Executive Motor Control Across the Lifespan: Clinical Insights from Attention Deficit Hyperactivity Disorder, Concussion and Mild Cognitive Impairment

by

Drew Halliday
M.Sc., University of Victoria, 2016
B.A., University of Victoria, 2011

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Abstract

The process of controlling executive and motor behaviours is central to one's ability to self-regulate and accomplish day-to-day goals across the lifespan. Executive and motor control share a set of underlying neural substrates that support a common set of processes, including planning, sequencing and monitoring of behaviour. They share a bidirectional relationship, such that gains or deficits in one area can have profound effects on the other. This doctoral dissertation examines the interplay between executive and motor control at three distinct stages of life and in the context of neurological conditions whose clinical manifestations shed additional light on the nature of the constructs. Central to each investigation is the methodological theme of intraindividual variability, as a means of leveraging valuable data within-persons. Chapter 2 examines executive and motor control in typically developing children and children with attention-deficit/hyperactivity disorder (ADHD). Findings suggest that dysregulation of motor processes accounts for hyperactive symptoms in ADHD and detracts from higher-order executive control. Chapter 3 examines the impact of mild traumatic brain injury (mTBI) in young adult varsity athletes, who routinely practice executive motor control by virtue of their level of play. Findings suggest that the impacts of mTBI are discernible through a dampened electrophysiological response during computerized tests of higher order executive functioning, and may not outweigh the otherwise myriad health benefits of athletic engagement. Chapter 4 examines the impact of dementia on executive motor control during gait dual-tasking in older adults. Findings suggest that the consistency of performance across multiple indicators of gait is sensitive to dementia, and that engagement in cognitive and social lifestyle behaviours is protective against likelihood of both dementia and mild cognitive impairment (MCI) classification. On mass, these findings highlight the importance of assessing executive motor control to understand the pathophysiology of neurological conditions. The potential benefits that may generalize from one area to the other offer unique opportunities for preventative and rehabilitative efforts.

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Chapter 1

General Introduction

Executive motor control can be conceptualized as an interaction of systems comprising executive cognitive control and those comprising motor function, involving overlapping processes such as inhibition, planning, sequencing and monitoring (van der Fels, te Wierike, Hartman, Elferink-Gemser, Smith & Visscher, 2015). Executive and motor control share an intricate relationship across the lifespan, supported by shared neural substrates (e.g., frontal cortex, cerebellum, basal ganglia) that underpin these shared control processes (Cisek & Kalaska, 2010). Contemporary research continuously points to movement as a means of enhancing and preserving cognitive function, almost universally and regardless of developmental life stage or health condition (e.g., Hayes, Rye, DiSipio et al., 2013; Hillman, Erickson & Kramer, 2008; Tomporowski, 2003). The mechanisms by which movement affect cognition and vice versa are therefore an area of active exploration, given implications for our basic understanding of the relationship between the two domains, as well as the pathophysiology and ensuing potential for rehabilitation strategies in numerous, prevalent health conditions. Across the lifespan, conditions such as Attention Deficit Hyperactivity Disorder (ADHD), mild Traumatic Brain Injury (mTBI) and Mild Cognitive Impairment (MCI) represent some of the most pervasive harbingers to cognitive and motor functioning, each with unique literatures elucidating novel aspects of the motor-cognition relationship. These conditions demonstrate the potentially devastating functional limitations associated with deficits in executive motor control. At the same time, hope is offered through intervention and rehabilitation initiatives that might leverage the generalizable benefits from one modality

to the other, and from each modality to health and well-being overall. Importantly, normative development during certain life stages may also be supported by enrichment strategies emphasizing executive motor control, for downstream benefits to neurocognitive functioning and quality of life.

This doctoral dissertation investigates the relationship between executive and motor control during different developmental stages across the lifespan, and further investigates the influence of neurological conditions, as well as the protective role of lifestyle factors. Common across these separable investigations are themes of intraindividual variability, executive motor functioning and individual differences.

Lifespan Development

Executive control develops rapidly throughout childhood in accordance with neural networks comprising frontal-parietal and neocerebellar regions (Diamond, 2000; Edin, Macoveanu, Olesen, Tegner, & Klingberg, 2007; Luna et al., 2015; Sherman, Rudie, Pfeifer, Masten, McNealy & Dapretto, 2014), with particularly rapid development during mid-childhood and ongoing development during adolescence for more complex functions (Anderson, Anderson, Northam, Jacobs & Catroppa, 2001; Semrud-Clikeman & Ellison, 2009). The co-activation of critical structures (e.g, prefrontal cortex, basal ganglia and cerebellum) observed during cognitive and motor tasks, as well as the shared processes of sequencing, planning and monitoring, suggest that executive and motor control processes develop and operate in tandem (Roebers & Kauer, 2009; van der Fels et al., 2015). The development of executive and motor control through childhood and adolescence is critical for success with the academic and social demands that characterize these periods of life. Without the ability to regulate and direct one's executive resources,

it becomes challenging to adapt to the unpredictable environmental demands that are part and parcel of dynamic, moment-to-moment social and academic learning environments, as is seen in ADHD.

Peak maturity of executive control is seen by young adulthood (Boelema, Harakeh, Zeena et al., 2014; Hartshorne & Germine, 2015), after which neurological conditions impacting the control of executive resources are more likely ascribed to an acquired etiology (e.g., TBI), or to a developmental condition that has gone unnoticed. The maintenance of executive and motor control becomes particularly crucial again in older adulthood, in order to maintain independence and quality of life. Age-related changes to neurocognitive functioning in late-life are arguably more variable between-persons than in early-life, particularly as chronological age represents merely a proxy for an individual's overall health status that has accumulated over the lifespan, including their neurological health (e.g., "BioAge"; DeCarlo, Tuokko, Williams, Dixon, & MacDonald, 2014). Accordingly, normative neurocognitive changes in late-life follow a less predictable course, with much focus having been placed on the role of compensatory and neuromodulatory changes observed during functional neuroimaging (see Grady, 2012 for a review), rather than on reliable structural changes per say.

Irrespective of developmental life stage, the quest for optimal brain health for downstream cognitive, psychological and quality of life benefits is intuitive. The protective benefits from various lifestyle activities that influence executive and motor control (e.g., athletics, performance art) are most readily apparent during the developmental stages of life where the greatest changes in these networks are seen (e.g.,

Luna et al., 2015). Thus, intervention efforts for enhancing executive and motor control via cognitive and brain reserve are most abundant during these periods of life.

Executive Functioning

Executive functioning (EF) refers to a complex set of interconnected self-regulatory control processes routed in neurocognitive functioning, that work separately and in tandem to produce goal-oriented behaviours. Given the complexity of the overarching construct, it is no surprise that the neural substrates of EF are so widely distributed. At the constituent level, EF is expressed through higher-order cognitive processes such as the inhibition of prepotent responses, or the switching of one's attentional focus from a stimulus with one set of properties to another stimulus with a different set of properties. Laboratory studies of EF have contributed to our understanding of the construct through computer-based paradigms that isolate a given executive process, which have subsequently been built upon to form measurement models that imply an underlying structure of the relationships between these constituent processes (e.g., Friedman & Miyake, 2017; Miyake, Friedman, Emerson, Witzki, Howerter & Wager, 2000). Such paradigms are also amenable to functional neuroimaging methodology, which has further contributed to an understanding of the underlying neurophysiological patterns associated with these executive components.

A distinct and complementary line of research in EF pertains to clinical observations and behavioural rating scales associated with macro-level executive behaviours (e.g., Behavior Rating Inventory of Executive Function - BRIEF, Comprehensive Executive Function Inventory - CEFI). Based on the consistency with which certain clinical populations tend to experience challenges in these areas, numerous

behavioural rating scales have been developed to exemplify these day-to-day difficulties, for which lab-based measures of EF may lack the requisite ecological validity. For example, although individuals from various clinical populations may report difficulties with organization, planning and self-regulation, such difficulties are difficult to elicit reliably using lab-based measures or performance-based clinical assessments. For some macro-level executive behaviours, standardized clinical assessments have withstood the test of time and may be more easily linked to daily behavioural challenges (e.g., Wisconsin Card Sort Test to elicit one's flexibility in generating and switching between problem solving strategies).

Intraindividual Variability

Intraindividual variability (IIV) metrics of performance have emerged as increasingly central to understanding motor-cognition relationships within the aforementioned neuropathological phenomena, and in terms of early- and late-life development (e.g., Kofler, Rapport, Sarver et al., 2013; Luna, Marek, Larsen, Tervo-Clemmens, & Chahal, 2015; MacDonald, Nyberg, & Bäckman, 2006). This is because IIV seems to capture aspects of functioning that are orthogonal to, and at times more sensitive than, conventionally used metrics derived in central tendency. Where executive and motor dysregulation are implicated, increases in IIV are more likely to follow.

