27) = 0.945, p = 0.340, \eta_p^2 = 0.034$	$F(1,27) = 0.253, p = 0.619, \eta_p^2 = 0.009$
Average FM-Theta ITPC	$F(1,27) = 0.157, p = 0.695, \eta_p^2 = 0.006$	$F(1,27) = 0.588, p = 0.450, \eta_p^2 = 0.021$	$F(1,27) = 3.481, p = 0.073, \eta_p^2 = 0.114$
P3 Amplitude	$F(1,23,) = 2.904, p = 0.102, \eta_p^2 = 0.112$	$F(1,23) = 2.200, p = 0.152, \eta_p^2 = 0.087$	$F(1,23) = 2.102, p = 0.161, \eta_p^2 = 0.084$
P3 Latency	$F(1,23) = 2.614, p = 0.120, \eta_p^2 = 0.102$	$F(1,23) = 0.081, p = 0.778, \eta_p^2 = 0.004$	$F(1,23) = 2.751, p = 0.111, \eta_p^2 = 0.107$
N2 Amplitude	$F(1,23) = 0.049, p = 0.827, \eta_p^2 = 0.002$	$F(1,23) = 1.51, p = 0.231, \eta_p^2 = 0.062$	$F(1,23) = 0.017, p = 0.896, \eta_p^2 = 0.001$
N2 Latency	$F(1,23) = 0.175, p = 0.680, \eta_p^2 = 0.008$	$F(1,23) = 1.42, p = 0.245, \eta_p^2 = 0.058$	$F(1,23) = 0.484, p = 0.494, \eta_p^2 = 0.021$

Note. Type 3 Sums of Squares.

