The Cognitive Sequelae of Paediatric Concussion: Understanding Outcomes and Exploring Opportunities for Intervention

by

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Abstract

Background: Children and youth are at risk of experiencing persistent cognitive challenges after concussion. However, there is a lack of characterization of these outcomes and a paucity of treatment interventions.

Objective: **(1)** To characterize working memory post-paediatric concussion; and, **(2)** to explore the therapeutic potential of transcranial direct current stimulation (tDCS) for youth experiencing persistent cognitive symptoms.

Methods: **(1)** Systematic review methodology was applied to synthesize the literature on working memory outcomes. **(2)** A pilot quasi-randomized control trial was conducted to explore the feasibility, tolerability, and clinical efficacy of tDCS.

Results: **(1)** Working memory is vulnerable to insult in paediatric concussion, yet outcomes are variable. **(2)** tDCS shows the potential to enhance cognitive skill acquisition. Barriers to feasibility must be addressed.

Conclusions: This dissertation contributes to a better understanding of the cognitive outcomes of paediatric concussion and will inform future research exploring therapeutic interventions for persisting cognitive symptoms in youth.

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1 Introduction

1.1 Purpose and objectives

Youth are disproportionately affected by concussions, in relation to incidence, as well as the severity and sequelae of concussion-related symptoms. Approximately 30% of youth continue to experience concussion symptoms at 1-month post-injury (Zemek, Barrowman, Freedman, Gravel, Gagnon, McGahern, et al., 2016), and approximately 12% at 3-months post-injury (Barlow, Crawford, Brooks, Turley, & Mikrogianakis, 2015), which can restrict their ability to participate in daily activities, leading to significant decreases in health-related quality of life (Novak et al., 2016). Cognitive symptoms can be especially detrimental as they are critically related to functional areas that are of high importance to the youth population, including academics and social life. Despite the increased vulnerability of youth to these injuries, concussion research has focused predominantly on adults. As a result of this focus, the cognitive sequelae of concussion from a paediatric lens remains poorly defined both in relation to (1) the nature of cognitive challenges that can result from injury, and (2) the effective therapeutic interventions that can facilitate cognitive recovery post-injury. Not surprisingly, the need to better understand concussion uniquely from a paediatric lens was identified as a research priority in the most recent international consensus statement on sport concussion (McCrory et al., 2017). This dissertation directly addresses this need with the ultimate goal of informing the treatment of youth experiencing persisting cognitive symptoms after concussion.

The specific objectives of this dissertation are:

A. To systematically characterize the post-concussion sequelae of a core higher-order cognitive function, namely working memory, in a paediatric population.
B. To explore the feasibility, tolerability, and potential clinical efficacy of transcranial direct current stimulation (tDCS) as a potential intervention factor for facilitating recovery in youth experiencing persisting cognitive symptoms post-injury.

1.2 Terminology

Concussion is the predominant concept referred to throughout this dissertation. **Concussion** is defined as a traumatic brain injury consisting of a complex pathophysiological process induced by an external biomechanical force, resulting in the disruption of cortical activity and short-term impairment of neurological function, without substantial structural injury, as outlined in The 5th International Concussion in Sport Consensus Statement (McCrory et al., 2017). Specific to children and youth, **persistent post-concussion symptoms (PPCS)** are defined as any symptoms lasting over 28 days (or 4 weeks) after injury (McCrory et al., 2017; Zemek et al., 2016).

The secondary concept covered within this dissertation is **non-invasive brain stimulation (NIBS).** This refers to a category of neuroscience technologies that modify cortical activity through the administration of a magnetic or electrical current. These technologies are used to provide insight into neural plasticity and underlying brain structures, as well as to modify behaviour and promote skill acquisition (Brunoni et al., 2012; Page, Cunningham, Plow, & Blazak, 2015). This dissertation focuses on one type of NIBS, namely **transcranial direct current stimulation (tDCS)**, that utilizes a low-level electrical current to modulate cortical activity by promoting or hindering the occurrence of action potentials in a targeted brain region (Stagg & Nitsche, 2011; Woods et al., 2016). **Adaptive plasticity** is referred to within the context of NIBS technologies. This term encompasses any plasticity mechanisms occurring on the neural level which lead to beneficial functional outcomes (Cramer et al., 2011; Kolb & Muhammad, 2014).

Finally, the terms **children** and **youth** are used throughout this dissertation. **Children/child** is described as an individual aged 12 and younger, and **youth** refers to an individual between the ages of 13-18. The exception of this is in Manuscript 2 (Chapter 4), where 'youth' was extended to age 21 in order to ensure that important information from studies employing an age range that extended above of age 18 was included.

1.3 Thesis organization and research design

This thesis contains a total of five chapters. **Chapter 1**, the current chapter, introduces the reader to the key concepts and terminology of the fields of paediatrics, concussion and NIBS and provides an overview of the thesis structure. **Chapter 2** presents a summary of the literature on paediatric concussion and on the therapeutic potential of non-invasive brain stimulation technology. Chapters 3 and 4 are composed of two independent studies. **Chapter 3** (i.e., Study One), is entitled *"Working Memory Outcomes of Paediatric Concussion"* and used systematic review methodology to characterize the nature of working memory performance following paediatric concussion. **Chapter 4** (i.e., Study Two) is entitled *"The Effect of Transcranial Direct Current Stimulation on Cognitive Performance in Youth with Concussion: A Pilot and Feasibility Study"* and employed a pilot quasi-randomized double-blinded control trial design with two arms: active and sham tDCS. The objectives of the pilot trial were to explore: (1) the potential clinical efficacy and (2) the feasibility of implementing a multi-session tDCS intervention for persisting cognitive symptoms in youth with concussion. **Chapter 5** provides a summary and conclusion of the overall thesis, including a discussion of the implications of the work and directions for future research.

Chapter 2

2 Literature Review

2.1 Concussion: A global public health concern

According to the World Health Organization (WHO), concussions represent a global public health concern; over 150,000 individuals are diagnosed with concussion annually in Ontario alone, and these injuries represent 75-85% of the almost 2 million traumatic brain injuries (TBIs) occurring each year in the United States (Faul, Xu, Wald, & Coronado, 2010; Levin & Diaz-Arrastia, 2015; National Center for Injury Prevention and Control, 2003; Ontario Neurotrauma Foundation, 2016). Concussions have historically been perceived as relatively inconsequential, likely due to the lack of a neuropathological marker for these injuries (Levin & Diaz-Arrastia, 2015; McCrory et al., 2013; National Center for Injury Prevention and Control, 2003). However, the resulting potential detrimental effects have become increasingly recognized in clinical practice, research, and the media, leading to their classification as a "silent but serious epidemic" (Parachute Canada, 2015).

Concussions typically result in a range of immediate symptoms spanning emotional (e.g., sadness, irritability), cognitive (e.g., problems concentrating and remembering), and physical (e.g., 'clumsy' movements and fatigue) domains (Konrad et al., 2011; Levin & Diaz-Arrastia, 2015; McHugh et al., 2006; Rabinowitz & Levin, 2014). The typical prognosis for these immediate clinical symptoms is promising. Although developing evidence suggests that physiological and neural mechanisms impacted by injury may take longer to recover following concussion than abilities assessed by clinical measures of recovery (Dettwiler et al., 2014; Kamins et al., 2017), the majority (80-90%) of concussion cases resolve from a symptomology perspective within the initial 2 to 4-weeks post-injury (Davis et al., 2017; McCrory et al., 2013, 2017). However, despite this common recovery trajectory, research has shown that these symptoms can often persist longer than expected in a subset of affected individuals, significantly compromising their ability to function in daily life (Barlow et al., 2010; Carroll et al., 2004; Davis et al., 2017; Goldberg & Madathil, 2015; Levin & Diaz-Arrastia, 2015). There is a pressing need to better understand the nature of the immediate and persisting deficits, as well as to explore novel therapeutic interventions to address this symptomology, so that affected individuals can return to valued activities as quickly as possible.

2.2 Neurophysiological and neuropathological profile of concussion

Concussions are highly heterogeneous injuries, however, all severities of TBI can be divided into primary and secondary injury phases (Andriessen, Jacobs, & Vos, 2010; Choe, 2016; Hadanny & Efrati, 2016; Seifert & Shipman, 2015). The **primary injury** involves the immediate damage to the brain through a biomechanical force. This force may take the form of a typical 'blow to the head' through a direct contact force, or may involve inertial, acceleration-deceleration forces (Choe, 2016; Hadanny & Efrati, 2016; McCrory et al., 2017; Meaney & Smith, 2011). Often these types of biomechanical forces will occur together, amplifying the impact of the injury. While both forces can occur as a result of impact loading, where the head hits or is hit by an external surface (e.g., when a hockey puck collides with someone's head in a game), only inertial forces can result from impulsive loading, occurring without physical contact to the head (e.g., experiencing whiplash from colliding chests with another player). These forces result in two primary injury types: (1) focal cortical damage at the site of impact/injury and (2) widespread cortical disruption and damage due to axonal shearing and strain from linear and, especially, rotational acceleration (Choe, 2016; Hadanny & Efrati, 2016; McCrory et al., 2017; Meaney & Smith, 2011; Seifert & Shipman, 2015). The focal brain damage is primarily a result of the collision of the brain with the bony protrusions of the skull and often involves some form of skull fracture, resulting in hemorrhages, contusions, and other cortical injuries that typically would result in a brain injury of greater severity than concussion (Meaney & Smith, 2011). Inertial forces are much more commonly associated with concussion and mild TBI (Meaney & Smith, 2011). The linear and rotational acceleration introduced by an inertial force induces strain between cortical and subcortical layers during rapid movement of the head which in turn causes shearing forces in the brain, disrupting axonal connections and often resulting in a mild form of diffuse axonal injury (DAI) (Choe, 2016; Cubon, Putukian, Boyer, & Dettwiler, 2011; Hadanny & Efrati, 2016; Meaney & Smith, 2011; Seifert & Shipman, 2015).

The **secondary injury** consists of a series of cellular events that are triggered by the initial injury, ramifying the negative consequences of this primary damage. These events include changes in metabolic processes, increases in inflammation, and excitotoxicity (Choe, 2016; Hadanny & Efrati, 2016; Meaney & Smith, 2011; Werner & Engelhard, 2007). While these processes can result in significant cell death in many forms of TBI, the neural damage and disruption caused by concussion is typically more transient, involving cerebral dysfunction without extensive cellular atrophy (Choe, Babikian, DiFiori, Hovda, & Giza, 2012; Hadanny & Efrati, 2016). Therefore secondary injury in concussion presents more as changes in metabolic processes such as ionic imbalance and excessive neurotransmitter release, putting the brain in a state of heightened vulnerability and impacting neural activity and neural connections without causing substantial cellular death (Baillargeon, Lassonde, Leclerc, & Ellemberg, 2012; Choe, 2016; Hadanny & Efrati, 2016; Seifert & Shipman, 2015). Despite contributing to this state of vulnerability, the neuropathological changes that accompany concussion are promising, as they suggests that a substantial amount of the damage caused by injury is reversible (Anderson, Spencer-Smith, & Wood, 2011).

As concussion primarily manifests as functional changes in neural activity, within cortical regions and/or across neural networks, it typically does not present on clinical structural neuroimaging protocols such as conventional computed tomography (CT) imaging or structural magnetic resonance imaging (MRI) (Choe, 2016; Levin & Diaz-Arrastia, 2015; McCrory et al., 2013, 2017). However, diffusion tensor imaging (DTI) techniques have shown potential clinical utility in identifying white matter damage that correlates with functional outcomes after concussion, and further, that differentiate the white matter profile of clinical populations with concussion from healthy controls at both acute and chronic stages of recovery (see Aoki, Inokuchi, Gunshin, Yahagi, & Suwa, 2012 and Eierud et al., 2014 for review). Further, these white matter changes have been shown to correlate with the presence of post-concussion symptoms, both in paediatric (Chu et al., 2010) and adult populations (Dean, Sato, Vieira, McNamara, & Sterr, 2015). Future work is needed to explicitly explore the impact of injury history on DTI imaging outcomes, as highlighted by Gardner et al. (2012) in their systematic review.

Changes in neural activity, as measured by functional MRI (fMRI), can also be used to examine otherwise elusive characteristics of the underlying neural pathology associated with concussion. Clinical populations who have experienced a concussion typically show different blood oxygen level dependent (BOLD) responses than controls (see McDonald, Saykin, & McAllister, 2012 for review). These functional changes have been observed in both paediatric (Keightley et al., 2014; Krivitzky et al., 2011; Lovell et al., 2007; Toledo et al., 2012; Westfall et al., 2016) as well as adult populations (Chen et al., 2004; Dettwiler et al., 2014; Iraji et al., 2015; Wylie et al., 2015), and have been documented from the acute and subacute (Iraji et al., 2015; Krivitzky et al., 2011; Lovell et al., 2007; Wylie et al., 2015), through to the chronic stages of recovery (Chen et al., 2004; Dettwiler et al., 2014; Westfall et al., 2016). Further, these activity changes have been shown to correlated with clinical recovery trajectories and symptom profiles (Chen et al., 2004; Lovell et al., 2007; McDonald et al., 2012). As with the DTI literature, there is a lack of understanding regarding the impact of injury history on imaging outcomes. With regards to the nature of functional changes, hyperactivity (i.e., increased BOLD signal fluctuation) both within and between cortical regions is often observed following concussion (Bryer, Medaglia, Rostami, & Hillary, 2013; Dettwiler et al., 2014; Krivitzky et al., 2011; Lovell et al., 2007; McAllister et al., 1999, 2001; Westfall et al., 2016; Wylie et al., 2015). Although increased neural activity following injury can be interpreted from multiple theoretical perspectives, a predominant hypothesis is that the increased activity represents an adaptive process where previously less engaged or unengaged cortical resources become active under certain task demands to compensate for damaged cortical regions and neural connections (Bryer et al., 2013; Hillary et al., 2010; Medaglia et al., 2012). In support of this compensation theory, greater BOLD activation has been consistently correlated with improved performance on executive function (EF) tasks among those who have sustained concussion in paediatric and adult populations (Keightley et al., 2014; see McDonald, Saykin, & McAllister, 2012 for review).

However, the direction of activation differences (i.e., hyper versus hypo activation) are not as consistent in concussion and mTBI as compared to more severe brain injuries. Hypoactivation has also been observed following concussion and mTBI in the same brain regions which showed hyperactivation, such as the prefrontal cortex (see Bryer et al., 2013 for review). These activation differences seem to depend on task demands, with hypoactivation most commonly observed during conditions of low cognitive load (Bryer et al., 2013), as well as at resting state (Johnson et al., 2012). These aberrant cortical activity patterns imply that the recruitment and allocation of cognitive resources is affected by concussion, which may be influencing behaviour and cognitive symptoms (Bryer et al., 2013; van der Horn et al., 2015). Further, these abnormal activation patterns can persist even when functional deficits are no longer present, suggesting that the cerebral disruption that follows concussion may last for longer than could previously be estimated by behavioural assessments, forcing this population to continue to utilize compensatory neural strategies (Dettwiler et al., 2014; Slobounov et al., 2010; Westfall et al., 2015; Wylie et al., 2015).

2.3 Neuroplasticity following traumatic brain injury

Recovery following brain injury is dependent on two core domains of plasticity: neural plasticity and functional plasticity (Kolb & Muhammad, 2014; Levin, 2003; Nudo, 2013). Neural plasticity can be defined as the brain's ability to adapt to intrinsic and extrinsic events through physiological processes at the neurochemical and neuroanatomical levels, including neural recovery mechanisms such as regeneration or axonal sprouting (Cramer et al., 2011; Kolb & Muhammad, 2014; Nudo, 2013). Functional plasticity refers to larger-scale behavioural changes and/or recovery in response to these events (Kolb & Muhammad, 2014; Nudo, 2013). Although they are integrally related, recovery at the neural level does not always lead to recovery at the functional level, and functional recovery does not always imply neural recovery (Anderson et al., 2011). While plasticity-induced changes are elicited in response to injury and are often beneficial, these changes are fundamentally neutral with respect to the nature of outcomes they produce (Dennis et al., 2013). Plasticity that contributes to improved functional outcomes is considered adaptive plasticity, whereas that leading to negative consequences is considered maladaptive plasticity (Cramer et al., 2011). Plasticity mechanisms are always occurring in conjunction with homeostatic mechanisms which regulate the body and behaviour, and therefore behavioural outcomes must be understood as a product of interactions between plasticity mechanisms, homeostatic mechanisms, and the environment (Broderick, John, & Craddock, 2013; Dennis et al., 2013, 2014).

Adaptive recovery processes can be classified in one of two primary categories: restitution of function and substitution of function. **Restitution** refers to the reinstatement of damaged neurons and neural pathways and therefore the retrieval of lost function during recovery from brain injury, whereas **substitution** refers to the adaptive transfer of functions from injured brain tissue and neural pathways to healthy regions (Anderson et al., 2011; Cramer et al., 2011; Nudo, 2013). Restitution of function primarily consists of a series of molecular and cellular processes involving biochemical mechanisms and alterations in protein synthesis to promote recovery, including regeneration of damaged neurons and axonal connections, sprouting of axons to reach new target sites, and denervation supersensitivity to increase neural communication (Anderson et al., 2011). Substitution involves larger-scale structural changes such as anatomical reorganization leading to functional adaptation, e.g., changes in intra or interhemispheric neural pathways to recover impaired function from damaged cortical regions. While substitution processes involve the adaptation of new neural strategies to support function, they do not necessarily involve neural recovery (Anderson et al., 2011). Notably, a variety of intrinsic and extrinsic factors can influence these neural and functional plasticity processes and therefore the recovery prognosis. This includes injury, age, and environmental factors, as well as interventions and rehabilitation treatment (Cramer et al., 2011; Kolb & Muhammad, 2014; Nudo, 2013).

2.3.1 The vulnerability of the young brain

Children and adolescents are disproportionately affected by concussions, consistently experiencing higher injury rates than adults (Cassidy et al., 2004; Morrish & Carey, 2013). Further, this demographic group typically experiences more severe symptomology and more protracted recovery rates. Specifically, between 30-60% of youth continue to experience symptoms one-month post injury, and 13% continue to experience symptoms at 3 months, a rate much higher than the typical recovery time of 1-2 weeks seen in adult populations (Barlow et al., 2010; Davis et al., 2017; McCrory et al., 2017; Zemek et al., 2016). This long-term burden can severely restrict a child's ability to participate in social, academic, and extra-curricular settings, and can result in significant decreases in feelings of self-worth and overall quality of life (Barlow et al., 2010; Davis et al., 2017; Yeates, 2010).

Neuroplasticity and recovery from brain insult in the pediatric demographic is unique, and must be understood within the context of the developing nervous system (Dennis et al., 2013, 2015). Based on what was known about age-dependent differences in neuroplasticity, the 'Kennard Principle' represented a widely held belief that earlier brain injury would result in better functional outcomes than brain injury later in life (Dennis & Thompson, 2013; Dennis, 2010; Schneider, 1979). Although disproven in relatively recent years, this principle guided a large amount of early assumptions and research in the field of brain injury, leading medical professionals to underestimate the effects of these injuries in the pediatric population. In accordance with the increased likelihood of extensive and persistent symptomology following concussion in this demographic, it appears that the developmental nature of the pediatric brain may actually cause it to be more susceptible to long-lasting damage than is the case with adults (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005; Choe et al., 2012; Dennis et al., 2013, 2014). The same processes that encourage neural development during the childhood and adolescent years, such as synaptic pruning and apoptosis, can also make the young brain more susceptible to prolonged negative outcomes after injury as these core developmental processes can be modified or halted as a result of early brain insult (Anderson et al., 2011; Dennis et al., 2013, 2014). As at any age, many intrinsic and extrinsic factors can influence the recovery process, and neither an 'early plasticity' or 'early vulnerability' hypothesis can fully account for the range of functional outcomes possible after pediatric brain injury (Anderson et al., 2011). However, it is important to consider the factors that may increase this population's susceptibility to poor outcomes.

The potential increased vulnerability of the young brain can be explained by its lack of structural and functional maturity, as well as by the ability of neural damage at this age to interrupt and interact with the rest of the neural developmental trajectory (Anderson et al., 2011; Dennis et al., 2013, 2014). From a structural perspective, the protracted myelination patterns observed throughout childhood and adolescence, especially in cortical regions involved in higher cognitive function such as the frontal regions, can make neurons and fibre tracks more susceptible to damage as they are lacking the protective, insulating fatty layer that increased myelination provides (Asato, Terwilliger, Woo, & Luna, 2010; Lenroot & Giedd, 2006; Nagy, Westerberg, & Klingberg, 2004). As inter-cortical fibre connections are formed primarily of myelin, this makes children especially vulnerable to DAI from the shearing forces that are so common in concussion (Meaney & Smith, 2011).

Injury anywhere in the brain during development can have widespread influences on whole-brain development. The interactive specialization (IS) theory of functional brain development states that in addition to the maturation of focal brain regions, cognitive abilities emerge through the interaction between cortical regions, with these neural pathways becoming more specialized with time and use (Crone & Ridderinkhof, 2011; Johnson, 2011). Therefore, focal or diffuse damage following pediatric brain injury can interfere with this interactive process, causing aberrant functional specialization in the brain and disrupting the establishment of functional neural networks (Anderson et al., 2011). In support of the IS theory, lesion research has demonstrated that typical development of many cortical regions is dependent on whole-brain integrity (Crone & Ridderinkhof, 2011), and additionally, DAI has shown to be more damaging than focal injury in pediatric populations due to the disruption of intra-cortical communication (Anderson et al., 2011). Further, many *critical periods* exist throughout development where the nervous system is especially sensitive to environmental inputs and experiences, and therefore injuries sustained during this time period can have an even greater influence on active brain development both at the time of injury and for the rest of the developmental trajectory (Dennis et al., 2013).

Finally, early brain insult is thought to be especially detrimental for the functional skills that have not yet emerged at the time of injury. Considering the protracted trajectory of skill acquisition through childhood and adolescence, brain insult at an early age may not have any visible functional implications until a certain skill is expected to emerge (i.e. “growing into a deficit”). Further, early cortical disruptions may result in a persistent gap in acquiring cognitive skills on an appropriate maturational timeline (i.e. “arrested development”) (Andersen, 2003; Anderson et al., 2011; Dennis et al., 2013; Meekes, Jennekens-Schinkel, & van Schooneveld, 2006; Schneider, 1979). The delayed negative ramifications may also contribute to the underestimation of the detrimental effects of pediatric TBI.

2.4 Neuropsychological profile of concussion

The neuropsychological profile of individuals post-concussion is highly heterogeneous, depending on various pre- and post-injury factors, both individual and contextual, as well as on characteristics of the injury itself (Daneshvar et al., 2011; Yeates, 2010). Just as no two concussions will involve an identical insult to the brain, no two concussions will present the same in relation to neurocognitive outcomes. Notably, cognitive challenges are reported more frequently and for a longer time period following injury in pediatric populations compared to adults (Barlow et al., 2010; Daneshvar et al., 2011; Zemek et al., 2016). While these challenges can span all aspects of cognitive functioning, the typical cognitive changes that result from concussions can be explained from a neuroanatomical perspective. The frontal lobes are the most commonly damaged region following TBI (Eierud et al., 2014; McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017; Werner & Engelhard, 2007). They are especially vulnerable to neural damage in concussion due to (1) their large size relative to other cortical regions, (2) their close proximity to the bony protrusions at the front of the skull, and finally, unique to pediatric and young adult populations, (3) the protracted maturation of this cortical region in regards to myelination and connectivity with more posterior and subcortical brain regions (Choe, 2016; Eierud et al., 2014). Further, the widespread damage to axonal connections common to the concussion injury profile can disrupt the speed and integrity of cross-cortical communication in functional networks that are essential for complex cognitive functioning (Aoki et al., 2012; Choe, 2016; Choe et al., 2012).

As a result of this injury profile, individuals with concussion often demonstrate worse performance than healthy controls on cognitively challenging tasks that require coordinated activity and efficient communication across the brain. These complex cognitive challenges commonly present themselves in neuropsychological testing and laboratory settings as difficulty with task switching, problems dividing and sustaining attention, and difficulties with working memory (Babikian et al., 2011; Baillargeon et al., 2012; Bryer et al., 2013; Chen et al., 2012; D. Howell, Osternig, Van Donkelaar, Mayr, & Chou, 2013; Krivitzky et al., 2011; Kwok, Lee, Leung, & Poon, 2008; Moore et al., 2016; Ozen, Itier, Preston, & Fernandes, 2013). Further, individuals with concussion typically show compromised information processing speed and therefore slower reaction times in these cognitively overwhelming situations (Babikian et al., 2011; Bernstein, 2002; Karr, Areshenkoff, & Garcia-Barrera, 2014; Register-Mihalik, Littleton, & Guskiewicz, 2013; Sinopoli et al., 2014). Due to these cognitive difficulties, affected individuals often experience challenges on dual task paradigms, which require performance of two tasks simultaneously, introducing loads on sustained attention and cognitive control in addition to the specific demands of each of the combined tasks (Cicerone, 1996; De Monte et al., 2005; Howell, Osternig, & Chou, 2013; Register-Mihalik et al., 2013; Sinopoli et al., 2014). Dual tasks can range from cognitive-motor dual tasks, where experimenters are typically assessing how the cognitive demand of a co-occurring cognitive task may interfere with motor outcomes of interest (e.g., postural sway while performing numerical subtraction during a postural control task), to cognitive-cognitive dual tasks, where experimenters are assessing how the increased load of two co-occurring tasks impacts cognitive performance on each task (e.g., accuracy and reaction time during a dual working memory task). These tasks create cognitive demands representative of ecologically valid cognitive strain, providing better insight into the challenges this population may face in everyday life. They can be essential for revealing cognitive difficulties in this population that may not present on isolated cognitive activities (Register-Mihalik et al., 2013; Sinopoli et al., 2014).

Changes in cognitive performance after concussion have been documented from the acute and subacute periods immediately following injury, into the chronic period upwards of 1-2 years post injury for a subset of individuals (Daneshvar et al., 2011; McInnes et al., 2017). Further, for children and youth, residual effects of these cognitive difficulties can continue to impact subsequent development across the lifespan (Babikian et al., 2011; Babikian, Merkley, Savage, Giza, & Levin, 2015; Howell et al., 2013; Lax et al., 2015; Loher, Fatzer, & Roebers, 2014; Moore et al., 2016). Attention, working memory, task switching, and dual tasking all constitute higher-level, ‘top-down’ mental processes involved in coordinating multiple basic cognitive activities in order to attain goals (Diamond, 2012). These complex cognitive skills are often referred to as executive functions (EF) (Diamond, 2012; Jurado & Rosselli, 2007). More complex EFs, such as reasoning and planning, arise through a combination of these core EF skills. These abilities are especially of interest when considering an individual’s capacity to function in everyday life, as they are intrinsically related to social and academic success, and are also implicated in mental and physical health as well as cognitive and psychological development (Diamond, 2012; Manchester, Priestley, & Jackson, 2004).

2.4.1 Working memory outcomes of concussion

Working memory is a core component of executive function and higher level cognition (Mccabe, Roediger, Mcdaniel, Balota, & Hambrick, 2010) involving the short-term retention and manipulation of information to perform a task (Baddeley, 2003). Working memory is critical for daily activities and demands, including those involving cognitive “cold” processing, such as following instructions and sustaining conversations, as well as those involving affective “hot” processing, such as perceiving and responding to emotional information (Hofmann, Schmeichel, & Baddeley, 2012). Notably, decreases in working memory abilities have been correlated with various negative outcomes including diminished academic performance (St Clair-Thompson & Gathercole, 2006) and compromised peer relationships (Kofler et al., 2011; Phillips, Tunstall, & Channon, 2007). Considering the widespread network engagement of both the frontal and parietal regions during working memory activities (Hampson, Driesen, Roth, Gore, & Constable, 2010; Owen, McMillan, Laird, & Bullmore, 2005), it is to be expected that persisting challenges with working memory are being increasingly recognized subsequent to concussion and mTBI (Bryer et al., 2013; Chen et al., 2012; Keightley et al., 2014; Krivitzky et al., 2011; Moore et al., 2016; Ozen et al., 2013; Westfall et al., 2015). However, the exploration of performance in this cognitive domain post-concussion and mTBI is relatively new. Further, working memory is typically assessed as part of larger neuropsychological evaluations, and therefore is not always the primary focus of concussion research studies. As a result of this, the specific nature of these difficulties in regards to both the type of working memory that is most challenging (e.g., visuospatial versus verbal working memory) and the component of working memory performance most commonly affected (e.g., accuracy, inhibition, reaction time), is not well understood, especially in the pediatric population. There is a pressing need to characterize working memory performance post-injury in order to best understand the potential cognitive challenges youth may face, as well as to develop the most effective treatment protocol to facilitate recovery.

2.4.2 Current treatment interventions for persisting cognitive symptoms following concussion

Research on concussion, especially that focused on the pediatric population, is still very new. Therefore, it is not surprising that there is currently a paucity of effective therapeutic interventions to facilitate recovery for individuals experiencing persisting cognitive symptoms following concussion (Hadanny & Efrati, 2016). Typical treatment protocols prescribe increased rest and extended periods of inactivity until asymptomatic, when activity can be gradually reintroduced (McCrory et al., 2013), however meta-analyses have shown that evidence supporting this protocol is limited and contradictory (Schneider et al., 2013; Silverberg & Iverson, 2012). In the context of treating persisting symptoms (i.e., symptoms lasting over 10-14 days in adults and >4 weeks in children (McCrory et al., 2017), this typical procedure can increase the risk of secondary problems, such as heightened anxiety and irritability, and can even contribute to symptom maintenance (Schneider et al., 2013), as it keeps individuals from engaging in their daily lives in a meaningful manner. This conflicting evidence has been reflected in the most recent concussion consensus statement, which refers to the insufficient evidence that extended rest while symptomatic is useful in attaining rehabilitation goals. It is now advised in the statement that patients be encouraged to slowly return to activity after a short period of rest (24-48 hours) in the acute phase following injury (McCrory et al., 2017). Active rehabilitation programs which gradually introduce aerobic activity into the daily lives of affected individuals have been shown to be a promising means to promote recovery and diminish the frequency of occurrence of persisting symptoms (Gagnon, Galli, Friedman, Grilli, & Iverson, 2009; Hadanny & Efrati, 2016). Considering this shifting perspective on concussion rehabilitation, there is a pressing need to continue to explore potential therapeutic interventions that can modify the recovery trajectory.

2.5 Non-invasive brain stimulation technologies: Their role in a rehabilitation setting

Non-invasive brain stimulation (NIBS) technologies have become a central focus of neuroscience research due to their ability to modulate cortical functions and enhance cognitive abilities. They have been widely used to better understand basic principles of neuroplasticity and human cognition (Filmer, Dux, & Mattingley, 2014), as well as to improve skill learning and cognitive control (Filmer, Mattingley, & Dux, 2013; Martin et al., 2013; Sarkis, Kaur, & Camprodon, 2014; Strobach, Soutschek, Antonenko, Flöel, & Schubert, 2015). This is done by increasing or decreasing the threshold for action potentials in neurons, capitalizing on principles of neuroplasticity (Page et al., 2015; Stagg & Nitsche, 2011). NIBS technologies are being progressively recognized for their therapeutic potential in the context of rehabilitation, primarily due to their promising utility to promote the recovery of cognitive or motor function following injury (Cramer et al., 2011; Hummel & Cohen, 2006; Page et al., 2015; Shin, Dixon, Okonkwo, & Richardson, 2014).

Within the context of recovery after brain injury, NIBS technologies can be viewed as an intervention factor that can interact with pre-existing neural and functional plasticity mechanisms in order to promote adaptive plasticity and therefore improve functional outcomes (Cramer et al., 2011; Li et al., 2015; Nudo, 2013; Shin et al., 2014). Through modulating neuronal firing, NIBS technologies can facilitate increases in synaptic strength and the modification of network connections, as well as influence neurotransmitter release and excitotoxcity processes, therefore interacting with all core aspects of cerebral dysfunction present following concussion (Choe, 2016; Li et al., 2015; Shin et al., 2014). NIBS technologies have the most promising clinical utility when used in conjunction with pre-existing neurorehabilitation interventions, as they can reinforce adaptive neural activity elicited by engaging in these paradigms, and therefore promote long-term cortical changes through long-term potentiation (LTP) mechanisms (Li et al., 2015; Shin et al., 2014).

2.5.1 Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is the least invasive and most cost-effective form of brain stimulation, contributing to its prevalent use in rehabilitation research (Brunoni et al., 2012). It modulates cortical activity to promote neuroplasticity through the administration of a low-electrical current. This current acts on the neuronal resting membrane potential to influence ion exchange through the voltage-gated calcium (Ca^{2+}) and sodium (Na^{+}) channels to promote (anodal tDCS) or deter (cathodal tDCS) the occurrence of an action potential, impacting communication patterns within and between brain regions (Paulus, 2003; Stagg & Nitsche, 2011) (see Figure 2.1). Influencing neuronal communication patterns can modulate the strength of synaptic connections, which can effectively promote skill acquisition, and eventually result in functional and structural changes (Kolb & Muhammad, 2014).

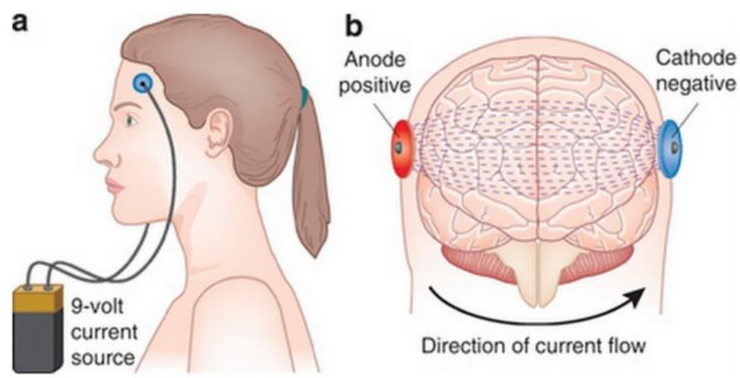

Figure 2.1. Overview of the mechanisms of tDCS provided by George & Aston-Jones, 2009.

2.5.1.1 Applications of tDCS. tDCS has successfully been used in the promotion of skill learning and cognitive and motor performance (Cantarero et al., 2015; Ciechanski & Kirton, 2017; Ohn et al., 2008), as well as in rehabilitation therapy (Brunoni et al., 2012; Convento, Russo, Zigiotto, & Bolognini, 2016; Hummel & Cohen, 2006; Li et al., 2015; Page et al., 2015). Its subthreshold, non-invasive properties make it safe and feasible to use with adults and children (Palm et al., 2016), both healthy controls and clinical populations (Bikson et al., 2016; Poreisz, Boros, Antal, & Paulus, 2007). The utility of tDCS can be attributed to the fact that electrodes can be placed in different locations on the scalp to concentrate current flow to specific brain regions of interest (Stagg & Nitsche, 2011). Therefore, behavioural changes will be dependent on the specializations of the stimulated or inhibited cortical region, a factor that is critical for its use in a rehabilitation context as it facilitates the targeting of cortical areas corresponding with behaviours and skills of interest. This allows researchers and clinicians to see predictable changes in behaviour based on what is known about brain-behaviour relationships.