In TBI populations, elevated IIV on reaction time tasks was initially demonstrated in the late 1980s and into the early 2000s (e.g., Hetherington, Stuss & Finlayson, 1996; Stuss, Stethem, Hugenholtz, Picton, Pivik & Richard, 1989; Stuss, Murphy, Binns & Alexandar, 2003; Stuss, Pogue, Buckle & Bondar, 1994). These earlier studies suggested that IIV was particularly susceptible to frontal lobe damage (Stuss et al., 2003) and that it

remained elevated up to 10 years following a TBI (Hetherington et al., 1996). More recent work examining IIV in reaction time tasks and white matter hyperintensities using MRI has demonstrated strong associations between IIV and frontal regions, and an absence of white matter associations with IIV in temporal, parietal and occipital regions (Bunce, Anstey, Christensen, Dear, Wen & Sachdev, 2007). Although replication is required to solidify the merit of these findings, this work suggests that the attentional mechanisms supported by frontal systems are particularly central to behavioural IIV during speeded cognitive tasks.

In the cognitive aging literature, IIV emerged as sensitive to neurological insults (e.g., progressive neuropathology, cerebrovascular accidents) and has been employed in numerous studies, with expansion outside of cognitive behavioural performance and into other domains of function (e.g., heart rate, gait, functional brain activity). Observations of increased IIV in Parkinson's disease further suggest that motor and cognitive domains have functional coupling and that this can be measured with IIV, such that compromises in one domain impact the other (de Frias, Dixon, Fisher, & Camicioli, 2007). At times, IIV has been uniquely predictive of neurological status (e.g., Hultsch, MacDonald, Hunter, Levy-Becheton & Strauss, 2000) and chronological age in late-life (e.g., Garrett, Kovacevic, McIntosh & Grady, 2010), suggesting that it captures information that is orthogonal to more commonly employed measures routed in central tendency (e.g., the dynamic range within a focal population of neurons). Perhaps most importantly from the standpoint of early identification of the dementia prodrome, systematic review evidence suggests that IIV shows considerable potential in identifying those at risk of adverse

health outcomes (Haynes, Bauermeister & Bunce, 2017), with sufficient time to address modifiable risk factors and put in place appropriate supports.

In the context of childhood development and ADHD, IIV appears to be the rule rather than the exception (e.g., Kofler et al., 2013; Luna et al., 2015; Tamm, Narad, Antonini, O'Brien, Hawk Jr. & Epstein, 2012), with variability metrics now built into performance-based measures of sustained attention that are commonly administered during clinical assessment (e.g., the Conners Continuous Performance Task). IIV in the ADHD literature tends to be operationalized using an Ex-Gaussian distribution and by examining tau. Although a direct comparison of IIV in the TBI, aging and ADHD literatures has not been conducted, it appears that tau is more commonly accepted as a cognitive index of attentional lapsing in ADHD, relative to related operationalizations that are more commonly employed when the affected neural substrates are more circumscribed (e.g., the residualized intraindividual standard deviation). Neuroimaging studies are likely to enhance our understanding of the neural mechanisms driving IIV in the ADHD population, with recent work linking increased IIV to decreased white matter integrity in the cingulum and frontostriatal tracts (Lin, Gau, Huang-Gu, Shang, Wu & Tseng, 2018), and to frontoparietal hypoactivation and somatomotor hyperactivation (Cortese, Kelly, Chabernaud et al., 2012).

Individual Differences

In the context of this dissertation, individual differences refers to a methodological approach that seeks to explain why individuals from a given population (i.e., those who share meaningful sociodemographic features) differ on an outcome variable (e.g., symptom severity), based on additional factors across which they may also

differ (e.g., lifestyle factors). For example, an individual differences study may seek to understand what accounts for the magnitude of an individual's ADHD symptoms on the basis of their family's socioeconomic status, average quality of sleep, performance on an attention task and maternal age at pregnancy. This approach leverages within-person information and contrasts with more experimental approaches that employ between-person analyses in attempts to draw more causal conclusions. For example, an experimental study emphasizing between-person differences may compare the performance on a sustained attention task between a group of children with ADHD and a group of children without ADHD, in order to point toward deficits in sustained attention as central to the symptomatology associated with ADHD.

Although both approaches have their respective merits and shortcomings, I argue that the individual differences approach (a) is better suited towards psychological and cognitive processes that are distributed along a continuum, and that it (b) affords a more powerful investigation of developmental phenomena, especially when longitudinal designs are employed. Importantly, individual differences research is also more congruent with contemporary conceptualizations of psychopathology that we increasingly understand from a dimensional rather than a binary perspective. Although clinical practice has been slow to adopt this perspective for a multitude of reasons, I believe individual differences research stands to refine the way we assess and treat mental and neurological health conditions moving forward. Moreover, an individual differences approach may help reduce mental health stigma from an advocacy standpoint, towards a more inclusive and progressive way of thinking.

Chapter 2

Intraindividual Variability in Executive and Motor Control Tasks in Children with Attention Deficit Hyperactivity Disorder

2.1 Abstract

Background: Attention Deficit Hyperactivity Disorder is a common neurodevelopmental condition that is typically diagnosed using behavioural rating measures that are subject to bias or by performance measures, which tend to lack specificity. Emerging evidence points to the role of intraindividual variability (IIV) during executive control tasks as a reliable endophenotype of ADHD, and to the role of motor regulation in the pathophysiology associated with hyperactive-impulsive behaviours. This study sought to better understand the relationship between executive and motor control in mid- to late-childhood in children with and without ADHD. Method: Ninety-seven children ages 6 to 13 years completed a battery of standardized and experimental tasks of executive and motor control. Primary caregivers of these children completed a semi-structured interview, as well as behavioural rating forms relating to ADHD symptoms and executive functioning. Results: In terms of developmental differences, children with ADHD demonstrated greater gains in cognitive interference control with age, relative to typically developing children; however, they maintained lower motor performance across development. Motor IIV accounted for a significant proportion of variance in ADHD symptoms of hyperactivity, above and beyond age and motor dexterity. Response time inconsistency from executive measures with relatively low levels of cognitive demand were more sensitive to ADHD symptoms when assessed continuously, rather than in a binary fashion. Conclusions: On mass, IIV metrics appear to tap into the motor regulation challenges associated with ADHD, as well as attentional lapsing at lower levels of cognitive demand.

2.2 Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by a persistent pattern of inattentiveness and/or hyperactivity-impulsivity that interferes with daily functioning (APA, 2013). ADHD represents the most commonly diagnosed neurodevelopmental condition in childhood, with between three to nine percent of children and adolescents meeting diagnostic criteria (Greydanus, Pratt & Patel, 2007). Hallmark symptoms of ADHD include inattention/distractibility, impulsivity/hyperactivity, and problems with regulating motor behaviour. However, despite the predominance and negative impact of motor symptoms (Hervey, Epstein, Curry et al., 2006; Willcutt, Doyle, Nigg, Faraone & Pennington, 2005), few have investigated whether motor atypicalities can be used as an endophenotype for ADHD or how they may explain hyperactive/impulsive behaviours. Although difficulty with motor regulation in the form of hyperactivity and impulsivity is a hallmark of ADHD (Archibald, Kerns, Mateer & Ismay, 2005; L'hermitte, 1983; Rubia, Taylor & Taylor, 1999; Macoun & Kerns, 2016), motor ability and the overlap between executive control and motor function has been understudied in this population (Bidwell, Willcutt, DeFries, & Pennington, 2007; Castellanos & Tannock, 2002; Pinto, Asherson, Ilott, Cheung, & Kuntsi, 2016). Executive motor control can be conceptualized as an interaction of systems comprising executive cognitive control and those comprising motor function, involving planning, sequencing and monitoring (van der Fels, te Wierike, Hartman, Elferink-Gemser, Smith & Visscher, 2015). Deficits in the executive control of motor behaviour have been documented in ADHD, including problems with motor inhibition, preparation, response selection, and motor adjustment (Oosterlan, Logan & Seargent

1998; Schachar, Crosbie, Barr et al., 2005; Sergeant & Vandermeere, 1998). These atypicalities are thought to be due to dysfunction in the networks that subserve executive and motor functions, including under-activation in frontal striatal networks (Castellanos & Proal, 2012; Cortese, Kelly, Chabernaud et al., 2012; Cubillo, Halari, Smith, Taylor, & Rubia, 2012; de Zeeuw, Mandl, Hulshoff Pol, van Engeland, & Durston, 2012; Zang et al., 2005). Notably, dysfunction within frontal-striatal networks has also been directly linked to clinical symptomatology and motor control deficits in ADHD (Booth et al., 2005; Bush, Valera, & Seidman, 2005; Cubillo et al., 2012; Dickstein, Bannon, Castellanos, & Milham, 2006; Klimkeit, Mattingley, Sheppard, Lee, & Bradshaw, 2005; Rubia, Taylor & Taylor, 1999; Rubia, Smith, Brammer, Toone, & Taylor, 2005; Zang et al., 2005; Vaidya, Bunge, Dudukovic et al., 2005; Suskauer, Simmonds, Fotedar, et al., 2008).