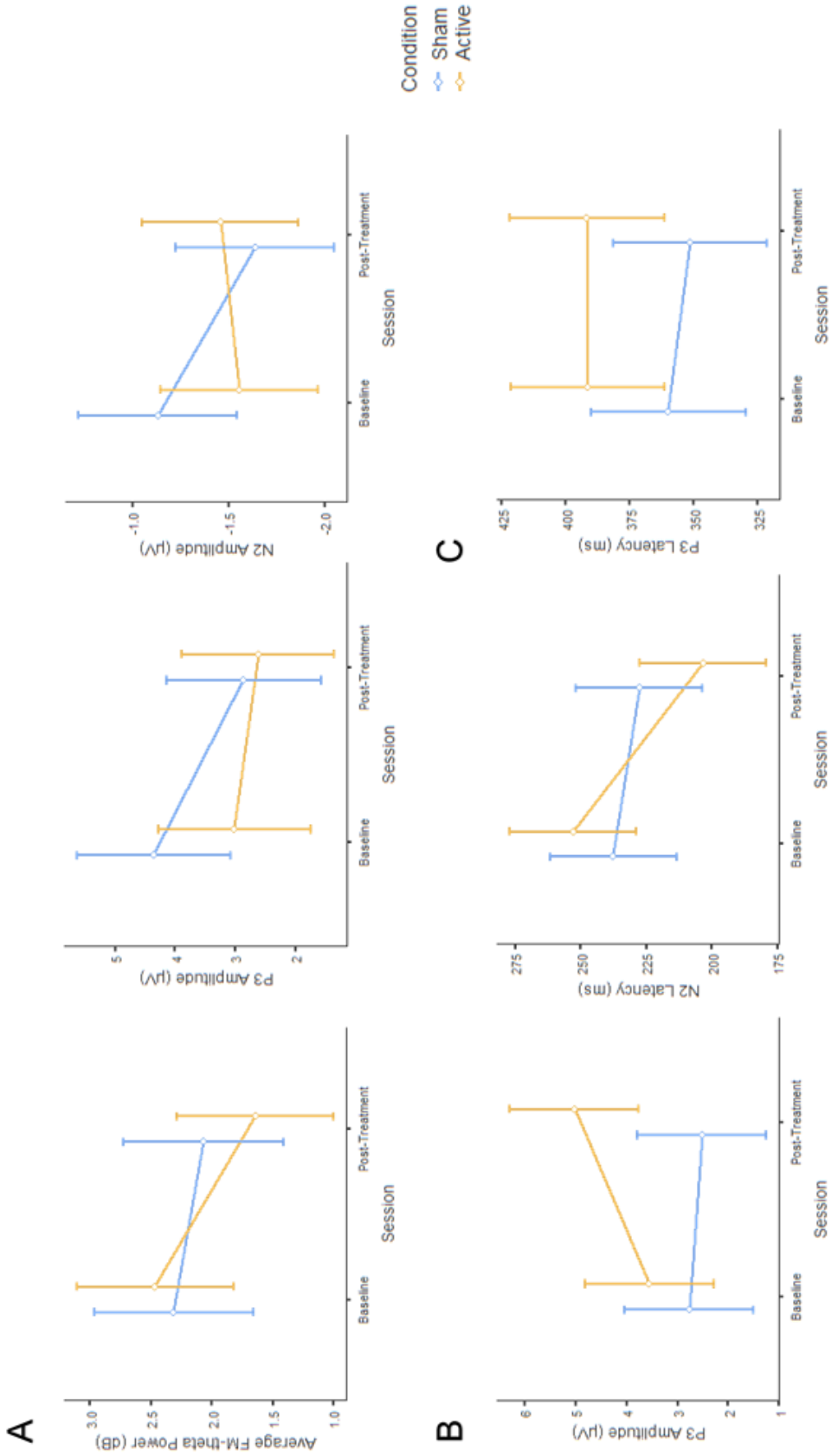

Figure 8. A.) Estimated marginal means plot for significant 3AOB repeated-measures ANOVA; B.) Estimated marginal means plots for significant DPX "A" Cue repeated-measures ANOVA; C.) Estimated marginal means plots for significant DPX "B" Cue repeated-measures ANOVA.

There were no significant main effects of Group or Session and no significant Group by Session interactions for any of the EEG measures on the n-back task.

Multiple Linear Regression to Predict Treatment Outcomes

Repeated-measures ANOVAs of Behavioral Measures. Table 6 shows the changes in the reaction time (RT) and accuracy for the n-back and DPX tasks. Assumptions of homogeneity of variance and sphericity were not violated. There was a significant main effect of Session for all of the behavioral measures (N-back accuracy: $F(1,23) = 14.43, p < 0.001, \eta_p^2 = 0.386$; DPX "A" cue RT: $F(1,20) = 8.60, p = 0.008, \eta_p^2 = 0.301$; DPX "B" cue RT: $F(1,16) = 10.55, p = 0.005, \eta_p^2 = 0.397$) except the N-back RT($F(1,23) = 3.15, p = 0.089, \eta_p^2 = 0.120$). For the change in N-back RT post-hoc t-tests with Bonferroni's correction for multiple comparisons revealed that the average reaction time decreased by 34.3 ms from baseline to post-treatment testing ($t(23) = 1.77, p_{bonferroni} = 0.089$). Similarly, post-hoc t-tests with Bonferroni's correction for multiple comparisons found that the average accuracy on the n-back increased by 9.61% from baseline to post-treatment testing ($t(23) = -3.80, p_{bonferroni} < 0.001$). Post-hoc t-tests with Bonferroni's correction for multiple comparisons also revealed that the average RT on the DPX "A" and "B" cues decreased by 77.7 ms ($t(20) = 2.93, p_{bonferroni} = 0.008$) and 117 ms ($t(16) = 3.25, p_{bonferroni} = 0.005$).

Linear Regressions for N-back. Table 7 presents the model coefficients for the first set of nested models used to regress the change in response accuracy for the n-back task. Assumptions of homogeneity of variance, normality, linearity, and independence were not violated in all linear models. The first model, which included only the control variables, was not significant ($F(4,20) = 0.452, p = 0.769$) and there were no significant predictors

of change in response accuracy. The second model, which included the average FM-theta power during and average FM-theta ITPC along with the control variables, was also not significant overall ($F(6,18) = 1.629, p = 0.197$). However, from model one to model two, there was a significant change in the variance explained by the model ($F(2,18) = 3.73, p = 0.044$). Model 2 overall explained 13.6% ($Adjusted\ R^2 = 0.136$) of the