2.5.1.2 tDCS can interact with cognitive processes. tDCS has been extensively used to improve cognitive performance in healthy controls and clinical populations. One of the most prominent uses of tDCS in this capacity is in the area of executive functions (Coffman, Clark, & Parasuraman, 2014; Sarkis et al., 2014), including skills such as working memory, sustained attention, and inhibitory control (Diamond, 2012; Elliott, 2003; Jurado & Rosselli, 2007). Across these challenging EF paradigms, tDCS is often administered to prefrontal areas, the cortical areas primarily responsible for executive control and coordinating the allocation of cognitive resources (Stuss, 2011). Many studies have identified the beneficial effect of tDCS on isolated cognitive tasks engaging single components of executive function abilities, supporting the potential of this technology to influence neuroplasticity and enhance cognitive performance and skill acquisition (Brunoni & Vanderhasselt, 2014; Coffman et al., 2014; Ditye, Jacobson, Walsh, & Lavidor, 2012; Flöel, 2014; Fregni et al., 2005; Hill, Fitzgerald, & Hoy, 2016; Kuo & Nitsche, 2012; Ohn et al., 2008; Sarkis et al., 2014).

Further, tDCS has been used extensively to improve performance on diverse dual task paradigms, ranging from cognitive-motor dual tasks to cognitive-cognitive dual- asks. Anodal tDCS to the dorsolateral prefrontal cortex (DLPFC) has been shown to improve balance, gait, and postural control while a cognitive task is concurrently performed in healthy controls and clinical populations (Manor et al., 2015; Swank, Mehta, & Criminger, 2016; Zhou et al., 2015; Zhou et al., 2014), as well as to increase cognitive performance during multitasking and divided attention paradigms inducing cognitive overload (Filmer et al., 2013; Strobach et al., 2015), including dual working memory paradigms (Martin et al., 2013; Martin, Liu, Alonzo, Green, & Loo, 2014). The promising findings of tDCS in dual task paradigms suggest that tDCS administration has the ability to improve cognitive performance through modulating overarching processes of executive control.

2.6 The potential clinical utility of tDCS for persisting cognitive concussion symptoms

tDCS has the potential of being an excellent rehabilitative tool as it can be used to target and induce beneficial changes in neuronal communication and firing in the specific brain region that appears to be vulnerable in concussion and extensively implicated in the EFs that are consistently negatively impacted in these injuries: the prefrontal cortex (PFC). Recent reviews have shown that NIBS technologies have clinical utility in improving recovery from TBI in adults in multiple domains, including general cognitive abilities and executive functioning (Clayton, Kinley-Cooper, Weber, & Adkins, 2016; Li et al., 2015; Shin et al., 2014), as well as for improving persisting concussion symptoms (Koski et al., 2015); however the literature is still in its infancy. More research is needed to know the therapeutic potential of tDCS across varying severities of TBI as well as on executive function tasks more representative of daily cognitive demands. Additionally, there is a pressing need to further characterize the therapeutic effects of tDCS within the unique developmental context of a paediatric population.

Considering the well-supported ability of tDCS to interact with the injury mechanisms of concussion and to enhance performance on the same complex cognitive functions that are typically compromised in youth with persisting symptoms, its ability to facilitate cognitive recovery following concussion must be explored in order to improve the lives of affected youth. Finally, in order to harness the promising clinical utility of NIBS technologies and design the most effective therapeutic interventions for individuals with persisting concussion symptoms, the specific nature of these symptoms must be well characterized. While the body of evidence on concussion symptomology is growing, future research must focus on synthesizing this information through structured review strategies in order to better establish the cognitive profile of these injuries and, consequently, design the most appropriate interventions.

Chapter 3
Working Memory Outcomes of Paediatric Concussion

3 Abstract

Background: The potential for paediatric concussion to result in persisting detrimental effects on cognitive performance is becoming increasingly recognized, with executive functions (EFs), including working memory, being the most commonly impacted cognitive domain. Working memory involves the short-term retention and manipulation of information to perform a task. Despite its vulnerability to injury, the specific nature of post-injury working memory challenges is not well understood in the paediatric population. It is essential that post-injury working memory performance is better characterized in order to understand how the unique neuropsychological profile of affected children and youth may impact their ability to participate in daily life.

Objective: The aim of this review was to systematically characterize the working memory profile of children and youth who have experienced concussion, through synthesizing existing literature on the neuropsychological outcomes of these injuries.

Methods: A peer-reviewed (PRESS 2015 guidelines) and standardized search strategy combining the key concepts of concussion/mTBI, working memory, and paediatrics was implemented across four academic databases (MedLine, Embase, PsycINFO, CINAHL) in order to identify studies reporting on working memory performance following paediatric concussion. Narrative synthesis was applied to summarize the findings of included studies and explore trends in the literature.

Results: Working memory is a cognitive skill that is vulnerable to insult following paediatric concussion, however the nature of these outcomes are highly variable. No clear trends emerged regarding the type or component of working memory that may be especially susceptible to the impact of concussion. Factors related to working memory outcomes included, but were not limited to: age at injury, time since injury, functional and structural cortical properties, and daily functional behaviours.

Implications and Conclusion: The findings of this review made a significant contribution to a more comprehensive understanding of the cognitive sequelae of paediatric concussion. Further,

they highlighted critical areas for future research, which can aim to reduce the heterogeneity in the literature. Together, this will enable children and youth to receive the most appropriate care post-concussion.

3.1 Introduction

Concussion and mild traumatic brain injuries (mTBI) are a rising public health concern (National Center for Injury Prevention and Control, 2003). 94,000 concussions are reported annually in Canada alone, and further, this number is likely a broad underrepresentation of the actual incidence rate, as these injuries are vastly underreported and not tracked appropriately (Billette & Janz, 2011; Kroshus, Baugh, Daneshvar, & Viswanath, 2014; McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). While definitions vary, concussions and uncomplicated mTBIs refer to brain injuries resulting in a change in the Glasgow Coma Scale (GCS) score within the range of 13-15, independent of any cranial damage (e.g., skull fracture) or abnormalities on neuroimaging findings (e.g., contusions or hemorrhages) (Iverson et al., 2012; McCrory et al., 2013, 2017; Williams, Levin, & Eisenberg, 1990). These injuries are caused by an external biomechanical force, resulting in a functional disruption in cortical activity that is typically accompanied by a variety of clinical symptoms spanning affective, physical, and cognitive domains (Ayr, Yeates, Taylor, & Browne, 2009; McCrory et al., 2013, 2017; Zemek, Barrowman, Freedman, Gravel, Gagnon, McGahern, et al., 2016). Due to the overlapping in injury criteria, "uncomplicated mTBI" will be included within the term "concussion" throughout the rest of this manuscript. The ability of these injuries to cause a lasting impact on an individual's capacity to participate in everyday life has become increasingly recognized (McCrory et al., 2013, 2017; Yeates, 2010), supporting the necessity of better understanding the functional ramifications of concussion.

3.1.1 Vulnerability of youth to concussion and persisting symptoms

Age appears to play a critical role in the incidence of concussion (Baillargeon et al., 2012; Cassidy et al., 2004; McCrory et al., 2013, 2017; Morrish & Carey, 2013). These injuries occur at a rate of 3.3 per 100,000 youth (aged 12-19) in Canada, which is a notably higher injury rate than that observed in adults (rate of 2.1/100,000 in those aged 20-64), and the elderly (rate of 1.1/100,000 in those aged 65+) (Billette & Janz, 2011). In Ontario specifically, there has been over a 4-fold increase in emergency room visits for paediatric concussion in the ten year period following 2003, rising to almost 35,000 annual visits in 2013 (Zemek et al., 2017). Additionally, evidence suggests that youth may be at the greatest risk for developing persisting symptoms after concussion, especially in the cognitive domain (Baillargeon et al., 2012), amplifying the debilitating impact of these injuries (McCrory et al., 2017; Zemek et al., 2016). The expected clinical recovery trajectory for children and youth with concussion is 2-4 weeks, almost double the 7-10 day recovery window typically seen in adult populations (Barlow et al., 2010; Davis et al., 2017; McCrory et al., 2017; Zemek et al., 2016). Further, over 30% of youth fail to recover in this expected timeline, continuing to experience symptoms at 1-month post-injury (Barlow et al., 2010; Davis et al., 2017; McCrory et al., 2017; Zemek et al., 2016). Any symptom lasting over 28 days in children and youth is considered a ,,lll; post-concussion symptom (PPCS) (Ayr et al., 2009; Zemek et al., 2016) . Experiencing these symptoms can substantially limit an individual’s ability to carry out daily activities, and is negatively correlated with health-related quality of life (Daneshvar et al., 2011; McCrory et al., 2013, 2017; Yeates, 2010; Yeates et al., 2012; Fineblit, Selci, Loewen, Ellis, & Russell, 2016; Novak et al., 2016). Anecdotally, youth often report these symptom-driven functional limitations in response to the question “what is the worst thing for you about having a concussion” (Stein et al., 2016, p. 387-388).

Despite the vulnerability of youth to concussion and related negative outcomes, the majority of concussion research has focused on adult populations. The impact of these injuries in youth must be understood within the unique context of the developing brain, and therefore findings from adult research cannot be directly applied to the paediatric population (Anderson et al., 2011; McCrory et al., 2017). The critical need to understand the distinct impact of concussion in children and youth has led to the most recent international consensus statement on concussion in sport listing the paucity of research on paediatric outcomes as a pressing priority to be addressed (McCrory et al., 2017).

3.1.2 Cognitive post-concussion symptoms

Widespread cognitive challenges are one of the most prevalent and detrimental clinical outcomes of concussion (Novak et al., 2016; Yeates et al., 2012). A recent scoping review found that approximately half of individuals experience long-term cognitive impairment after a single mTBI (McInnes et al., 2017). While all cognitive functions are at risk of damage post-injury, the diffuse disruption in cortical activity characteristic of the neuropathology of concussion puts complex cognitive abilities requiring efficient communication within and between cortical regions at an elevated risk for disruption (Babikian et al., 2011; Baillargeon et al., 2012; Howell, Osternig, Van Donkelaar, Mayr, & Chou, 2013; Kwok, Lee, Leung, & Poon, 2008; Ozen, Itier, Preston, & Fernandes, 2013). These abilities generally fall in the category of executive functions (EFs), or higher-order cognitive skills responsible for regulating, planning, and organizing behaviour to achieve goals, including abilities such as inhibition, set shifting (i.e., cognitive flexibility), task switching or dual tasking, and working memory (Best & Miller, 2010; Diamond, 2012; Elliott, 2003). The critical involvement of EFs in goal-directed behaviour makes them essential for almost all aspects of daily functioning, with EF abilities associated with school readiness, quality of life, math and reading competency, social competency, job productivity, and more (see Diamond, 2012 for review). Considering the importance of functional participation to the quality of life of youth (Fineblit et al., 2016; Novak et al., 2016; Yeates, 2010), there is a definite need to better understand the impact of paediatric concussion on various EF outcomes.

3.1.3 Overview of working memory

Working memory is a core EF involving the temporary (i.e., seconds to minutes) retention and manipulation of information (Baddeley, 2003; Eriksson, Vogel, Lansner, Bergstrom, & Nyberg, 2015; Ma, Husain, & Bays, 2014). This cognitive skill allows mental representations to be held in a briefly accessible state, letting that information be used to meet various cognitive demands (Eriksson et al., 2015). Working memory is fundamentally limited in capacity, with an individuals' working memory "span" referring to the maximum number of items they can hold in this active memory state (Luck & Vogel, 2013). Working memory is understood as a complex system, with different core cognitive processes supporting the encoding, maintenance, and retrieval of information. This includes selective and sustained attention as well as perceptual and long-term memory representations (Baddeley, 2003; D'Esposito & Postle, 2015; Eriksson et al., 2015).

As with many other cognitive abilities, working memory skills increase exponentially during the first two decades of life, growing by an average of 23 standard points from age 5 to 19, which is almost 6 times the increases seen during adulthood (Alloway & Alloway, 2013; Pelegrina et al., 2015). While the basic structure of the working memory system appears to be formed by age six (Gathercole, Pickering, Ambridge, & Wearing, 2004), more complex aspects such as the ability to manipulate spatial representations and self-monitor and organize representations strategically (i.e., working memory tasks placing demands on executive controls), continue to develop past late adolescence (Luciana, Conklin, Hooper, & Yarger, 2005; Pelegrina et al., 2015), with a peak in working memory abilities seen in the early 30s (Alloway & Alloway, 2013; Cansino et al., 2013).

Working memory abilities are critically related to fluid intelligence (Unsworth, Fukuda, Awh, & Vogel, 2014) and general 'hot' and 'cold' cognition (Johnson et al., 2013). Examples of "cold" cognition include mathematical skills (Bull, Espy, & Wiebe, 2008; Dumontheil & Klingberg, 2012; Simmons, Willis, & Adams, 2012), academic achievement, especially in math and English (St Clair-Thompson & Gathercole, 2006), and decision making (Hinson, Jameson, & Whitney, 2003), where examples of "hot" cognition include emotional regulation (Schmeichel, Volokhov, & Demaree, 2008), and the processing of social cues (Phillips et al., 2007). Notably, working memory has been shown to account for unique or greater variance in subsequent academic achievement than other educational baseline assessments (Gathercole, Brown, & Pickering, 2003) and complete IQ scores (Alloway & Alloway, 2010), respectively. Therefore, working memory abilities are essential to an individual's ability to function in daily life.

3.1.3.1 Cognitive models of working memory. Cognitive models are widely utilized to represent the complexity of working memory. While a myriad of definitions and theoretical models have been used to describe this cognitive function (Cowan, 2017; D'Esposito & Postle, 2015; Eriksson et al., 2015), the two pervasive theoretical approaches conceptualize working memory through either a multicomponent model or a state-based model (D'Esposito & Postle, 2015a; Oberauer, 2002; Repovs & Baddeley, 2006).

The multicomponent model of working memory was originally developed by Baddeley and Hitch in 1974, based on evidence that working memory is supported by a collective cognitive system with various subsystems, each of which processes and inputs sensory information in a unique manner to support the temporary storage of these representations (see Baddeley, 2003, 2012 for review). This collective system involves four subcomponents: the central executive, the visuospatial sketchpad, the phonological loop, and the episodic buffer (Repovs & Baddeley, 2006). The central executive acts as a source of attentional control, monitoring and guiding the other subsystems through sustaining, diving, and switching attention onto relevant, goal-directed information (Baddeley, 2012; Eriksson et al., 2015; Repovs & Baddeley, 2006). The visuospatial sketchpad and phonological loop both facilitate the maintenance and manipulation of this goal-relevant information, with the visuospatial sketchpad supporting the feature-based retention of visual and spatial information, and the phonological loop supporting the maintenance of auditory information through a phonological store and articulatory rehearsal process (Baddeley, 2012; Repovs & Baddeley, 2006). Based on this model, the information being held within working memory is therefore limited to whichever mental representations were being rehearsed in these specialized buffers (Eriksson et al., 2015). Finally, the episodic buffer then acts as an intermediary between the rest of the subsystems and long-term memory, integrating information from the different processing codes of each subsystem into complex, comprehensive representations (Baddeley, 2012; Eriksson et al., 2015; Repovs & Baddeley, 2006). Multi-component models effectively describe how, through the guidance of a primary executive component, the working memory system allows for the encoding and maintenance of a variety of sensory information, in order to meet cognitive demands and update long-term memory representations.

State-based models share many similarities with multi-component models, including a belief in the critical role of attentional processes in working memory. However, rather than focusing on how various subsystems can support the encoding and maintenance of sensory information, state-based models commonly theorize that the allotment of attention to relevant internal mental representations (e.g., perceptual or long-term memory representations) facilitates the maintenance of information in working memory (Oberauer, 2002, 2013; Eriksson et al., 2105; D'Esposito & Postle, 2015). These models therefore do not propose any formal distinction between the processes that support working memory representations and those supporting long-term memory or perceptual representations, or even between the representations themselves (Eriksson et al., 2015). Through selective attention, mental representations can be brought to an accessible state to support the encoding of new, related, information, or to support recall. The critical role of attentional allocation proposed in state-based models is supported by behavioural and neural evidence that information can be held in different states of representation within working memory (D’Esposito & Postle, 2015; Oberauer, 2002, 2013).

Many models have theorized about the specific role of attention within working memory and its influence on working memory capacity (Cowan, 2000, 2010; Cowan et al., 2005; Mcelree &

Dosher, 1989; Oberauer, 2013). To conceptualize evidence on the different attentional states of working memory, Oberauer (2002, 2009) introduced a circular, three-component model, comprised of the following attentional regions within which information can be held in an accessible state: (1) the focus of attention, (2) the region of direct access, and (3) the activated part of long-term memory. Within this model, attention can be focused on specific components of the immediately accessible items in the region of direct access (Oberauer, 2002, 2009). This attentional focus can then act as a cue to recruit related representations from long-term memory (Oberauer, 2002, 2009). Similar theoretical propositions exist for the recruitment of sensory information to support working memory (Oberauer, 2002, 2009). While various models exist within the state-based theoretical approach, state-based models generally conceptualize working memory as a combination of various mental representations selected through our attentional processes, categorized by their differing levels of accessibility for cognitive operations (Cowan, 2000, 2010; Cowan et al., 2005; D'Esposito & Postle, 2015; Eriksson et al., 2015; Oberauer, 2002, 2009, 2013) .

3.1.3.2 Cognitive neuroscience of working memory. Common across all cognitive models of working memory is the concept that its function is reliant on numerous independent, higher-order, cognitive abilities (D'Esposito & Postle, 2015; Eriksson et al., 2105; Cowan, 2017); therefore, it follows that working memory is supported by a diverse cortical network, characterized primarily by focal, persistent, activity in the prefrontal and parietal cortices (D'Esposito & Postle, 2015; Darki & Klingberg, 2015; Eriksson et al., 2015; Lara & Wallis, 2015; Owen et al., 2005; Roux & Uhlhaas, 2014). The cortical network underlying working memory involves the simultaneous operation of many specific neural mechanisms, each supporting one or many of the subcomponents of the cognitive skill, as part of a greater system in the brain focused on executing goal-directed behaviour (D'Esposito & Postle, 2015). Evidence for the critical role of the prefrontal and parietal regions in working memory comes from findings that excitatory non-invasive brain stimulation over the prefrontal regions can transiently improve working memory performance (see Brunoni & Vanderhasselt, 2014 for review), and further, that functional connectivity between posterior and frontal regions, both at rest and during a working memory task, is positively correlated with task performance (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006).

While task-specific focal cortical activity is concentrated in prefrontal and parietal regions during working memory, many other regions contribute to the active maintenance and storage of information, including modality-specific activity in the sensory cortices, such as the visual cortex (Eriksson et al., 2015; Sreenivasan, Curtis, & Esposito, 2014). Research suggests that it may actually be in these sensory cortices that information is held during working memory, with the prefrontal cortex playing a larger role in engaging the executive processes needed to remain focused on goal-relevant information, than in the maintenance itself (Lara & Wallis, 2015; Sreenivasan et al., 2014). Dynamic communication between isolated focal brain regions is therefore essential to facilitating the complex cognitive interactions that support working memory.

On a systems level, the neural mechanisms supporting working memory, as outlined in D'Esposito & Postle, 2015, include the following: (1) persistent neural activity in the prefrontal regions, allowing the encoding maintenance of cognitive representations without sensory input and/or supporting the executive processes needed for this maintenance (Olesen, Westerberg, & Klingberg, 2003; D'Esposito & Postle, 2015; Lara & Wallis, 2015; Riley & Constantindis, 2016), (2) pervasive functional connectivity through long-range synchronized neural activity across brain areas, facilitating communication between the variety of frontal and posterior brain areas supporting the different subcomponents of working memory, including the sensory cortices (Lara & Wallis, 2015; Pasternak & Greenlee, 2005; Roux & Uhlhaas, 2014) (3) hierarchical organization of perceptual representations in the prefrontal cortex, and top-down signaling from prefrontal regions, biasing downstream working memory processes to focus on goal-relevant information (Baddeley, 2012; D'Esposito & Postle, 2015; Eriksson et al., 2015; Oberauer, 2013), and (4) neuromodulators including dopamine which have a regulatory effect on working memory function through influencing prefrontal cortex function (D'Esposito & Postle, 2015).

Considering the breadth of cortical and subcortical regions implicated in working memory, it follows that the growth of working memory abilities across development is dependent on more general trends in the maturation of gray and white matter. Longitudinal studies have found that improvements in working memory across development are highly interrelated with the maturation of grey and white matter in the fronto-parietal network, as well as subcortical structures (Darki & Klingberg, 2015; Ullman, Almeida, & Klingberg, 2014). While activity in the frontal and parietal cortices is positively correlated with current working memory capacity

(Geier, Garver, Terwilliger, & Luna, 2009; Ullman et al., 2014), white matter fractional anisotropy in these regions has shown to be predictive of future working memory capacity (Darki & Klingberg, 2015). Further, the emergence of working memory capacity across development is positively correlated with cortical thinning and synchronized activity in the frontal and parietal regions (Darki & Klingberg, 2015), as well as activity in the thalamus and caudate nucleus (Ullman et al., 2014). The critical reliance of working memory abilities on more general cortical maturation further supports the need to understand paediatric working memory function and dysfunction uniquely from a developmental lens.

3.1.4 Working memory outcomes of paediatric concussion

The widespread disruption in cortical activity and functional connectivity characteristic of the concussion injury profile increases the susceptibility of working memory to damage following injury, as this disruption can negatively impact the integrity and operation of the diffuse fronto-parietal network supporting this cognitive function (Choe, 2016). This is supported by research finding that compromised working memory performance post-concussion is correlated with injury-related changes in cortical activity and functional connectivity (van der Horn et al., 2015), as well as with structural changes in white matter integrity (Treble et al., 2013). The potential for damage is increased in the paediatric population, as cortical networks are at increased vulnerability to disruption due to their lack of functional and structural maturity (Anderson et al., 2011). Cortical damage and disruption during this period can therefore have a negative impact on all subsequent cortical development, putting children and youth at increased risk for a persisting gap in their acquisition of new cognitive skills (Anderson et al., 2011). Working memory challenges have been well-documented following paediatric TBI (Phillips, Parry, Mandalis, & Lah, 2017). While persisting challenges with working memory after paediatric concussion are being increasingly recognized (e.g., Baillargeon et al., 2012; Keightley et al., 2014; Sinopoli et al., 2014), the exploration of working memory performance post-injury is relatively new, and it is often assessed as part of larger neuropsychological evaluations. Because of this, the nature of working memory outcomes post-paediatric concussion are not well understood.

To date, no systematic review has been published specifically characterizing working memory outcomes after paediatric concussion. It is essential to better characterize the impact of paediatric concussion on working memory, in order to best understand how the unique neuropsychological profile of affected children and youth may impact their ability to participate in daily life, and further, to inform appropriate treatment interventions to address these needs.

3.2 Review objectives and research questions

The objective of this systematic review was to characterize and critically appraise the evidence on the working memory outcomes of paediatric concussion.

The primary research question was:

(1) Do children and youth who have experienced a concussion present with aberrant working memory abilities post-injury?

Secondary research questions included:

(2) If working memory is impacted by paediatric concussion, what is the nature of these outcomes in relation to the recovery trajectory and the type of working memory impacted?

(3) Are specific pre-injury, injury, or post-injury factors related to working memory outcomes?

(4) What types of methodological approaches are currently being used to assess working memory outcomes following concussion? What is the influence of these methodological approaches on working memory outcomes?

(5) What is the quality of the research which has been conducted to assess the impact of paediatric concussion on working memory performance?

In the context of the PICO model, as per PRIMSA guidelines, the **population** of interest for this systematic review was children and youth aged 21 and under. The **intervention** factor was not a clinical intervention, but was the injury factor of experiencing a concussion. The **control** was either a comparison group who had not received a concussion, pre-injury abilities, or population norms. The **outcome** of interest was working memory performance.

3.3 Review methods

The PRISMA statement for the preferred reporting of systematic reviews and meta-analyses was followed throughout protocol development and manuscript production (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

3.3.1 Search strategy

The search strategy was developed with the assistance of a medical research librarian, and was then peer reviewed by a separate medical research librarian according to the PRESS Peer Review of Electronic Search Strategies 2015 Guidelines (Mcgowan et al., 2016). This search strategy was then implemented across the following academic databases: MedLine (including ePub ahead of print, in-process & other non-indexed citations, 1946-August 2nd 2017), Embase (1946-August 2nd 2017), PsycINFO (1806-August 2nd 2017), and CINAHL (August 2nd 2017).

While this thesis was interested in synthesizing literature on working memory performance following paediatric concussion, we chose to take a broad scope and conduct a search encompassing concussion as well as mTBI, as these terms are used interchangeably in the literature (Kimbler, Murphy, & Dhandapani, 2011). Since concussion and uncomplicated mTBI shared very similar definitions (see section 4.1), citations were restricted to the uncomplicated subset of mTBI at the inclusion/exclusion stage when enough detail was provided to be able to do so.

The search strategy included subject headings and search terms comprehensively covering the subtopics of concussion and mTBI (e.g., Post-concussion syndrome/ and mild adj3 “traumatic brain injur*”), paediatrics (e.g., Child/ and adoelscen*), and working memory (e.g., working adj3 memor*, Memory, short-term/). See Appendix A for the complete search strategy.

3.3.2 Inclusion and exclusion criteria

The final **inclusion criteria** at the full-text stage were as follows: (i) studies must have solely reported on concussion or mTBI or have isolated mTBI results from other injury severities; (ii) population aged 21 years and under; (iii) included at least one working memory outcome measure with extractable results; and (iv) primary source peer reviewed studies written in English. However, in order to ensure that no relevant results were omitted, substantially broader inclusion criteria were applied at the title and abstract screening phase, with any study including a memory measure or neuropsychological measure moving to full-text screen, as well as any study where authors did not explicitly specify in their abstract that they were looking at a non-paediatric population only. **Exclusion criteria** applied at the title and abstract and full-text screen phases involved (i) studies only reporting on baseline or pre-injury working memory outcomes, (ii) studies that explicitly indicated examining complicated mTBI only[1], and (iii) reviews, commentaries, book chapters, position statements, conference publications, as well as case studies with less than five participants.

3.3.3 Search outcome

Through the search process a total of 1125 citations were identified across the four academic databases. 147 duplicates were identified and removed through the 'close duplicate' function on RefWorks (ProQuest LLC, 2017), and an additional 265 duplicates were identified through hand searching the results, leaving a total of 713 articles for title and abstract screen. Two reviewers independently screened the titles and abstracts according to the a-priori inclusion and exclusion criteria using the Covidence review management software (Covidence, 2017). Raters reached 80.14% interrater reliability. This is an expected reliability rate considering our purposely broad inclusion criteria at the title and abstract screen phase. It should also be noted that within Covidence a classification of a 'yes' and a 'maybe' response is identified as a conflict, despite the fact that the decision for both responses is to move the article to full-text screen and therefore does not represent a true conflict. All conflicts were resolved using the inclusion and exclusion criteria by a third reviewer who was otherwise uninvolved in the screening process. After title and abstract screen, 256 citations required a full-text screen, however N=58 were incomplete references which could not be identified through any academic libraries, leaving a total of N=198 complete references for full-text review. The second reviewer screened a subset of 15% of the

[1] Most studies did not provide enough detail to determine if they were solely examining uncomplicated mTBI. In order to ensure that this review comprehensively described the literature on working memory outcomes of concussion, papers were not excluded based on this lack of detail. This is outlined as a limitation of the literature and of this review (see section 3.5.5 and 3.5.6).

full-text articles to ensure reliability at this stage. Full text articles were initially screened for the age criteria. N=91 papers were excluded for not including or not separating a population aged 21 and under. Subsequently, N=47 studies were excluded for not including a working memory measure or not separating working memory findings. N=16 papers were excluded for not examining or separating concussion/mTBI findings. N=10 studies were excluded as they were reviews or commentary pieces. Finally, N=1 study was excluded as it was a case study with less than five participants. This left a total of N=33 articles for synthesis. See Appendix B for a flowchart of the search outcome.

3.3.4 Data extraction process

Data was extracted based on pre-determined factors that addressed our research questions including: Research group and geographical location, study design (including study type, overall methodological design, and primary aims), participant characteristics (including age, gender, concussion or mTBI diagnosis criteria for cases only, as well as age at injury, time since injury, injury mechanism, and injury history when available), outcome measures used, working memory outcomes (including change in outcomes over time for prospective cohort studies), and, finally, any factors related to working memory outcomes, if applicable.

3.3.5 Quality assessment

A quality assessment of all included articles was conducted by KQ and validated by AM using the National Institute of Health (NIH)'s National Heart, Lung, and Blood Institute (NHLBI)'s Quality Assessment of Observational Cohort and Cross-Sectional Studies (NHLBI, 2014). This tool is designed to assess risk of bias as well as internal validity (NHLBI, 2014). Studies were evaluated on each of the tool items as "yes", "no", "not applicable" and were then given an overall classification of "good", "fair", and "poor" based on the NHLBI's assessment guiding principles. A paper was rated as "good" quality when there were two or more "yes" than "no"/"doesn't specify" responses on all eligible criteria. A "fair" was defined as having equal "yes" and "no" responses, plus/minus one. A paper was deemed "poor" quality when there were two or more "no"/"doesn't specify" responses than "yes" responses, on all eligible items. "N/A" responses were treated neutrally. The exception to the above was for question #13 of the assessment, where a negative response actually indicates better study quality. When determining study quality, negative answers to question #13 were treated as a 'yes'.

3.3.6 Narrative synthesis

The studies included in the current review were highly heterogeneous in regards to the outcome measure used to assess working memory, the study design, as well as sample characteristics. Consequently, it was not appropriate to pool the review data into any statistical analysis. Narrative synthesis was therefore used to summarize the data considering the wide variety of study designs captured in the current review (Ryan R; Cochrane Consumers and Communication Review Group, 2013). Narrative synthesis is an interactive process involving an exploration of the similarities and differences between study findings, as well as identifying any visible trends in study findings. Identifying factors influencing these similarities and differences subsequently allows for the recognition of explanations for trends in the data.

3.4 Results

3.4.1 Study Characteristics

3.4.1.1 Concussion diagnosis. Concussion/mTBI diagnosis criteria utilized in the included studies were as follows: the GCS[2] (N=15), the American Congress of Rehabilitation Medicine criteria (N=5), the American Academy of Neurology guidelines (N=2), the WHO task force definition (N=4), the concussion consensus (3rd International Consensus Conference on Concussion in Sport in Zurich, 2008) (N=2), the ThinkFirst Concussion Questionnaire (N = 2), Abbreviated Injury Scale head scores (N=1), Centres for Disease control criteria (N=1), post-traumatic amnesia and surgeon standardized assessment (N=1), and solely clinical diagnosis of mTBI (N=3). N=3 studies utilized multiple confirmatory measures, accounting for the high total number. N=2 studies differentiated between complicated and uncomplicated mTBI, with one study using visible neuropathology as the differentiating factor, and the other using Yeates & Taylor's 2005 definition, which referred to Paediatric Coma Scores for the diagnosis criteria. 17/33 studies assessed imaging, and of these, 15/17 excluded based on positive neuroimaging findings or reported an absence of neuropathology on neuroimaging. However, 2/15 of these

[2] As the GCS is included as a diagnostic criteria in many definitions of concussion, this refers to any studies who used the GCS outside of the context of another assessment.

studies only had neuroimaging findings for a subset of their participants. Eight studies explored working memory outcomes in a sports-related concussion population[3]. Of these studies, six of these studies used a sample of non-injured athletes as their control group, while the remaining two studies used a general sample of healthy controls. Ten studies examined the impact of mTBI on working memory outcomes in the context of other injury severities, providing insight into the relative influence of severity scores. Only one study explored the impact of injury history on cognitive outcomes.

3.4.1.2 Study design. The three study designs captured in the review were prospective cohort studies (N=13), cross-sectional studies (N=19), and a pre-post intervention study (N=1). Working memory was one of the primary outcomes of interest in N=12 studies, whereas working memory was a secondary outcome in the remaining N=21 studies. Three pairs of studies (Anderson & Catroppa, 2007 and Catroppa, Anderson, Ditchfield, & Coleman, 2008; Mayer et al., 2012 and Mayer, Hanlon, & Ling, 2015; Sinopoli et al., 2014 and Urban et al., 2017) used the same participant sample, however as they each had independent research objectives they are treated as separate experiments throughout the reporting of review findings.

3.4.1.2.1 Exploring neuroimaging findings. A total of N=6 studies explored associations between neuroimaging outcomes and working memory performance. Of these, N=5 explored functional imaging findings and N=1 examined structural imaging findings. All of the former utilized functional magnetic resonance imaging (fMRI). The latter used magnetic resonance imaging (MRI) to assess cortical thickness through T1 imaging, as well as explored other structural properties through several scans including diffusion tensor imaging (DTI), susceptibility weight imaging (SWI), and fluid-attenuated inversion recovery (FLAIR).

3.4.1.2.2 Long-term follow-up or longitudinal design. In this review, a long-term follow-up was defined as an isolated assessment taking place at least 6 months after injury. A longitudinal design referred to any study that included multiple follow-ups at different points in time, which

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[3] A study was categorized as examining sports-related concussion if sport was the mechanism of injury for 85% and above of the study sample.

could occur within the first year after the initial assessment. A total of N=11 studies implemented a long-term follow-up, at time points ranging from 6 months to over 23 years post-injury. Further, of the N=13 prospective cohort studies, N=11 assessed working memory outcomes at multiple time points; all of these included a baseline assessment occurring within the first month post-injury, and one to four follow-up assessments, occurring from 10 days to up to 24 months post-injury.

3.4.1.2.3 Correlation with pre-injury, injury, or post-injury factors. Multiple studies explored the associations among working memory performance and pre-injury, injury, or post-injury factors, and separated these correlations by injury severity. The following factors were considered: age at injury (N=5 studies), time since injury (subset of prospective cohort studies [N=11] and N=2 additional studies), premorbid neurodevelopmental disorders (N=1), presence of post-morbid neuropsychiatric disorder (N=2), injury symptom validity (N=1), daily functional outcomes (N=1), speech and language outcomes (N=1), math abilities (N=1), concussion history (N=1), premorbid adaptive functioning and socioeconomic status (SES) (N=1).

3.4.2 Frequency and nature of working memory challenges post-paediatric concussion

A total of N=27 studies compared working memory performance in children and youth with concussion to that of healthy controls or to normative values, providing insight into how working memory performance may differ following injury. Of these studies, N=12 (**44.44%**) reported significantly different working memory performance in the concussion sample compared to controls or normative values. N=14 studies did not find significant differences between the two groups, and one found that the concussion group performed better on the working memory assessment than the healthy control group (Maillard-Wermelinger et al., 2009).

3.4.2.1 Impact of working memory type and measure. Of the N=12 studies that found working memory had been impacted by concussion, N=4 assessed visual working memory (Catale, Marique, Closset, & Meulemans, 2009; Hammeke et al., 2013; Loher, Fatzer, & Roebers, 2014; Moore et al., 2016), N=2 assessed verbal working memory (Baillargeon, Lassonde, Leclerc, & Ellemberg, 2012; Barrett, McLellan, & McKinlay, 2013), N=2 assessed visuospatial working memory in a single and dual task condition (deficits only found in dual task) (Sinopoli et al., 2014; Urban et al., 2017), N=1 assessed visuospatial and verbal working memory (deficits only found in visuospatial) (Van Beek, Ghesquière, Lagae, & De Smedt, 2015), N=1 assessed verbal and visual working memory and found deficits on both measures (Keightley et al., 2014), N=1 used a clinical measure (Digit Span) (Scherwath et al., 2011), and N=1 utilized a parent-report measure (Sesma, Slomine, Ding, & McCarthy, 2008). Six studies out of the total N=12 included a sports-related concussion population (Baillargeon et al., 2012; Hammeke et al., 2013; Keightley et al., 2014; Moore et al., 2016; Sinopoli et al., 2014; Urban et al., 2017).