Intraindividual variability (IIV) is a metric that is sensitive to motor dysfunction in ADHD, defined as moment-to moment fluctuations in behaviour and test performance (Hultsch, MacDonald, and Dixon, 2002). Although IIV has historically been considered to reflect artifact or noise in test performance, it is now proving to be an important indicator of neural integrity (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; MacDonald et al., 2006). IIV has been conceptualized as a behavioural marker of brain integrity, particularly in relation to attention and EF processes; a finding which has been supported in the clinical, developmental and neuroimaging literatures (Kelly et al., 2008; MacDonald, Li, & Bäckman, 2009; Suskauer et al., 2008; Adamo, Martino, Di, et al., 2014; Ali, Kerns, Mulligan, Olson, & Astley, 2017; Haynes, Bauermeister, & Bunce, 2017). IIV is a

consistent finding that discriminates children with ADHD from typically developing (TD) children (Kofler et al., 2013; Tamm, Narad, Antonini, O'Brien, Hawk Jr., & Epstien, 2012; Nikolas & Nigg, 2014) and is a robust and stable cognitive feature of ADHD that has been associated with EF deficits, hyperactivity/impulsivity, deficient motor inhibition, and motor-execution problems (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Gilbert, Isaacs, Augusta, MacNeil & Mostofsky, 2011; Castellanos & Tannock, 2002; Kofler et al., 2013; Antonini et al., 2013; Gomez-Guerrero, Martin, Mairena et al., 2011; Klotz, Johnson, Wu, Isaacs, & Gilbert, 2012; Kofler et al., 2014; Macoun & Kerns, 2016). Recent imaging studies have linked increased IIV to decreased white matter integrity in the cingulum and frontostriatal tracts (Castellanos, Kelly, & Milham, 2009; Fassbender, Zhang, Buzy et al., 2009; Weissman, Roberts, Visscher, & Woldorff, 2006; Lin, Gau, Huang-Gu, Shang, Wu & Tseng, 2018), in addition to frontoparietal hypoactivation and somatomotor hyperactivation (see Cortese et al., 2012 for a review); consistent with the neuropathology of ADHD.

On mass, it appears that the interface between executive control and motor function is central to the pathophysiology of ADHD and that challenges in one area (e.g., motor regulation) may impede functioning in the other (e.g., behavioural control). Further, it appears that IIV performance metrics may capture subtleties in both the executive and motor components of the disorder and yield additional information regarding their interactions. The extant literature on IIV in ADHD is largely based on examining tau from an Ex-Gaussian distribution, reflecting response times that are atypically and inconsistently slow, and which are thought to reflect attention lapses (e.g., Kofler et al., 2013). A separate literature examining IIV has employed the residualized

intraindividual standard deviation (rISD) with between-subject confounds removed (e.g., differences in learning rates, differences attributable to age), as an overall index of neural integrity that may be equally if not more sensitive to motor dysfunction (e.g., Hultsch, MacDonald, Hunter, Levy-Becheton & Strauss, 2000, MacDonald, Li & Bäckman, 2009; MacDonald, Nyberg, & Bäckman, 2006). We recently demonstrated that IIV in simple motor speed (finger tapping) indexed with rISD was systematically associated with working memory performance in individuals with neurological impairment, such that on occasions when these individuals were more variable in their tapping speed, they were also slower in their working memory performance (Halliday, Stawski & MacDonald, 2016). The rISD metric has been predominantly employed in studies of cognitive aging and its utility in capturing motor and executive dysfunction in ADHD remains relatively unexplored. Importantly, the rISD metric removes between-subject confounds that may conflate mean and variance and is established as a marker of neural integrity across a multitude of tasks (e.g., MacDonald et al., 2006; 2009; Walhovd & Fjell, 2007). This precedent suggests that rISD may more reliably index neural integrity rather than cognitive events like attention lapsing, which may be less driven by endogenous processes.

Development of Executive and Motor Control

In order to better understand the relation between executive function and motor control (including IIV) in ADHD, as well as their utility as potential endophenotypes for the disorder, an understanding of how these processes typically develop is required. Neurological development in mid- to late-childhood is characterized by ongoing synaptic pruning and myelination of brain areas that form neural networks (Semrud-Clikeman &

Ellison, 2009). While networks subserving primary sensory and motor functions develop early, networks comprising the frontal-parietal and neocerebellar regions that subserve more complex motor behaviours continue to mature and differentiate well into adolescence (Diamond, 2000; Edin, Macoveanu, Olesen, Tegner, & Klingberg, 2007; Luna et al., 2015; Sherman, Rudie, Pfeifer, Masten, McNealy & Dapretto, 2014). The executive and complex motor behaviours that emerge from these networks therefore also unfold in a protracted manner with a period of rapid development between ages 6-8 years and ongoing development past age 12 years for more complex motor functions (Anderson, Anderson, Northam, Jacobs & Catroppa, 2001; Semrud-Clikeman & Ellison, 2009). The co-activation of prefrontal cortex, basal ganglia and cerebellum observed during cognitive and motor tasks, as well as the shared processes of sequencing, planning and monitoring, suggest that executive and motor control processes develop and operate in tandem (Roebers & Kauer, 2009; van der Fels et al., 2015). Longitudinal evidence suggests that the developmental trajectory in children with ADHD may be delayed by as much as 2-3 years, with the greatest delay observed in prefrontal regions (Shaw, Eckstrand, Sharp, et al., 2007; Shaw, Lerch, Greenstein, et al., 2006), and with peak cortical thickness attained by 10.5 years in children with ADHD, relative to TD children who attain peak thickness by 7.5 years (Shaw et al., 2007).

Although, the developmental relationship between motor and executive control processes is complex, it is clear that motor and executive control systems are strongly interconnected and crucial for regulating behaviour (Cisek & Kalaska, 2010). With respect to IIV, motor variability differs across childhood and seems to exhibit a U-shaped trajectory across the lifespan (Luna et al., 2015; Unsworth, 2015; Grady, 2012; Williams,

Hultsch, Strauss, Hunter & Tannock, 2005). Higher IIV in early development is thought to reflect normal processes associated with early brain maturation; however, later in childhood, high levels reflect atypical cognitive function (Leth-Steensen, Elbax & Douglas, 2000; Williams et al., 2005), including those associated with symptoms of ADHD (e.g., impulsivity, attention deficits, etc.). Direct empirical evidence that IIV may be sensitive to the integrity of motor systems has been limited to individuals with Parkinson's Disease thus far (de Frias, Dixon, Fisher & Camicioli, 2007). The extent to which IIV is sensitive to motor systems in ADHD is less clear. Similarly, the extent to which IIV in executive and motor systems stabilizes across childhood is also unclear. This has important implications for understanding how executive and motor systems may ultimately deviate from an otherwise typical developmental trajectory, in disorders such as ADHD.

This study sought to examine (1) the relationship between executive and basic motor control in children with ADHD compared to those without, and (2) whether IIV in executive and motor performance is uniquely predictive of hyperactive/impulsive symptoms in ADHD. *A priori* hypotheses included that ADHD participants would show higher levels of IIV on executive and motor tasks, consistent with what is seen in younger children, due to delayed development of the neural systems that subserve these functions in ADHD (e.g., Shaw et al., 2006; 2007). Additional hypotheses included that IIV on motor tasks would be more predictive of hyperactive/impulsive ADHD symptoms than mean values for motor dexterity and motor sequencing. It was also was anticipated that IIV would be more predictive of ADHD symptoms than conventional metrics of executive control, given converging evidence that IIV is a robust endophenotype that

uniquely captures hallmark ADHD symptoms (Kofler et al., 2013; Tamm et al., 2012; Nikolas, 2015).

2.3 Method

2.3.1. Participants

This study employed data collected from 97 children between the ages of 6 and 13 years, recruited through community and school-board advertisements. All participants were screened for parent-reported neurological and mental health conditions as well as learning disorders. Table 2.1 presents several demographic variables of interest. Thirty-one participants had a formal diagnosis of ADHD and 66 participants were classified as typically developing (TD). ADHD diagnoses were provided by a range of healthcare providers (e.g., pediatricians, psychologists) and were corroborated using the ADHD Rating Scale V (DuPaul, Power, Anastopoulos & Reid, 2016) and the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL DSM-5; Kaufman, Birmaher, Axelson, Perepletchikova, Brent & Ryan, 2016) upon enrollment to the study. Both scales are based on criteria from DSM-5. Intellectual ability was screened using the Kaufman Brief Intelligence Test Second Edition (KBIT-2; Kaufman & Kaufman, 2004) and all participants enrolled obtained overall intellectual scores in the average range. Groups did not differ in overall intellectual ability (mean ADHD SS = 106.4; mean TD SS = 109.8; $F(1,89)=0.741$, $p=.39$) or age (mean ADHD age = 9.3 years, mean TD age = 9.3 years). Annual income for both groups was most commonly reported in the above $100,000 range. Given the high rates of comorbid learning disorder and oppositional defiant disorder in children with ADHD, participants were not excluded if they presented with these conditions, but were excluded on the basis of additional neurological or mental

Table 2.1. Demographic differences between children with Attention-Deficit Hyperactivity Disorder (ADHD) and typically developing (TD) children.

Demographic Variable	**ADHD**	**TD**
Percent male	75.0	58.0
Average age	9.0	10.0
Average IQ	106.4	109.8
Percent comorbid LD (parent-reported)	6.4	0.0
Percent comorbid ODD (parent-reported)	0.0	0.0
Household income less than $40,000 (%)	7.5	8.0
Household income $40,001-75,000 (%)	15.1	24.0
Household income $75,001-90,000 (%)	22.6	24.0
Household income $90,001-100,000 (%)	5.7	8.0
Household income more than $100,000 (%)	49.1	36.0

health conditions (e.g., clinically significant anxiety, autism spectrum disorder, fetal alcohol spectrum disorder). Overall, of 114 number of children screened, 14 were excluded due to presence of another neurodevelopmental disorder (*n*=7), clinically significant mental health condition (*n*=1), being out of the targeted age range (*n*=2) or expressing discomfort with adhering to the 48-hour medication washout period (*n*=4).