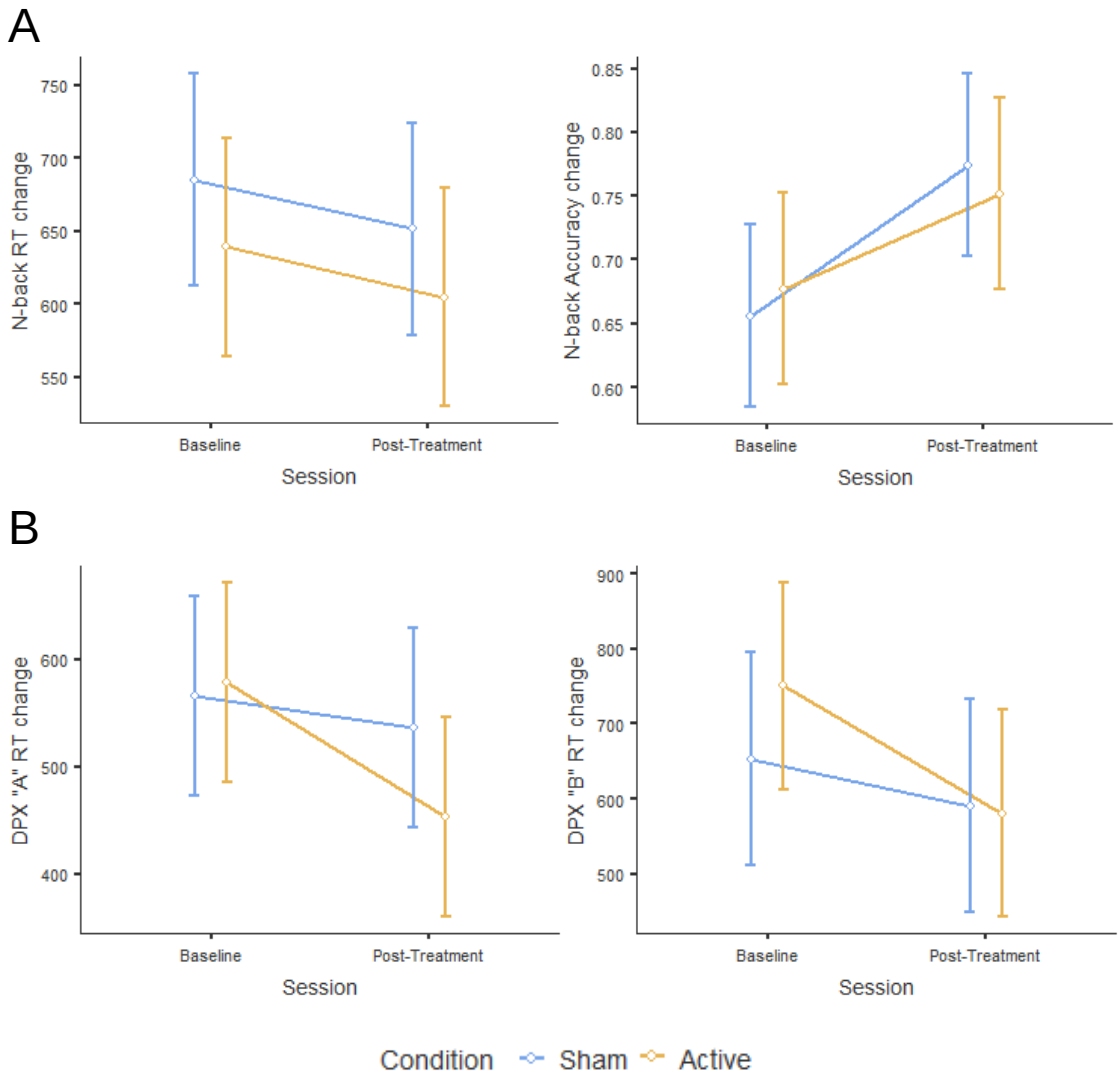

Figure 9. A.) Estimated marginal means plots for the n-back accuracy and reaction time (RT); B.) Estimated marginal means plots for DPX "A" and "B" cue reaction time (RT).

Table 6. Statistical values for repeated-measures ANOVAs for Behavioral Results of EEG-paired Cognitive Control Tasks

	Main Effect of Session	Main Effect of Condition	Session * Condition Interaction
N-back RT	$\boldsymbol{F(1,23) = 3.15, p = 0.089, \eta_p^2 = 0.120}$	$F(1,23) = 0.942, p = 0.342, \eta_p^2 = 0.039$	$F(1,23) = 0.000, p = 0.987, \eta_p^2 = 0.000$
N-back Accuracy	$\boldsymbol{F(1,23) = 14.43, p < 0.001, \eta_p^2 = 0.386}$	$F(1,23) = 0.000, p = 0.986, \eta_p^2 = 0.000$	$F(1,23) = 0.76, p = 0.391, \eta_p^2 = 0.032$
DPX "A" RT	$\boldsymbol{F(1,20) = 8.60, p = 0.008, \eta_p^2 = 0.301}$	$F(1,20) = 0.37, p = 0.549, \eta_p^2 = 0.018$	$F(1,20) = 3.32, p = 0.084, \eta_p^2 = 0.142$
DPX "B" RT	$\boldsymbol{F(1,16) = 10.55, p = 0.005, \eta_p^2 = 0.397}$	$F(1,16) = 0.24, p = 0.633, \eta_p^2 = 0.015$	$F(1,16) = 2.26, p = 0.152, \eta_p^2 = 0.124$

Note. Type 3 Sums of Squares; RT = "Reaction Time".

variance in change in response accuracy compared to Model 1 which explained 0% of the variance. Examining the AIC values for each model shows that despite the significant change in R^2 between Model 1 and Model 2, Model 1 had a lower AIC value. However, given the difference in AIC is 4.7 and there was a significant change in R^2 was significant Model 2 is preferred in this circumstance. The results for Model 2 are discussed below.

The only significant predictor of change in response accuracy was the average FM-theta ITPC ($B = 0.573, t(18) = 2.512, p = 0.022$). In other words, for every 1 unit increase in FM-theta ITPC there is an expected increase of 57.3% in change in response accuracy. Still, while this number is quite astonishing, it is important to point out the ITPC only ranges from 0 to 1. Therefore, a better representation of this finding would be for every .1 increase in ITPC there is an expected 5.73% increase in change in response accuracy.