Of the N=15 studies that did not find working memory impairments in the concussion population, N=1 assessed visual working memory (Chapman et al., 2006), N=3 assessed verbal working memory (Dennis & Barnes, 2000; Roncadin, Guger, Archibald, Barnes, & Dennis, 2004; Westfall et al., 2015), and N=11 utilized a standardized clinical assessment of working memory (Anderson & Catroppa, 2007; Catroppa et al., 2008; Hessen, Nestvold, & Anderson, 2007; Kaufmann, Fletcher, Levin, Miner, & Ewingcobbs, 1993; Maillard-Wermelinger et al., 2009; Mayer et al., 2012; Mayer et al., 2015; Papoutsis, Stargatt, & Catroppa, 2014; Ponsford et al., 2001; Sim, Terryberry-Spohr, & Wilson, 2008; Studer et al., 2014), which in N=9 of cases was some variation of the Digit Span test. A total of two of these studies used a sports-related concussion population (Sim et al., 2008; Westfall et al., 2015).

3.4.2.2 Accuracy versus reaction time. Of the 12 studies that found compromised working memory performance post-concussion, N=8 reported a difference in accuracy only (Baillargeon et al., 2012; Barrett et al., 2013; Catale et al., 2009; Keightley et al., 2014; Loher et al., 2014; Moore et al., 2016; Scherwath et al., 2011; Van Beek et al., 2015), N=2 reported a difference in reaction time only (Sinopoli et al., 2014; Urban et al., 2017), N=1 reported a difference on both measures (Hammeke et al., 2013), and N=1 used a parent-report measure that did not assess these metrics (Sesma et al., 2008). Notably, only a subset of N=3 papers within the N=8 that reported an accuracy difference also included a reaction time metric in their task, while both studies that reported reaction time differences also had an accuracy measure. Within the two studies reporting reaction time changes, these deficits only presented themselves during dual task working memory conditions, in comparison to single task conditions. Notably, while all 27 studies included an accuracy metric, only seven studies assessed reaction time. In addition to the three studies which found that reaction time was impacted, three of the studies that included both metrics found that reduced performance was only observable in the accuracy metric. The final reaction time study did not find that either measure was significantly impacted by injury. Across all studies, accuracy was therefore reported as impacted 33.33% of the time (9/27 studies), and reaction time 42.86% of the time (3/7 studies).

3.4.2.3 Working memory outcomes in the context of other TBI severities. Of the ten studies that examined working memory abilities in the context of other TBI severities, injury severity did not appear to be a consistent predictor of working memory outcomes. Anderson & Catroppa (2007), Catroppa et al. (2008), and Kaufmann et al. (1993) found no significant effect of injury severity on working memory abilities. Additionally, while Barret et al. (2013) and Scherwath et al. (2011) found that their working memory/attention domain score was significantly lower in the moderate/severe and concussion groups compared to controls, they either did not specify (Barret et al., 2013), or did not find any significant differences between injury groups (Scherwath et al., 2011). Conversely, Chapman et al. (2006), Dennis and Barnes (2000), Levin et al. (2004), Roncadin et al. (2004), and Sesma et al. (2008), found that injury severity did significantly influence outcomes. Sesma et al. (2008) found that the working memory domain was the only area of the BRIEF that elucidated significant differences between controls and injury groups at three and 12 months post-injury, with all injury groups scoring lower than controls. However, while the severe injury group scored significantly lower than the mild and moderate groups at three months post-injury, there were no significant differences between injury groups by 12 months post-injury. Chapman et al. (2006), Dennis and Barnes (2000), Levin et al. (2004), and Roncadin et al. (2004), all found that the concussion group showed the best working memory outcomes, compared to moderate and severe injury groups. While concussion performance was still significantly lower than healthy controls in Levin et al. (2004), the concussion group showed performance within normal ranges in Chapman et al. (2006), Dennis and Barnes (2000), Roncadin et al. (2004). Notably, Levin et al. (2004) and Roncadin et al. (2004) found that performance of the moderate TBI group was not significantly different from that of the mild and severe TBI groups, indicating that a high degree of overlap existed between severity categories on neurocognitive outcomes. Chapman et al. (2006) and Dennis and Barnes (2000) and did not include a moderate TBI group.

3.4.3 Pre-injury, injury, and post-injury factors related to working memory outcomes

3.4.3.1 Age at injury. Five studies examined the impact of age at injury on post-injury working memory outcomes. Two found it not significantly related to working memory abilities

(Anderson & Catroppa, 2007; Roncadin et al., 2004). Levin et al. (2004) found that children who were older when injured had slower improvements in working memory scores across time than those who were younger. Similarly, when Baillargeon et al. (2012) examined the neurocognitive performance of children, adolescents, and adults after injury, they found that their adolescent subgroup were the only ones who showed significantly reduced working memory performance compared to healthy controls. Conversely, Moore et al. (2016) found that children who sustained their injury earlier in life showed the greatest challenge in their discrimination abilities on the N-Back task.

3.4.3.2 Time since injury. Thirteen studies (N=11 prospective cohort studies) explicitly examined the impact of time since injury on working memory performance. Four did not find any significant difference between groups at initial assessment, and this remained stable across follow-up assessments (Mayer et al., 2012; Mayer et al., 2015; Sim et al., 2008; Studer et al., 2014). An additional study found that time since injury did not correlate significantly with working memory performance (Roncadin et al., 2004). One study did not adequately report on working memory performance at follow-up time-point (Scherwath et al., 2011). One study found that their control group showed worse performance than the children with concussion, however the magnitude of group differences declined over time as both groups showed consistent improvements in working memory (Maillard-Wermelinger et al., 2009). Notably, this study was one of the only studies using an orthopedic injury control group. Another study assessed working memory solely through parent report on the Behavior Rating Inventory of Executive Function (BRIEF), but found that it was the only domain where performance was rated as significantly worse than controls across all time points (Sesma et al., 2007). Interestingly, an additional study found that working memory deficits in the concussion group were not apparent until 12 weeks post-injury, with small performance decreases accumulating over time (Loher et al., 2014). Conversely, the remaining for studies found that working memory performance consistently increased with time since injury (Hammeke et al., 2013; Levin et al., 2004), that time since injury was positively correlated with performance accuracy on the 0-Back and 1-Back conditions of the N-Back (Westfall et al., 2015), and further, that pre-injury ADHD appeared to increase neurocognitive recovery (Levin et al., 2008). Only 2/13 studies reported on the presence or absence of concussion symptoms at the time periods of assessment. Both Hammeke et al. (2013)

and Studer et al. (2014) found that the youth with concussion reported significantly higher symptoms than controls in the acute period only.

While the long-term follow-up studies did not include multiple follow-ups, and further, did not correlate differences in time since injury with outcomes (with the exception of Roncadin et al., 2004 and Westfall et al. 2015, reported above), it is still interesting to consider their results within this topic as they provide insight into how working memory outcomes may differ at variable post-injury time points. 10 of the long-term follow-up studies compared working memory performance to healthy controls. At 6 months to 4 years post-injury, children with concussion showed worse performance accuracy than controls in the majority of studies (Baillargeon et al., 2012; Catale et al., 2009; Moore et al., 2016). However, by five years post-injury onwards results were more variable; Anderson and Catroppa (2007), Catroppa et al. (2008), Chapman et al. (2006[4]), Dennis and Barnes (2000), and Papoutis et al. (2014) did not find any differences between their concussion injury groups and healthy controls, however Barret et al. (2013) found that working memory/attention domain scores were lower in the concussion group as compared to healthy controls at this age. At 23 years post-injury, working memory performance on the digit span was within normal ranges, however, within this range the lowest scores were observed within subgroup who had receive their concussion in childhood as compared to adulthood (Hessen et al., 2007). Again, only Moore et al. (2016) addressed the presence or absence of concussion symptoms at the long-term follow-up time points. None of their participants reported any symptoms.

3.4.3.3 Injury history. Westfall et al. (2015) found no significant working memory performance differences between those with or without a history of previous concussion. No other studies directly examined the impact of this variable.

3.4.3.4 Structural and functional cortical properties. There was some consistency across imaging studies regarding the brain regions which appeared to be critically implicated in

[4] Chapman et al. (2006) required their participants to be at least 2 years out of injury, but most participants were in the range of 5 years out of injury.

working memory performance after concussion. This will now be reviewed in the context of the frontoparietal working memory network.

3.4.3.4.1 Frontoparietal network. Westfall et al. (2015) found that, during the most challenging working memory condition compared to a baseline condition, the concussion group generally showed increased activity in the frontoparietal working memory network, with this activity expanding outside of the network boundaries observed in healthy controls. This included increased activity in critical regions such as the left precentral gyrus and the left sub-lobar insula. Notably, activity in these two regions was positively correlated with performance on the least challenging working memory condition for the concussion group only. Interestingly, dissimilarities in cortical activation patterns were present despite the lack of significant differences in behavioural performance between the concussion group and healthy controls. Hammeke et al. (2013) found that while the concussion group showed decreased cortical activation at 13 hours post-injury, this trend generally reversed, with the concussion group showing increased cortical activity at seven weeks post-injury. This pattern was most consistently apparent in the right inferior frontal gyrus within the frontoparietal network.

3.4.3.4.2 The DLPFC. The DLPFC is a subcomponent of the frontoparietal network which appeared to be independently implicated in working memory outcomes. From a structural perspective, Urban et al. (2017) found a significant relationship between cortical thickness in the left DLPFC and working memory performance on a visuospatial N-Back task of working memory. In the control group, better accuracy on the 0-back condition of the single-task working memory paradigm was correlated with increased cortical thickness in the left DLPFC region. However, in the concussion injury group, they found a negative correlation between task accuracy and left DLPFC cortical thickness in the 1-back condition. Conversely, in the dual task condition, thinner left DLPFC was associated with slower reaction times within this group. Notably, the concussion group showed thinner left DLPFC overall, which could begin to explain the differing impact of cortical thickness across study groups.

From a functional lens, Keightley et al. (2014) found that the healthy control group showed greater activation in the DLPFC across all task conditions, compared to those with concussion. During their verbal working memory task condition, greater activation in the left DLFPC was significantly correlated with greater task accuracy for both groups, however, within the visual working memory, this correlation was only significant for the injured group, and expanded to include the right DLPFC as well. These results suggested that heightened activity in the DLPFC was a facilitating factor for working memory performance in youth with a history of concussion.

Similarly, Sinopoli et al. (2014) found that, compared to healthy controls, the concussion group showed reduced activity in the DLPFC during single-task working memory performance. However, group differences in activation levels appeared to be load dependent, as the concussion group showed increased activity in the right DLPFC than did healthy controls on the most challenging working memory task level (i.e., N-2 in their N-Back task). In line with Keightley et al. (2014), they found that greater activity in the right DLPFC was correlated with increased accuracy on the more challenging levels of their working memory task (i.e., N-2). Interestingly, they found that the same increased activity was correlated with slower reaction times in this group. During dual task performance (i.e., working memory task paired with a motor task), Sinopoli et al. (2014) found similar patterns of overall increased activity in the DLPFC in the healthy control group, when contrasted with baseline performance. Again, these differences appeared to be load dependent. When contrasting level N-2 with N-1, the control group showed greater activation in the left DLPFC whereas the injured group had greater activity in the right DLPFC. No correlations between activation patterns and accuracy or reaction time were found in the concussion group during the dual task condition.

3.4.3.4.3 Cerebellum. While Krivitzky et al. (2011) found minimal group differences in cortical activity, the cerebellum was one region which was able to elucidate meaningful disparities between the injured population and healthy controls; however these were only seen during task conditions which placed demands on inhibitory control in addition to working memory. In their moderately challenging inhibitory task condition, individuals with concussion showed increased bilateral posterior cerebellum activation compared to controls. Region of interest analysis also found generally greater cerebellar activation in the concussion group during inhibitory control conditions. Further, increased activity in the posterior cerebellum was negatively correlated with the metacognition index of the BRIEF, which includes a working memory scale.

3.4.3.5 Psychiatric conditions. Two studies investigated the relationship between working memory performance and the presence of post-injury psychiatric conditions. Guo et al. (2017)

were interested in exploring what neurocognitive factors were connected with the onset of post-traumatic stress disorder (PTSD) after paediatric TBI. They assessed working memory through the Digit Span backwards subtest of the WISC-IV, and found that, along with sex and sustained attention factors, scores on this measure at three months post-injury accounted for 19% of PTSD symptom variance at six months in the subgroup youth with concussion. Interestingly, deficits in sustained attention and working memory had opposing effects on PTSD symptoms: challenges in sustained attention predicted increased PTSD symptoms, whereas challenges in working memory actually protected against the onset of PTSD symptoms. However, the separation that emerged between sustained attention and working memory in the regression analysis suggested that the working memory construct may be more representative of one of its sub-constructs, such as auditory or verbal learning, since working memory itself is so closely related to attention. This is supported by the fact that challenges with verbal learning was an additional protective factor for the onset of PTSD symptoms in the moderate TBI group.

Max et al. (2013) looked at the relationship between novel psychiatric disorder (NPD) and concurrent neuropsychological functioning. They assessed working memory through a visual, letter-based, N-Back task, and found that working memory, along with verbal memory, were the only neurocognitive factors that significantly accounted for any variance in NPD once SES was controlled for, with those without NPD performing significantly more accurately on the working memory task.

3.4.3.6 Functional outcomes. One study explored the relationship between working memory performance post-injury and self- and/or family-reports of executive behaviours in daily life. Maillard-Wermelinger et al. (2009) explored the predictive ability of a spatial working memory performance from the Cambridge Neuropsychological Testing Automated Battery (CANTAB) for parent-reported BRIEF domain scores at three and 12 months post-injury. At three months post-injury, higher scores on the working memory subtest of the CANTAB in the concussion group predicted lower t-scores scores on the Shift, Emotional Control and Organization of Materials scales and the Behavior Regulation Index of the BRIEF. These relationships were stronger in the concussion group than in healthy controls. At 12 months post-injury, relationship strength no longer differed between those with concussion and healthy controls. However, spatial working memory was still a key predictive factor, accounting for variance on the Inhibit, Emotional Control, Working Memory, and Monitor scales, as well as on the Metacognition and

Behavioral Regulation indexes, and the Global Executive Composite. The authors interpreted these findings to suggest that standardized assessments of working memory do appear to have ecological validity in predicting critical executive abilities in daily life.

3.4.3.7 Additional outcomes. Four studies explored the relationship between working memory performance and a variety of additional pre- and post-injury factors not captured in the categories above. Dennis & Barnes (2000) found a trend towards working memory predicting the significantly lower speech act abilities observed in their concussion group. Speech acts are a key component of pragmatic language, i.e., the language abilities that support communication in daily life, which involves using dialogue intentionally to influence the mental state of a communication partner. Van Beek et al. (2015) found that reduced mathematical abilities observed in their concussion group compared to healthy controls disappeared when visuospatial working memory was controlled for, suggesting that working memory is critically related to mathematical abilities post-injury; a relationship that is well established in healthy controls (see section 3.1.3).

Kirkwood et al. (2011) found that digit span scores have promising utility in identifying non-credible (i.e., low effort) performance in older children and adolescents, which substantiated the significant relationship between working memory performance and the cognitive impact of concussion. Anderson & Catroppa (2007) correlated post-injury working memory performance with SES and premorbid adaptive functioning, as measured by the Vineland Adaptive Behavior Scale (VABS), but did not find that these factors significantly predicted working memory outcomes.

3.4.4 Quality assessment

All 33 studies included in the review were assessed for their quality using the NHLBI's Quality Assessment of Observational Cohort and Cross-Sectional Studies[5], which allows for the

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[5] Since the pre-post intervention study did include a healthy control group, it was evaluated with the Quality Assessment of Observation Cohort checklist.

evaluation of bias and internal validity. 18/33 (54.55%) were rated as a "good" quality study, 9/33 (27.27%) were rated as a "fair" quality study, and 6/33 (18.18%) were rated as a "poor" quality study, according to the NHLBI' criteria, suggesting that there was substantial potential for bias in the included studies. As guided by the NHLBI questions, a common weakness of the included studies was with regards to the exposure assessment measure, and the consistency of assessment and inclusion and exclusion criteria across all study groups. 16/33 (48.48%) of studies did not include at least one of the following in their exposure measure: (1) validation of concussion diagnosis with an additional measure at time of study, (2) application of concussion diagnosis criteria to control group, (3) substantiation of diagnosis through imaging data with specified exclusion of individuals those with positive imaging findings. While not all of these are feasible depending on the study design and participant group, the prevalence of these omissions raises questions regarding the validity of injury diagnoses. Further, although concussion can vary in severity, most studies did not explore the impact of any injury severity indices within their concussion group. Additionally, the studies often presented with a lack of detail about: (1) recruitment yield in the context of the eligible participant pool, as well as sample size calculations or rationales, (2) the nature of blinding of experimenters to participant injury status. The NHLBI's rating criteria is designed so that cross-sectional studies are rated more poorly, therefore the lack of long-term follow up in the majority of studies included in the review contributed substantially to the lower quality ratings.

Strengths of the studies included the use of valid, reliable, working memory outcome measures, which were administered consistently across both study groups (32/33, 96.97%), as well as assessment and control for potential confounding factors (31/33, 93.94%). Further, almost all studies clearly stated their research aims and questions (32/33, 96.97%).

3.5 Discussion

The overall aim of this systematic review was to explore the presence of working memory challenges following paediatric concussion, and to (i) characterize the nature of working memory outcomes following pediatric concussion in regards to the type and aspect of working memory impacted and the recovery trajectory, (ii) explore if these outcomes were related to any specific pre-injury, injury, or post-injury factors, (iii) examine the type of methodological approaches being implemented to evaluate working memory performance, as well as the impact of measurement type on working memory outcomes, and (iv) assess the quality of the current body of research. This review is the first to systematically synthesize and appraise the literature on paediatric outcomes of concussion.

3.5.1 Presence and nature of working memory challenges post-paediatric concussion

Overall, the findings of the current review provide substantial evidence that working memory is a neurocognitive ability that has the potential to be vulnerable to insult following paediatric concussion. However, the nature and severity of these challenges appear to be highly heterogeneous. Less than half of the studies (12/27, 44.44%) included in the current review found that working memory performance in individuals who had experienced a paediatric concussion was significantly lower than that of healthy controls, and these studies varied substantially with regards to the type and component of working memory that appeared challenging for this clinical population.

3.5.1.1 Type and aspect of working memory most commonly impacted post-injury.

3.5.1.1.1 Working memory type. The lack of clear trends regarding the type or aspect of working memory that is most prone to disruption after a concussion can likely be attributed to the high degree of heterogeneity in the methodological approaches employed in the literature. However, some preliminary patterns could be identified which merit further exploration. Specifically, studies employing visual/spatial and dual task experimental working memory paradigms tended to report significantly lower performance in the concussion versus healthy control group than those employing verbal and single task working memory paradigms. While exploratory, there are potential developmental reasons why varying modalities of working memory may be differentially impacted by concussion. Research supports the functional independence, or “developmental fractionation,” of working memory subsystems in childhood and adolescence, suggesting that subsystems supporting auditory versus visual/spatial information could be differentially impacted by injury (Alloway, Pickering, & Elizabeth, 2006; Tsujimoto, Kuwajima, & Sawaguchi, 2007). Although verbal and visual/spatial working memory share many core mechanisms which are established by early childhood, they are also supported by unique cognitive processes that develop at different rates (Bayliss, Jarrold, Baddeley, Gunn,

& Leigh, 2005; Gathercole et al., 2004; Hale, Bronik, & Fry, 1997; Thomason et al., 2008). Across adulthood, visual/spatial working memory has been shown to decline at a steeper rate than verbal working memory skills, further supporting the independence of these cognitive abilities (Alloway & Alloway, 2013). Mechanisms supporting more complex aspects of visual/spatial working memory, including the retention and manipulation of multiple spatial units, show protracted maturation that continues into early adolescence (Luciana et al., 2005). This delayed development can be attributed to the fact that these complex tasks engage the executive aspects of working memory (e.g., strategic organization), referred to as the 'central executive' in the Baddeley & Hitch cognitive model, and therefore follow the general protracted maturation of executive function abilities (Alloway et al., 2006; Baddeley, 2003; Luciana et al., 2005). Since cognitive skills which have not yet emerged at the time of injury are especially vulnerable to insult (Anderson et al., 2011), it follows that working memory for complex visual/spatial stimuli may be impacted at a greater rate in the paediatric population. Age at injury and time since injury are also critical to consider as influencing factors in these differing outcomes (see Section 3.5.2).

Dual task performance deficits reported in this review further support the vulnerability of executive aspects of working memory to insult following paediatric concussion. The lack of findings on single task paradigms in the included studies suggest that the components of working memory related to attention and the overall allocation of cognitive resources may be the most sensitive to the diffuse cortical disruption resulting from concussion. Youth with concussion present with challenges on other attentional tasks, as well as on dual task conditions outside of the realm of working memory, further supporting that general challenges with attention and cognitive control may play a critical role in the working memory profile of youth post-concussion (Howell et al., 2013; Register-Mihalik et al., 2013). Similar to the protracted maturation of visual/spatial working memory, the complex cognitive processes underlying dual task performance continue to develop into late adolescence and even early adulthood, and therefore are at a heightened risk of being negatively impacted by injury. While the basic structure of the working memory system appears to be established as early as age six, with children reaching adult levels of accuracy during working memory maintenance task by age 10-12, working memory performance during conditions of distraction do not reach adult levels of performance until late adolescence (Gathercole et al., 2004; Schleepen & Jonkman, 2010).

3.5.1.1.2 Accuracy versus reaction time. The most commonly reported working memory performance difference was compromised task accuracy; however, the presence of accuracy changes can be attributed to the fact that the majority of studies omitted an assessment of reaction time. When both were considered, accuracy and reaction time were impacted relatively equally. Although accuracy and reaction time are highly interrelated, they can also provide insight into different cognitive processes. Accuracy scores may be more reflective of core components of working memory itself, including an individual's capacity to effectively encode, maintain, and manipulate sensory information, whereas reaction time may be more reflective of general processing speed or cognitive efficiency (Alloway & Alloway, 2013; Baddeley, 2003; Ohn et al., 2008). The distinctive nature of these working memory components is represented on a developmental level. Studies exploring working memory changes across childhood report that while interrelated, working memory storage capacity and speed do show independent developmental trajectories (Bayliss et al., 2005; Pelegrina et al., 2015), and could therefore be uniquely affected by paediatric injury. Specifically, while age-dependent improvements in accuracy scores are critically related to working memory load, changes in reaction time across development are not consistently influenced by the content of working memory itself, and appear to be more representative of a global increase in processing speed (Bayliss et al., 2005; Pelegrina et al., 2015; Schleepen & Jonkman, 2010).

Processing speed is known to be an area impacted by concussion across various challenging cognitive activities (Babikian, McArthur, & Asarnow, 2013; Belanger & Vanderploeg, 2005; Cicerone, 1996; Echemendia, Putukian, Mackin, Julian, & Shoss, 2001; Register-Mihalik et al., 2013). This cognitive metric is highly correlated with white matter integrity (Charlton et al., 2006; Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006; Turken et al., 2008), and therefore, as white matter is vulnerable to insult in concussion, changes in processing speed are attributed to the diffuse cortical disruption resulting from these injuries, hindering effective cross-cortical communication (Choe, 2016; Choe et al., 2012; Niogi et al., 2008). Therefore, the limited use of reaction time metrics in the literature may have restricted the ability of the included studies to identify working memory performance changes after paediatric concussion. Research on adult populations has shown that processing speed is highly correlated with working memory performance, accounting for approximately 15% of performance variability, substantiating its influential role in performance outcomes post-injury (Brown, Gow, & Deary, 2012). Additional research should be done to characterize if paediatric concussion has a differential impact on accuracy versus reaction time metrics.

Despite their respective differences, both reaction time and accuracy are critically related to attentional processes. The role of attention in both performance metrics is in line with state-based models of working memory, as well as with the 'central executive' in multicomponent models (Baddeley, 2003; Cowan, 2017; D'Esposito & Postle, 2015b; Eriksson et al., 2015; Oberauer, 2013). The latter share a mutual consensus of the primary role of attention in guiding which information is maintained and rehearsed (Baddeley, 2003; Cowan, 2017; D'Esposito & Postle, 2015b; Eriksson et al., 2015; Oberauer, 2013) . To meet the task demands of a working memory paradigm, individuals must be able to efficiently switch their attention between mental representations of different sensory information; therefore age-dependent differences in working memory accuracy have been attributed to developmental changes in the ability to switch the focus of attention (Pelegrina et al., 2015). Further, reaction times are critically related to attentional processes, with a breadth of research showing that response times are longer with increasing attentional demands (Sigman & Dehaene, 2006; Tombu & Jolicœur, 2003; Tun & Lachman, 2008; Verhaeghen & Cerella, 2002). The common role of attention in working memory accuracy and reaction time provides a potential explanation for the comparable impact of concussion on both of these metrics.

3.5.1.1.3 Clinical outcome measures. Notably, the majority of studies that found that working memory abilities were not significantly impacted by concussion used a standardized clinical outcome measure to assess performance (11/15, 73.33%, 9 of which used the Digit Span), suggesting that these measures may not be sensitive to the cognitive challenges that can emerge after these injuries. The reliability and validity of neuropsychological testing to assess the cognitive outcomes of concussion is controversial, due to the subtle nature of the resulting changes, and to their ability to be impacted by situational and individual factors, including other concussion symptoms (Kontos, Sufrinko, Womble, & Kegel, 2016; Randolph, Mccrea, & Barr, 2005). As a result of this, there is currently no "gold standard" for the assessment of cognitive symptoms post-injury (Goldberg & Madathil, 2015).

There are various possible reasons for why clinical outcome measures such as the Digit Span may not have identified working memory challenges in youth with concussion. Firstly, clinical assessments of working memory are typically included within a larger, comprehensive neuropsychological test battery. They are therefore designed to assess a very specific construct of working memory, and by nature offer a more restricted recording of performance than continuous recall tasks such as the N-Back. Further, neuropsychological tests were designed to assess notable deviations in cognitive performance from the population norm, and therefore may not be appropriate for the subtle fluctuations in cognitive abilities that can result from these mild injuries (Randolph et al., 2005). Secondly, different classes of working memory tasks exist, including complex span tasks, updating tasks, and recall tasks. While it appears that all these tasks do assess the overarching construct of working memory capacity (Wilhelm, Hildebrandt, & Oberauer, 2013), research on the congruence of these different task classes has been controversial (Redick & Lindsey, 2013; St Clair-Thompson, 2010; Zokaei, Burnett Heyes, Gorgoraptis, Budhdeo, & Husain, 2015). It is possible that youth with concussion may have more difficulty on one of these task classes, and a better understanding how these classes differ with regards to the cognitive constructs they assess will provide insight into the specific nature of cognitive challenges that result from concussion. Further, as previously mentioned, these discrete complex span tasks typically do not include assessments of reaction time, which is a metric of cognitive performance highly related to performance changes after concussion.

The ability of dual task paradigms to reveal compromised cognitive performance in a youth concussion population that could not be identified in a single task condition provides additional evidence that the cognitive challenges that result from these injuries are at risk of not being identified on isolated cognitive tasks (Bigler, 2008; Kontos et al., 2016; Mangeot, Armstrong, Colvin, Yeates, & Taylor, 2002). The findings of the current review suggest that working memory difficulties post-concussion may be more subtle that can be detected by more traditional neuropsychological measures, and that experimental paradigms which introduce greater and more sustained demand on working memory are likely more sensitive to these changes. However, it is important for future research to better elucidate how performance differences on these experimental paradigms actually impact an individual’s ability to participate in daily life, i.e., what is a clinically meaningful difference in working memory performance for this population.

3.5.1.1.4 Outcomes in the context of other TBI severities. Studies which examined working memory outcomes among different injury populations provide important insight into which aspects of these cognitive outcomes are injury-specific and which may be more attributable to the general experience of sustaining a TBI. Notably, it did not appear that injury severity was consistently related to working memory outcomes, as some groups did not find an impact of injury severity on performance. It is interesting to note that all of the studies that did not find an effect of severity either used GCS scores or solely clinical diagnosis to define their injury groups. Additionally, 4/5 of these studies utilized the Digit Span to assess working memory, whereas none of the other papers examining the impact of severity used this measure, further suggesting that the Digit Span may not be sensitive to the subtleties of working memory performance differences that can result from TBIs. Of those that did find a difference, it generally appeared that while individuals of all TBI severities performed worse than healthy controls, individuals with concussion consistently performed better than the other injury groups, as is to be expected. However, this trend was not always significant. The inconsistent impact of injury severity on working memory documented in this review suggest that while some of the cognitive outcomes of brain injury may be generalizable across all severity categories, certain assessment measures may be better suited to reveal performance differences between injury severities.

3.5.2 Influence of age at injury and time since injury on working memory outcomes

Age at injury did not appear to be a consistent predictor of working memory outcomes post-paediatric concussion. Two studies did not find any significant correlation between working memory outcomes and age at injury, while the other three studies did. One study reported that those injured earliest in childhood had the lowest performance on the working memory task (Moore et al., 2016); conversely, the other two showed that those injured later in their youth had the most compromised working memory performance (Baillargeon et al., 2012) and recovery trajectories (Levin et al., 2004). Notably, there was substantial overlap between the age range of participants in Moore et al. (2016) and Levin et al. (2004), suggesting that it was unlikely that these opposing findings were a product of occurring within different critical development stages, however future work should explore this possibility. The variable impact of age at injury found in the current review disputes the previously-held view that earlier time of insult in childhood always leads to better functional outcomes (Dennis, 2010; Dennis et al., 2013). Comprehensive reviews exploring neuroplasticity following paediatric brain injury identify recovery as a continuum, where multiple injury and environmental factors interact and contribute either to adaptive or maladaptive outcomes (Anderson et al., 2011). While age is a core injury factor which influences the functioning of different mechanisms of neuroplasticity, it alone cannot predict recovery trajectories (Anderson et al., 2011).

Additionally, there was a lack of consensus in the literature regarding the impact of time since injury, or the recovery trajectory, for challenges with working memory resulting from paediatric concussion. While four studies found that working memory performance showed improvements with time since injury (Hammeke et al., 2013; Levin et al., 2004, 2008; Maillard-Wermelinger et al., 2009; Westfall et al., 2015), six studies found that working memory performance did not show any consistent temporally-based gains (Mayer et al., 2012; Mayer et al., 2015; Sesma et al., 2007; Sim et al., 2008; Studer et al., 2014; Roncadin et al., 2004). A final study found that working memory challenges did not present themselves until around three months post-injury (Loher et al., 2014). Studies utilizing long-term follow-up designs showed that although deficits do still appear at one year post-injury (Baillargeon et al. 2012; Catale et al., 2009; Moore et al., 2016), the majority reported that they are no longer significant at the five as well as the 23-year mark (Anderson & Catroppa, 2007; Catroppa et al., 2008; Chapman et al., 2006; Dennis and Barnes, 2000; Hessen et al., 2007; Papoutis et al. 2014).

Most research on neuroplasticity following paediatric brain injury has focused on moderate and severe TBI. However, as the potential lasting impact of concussion becomes increasingly recognized, it is important to consider how neuroplasticity patterns may apply to children and youth who fail to recover quickly from these milder brain injuries. After paediatric brain injury, three common patterns emerge, which are critically related to age at injury and time since injury. Individuals may either "grow into a deficit", i.e., present with uncompromised performance immediately after injury, but begin to present with cognitive challenges as certain complex skills are expected to emerge, or show immediate challenges, which slowly resolve over time (Anderson, 2003; Anderson et al., 2011; Dennis et al., 2014; Schneider, 1979). The third pattern is potentially the most detrimental, in which early disruptions to cognitive skill acquisition result in a persistent developmental gap, as children are unable to gain new skills due to the lack of establishment of cognitive precursors (Anderson, 2003; Anderson et al., 2011; Dennis et al., 2014; Schneider, 1979).

The recovery pattern which a given individual will present with is influenced by their developmental stage in relation to two key factors: brain maturity and level of skill maturity, as well as by the level of skill complexity (Anderson et al., 2011; Dennis et al., 2013, 2014). Cognitive skills which have not yet been established are the most vulnerable to damage by injury, and complex skills supported by diffuse cross-cortical communication are less likely to recover (Anderson et al., 2011; Dennis et al., 2013, 2014). Therefore, age at injury plays a critical role in dictating which skill sets will be the most susceptible to the negative impact of the cortical disruption that accompanies concussion. As previously discussed, the executive components of working memory would therefore be most susceptible in the paediatric population, as these continue to develop into late adolescence (Alloway & Alloway, 2013; Gathercole et al., 2004; Schleepen & Jonkman, 2010). Considering these recovery patterns, timing of assessment will also have a significant impact on an individual's neurocognitive profile. Studies assessing working memory immediately after injury may be capturing transient disruptions in cognitive performance that will resolve naturally with time, whereas studies assessing performance months out of injury may not accurately represent earlier challenges (Anderson et al., 2011).

The heterogeneity regarding the impact of age at injury and time since injury found in the current review can likely be attributed to these differing recovery trajectories; however, cohesive explanations could not be established. Baillargeon et al. (2012), Moore et al. (2016), and Levin et al. (2004) all assessed their affected participants at approximately six months post-injury (with Levin et al., 2004, including more follow-up points), and therefore should have all been at a similar point on the recovery trajectory. However, only Baillargeon et al. (2012) included a teenage population in their study, which restricted the ability of Moore et al. (2016) and Levin et al. (2004) to assess the vulnerability of this age group. Further, Baillargeon et al. (2012) only included a male population, further differentiating their results. Moore et al. (2016) and Levin et al. (2004) both used an N-Back task to assess working memory performance; however, the stimuli used in Moore et al. (2016) were shapes, whereas the stimuli in Levin et al. (2004) were letters. While it is possible that the processing of these stimuli follow different developmental trajectories, it is more likely that other environmental factors not explicitly assessed in these studies may explain the opposing effects of age at injury in these study groups.

Of the studies that found a significant correlation between time since injury and working memory performance, two included assessments within the acute to subacute periods (Hammeke et al., 2013; Loher et al., 2014), three included measurements in the chronic period (Levin et al., 2004, 2008; Westfall et al., 2015), and one included assessments spanning all periods (Maillard-Wermelinger et al., 2009), which could explain the variability in results. While Hammeke et al. (2013) found that working memory performance improved from the acute to subacute period, Loher et al. (2014) found that challenges began to present themselves across the subacute to chronic period. Levin et al. (2004, 2008) found that decreases in performance began to resolve across the chronic period, and additionally, Westfall et al. (2015) found that time since injury during this period was positively correlated with task accuracy. Finally, Maillard-Wermelinger et al. (2009) found that all of their participants showed consistent performance increases across the recovery periods. In the context of the three recovery patterns, Hammeke et al. (2013) may have been assessing the immediate challenges that result from concussion that can naturally resolve with time since injury, whereas Levin et al. (2004, 2008), Westfall et al. (2015), and Maillard-Wermelinger et al. (2009) were assessing the sustainability of these initial insults. The findings of Loher et al. (2014) seem to suggest that individuals may grow into their cognitive deficits over the first few months post-injury, however in the context of Levin et al. (2004, 2008), Westfall et al. (2015), and Maillard-Wermelinger et al. (2009), these challenges to do not appear to persist. The protracted recovery of working memory abilities during the chronic period of injury is in line with the recovery trajectory of other persistent neurocognitive challenges resulting from concussion (Howell et al., 2013; McCrory et al., 2017; McInnes et al., 2017). Future research should aim to better identify the impact of time since injury within the context of developmental stage to understand the extent to which paediatric concussion can impact typical developmental trajectories, to best predict recovery outcomes. Additionally, the lack of reporting on the presence or absence of concussion symptoms in the majority of these studies substantially limited the ability to understand which injury-related factors may be contributing to cognitive outcomes across the recovery trajectory, as post-concussive symptoms are critically related to cognitive performance (Chen, Johnston, Collie, Mccrory, & Ptito, 2007).