After a minimum 48-hour medication washout period, participants underwent a comprehensive assessment battery consisting of both standardized and experimental tests of executive function and motor control during a single testing session lasting approximately 2 hours with a break. A primary caregiver for each participant completed a semi-structured clinical interview (KSADS-V ADHD and ODD Modules; Kaufman, Brimaher, Brent et al., 2013), as well as a demographic questionnaire (Child History Questionnaire) and two behavioural rating scales (DuPaul ADHD Rating Scale 5; DuPaul, Power & Anastopooulos 2016; Comprehensive Executive Function Inventory; Naglieri & Goldstein, 2013).

Relative to parents of TD children, parents of children with ADHD reported more ADHD symptoms on the DuPaul ADHD Rating Scale, both in terms of inattentiveness ($F(1,90)=62.920$, $p<.001$; TD mean t-score =54.1, $SD=12.4$; ADHD mean t-score =74.4, $SD=8.9$) and hyperactivity/impulsivity ($F(1,90)=58.834$, $p<.001$; TD mean t-score =54.0, $SD=13.3$; ADHD mean t-score =75.7, $SD=10.9$). This same pattern was observed based on the K-SADS semi-structured interview, in terms of inattentiveness ($F(1,90)=56.545$, $p<.001$) and hyperactivity/impulsivity ($F(1,90)=39.946$, $p<.001$). Groups did not differ in terms of parent-reported criterion A ODD symptoms (i.e., angry/irritable mood, argumentative/defiant behaviour and/or vindictiveness) ($F(1,20)=0.002$, $p>.05$), criterion B ODD symptoms (i.e., degree of functional impairment) ($F(1,20)=0.069$, $p>.05$), or parent-reported diagnosis of LD ($F(1,93)=0.359$, $p>.05$). Parents of children with ADHD also reported significantly lower executive functioning on each of the CEFI subscales (i.e., attention, emotion regulation, flexibility, inhibitory control, initiation, organization, planning, self-monitoring, working memory) (all ps$<.001$). No significant age or age by group interaction effects were observed.

2.3.2. Measures

Participants were tested individually in a quiet room free of distractions using a fixed battery of tests administered in a counterbalanced order. The Multi-Source Interference and Jelly Bean Tasks each include a simple and a more complex condition and a full description is provided subsequently. Briefly, the simple conditions in these tasks involved congruent perceptual-motor responding, where the interference effects from the additional stimuli were relatively minimal. In contrast, the complex conditions

involved incongruent perceptual-motor responding, where the interference effects from the additional stimuli were greater.

Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), ADHD and ODD Modules. The K-SADS is a widely used semi-structured interview for primary caregivers (Kaufman et al., 2013). It is designed to capture important diagnostic information pertaining to a range of childhood and adolescent psychiatric issues (e.g., depression, anxiety, oppositional defiance disorder, conduct disorder), by asking primary caregivers to rate behaviours on a scale of 1 (never) to 3 (frequently). The K-SADS ADHD and Oppositional Defiant Disorder modules were administered.

Items are mapped onto Diagnostic and Statistical Manual, 5th edition (DSM-5) criteria for ADHD, with total symptom scores derived by multiplying the number of items endorsed under a given frequency and then summing the total values. This is done separately for inattentive, hyperactive/impulsive and combined symptoms for the purposes of examining ADHD symptoms across a continuum of severity (i.e., relative to binary classification).

DuPaul ADHD Rating Scale 5. This standardized rating scale is designed to determine the frequency and severity of ADHD symptoms and impairments. Parents and teachers were asked to rate their child's behaviours in the home environment and these ratings are then reviewed against DSM-5 criteria for ADHD (DuPaul et al., 2016). For the purposes of this investigation, teacher forms were not included, as the sample of returned forms was relatively small.

Comprehensive Executive Function Inventory (CEFI). This standardized rating scale is designed to measure executive functioning abilities in children as observed

by their parents and teachers. It contains a full-scale score, in addition to 9 subscales (attention, emotion regulation, flexibility, inhibitory control, initiation, organization, planning, self-monitoring, working memory). This subtest has a strong normative base, and is psychometrically sound (Naglieri & Goldstein, 2014). For the purposes of this investigation, teacher forms were not included, as the sample of returned forms was relatively small.

The Kaufman Brief Intelligence Test, 2nd edition (KBIT-2). This is an individually administered measure of cognitive function that yields summary scores for verbal reasoning, visual reasoning and overall intellectual ability. Specific subtests include measures assessing vocabulary, verbal analogies, and matrix reasoning. This measure has a strong normative base, and is psychometrically sound (Kaufman & Kaufman, 2004). The KBIT-2 was used for screening purposes and all participants obtained scores in the average range.

Multi-Source Interference Task (MSIT). This is an experimental task of cognitive interference, in which participants are presented a series of three numbers, with one number differing from the other two, and are asked to respond to the value of the number that differs. During control trials (simple interference), the value and location of the different number are congruent. During interference trials (complex interference), the value and location are incongruent. Participants are presented with 15 trials that are grouped into 3 blocks per condition. This measure does not have a normative base, but shows strong psychometric properties in the literature (Bush, Shin, Holmes, Rosen & Vogt, 2003; Bush & Shin 2006).

Jelly Bean Task. This is a computerized task of cognitive interference, in which participants are presented with an arrow in either the left, centre or right side of the screen and are asked to respond using three buttons that match in colour and spatial location to the arrows. During the control condition (simple interference), they are required to match arrows to keys (e.g., green left arrow to green left button) and in the interference condition (complex interference), they are asked to respond using opposite buttons for the right and left arrows (i.e., right button for left arrow and left button for right arrow). This is an experimental measure that does not have a normative base or previously established psychometric properties.

Wack-a-Mole. This is a computerized go/no-go task that measures inhibitory control, where children are required to respond to target stimuli or to refrain from a response when a non-target stimulus appears instead. Baseline blocks are used to help participants develop a prepotent response to the stimuli and to measure reaction time, due to the absence of non-target stimuli. Following these baseline blocks, test blocks are used to measure both the number of omission errors (i.e., no response for target stimuli) and commission errors (i.e. response to non-target stimuli). This is an experimental measure that does not have a normative base or previously established psychometric properties.

Computerized Finger Tapping. This is an experimental version of computerized finger tapping, in which participants are asked to tap a button using their index finger as quickly as possible for 30 seconds to assess fine motor speed. The task is alternated between dominant and nondominant hands for a total of three attempts per hand. This measure does not have a normative base or previously established psychometric properties.

Grooved Peg Board. In this task, participants are asked to place a series of metal pegs into a peg board as quickly as possible. The task is repeated for both right and left hands and is used to measure fine motor dexterity. This standardized measure has a strong normative base and previously established psychometric properties in the literature (Strauss, Sherman & Spreen, 2006).

Manual Motor Sequences from the Developmental Neuropsychological Assessment, 2nd edition (NEPSY-II). This is a standardized measure designed to assess the ability to imitate a series of rhythmic movement sequences using one or both hands, and involves elements of both motor planning and sequencing. The child repeats a series of hand movements demonstrated by the examiner until the required number of movements is completed. This subtest has a strong normative base, and is psychometrically sound (Korkman, Kirk & Kemp, 2007a).

2.4 Results

2.4.1 Analysis Overview

Executive and motor differences between ADHD and TD participants were examined, in addition to differences between younger (6-9 years) and older children (10-13 years), using a 2 (age) x 2 (group status) ANOVA to examine the effects of these between-group differences on each of the motor and executive control outcome measures. Age was dichotomized using a median split in order to maximize degrees of freedom and considering the differences in rates of EF development between mid- and late-childhood (Semrud-Clikeman & Ellison, 2009). Table 2.2 summarizes the main effects and interactions and Table 2.3 summarizes average performance levels for the computerized tasks that were amenable to computation of IIV metrics.

2.4.2. Operationalizations of Intraindividual Variability

IIV was operationalized using Ex-Gaussian (specifically, tau) and residualized intraindividual standard deviation (rISD) computations. The decision to include both operationalizations was motivated by the precedent that tau reflects attention lapsing in the ADHD literature (e.g., Kofler et al., 2013) and that rISD reflects motor dysfunction (e.g., de Frias et al., 2007; Halliday et al., 2016). IIV estimates were computed on correct RT trials only, which is commonly employed in IIV methodology in order to circumvent the potential influence of incorrect trials (e.g., Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Halliday et al., 2016). IIV estimates were computed for the MSIT, Jelly Bean, Wack-a-Mole and Computerized Finger Tapping tests.

Tau estimates were derived using Quantile Maximum Likelihood Estimation (QMLE) software (Heathcote, Brown & Mewhort, 2002). RISD estimates were derived by first partialling systematic within- (e.g., learning across trials) and between-person (e.g., age) sources of variance in mean RT. Next, intraindividual standard deviations were computed across these residualized estimates.