Table 8 shows the model coefficients for the second set of nested models used to regress change in reaction time for the n-back tasks on FM-theta power and ITPC. The first model that contained only the control variables was non-significant ($F(4,20) = 0.156, p = 0.958$) as was the second model that included the control variables and average FM-theta power and average FM-theta ITPC ($F(6,18) = 0.909, p = 0.510$). The third model, which included all of the previous variables and an interaction term between the average FM-theta power and average FM-theta ITPC was also non-significant ($F(7,17) = 1.741, p = 0.166$). However, from model two to model three there was a significant change in the overall variance explained ($F(1,17) = 5.40, p = 0.033$) and model three explained 17.77% ($Adjusted\ R^2 = 0.1777$) of the variance in change in reaction time. Examination of the AIC values for this set of nested models shows that Model 3, with all

measures included as well as the interaction between FM-theta Power and FM-theta ITPC had the lowest AIC value (Model 1: $AIC = 308$; Model 2: $AIC = 306$; Model 3: $AIC = 301$). This combined with the significant change in R^2 from Model 2 to Model 3 presents Model 3 as the best fitting model to the data. The results for Model 3 are discussed below.

Table 7. Model Coefficients for Multiple Linear Regression Predicting Change in Response Accuracy for the N-back task

	Model 1			Model 2		
Variable	B	SE(B)	β	B	SE(B)	β
Age	0.002	0.002	0.218	0.001	0.002	0.097
Time Since Injury	-0.001	0.007	-0.046	0.000	0.006	0.001
Years of Education	-0.006	0.010	-0.119	-0.013	0.010	-0.266
Condition:						
Active – Sham	-0.037	0.053	-0.297	-0.019	0.050	-0.153
Average FM-theta Power				0.001	0.028	0.008
Average FM-theta ITPC				0.537*	0.228	0.566
R^2		0.083			0.352	
$Adjusted\ R^2$		-0.100			0.136	
$F\ for\ change\ in\ R^2$					3.73*	
AIC		-24.9			-29.6	

Note. $* p < 0.05$ $** p < 0.01$

There was a significant average FM-theta power by average FM-theta ITPC interaction when predicting change in reaction time ($B = -375.394, t(17) = -2.324, p = 0.033$). In other words, the effect of average FM-theta power on change in reaction time varies at different levels of average FM-theta ITPC (see Figure 9). At the mean of average FM-theta ITPC, every 1 dB increase in FM-theta power results in an expected increase of 23 milliseconds (ms) in change in reaction time. At one standard

deviation above the mean of average FM-theta ITPC, for every 1 dB increase in FM-theta power there is an expected decrease of 25 ms in change in reaction time. And at one standard deviation below the mean of average FM-theta ITPC, with every 1 dB increase in FM-theta power there is an expected increase of 72 ms in change in reaction time. Put

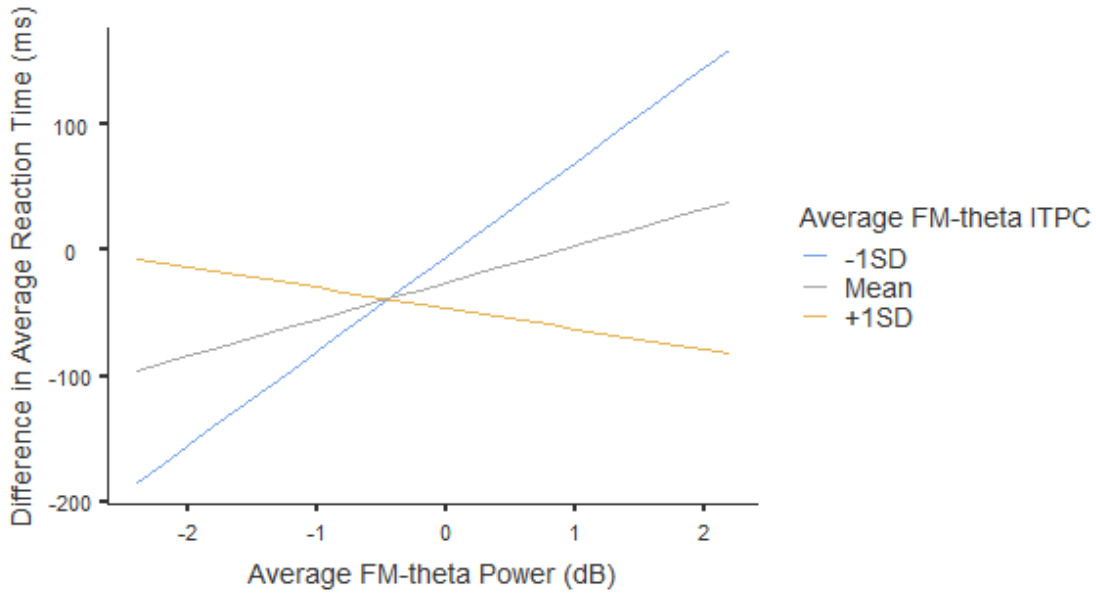

Figure 10. Graph of the interaction effect of Average FM-theta Power (dB) and Average FM-theta ITPC on Differences in Average Reaction Time (ms)

another way, the significant interaction indicates that with higher phase synchrony *and* higher power in FM-theta at baseline the overall change in reaction time is negative, meaning participants were faster at responding to stimuli during post-treatment compared to baseline. On the other hand, lower phase synchrony and higher power in FM-theta results in an overall change in reaction time that is positive, meaning individuals were slower to react to stimuli during their post-treatment compared to baseline.