3.5.3 Correlation of working memory outcomes with pre-injury, injury, and post-injury factors

Multiple studies found that a variety of factors either influenced, or were impacted by, working memory performance, suggesting that these outcomes should not be considered in isolation.

3.5.3.1 Pre-injury neurodevelopmental disorder. One study explored the impact of pre-injury neurodevelopmental disorder, specifically ADHD, on the presence and recovery trajectory of working memory challenges post-injury (Levin et al., 2008). While they only compared those with complicated versus uncomplicated mTBI, they found that individuals with pre-injury ADHD experienced a quicker recovery of working memory skills post-injury across both injury groups (Levin et al., 2008). This finding opposed the literature, as individuals with pre-injury ADHD often present with worse outcomes post-injury, and experience longer recovery trajectories (Bonfield, Lam, Lin, & Greene, 2013; Mautner, Sussman, Axtman, Al-farsi, & Al-adawi, 2015). Considering the high prevalence of pre-injury ADHD in youth with concussion, the impact of this condition on cognitive outcomes must be better understood in order to characterize unique modifiers of an individual's recovery trajectory.

3.5.3.2 Daily cognitive demands. Working memory performance post-injury was significantly correlated with everyday behaviours, including speech acts (Dennis & Barnes, 2000) and actions described in caregiver reports on the BRIEF, an assessment of executive function in daily life (Maillard-Wermelinger et al., 2009). Further, working memory proved useful as a measure of malingering, showing specificity and sensitivity in identifying credible versus non-credible cognitive performance post-injury (Kirkwood et al., 2011). Finally, working memory was found to account for variability in mathematical abilities post-injury (Van Beek et al., 2015). The critical relationship between this ability and a wide array of daily cognitive demands, including academic achievement and social performance, is well supported (e.g., Johnson et al., 2013; Phillips et al., 2007; Schmeichel et al., 2008; Unsworth et al. 2014). The findings of the current review suggest that changes in working memory abilities following concussion may underlie more global functional challenges that can result from injury. Notably, the variety of factors assessed by these studies provided insight into the breadth of areas that can be influenced by working memory abilities, supporting the need to better assess and therefore understand the potential impact of working memory challenges post-concussion on the daily demands of affected individuals.

3.5.3.3 Post-injury psychiatric disorder. Post-injury working memory abilities were found to have an opposing effect on the presence of two different psychiatric disorders, with decreased working memory performance being protective against the development of PTSD symptoms, but increased working memory performance accuracy observed in those that do not develop NPD post-injury. Working memory capacity has been implicated in a variety of other psychiatric disorders, including schizophrenia and major depression (Lee & Park, 2005; Rose & Ebmeier, 2006). Considering that challenges with mental health are prevalent following paediatric concussion (Ayr et al., 2009; McCrory et al., 2013), additional research must be done to best understand how the cognitive outcomes of concussion may be implicated in these affective outcomes.

3.5.3.4 Structural and functional cortical properties. Studies exploring the relationship between neuroimaging findings and performance in the current review substantiate the critical role of the frontoparietal network in working memory abilities. Four studies found that functional and structural characteristics of this network were significantly correlated with working memory performance, with a fifth study reporting on correlations between working memory performance and the cerebellum, a region outside of the traditional working memory cortical network.

Studies examining functional activity in the frontoparietal network reported inconsistent increases and decreases in cortical activity. These changes were related to working memory performance, and often influenced by components of the task itself, including task load. Westfall et al. (2015) and Hammeke et al. (2013) found increased activity in the frontoparietal network in their concussion group, however Hammeke et al. (2013) found that these activation patterns changed across the recovery trajectory, with reduced activation compared to controls documented immediately after injury. Within the DLPFC specifically, both Keightley et al. (2014) and Sinopoli et al. (2014) found that the concussion group showed decreased activation overall; however, for Sinopoli et al. (2014) these changes were load-dependent, with increased activity in the DLPFC on the most challenging working memory condition. Westfall et al. (2015), Keightley et al. (2014), and Sinopoli et al. (2014) all found that increased activation was correlated with better task accuracy for the concussion group, however Westfall et al. (2015) found this correlation was significant in the least challenging conditions only, whereas Keightley et al. (2014) and Sinopoli et al. (2014) found the correlation in the most challenging level of their single task condition.

Previous studies in adult populations have found that changes in functional activity are correlated with working memory performance; however, as found in the current review, activation changes are highly variable, and often load-dependent (see McDonald et al., 2012 for review). A review by Bryer et al. (2013) found general trends towards individuals with concussion showing increased activation during complex, continuous tasks, and reduced activation during discrete tasks or during the less challenging conditions of continuous tasks. The general, or task-reliant, correlations between increased activity and better cognitive performance documented in the current review by Westfall et al. (2015), Keightley et al. (2014), and Sinopoli et al. (2014) support these load-dependent trends in activation differences, and provide further evidence that increased cortical activity may be a compensatory mechanism employed post-injury during complex cognitive performance. Previous literature examining functional activity during working memory have found that disparities in activation patterns persist between individuals with a history of concussion versus healthy controls despite a lack of significant differences in behavioural performance scores, suggesting that differences in neural activity may still be required for affected individuals to present similarly to healthy controls (Chen et al., 2004; Dettwiler et al., 2014; McAllister et al., 1999; McAllister, Flashman, McDonald, & Saykin, 2006). This was further supported by Westfall et al. (2015), who found no significant cognitive performance differences between their groups. Further, the DLPFC has been extensively documented as being a critical neural hub for the control and allocation of cognitive resources (Wagner, Maril, Bjork, & Schacter, 2001), and therefore increases in activation in this area suggest that youth with concussion may require a greater engagement of this region to effectively allocate cognitive resources and perform complex cognitive tasks. Considering the heterogeneity in the current review, additional studies should further characterize the relationship between cortical activation and behavioural working memory performance after injury.

In line with the concept of compensatory mechanisms, Krivitzky et al. (2011) found greater bilateral cerebellar activation in their concussion versus healthy control population during challenging working memory conditions that were paired with an inhibitory control task. The role of the cerebellum in working memory has been well documented (Eriksson et al., 2015; Owen et al., 2005) in the maintenance of verbal information and in supporting more general aspects of working memory performance (Stoodley & Schmahmann, 2009; Tomlinson, Davis, Morgan, & Bracewell, 2014) . Specifically, as increased activation was only documented during inhibition conditions, findings suggested that this region is implicated in the executive components of working memory in youth with concussion, in line with previous findings in healthy controls (Stoodley & Schmahmann, 2009). Further, the increased bilateral cerebellar activation in youth with concussion suggests that broad activation of this area may be required to support challenging task performance post-injury.

The correlation between working memory performance and cortical thickness in the left DLPFC documented by Urban et al. (2017) substantiates the potential clinical efficacy of assessing microstructural cortical changes to explore the underlying neuropathology of the working memory outcomes of paediatric concussion. As these injuries typically involve diffuse, cortical disruption, they often do not present on traditional structural imaging scans such as computed tomography (CT) imaging or structural magnetic resonance imaging (MRI) (Choe, 2016; Levin & Diaz-Arrastia, 2015; McCrory et al., 2013, 2017). This introduces significant challenges for a clinician's ability to diagnose the injury and assess pathology and expected injury prognosis. Diffusion tensor imaging (DTI) techniques allow for an assessment of microstructural white matter cortical properties, and have shown potential utility in identifying changes in white matter resulting from injury that can distinguish the affected population from healthy controls (Aoki et al., 2012; Eierud et al., 2014; Levin et al., 2010).

Cortical thickness measurements also assess microstructural properties, and provide the added benefit of assessing gray matter properties along with white matter (Hutton, Vita, Ashburner, Deichmann, & Turner, 2008). In adults post-concussion, cortical thinning has been documented after concussion in adults in regions critical to working memory performance, including the frontal and parietal regions (Govindarajan et al., 2016; List, Ott, Bukowski, Lindenberg, & Rubin, 2015). Cortical thinning has also been related to clinical outcomes in diseases with cognitive involvement, including Alzheimer's (Dickerson et al., 2009; Singh, Chertkow, Lerch, Evans, & Dorr, 2006). Cortical thickness is a cortical property that undergoes extensive change and maturation throughout development (Soelen et al., 2012; Sowell, Trauner, Gamst, & Jernigan, 2002) and therefore may provide critical insight into the unique developmental impact of concussion. The findings of Urban et al. (2017) support that cortical thickness is a microstructural property that appears to be sensitive to the neuropathology of concussion. Further, the relationship between left DLPFC and working memory performance documented in their study substantiates the critical implication of the structure and function of the DLPFC in complex working memory tasks, as well as the susceptibility of this region to injury. They found that cortical thickness had a differing impact on working memory depending on task load and working memory metric (i.e., accuracy and reaction time). Future work should aim to better characterize the behavioural consequences of cortical thickness changes post-concussion.

3.5.4 Implications for clinical practice

The findings of this review provide evidence that working memory is an essential area of cognitive functioning to monitor after paediatric concussion, as almost half of the included studies found that performance was significantly worse in the injury population than in healthy controls or compared to population norms. Of note, the studies that were not sensitive to the effects of working memory on concussion used clinical measures, primarily the Digit Span, which suggests that traditional neuropsychological measures of working memory may not be sensitive and/or cognitively challenging enough to assess the subtle but significant working memory difficulties experienced by individuals with concussion. As limited clinical measures did not consistently find the performance differences seen through experimental paradigms in the current study, clinicians should consider administering extensive working memory paradigms more representative of daily cognitive demands, in combination with these clinical assessments . Further, this review suggests that self-reported post-injury cognitive challenges should not be ignored if they do not present on neuropsychological testing. As findings regarding the recovery trajectory of these outcomes were highly diverse, clinicians should ensure to continuously assess working memory functioning at multiple reassessment time points if an individual self-reports cognitive challenges after their injury . Finally, this review provide evidence that working memory outcomes impact, and are impacted by, a wide variety of factors including language outcomes, daily executive functions, and the presence of psychiatric disorders. This suggests that clinicians should not treat working memory outcomes in isolation, and should be aware and monitor the other functional domains that these changes could be impacting. This review plays a critical role in the characterization of cognitive outcomes of paediatric concussion, an essential step in ensuring that clinical diagnostic tools and treatment plans are best suited for this population.

3.5.5 Strengths and limitations of review papers

The findings of this review must be interpreted within the context of the limitations of the included studies. Consistent with a predominant weakness in the paediatric TBI working memory literature found by Phillips et al. (2017), the majority of studies utilized limited assessments of working memory, and did not approach the research from a theoretical framework. The lack of controlled assessment of multiple aspects of working memory, along with the limited theoretical interpretation, restricted our ability to draw conclusions about which component of working memory is most susceptible to injury. These types of conclusions are essential to be able to best understand the underlying causes of these cognitive challenges, and subsequently inform clinical interventions aimed at rehabilitating this compromised performance. Studies were also highly heterogeneous with regards to factors including age at injury, time since injury, and the working memory outcome measure employed. As found in Phillips et al. (2017), this made drawing cohesive conclusions very challenging, as many unrelated factors could be impacting any disparity in outcomes documented in the included studies. Further, while studies explored the relationship between working memory performance and a variety of pre-injury, injury, and post-injury factors, this consequently resulted in a low number of citations for each factor, limiting the ability to best understand these associations. The majority of studies did not utilize a measure of effort to describe their clinical sample, which is important to consider when interpreting cognitive performance post-concussion, as approximately 17-37% of children with concussion exhibit questionable effort during standardized testing (Kirkwood & Kirk, 2010). Finally, only three papers which explored the impact of time since injury on cognitive outcomes assessed the presence or absence of post-concussion symptoms, which substantially restricts the ability to understand their study populations and the factors that may be influencing these outcomes.

As highlighted through the quality assessment, around half of the studies did not include a thorough assessment with regards to the exposure criteria (i.e., concussion). As only 15/33 studies excluded participants based on positive neuroimaging findings, it cannot be assumed that studies only examined individuals with uncomplicated mTBI, restricting our ability to best understand the relationship between concussion/mTBI and working memory outcomes. Further, the included studies did not consistently apply assessment measures and inclusion and exclusion criteria across injury and control groups, introducing potential bias. Only four studies used an orthopaedic injury control group, which is often thought of as more appropriate than a general healthy control group as it controls for non-specific injury-related factors, such as the experience of sustaining a traumatic injury, and the ensuing exposure to various medical centers and treatments (Yeates, 2010). Further, youth with mTBI and orthopedic injuries present with similar premorbid behavioural disorders that differ from the general population, including attention problems (Yeates, 2010), all of which could impact performance on cognitive testing. However, the added value of using an orthopedic control population has been questioned in both paediatric (Beauchamp, Landry-roy, Gravel, & Beaudoin, 2017) and adult populations (Mathias, Dennington, Bowden, & Bigler, 2013), and therefore more work needs to be done to best understand the best comparison group for research on youth with mTBI. Despite this, most studies did ensure that injury and control groups were well matched on age and sex, as well as on at least one additional demographic or neuropsychological factor. Further, almost all studies examining a sports-related concussion population used athletes as controls. While this review suggested that experimental paradigms (e.g., the N-Back), may be more sensitive to the cognitive outcomes of concussion than clinical paradigms, the fact that almost all studies using a clinical assessment employed the same measure (i.e., the Digit Span) does limit the ability to generalize these conclusions to all clinical measures. Additionally, a small minority of studies included a measure of reaction time in addition to their measure of working memory accuracy. Considering the vulnerability of processing speed to insult following brain injury, this may have substantially restricted the ability to identify changes in working memory performance resulting from concussion.

3.5.6 Strengths and limitations of current review

This review also included some methodological limitations. We only included peer-reviewed studies written in English, which may have restricted our ability to synthesize relevant information from conference abstracts or other areas of grey literature, as well as work in different languages. Further, we did not apply any statistical synthesis methodology; however, this would not have been appropriate considering the high degree of heterogeneity in the literature. We combined data from studies examining concussion as well as mTBI. As the definition of ‘uncomplicated mTBI’ is more comparable to that of concussion, we restricted the review to cases of uncomplicated mTBI where possible, for increased cohesiveness. However, the majority of studies did not provide enough detail to do so. We also combined data from sports and non-sport related concussion. As all of these definitions are often used interchangeably (concussion versus mTBI), or as a subcategory of another (sports-related concussion to concussion, uncomplicated mTBI to mTBI) this combination was appropriate, however findings should be interpreted with caution. Despite these restrictions, strengths of the review were the broad inclusion of studies where working memory was not required to be the primary outcome of interest, increasing our ability to capture and therefore best understand the variability of working memory outcomes that can result from these injuries.

3.5.7 Future directions

Future research in this area should focus on reducing the heterogeneity in the literature through employing more comprehensive and theoretical working memory assessments, in order to better understand the components of working memory most commonly impacted by injury, as well as the underlying causes of this impact. Specifically, future work should include assessments of reaction time, and direct comparisons between different types of working memory (i.e., verbal versus visual/spatial), as well as different components of working memory (i.e., differing load levels, etc.), in order to identify where these performance challenges most commonly present. Further, considering that clinical paradigms did not consistently identify working memory performance changes in this review, research should , focus on understanding what potential performance differences on experimental paradigms represent and how they may impact daily functional performance. If these performance differences appear to be having a substantial impact of everyday performance, research should subsequently focus on updating and tailoring clinical neuropsychological assessments to capture the subtle differences in cognitive abilities that can result from concussion.

Studies should also employ longitudinal designs in order to better understand performance changes across the acute, subacute, and chronic periods, as well as define the expected recovery trajectory. Research should also focus on defining the relationship between working memory and pre-injury, injury, and post-injury factors, including better understanding the underlying neural pathology of these deficits and the impact of injury mechanism. Further, while this review focused on working memory specifically, it is important to acknowledge that all executive functions (e.g., attention, processing speed) work in concert with each other, and are influenced by factors including mood, and post-concussion symptoms. Given the heterogeneity of symptoms that can result from concussion, all of these factors and abilities should be considered together to best understand the impact of a concussion on an individual's ability to function in daily life. Together, these recommendations will allow for a more comprehensive characterization of the nature of working memory challenges after paediatric concussion, as well as of the factors that may impact or be impacted by cognitive performance, and the expected recovery trajectory.

3.5.8 Conclusion

This was the first review to systematically synthesize the literature on working memory outcomes following paediatric concussion. The findings of this review suggest that working memory is a cognitive ability that may be vulnerable to disruption from concussion; however, demonstrated that the presence and nature of this disruption is highly heterogeneous, and appears dependent on pre-injury, injury, and post-injury factors, as well as on how it is assessed. This review will inform future work which can use a variety of different working memory tasks, including those which are more cognitive demanding, to best understand which components of working memory may be impacted by concussion, and further, which injury or non-injury related factors may impact these outcomes. This will inform clinical assessment guidelines and treatment recommendations to ensure that children and youth are receiving appropriate cognitive rehabilitation following injury.

Chapter 4
The Effect of Transcranial Direct Current Stimulation on Cognitive Performance in Youth with Concussion: A Pilot and Feasibility Study

4 Abstract

Background: Concussions are a significant global public health concern, with the best available North American statistics showing that these injuries represent 75-85% of the over 1.7 million traumatic brain injuries occurring annually in the United States. Notably, children and youth are disproportionately affected by concussion, having substantially higher injury rates and slower recovery times than adults. Despite increased recognition of the persisting cognitive challenges in working memory and attention that can result from these injuries, therapeutic interventions to treat these symptoms are not well developed. Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation which regulates cortical activity to promote adaptive plasticity for cognitive recovery and skill reacquisition. While it has been shown to be a promising tool for brain injury recovery in children and adults, the feasibility and efficacy of a tDCS intervention for a youth concussion population remains unknown.

Objective: In the current study, we explored the (1) potential clinical efficacy and (2) feasibility of implementing a multi-session tDCS intervention for persisting cognitive symptoms in youth with concussion.

Methods: We implemented a pilot quasi-randomized control design to investigate whether three sessions of tDCS to the left dorsolateral prefrontal cortex (1) influenced performance on a dual visuospatial-auditory N-back working memory task (i.e. accuracy and reaction time), and (2) was a feasible and tolerable intervention for youth with persistent post-concussion cognitive symptoms (i.e. questionnaire-based measures of the subjective experience of using the device).

Considering the pilot sample size, the influence of tDCS was primarily assessed through data visualization, descriptive statistics, and exploratory analyses.

Results: A total of 12 youth participated in the study. Data analysis showed that: (1) participants with persisting concussion symptoms demonstrated significant improvements in cognitive performance on a challenging dual task across three sessions, with a trend towards tDCS

enhancing increases in task accuracy; and, (2) participants reported receiving tDCS as tolerable, further supported by the lack of participant attrition and adverse effects.

Implications and Conclusion: This study is an initial step towards the development of novel therapeutic interventions for youth with persistent concussion symptoms. Our results will inform future clinical trials aimed at best understanding how to merge clinical practice and advancements in brain stimulation technology for youth with concussion.

4.1 Background

4.1.1 Concussion as a public health concern for youth

Concussion involves the disruption of cortical activity by an external biomechanical force, and typically results in a range of immediate symptoms which can impact cognitive, physical, and emotional domains (Konrad et al., 2011; McCrory et al., 2013, 2017; Rabinowitz & Levin, 2014). The high prevalence of these injuries has led to their classification as a rising public health concern, with almost 150,000 individuals diagnosed annually in Ontario alone (Ontario Neurotrauma Foundation, 2016). Further, these injuries are vastly underreported and not tracked appropriately, and therefore this number is likely a broad underrepresentation of the actual incidence rate (Kroshus et al., 2014; McCrea et al., 2004). Notably, children and youth are disproportionately impacted by these injuries, experiencing higher incidence rates, more severe symptomology, and slower recovery times than adults (Baillargeon et al., 2012; Billette & Janz, 2011; Dougan, Horswill, & Geffen, 2014; Morrish & Carey, 2013; Scopaz & Hatzenbuehler, 2013; Zuckerman et al., 2012). The majority of youth show symptom resolution within 4 weeks post injury, almost double the symptom resolution trajectory of 1-2 weeks seen in adult populations (McCrory et al., 2017). Additionally, up to 30% of youth continue to experience symptoms outside of this expected recovery window (Barlow, 2016; Zemek et al., 2016). Symptoms lasting over 28 days post injury are defined as persistent post-concussion symptoms (PPCS) (Ayr, Yeates, Taylor, & Browne, 2009; Zemek et al., 2016). Experiencing these symptoms can negatively impact an individual’s ability to participate in daily life (Daneshvar et al., 2011; McCrory et al., 2013, 2017; Yeates, 2010; Yeates, Kaizar, et al., 2012), and is correlated with decreased health-related quality of life (Fineblit et al., 2016; Novak et al., 2016).

4.1.1.1 Persisting cognitive symptoms post-concussion. The cognitive challenges that result from concussion can be especially detrimental for youth, due to the extensive impact on all aspects of daily functioning (Yeates, 2010). As a result of the widespread cortical disruption that is characteristic of the concussion injury profile, affected youth typically show reduced performance on complex cognitive tasks requiring efficient communication within and between cortical networks (Babikian et al., 2011; Baillargeon et al., 2012; Howell, Osternig, Van Donkelaar, Mayr, & Chou, 2013; Kwok, Lee, Leung, & Poon, 2008; Ozen, Itier, Preston, & Fernandes, 2013). These tasks involve cognitive skills which can be categorized as executive functions, the higher-order cognitive abilities responsible for coordinating multiple cognitive activities in order to attain goals (Elliott, 2003). Anatomically, neural activity during these tasks occurs primarily in the frontal regions, a brain region which is also highly susceptible to injury in concussion (Choe, 2016; Dettwiler et al., 2014; Stuss & Alexander, 2000). In test settings, challenges with executive functions often present as decreased accuracy and increased information processing speed (i.e., reaction times) on cognitive tasks involving dividing and sustaining attention, task switching, and working memory (Chen et al., 2012; Green et al., 2017; Howell et al., 2013; Karr et al., 2014; Krivitzky et al., 2011; McInnes et al., 2017; Ozen et al., 2013; Sinopoli et al., 2014; Urban et al., 2017). Working memory is a core cognitive skill, involving the goal-directed retention and manipulation of information (Baddeley, 2003; Eriksson et al., 2015). The integrity of working memory abilities has critical functional implications for a range of everyday academic and social demands, with challenges in working memory performance correlated with reduced academic achievement, difficulties with emotional regulation and decision making, and compromised peer relationships (Alloway & Alloway, 2013; Gathercole et al., 2003; Hinson et al., 2003; Johnson et al., 2013).

Changes in cognitive performance following youth concussion can be subtle, and therefore are at risk of not being identified through isolated cognitive tasks (Bigler, 2008; Grindel, Lovell, & Collins, 2001; Kontos et al., 2016; Mangeot et al., 2002). Individuals who have suffered a concussion often perform within the age-appropriate/average range on traditional neuropsychological assessments but still experience various challenges in everyday life (Mangeot et al., 2002; Randolph et al., 2005). However, a number of research studies using more cognitively demanding tasks with increased complexity and task loading, such as dual task paradigms, have found reduced performance in youth with concussion. This suggests that traditional measures may not be sensitive enough to capture some of the more subtle concussion-related symptoms. The dual task paradigm requires individuals to perform two tasks simultaneously and therefore introduces additional demands on sustained attention and cognitive control that are additional to the demands of the individual cognitive tasks to be combined (Jaeggi et al., 2007; Salminen, Mårtensson, Schubert, & Kühn, 2016; Sigman & Dehaene, 2006; Tombu & Jolicœur, 2003). By requiring the simultaneous processing of co-occurring stimulus modalities, dual tasks provide insight into how multiple cognitive and neural systems interact (Sigman & Dehaene, 2006; Tombu & Jolicœur, 2003). This allows for a more comprehensive understanding of the integrity of cognitive functioning and, therefore, a more reliable assessment of the cognitive impact of diffuse cortical injuries such as concussion (Howell, Osternig, & Chou, 2013; Register-Mihalik, Littleton, & Guskiewicz, 2013; Sinopoli et al., 2014). In youth with concussion, dual task paradigms have been shown to elucidate cognitive challenges, as well as abnormal cortical activity, that do not present in single-task paradigms (Howell et al., 2013; Register-Mihalik et al., 2013; Sinopoli et al., 2014).

4.1.1.2 Assessing working memory and dual tasking abilities post-concussion in experimental settings. The N-Back task is an extensively employed paradigm used to investigate working memory performance and assess its underlying neural mechanisms (Jaeggi, Buschkuehl, Perrig, & Meier, 2010; Kane, Conway, Miura, & Colflesh, 2007). In this task, participants are presented with a stream of stimuli and are instructed to make a response whenever a stimulus matches the one presented N trials prior, with N = 0, 1, 2, 3+ trials. This paradigm places demands on many key working memory processes depending on the N level. In level N-0, participants are told which stimulus to respond to, therefore this condition induces the lowest cognitive load as it does require the active retention and manipulation of information. Due to its minimal demands on memory, this condition is often used as a baseline or control, to ensure that participants are actively engaging with the task (Jaeggi et al., 2007). In the rest of the levels, participants must monitor and update the stimuli they are retaining (i.e. sustained attention), and actively manipulate this information to meet task demands (Jaeggi et al., 2010; Kane et al., 2007; Owen et al., 2005). Due to the minimal distance between stimulus and response trials in level N-1, this level predominantly engages sustained attention mechanisms (Pelegrina et al., 2015). N-2, N-3, and above most effectively place demands on the most complex, executive aspects of working memory, involving the active manipulation of information (Jaeggi et al., 2010; Kane et al., 2007; Pelegrina et al., 2015).

The N-Back paradigm has been shown to elicit robust cortical activity in regions typically underlying working memory function, including the dorsolateral and prefrontal cortex, the medial and lateral posterior parietal cortex, and the frontal poles (Owen et al., 2005). It has also been shown to be sensitive to the effects of concussion in the pediatric population, with lower performance on the higher load conditions (Keightley et al., 2014; Sinopoli et al., 2014). Dual N-Back tasks introduce additional cognitive strain on working memory and attentional processes, making it even more demanding and potentially more sensitive to post-concussion cognitive effects as they require diffuse and integrated communication between multiple neural systems, an ability which is especially vulnerable to the injury mechanism of concussion (Choe, 2016). They may also be more ecologically valid since individuals are often required multi-task in everyday life and this is one of the most commonly reported difficulties post-concussion (Howell et al., 2013; Register-Mihalik et al., 2013; Sinopoli et al., 2014).

4.1.1.3 Paucity of treatment interventions. Despite the incidence and detrimental impact of PPCS in youth, surprisingly few treatment interventions exist to address these symptoms. The most recent consensus statement on concussion addresses the limited and contradictory evidence for typical concussion treatment protocols advising prolonged rest and extended periods of inactivity until asymptomatic (McCrory et al., 2017). These procedures have been shown to increase the risk of secondary problems, such as heightened anxiety and irritability, and even contribute to symptom maintenance, as they keep children away from the activities that they want and love to do (Schneider et al., 2013; Silverberg & Iverson, 2012). The statement therefore positions active rehabilitation interventions, involving the graduated return to activity during the symptomatic period, as the most effective approach to concussion recovery (McCrory et al., 2017). In line with this recent shift in recovery protocol, there is an urgent need to identify effective and feasible therapeutic interventions to improve the injury prognosis of youth experiencing PPCS.

4.1.2 Non-invasive brain stimulation technologies

Non-invasive brain stimulation (NIBS) technologies have become a central focus of neuroscience research due to their ability to modulate cortical functions and enhance cognitive abilities. They have been widely used to improve skill learning and cognitive control through increasing or decreasing the threshold for action potentials in neurons, capitalizing on principles of neuroplasticity (Stagg & Nitsche, 2011). Recently, NIBS technologies have been increasingly recognized for their therapeutic potential in the context of rehabilitation, primarily due to their promising utility in promoting cognitive and motor skill re-acquisition following brain injury (Ciechanski & Kirton, 2017; Hummel & Cohen, 2006a; Kirton, 2013; Page et al., 2015; Shin et al., 2014). While the evidence to support the use of NIBS technology to improve recovery from brain injury in adults is emerging (see Li et al., 2015 for review), little is known about its rehabilitative potential in the youth population (Chung & Lo, 2015). The current study addresses this gap by exploring the potential clinical efficacy, as well as the feasibility, of using transcranial direct current stimulation (tDCS), a prevailing NIBS technology, to improve working memory in youth with persistent concussion symptoms.

***4.1.2.1* Transcranial direct current stimulation (tDCS).** tDCS is a safe and commonly used form of NIBS (Bikson et al., 2016). It has the potential to be an excellent rehabilitative tool when used in conjunction with active rehabilitation interventions (Page et al., 2015), as it can be used to target and induce beneficial changes in neuronal communication and firing in the specific brain region that is vulnerable to injury in concussion and extensively implicated in most executive functions: the frontal cortex (Choe, 2016; Filmer et al., 2013; Sarkis et al., 2014). It is the least invasive of NIBS technologies, and further, is portable and inexpensive, increasing its practical applicability (Brunoni et al., 2012).

tDCS modulates cortical activity through the administration of a low, subthreshold, direct electrical current through saline-soaked electrodes on the surface of the skull (Paulus, 2003; Stagg & Nitsche, 2011; Woods et al., 2016). It is comprised of an anode, which delivers an excitatory electrical current, and a cathode, delivering an inhibitory electrical current (Stagg & Nitsche, 2011; Woods et al., 2016). The charge of these currents modifies the resting membrane potential of a neuron, therefore acting on the voltage-gated calcium (Ca^{2+}) and sodium (Na^{+}) channels of the neuronal membrane to influence ion exchange, and encouraging (anodal tDCS) or hindering (cathodal tDCS) the chances of an action potential (Stagg & Nitsche, 2011). Action potentials increase the synaptic strength between two adjacent neurons, which is the basis of synaptic plasticity and can eventually result in structural changes in the cortex (Kolb & Muhammad, 2014). By promoting task-relevant brain activity during a cognitive activity, tDCS can cause transient, immediate improvements in performance, as well as long-term, sustained benefits in skill acquisition, through an interaction with consolidation mechanisms (Reis et al., 2009; Ruf, Fallgatter, & Christian, 2017). The potential for tDCS to interact with consolidation is greatest in multi-session paradigms where individuals have more opportunity to engage these learning mechanisms and acquire new skills (Reis et al., 2009; Reis & Fritsch, 2011; Sarkis et al., 2014). However lasting changes have also been observed after single-session interventions (Lefebvre et al., 2017; Lefebvre, Laloux, Peeters, & Desfontaines, 2013).

4.1.2.1.1 Applications of tDCS. The widespread use of tDCS can be attributed to the fact that electrodes can be placed in multiple varying arrays on the scalp to concentrate current flow to a specific and desirable brain region of interest (Stagg & Nitsche, 2011). Behavioural changes are therefore dependent on the specializations of the stimulated or inhibited cortical region, facilitating the targeting of cortical areas corresponding with behaviours and skills of interest (Brunoni et al., 2012; Filmer et al., 2013; Woods et al., 2016). In the context of rehabilitation, tDCS, and other NIBS technologies, can be understood as intervention or rehabilitation factors which can promote pre-existing adaptive neural and functional plasticity mechanisms following brain injury, encouraging skill reacquisition and thus facilitating recovery from injury (Chen & Schlaug, 2016; Clayton et al., 2016; Kolb & Muhammad, 2014; Li et al., 2015; Page et al., 2015).

tDCS has shown promising utility for the improvement of cognitive performance and skill acquisition in the domain of executive function, in both healthy controls and clinical populations. tDCS facilitates this improvement through modulating (typically, promoting) cortical activity in the frontal regions, especially in the dorsolateral prefrontal cortex (DLPFC), either before or during the completion of a cognitive task. tDCS has been shown to cause immediate and sustained improvements in working memory performance, as defined by shorter reaction time and increased accuracy (Brunoni & Vanderhasselt, 2014; Hill, Fitzgerald, & Hoy, 2016; Mancuso, Ilieva, Hamilton, & Farah, 2016; Ruf et al., 2017; Zaehle et al., 2011), with these changes documented up to nine months post-intervention (Ruf et al., 2017). Further, the technology has been used to improve dual task performance through modulating overarching processes of executive control during conditions of cognitive overload (Filmer et al., 2013; Strobach et al., 2015). Specifically, the application of anodal (i.e., excitatory) tDCS to DLPFC has been shown to improve balance, gait, and postural control, while a cognitive task is concurrently performed (Manor et al., 2015; Swank, Mehta, & Criminger, 2016; Zhou et al., 2015; Zhou et al., 2014). It has also been shown to increase executive control and cognitive performance during multitasking and divided attention paradigms (Filmer et al., 2013; Strobach et al., 2015), including dual working memory tasks (Martin et al., 2013; Martin, Liu, Alonzo, Green, & Loo, 2014). Notably, changes induced by tDCS have shown transferability to related tasks of executive functioning (Ruf et al., 2017).

The ability of dual working memory conditions to engage extensive executive functions has been well substantiated (Jaeggi et al., 2007; Salminen, Kuhn, Frensch, & Schubert, 2016; Salminen, Strobach, & Schubert, 2012; Sinopoli et al., 2014). Training on these challenging paradigms has been shown to lead to global improvement on multiple related measures of executive function (Salminen et al., 2012), and also to structural changes in cortical networks involved in higher cognition (Salminen, Mårtensson, Schubert, & Kühn, 2016). Previous work with tDCS has found that the enhancing effects of this technology are augmented in conditions inducing a greater cognitive load than single task conditions (Manor et al., 2015; Meiron & Lavidor, 2013), suggesting that utilizing dual working memory paradigms may augment the beneficial effects of tDCS. The transfer of dual working memory training to other complex cognitive abilities suggests that better understanding how to modulate performance on these tasks with tDCS interventions has important clinical utility for populations experiencing deficits in these abilities, such as youth with persisting cognitive symptoms.