2.4.3. Data Screening

Technical issues with the response apparatus used in the Jelly Bean Task resulted in 2 cases with invalid data. All data were screened for outliers ± 3 SD from the group mean. Data were also treated as missing in cases of below chance responding. In total, 4 cases were excluded from the Finger Tapping task (3/66 TD, 1/31 ADHD), 8 cases were excluded from the MSIT control condition (4/66 TD, 4/31 ADHD), 10 cases were excluded from the MSIT interference condition (4/66 TD, 6/31 ADHD), 18 cases were excluded from the Jelly compatible condition (13/66 TD, 5/31 ADHD), 34 cases were

excluded from the Jelly incompatible condition (24/66 TD, 10/31 ADHD) and 7 cases were excluded from the Wack-a-Mole task (4/66 TD, 3/31 ADHD).

2.4.4. Group Differences in Motor Performance

In terms of average simple motor speed (finger tapping), no group differences were observed between children with and without ADHD ($F(1,87)=0.067$, $p=.80$); however, across both groups older children were significantly faster than younger children ($F(1,87)=34.370$, $p<.001$). A similar pattern was observed with variability in simple motor speed, with no group differences (ADHD vs. TD) observed based on rISD or tau, but with younger children exhibiting more variability relative to older children on both metrics of IIV (i.e., tau and rISD) (Table 2.2 and 2.3). In terms of motor dexterity (Grooved Pegboard, total seconds, dominant hand), there was a trend towards group differences ($F(1,89)=3.172$, $p=.08$) such that children without ADHD ($m=86.9$, $SD=22.2$) were faster than children with ADHD ($m=94.7$, $SD=30.5$). Older children ($m=76.4$, $SD=14.8$) were also significantly faster than younger children ($m=101.9$, $SD=26.9$) in terms of motor dexterity (Grooved Pegboard). In terms of motor sequencing (NEPSY motor sequences, total correct), there was a trend towards group differences ($F(1,64)=2.983$, $p=.09$) such that children without ADHD ($m=52.3$, $SD=5.6$) completed more correct sequences than children with ADHD ($m=49.9$, $SD=8.4$). Older children ($m=53.6$, $SD=4.1$) also completed significantly more correct sequences than younger children ($m=49.3$, $SD=8.2$). The age by group interactions in each of these tasks and metrics were not significant, suggesting that developmental gains in motor function were equivocal in both groups.

2.4.5. Group Differences in Inhibitory and Interference Control

Table 2.2. Descriptive statistics for each group, depicting mean performance values and corresponding standard deviations.

		Young-Young				**Young-Old**			
		ADHD		*Control*		*ADHD*		*Control*	
Tap	RT rISD	9.86	± 4.29	8.67	± 5.05	5.90	± 3.51	4.43	± 1.67
	RT Tau	58.00	± 40.53	46.59	± 33.05	43.58	± 40.33	28.59	± 27.88
	RT Mean	318.30	± 50.89	331.02	± 80.03	243.13	± 25.52	237.84	± 58.01
Wack-a-Mole	RT rISD	10.11	± 4.63	9.44	± 3.30	7.73	± 2.94	6.53	± 2.45
	RT Tau	146.36	± 60.76	162.84	± 81.70	152.90	± 66.70	132.74	± 56.95
	RT Mean	609.96	± 137.51	620.76	± 94.44	511.24	± 82.16	468.05	± 65.90
	Accuracy	0.96	± 0.06	0.98	± 0.02	0.99	± 0.01	1.00	± 0.01
MSIT Control	RT rISD	11.42	± 3.84	9.68	± 2.77	7.01	± 1.99	5.63	± 2.24
	RT Tau	161.91	± 87.98	215.69	± 95.15	167.05	± 117.71	202.41	± 120.68
	RT Mean	973.93	± 143.09	950.71	± 202.86	735.00	± 110.15	644.08	± 135.08
	Accuracy	0.87	± 0.14	0.95	± 0.05	0.98	± 0.03	0.99	± 0.02
MSIT Interference	RT rISD	10.63	± 2.29	10.44	± 2.33	8.59	± 1.52	8.11	± 2.00
	RT Tau	241.28	± 180.40	190.60	± 159.75	229.77	± 118.83	211.20	± 98.91
	RT Mean	1466.92	± 207.30	1530.40	± 196.09	1285.09	± 167.22	1189.29	± 209.75
	Accuracy	0.63	± 0.30	0.78	± 0.17	0.91	± 0.07	0.94	± 0.06
Jelly Compatible	RT rISD	10.69	± 1.16	9.43	± 1.43	8.40	± 1.67	7.99	± 1.56
	RT Tau	28.80	± 21.21	26.13	± 24.63	50.61	± 47.96	42.44	± 42.08
	RT Mean	701.05	± 44.46	715.41	± 71.40	622.13	± 69.20	588.77	± 91.83
	Accuracy	0.78	± 0.16	0.78	± 0.14	0.92	± 0.09	0.94	± 0.09
Jelly Incompatible	RT rISD	10.89	± 1.40	9.53	± 1.66	8.91	± 1.49	9.24	± 1.33
	RT Tau	16.61	± 1.99	24.76	± 17.40	17.55	± 10.88	32.25	± 36.71
	RT Mean	738.57	± 35.28	754.22	± 46.78	723.64	± 43.01	670.00	± 67.32
	Accuracy	0.63	± 0.11	0.64	± 0.11	0.78	± 0.13	0.85	± 0.10

During an inhibitory control task (Wack-a-mole), children with ADHD were less accurate (hits) relative to children without ADHD, and younger children were also less accurate than older children (Table 2.2 and 2.3). No group differences were observed in response time variability based on rISD or tau during inhibitory control (Wack-a-mole);

Table 2.3. Summary of ANOVA models examining differences in performance as a function of group status and age as well as the interaction of these two variables.

	Group		**Age**		**Interaction**	
Variables	*F-statistic*	*p-value*	*F-statistic*	*p-value*	*F-statistic*	*p-value*
TAP						
RT rISD	2.253	.137	21.459	.000	.025	.875
RT Tau	2.962	.089	4.468	.037	.054	.817
RT Mean	.067	.796	34.370	.000	.393	.532
WACK						
RT rISD	1.641	.204	13.150	.000	.128	.722
RT Tau	.014	.906	.571	.452	1.380	.243
RT Mean	.566	.454	34.141	.000	1.574	.213
Accuracy	6.288	.014	12.579	.001	1.012	.317
MSIT-Control						
RT rISD	6.148	.015	45.163	.000	.081	.776
RT Tau	3.251	.075	.027	.870	.139	.710
RT Mean	2.160	.145	49.339	.000	.760	.386
Accuracy	14.333	.000	29.027	.000	6.417	.013
MSIT-Interference						
RT rISD	.408	.525	17.142	.000	.075	.785
RT Tau	1.179	.281	.020	.887	.254	.616
RT Mean	.104	.747	27.353	.000	2.537	.115
Accuracy	5.959	.017	36.609	.000	2.371	.127
Jelly-Compatible						
RT rISD	4.653	.034	23.094	.000	1.193	.278
RT Tau	.359	.551	4.439	.039	.092	.762
RT Mean	.239	.626	28.015	.000	1.510	.223
Accuracy	.108	.743	27.190	.000	.076	.784
Jelly-Incompatible						
RT rISD	1.363	.248	6.593	.013	3.694	.060
RT Tau	1.867	.178	.254	.616	.153	.697
RT Mean	1.215	.275	8.273	.006	4.039	.049
Accuracy	1.558	.217	30.678	.000	.662	.419

however, younger participants were slower and more variable, based on rISD (Table 2.2 and 2.3). Significant group differences were observed in response time variability based on rISD during simple (MSIT Control, Jelly Compatible), but not complex interference control tasks (MSIT Interference, Jelly Incompatible), with ADHD participants showing greater variability relative to TD participants (Table 2.2 and 2.3). Significant age differences were also observed in response time variability based on rISD during both simple and complex interference controls tasks, such that younger participants were more variable than older participants. In terms of tau, age differences emerged for one measure of simple interference (Jelly Compatible), such that younger participants were more variable than older participants (Table 2.2 and 2.3). Age differences were observed based on mean response time, with older participants performing faster than younger participants on all measures of interference control.

A significant group by age interaction was observed based on accuracy on one measure of simple interference control (MSIT control condition: $F(1,84)= 6.417$, $p<.05$), such that ADHD participants showed greater developmental gains compared to TD participants (Figure 2.1). Significant group by age interactions were also observed based on rISD ($F(1,54)=3.694$, $p=.06$) and mean response times ($F(1,54)=4.039$, $p=.05$) on one measure of complex interference control (Jelly incompatible). In this case, the ADHD participants showed greater developmental gains in performance consistency, but were significantly slower on average relative to TD participants at the older end of the developmental period (Figure 2.1).