Linear Regressions for DPX. Examination of the overall model fit for the series of multiple linear regressions ran to predict changes in RT for the DPX "B" cue condition

Table 8. Model Coefficients for Multiple Linear Regression Predicting Change in Reaction Time for the N-back task

	Model 1			Model 2			Model 3		
Variable	B	SE(B)	β	B	SE(B)	β	B	SE(B)	β
Age	-0.444*	1.65*	-0.061*	1.62*	1.81*	0.223*	0.830*	1.66*	0.115*
Time Since Injury	-2.057*	5.41*	-0.085*	-2.12*	5.09*	-0.087*	1.070*	4.77*	0.044*
Years of Education	-4.885*	8.13*	-0.136*	-7.33*	8.18*	-0.204*	-6.509*	7.34*	-0.181*
Condition:									
Active – Sham	-3.125*	41.26*	-0.034*	-30.85*	40.73*	-0.333*	-43.87*	36.94*	-0.474*
Average FM-theta Power				45.66*	22.77*	0.524*	23.301*	22.57*	0.336*
Average FM-theta ITPC				-289.63*	186.32*	-0.381*	-167.594*	175.09*	-0.208*
Average FM-theta Power *							-375.394*	161.55*	-0.525*
Average FM-theta ITPC									
R^2		0.030*			0.233*			0.418*	
$Adjusted\ R^2$		-0.164*			-0.023*			0.178*	
$F\ for\ change\ in\ R^2$					2.37*			5.40*	
AIC		308*			306*			301*	

Note. * $p < 0.05$ ** $p < 0.01$

shows that neither Model 1 ($F(4,13) = 0.490, p = 0.743$) nor Model 2 ($F(6,11) = 0.278, p = 0.936$) had good overall fit. Furthermore, there were no significant predictors in either model, and the adjusted R^2 values for both models were not significant. This is more than likely due to the lack of necessary degrees of freedom caused by missing data. Therefore, the model coefficients will not be presented, and the models will not be discussed further.

Table 9. Model Coefficients for Multiple Linear Regression Predicting Change in Reaction Time for the DPX "A" Cue

	Model 1			Model 2		
Variable	B	SE(B)	β	B	SE(B)	β
Age	-5.13*	2.32	-0.492	-4.40	2.34	-0.422
Time Since Injury	-5.17	6.83	-0.148	-7.50	7.04	-0.214
Years of Education	8.43	9.37	0.176	11.58	9.46	0.242
Condition:						
Active – Sham	-162.18*	57.05	-1.238	-173.4**	56.67	-1.324
Average FM-theta Power				28.13	26.48	0.281
Average FM-theta ITPC				68.80	253.66	0.072
R^2		0.362			0.453	
$Adjusted\ R^2$		0.212			0.235	
$F\ for\ change\ in\ R^2$					1.26	
AIC		278			279	

Note. $* p < 0.05 ** p < 0.01$

Tables 9 displays the model coefficients for the sets of nested models used to regress change in reaction time for the DPX "A" cue condition. Assumptions of homogeneity of variance, normality, linearity, and independence were not violated in all linear models. Neither the first model nor second model was significant (Model 1:

$F(4,17) = 2.41, p = 0.089$; Model 2: $F(6,15) = 2.07, p = 0.118$). There was no significant change in R^2 from Model 1 to Model 2 ($F(2,15) = 1.26, p = 0.313$). Examination of the AIC for both Models reveals Model 1 had a lower AIC value ($AIC = 278$) than Model 2 ($AIC = 279$). With a difference in AIC of 1 there is no considerable evidence to support for adding FM-theta power and ITPC to the model. Therefore, Model 1 is deemed the better fitting model. The results for Model 1 are discussed below.

There was a significant effect of Age ($B = -5.13, t(17) = -2.209, p = 0.041$) and Condition ($B = -162.18, t(17) = -2.843, p = 0.011$). That is to say, that for every increase of 1 year in age, there is an expected decrease of -5.13 ms in change in RT for "A" cue condition from baseline to post-treatment testing. Additionally, there is a significant difference in change in reaction time between the active and sham tDCS conditions with the average change in RT for the active tDCS condition decreasing by -75.63 ms while the sham tDCS condition increased by 86.55 ms. The change in significance for Condition in the present analysis compared to the repeated-measures ANOVA may be caused by additional predictors explaining residual variance.

DISCUSSION

Differences in EEG Biomarkers between Control and mmTBI Individuals

FM-theta power, FM-theta ITPC, and ERP components from the DPX "A" and "B" cue conditions were collected from two distinct groups: a healthy control sample and a mmTBI sample. However, as was depicted in Table 4 the cluster analysis did *not* cluster the participants into groups that aligned with their membership as control or mmTBI. Therefore, the first hypothesis was not supported by the results of the analysis. Instead, the cluster analysis formed two distinct groups based on greater or lesser activation of FM-theta and ERP components. While this result is not what was hypothesized, the clusters created reflect marked differences in the EEG biomarkers used for the analysis.