4.1.2.1.2 Feasibility of utilizing tDCS in a youth concussion population. Comprehensive reviews support that tDCS is safe and tolerable, and has potential clinical applicability in both clinical and typically developing pediatric populations (Bikson et al., 2016; Kirton, 2013; Palm et al., 2016). In a rehabilitation context, tDCS has shown promising utility in promoting positive clinically-relevant outcomes in a variety of neurodevelopmental (including ADHD and autism), psychological (including schizophrenia and depression), and movement disorders (including stroke, dystonia, and cerebral palsy), as well as in epilepsy, dyslexia, and headache (Krishnan, Santos, Peterson, & Ehinger, 2015; Palm et al., 2016). Applications have included promoting motor learning (Ciechanski & Kirton, 2017), and improving performance on executive function tasks involving inhibition and working memory (Prehn-Kristensen et al., 2014; Soff, Sotnikova, Christiansen, & Becker, 2017). Studies including reports on adverse effects and tDCS tolerability have shown that tDCS appears to be safe and feasible to implement in a paediatric population, with no serious adverse effects and low participant attrition rates (Krishnan et al., 2015; Palm et al., 2016). During tDCS, children and youth report experiencing sensations comparable to those of adult populations, including itching at the site of the electrodes and slight headache (Ciechanski & Kirton, 2016; Gillick et al., 2018; Gillick et al., 2015; Krishnan, Santos, Peterson, & Ehinger, 2015; Palm et al., 2016). Overall, children and youth report tDCS as tolerable, comparative to other everyday life events such as watching TV and going on a long car ride (Ciechanski & Kirton, 2017).

Despite these promising results, the majority of research on tDCS has explored its tolerability and feasibility in adult populations. In paediatric populations, early rehabilitation and intervention following injury can be critical in promoting adaptive plasticity mechanisms and minimizing the risk of persisting post-injury gaps in acquiring cognitive skills (Anderson et al., 2011; Dennis et al., 2014). Therefore, it is essential that further research be done to better understand how to safely and effectively implement these technologies in children and youth, in order to maximize clinical outcomes for this population.

4.1.2.1.3 Clinical utility of tDCS for persisting cognitive symptoms in a youth concussion population. Recent reviews have shown that NIBS technologies have clinical utility in improving recovery from TBI in adults in multiple domains, including general post-concussion symptoms and cognitive abilities in the area of executive functioning (Clayton et al., 2016; Kolb & Muhammad, 2014; Koski et al., 2015; Li et al., 2015; Page et al., 2015); however, the literature is still in its infancy. Further research is needed to know the therapeutic potential of tDCS across varying severities of TBI and across different demographic groups, as well as to better understand the impact of tDCS on executive function tasks more representative of daily cognitive demands. Considering the ability of tDCS to enhance performance on the same complex cognitive functions typically compromised in youth with persistent cognitive concussion symptoms, its ability to facilitate cognitive recovery following concussion must be explored in order to improve the lives of affected youth.

4.2 Study objectives, research questions, and hypotheses

The objectives of this pilot study were to explore: (1) potential clinical efficacy and (2) feasibility of implementing a multi-session tDCS intervention for persisting cognitive symptoms in youth with concussion. Specifically, the research questions were as follows:

1) Does anodal tDCS to the left DLPFC influence cognitive performance on a working memory dual task in youth with persisting cognitive symptoms post-concussion?
2) How do youth with PPCS rate the subjective experience of receiving tDCS? Were any feasibility barriers identified?

It was hypothesized that all participants would show performance improvements (as operationalized by higher accuracy and faster reaction time) on the working memory dual task across the three study sessions, with tDCS enhancing learning-related changes in either accuracy, reaction time, or both. Further, it was hypothesized that a tDCS intervention would be feasible for youth with PPCS, and further, that youth would find the experience of receiving tDCS as tolerable.

In the context of randomized control trial methodology, the **population** of interest was youth with concussion, ages 13-18 years, who were still experiencing self-reported cognitive symptoms at the 1-month post-injury mark. The **intervention** was three separate sessions (20 minutes per session) of anodal (excitatory) tDCS over the DLPFC during the completion of a cognitive dual task. The **control** was 20 minutes of sham tDCS over the same DLPFC region during the dual task. The **outcome** of interest was performance, as measured by reaction time and accuracy, on a dual working memory task across the three experimental sessions, as well as questionnaire-based ratings of the subjective experience of receiving tDCS.

4.3 Methods

4.3.1 Overview of research design

A pilot quasi-randomized double-blinded control design was applied to investigate whether three sessions of tDCS to the left dorsolateral prefrontal cortex, paired with a dual visuospatial-auditory N-back working memory task, (1) influenced cognitive performance, and (2) was a feasible and tolerable intervention for youth with persistent cognitive symptoms post-concussion. While a 48-hour window between the three experimental sessions for each participant was desired, anytime in the 24-72-hour period was acceptable, due scheduling constraints. Average time between sessions was 51.17 hours. At the first study session, capacity assessment was performed and all participants gave written consent. Participants also completed demographic and medical measures and underwent neuropsychological testing. At each study session, all participants completed a tDCS safety screening questionnaire, to ensure that they did not have any contraindications to receiving the stimulation, as well as a measure of concussion symptom severity. Participants completed a familiarized phase in which they practiced the cognitive task prior to the experiment. After familiarization, participants performed the cognitive task while receiving either real or sham tDCS dependent upon group assignment. Finally, participants completed debriefing questionnaires to document their tDCS experience. See Table 1 for a detailed overview of the structure of each study session.

Table 4.1

Summary of Study Protocol

Session 1	***Session 2***	***Session 3***
Consent and tDCS safety screening questionnaire	tDCS safety screening questionnaire	tDCS safety screening questionnaire
Demographic and medical questionnaire	---	---
Edinburgh handedness inventory	---	---
Post-concussion symptom inventory	Post-concussion symptom inventory	Post-concussion symptom inventory
Medical Symptom Validity Test (MSVT)	---	---
Full-Scale IQ-II (FSIQ-II) of the WASI-II	---	---
Digit span (WISC-V/WAIS-IV)	---	---
Quasi-randomization	---	---
N-Back task practice	N-Back task practice	N-Back task practice
tDCS set up	tDCS set up	tDCS set up
tDCS and N-Back task	tDCS and N-Back task	tDCS and N-Back task
tDCS adverse effects questionnaire	tDCS adverse effects questionnaire	tDCS adverse effects and tolerability questionnaires

Total session time = 2-3 hours	Total session time = 1 hour	Total session time = 1 hour

4.3.2 Participants and recruitment

4.3.2.1 Inclusion and exclusion criteria*.* Participants were eligible for participation if they were between the ages of 13-18 years, with a medical diagnosis of concussion by a community physician received at least one month prior to the time of study. Further, all participants had to be experiencing self-reported persistent cognitive concussion symptoms at the time of participation. The age range in this study was chosen based on a recent prospective, multi-center cohort study which correlated many demographic variables with concussion prognosis to develop a 12-point PPCS risk score model, and found that being between the ages of 13 to 18 years was a central and significant predictor of negative outcomes (Zemek et al., 2016). As no objective marker of persistent-post concussion symptoms exists (Zemek et al., 2016), the presence of persisting cognitive concussion symptoms was determined by self-report during a pre-screening phone call and by the baseline post-concussion symptom inventory. As the majority of typically developing controls (>85%) have been shown to rate themselves in the 0 (not a problem) range on the cognitive component of the PCSI (Hunt, Paniccia, Reed, & Keightley, 2016), anyone who rated themselves within the 1-6 range (i.e., anything above 'not a problem') on at least one of the five cognitive items on the PCSI (i.e., #14- feeling slowed down, #15-feeling mentally "foggy", #16-difficulty concentrating, #17-difficulty remembering, #18-get confused with directions or tasks, and #19-answer questions more slowly than usual) was classified as having persistent cognitive symptoms.

Participants were deemed ineligible for participation on the basis of having any comorbid neurological conditions, in order to minimize the amount of confounding factors, as concussion is in itself a highly heterogeneous injury. As in other studies assessing working memory in a concussion population (Keightley et al., 2014), participants were also excluded on the basis of premorbid diagnoses of learning disabilities or of a developmental disorder. Given that a premorbid diagnosis of ADHD is present in a significant portion of youth experiencing persistent symptoms (Zemek et al., 2016), participants were not excluded based on this diagnosis, however this information was recorded in a demographic and medical questionnaire for further consideration during data analysis. Additionally, participants were excluded on the basis of uncorrectable vision and/or hearing impairments, such as a report of severe sensorineural hearing loss, to ensure they were able to engage with the experimental task. Finally, participants were screened for the general exclusion criteria for non-invasive brain stimulation, including the presence of metallic implants, pacemakers, medication infusion devices, as well as epilepsy and conditions increasing the risk of syncope (Bikson et al., 2016; Brunoni et al., 2012; Woods et al., 2016) .

4.3.2.2 Recruitment strategies. The primary (1) recruitment strategy involved collecting a convenience sample through all concussion research, clinical, and educational programs at Holland Bloorview Kids Rehabilitation Hospital. The secondary (2) recruitment strategy involved contacting concussion clients and participants from concussion educational programs who had previously said they were interested in learning more about concussion research at the hospital. Finally (3), recruitment was done through advertising materials throughout the hospital and on the hospital webpage. Potential participants who were referred to the study team either through (1) the concussion programs, (2) the concussion research list, or (3) through self-referral from advertising materials were contacted over the phone to discuss the study. Potential participants were asked to answer preliminary screening questions to determine their eligibility. If participants remained interested and eligible at the screening phone call, they were sent an information package with further details about participating, and were instructed to contact the study team to schedule their study sessions. The study team followed-up with participants who had not been in contact 1-week after the information letter was sent out. Participants were provided with a gift card as a token of appreciation for their time, as well as with high school volunteer hours equivalent to the duration of travel time and length of each session.

4.3.3 Participant characteristic measures

4.3.3.1 Participant demographic and injury characteristics. At the first study session participants completed a demographic and medical questionnaire asking about age, grade, sex, concussion characteristics (i.e. date of injury, number of injuries, mechanism of injury, etc.), academic history, and pre-morbid diagnoses (e.g. learning disability, depression, etc.). They were also administered the Edinburgh Handedness Inventory – Short Form (Veale, 2014), which was used to classify participants as left, right, or mixed-handed. At every study session participants completed the 22-item Post-Concussion Symptom Inventory (PCSI), to monitor how concussion symptomology varied over the course of the intervention. The PCSI is a measure of concussion symptom severity and cognitive performance that is a well-validated tool for assessing the severity of physical, emotional, and cognitive symptoms (Sady, Vaughan, & Gioia, 2014).

4.3.3.2 Participant neuropsychological characteristics. At the first study session, participants completed neuropsychological tests assessing IQ, working memory, and effort/malingering. A measure of effort was needed as research shows that approximately 17-37% of children with concussion exhibit questionable effort during standardized testing (Kirkwood & Kirk, 2010). See Table 2 for a summary of tests administered.

Table 4.2

Summary of Neuropsychological Tests Administered to Study Participants

Test Name	***Function***
Medical Symptom Validity Test (MSVT)	Measure of effort/malingering
Full-Scale IQ-II (FSIQ-II) of the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II)	Estimate of general intelligence, includes a verbal and a visual measure
Digit Span from the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV; >16 years) or Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V; 6-16 years)	Measure of attention span and working memory

4.3.3.3 Participant stratification. Participants were assigned to the experimental or control tDCS groups based on demographic variables and neuropsychological test scores. Specifically, they were assigned based on five strata: age (matched +/- 1 year), sex, handedness, IQ (matched +/- 5 points), and digit span performance (matched +/- 2 points). During the data analysis stage, 2-sided t-tests were performed on the scores of each of these measures to ensure effective stratification (a-prior significance level of $p < 0.05$).

4.3.4 Description of participant sample

A total of N = 12 (10 F, 2 M) participants completed the pilot and feasibility study. While the tolerability and feasibility data include all 12 participants, the N-Back data is comprised of a subset of N = 10 (8 F, 2 M) participants, due to changes in the N-Back experimental design that were implemented after the first two participants completed the study. Descriptive statistics on participant demographic and concussion injury characteristics are outlined in Table 3. Based on the laterality quotient, within the total sample (N =12), N = 7 (58.33%) were right handed, N = 3 (25.0%) were mixed handed, and N = 2 (16.67%) were left-handed. Within the N-Back data subset (N = 10), N = 5 (50.0%) were right handed, N = 3 (30.0%) were mixed handed, and N = 2 (20.0%) were left-handed.

4.3.4.1 Injury characteristics and concussion symptomology. All participants were at minimum >4 weeks out of their concussion, however time since injury was variable. Within the total sample (N = 12), N = 3 (25.0%) of participants were between one to less than three months out of their injury, N = 3 (25.0%) were three to less than six months out of injury, N = 1 (8.33%) were six months to less than one year out of injury, N = 3 (25.0%) were one year to less than three years out of injury, and N = 2 (16.67%) were over three years out of their injury. N = 5 (41.67%) participants had a sports-related concussion.

Within the N-Back data subset (N = 10), N = 2 (15.38%) of participants were between one to less than three months out of their injury, N = 3 (23.08%) were three to less than six months out of injury, N = 2 (15.38%) were six months to less than one year out of injury, N = 3 (23.08%) were one year to less than three years out of injury, and N = 2 (15.38%) were over three years out of their injury. N = 3 (25.0%) participants had a sports-related concussion.

4.3.4.2 Additional academic and medical characteristics. N = 3 participants of the total sample had attended a gifted program, N = 4 had an Individual Education Plan (IEP), N = 2 had premorbid undiagnosed issues with attention, and N = 4 had a history of psychiatric illness. An additional N = 1 participant was diagnosed with premorbid ADHD; however, this participant was not a part of the N-Back data subset.

Table 4.3

Participant Demographic and Injury Characteristics, Across Both tDCS Groups

Demographic and Injury Characteristics	*Mean*	*SD*	*CI (95%)*
Test age	15.90[A] 15.84[B]	1.33[A] 1.16[B]	0.85[A] 1.01[B]
Grade	10.42[A] 10.40[B]	1.16[A] 1.26[B]	0.74[A] 0.90[B]
Handedness (Laterality quotient)	47.92[A] 41.25[B]	66.96[A] 71.94[B]	42.55[A] 51.46[B]
Number of previous diagnosed concussions	1.50[A] 1.60[B]	1.09[A] 1.17[B]	0.69[A] 0.84[B]
Longest symptom duration since most recent concussion (months)	14.88[A] 15.65[B]	14.81[A] 16.08[B]	9.40[A] 11.50[B]
Average baseline PCSI score (All items)	2.06[A] 2.25[B]	1.20[A] 1.81[B]	0.76[A] 1.29[B]
Average baseline PCSI score (Cognitive items)	2.61[A] 2.67[B]	1.17[A] 2.04[B]	0.74[A] 1.46[B]

A = Total sample values (N =12)

B = N-Back data subset (N = 10)

4.3.4.3 Neuropsychological profile. Participant neuropsychological test results are shown in Table 4. All participants had a within or above average IQ score based on the FSIQ-II of the WASI-II. Two participants failed the MSVT measure of effort, with N = 1 participant presenting with poor effort and poor memory and N = 1 participant presenting with poor effort and good memory. An additional N = 1 participant presented with poor memory, but good effort. Participants who failed the effort component of the MSVT were equally distributed between tDCS groups.

Table 4.4

Participant Neuropsychological Test Results, Across Both tDCS Groups

Neuropsychological Test Results	***Mean***	***SD***	***CI (95%)***
WASI-II Vocabulary T-Score	62.33[A] 62.90[B]	9.75[A] 10.61[B]	6.19[A] 7.58[B]
WASI-II Vocabulary Scaled Score	13.75[A] 13.9[B]	2.86[A] 3.12[B]	1.82[A] 2.22[B]
WASI-II Matrix Reasoning T-Score	52.92[A] 54.30[B]	9.02[A] 8.71[B]	5.73[A] 6.23[B]
WASI-II Matrix Reasoning Scaled Score	11.08[A] 11.5[B]	2.68[A] 2.59[B]	1.70[A] 1.85[B]
WASI-II FSIQ-2 Total Scaled Score	24.83[A] 25.4[B]	4.59[A] 4.83[B]	2.92[A] 3.46[B]
WASI-II FSIQ-2 Percentile Rank	74.42[A] 76.70[B]	22.71[A] 23.94[B]	14.43[A] 17.13[B]
WAIS-IV Digit Span Scaled Score	9.50[A] 9.33[B]	3.87[A] 4.73[B]	6.16[A] 11.74[B]
WISC-V Digit Span Scaled Score	11.0[A] 10.71[B]	2.62[A] 2.69[B]	2.19[A] 2.49[B]

A = Total sample values (N =12). N = 4 individuals were tested with the WAIS-IV, and N = 8 individuals were tested with the WISC-V.

B = N-Back data subset (N = 10). N = 3 individuals were tested with the WAIS-IV, and N = 7 individuals were tested with the WISC-V.

4.3.4.4 Participant stratification. Participants were quasi-randomized into the real or sham tDCS group on the basis of demographic and neuropsychological factors; specifically, age, sex, handedness, IQ, and digit span performance. Within the total sample (N = 12), N = 7 (6 F, 1 M) participants were allocated to the real tDCS group, and N = 5 (4 F, 1 M) were in the sham tDCS group. Within the subset of N-Back data (N = 10), N = 5 (4 F, 1 M) were in the real tDCS group and N = 5 (4 F, 1 M) were in the sham tDCS group. Independent Welch's t-tests were conducted to compare scores between the real and sham tDCS groups on the demographic and neuropsychological quasi-randomization factors. No significant differences existed between groups on any of the factors ($p < 0.05$), both within the total sample (N = 12), as well as the N-back data subset (N = 10), suggesting that participants were appropriately stratified between groups. See Tables 5 and 6 for a breakdown of participant demographic and injury characteristics as well as neuropsychological test results by tDCS group.

Table 4.5

Participant Demographic and Injury Characteristics, Within Each tDCS Group

Demographic and Injury Characteristics	***Mean***	***SD***	***CI (95%)***
Test age	16.22^{A}	1.42^{A}	1.76^{A}
	15.47^{B}	1.47^{B}	1.82^{B}
Grade	10.80^{A}	1.30^{A}	1.62^{A}
	10.00^{B}	1.22^{B}	1.52^{B}
Handedness	2.50^{A}	84.50^{A}	104.92^{A}
(Laterality quotient)	80.00^{B}	27.39^{B}	34.00^{B}
Number of previous diagnosed concussions	1.40^{A}	1.14^{A}	1.42^{A}
	1.80^{B}	1.30^{B}	1.62^{B}
Longest symptom duration since most recent concussion (months)	15.50^{A}	13.81^{A}	17.15^{A}
	15.80^{B}	19.77^{B}	24.54^{B}
Average baseline PCSI score	1.11^{A}	1.04^{A}	1.30^{A}
(All items)	3.38^{B}	1.74^{B}	2.17^{B}

Average baseline PCSI score (Cognitive items)	1.47[A] 3.87[B]	1.38[A] 1.96[B]	1.72[A] 2.43[B]

A = Real tDCS Group (N = 5) subset of the N-Back dataset

B = Sham tDCS Group (N = 5) subset of the N-Back dataset

Table 4.6

Participant Neuropsychological Test Results, Within Each tDCS Group

Neuropsychological Test Results	***Mean***	***SD***	***CI (95%)***
WASI-II Vocabulary T-Score	61.20[A] 64.60[B]	8.56[A] 13.15[B]	10.62[A] 16.32[B]
WASI-II Vocabulary Scaled Score	13.4 [A] 14.4 [B]	2.51 [A] 3.85 [B]	3.12 [A] 4.78 [B]
WASI-II Matrix Reasoning T-Score	57.00[A] 51.60[B]	10.70[A] 6.15[B]	13.29[A] 7.63[B]
WASI-II Matrix Reasoning Scaled Score	12.2 [A] 10.8 [B]	3.27 [A] 1.79 [B]	4.06 [A] 2.22 [B]
WASI-II FSIQ-2 Total Scaled Score	25.6 [A] 25.2 [B]	4.72 [A] 5.50 [B]	5.86 [A] 6.82 [B]
WASI-II FSIQ-2 Percentile Rank	79.20[A] 74.20[B]	19.45[A] 29.93[B]	24.15[A] 37.16[B]
WAIS-IV Digit Span Scaled Score	12.00[A] 4[B]	1.41[A] N/A[B]	12.71[A] N/A[B]

WISC-V Digit Span	10.67[A]	2.08[A]	5.17[A]
Scaled Score	10.75[B]	3.40[B]	5.42[B]

A = Real tDCS Group (N=5) subset of the N-Back dataset. N = 2 individuals were tested with the WAIS-IV, and N = 3 individuals were tested with the WISC-V.

B = Sham tDCS Group (N = 5) subset of the N-Back dataset. N = 1 individuals were tested with the WAIS-IV, and N = 4 individuals were tested with the WISC-V.

4.3.5 tDCS protocols

tDCS was administered using a Soterix Medical 1x1 Limited Total Energy (LTE) Stimulator for Susceptible Subjects (Soterix Medical, 2016). For the experimental group, anodal tDCS was delivered for 20 minutes at 1.5 milliamps (mA) over the left DLPFC, defined as area F3 on the 10-20 electrode reference system. The control group received sham tDCS, also for 20 minutes over the left DLPFC. In both groups, the cathode was placed over the right supraorbital region, defined as area Fp2 on the 10-20 system (see Figure 4.1, Klem, Luders, Jasper, & Elger, 1999; Palm et al., 2016). The 1x1 LTE Stimulator contains an auto-sham feature which ramped up the intensity to maximum stimulation (i.e., 1.5 mA) over 30 seconds at the beginning of the experiment, creating the tickle sensation that occurs during the early phase of tDCS administration, and then automatically ramped the stimulation down to baseline. Ramping was repeated at the end of the 20 minutes to mimic the sensations experienced during the final ramp down phase of anodal tDCS. The participants and the experimenter were blinded to the experimental condition (anodal versus sham tDCS), creating a double blinded experiment and minimizing the possibility of participant and experimenter effects on cognitive performance. The blinded experimenter was KQDEL, and at minimum one other study team member was present at each session to pre-set the tDCS device to the correct condition and assist with tDCS administration (e.g., 10-20 measurements).

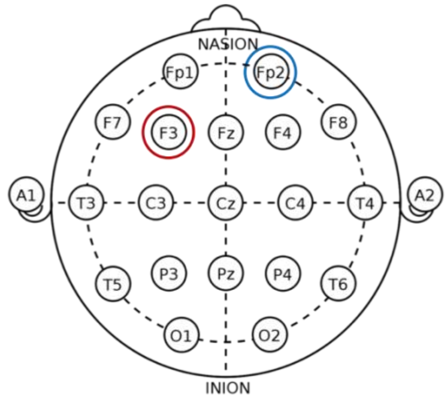

Figure 4.1. The left DLPFC region (anode placement) as defined by area F3, and the right supraorbital region (cathode placement) as defined by area Fp2, on the 10-20 electrode reference system. Adapted from Klem et al., (1999).

4.3.6 tDCS tolerability and feasibility

After each study session, participants completed a tDCS adverse effects questionnaire, probing the degree to which they experienced the ten most commonly-reported tDCS side effects: itching, pain, burning, warmth/heat, pinching, metallic/iron taste, fatigue, headache, nausea, and dizziness (Aparicio et al., 2016; Fertonani, Ferrari, & Miniussi, 2015). A 5-point scale was used to operationalize the degree of intensity, spanning 'none', 'mild', 'moderate', 'considerable', and 'strong'. The questionnaire also included probing items about how long the sensation lasted, how much sensations affected performance, and the location where the sensations were experienced. Further, at the final study day, the questionnaire also included a section asking participants which tDCS group they thought they were in, in order to assess the effectiveness of participant blinding. The questionnaire was slightly modified from that proposed in Fertonani et al. (2015), through the addition of three frequently reported symptoms identified through a systematic review and meta-analysis of adverse effects in tDCS studies (Aparicio et al., 2016). At the final study session, participants were also asked to rate the subject tolerability of tDCS, by comparing the experience to seven common childhood events (modified from the questionnaire developed by Garvey, Kaczynski, Becker, and Bartko, 2001).

Recruitment rates, participant attrition, and PCSI data were also considered within the context of tolerability and feasibility. A detailed contact log was kept during the recruitment and data collection process, including reasons for declining participation, in order to best understand any barriers to feasibility. PCSI scores were monitored as a control to ensure that tDCS administration was not having a negative impact on pre-existing concussion symptoms.

4.3.7 Cognitive performance measure: N-Back experimental task

We administered an auditory-visuospatial dual N-Back task was at four levels of difficulty. The task was implemented using custom Python 2.7 scripts developed in the lab (Python Software Foundation), and was presented on a Lenovo laptop computer with a 15.5-inch (diagonal) screen and a built-in keyboard. The N-Back task was adapted from Jaeggi et al. (2007) to be appropriate for a behavioral experiment outside of an fMRI scanner, and further, to suit the clinical pediatric population of this study. Modifications were informed through pilot testing with healthy controls, as well as through the guidance of LR, a clinical neuropsychologist with expertise in pediatric brain injury.

During the N-Back working memory task, participants were presented with sequences consisting of concurrent auditory and visual stimuli. Auditory stimuli were 9 consonant letter names of the English alphabet as spoken by an adult female: C, G, H, K, L, P, Q, T, and Z. Consonant letter names were chosen based on their distinctiveness (modified from Jaeggi et al., 2007). Auditory stimulus loudness was normalized in MATLAB (Version R2014b, MathWorks Inc.). Each visual stimulus was a white square position in one of 9 possible locations on a black 3-by-3 grid (see Figure 4.2). Trials were presented consecutively with a stimulus duration of 500 ms and an inter-stimulus interval (ISI) of 2500 ms, so that each trial was 3000 ms long. Participants were tasked with pressing a keyboard on the laptop if the stimulus in the present trial matched the stimulus presented in the trial directly previous (level N-1), two trials back (level N-2), or three trials back (level N-3). Different keys were assigned to visual and auditory matches, and participants made key-press responses on the side of the keyboard congruent with their dominant hand. As in Jaeggi et al. (2007), an N-0 level was also included to serve as a control task. In each level N-0, participants were introduced to a pair of auditory and visual targets and pressed the buttons on any trial in which the auditory or visual stimuli matched the targets.

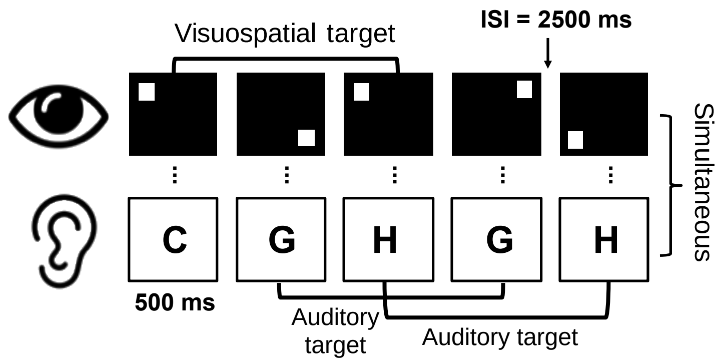

Figure 4.2. Example of an N-2 trial in the N-Back task.

The N-back task consisted of 12 blocks, with each block containing one 45-trial sequence of one of the four N-back levels: N-1, N-2, N-3, or N-0, with difficulty level always being equal in each of the visual and auditory modalities. The order of the 12 blocks was quasi-randomized such that no two consecutive blocks were the same N-back level. The trial sequences were generated using custom MATLAB scripts developed by our group. Our approach ensured that all 45-trial quasi-randomized sequences contained exactly 15 hits (i.e., 33% hits) within both the auditory and visual modality, with a total of 5 hits within each the visual and auditory stimuli occurring in both modalities on the same trial. Further, the script generation was programmed so that there would be exactly seven lures within each stimulus modality in a 45-trial sequence (i.e., 15.56% lures). Lures were defined as no-match trials at the current task level, but served as matches for a different level not tested in that block. Button presses on match trials were tabulated as hits, and button presses on no-match or lure trials as false alarms. Block order and sequences were quasi-randomized for each participant and for each session.

Prior to beginning the 12-block dual N-Back task, participants practiced the task by completing training sequences using the same experimental set-up. During task practice, participants completed sequences with visual stimuli only, then with auditory stimuli only. For each modality, participants were presented with one 20-trial familiarization block at each level: N-0, then N-1, then N-2, then N-3. Participants were not permitted to progress to the next familiarization block until they had reached a task accuracy of d’ >= 1.7. This threshold was determined through pilot testing, to ensure that participants could demonstrate an understanding of the task without over-training to reach higher performance. While order of presentation of the

N-Back level remained consistent during the practice, the 20-trial sequences were quasi-randomized for each participant and for each session.

4.4 Data Analysis

4.4.1 Data analysis approaches for pilot and feasibility studies

In the context of clinical research, pilot studies are critical precursors to large-scale clinical trials, as they can inform future work by addressing uncertainties around the feasibility of study methodology, as well as by providing estimates of treatment effects that may merit follow-up (Moore, Carter, Nietert, & Stewart, 2011; Thabane et al., 2010). However, due to their preliminary and exploratory nature, pilot studies typically involve small sample sizes, and consequently often lack the statistical power needed for estimating effects (Kianifard & Islam, 2011; Lee, Whitehead, Jacques, & Julious, 2014). Analysis approaches must therefore be appropriately tailored to the nature of the pilot sample size. It is recommended within pilot study methodology that analysis primarily involves a descriptive approach (Lancaster, Dodd, & Williamson, 2001), and further, that hypothesis testing should be interpreted as preliminary, with a focus on estimating effects through confidence intervals (Chen et al., 2016; Kianifard & Islam, 2011; Lancaster et al., 2001; Lee et al., 2014) .

These recommendations are followed in this study's approaches to data analyses. All data were analyzed with RStudio software, version 1.0.136 (RStudio team, Boston, MA, 2016). The significance threshold was set to $p<0.05$ for all statistical tests. Significance values between 0.2 to 0.05 were reported as marginally significant, considering that the power of a statistical test can be increased in the context of pilot trials (Kianifard & Islam, 2011).

4.4.2 Analysis of participant characteristics

Descriptive statistics (mean, SD, 95% CI) were generated for all numeric participant demographic and injury characteristics, as well as for all neuropsychological test results. Independent Welch's t-tests ($p < 0.05$) were performed on all a-priori identified participant stratification factors (i.e., age, sex, handedness, IQ, and digit span performance) to assess the efficacy of quasi-randomization.

4.4.3 Analysis of N-Back data

4.4.3.1 Accuracy performance metrics. In order to best understand performance accuracy on N-Back tasks, an individual's correct responses to targets (i.e., hits, with misses being omission errors) must be interpreted relative to their incorrect responses to non-targets (i.e., false alarms, or commission errors) (Haatveit et al., 2010; Meule, 2017). This can be done through a net score calculation (i.e., hits – false alarms), defined as the *Pr* discrimination index (Snodgrass & Corwin, 1988). The mathematical formla for *Pr* is as follows:

$$Pr = Hit\ Rate - False\ Alarm\ Rate$$

However, net scores are at risk of being highly skewed when the probability of performing a hit differs from that of performing a false alarm (Haatveit et al., 2010). *D'* is another discrimination index which allows for the direct comparison of hits and false alarms despite their differing probability distributions, through taking the normalized, or z-score transformed, value of each rate, giving the percent probability in a normal distribution (Haatveit et al., 2010; Macmillan & Creelman, 1990; Snodgrass & Corwin, 1988). The mathematical formula for d' is therefore as follows:

$$d' = Z_{hit\ rate} - Z_{false\ alarm\ rate}$$

In the context of signal detection theory, the *d'* discrimination index can be interpreted as the distance between the signal and the noise probability distribution and the noise probability distribution alone, which provides insight into the executive abilities necessary to complete a dual N-Back task (Haatveit et al., 2010). The validity of this metric as a measure of working memory has been supported in patients with schizophrenia, with the N-Back level N-2 *d'* score outperforming the Digit Span Backward and Letter-Number Sequencing subtests from the WAIS-III, and further, resisting influence from demographic variables or IQ (Haatveit et al., 2010).

4.4.3.2 Cognitive performance. On each study day, cognitive performance was assessed with accuracy (*d'*) and reaction time values. Hit rate (i.e., number of correctly identified hits divided by all possible hits) and false alarm rate (i.e., number of incorrect hit responses to non-targets divided by all possible non-targets) calculations were performed on the raw values of participant's behavioural responses in the visual and auditory domains. These values were then inputted into the d' formula. As in (Haatveit et al., 2010), perfect hits (i.e., hit rate of 1.0) were adjusted using the formula 1-1/(2*n*), and zero false alarms were adjusted with the formula 1/(2*n*), where *n* is the total number of hits or false alarms. Based on the ratio of hits and false alarms in the N-Back paradigm employed in the current study, the greatest possible *d'* value that could be achieved (i.e., perfect hit rate, zero false alarms) was +4.52, and the lowest possible *d'* value (i.e., zero hits, all false alarms) was -4.52. The average of a participant's visual and auditory *d'* value was used for all subsequent accuracy analyses. Only reaction time values (in milliseconds) for correctly identified hits were considered in our analyses (as in Jaeggi et al., 2007).

Aligned with pilot study methodology, visualizations of N-Back accuracy (*d'*) and reaction time data were conducted to identify trends in cognitive performance across study days. Trends identified through visualization were further explored primarily through descriptive statistics, as well as limited statistical testing on visually identified points of interest. Statistical testing included either within-subjects paired, or between-subjects independent t-tests, as well as two- and three-way repeated measures ANOVAs. One-tailed t-tests were conducted when exploring performance changes across the three study sessions, as a substantial body of literature supports that individuals improve on the N-Back task with practice. Two-tailed t-tests were conducted for all other estimations of effect. Two-way repeated measures ANOVAs were conducted across both tDCS groups, with independent variables of study day and N-Back level, and dependent variable of either accuracy (*d'*) or reaction time. Three-way repeated measures ANOVAs were conducted to explore the impact of tDCS, with independent variables of study day, N-Back level, and tDCS group, and dependent variables of either accuracy (*d'*) or reaction time. In order to minimize the ANOVA levels considering the small sample size, two-way repeated measures ANOVAs with independent variables study day and tDCS group and dependent variables accuracy (*d'*) or reaction time were also conducted within N-Back levels N-2 and N-3.

4.4.3.3 Learning effects. In order to better understand participant's performance change across study days, overall learning effects were calculated for accuracy (*d'*) and reaction time values on study Day 2 and study Day 3, using the transformation: [(Day 2 or 3-Day 1)/Day 1] x 100%. Learning effects were baselined to each participant's individual study Day 1 performance to control for the marginally significant differences that existed between tDCS groups on study Day 1. Approaches to data analysis were the same as the methods applied to the cognitive performance data, including visualization, descriptive statistics, and exploratory statistical analyses encompassing t-tests and ANOVAs, with the dependent variables being the transformed accuracy (*d'*) and reaction time learning effect values.

4.4.4 Analysis of tolerability and feasibility data

Severity ratings from each study day on the tDCS side-effects outlined in the tDCS adverse effects survey were summarized as frequency percentages both across and within tDCS groups. In order to explore group differences in tDCS side-effect severity ratings, two-tailed independent t-tests were conducted on the frequency data within each symptom severity rating category. Tolerability ratings from study Day 3 were also summarized as frequency data across and within tDCS groups. PCSI symptom severity data was analyzed in the context of feasibility data both across and within tDCS groups, through two-sided paired t-tests comparing symptom severity scores on study Day 1 to study Day 3.

4.5 Results

4.5.1 Cognitive performance: N-Back data

Accuracy and reaction time data from the dual N-Back task was analyzed both collapsed across tDCS groups as well as within each group. The former analysis provided insight into the impact of task practice on cognitive performance, while the latter analysis allowed for the exploration of the effects of tDCS on practice-induced changes.