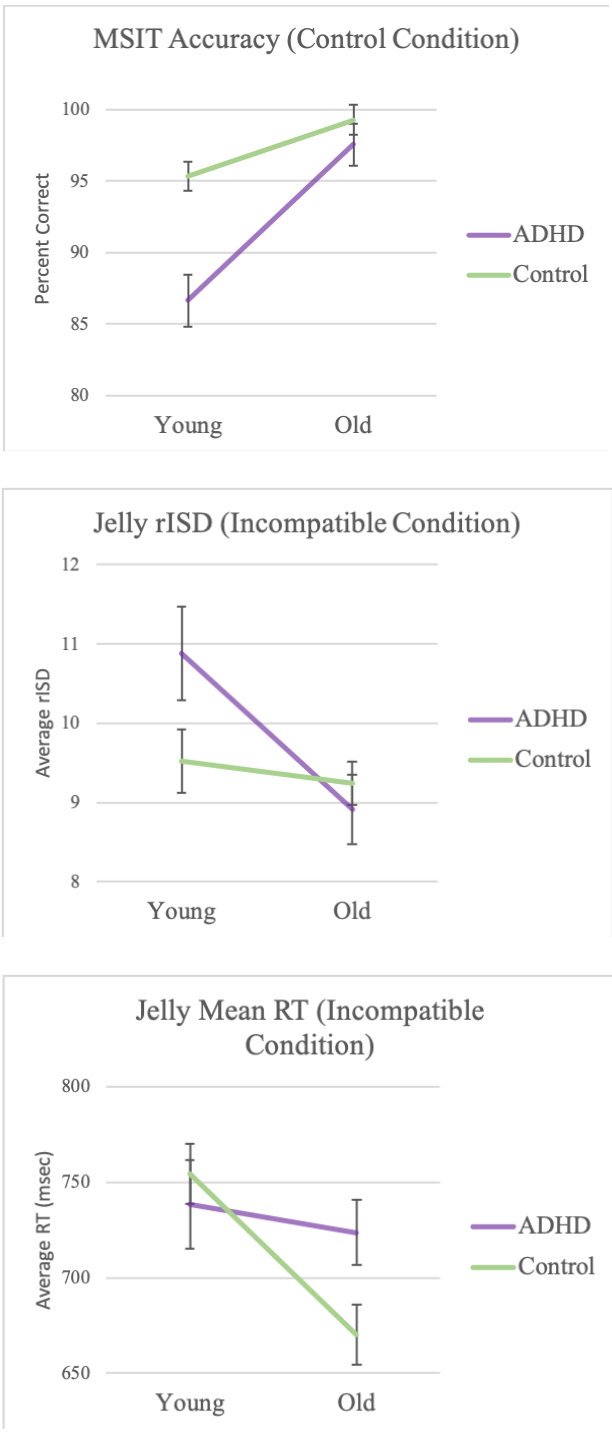

Figure 2.1. Interaction between age (young-young, less than 110 months and young-old, greater than 110 months) and group status (control and ADHD) based on (a) MSIT control accuracy performance, (b) Jelly incompatible rISD, and (c) Jelly incompatible mean RT.

2.4.2. Predicting ADHD Symptoms with Motor Variability and Executive Performance

ADHD symptoms were examined using a series of hierarchical linear regression models, with predictor variables comprising motor (Grooved Pegboard, NEPSY Manual Motor Sequences, finger tapping) and executive/motor performance (MSIT, Jelly, Wack-a-Mole). Symptom count from the K-SADS was modelled as a function of motor dexterity (Grooved Pegboard) or motor sequencing (NEPSY Manual Motor Sequences), alongside motor variability (finger tapping rISD). Table 2.4 displays the unstandardized regression coefficients, intercepts, β (standardized coefficients), SE B, semi-r and p values for each stage of the hierarchical regression model. Motor variability (rISD) was a significant predictor of hyperactive/impulsive ADHD symptoms, after accounting for age and motor dexterity (β=0.22, $p<.05$, one-tailed; full model: $F(3,86) = 4.937$, $p = .003$); however, motor dexterity (mean values) was not significantly predictive in this model (β=0.17, $p>.05$). Conversely, motor variability (rISD) failed to account for significant variance in hyperactive/impulsive symptoms after accounting for motor sequencing (β=0.07, $p>.05$; full model: $F(3,62) = 2.472$, $p = .074$); however, motor sequencing was significantly predictive of hyperactive/impulsive symptoms in this model (β=-0.25, $p<.05$, one-tailed). In terms of total K-SADS symptom count (i.e., combined across both inattentive and hyperactive/impulsive), motor variability failed to account for significant variance, beyond variance that was explained by clinical measures of motor dexterity or motor sequencing. Similarly, inattentive symptoms were not reliably predicted by motor dexterity, sequencing or variability.

Table 2.4. Hierarchical regression on K-SADS scores, modelled separately as a function of age and (a) motor, for Hyperactive/Impulsive symptoms or (b) executive scores for total symptoms. In each model motor or response time variability were entered at stage two of the model, after variance in K-SADS associated with stage one predictors was accounted for.

Motor					
Variables	**B**	**SE B**	**β**	**semi-r**	**p**
Stage 1					
Age	-.045	.027	-.198	-.176	.099
Grooved Peg	.045	.029	.186	.166	.121
Stage 2					
Tap rISD	.313	.167	.218	.198	.064
Stage 1					
Age	-.020	.028	-.097	-.090	.475
NEPSY	-.227	.117	-.262	-.237	.057
Stage 2					
Tap rISD	.110	.236	.065	.059	.642
Executive					
Variables	**B**	**SE B**	**β**	**semi-r**	**p**
Stage 1					
Age	-.012	.047	-.030	-.029	.793
Control Acc	-41.426	18.399	-.259	-.239	.027
Stage 2					
Control rISD	.814	.481	.268	.183	.094
Stage 1					
Age	.044	.054	.109	.091	.412
Interference Acc	-26.621	9.491	-.370	-.298	.006
Stage 2					
Interference rISD	.132	.626	.029	.024	.833
Stage 1					
Age	-.035	.060	-.082	-.067	.561
Compatible Acc	-12.342	11.669	-.149	-.121	.294
Stage 2					
Compatible rISD	1.830	.815	.295	.253	.028
Stage 1					
Age	.061	.074	.131	.110	.411
Incompatible Acc	-20.963	12.301	-.269	-.222	.094

Stage 2					
Incompatible rISD	1.187	1.010	.167	.157	.245
Stage 1					
Age	-.007	.047	-.016	-.015	.888
Wack Acc	-133.689	46.830	-.329	-.297	.005
Stage 2					
Wack rISD	1.181	.493	.365	.254	.019

Total symptom count from the K-SADS was subsequently modelled with age and measures of executive/motor control (Wack-a-Mole, MSIT, Jelly) in order to examine the unique predictivity of IIV in predicting ADHD symptoms above and beyond these variables. The accuracy and rISD measures for a given condition were selected for each model, with correlation values examined to rule out the possibility of collinearity. Correlation values ranged between -.329 to -.740. IIV (indexed with rISD) was a significant predictor of total ADHD symptoms after accounting for age and executive control, indexed with either Wack-a-mole accuracy (β=0.37, $p<.05$; full model: $F(3,81) = 5.71$, $p<.001$, $\Delta R^2 = 0.06$, $p<.05$), MSIT control accuracy (β=0.27, $p<.05$, one-tailed; full model: $F(3,83) = 3.26$, $p = .026$, $\Delta R^2 = 0.03$, $p<.05$, one-tailed) or Jelly compatible accuracy (β=0.30, $p<.05$; full model: $F(3,74) = 2.88$, $p = .042$, $\Delta R^2 = 0.06$, $p<.05$). At greater levels of cognitive demand (i.e., MSIT interference, Jelly incompatible), IIV was not reliably predictive of K-SADS scores (Table 2.4). These effects were highly similar when examining hyperactive/impulsive and inattentive scores in isolation. Importantly, tau was not significantly predictive of K-SADS scores, when used as the index of response time variability, for either inattentive or hyperactive/impulsive symptoms separately, or when combined as total symptom count.

2.5 Discussion

ADHD is a relatively common neurodevelopmental disorder characterized by inattentive and/or hyperactive/impulsive symptoms; behaviours which occur in ADHD but also in other neurodevelopmental disorders and undiagnosed conditions (Sinzig, Bruning, Morsch, & Lehmkuhl, 2008; Stojanovski, Felsky, Viviano et al., 2019; Davis, Desrocher, & Moore, 2011). Challenges in accurately identifying ADHD and the search for endeophenotypes for the disorder has been plagued by a reliance on behavioural measures, which tend to be subjective (Sims & Lonigan, 2012) and by objective performance measures, which are not particularly sensitive (Sims & Lonigan, 2012; Berger, Slobodin, & Cassuto, 2017; Matier-Sharma, Perachio, Newcorn, Sharma & Halperin, 1995). Therefore, identification of specific endophenotypes for ADHD holds value for increasing diagnostic precision, permitting early identification/intervention, and reducing long-term morbidity (Galéra, Bouvard, Lagarde et al., 2012; Lee, Yang, Chen et al., 2016; Coghill, Banaschewski, Soutullo, Cottingham, & Zuddas, 2017; Sonuga-Barke, Koerting, Smith, McCann, & Thompson, 2011).

A hallmark of ADHD is difficulties with motor regulation, which may underlie impulsive and hyperactive symptoms and hold potential as a possible endophenotype of ADHD. In particular, IIV in motor behaviour has emerged as a potentially sensitive metric in the assessment of ADHD that may ultimately prove to be an objective metric for assessment purposes (e.g., Kofler et al., 2013; Suskauer et al., 2008). Given that IIV varies across typical childhood development, this investigation sought to better understand the relationship between motor and executive/motor development in TD children when compared to those with ADHD. To this end, we investigated the

performance of children between the ages of 6 to 13 years, with and without a diagnosis of ADHD on standardized measures of motor control, as well as experimental measures of executive/motor control. We employed mean values and calculations of IIV based on the ex-Gaussian approach (tau), which is commonly utilized in the ADHD literature (e.g., Kofler et al., 2013). We also employed the rISD approach, which has a stronger precedent in the older adult literature, but which may be more suited to capturing motor dysfunction (e.g., de Frias et al., 2007; Hultsch et al., 2000, MacDonald et al., 2006; 2009).