One possible explanation for this result is the fact that TBI is a rather heterogeneous disease that encompasses a variety of conditions (Lingsma et al., 2010). This perspective is readily supported by the work of Rosenbaum and Lipton (2012), that showed that of the 80-100% of individuals that experience post-concussive symptoms, approximately 20% recover within 24 hours and 85% recover within a week. Additionally, current statistics indicate that only a small minority (between 3-15%) of individuals that experience a mild TBI display prolonged limitations to cognitive functioning a month after the initial injury (Arciniegas, 2011; Nuwer et al., 2005). Further research by Goldstein and colleagues (2010), who used a cluster analysis to identify subgroups with a TBI sample, concluded that cognitive deficits among TBIs is variable (Goldstein, Allen, and Caponigro 2010). Furthermore, a review by Moldover, Goldberg, and Prout (2004) found that post-TBI depression is also rather heterogeneous with individuals displaying depression months after their TBI and other individuals not showing pronounced depressive symptoms until

potentially years after their initial injury. Other research has also pointed to several factors that significantly influence how the brain recovers in response to a TBI.

It is well documented that even before a TBI occurs there are several premorbid factors to consider when examining the heterogeneity of TBIs. As Rosenbaum and Lipton (2012) summarize, "premorbid factors including, but not limited to age, gender, IQ, socioeconomic status, ethnicity, education, genotype, psychiatric history, prior head injury, substance abuse and anthropometrics vary greatly across mTBI patients" (p. 257). Additional variability occurs when considering the biomechanical forces that result in a TBI. A TBI can be caused by one of three forces: linear acceleration, rotational acceleration, and impact deceleration (Blennow et al., 2016). The primary consequence of these variable biomechanisms is differences in impact and inertia forces on the brain. As Rosenbaum and Lipton (2012) explain, higher impact forces could theoretically result in skull fractures and brain contusion while increased inertia forces would result in diffuse axonal injury.

Clearly, the heterogeneity of TBI is rather apparent and therefore its effect on overall cognitive function, both in the acute and chronic stages, must also be recognized. While EEG has been heralded as a strong approach to diagnosing the severity of TBIs, critics have suggested EEG is limited due to distance from the location of injury (Lingsma et al. 2010). That is to say that since the prominent alteration in the chronic stages of injury is DAI (located in the white matter; see Kinnuen et al., 2011) and EEG records electrical activity at the scalp, the true extent to which it can assess the severity of the injury is limited (Lingsma et al. 2010). Cohen, Cavanagh, and Slagter (2011) illustrated this when they argued that dipoles located in different regions of the brain could manifest the same EEG

signal recorded at the scalp. Additionally, as Arciniegas (2011) defends "EEG changes, when present at all, often are subtle and not infrequently still within the range of normal findings in the general population" (p. 45). Taken together it must be recognized that EEG has its limitations when detecting cognitive differences caused by a TBI. Therefore, using those changes when attempting to differentiate between a TBI sample and a control sample may not be a reliable avenue for differentiating groups. Future research should attempt to classify groups on a variety of measures, such as behavioral measures, questionnaire data, along with EEG biomarkers.

The above evidence provides one possible explanation for the results of the cluster analysis. Since the majority of the TBI participants recruited for the present study were classified as having sustained a mild TBI ($n = 23$) it is possible that changes in EEG activity are not as prominent as was hypothesized. Therefore, attempting to categorize individuals into a control sample and a TBI sample based solely on EEG biomarkers may not be robust. To be clear, the presented evidence does not discredit EEG as a potential tool to aid in research surrounding TBI, but rather points to one of its limitations with regards to distinguishing between control and TBI persons.

Differences in EEG Biomarkers as a Result of Active tDCS

A series of repeated-measures ANOVA were used to examine changes in the TBI sample between baseline and post-treatment testing to determine if active tDCS would result in any significant changes to EEG biomarkers. The most promising result is shown in the significant effect of condition and session for the two DPX components that were analyzed.

The significant increase in the P3 amplitude for the active tDCS group suggests that the participants showed increased cognitive resource allocation as described by Sur and Sinha (2009). Moreover, the decrease in the N2 latency reflects faster conflict monitoring in the "A" cue condition. Taken together, the changes seen in these two components indicate that individuals in the active tDCS condition are showing greater cognitive control. In terms of the DPX task itself, the decrease in N2 latency could represent participants anticipating a conflict to emerge after the "A" cue has been presented. This anticipated conflict is represented by the differences in responses participants must give depending on if the probe that follows the cue is in the "aX" or "aY" formation. Similarly, the increase in the P3 amplitude for the "A" cue condition displays participants anticipatory activation of the CCN in order to respond quickly and accurately depending on which probe appears following the cue. Therefore, the changes in these ERP components for the only active tDCS condition shows that active stimulation results in increased cognitive control abilities for the mmTBI sample, thereby supporting hypothesis 2. However, this same significant effect of Condition was not seen in any of the other EEG-paired cognitive tasks. One possible explanation for this non-transfer of significant effects is near versus far transfer.