4.5.1.1 Cognitive performance trends across both tDCS groups.

4.5.1.1.1 N-Back levels N-0 and N-1: Accuracy (D'). As expected, visualization indicated that participants appeared to be performing at ceiling level on the N-0 and N-1 N-Back levels, and further, that individuals did not show any significant improvements in accuracy (*d'*) on these levels across study days (see Figure 4.3). As N-0 is a simple control task, and N-1 predominantly engages the sustained attention component of working memory, it was anticipated that participants would demonstrate near perfect performance on Day 1, and therefore no substantial improvements were expected. The observed ceiling performance supports that all participants were actively engaged in the cognitive task. Descriptive statistics and two-sided paired t-tests comparing accuracy (*d'*) performance on study Day 1 and study Day 3 supported the lack of significant performance improvements on N-0 and N-1, with accuracy (*d'*) performance levels demonstrating a non-significant change from a mean of 3.66 (*SD* = 1.02) on study Day 1 to a mean of 3.87 (*SD* = 0.29) on study Day 3 within N0, *t*(9) = -0.60, *p* = .56, and similarly, a non-significant change from a mean of 3.66 (*SD* = 0.39) on study Day 1 to a mean of 3.48 (*SD* = 0.27) on study Day 3 within N1, *t*(9) = 1.49, *p* = .17. N-Back Levels N-2 and N-3 were therefore subsequently solely analyzed to understand practice and tDCS effects on N-Back performance. This decision was further supported by the fact that N-Back levels N-2 and N-3 most effectively engage the most complex, executive aspects of working memory (see Section 4.1.1.2).

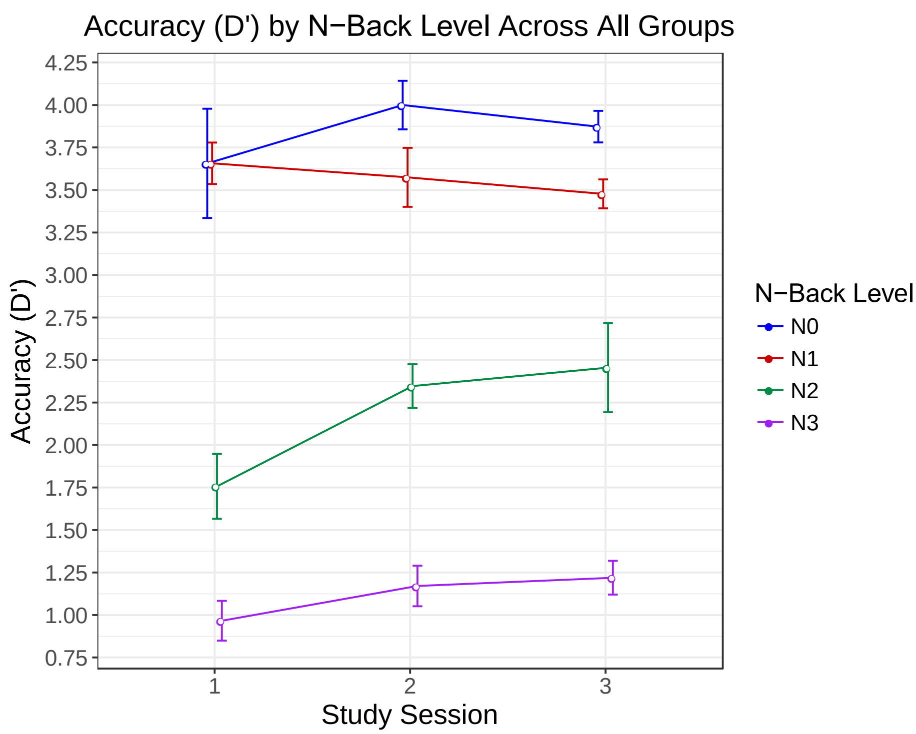

Figure 4.3. Accuracy (*d'*) performance across study days and collapsed across tDCS groups, amongst all N-Back levels.

4.5.1.1.2 N-Back levels N-0 and N-1: Reaction time. Visualization of reaction time across all N-Back levels indicated similar trends of minimal performance change across study days in N-Back Levels N-0 and N-1 (see Figure 4.4). Descriptive statistics and paired two-sided t-testing comparing performance on study Day 1 to study Day 3 showed that within N-0, performance fluctuated non-significantly from a mean of 950.94 ms (*SD* = 136.76) on study Day 1 to a mean of 918.31 ms (*SD* = 155.94) on study Day 3, *t*(9) = -0.59, *p* = .57. Within N-1, there was a larger change in reaction time, from 1222.60 ms (*SD* = 83.96) on study Day 1 to 1105.19 (*SD* = 124.86) on study Day 3. Paired two-sided t-testing indicated that the decreases in reaction time were significant within N-1, $t(9) = 2.45$, $p = .037$. However, these changes were substantially smaller than the reaction time changes observed in N-Back levels N-2 and N-3 (see Section 3.5.1.1.4). As with accuracy (*d'*), N-Back levels N-2 and N-3 were subsequently analyzed independently to best understand changes in N-Back performance across study days.

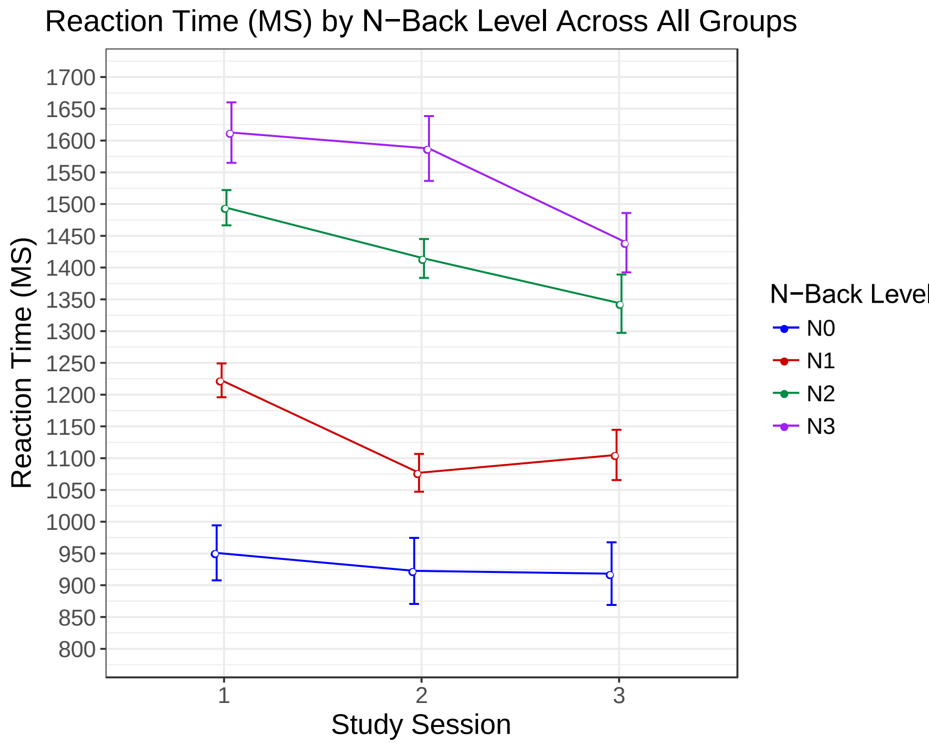

Figure 4.4. Reaction time across study days and collapsed across tDCS groups, amongst all N-Back levels.

4.5.1.1.3 N-Back levels N-2 and N-3: Accuracy (D'). Trends for increased accuracy (*d'*) across session days were seen when accuracy performance on N-Back levels N-2 and N-3 were plotted on their own (see Figure 4.5), supported by descriptive statistics indicating that accuracy (*d'*) increased from a mean of 1.76 (*SD* = 0.50) on Day 1 to 2.46 (*SD* = 0.77) on Day 3 within N-2, and from a mean of 0.97 (*SD* = 0.40) on Day 1 to 1.22 (*SD* = 0.29) on Day 3 within N-3. One-sided paired t-tests comparing accuracy (*d'*) on study Day 1 to study Day 3 were conducted on these visually identified trends within each N-level to better understand the nature of these changes. Within level N-2, participants had significantly higher accuracy on Day 3 compared to

Day 1, *t*(9) = 2.23, *p* = .027, and within level N-3, participants were performing with marginally higher accuracy on day 3 compared to day 1, *t*(9) = 1.48, *p* = .086. These results supported the performance improvements observed through visualization. Further, visualization indicated that there was a substantial impact of N-Back level on accuracy (*d'*) performance, with participants performing more accurately within N-2 compared to N-3, which was further substantiated by the descriptive statistics addressed above.

A two-way repeated measures ANOVA was conducted to further explore the influence of N-Back level and Day on performance accuracy (*d'*). There was a significant main effect of N-Back level [F(1,9) = 73.09, p = 1.3e-5] and Day [F(2,18) = 3.89, p = 0.039]. Additionally, there was a trend towards an interaction between N-Back level and Day [F(2,18) = 2.55, p = 0.11]. Together, these results indicated that participants are able to make significant increases in overall accuracy (*d'*) on the N-Back across study days, particularly for the N-2 versus N-3 condition.

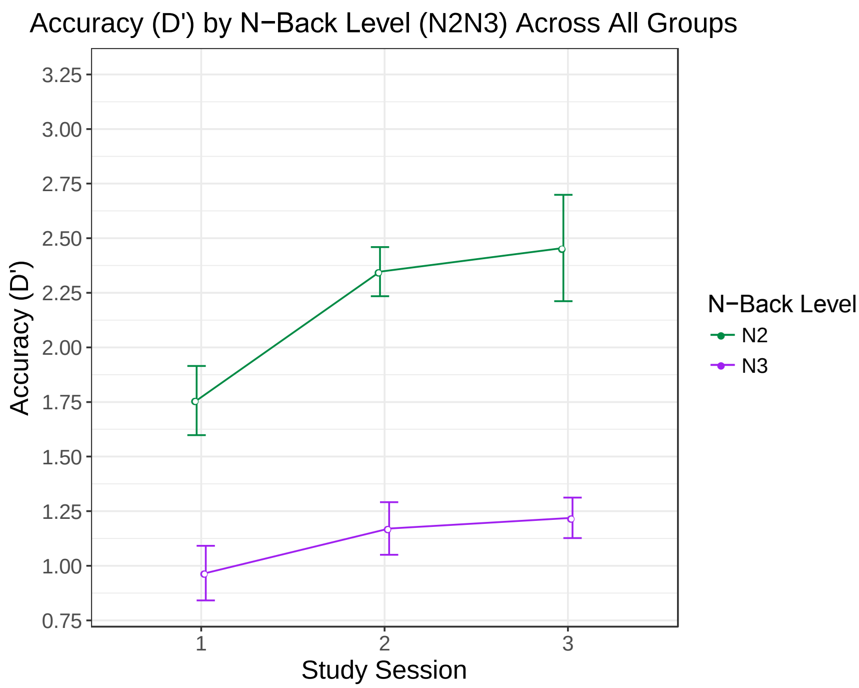

Figure 4.5. N-Back accuracy (*d'*) by study day, collapsed across tDCS groups, between N-Back levels N2 and N3.

4.5.1.1.4 N-Back levels N-2 and N-3: Reaction time. Trends for reduced reaction times across session days were observed within N-Back levels N-2 and N-3 when these levels were plotted independently (see Figure 4.6). These visually-observed trends were supported by descriptive statistics, which indicated that, within N-2, reaction time decreased from a mean of 1494.27 ms (*SD* = 80.41) on study Day 1, to a mean of 1343.20 ms (*SD* = 132.92) on Day 3. Further, within N-3, reaction times decreased from a mean of 1612.53 ms (*SD* = 115.05) on Day 1 to 1439.29 ms (*SD* = 93.30) on Day 3. One-sided paired t-tests were run comparing reaction time performance on Day 3 versus Day 1 within each N-Back level, in order to better understand the nature of these trends. Participants had significantly shorter reaction times on study Day 3 compared to study Day 1, both within N-2, $t(9) = -2.77$, $p = .011$, as well as within N-3, $t(9) = -3.96$, $p = .0016$. Visualization demonstrated that reaction time appeared to be influenced by N-Back level difficulty, with substantially longer reaction times in N3 compared to N2. The impact of N-Back level on reaction time is supported by the descriptive statistics outlined above.

A two-way repeated measures ANOVA was conducted to explore the impact of N-Back level and Day on reaction time performance on N-2 and N-3 collapsed across tDCS group. There was a significant main effect of N-Back level [F(1,9) = 12.27, p = 6.7e-3] and Day [F(2,18) = 11.92, p = 5.0e-4]. Together, these results indicate that participants are making significant decreases in overall reaction time on the N-Back across study sessions, and further, that reaction time decreases with decreasing N-Back level difficulty, especially within level N-2 and N-3.

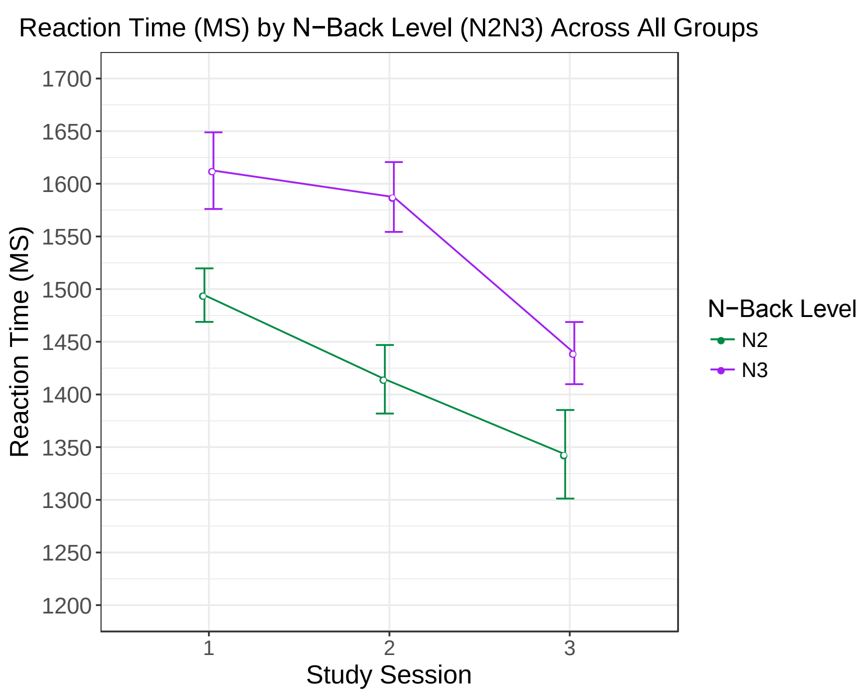

Figure 4.6. N-Back reaction time by study day, collapsed across tDCS groups, between N-Back levels N2 and N3.

4.5.1.2 Cognitive performance trends between tDCS groups.

4.5.1.2.1 N-Back levels N-0 and N-1: Accuracy (D'). Two-sided paired t-tests were conducted to compare accuracy (*d'*) performance between study Day 1 and study Day 3 within each tDCS group, to explore if the null effects found across both groups within these levels were influenced by tDCS group allocation (see Figure 4.7 for visualization of accuracy across all study days and N-Back levels, between tDCS groups). Visualization indicated that both tDCS groups appeared to be demonstrating ceiling performance on N-Back levels N-0 and N-1. Consistent with findings collapsed across tDCS groups, two-sided paired t-tests comparing performance on study Day 1 to study Day 3 indicated that within the real or sham tDCS groups no significant differences in performance across session days in N-Back levels N-0 [real tDCS group, $t(4) = -0.99$, $p = .38$; sham tDCS group $t(4) = -0.046$, $p = .97$] and N-1 [real tDCS group, $t(4) = 0.66$, $p = .54$; sham tDCS group $t(4) = 1.47$, $p = .22$]. Further, independent two-sided t-tests comparing performance between tDCS groups indicated that performance was not significantly different between groups on study Day 1 [$t(8) = -0.092$, $p = .93$] and study Day 3 [$t(8) = 1.41$, $p = .19$] within N-0, as well as on study Day 1 [$t(8) = 1.40$, $p = .20$] and study Day 3 [$t(8) = 1.84$, $p = .10$] within N-1. As expected, there was a consistent lack of significant performance change in N-Back levels N-0 and N-1 within both tDCS groups. As such, the subsequent analyses were focused solely on performance in N-Back levels N-2 and N-3.

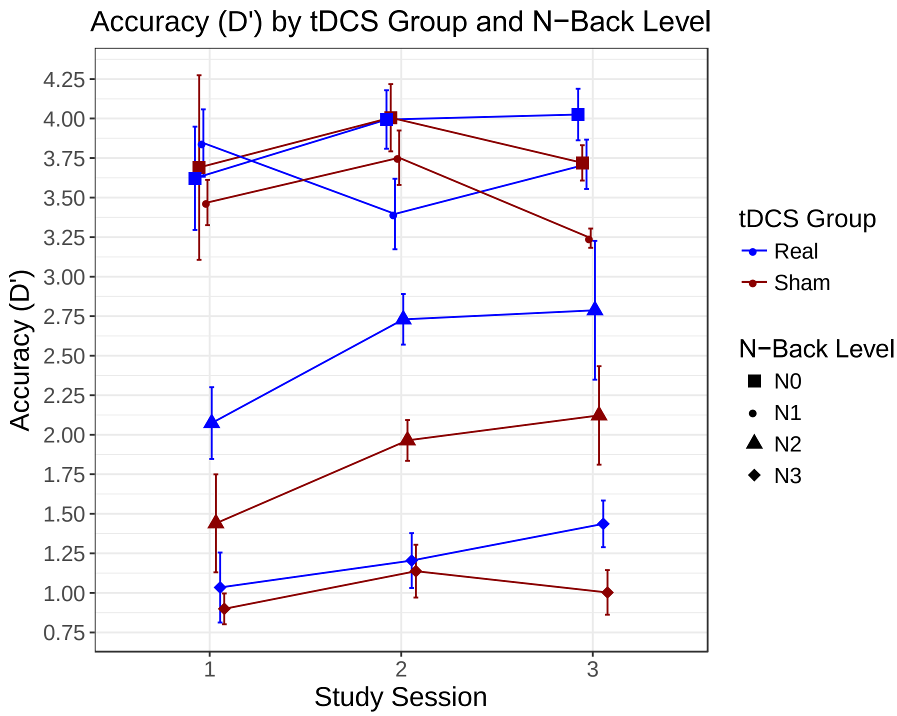

Figure 4.7. N-Back accuracy (*d'*) across study days, N-back levels and tDCS groups.

4.5.1.2.2 N-Back levels N-0 and N-1: Reaction time. As with performance accuracy (*d'*), two-sided paired and independent t-tests were conducted to explore if tDCS group impacted the nature performance changes within levels N-0 and N-1 (see Figure 4.8 for visualization of accuracy across all study days and N-Back levels, between tDCS groups). In line with trends from the collapsed group analyses, paired t-tests comparing reaction times on study Day 1 to study Day 3 indicated that there were no significant changes in N-0, both with the real tDCS group, $t(4) = 0.0095$, $p = .99$, as well as the sham tDCS group, $t(4) = 1.55$, $p = .20$. Further, significant reductions in reaction time observed across both tDCS groups within N-1 were no longer apparent when the real tDCS group was analyzed independently, $t(4) = 0.98$, $p = .38$. Additionally, the trend was only marginally significant within the sham tDCS group, $t(4) = 2.73$, $p = .053$. Two-sided independent t-tests comparing performance between groups showed that performance between groups was not significantly different within Day 1 [$t(8) = -0.62$, $p = .55$] or Day 3 [$t(8) = -0.075$, $p = .94$] in level N-0, as well as within Day 1 [$t(8) = -0.22$, $p = .83$] or Day 3 [$t(8) = 0.45$, $p = .66$] in level N-1. These results confirmed that performance changes on levels N-0 and N-1 were not influenced by tDCS group allocation, and substantiated the decision to focus all further analyses on N-levels N-2 and N-3.

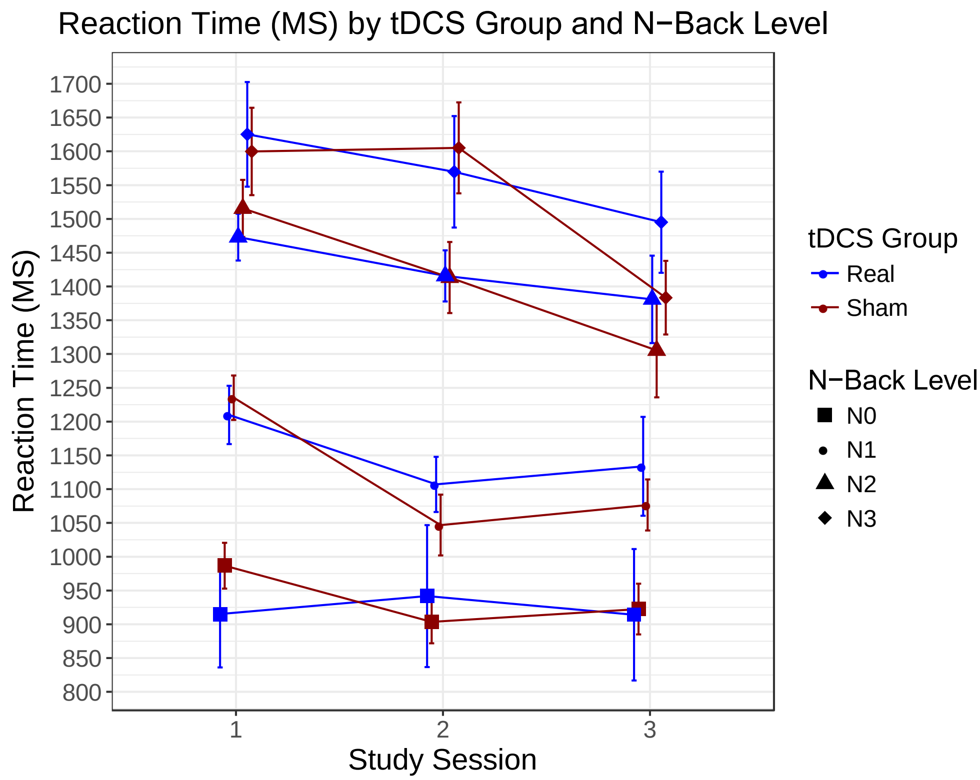

Figure 4.8. N-Back reaction time across study days and between tDCS groups, across all N-Back levels.

4.5.1.2.3 N-Back levels N-2 and N-3: Accuracy (D'). Visualization of between-group differences in performance accuracy (*d'*) across session days indicated that tDCS may be influencing the size, rate, and direction of changes in performance accuracy (*d'*) (see Figure 4.9).

Within N-2, both tDCS groups showed similar trends for overall improvements in accuracy across study sessions. These trends were supported by the descriptive statistics. Within the real tDCS group, mean accuracy (*d'*) increased from a mean of 2.07 (SD = 0.48) on study Day 1, to a mean of 2.79 (SD = 0.96) on study Day 3. Further, within the sham tDCS group, mean accuracy (*d'*) increased from a mean of 1.44 (SD = 0.56) to a mean of 2.12 (SD = 0.61). One-sided paired t-tests were run within each tDCS group comparing accuracy performance on from study Day 1 to study Day 3, to explore the significance of these changes in accuracy. In line with these visually identified trends, both groups showed similar marginally trends towards increases in accuracy [within real tDCS group, $t(4) = 1.44$, $p = .11$, and within sham tDCS group $t(4) = 1.54$, $p = .099$].

While overall performance improvements, as well as the rate of these improvements, appeared similar between both groups, there was a trend toward the real tDCS group consistently performing more accurately than the sham tDCS group at all study sessions within N2. This was supported by descriptive statistics, with the real tDCS group having a mean accuracy of 2.07 (*SD* = 0.48) on study Day 1, compared to the sham group, who was performing with a mean accuracy of 1.44 (*SD* = 0.56). These between-group performance discrepancies were sustained across all sessions, with the real tDCS group performing with a mean accuracy of 2.73 (*SD* = 0.35) on study Day 2, where the sham tDCS group was performing with a mean accuracy of 1.96 (*SD* = 0.30), and finally, the real tDCS group having a mean accuracy of 2.79 (*SD* = 0.96) and the sham tDCS group having a mean accuracy of 2.12 (*SD* = 0.61) on study Day 3. The real tDCS group was therefore able to immediately perform close to the accuracy level that it took the sham group three sessions of practice to achieve. Two-sided independent t-tests comparing performance accuracy on study sessions between the real and sham tDCS groups further substantiated these trends, with the real tDCS group performing with marginally significantly higher accuracy than the sham tDCS group on study Day 1, $t(8) = 1.96$, $p = 0.085$, and significantly higher accuracy than the sham tDCS group on study Day 2, $t(8) = 2.93$, $p = .019$. A two-sided independent t-test indicated that performance differences between groups were no longer significant on Day 3 [$t(8) = 0.94$, $p = .37$], which was likely due to the increased performance variability within groups, as indicated by the larger standard error of the mean on Session 3 compared to Sessions 1 and 2.

Within N-3, visualization indicated that the tDCS groups showed different trends for changes in performance accuracy across study days. While the real tDCS group demonstrated a trend for continued increases in accuracy across the three days, performance gains in the sham tDCS group appeared to plateau, returning to baseline performance levels after any observable changes on study Day 2. These differing trends were supported by descriptive statistics. While the real tDCS group had an increase in mean accuracy from 1.03 (*SD* = 0.50) on study Day 1 to 1.44 (*SD* = 0.37) on Day 3, then sham tDCS group had a much smaller increase in mean accuracy, changing from 0.90 (*SD* = 0.15) on study Day 1 to 1.00 (*SD* = 0.24) on study Day 3. Two-sided paired t-tests comparing accuracy performance from study Day 1 to study Day 3 further substantiated these differing trends in performance change. While neither group had significant increases in performance accuracy, the real tDCS group [$t(4) = 1.23$, $p = .29$] was closer to the marginal significance threshold than the sham tDCS group [$t(4) = 1.54$, $p = .42$]. These results suggest that tDCS may be impacted the overall level of performance improvements within level N-3. Further, a two-sided independent t-test indicated that the visual trend towards increased accuracy in the real tDCS group compared to the sham tDCS group on study Day 3 was approaching the marginal significance threshold, $t(8) = 1.20$, $p = 0.26$.

A three-way repeated measures ANOVA was conducted to further understand the influence of tDCS group, study day, and N-Back level on performance accuracy. There was a significant main effect of N-Back level [$F(1,8) = 109.082$, $p = 6.1e\text{-}6$] and a significant interaction between N-Back level and tDCS group [$F(1,8) = 5.43$, $p = 0.048$].

Additionally, two-way repeated measures ANOVAs were conducted to explore the effects of tDCS group and Day within each N-Back level. Within N-Back level N-2, there was a marginally significant main effect of Day [$F(2,16) = 3.64$, $p = 0.050$]. Within level N-3, there was a trend towards a main effect of Day [$F(2,16) = 1.73$, $p = 0.21$].

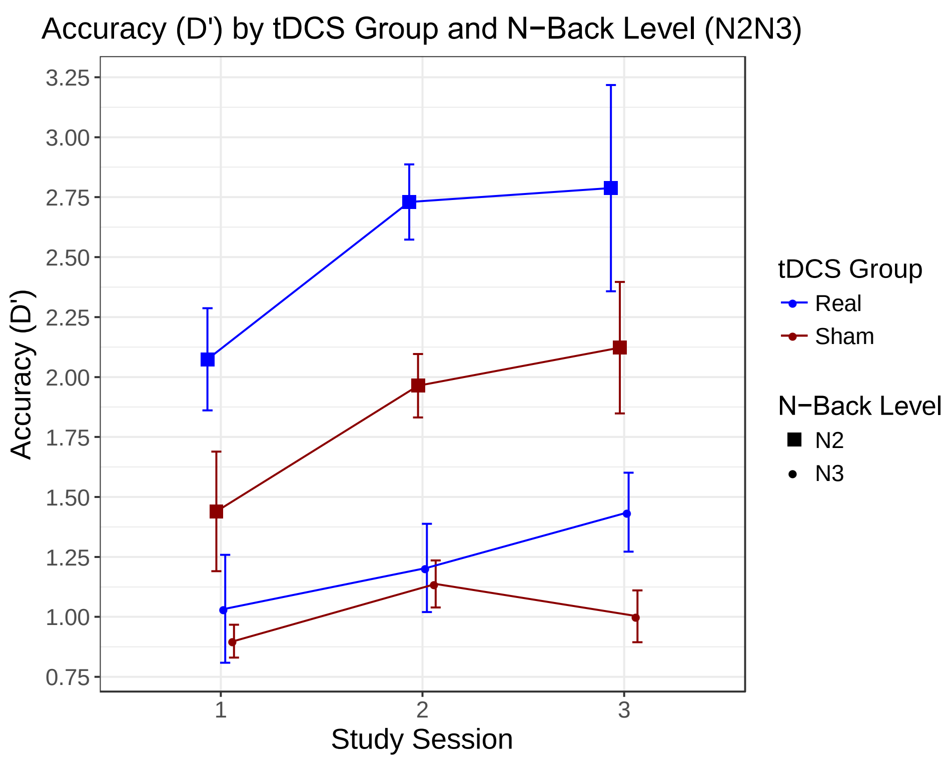

Figure 4.9. N-Back accuracy (*d'*) across study days and between tDCS groups, within N-Back levels N-2 and N-3.

4.5.1.2.4 N-Back levels N-2 and N-3: Reaction time. Similarly to accuracy (*d'*), visualization of between-group differences in reaction time across study days indicated that both groups showed similar trends in decreasing RT which did not appear to be substantially influenced by tDCS (see Figure 4.10). However, tDCS did appear to be having a potential impact on the size and rate of these changes at certain time points, which will be explored further here.

Within N-2, both groups showed similar trends for continued decreases in RT across study days. However, the sham tDCS group appeared to be demonstrating a greater overall decrease in performance than the real tDCS group. While reaction times in the real tDCS group decreased from a mean of 1473.02 (SD = 60.97) on study Day 1 to a mean of 1380.97 (SD = 80.21) on study Day 3 in the real tDCS group, reaction times decreased from a mean of 1515.53 (SD = 87.34) to a mean of 1305.44 (SD = 176.74) in the sham tDCS group. One-sided paired t-tests were conducted within each tDCS group to compare performance differences on Day 3 compared to Day 1. While within the real tDCS group there was a marginally significant trend towards faster RTs on Day 3 compared to Day 1 [$t(4) = -2.01$, $p = .057$], the sham tDCS group did have significantly faster RTs on Day 3 compared to Day 1 [$t(4) = -2.15$, $p = .049$]. However, these differences in significance were minor, likely due to the larger reaction time response variance in the sham tDCS group on study Day 3. Two-sided independent t-tests comparing performance differences between groups indicated that groups were not significantly different in their performance on Day 1 [$t(8) = -0.35$, $p = .74$] or on Day 3 [$t(8) = 0.45$, $p = .66$], suggesting that visually-identified trends may not representative of overall differences in performance.

Within N-3, visualization indicated that real tDCS may be enhancing the rate at which decreases in RT performance are obtained between study Day 1 and Day 2, with the real tDCS group showing a trend for lower RT than the sham tDCS group on Day 2, despite highly similar performance on Day 1. This visual trend is supported by descriptive statistics, as the real and sham group had almost identical means on Day 1 (real, M = 1625.19, SD = 102.38; sham, M = 1599.87, SD = 138.91), yet by Day 2 the real group was notably faster (real, M = 1569.75, SD = 85.84; sham, M = 1605.17, SD = 121.64). However, a two-sided independent t-test comparing RT between tDCS groups within N-3 on Day 2 indicated that these performance differences were not significant, $t(8) = -0.22$, $p = .83$. Further, by Day 3, any performance-enhancing effects of tDCS seem to disappear, with the sham group showing a steeper performance change rate, and lower RT, than the real tDCS group. Notably, despite these visual trends, a two-sided independent t-test comparing RT between tDCS groups within N-3 on Day 3 indicated that performance differences at this time point were only marginally significant, $t(8) = 0.66$, $p = .53$.

A three-way repeated measures ANOVA was conducted to further understand the influence of tDCS group, study day, and N-Back level on reaction time. There was a significant main effect of N-Back level [$F(1,8) = 11.02$, $p = 0.011$] and Day [$F(2,16) = 12.97$, $p = 4.5e-4$]. Further, there was a trend towards an interaction between tDCS group and Day [$F(2,16) = 1.79$, $p = 0.21$]. Additionally, two-way repeated measures ANOVAs were conducted within each N-Back level. Within N-2, there was a significant main effect of Day on reaction time [$F(2,16) = 6.05$, $p = 0.011$]. Within N-3, there was also a main effect of Day [$F(2,16) = 10.97$, $p = 1.0e-3$], as well as a trend towards an interaction between tDCS group and Day [$F(2,16) = 1.71$, $p = 0.21$].

Overall, these findings suggest that while participants are able to make significant decreases in reaction time across study Days, these changes do not appear to be consistently influenced by tDCS group allocation.

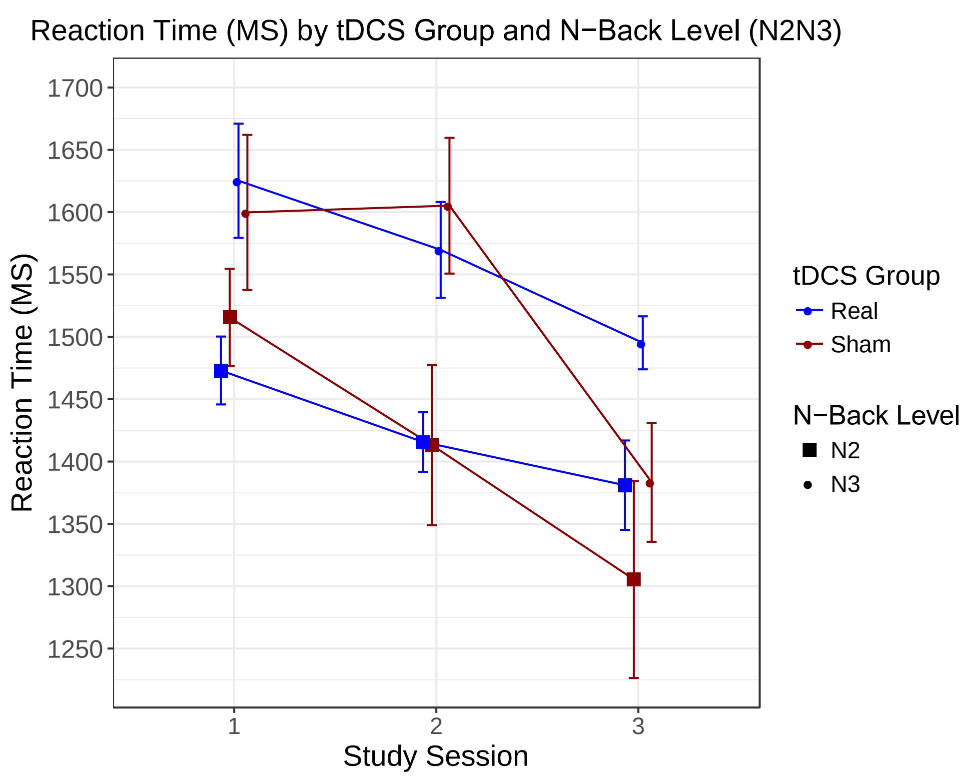

Figure 4.10. N-Back reaction time across study days and between tDCS groups, within N-Back levels N-2 and N-3.

4.5.1.2 Learning effects between tDCS groups. In order to better understand the influence of tDCS on performance changes across study days, overall learning effects (i.e., percent change in performance from day 1) were calculated and compared between groups within N-Back levels N-2 and N-3.