With respect to motor function, we observed trends in the expected direction, such that children with ADHD performed worse in terms of consistency in motor speed, speed of motor dexterity, and accuracy in terms of motor sequencing. Contrary to expectations, TD children did not demonstrate greater developmental gains in motor control relative to ADHD children; instead, group differences in motor performance remained consistent across the developmental period from 6 to 13 years of age. In terms of executive performance, children with ADHD exhibited greater variability during simple but not complex cognitive interference tasks and these effects were observed primarily using rISD. The observation of stronger rISD effects relative to tau during interference control suggests that variability may be driven more by motor dysfunction than attention lapsing during interference measures. Given that the rISD effects were strongest during the simple interference tasks, this further suggests that motor dysfunction may interfere with cognitive control at relatively low demands on interference control.

In terms of developmental differences between groups, children with ADHD demonstrated lower accuracy on a simple cognitive interference task (MSIT control)

prior to age 9, after which their performance became less distinguishable and not reliably different from TD children. Similarly, during a more complex cognitive interference task (Jelly incompatible), children with ADHD demonstrated greater variability in response times prior to age 9, after which they became indistinguishable from TD children. Interestingly, their reaction time was significantly slower than TD children after age 9 only, suggesting that greater consistency in performance may have come at a loss of overall speed. This is in keeping with reports that individuals with lower motor coordination may have difficulties with speed-accuracy trade-off (Michel, 2012) and that dysfunction of motor systems may detract from executive resources (Suskauer et al., 2008); however, it also suggests that the relationship between motor and executive control may look different across childhood development. With greater executive demands, children with ADHD appear to take more time to process information that interferes with their intended goal, to do so in a manner that is careful and considerate. Given the consistent differences in motor regulation observed between TD and ADHD children and the fact that consistency of executive performance differed between groups in the younger age bracket only, these findings suggest that children with ADHD may learn to compensate for their motor dysregulation during executive control through different means; by responding less consistently earlier in childhood, and by responding more slowly in later childhood. These findings may reflect maturation in error monitoring, which has been shown to differ in childhood ADHD (Gupta & Kar, 2009; Wiersema, van der Meere & Roeyers, 2005). These findings also suggest that there are differences in the developmental trajectories for aspects of executive performance between TD and ADHD children, and that ADHD children may experience greater

developmental gains during mid-childhood, following a period of initially protracted development. In line with the assertion that executive control processes undergo rapid development from 6-8 years of age (Anderson et al., 2001; Semrud-Clikeman & Ellison, 2009), these findings suggest that this window of development is characterized by gains in executive control (implicated by both consistency and accuracy), but that the efficiency of this control (implicated by overall speed) remains below age expectations in late-childhood.

With executive motor tasks that involved cognitive interference and inhibition, IIV in response times was predictive of total ADHD symptoms and was more sensitive than accuracy-based measures (e.g., simple error rates). This was the case in the control condition types only (with fewer interference and inhibition demands), and was consistent across hyperactive, inattentive and combined symptom counts. The fact that this trend was observed in simple but not complex interference tasks suggests that response time variability may be capturing difficulties with regulation (e.g., motor and/or attentional) at lower levels of cognitive demand. Given that this was observed with rISD but not tau, and to the extent that the two metrics are driven by different phenomena (rISD by motor dysregulation and tau by attentional lapsing), these results further suggest that motor regulation impedes executive performance at lower levels of cognitive demand. In contrast, at higher levels of cognitive demand, children with ADHD appear better able to regulate. Overall, these findings suggest that IIV metrics are more sensitive to ADHD symptoms when derived from simple executive tasks, where the demands are lower and more susceptible to motor and/or executive dysregulation (e.g., Sauskauer et al., 2008). Accordingly, IIV metrics may help inform diagnostic testing for ADHD.

A more thorough assessment of motor dysregulation may ultimately improve ADHD diagnosis and help account for aspects of executive dysfunction that are also observed. ADHD diagnoses have traditionally been based on symptom checklists and ultimately made in a binary fashion (i.e., an individual is either diagnosed with ADHD or not); however, in actual fact, the symptoms comprising ADHD exist along a continuum. When symptoms of ADHD hyperactivity (e.g., excessive fidgeting, interrupting of others) were rated continuously, motor variability (indexed with rISD in finger tapping) was predictive of individual differences beyond differences explained by motor dexterity, suggesting that consistency in simple motor speed is more sensitive to hyperactive behaviours than overall speed. Motor sequencing was more predictive of hyperactive symptoms than motor variability (indexed with rISD in finger tapping) and this may relate to the added executive demands inherent in motor sequencing that necessitate involvement of neural regions extending beyond those involved in simple motor speed (e.g., supplementary motor areas). Interestingly, performance on the motor tasks was not reliably predictive of inattentive symptoms, further suggesting that it uniquely captures symptoms of hyperactivity and impulsivity. Similarly, the variability effects during speed of simple interference control emerged most strongly for the rISD metric. Overall, these findings support the hypothesis that the hyperactivity and impulsivity observed in ADHD may be driven by greater difficulties with motor regulation.

2.5.1. Limitations and Future Directions

This study was limited in part by the technical issues experienced during the Jelly Bean task; however, data were missing completely at random and reliable patterns were still observed nevertheless. Our study was limited to a relatively affluent sample, and thus

the results may not generalize to a more diverse population. IIV in the ADHD literature is primarily comprised of studies examining tau from the Ex-Gaussian distribution and thus, it is interesting that the current findings were driven largely by the rISD operationalization. Future studies may consider employing more nuanced experimental paradigms to shed additional insight on whether these different operationalizations of IIV (i.e., rISD and tau) are driven by separable processes. Similarly, additional work characterizing the relationship between motor control and EF tasks with less motor output (e.g., verbal fluency, colour-word interference) would be useful to better understand the non-overlap between motor and executive performance. Employing motor tasks involving greater executive control would be equally useful. Understanding these relationships in the context of additional demographic (e.g., broader age range, including adolescents post-puberty) and clinical group status variables (e.g., developmental coordination disorder) will be important in understanding the nature of these constructs as well as their potential compromises in other neurodevelopmental conditions.

Chapter 3

Electrophysiological Variability During Executive Functioning is More Sensitive than Self-Report Ratings in Athletes Mild Traumatic Brain Injury

3.1 Abstract

Background: Sports participation and athleticism confer a host of protective health benefits, with emerging evidence for additional neurocognitive gains related to executive functioning (EF). Mild Traumatic Brain Injury (mTBI) impacts EF most commonly and is more likely to be sustained in certain athletic undertakings. Neural variability is an emerging proxy of brain health that indexes the brain's dynamic range and ability to connect with other regions and has yet to be characterized in mTBI or athleticism. This study examined whether neural variability was attenuated after mTBI and explored its predictive utility alongside clinical measures of EF. Method: Seventy seven young adults (18-25 years of age) were recruited from varsity-level sports teams and undergraduate courses, and were classified as either sedentary controls (n=33), athletes with mTBI (n=21) or athletes without mTBI (n=23). Participants completed laboratory measures of attention switching, response inhibition and updating working memory while undergoing electroencephalography (EEG) recordings to index neural variability (based on standard deviation), in addition to behavioural ratings of executive difficulties and post-concussive symptoms. Results: Athletes with mTBI reported more difficulties in terms of inhibition, working memory and organization of materials. Athletes with mTBI exhibited a restricted dynamic range of neural variability during error monitoring and attention switching. This restricted range was more predictive of the mTBI group status than the clinical measures of EF. Conclusions: MTBI appears to attenuate the dynamic range of neural activity during EF, in young adult athletes. This suggests that athleticism may not buffer against the associated neurocognitive impacts of an mTBI. Neural variability represents a promising assessment metric for mTBI assessment.

3.2 Introduction

Executive functioning (EF) refers to a complex set of interconnected self-regulatory control processes routed in neurocognitive functioning, that work separately and in tandem to produce goal-oriented behaviours. Although the precise nature of the construct itself remains under investigation, EF seems to be highly important to successful daily functioning and independence (Baggetta & Alexander, 2016; Jurado & Rosselli, 2007; Lezak, 1982) and has therefore been of relative priority for assessment and rehabilitation in many clinical populations. EF continues to be studied at multiple levels of the nervous system, with evidence for the role of genetics (Friedman, Miyake, Altamirano et al., 2016) and large-scale neural networks, which give rise to the basic underpinnings (e.g., processing speed) of higher order cognition, and to EF itself. At the behavioural level, EF is examined in terms of constituent processes (e.g., shifting, working memory, inhibition) with broadly understood neural correlates (Manard, Bahri, Salmon & Collette, 2016), and at the macro-behavioural level, where the purported neural correlates are more tenuous, given the complexity of the processes (e.g., problem solving). In general, EF relies on widely distributed neural networks that comprise not only frontal-parietal connections, but also connections to subcortical (e.g., basal ganglia) and cerebellar areas (Miller & Cohen, 2001; Wager & Smith 2003). This wide distribution means that EF difficulties are often impacted in the face of neurological injury, although there is much heterogeneity across populations who experience executive dysfunction (Garcia-Barrera, 2019).