Briefly stated, near transfer refers to improvement of capabilities on untrained cognitive control and working memory tasks that are similar to the tasks that participants were trained on (see Linares et al., 2019). Far transfer refers to improvements on other cognitive abilities that are less closely associated with the trained task (Linares et al., 2019). It has been shown that cognitive training on working memory tasks paired with active tDCS in healthy populations has led to near transfer of working memory abilities (Filmer et al., 2016, 2017; Ruf et al., 2017). However, the research concerning these findings within EEG

and using a TBI population is limited. In the context of the present study, near and far transfer occurs when comparing the tasks run during the baseline and post-treatment testing (i.e. 3AOB, n-back, and DPX tasks) with those ran during the stimulation protocol (i.e. multimodal n-back, and AX-CPT tasks).

When comparing the DPX task to the AX-CPT the possibility for near transfer of working memory is apparent. The DPX being a variant of the AX-CPT tasks the cognitive processes engaged and the procedures for responding in these two tasks is arguably similar. Therefore, if subjects improve on the AX-CPT task during stimulation, similar gains may be seen in a task that is similar in nature. A parallel idea can support the results found in the significant results of the 3AOB task and the lack of significant results for the n-back task run at baseline and post-treatment.

While Condition was not significant for the 3AOB analyses there was a main effect of Session for the FM-theta Power with the average power decreasing from baseline to post-treatment. This result could demonstrate far transfer of working memory and cognitive control capabilities. The auditory component of the multimodal n-back task required participants to attend and remember the numbers they heard in order to identify matches. The cognitive networks involved in auditory working memory and cognitive control were therefore engaged in this task. When participants completed the 3AOB task at baseline and post-treatment these same networks were recruited to attend to certain stimuli while ignoring others. To summarize, the cognitive processes employed in the 3AOB task were the same as those employed in the auditory component of the multimodal n-back resulting in a significant change in FM-theta. However, a discrepancy arises when considering the null results of the n-back task ran during the testing sessions.

While at first glance the two versions of the n-back task appear similar there are marked differences between them. For one, the multimodal element of the n-back task ran during stimulation is more complicated than the one ran during the baseline and post-treatment testing. This could imply that cognitive control may not have been needed when completing the n-back task administered during the testing sessions. Additionally, the cognitive processes involved in each task are rather distinct. The multimodal n-back involves auditory and visual processing. Meanwhile, the n-back task run during testing sessions is simply visual. And critically, the visual processing that occurs in each of the n-back tasks recruit different visual pathways within the brain.

It is well known that visual processing occurs in two independent pathways: the dorsal and ventral. An object's spatial position is processed in the dorsal pathway while the objects features, such as its shape, color, and texture are processed through the ventral pathway (Zachariou et al., 2014). The visual component of the n-back task run during the stimulation session utilizes the dorsal pathway since participants must remember the object's spatial location when attempting to recognize a match. Meanwhile, the visual n-back task ran during the testing sessions relies on the ventral pathway to hold the objects features in mind when attempting to find a match. This dissimilar activation pattern may be responsible for the lack of significant results seen in the analysis of changes in the n-back.

As the participants are trained on the multimodal n-back task their brain develops a cognitive strategy in order to improve on the task. This will include activation of the regions pertaining to cognitive control. However, when presented with a novel n-back that does not utilize the same pathways as the ones recruited during the multimodal n-back task,

changes in cognitive control were not observed therefore resulting in no significant change from baseline to post-treatment testing.

These results provide support for the idea that transfer occurs through strengthening cognitive processes during training that overlap with cognitive processes used for testing (Klingberg, 2010; Linares et al., 2019). As Linares et al. (2019) describe, "the greater the overlap between the cognitive abilities engaged in the trained process and the transfer tasks, the greater the likelihood of obtaining transfer effects" (p. 3). What remains unique about this particular analysis is that the cognitive processes used in the tasks are directly measured adding to the validity of the results found. Specifically, the FM-theta activation seen in the DPX and 3AOB task support the idea that cognitive processes used in training can result in transfer of cognitive control to untrained tasks. Furthermore, the significant effect of Condition on the DPX tasks provides strong evidence for the use of tDCS to augment these cognitive processes to further increase the gains received from cognitive control training in an mmTBI sample.

EEG Biomarkers as Predictors of Treatment Outcomes

Recent findings have already confirmed the predictive power of FM-theta activity in working memory and cognitive control tasks (Cavanagh et al., 2009; Enriquez-Geppert et al., 2014; Maurer et al., 2015). The results of the multiple linear regressions used to predict change in reaction time and accuracy for the n-back task support these general findings. In particular, FM-theta ITPC appears to be the main predictor of the change in reaction time and accuracy, which supports the findings of Berger et al. (2019) Cavanagh and Frank (2014). and Papenberg et al. (2013). That is to say that the phase synchrony of

the FM-theta correlates with increased task complexity, which requires higher levels of cognitive control.