4.5.1.2.1 Accuracy (D'). Visualization of overall learning effects for accuracy (*d'*) between groups indicated that there was substantial variability in size and direction of changes in learning effect across study days, and further, that this variability appeared to be influenced by tDCS group allocation as well as N-Back level (see Figure 4.11).

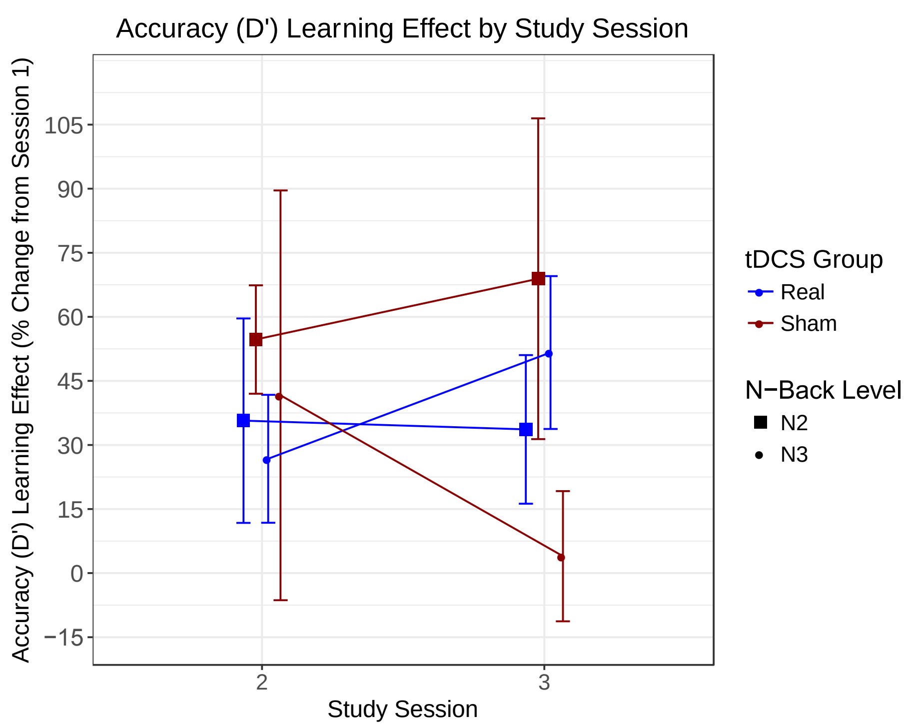

Figure 4.11. Overall accuracy (*d'*) learning effect (i.e., % change from study Day 1) across study days and between tDCS groups, across N-Back levels N-2 and N-3.

Within N-2, tDCS groups showed slightly differing trends in the direction of the learning effect across study days, with the real tDCS group not showing any visible increase in learning effect, and the sham tDCS group showing a small increase in percent accuracy change on Day 3 compared to Day 1 (see Figure 4.12). These differing trends were further supported by descriptive statistics, as the percent change in accuracy decreased from a mean of 35.69% (*SD* = 53.54%) on Day 2 to a mean of 33.65% (*SD* = 38.91%) on Day 3 in the real tDCS group, compared to the increase from a mean of 54.69% (*SD* = 28.38%) on Day 2 to a mean of 68.94% (*SD* = 83.98%) on Day 3. However, the high degree of variability that existed in the data suggested that tDCS was not likely having an influence on the nature of these trends, and therefore no further exploratory statistics were conducted. This was to be expected, as the rate of performance gains across the three study days did not appear to differ between the real and sham tDCS group on N2 (see Figure 4.9).

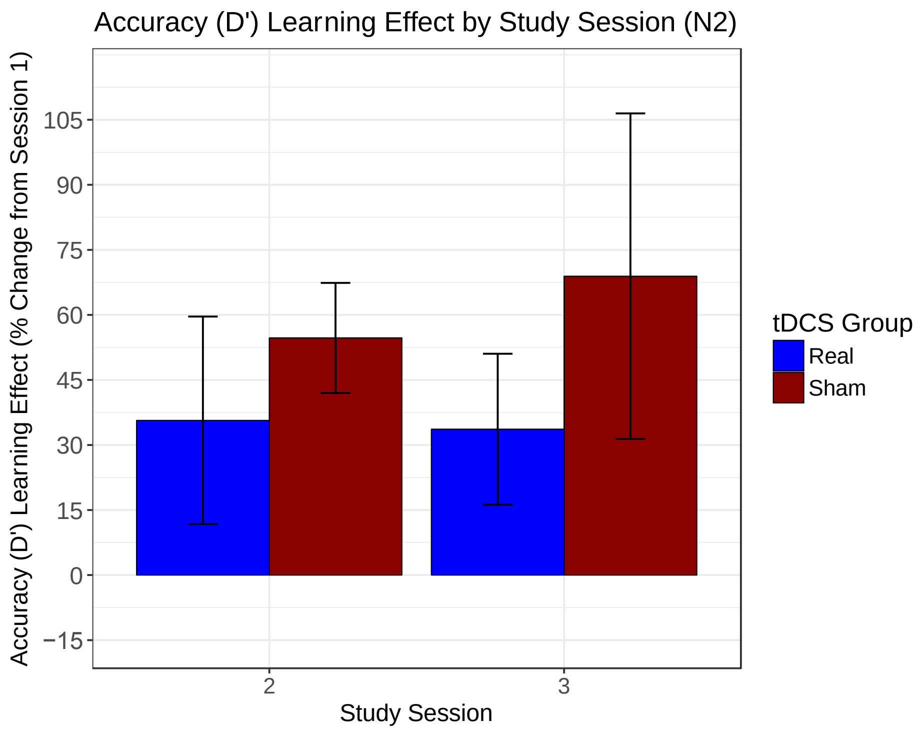

Figure 4.12. Overall accuracy (*d'*) learning effect (i.e., % change from study Day 1) across study days and between tDCS groups, within N-Back level N-2.

Within N-3, visualization of the overall learning effect revealed a disparity between the real and sham tDCS groups, with the real tDCS group showing a greater percentage change in learning from Day 1 on Day 3 compared to Day 2, compared to the sham tDCS group, who presented with a decreased percent change in learning by Day 3 (see Figure 4.13). These visually observed trends were supported by descriptive statistics, with percent change in accuracy increasing from a mean of 26.76% (*SD* = 33.45) to a mean of 51.64% (*SD* = 40.0) in the real tDCS group, compared to a substantial decrease in percent accuracy change from a mean of 41.63% (*SD* = 107.24) on Day 1, to a mean of 3.95% (*SD* = 34.08) on Day 3 in the sham tDCS group. A one-sided independent t-test revealed that there was a marginally significant trend in the predicted direction, with the overall learning effect (i.e., percent change in accuracy) marginally greater in the real tDCS group compared to the sham tDCS group on study Day 3, $t(8) = -1.17$, $p = .14$.

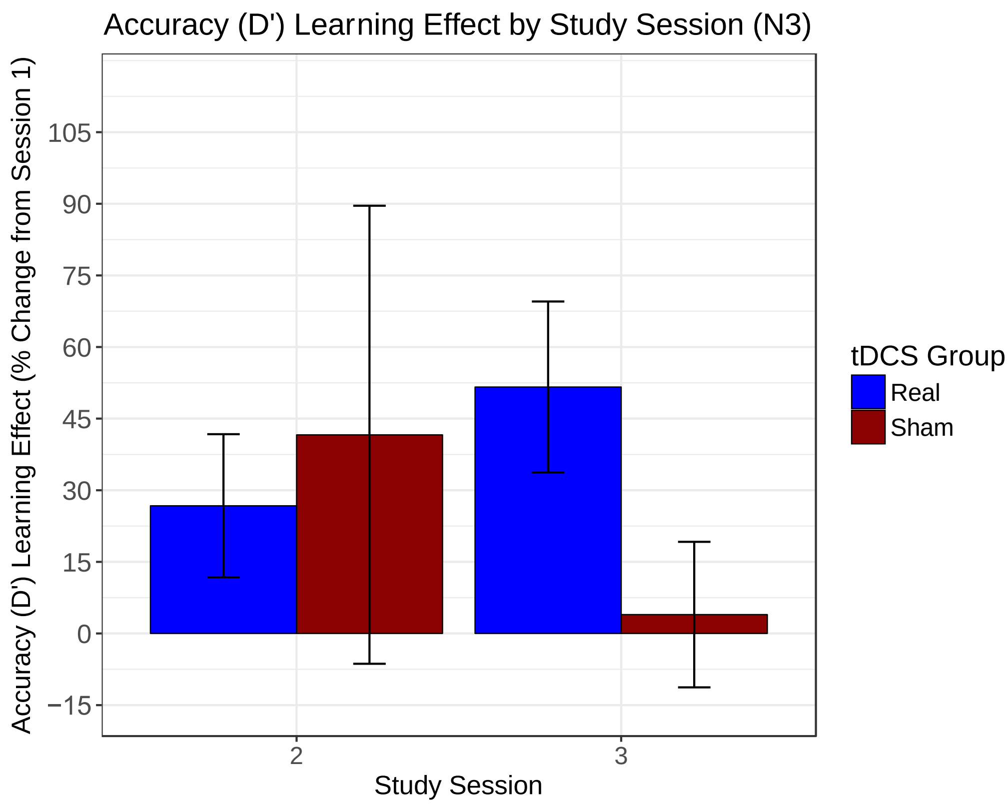

Figure 4.13. Overall accuracy (*d'*) learning effect (i.e., % change from study Day 1) across study days and between tDCS groups, within N-Back level N-3.

A two-way repeated measures ANOVA was conducted within each N-Back level to further explore the effects of day and tDCS group on the overall learning effect. Within N-2, there was a marginally significant effect of day [$F(2,16) = 3.60$, $p = 0.051$], indicating that percent change in accuracy was larger on Day 3 than Day 1. Within N-3, there were no significant or marginal effects of day or tDCS group.

Overall, these results suggest that tDCS may be having a marginally beneficial effect on participant's overall learning capacity within the most challenging N-Back level, N-3. These findings support the trends observed in the raw accuracy (*d'*) data (see Section 3.5.1.1.3).

4.5.1.2.2 Reaction time. Visualization of the overall learning effect for reaction time between both groups showed that both tDCS groups had similar trends for larger decreases in reaction time on study Day 3 compared to study Day 1 (see Figure 4.14). As observed with the raw reaction time scores (see Section 3.5.1.1.4), the degree of overlap and variability in the data suggested that these trends did not appear to be substantially influenced by tDCS. However, it did appear that the sham tDCS group may be experiencing greater changes in overall learning effect compared to the real tDCS group, especially within N-Back level N-3. These trends were supported by descriptive statistics, with a change from a mean percentage change in reaction time from -4.10% (*SD* = 4.46) to -6.31% (*SD* = 4.77) in the real tDCS group, compared to a change from a mean of -6.83% (*SD* = 7.48) to -14.25% (*SD* = 8.98) in the sham tDCS group within level N-2, and a change from a mean percentage change in reaction time from -3.47% (*SD* = 5.69) to -8.16% (*SD* = 2.37) in the real tDCS group, compared to a change from a mean of -0.014% (*SD* = 10.03) to –13.92% (*SD* = 8.07) in the sham tDCS group within level N-3. However, the high degree of variability in the data in conjunction with the similar between-group trends suggested that tDCS group allocation was not having a substantial impact on the nature of these changes, and therefore no further exploratory statistics were conducted.

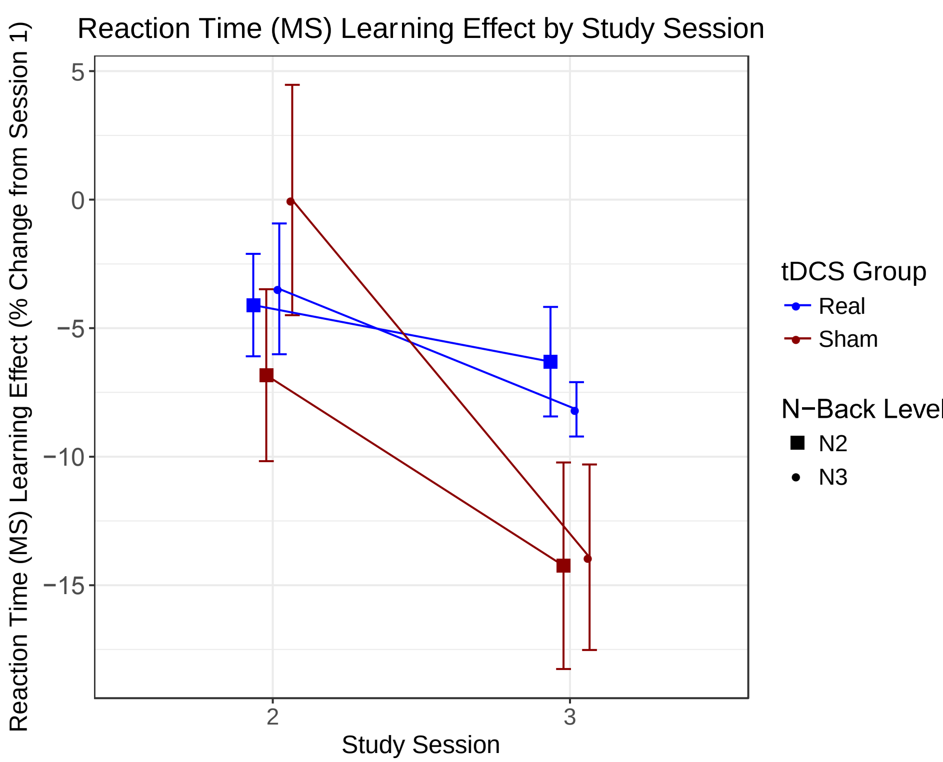

Figure 4.14. Overall reaction time learning effect (i.e., % change from study Day 1) across study days and between tDCS groups, across N-Back levels N-2 and N-3.

4.5.2 Tolerability and feasibility data

4.5.2.1 Recruitment and attrition rates. Of the N = 12 individuals that chose to participate in the pilot study, there was a 0% participant attrition rate. However, recruitment was identified as a substantial barrier to feasibility during the course of this study. While participants often declined participation for multiple reasons, the two primary reasons for refusal included, (1) scheduling constraints, and (2) discomfort with participating in a study involving brain stimulation. Other reasons for not participating included (3) not meeting the eligibility criteria (primarily, not experiencing appropriate concussion symptoms). A total of N = 41 families were identified through convenience sampling and contacted with information to participate in this study, of which a total of N = 8 (19.51%) individuals participated. Of the N = 33 that did not choose to participate, N = 10 (24.39%) were not eligible, N = 9 (21.95%) declined due to scheduling constraints, N = 8 (19.51%) declined due to tDCS, and N = 6 (14.63%) declined for various other reasons.

A total of N = 85 families were contacted (N = 56 [65.88%] through email, and N = 29 [34.12%] through phone contact) from a database of clients who had previously expressed interested in hearing about concussion research, of which a total of N = 4 (4.71%) individuals participated. Email had a low response rate (N = 7 responses [12.50%]) and N = 3 (10.34%) individuals had out of date contact information, or otherwise could not be contacted by phone. Of the total N = 29 individuals who were contacted but chose not to participate, N = 16 (55.17%) were not eligible, N = 4 (13.79%) declined due to scheduling constraints, N = 5 (17.24%) were no longer interested in research, and N = 4 (13.79%) were lost to follow-up.

While the lack of participant attrition supported the feasibility of a tDCS intervention, recruitment challenges indicated that it may not be possible for a substantial amount of youth with persisting concussion symptoms to attend a clinic or research center for three sessions of tDCS within a one-week time period. Further, it suggested that attitudes and knowledge about tDCS should be addressed through education and knowledge translation activities in order to reduce the negative perspectives families may have about these types of brain stimulation technologies.

4.5.2.2 Safety and tDCS side effects across tDCS groups. No serious adverse effects occurred during the course of the study. The frequency at which the ten most common tDCS side effects and sensations were given a certain severity rating across the three study sessions is summarized in Table 7. While 69.44% of participants did not report that they experienced any side effects not represented on the list, the following additional symptoms were reported by the remaining 30.56% of participants: pins and needles (mild, N = 1), stinging/pinching (Day 1 = considerable, Day 2 =strong, Day 3 = mild, N = 1), insect stings (moderate, N = 1), brain fog (mild, N = 1). Across all three study days, participants rated tDCS as affecting their performance at the following degrees: "Not at all" (36.11%), "Slightly" (25.0%), "Considerably" (22.22%), "Much" (16.67%), "Very Much" (0%). 100% of participants indicated that they felt the sensations on the head, while N=2 (16.67%) of participants indicated that they also felt the sensations in other parts of the body, including on the knee, as well as general warmth and nausea in the whole body.

Table 4.7

tDCS Side Effect Severity Ratings Collapsed Across Study Days and tDCS Groups

Side Effect	***None***	***Mild***	***Moderate***	***Considerable***	***Strong***
Itching	5.56%	33.33%	33.33%	22.22%	5.56%
Pain	30.55%	41.67%	11.11%	16.67%	0%
Burning	19.44%	36.11%	25.0%	11.11%	8.33%
Warmth/Heat	47.22%	36.11%	8.33%	8.33%	0%
Pinching	55.56%	30.56%	5.56%	5.56%	2.78%
Metallic/Iron Taste	100%	0%	0%	0%	0%
Fatigue	47.22%	25.0%	27.78%	0%	0%
Headache	52.78%	19.44%	13.89%	8.33%	5.56%
Nausea	77.78%	11.11%	2.78%	8.33%	0%
Dizziness	83.33%	8.33%	5.56%	2.78%	0%

4.5.2.3 PCSI data across tDCS groups. PCSI symptom severity scores were considered within the context of feasibility and tolerability as a control to ensure that tDCS administration was not having a negative impact on pre-existing concussion symptoms. Two-sided paired t-tests were conducted to compare PCSI severity ratings on study Day 1 compared to study Day 3. Participants reported significantly less severe symptomology scores on Day 3 compared to Day 1 both across all concussion symptoms, $t(12) = 2.88$, $p = .014$, as well as within cognitive symptoms only, $t(12) = 3.66$, $p = 3.3e\text{-}3$, indicating that tDCS was not having a negative impact on concussion symptoms.

4.5.2.4 tDCS side effect ratings between tDCS groups. Side effect severity frequency data was also examined separately between tDCS groups, as summarized in Table 8. Notably, it appeared that severity ratings from the sham tDCS group were driving the more severe symptom ratings, compared to those from the real tDCS group. Two-sided independent t-tests were conducted within each symptom severity rating category to compare the frequency of severity ratings between the real and sham tDCS groups. No significant differences were found between groups for the frequency of 'none' $t(1.40)$ =, $p = 0.18$, 'mild' $t(-0.12)$ =, $p = 0.90$, or 'moderate' $t(-1.03)$ =, $p = 0.32$ severity ratings, however there were marginally significant trend towards the sham group reporting more symptoms in the 'considerable' $t(-1.87)$ =, $p = 0.078$ and 'strong' ranges $t(-1.84)$ = , $p = 0.097$.

Table 4.8

tDCS Side Effect Severity Ratings Collapsed Across Study Days and Between tDCS Groups

Side Effect	***None***	***Mild***	***Moderate***	***Considerable***	***Strong***
Itching	9.52%^{A}	28.57%^{A}	33.33%^{A}	28.81%^{A}	4.76%^{A}
	0%^{B}	40.0%^{B}	33.33%^{B}	20.0%^{B}	6.67%^{B}
Pain	38.10%^{A}	52.38%^{A}	4.76%^{A}	4.76%^{A}	0%^{A}
	20.0%^{B}	26.67%^{B}	20.0%^{B}	33.33%^{B}	0%^{B}
Burning	14.29%^{A}	38.10%^{A}	28.57%^{A}	19.05%^{A}	0%^{A}
	26.67%^{B}	33.33% ^{B}	20.0%^{B}	20.0%^{B}	20.0%^{B}

Warmth/Heat	57.14%[A] 33.33%[B]	33.33%[A] 40.0%[B]	9.52%[A] 6.67%[B]	0%[A] 20.0%[B]	0%[A] 0%[B]
Pinching	61.90%[A] 46.67%[B]	38.10%[A] 20.0%[B]	0%[A] 13.33%[B]	0%[A] 13.33%[B]	0%[A] 6.67%[B]
Metallic/Iron Taste	100%[A] 100%[B]	0%[A] 0%[B]	0%[A] 0%[B]	0%[A] 0%[B]	0%[A] 0%[B]
Fatigue	57.14%[A] 33.33%[B]	23.81%[A] 26.67%[B]	19.05%[A] 40.0%[B]	0%[A] 0%[B]	0%[A] 0%[B]
Headache	76.19%[A] 20.0%[B]	14.29%[A] 26.67%[B]	9.52%[A] 20.0%[B]	0%[A] 20.0%[B]	0%[A] 13.33%[B]
Nausea	100%[A] 46.67%[B]	0%[A] 26.67%[B]	0%[A] 6.67%[B]	0%[A] 20.0%[B]	0%[A] 0%[B]
Dizziness	85.71%[A] 80.0%[B]	9.52%[A] 6.67%[B]	4.76%[A] 6.67%[B]	0%[A] 6.67%[B]	0%[A] 0%[B]

A = Real tDCS severity ratings.

B = Sham tDCS group severity ratings.

4.5.2.5 PCSI data between tDCS groups. Changes in PCSI scores across study days were also monitored within each tDCS group, to ensure that pre-existing concussion symptoms were not differentially impacted depending on group allocation. Paired t-tests within each tDCS group comparing PCSI symptom severity scores on study Day 3 to study Day 1 indicated that both groups showed similar trends of significantly lower PCSI scores by Day 3 [real tDCS group: $t(2.96)$ =, $p = 0.025$ across all symptoms, $t(3.33)$ =, $p = 0.016$ across cognitive symptoms only; sham tDCS group: $t(3.03)$ =, $p = 0.039$ across all symptoms, $t(3.04)$ =, $p = 0.038$ across cognitive symptoms only]. This provided further support that tDCS did not negatively impacting pre-existing symptoms.

4.5.2.6 Integrity of blinding. Participants were asked to indicate which experimental group they believed they were allotted to over the three session days. Within the real tDCS group, N = 2 (28.57%) of participants thought they were in the real tDCS group, N = 2 (28.57%) of participants thought they were in the sham tDCS group, and N = 3 (42.86%) did not know which group they were in. Within the sham tDCS group, N = 3 (60.0%) of participants thought they were in the real tDCS group, N = 1 (20.0%) of participants thought they were in the sham tDCS group, and N = 1 (20.0%) did not know which group they were in. These results indicated that participants were effectively blinded to tDCS group allocation.

4.5.2.7 tDCS tolerability. When participants were asked to compare the subjective experience of receiving tDCS to seven common childhood events, tDCS was rated as relatively tolerable, similar to common childhood events such as attending a birthday party or going on a long road trip. When tolerability ratings were examined separately between real and sham tDCS groups, again it appeared that the less tolerable ratings were being driven by the sham tDCS group. Tolerability ratings within and across both tDCS groups are outlined in Table 9.

Table 4.9

tDCS Tolerability Ratings Within and Across tDCS Groups

Comparable Experience	***Real tDCS***	***Sham tDCS***	***Both Groups***
Playing a Game	14.29%	N/A	8.33%
Watching TV	N/A	N/A	N/A
Attending a Birthday Party	21.43%	20.0%	20.83%
Going on a Long Road Trip	50.0%	N/A	29.17%
Throwing Up	N/A	20.0%	8.33%
Going to the Dentist	N/A	20.0%	8.33%
Receiving a Shot at the Doctors	14.29%	40.0%	25.0%

4.6 Discussion

4.6.1 Summary of findings

4.6.1.1 Cognitive performance: Dual N-Back task. All youth demonstrated significant improvements in performance on the dual N-Back task across the three study days, as operationalized by increased accuracy (*d'*) and decreased reaction time (see Results: Figure 4.5 and Figure 4.6). These findings suggest that youth with PPCS have the ability to improve on novel cognitive skills through practice, providing further support that neurophysiological mechanisms critical to adaptive neuroplasticity and consolidation remain functional and active following paediatric concussion (Anderson et al., 2011; Choe, 2016; Choe et al., 2012). These results are promising, as they suggest that repetitive practice on cognitive tasks which are challenging for youth with PPCS can lead to significant enhancements in performance. Practice-based learning improvements have been extensively documented on single and dual N-Back tasks, as well as on other cognitive paradigms engaging core executive functions, both in healthy controls and clinical populations (Bigorra, Garolera, Guijarro, & Hervás, 2016; Constantinidis & Klingberg, 2016; Dunning, Holmes, & Gathercole, 2013; Hussey et al., 2016; Jaeggi et al., 2010; Klingberg, 2010; Lundqvist, Grundstro, Samuelsson, & Ro, 2010; Melby-Lervåg & Hulme, 2013; Salminen et al., 2016; Takeuchi et al., 2010). These performance improvements have primarily been explored through cognitive training paradigms, which allow for extensive practice on a cognitive task, with graduated increases in task difficulty. Cognitive training has been shown to have lasting, as well as generalizable, improvements in cognitive abilities (Beatty et al., 2015; Bigorra et al., 2016; Hussey et al., 2016; Jaeggi, Buschkuehl, Jonides, & Shah, 2011; Jaeggi et al., 2010; Johansson & Tornmalm, 2012; Melby-Lervåg & Hulme, 2013). The learning potential of youth with PPCS demonstrated in the current study suggests that cognitive training paradigms engaging core executive functions may be an important clinical tool for youth experiencing cognitive challenges after concussion.

While preliminary, there were trends towards tDCS enhancing dual task performance, through promoting gains in task accuracy (*d'*) (see Results: Figure 4.9). The beneficial effect of tDCS over the left DLPFC for task accuracy is in line with findings from previous research (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Boggio et al., 2006; Fregni et al., 2005; Giglia et al., 2014; Hussey, Ward, Christianson, & Kramer, 2015; Ohn et al., 2008; Ruf et al., 2017).

Notably, the influence of tDCS on performance accuracy appeared to differ depending on the level of task difficulty. Within N-2 level, a cognitive task of moderate difficulty, tDCS seemed to be having an effect on performance by consistently enhancing task accuracy across all study sessions; however it did not appear to influence the rate of improvements in accuracy, or the total performance improvement across the three sessions (see Results: Figure 4.9). Conversely, within N-3 level, a cognitive task of high difficulty, tDCS did appear to increase the overall level of performance improvements (i.e., total learning) observed across the study (see Results: Figure 4.13).

The immediate and sustained trends towards enhanced task accuracy in the real tDCS compared to sham tDCS group within N-2 is consistent with literature documenting that tDCS may facilitate within-session beneficial effects on cognitive performance through modulating task-relevant cortical activity (Brunoni & Vanderhasselt, 2014; Manor et al., 2015; Martin et al., 2013; Ohn et al., 2008; Strobach et al., 2015; Zaehle et al., 2011). Since the study design did not include a baseline condition (i.e., no tDCS), trends suggesting the immediate enhancing effects of tDCS must be interpreted with discretion. However, the lack of significant differences between study groups on all neuropsychological measures supports that these performance differences represent a true influence of tDCS group allocation. The impact of real tDCS on overall performance improvements within level N-3 provides further evidence that tDCS may have an effect on skill acquisition through an interaction with consolidation mechanisms (e.g., Ciechanski & Kirton, 2017; Reis et al., 2009).

While the enhancing effects of tDCS can occur through within-session performance improvements, an impact on total skill learning, or both concurrently (e.g., Ciechanski & Kirton, 2017; Ditye et al., 2012), there is a lack of consensus in the literature surrounding why tDCS may selectively have an effect through one of the two mechanisms. It is possible that the influence of tDCS on total learning may not be apparent in moderately challenging tasks where all individuals are eventually able to make similar improvements on task performance with practice. This is further substantiated by the fact that dual task paradigms can elucidate effects of tDCS that are not apparent in single task conditions (Manor et al., 2015; Strobach et al., 2015; Zhou et al., 2014), suggesting that some tasks may not be challenging enough for tDCS to have an observable enhancement on overall skill acquisition. Further, the impact of tDCS on performance is modulated by a variety of factors that can impact the activity state of the targeted neural network, including tDCS protocols and the nature of the cognitive task (Miniussi, Harris, & Ruzzoli, 2013; Stagg & Nitsche, 2011); an influence known as ‘state-dependency’ (Silvanto, Muggleton, & Walsh, 2008). As task level N-3 is substantially more challenging than N-2 (see *Figure 4.9*), these levels likely elicited different interactions between tDCS mechanisms and cortical activity, influencing the impact of tDCS on performance.

Unlike the observed changes in performance accuracy, tDCS did not appear to have an influence on reaction time in the current study (see Results: Figure 4.10). Previous research has found inconsistent effects of tDCS on these two performance measures (Brunoni & Vanderhasselt, 2014; Lewis & Bates, 2013). Interestingly, the variable effects of tDCS on accuracy and reaction time appear to differ between typically developing controls and clinical populations, with changes in reaction time being less pronounced in the clinical cohorts. However, reasons for these differences remain undefined (Hill et al., 2016). Working memory accuracy is thought to be representative of core components of the cognitive mechanism itself, including attentional abilities and decision making, as well as the encoding, maintenance, and selection of information (Alloway & Alloway, 2013; Baddeley, 2003; Ohn et al., 2008). Conversely, working memory reaction time is generally thought to reflect the efficiency of intra-cortical communication and cognitive processing (Alloway & Alloway, 2013; Baddeley, 2003). Consequently, tDCS-induced changes in accuracy can be considered more indicative of its influence on cognitive skill acquisition than differences in reaction time. The findings of the current study therefore provide further evidence that tDCS can have a promising influence on learning-related performance improvements, despite having an unidentifiable impact on the efficiency of cognitive processing. Notably, the fact that all participants showed highly significant decreases in reaction time on the N-Back task may have minimized any potential influence of tDCS on this metric.

The trends towards tDCS enhancing performance accuracy observed in this study provide further evidence that tDCS has the potential to increase improvements in cognitive function. As cortical activity was not measured in this study, no conclusive statements can be made about the mechanisms through which tDCS was facilitating these enhancing effects. However, the beneficial outcome of pairing anodal tDCS over the left DLPFC with a challenging dual working memory task suggested that tDCS may promote task-relevant cortical activity, as well as interact with learning and consolidation mechanisms underlying the performance enhancement observed across both tDCS groups (see Results: Figure 4.5 and Figure 4.6). Imaging studies support that changes in cortical activity induced by tDCS are not limited to the site of stimulation itself (Das, Holland, Frens, & Donchin, 2016; Hunter, Coffman, Trumbo, & Clark, 2013; Weber, Messing, Rao, Detre, & Thompson-Schill, 2014). Through an interaction with task-specific cortical networks engaged during performance, tDCS influences the activation of, and functional connectivity between, brain areas distal to the source of stimulation (Weber et al., 2014). The potential widespread effects of tDCS are especially apparent when stimulation is applied over critical ‘network hubs’, including areas such as the DLPFC (Hunter et al., 2013). N-Back tasks engage a diffuse and functionally connected cortical network, with activity concentrated primarily in the frontal (i.e., DLPFC) and parietal regions (Owen et al., 2005). Further, the additional cognitive strain induced by a dual task paradigm places added demands on widespread functional activity and connectivity throughout the cortex (Jaeggi et al., 2007; Sinopoli et al., 2014). Lasting changes in cognitive performance resulting from training on N-Back and dual task paradigms have been shown to be facilitated through the same adaptive plasticity mechanisms engaged through the administration of tDCS. This includes heightened activity in the frontal regions and increased functional coupling between core network areas, such as the frontal and parietal regions, as well as sensory areas supporting the processing of visual/spatial and auditory stimuli (Constantinidis & Klingberg, 2016; Klingberg, 2010; Kundu, Sutterer, Emrich, & Postle, 2013; Salminen et al., 2016; Takeuchi et al., 2010). Notably, increases in within-network functional connectivity appear to be critical to the transfer of training-induced effects to other cognitive tasks (Kundu et al., 2013).

Further, the positive outcomes resulting from the tDCS intervention employed in this study is in line with evidence that the potential for the influence of tDCS is greatest when stimulation is applied in core brain regions during complex tasks engaging diffuse cortical networks. Widespread functional disruption in cortical activity and connectivity is a core component of the concussion injury profile, with changes in activity patterns correlating with cognitive performance on tasks of executive functioning post-injury (Choe, 2016; Keightley et al., 2014; McCrory et al., 2013, 2017; see McDonald et al., 2012 for review). The potential ability of tDCS to directly influence network-wide activity patterns positions tDCS as a promising rehabilitative tool to address the underlying neurophysiological cause of functional challenges post-concussion. Despite the inability to make conclusive statements on changes in cortical activity, the tDCS-induced increases in cognitive performance observed in the current study suggests that tDCS may have the potential to impact this underlying pathology.

4.6.1.2 tDCS tolerability and feasibility. Overall, the current study provided evidence that tDCS is a safe and tolerable intervention for youth with PPCS. All 12 participants completed the three study sessions, with no serious adverse effects. Further, youth with PPCS reported tDCS as tolerable, comparable to common everyday experiences such as attending a birthday party or going on a long road trip (see Results: Table 9). These tolerability ratings were in line with those of other paediatric tDCS trials (Ciechanski & Kirton, 2017). Similarly, participants reported the severity of tDCS side effects primarily in the *'none'* to *'moderate'* range, with the most commonly experienced symptoms being mild itching and burning at the site of the electrodes, comparable to other pediatric (Ciechanski & Kirton, 2017; Gillick et al., 2015) and adult populations (Aparicio et al., 2016) (see Results: Table 7). Further, while concussion symptoms were not directly addressed with tDCS, participants demonstrated significant reduction in symptoms across the three study sessions. These findings confirmed that tDCS did not negatively impact pre-existing challenges, and further, suggest that there may be clinical merit in exploring the effects of tDCS on general post-concussion symptoms. Together, these results supported that tDCS is a safe and tolerable intervention for youth with PPCS.

Notably, there was a consistent trend towards the sham tDCS group driving the more negative tDCS side effect severity and tolerability ratings (see Results: Table 8). While a previous systematic review and meta-analysis of the tolerability of tDCS in neuropsychiatry trials found no differences in acceptability between active and sham stimulation (Aparicio et al., 2016), another study had a finding opposite to that of the current work, with anodal tDCS rated as marginally less tolerable than sham stimulation (Fertonani et al., 2015). However, this opposing finding came from a large sample of healthy controls, suggesting that tDCS sensations may differ within clinical populations. The disparity in severity ratings between tDCS groups observed in the current study suggests that these sensations could be attributed to factors other than the stimulation itself, such as the nature of the cognitive task, the experience of wearing the device, or premorbid concussion symptoms, further supporting the tolerability of the technology. Considering the degree of overlap between side-effect sensations commonly reported during tDCS and PPCS (i.e., headache, fatigue) (Hunt et al., 2016), it is plausible that pre-existing concussion symptoms were influencing individual's experience with the device.

Despite these promising tolerability results, potential deterrents to participation were identified through running the pilot study, including substantial scheduling constraints, as well as negative attitudes toward NIBS technologies. In future work, scheduling barriers could potentially be negated by combining the tDCS sessions with clinic appointments, or through utilizing shorter, cross-over designs, until further evidence regarding the clinical efficacy of tDCS for this population is gathered. Regarding attitudinal barriers, increasing awareness of health technologies through appropriate knowledge dissemination is a critical precursor to creating attitudinal and behavioural shifts and changes in practice (CIHR, 2015), and is therefore a needed focus as research continues to explore the rehabilitative potential of tDCS (Brunoni et al., 2012).

4.6.2 The clinical applicability for tDCS for youth with concussion

Recently, there has been an increasing recognition of the prevalence and detrimental impact of PPCS on the lives of affected youth. Youth frequently report symptom-driven functional limitations as "…the worst thing about having a concussion" (Stein et al., 2016, p. 387-388). There is an essential need to develop feasible, cost-effective, and clinically meaningful interventions to address the cognitive challenges that can be experienced by youth post-concussion (McCrory et al., 2017; Yeates, 2010). The current study provides preliminary evidence that tDCS has the possibility of being a beneficial intervention factor, facilitating faster and greater skill acquisition when used in conjunction with cognitive rehabilitation paradigms. Its potential ability to reduce time needed to regain cognitive skills also has important implications for decreasing clinical burden and reducing time for return to school and play, ensuring youth can get back to doing what they need, want, and love to do, safely, at a faster rate.

Capitalizing on adaptive neuroplasticity mechanisms following pediatric brain injury is critical. The lack of functional and structural maturity present in the young brain can increase an individual's risk for lasting challenges following injury, as focal or diffuse cortical damage can disrupt the interactions between cortical regions that are necessary to their functional specialization of cortical regions and for the establishment of neural networks (Andersen, 2003; Anderson et al., 2011; Johnson, 2011). This can have a negative impact on cognitive skills which have not yet fully matured at the time of injury, leading to a potentially persistent developmental gap in cognitive performance and skills acquisition between those with a history of concussion and healthy controls (Anderson et al., 2011; Meekes et al., 2006). Intervention and rehabilitation factors, such as tDCS, may have the potential to prevent/reduce these long-term effects by encouraging adaptive cortical activity within and between brain areas implicated in complex cognitive functioning (Kolb & Muhammad, 2014; Page et al., 2015).

4.6.3 Strengths and limitations

This study makes a novel contribution to the literature by taking a preliminary step toward a better understanding of how to use advancements in neuromodulation technology to develop effective therapeutic interventions for youth experiencing PPCS. Strengths of the study include its quasi-randomized, double-blinded control design, increasing the probability that any changes in cognitive performance can be attributed to the intervention factor: real or sham tDCS. Further, the study's multi-session design allowed for a greater exploration of the impact of tDCS on mechanisms underlying learning and skill acquisition than would a single-session design. Additionally, the cognitive dual task utilized here was representative of daily cognitive challenges that these youth experience, which do not always appear on typical neuropsychological testing and isolated cognitive tasks, increasing the clinical relevance of study findings to youth with concussion. Finally, the study included assessments of tolerability and adverse effects, providing critical insights into the feasibility of implementing tDCS as a potential therapeutic intervention for youth with concussion, and informing any necessary methodological considerations.

Limitations of this study included the small sample size, as this restricted the statistical power and the types of analyses that could be conducted, lessening the ability to draw conclusions about the impact of tDCS on cognitive performance, and therefore to influence clinical practice. Further, the use of convenience sampling led to a highly heterogeneous study sample, introducing a number of potentially confounding factors (e.g., symptom severity scores, injury history, time since injury). However, small and diverse sample sizes are typical and recommended with pilot studies, as their aim is to explore potential treatment effects as well as protocol feasibility in a small, but representative, sample before its implementation in a larger trial (Thabane et al., 2010). Further, heterogeneous samples are characteristic of concussion studies considering the diverse nature of these injuries. In the current study, intervention groups were not significantly different on any demographic, injury, or neuropsychological characteristics, limiting the probability that these factors were having a substantial impact on performance. A final limitation of the study is the lack of long-term follow up, as this restricted conclusions regarding the sustainability of any observed effects of tDCS. However, it was essential to explore the clinical efficacy and feasibility of a shorter tDCS intervention through pilot testing prior to incorporating a long-term follow-up. Despite these limitations, this study was the first to examine the therapeutic potential of tDCS in youth with persisting concussion symptoms. The findings will therefore be critical in informing future studies which can recruit larger, more homogeneous, samples and include a longer-term follow-up.

4.6.4 Future directions

While results were preliminary, the current study supported the potential clinical efficacy, feasibility, and tolerability of a tDCS intervention for youth experiencing persisting cognitive symptoms post-concussion. From a feasibility lens, future studies can focus on addressing identified barriers to the implementation of a tDCS intervention in this population, including influencing negative attitudes about NIBS technologies through education, and exploring other study protocols which could minimize the scheduling burden on clients and families.

Trends for tDCS enhancing improvements in task accuracy merit exploration in a larger sample with greater statistical power, in order to better assess if tDCS does have a significant impact on compromised cognitive performance post-concussion. Considering the variability in the cognitive data, a larger sample size would also facilitate more exploration of how the influence of tDCS may differ between accuracy and reaction time. Further, additional research should focus on operationalizing a minimum clinical meaningful difference in cognitive performance post-concussion, in order to have better guidelines through which to assess the significance of any effects of tDCS. Concussion can result in diffuse and heterogeneous changes in cortical function, including inconsistent increases and decreases in activity. Future research in this population should therefore investigate the differing impact of anodal and cathodal tDCS stimulation, in order to better understand which modulations in brain activity result in the most adaptive functional changes. Additionally, studies can further explore the influence of tDCS on cognitive skill learning through the use of adaptive N-Backs and other cognitive training paradigms, as these allow participants to maximize their performance improvements on a task, and minimize any challenges with ceiling effects. Finally, subsequent clinical trials should include a long-term follow up, as well as assessments of skill transfer to other executive functions, in order to better assess the sustainability and ecological validity of the effects of tDCS.

4.6.5 Implications and conclusions

This study addressed two prevalent rationales for conducting pilot studies: *scientific*, i.e., assessing safety, and exploring and estimating potential clinical effects of an intervention, and *process*, i.e., exploring the feasibility of executing the study (Thabane et al., 2010). The results of the current study suggest that the potential for tDCS to influence cognitive performance and cognitive skill acquisition merits being explored through a larger clinical trial, after addressing critical barriers and enablers to feasibility.

Chapter 5
General Discussion and Conclusions

5 Overall discussion

The overall objectives of this dissertation were: (1) To systematically characterize the post-concussion sequelae of a core higher-order cognitive function, working memory, in a paediatric population, and (2) to explore the feasibility, tolerability, and potential clinical efficacy of transcranial direct current stimulation (tDCS) as a potential intervention factor for facilitating recovery in youth experiencing persisting cognitive symptoms post-injury. Both of these objectives contributed to the general aim of better understanding concussion recovery amongst children and youth, in relation to expected recovery trajectories as well as potential modifying factors. This chapter provides a summary of the key findings of each study chapter (i.e., Chapter 3 and Chapter 4), and considers the implications of these findings within the broader literature on recovery from paediatric concussion and the clinical applicability of brain stimulation technologies. Further, it summarizes the overall strengths and limitations of the thesis, offers suggestions for future research, and discusses theoretical and clinical implications and conclusions.

5.1.1 Discussion of key findings

This thesis addressed multiple critical gaps in the literature. Firstly, there is a substantial lack of consensus regarding the nature of cognitive challenges that can result from paediatric concussion, especially when examining different cognitive skills in isolation, such as working memory. Further, research on the cognitive outcomes of concussion in adult populations is often generalized to the paediatric population; however, it is essential to comprehend the cognitive impact of concussion within the developmental context. The first study of this thesis (i.e., Chapter 3) addressed the need to better characterize the cognitive outcomes of concussion, especially from a paediatric lens, through conducting a systematic review of the literature documenting the working memory outcomes of concussion in children and youth. Understanding the critical influence of developmental factors on concussion recovery was addressed as a priority in the most recent international concussion consensus statement on concussion in sport (McCrory et al., 2017). In addition to characterizing the prevalence and nature of working memory performance differences, this review aimed to better understand which factors may modify, or be modified by, working memory performance post-injury. Due to the diverse nature of study designs and experimental paradigms employed in the 33 studies included in the review, narrative synthesis was used to explore trends in working memory performance. Just under half (44.44%) of studies that compared performance in children and youth with concussion to healthy controls or population norms found that working memory abilities were significantly lower in the injury population. The findings of this review provided evidence that working memory abilities have the potential to be vulnerable to the diffuse cortical disruption that accompanies concussion, and suggest that working memory should be monitored in individuals that self-report cognitive challenges post-injury. However, despite this vulnerability, the impact of paediatric concussion on working memory appeared to be highly variable, and influenced by non-injury related factors such as the type of assessment measure used. Notably, the majority of the studies that did not find working memory performance to be compromised post-injury utilized neuropsychological test, with most employing the Digit Span. Additionally, no clear conclusions could be drawn about the type or specific aspect of working memory that appears to be most vulnerable to insult.

Key factors that were correlated with working memory outcomes included: (1) age at injury; (2) time since injury; (3) structural and functional cortical properties; (4) post-injury psychiatric conditions; and, (5) everyday functional performance, such as speech acts, math abilities, and caregiver reports of executive function behaviours. However, the impact of these factors was highly variable, with a lack of cohesiveness in the literature regarding the impact of age at injury, the recovery trajectory, and the nature of underlying neural pathology. While the high degree of variability in the literature may be representative of the heterogeneity of concussion, some of this variability can likely be attributed to methodological problems in the literature. The reviewed studies used relatively limited assessments of working memory, and/or did not describe the specific nature of working memory outcomes in detail. Further, the studies themselves were variable with regards to the age at injury of their sample, the time since injury, and the factors they explored in relation to working memory outcomes. The synthesis provided by this review addressed the pressing need to better characterize the cognitive outcomes of concussion uniquely from a paediatric lens. It also provided important recommendations for future research regarding how to reduce the methodological variability in the literature and better inform clinical recommendations (see Section 3.5.7 for details).

A second predominant gap in the literature is that, despite the increased recognition of persisting cognitive challenges that can result from paediatric concussion, there is a paucity of therapeutic interventions targeted at promoting the reacquisition of cognitive skills and facilitating recovery (Hadanny & Efrati, 2016). The previously-held view that prolonged rest until post-concussion symptom resolution was the best approach to concussion management has been recently challenged due to a lack of evidence, especially in the context of persisting symptoms (McCrory et al., 2017; Schneider et al., 2013; Silverberg & Iverson, 2012). The most recent international consensus statement on concussion in sport cites preliminary evidence for the beneficial effects of various active treatment interventions, which introduce physical and/or cognitive activity while individuals are still symptomatic, as long as they do not exacerbate symptoms beyond a threshold that would put an individual at risk for further injury (McCrory et al., 2017) . In line with this theoretical shift in concussion management, the second study (i.e., Chapter 4) explored tDCS as a novel and innovative intervention factor which could enhance the effects of active cognitive rehabilitation paradigms post-injury. This pilot double-blinded quasi-randomized control trial provided data on the potential clinical efficacy, as well as tolerability and feasibility, of a multi-session tDCS intervention in a sample of 12 youth (10 female, 2 male) aged 13-18 years experiencing persisting cognitive symptoms post-concussion. While preliminary, the results of the trial suggested that a tDCS intervention is tolerable and feasible for this population, and appears promising in facilitating the reacquisition of complex cognitive skills which may have been negatively impacted by injury.

All youth improved their performance on the challenging dual working memory task across the three study days, as operationalized by increased accuracy and decreased reaction time. Aligned with pilot study methodology, visualization and descriptive statistics were used to explore trends in the data regarding the impact of tDCS on cognitive performance. Individuals receiving real tDCS appeared to perform consistently more accurately than the sham tDCS group across all study sessions on the moderate task difficulty level (N2), and further, demonstrated larger overall improvements in accuracy on the most challenging task level (N3). tDCS did not appear to impact changes in reaction time. With regards to tolerability and feasibility, participants rated the subjective experience of receiving tDCS, as well as its tolerability, similarly to other paediatric and adult populations, with the most common sensations being mild itching, burning, and pain at the site of the electrodes. Further, the experience was evaluated as comparable to everyday childhood experiences such as a long car ride. Notably, the most negative sensation ratings were being driven by the sham (i.e., control) tDCS group, further supporting the tolerability of the stimulation itself. Importantly, concussion symptoms decreased in both groups across the three study sessions, providing evidence that tDCS does not appear to have a detrimental effect on pre-existing concussion symptoms. A key barrier to feasibility identified through the pilot trial was the low recruitment rate. The two primary reasons that participants chose not to participate in the pilot trial were (1) scheduling constraints due to the three session design, and (2) apprehensive and/or negative attitudes towards brain stimulation technologies.

This study was an important first step in addressing a pressing need in the paediatric concussion literature to identify feasible, cost-effective, and clinically-meaningful intervention factors to facilitate the regaining of cognitive abilities post-injury. From an intervention standpoint, this trial provided substantial evidence that the potential for tDCS to improve cognitive performance and skill acquisition in youth with persisting cognitive symptoms post-concussion is promising, and worthy of being explored in a future clinical trial with a larger sample size. Further, from a feasibility perspective, findings demonstrated that tDCS was safe and feasible to implement in a youth concussion population. However, running the pilot trial also suggested that strategies to mitigate recruitment barriers must be implemented.

5.1.2 Contextualization of tDCS as an intervention factor for recovery from paediatric brain injury

Neural and functional plasticity and recovery following brain injury is a highly complex process, modulated by a variety of injury factors and environmental influences (Nudo, 2013). Brain insult incurred during childhood is compounded by the fact that it is occurring within the developmental landscape (Anderson et al., 2011; Dennis et al., 2014). While it is simplistic and inaccurate to assume that experiencing injury early in life will lead to better functional outcomes, age does play a critical factor in the recovery trajectory due to its critical implication with the onset of various cognitive functions (Dennis et al., 2014). The compounded impact of multiple factors that influence recovery can cause children with brain insult to be either especially vulnerable to maladaptive plasticity and negative functional outcomes, or to experience greater adaptive plasticity and better outcomes than adult populations (Anderson et al., 2011; Dennis et al., 2014; See Figure 5.1). Intervention factors are a subcategory of environmental influences which can modify the recovery trajectory and promote adaptive plasticity through addressing post-injury challenges, by targeting either functional behaviours or the underlying causes of these behavioural deficits (Anderson et al., 2011; Cramer et al., 2011; Kolb & Muhammad, 2014). Specifically, cognitive intervention paradigms provide individuals with engaging training environments to practice the complex skills that may have been negatively affected by injury. Cognitive training paradigms aim to positively impact functional outcomes thorough encouraging adaptive activity in dysfunctional neural systems, capitalizing on principles of neuroplasticity (Cramer et al., 2011). Cognitive training on complex executive functions has shown to result in result in sustained, as well as generalizable, behavioural improvements, which are accompanied by functional and structural cortical changes (Beatty et al., 2015; Hussey et al., 2016; Jaeggi et al., 2010; Salminen et al., 2016, 2012).

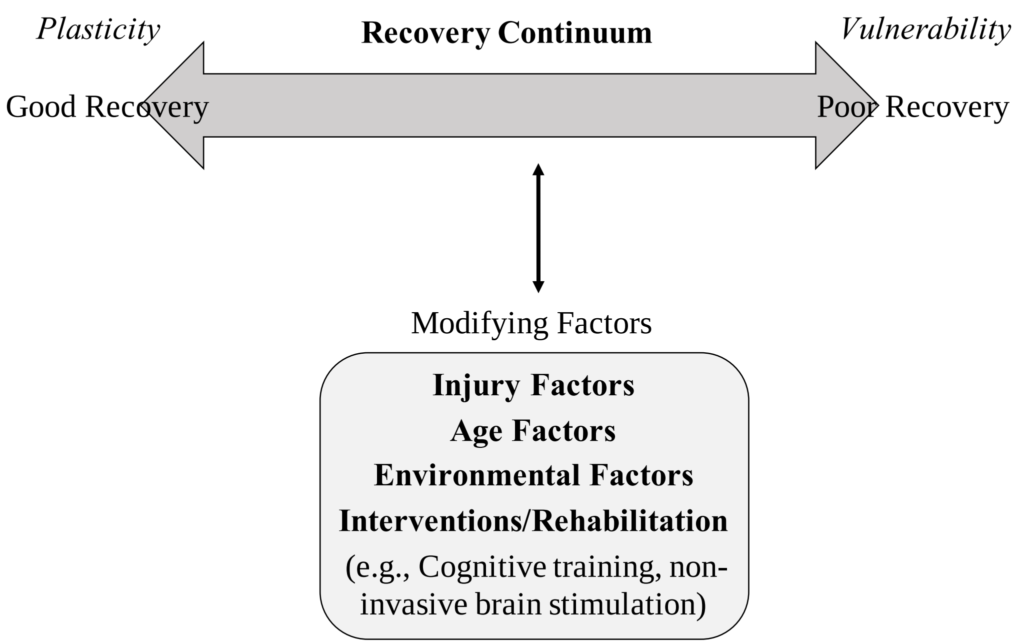

Figure 5.1 Factors influencing the recovery trajectory following paediatric brain injury. Adapted from Anderson et al. (2011).

NIBS technologies have therapeutic potential by acting through mechanisms engaged by cognitive training paradigms. When paired with behavioural interventions, NIBS technologies can be used to modulate cortical activity in task-related brain regions, leading to transient performance improvements, as well as lasting enhancements in skill acquisition, through promoting or hindering the chances of an action potential, and therefore influencing communication patterns within and between brain regions to encourage adaptive neuroplasticity.

While additional work is needed to characterize the long-term sustainability of tDCS-induced changes in cognition, from a developmental perspective, enhancing behavioural interventions and the regaining of cognitive skills with brain stimulation technologies (Brunoni et al., 2012) has the potential to reduce the persisting cognitive challenges that can result from experiencing a brain insult during critical developmental periods (Dennis et al., 2014). When used in conjunction with rehabilitation paradigms, including cognitive training, tDCS has been shown to promote skill learning along with adaptive changes in cortical structure and activity (Chen & Schlaug, 2016; Ditye et al., 2012; Keeser et al., 2011; Martin et al., 2013; Ruf et al., 2017; Zaehle et al., 2011; Zheng & Schlaug, 2015). Research on the ability for NIBS technologies including tDCS to cause lasting beneficial improvements in these structural and functional properties of the cortex is emerging, yet promising. Since cortical dysfunction is a core feature of the neuropathology of brain injury, brain stimulation technologies could be leveraged to directly modulate this dysregulation by promoting healthy cortical activity and strategically guiding neural plasticity in recovery (Brunoni et al., 2012; Li et al., 2015; Page et al., 2015). Maladaptive neuroplasticity following injury during these stages can have a persisting negative impact on subsequent development, as it can impact the integrity of neural networks and functional specialization in the cortex (Anderson et al., 2011; Dennis et al., 2014). Therefore, further research must be conducted to better understand the ability of tDCS to strategically guide recovery-induced changes in neural activity, as this could therefore be critical to reducing potential gaps in cognitive development, or the onset of delayed deficits.

The fourth chapter of this thesis provided evidence that tDCS may have potential in guiding adaptive neuroplasticity in youth experiencing persisting concussion symptoms. Specifically, it can have this effect through influencing cortical activity during dual working memory performance in a brain region vulnerable to insult in concussion and critically implicated in the performance of complex cognitive skills, the DLPFC. While the pilot study did not aim to assess the impact of tDCS on underlying neural pathology, behavioural differences in task accuracy suggested that tDCS may have been impacting the underlying neural mechanisms of working memory and dual task performance which may be affected by injury. Further, the third chapter of this thesis highlighted that working memory is a critical area of cognitive performance to monitor following paediatric concussion, positioning this skill as an important area to target with brain stimulation interventions. It also provided evidence regarding the impact of age at injury, in relation to critical developmental periods, on cognitive recovery, substantiating the importance of early intervention to prevent long-term challenges from injury.

5.1.3 A call for understanding the underlying causes of persisting cognitive symptoms

The potential to most effectively use brain stimulation technologies such as tDCS to promote cognitive recovery following brain injury relies on the ability to accurately address the underlying mechanisms. The injury mechanism of concussion is highly heterogeneous, involving diffuse cortical disruption that is often not visible on structural scans. This heterogeneity has attributed to a lack of consensus and understanding surrounding the nature of injury-related factors contributing to cognitive challenges. Abnormal cortical activity patterns (i.e., increased or decreased regional and network activation compared to controls) have been critically implicated in cognitive performance following injury (see Bryer et al., 2013; McDonald et al., 2012 for review). However, the specific nature of these cortical changes is highly variable, influenced by individual and injury factors as well as by task demands, restricting the ability to make conclusions regarding which component of these cortical changes may be maladaptive and contributing to functional performance challenges (see Bryer et al., 2013; McDonald et al., 2012 for review). Further, research aimed at understanding the cellular mechanisms underlying these changes in cortical activity is limited (Choe, 2016). Notably, non-injury-related factors have also been well supported to impact cognitive outcomes, especially in the realm of persisting symptoms (Barlow, 2016). These factors include premorbid child and family functioning (Yeates et al., 2012), pre-injury learning disability (Beauchamp et al., 2018), as well as pre-injury psychiatric problems, especially relating to anxiety (Broshek, Marco, & Freeman, 2015; Morgan et al., 2015; Ponsford et al., 2012). A lack of understanding of the specific factors contributing to persisting cognitive symptoms post-concussion have substantially limited the ability to develop clinically meaningful therapeutic interventions. Preliminary attempts have been made to categorize post-concussion syndrome based on an individual's predominant concussion symptoms (e.g., headache, dizziness, blurred vision), with the thinking that this can allude to different proposed pathophysiology and therefore guide treatment recommendations in an informed manner (Ellis et al., 2017). While this is a critical area of research to further develop, this work is still in its infancy. Understanding the mechanistic underpinnings of post-concussion symptoms can provide critical insight into barriers and facilitators to adaptive cognitive changes following injury, which can subsequently be used to maximize the effects of intervention factors such as tDCS.

The promising therapeutic applicability of tDCS and other brain stimulation technologies can be partly attributed to their ability to strategically up- or down-regulate cortical activity in specific cortical regions and networks during cognitive tasks of interest, based on what is known about the underlying neural pathology of different brain-based disorders (Brunoni et al., 2012). As the injury mechanisms of concussion become increasingly understood, tDCS interventions can be tailored to address the specific neural changes that are implicated in different cognitive challenges. This will also allow for more personalized treatment interventions based on the individual's specific cognitive challenges, a pillar of treatment identified as a priority in the consensus statement on concussion (McCrory et al., 2017). Additionally, as the impact of non-injury factors on cognitive outcomes is further defined, tDCS can be utilized as part of a holistic treatment approach targeting multiple biopsychosocial factors contributing to persisting symptomology.

This thesis made a preliminary contribution to better understanding the underlying mechanisms of cognitive challenges following concussion, both through examining the impact of modulating cortical activity on persisting cognitive concussion symptoms, and exploring injury factors related to working memory outcomes. The beneficial effect of excitatory tDCS to the left DLPFC on performance accuracy suggested that changes in cortical activity may contribute to differences in cognitive performance. The implication of cortical activation patterns in cognitive performance post-injury was additionally substantiated by the systematic review, which highlighted structural and functional cortical properties as a core factor relating to working memory outcomes. Despite these preliminary contributions, both studies highlight a better need to understand the mechanistic causes of persisting cognitive symptoms and provide direction for future research aiming to characterize these mechanisms in order to best design therapeutic interventions to address these issues.

5.1.4 Overall limitations and strengths of thesis

Study specific limitations were highlighted within Chapters 3 and 4. To summarize, the predominant limitations of this thesis were as follows:

1. Due to the inconsistent terminology used in the literature, the systematic review outlined in Chapter 3 combined data from mTBI and all types of concussion. This may have contributed to the resulting high degree of variability in the included studies. Efforts to increase cohesiveness were made by limiting the review to uncomplicated mTBI when there was enough detail to do so, and exploring trends in the differences between sports and non-sports related concussion. Including studies exploring both concussion and mTBI was essential to comprehensively capture the diverse nature of working memory outcomes post-injury.
2. The use of a narrative synthesis approach in the systematic review limited the ability to make conclusive, statistically-grounded statements regarding the working memory outcomes of paediatric concussion. However, this was the only appropriate data synthesis approach considering the high degree of variability regarding the methodological design employed in the working memory literature. Using this approach allowed for a better consideration of the multitude of factors that may be impacting cognitive outcomes.
3. Use of a small sample size in the pilot trial in Chapter 4 restricted the nature of statistical analysis that was appropriate to apply to the data, limiting the ability to draw conclusions about the potential clinical efficacy of tDCS as measured by its impact on cognitive performance. However, this was a result of exhausting all recruitment options, highlighting a critical barrier to feasibility. Utilizing a small sample size is appropriate for the preliminary analysis of clinical efficacy, as well as the exploration of the tolerability and feasibility of an intervention. Further, all data analysis was appropriately tailored to pilot study methodology. Results from this pilot trial will be essential for informing a larger clinical trial.
4. A convenience sample from one paediatric rehabilitation hospital was recruited for the pilot trial. Since we did not strategically recruit based on demographic or injury related factors such as age, sex, time since injury, injury history, or injury mechanism, our participant sample was highly variable. This introduced various potentially confounding factors into a small sample size. However, the control and experimental group were not statistically significantly different on any of these factors, suggesting that they did not impact our findings. Further, while diverse, this sample was representative of the heterogeneity of the youth concussion population.

5. The methods and methodological design relating to the clinical efficacy study objective of the pilot trial may have limited the ability to fully observe the effects of tDCS. The static nature of the cognitive task meant that participants may reach ceiling performance on some task levels, and restricted their ability to make continued improvements beyond the highest included difficulty level. Adaptive N-Back paradigms are better suited to assess learning on cognitive tasks, as they increase in difficulty relative to an individual's task performance. Further, the lack of long-term follow-up meant that the sustainability of cognitive effects could not be addressed. The use of adaptive paradigms and long-term follow-ups are important considerations for future research. Despite this, the employed methods were appropriate for a preliminary exploration of the cognitive effects of tDCS in this population. Further, participants had substantial room to improve their task performance on levels N2 and N3, suggesting it was of appropriate difficulty for this population.

These limitations effectively guide future research which can address these to further define the cognitive outcomes of concussion, as well as the role of brain stimulation technologies as part of a comprehensive brain injury treatment plan.

5.1.5 Future directions

This thesis highlighted the critical need for future research aimed at better understanding both the cognitive outcomes of paediatric concussion, as well as identifying potential intervention factors which can adaptively modify the recovery trajectory and promote the best possible outcomes for affected youth. Specific recommendations for future research addressed at the ends of Chapter 3 and Chapter 4, and will be further developed and discussed here.

The systematic review (i.e., Chapter 3) highlighted a lack of consensus regarding the working memory outcomes post-concussion, in regards to the nature of these challenges, the underlying contributing mechanisms, the recovery trajectory, and other related factors. The findings of the review can directly inform future research aimed at better understanding these outcomes from a paediatric lens. Specifically, studies should ensure to use more extensive working memory paradigms which would provide insight into which type and component of working memory appears to be most vulnerable to injury. They should also employ longitudinal designs to inform the expected recovery trajectory, and rigorously explore the pre-injury, injury, and post-injury factors that contribute to these outcomes.

The pilot clinical trial outlined in study two (i.e., Chapter 4) suggested merit in a larger clinical trial to explore the potential of tDCS as an intervention for persisting cognitive symptoms post-concussion, after addressing barriers to recruitment. To mitigate these barriers, future research should be sure to incorporate knowledge translation plans to communicate information about the use of tDCS and other brain stimulation technologies within a research context to clients, families, and clinicians. Increased knowledge about its safety, tolerability, and promising clinical effects will be critical to ensuring the engagement and trust of these key stakeholders in paediatric brain stimulation research. This is an essential precursor to the establishment of any further related interventions and research programs.

The pilot study will be essential to informing the larger clinical trial, which could include the following modifications and objectives: (1) a minimum sample size of N=30 (15 participants in each group), all between one month to one year post injury, (2) an adaptive N-Back paradigm, allowing better understanding of the impact of tDCS on cognitive training and learning, (3) a 10 session intervention, maximizing the ability to observe the interaction between tDCS and learning on a cognitive task, and (4) a long-term follow-up at a minimum one month post-training. This well-powered trial would allow for the application of more extensive statistical analysis, including a mixed multivariate analysis of variance (MANOVA) with group (anodal tDCS versus sham tDCS) as the between-subject variable and time (session 1, session 2, session 3+) as the within-subject variable. This would facilitate the exploration of the main effects of tDCS and of study session, as well as any potential interactions between these two factors. The increased power would also allow for a greater exploration of potential covariates which may be modulating the impact of tDCS, including sex, IQ and digit span performance, time since injury, and injury history. This design has the potential to clarify the influence of tDCS on cognitive skill learning in youth with persisting symptoms, including providing a better understanding of the differing impact of tDCS on accuracy and reaction time.

Outside of this subsequent trial, there are various other areas of research that must be explored in order to understand the effects of tDCS within the youth concussion population. Firstly, it is essential to study the generalizability of performance improvements induced by tDCS to other executive functions as well as daily behaviours within this unique population. Further, additional research should utilize neuroimaging methodologies to understand the functional and structural changes tDCS may be having on the brains of youth with concussion. Finally, considering the variable increases and decreases in cortical activity that can result from concussion, research should explore the differing effects of anodal (excitatory) versus cathodal (inhibitory) tDCS on cognitive performance. Together, these findings could eventually inform the clinical application of this intervention using similar methodology, after the validation of effects through additional trials.

Both the systematic review and the pilot trial underlined the need to better operationalize clinically meaningful differences in cognitive performance following concussion. In order to best assess the clinical efficacy of tDCS, research must explore if the changes in cognitive performance are important in the context of everyday cognitive demands. Further, the limited ability of standardized clinical assessments to identify challenges with working memory highlighted in the systematic review additionally support the need to understand what differences in performance identified on non-standardized, experimental assessments of working memory represent, and further, if they actually have an impact on functional performance in everyday life. A clinically meaningful difference can be better understood through additional research correlating (1) tDCS-induced cognitive changes as well as (2) post-concussion working memory outcomes with measures of daily executive behaviours. Additionally, both studies substantiate the critical need to understand the underlying mechanisms of post-injury cognitive challenges in order to design the most effective and personalized treatment interventions. Research characterizing cognitive outcomes and the influence of intervention factors such as tDCS should work in conjunction with pathophysiological research aiming to identify the mechanisms moderating persistent concussion symptoms to development the most appropriate treatment interventions.

5.1.6 Implications and conclusions

The knowledge produced in this thesis has applicability to various key partners involved in the recommended multidisciplinary management and rehabilitation of concussion (Ellis et al., 2017), including researchers, clinicians, as well as clients and families. The findings of Study One (i.e., Chapter 3) provided evidence that clinicians involved in the care of youth recovering from concussion should ensure that they monitor working memory abilities post-injury, and should consider the variety of other skills that could be negatively impacted by experiencing challenges in this cognitive domain. Clients and families should also be aware of these findings in order to be best informed of the potential cognitive sequelae of concussion, empowering them to advocate for academic accommodations at school and the best possible treatment in a rehabilitation setting. The results of this review are also applicable to researchers, as they emphasize the critical need for a better grasp of the nature, underlying causes, and impact of working memory outcomes post-concussion. Without this understanding, youth are at risk of not being assessed and treated appropriately after injury. Neglecting to address cognitive challenges in areas such as working memory with suitable interventions during development could lead to persisting cognitive problems and have a negative impact on all aspects of daily functioning (Dennis et al., 2014).

Study two (i.e., Chapter 4) of this thesis advises that researchers be aware of the potential of tDCS to contribute to this treatment landscape as an intervention factor to be used in conjunction with other cognitive interventions to facilitate skill reacquisition post-injury. It is hoped that the findings of this study will act as a catalyst for promoting future research employing larger-scale, rigorous clinical trials to better define the most effective applications of tDCS in a rehabilitation context, in order to promote the best possible outcomes for youth experiencing persisting cognitive symptoms post-concussion.

The increasingly recognized incidence of persisting cognitive challenges following youth concussion can have a substantial negative impact on health-related quality of life, as these symptoms prevent youth from engaging in activities that they need, want, and love to do (Fineblit et al., 2016; Novak et al., 2016). This thesis makes a significant contribution to better understanding the cognitive sequelae of concussion from a paediatric lens, by exploring the clinically efficacy of a novel therapeutic intervention factor for youth experiencing persisting cognitive symptoms, as well as by characterizing working memory outcomes post-injury. While the findings will not result in the immediate uptake of tDCS in a clinical setting, they will directly inform the development of future clinical trials which, in conjunction with pathophysiological research, will ultimately lead to a comprehensive description of the ways in which the underlying mechanisms of persisting concussion symptoms can be adaptively modified to promote the best possible outcomes for youth with concussion.

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Appendices

Appendix A: Search Strategy (MedLine)

	Keyword/Subject Heading	Search Results (#)
1	Post-concuss*.mp	1608
2	Concuss*.mp	9752
3	Postconcuss*.mp	1090
4	Mild adj4 head injur*.mp	1084
5	Mild adj4 brain injur*.mp	3838
6	Minor adj4 head injur*.mp	911
7	Minor adj4 brain injur*.mp	117
8	Closed adj4 head injur*.mp	4528
9	Diffus* adj4 injur*.mp	3142
10	Diffus* adj2 axonal.mp	1576
11	mTBI*.mp	1952
12	Mild adj3 TBI*.mp	1674
13	Mild adj3 "traumatic brain injur*".mp	3529
14	Minor adj3 "traumatic brain injur*".mp	65
15	Chronic adj2 brain injur*.mp	1016
16	Diffuse Axonal Injury/	611
17	Exp brain concussion/ or post-concussion syndrome/	6705
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	21642
19	Working adj3 memor*.mp	26219
20	Short-term adj3 memor*.mp	24693
21	Shortterm adj3 memor*.mp	26
22	Memor* adj3 span.mp	1351
23	Visual adj3 span.mp	370
24	Spatial adj3 span.mp	416
25	Auditor* adj3 span.mp	159
26	Visuospatial adj3 span.mp	55
27	Recognition adj3 memor*.mp	7544
28	Immediate adj2 memor*.mp	1340
29	Immediate adj2 recall*.mp	1533
30	Memory/ or Memory, short-term/	79141
31	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	98465
28	Child*.mp	2227564
29	Teen*.mp	27266
30	Adolescen*.mp	1925911
31	Young person*.mp	3161
32	Young people.mp	22190
33	Pre-schooler.mp	17

34	Preschooler.mp	289
35	Son.mp	17389
36	Sons.mp	14873
37	Daughter*.mp	23946
38	Schoolage*.mp	67
39	School-age*.mp	11676
40	Kid.mp	1632
41	Kids.mp	5196
42	Toddler*.mp	8863
43	Juvenil*.mp	83588
44	Puberty.mp	33469
45	Kindergar*.mp	5810
46	Girl.mp	52407
47	Girls.mp	82487
48	Boy.mp	54110
49	Boys.mp	77352
50	Pubescen*.mp	1999
51	P?ediatric*.mp	333470
52	School adj2 age*.mp	22453
53	High adj2 school*.mp	27935
54	Middle adj2 school*.mp	4944
55	Elementary adj2 school*.mp	8753
56	Pediatrics/	49710
57	Students/	47646
58	Minors/	2495
59	Adolescent/ or Exp Child/	2788697
60	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	3443971
61	16 and 27 and 60	307

Appendix B: Search Outcome

PRISMA 2009 Flow Diagram