When examining the results of the n-back accuracy analysis, higher FM-theta ITPC values were correlated with a greater positive change in accuracy. A similar finding was found in the significant interaction between FM-theta power and ITPC for the change in reaction time on the n-back task. Higher activation of FM-theta was not enough to improve performance on the n-back task. However, when individuals showed higher levels of phase synchrony, the higher levels of activation resulted in improved response times from baseline to post-treatment. Clearly, the ITPC of FM-theta acts, as was reported by Berger et al. (2019), and Cavanagh and Frank (2014), as a gating mechanism that allows the brain to recruit specific regions in order to perform under high cognitive control demand.

Furthermore, when individuals demonstrate higher levels of ITPC prior to cognitive training, those individuals are more likely to show gains in accuracy and reaction time after cognitive training. Still, these significant results were limited to the n-back task and did not appear in the DPX task. This may be due to a lack of cognitive control needed when addressing the cue stimuli within the task. That is to say that cognitive control was not needed when responding to the cues within the DPX task but may have been needed in probe elements of the task that were unable to be analyzed. Therefore, the ITPC and power of FM-theta may not have been strong predictors in reaction time for this specific component of the DPX task.

These results *do not*, however, support the claims made in hypothesis 4. To begin, there was no significant effect of Condition. Therefore, individuals with lower cognitive control functioning did not see significant improvement from the stimulation. This leaves

only gains from cognitive training as a possible avenue for improvement. Moreover, it was the individuals that showed relatively high levels of FM-theta activation and phase synchrony that showed significant improvement on task accuracy and reaction time when compared to baseline testing. Meanwhile, individuals with lower FM-theta activation and phase synchrony showed an expected increase in reaction time. Even though the average participant did improve on all of the cognitive tasks as a result of cognitive training, as was shown in the repeated-measures ANOVAs for the behavioral measures, this result was caused by differences in cognitive control ability at baseline and not by the active tDCS intervention.

Limitations

The primary limitation in the present study was sample size. Relatively low sample sizes, in general, make it difficult to find significant effects due to insufficient power. The current sample for the analyses were $n = 67$ and $n = 33$ respectively. Post-hoc power analysis run in G*Power (version 3.1; Faul, Erdfelder, & Lang, 2009) for the multiple linear regressions using Cohen's f^2 statistic as a measures of effect size found that the achieved power for changes in reaction time and accuracy in the n-back task, and change in reaction time in the DPX "A" cue were 0.60, 0.72, and 0.71 respectively. While these results are not terrible, larger samples sizes would be necessary to achieve higher power and reach the recommend .80 threshold for reliability.

A second limitation is the lack of continuity between the tasks that were administered at baseline and post-treatment testing and those that were administered during the stimulation sessions. While this did present an opportunity to examine near and far transfer effects, it was not possible to determine if stimulation actually augmented brain

activity on trained tasks as EEG was not collected during the stimulation sessions. In order to comprehend the true extent of the benefits gained through tDCS stimulation, future research should administer tasks that remain consist throughout the course of testing and stimulation.

A third limitation is the narrowed focus of the present study. Only theta band activity from 300-500 ms post stimulus onset was collected from a single electrode (FCz). While there was theoretical merit to this selection, there remains a vast number of other analyses that could be accomplished from examining the activation of other frequency bands. Studies have shown a significant change in delta band activity (Ulam et al., 2015) and alpha band activity (Straudi et al., 2019) in TBI samples. Additional findings had found significant results when examining the relationships between the phase synchrony between different regions of the brain (Berger et al., 2019; Cavanagh et al., 2019). There is an abundant array of opportunities to assess chronic stages of mmTBI populations utilizing EEG. Future research should continue pursuing multiple avenues to better understand how TBI affects the brain.

A final limitation is the inaccuracy of tDCS with respect to the TBI sample. As was stated above, the heterogeneity that exists within TBI makes it difficult to develop a one-size-fits-all approach to implementing a potential treatment for cognitive control deficits. Current research that utilizes High-Definition tDCS, a form of tDCS that utilizes brain mapping and unique electrode montages for more focal stimulation may provide more prominent results within an mmTBI sample (Turski et al., 2017). Understanding and taking individual differences into account will hopefully spur a greater response from the implementation of tDCS as a treatment for TBI as well as other chronic conditions.

CONCLUSION

The present study demonstrates the complexity of TBI due to the heterogeneity present from subacute to chronic stages of the condition. These results provide additional evidence to the importance of FM-theta activity in cognitive control and how cognitive training can be used to improve cognitive control functioning in an mmTBI. Moreover, the findings illustrate the potential for active tDCS as a treatment to aid in restoring cognitive control functioning after a TBI. Specifically, the potential near transfer of active tDCS stimulation in untrained tasks within an mmTBI sample. Lastly, the current findings show the importance of FM-theta phase synchrony in the context of cognitive control deficits seen in mmTBI. Future research should account for the heterogeneity present within this disease when attempting to develop a treatment for cognitive control deficits caused by TBI.

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