In addition to neurobiological and cognitive mechanisms, EF is influenced by a number of environmental factors (e.g., socio-economic status, music and second language

learning). Among these factors, mounting evidence indicates that engagement in athletic activity positively influences EF (Marchetti, Forte, Borzacchini, Vazou, Tomporowski & Pesce, 2015; Muraskin, Sherwin & Sajda, 2015; Verburgh, Scherder, Van Lange, & Oosterlaan, 2016). Best (2010) posits that there are three primary pathways through which exercise impacts EF in particular; (1) via the executive demands inherent in engaging games, (2) via the executive demands inherent in the coordination of complex motor tasks, and (3) via the physiological changes resulting from aerobic exercise. Recent research has demonstrated enhanced inhibitory (Bianco, Di Ruesso, Perri & Berchicci, 2017) and interference control (Wylie, Bashore, Van Wouwe et al., 2018) in athletes relative to controls, suggesting that the consistent execution of these processes during executive motor control generalizes outside of sports participation. Furly and Wood (2016) argue that the enhanced inhibitory control found in individuals with sports expertise is driven by working memory, which serves to control attention in a goal-directed manner. Presumably, the synaptic connections underpinning the executive processes that are engaged during strategic games are strengthened and optimized under physiological and perhaps even emotional duress. This results in a more highly tuned system overall, where the overall functional benefits are generalized to other applications of EF.

In spite of the established health and apparent neurocognitive benefits, participation in certain sports also brings with it an increased risk of mild Traumatic Brain Injury (mTBI), particularly when it involves a greater likelihood of forceful body contact (e.g., football, hockey, rugby; Coronado, McGuire, Faul, Sugerman & Pearson, 2012). The topic of mTBI sustained during sports participation has received much

attention in recent years, in light of the concerns and observations surrounding the subtle, but persistent cognitive and emotional changes that ensue in some cases. Among the cognitive domains, EF appears to be most commonly impacted in mTBI, based on meta-analytic results (Karr, Areshenkoff, & Garcia-Barrera 2014). Given the most common injury mechanisms of mTBI (i.e., coup-contrecoup and rotational forces resulting in diffuse axonal injury), the likelihood of multimodal trauma (e.g., orthopedic, emotional, neurological), and the distributed neural and cognitive architecture of EF, it is unsurprising that symptoms of executive dysfunction are so commonly reported following these types of injuiries. Moreover, the influences from one symptom domain can also exacerbate those from another (e.g., physical pain can detract from attentional resources; withdrawing from activities during recovery can lead to low mood, which can in turn impact information processing speed and attention). Ultimately, navigating the cost-benefit ratio of sports participation remains a careful decision, particularly when it involves individuals who have already sustained an mTBI and are more vulnerable to the impacts of multiple injuries. To support these decisions, it is important to understand the neurocognitive benefits and ramifications of athleticism and mTBI, respectively.

3.2.1. Assessing Executive Functioning with Electroencephalography and Intraindividual Variability

Electroencephalography (EEG) methodology has proven sensitive to the effects of both mTBI (e.g., diffuse axonal injury) and the neurocognitive benefits of athleticism (e.g., synaptogenesis), rendering it of particular utility in the context of sports-based mTBI. Several recent investigations have employed EEG to demonstrate electrophysiological differences between athletes and non-athletes that contribute to a

deeper level of understanding of the potential mechanisms behind the cognitive benefits that have been observed (e.g., Bianco et al., 2017; Muraskin et al., 2015). Similarly, EEG methodology has been effective in elucidating electrophysiological differences in sports-based mTBI. Research has fairly consistently demonstrated reductions in P3 amplitude and latency (Broglio, Moore & Hillman, 2011; Brush, Ehmann, Olson, Bixby & Alderman, 2018), with emerging consensus that EEG is sensitive to the longer-term impacts of mTBI, in the absence of clinical findings during conventional practice (Broglio et al., 2011; Brush et al., 2018). The electrophysiological impacts of mTBI have also been observed during resting state paradigms without stimulus evoked potentials, particularly when using power-based analyses (Conley, Cooper, Karayanidis et al., 2019). For example, Slobounov, Cao and Sebastianelli (2009) demonstrated reduced electrophysiological activity in athletes who sustained an mTBI beyond 7 days post-injury, in spite of no differences observed on neuropsychological testing. Notably, although examinations of EEG data in the frequency domain (including power-based analyses) have demonstrated sensitivity to the effects of mTBI, methodological standardization has precluded a synthesis across studies with heterogeneous approaches (Conley et al., 2019).

Intraindividual variability (IIV) is an assessment approach that has been most commonly employed to examine response time consistency in older adults (e.g., MacDonald, Hultsch & Dixon, 2003), children with Attention-Deficit Hyperactivity Disorder (ADHD; e.g., Kofler, Rapport, Sarver et al., 2013) and individuals with moderate to severe TBI (e.g., Karr, Garcia-Barrera & Areshenkoff, 2014; Stuss, Pogue, Buckle & Bondar, 1994). Typically, proportionately greater IIV in response time is

associated with clinical group status and poorer prognosis. Similar to behavioural IIV, IIV in neurophysiological processes (neural variability) has demonstrated utility over the past decade in capturing unique sources of variance that are complimentary to conventional metrics routed in central tendency. In contrast to IIV in behavioural performance, greater neural variability represented in functional brain activation seems to reflect a more highly tuned neural system. Theoretically, neural variability appears to capture the dynamic range that a population of neurons operates within, with greater variability reflective of an adaptive and more flexible nervous system that is better able to respond to unpredictable environmental demands (see Garrett, Samanez-Larkin, MacDonald, Lindenberger, McIntosh & Grady 2013 for a review). Neural variability has been operationalized through different means (e.g., standard deviation, mean square successive differences, multiscale entropy) and in different imaging modalities (e.g., EEG, functional magnetic resonance imaging: fMRI, magnetoencephalography: MEG, functional near infrared spectroscopy: fNIRS), and a thorough review of the advantages and considerations is beyond the scope of the current investigation. Regardless of the operationalization and modality, however, increased neural variability has generally been associated with positive outcomes, including increased integration and segregation of brain areas in development (McIntosh, Kovacevic & Itier, 2008), increased behavioural performance in simple (Garrett, Kovacevic, McIntosh & Grady, 2011) and complex cognitive tasks (Halliday, Mulligan, Garrett et al., 2017; Malin, Pugh, Buis et al., 2018), and with better recovery following TBI (Raja Beharelle, Kovacevic, McIntosh & Levine, 2012). More recent investigations have demonstrated both positive and negative associations in spatially complex analyses across resting-state networks (Bodmer,

Muckschel, Roessner & Beste, 2018; McDonough & Nashiro, 2014; Nomi, Bolt, Ezie, Uddin & Heller, 2017; Wang, Jann, Fan, et al., 2019). These investigations demonstrate that increased neural variability may also be associated with more advanced age in certain networks (e.g., the salience network; Nomi et al., 2017). Similarly, examinations of neural variability in neurodevelopmental disorders (e.g., Easson & McIntosh, 2019; Gonen-Yaacovi, Azari, Shahar et al., 2016; Nomi, Schettini, Voorhies, Bolt, Heller & Uddin, 2018) have demonstrated positive associations between neural variability and clinical symptoms in Autism Spectrum Disorder (Easson & McIntosh, 2019), as well as ADHD (Gonen-Yaacovi et al., 2016; Nomi et al., 2018). With respect to the various domains of EF, neural variability appears to benefit attention switching (Armbruster-Genc, Ueltzhoffer & Fiebach, 2016; Grundy, Barker, Anderson & Shedden, 2019) and cognitive interference (Halliday et al., 2017); however, it may have a detrimental impact on response inhibition (Armbruster-Genc et al., 2016).

3.2.2. Present Study

In spite of recent, promising demonstrations of neural variability as a measurement technique sensitive to novel aspects of brain function, its sensitivity to the neurocognitive benefits of athletic activity (e.g., increased synaptogenesis) and to the mechanisms of mTBI (e.g., diffuse axonal injury) remain unexplored. In theory, neural variability should be one mechanism common to both phenomena (i.e., athletic activity and mTBI) that may help account for some of the cognitive behavioural performance differences that are consistently seen in these populations. This study sought to examine how long-term engagement in competitive athletic activity influences EF and how this is impacted in the face of mTBI, using both behavioural and electrophysiological IIV.

Primary questions included (1) whether there are differences in the magnitude of electrophysiological IIV between athletes, non-athletes and athletes with prior mTBI, (2) whether these differences are uniform, or whether they differ based on sub-components of EF, (3) whether electrophysiological IIV is associated with behavioural performance and/or self-reported symptoms, and (4) whether electrophysiological IIV is uniquely predictive of cognitive status, above and beyond standardized assessment measures.

3.3 Method

3.3.1. Participants

This investigation employed data collected from 77 young adults (18-25 years of age), who were recruited through the University of Victoria's research participation platform, as well as presentations to various varsity athlete teams. For the purposes of reporting results, the term concussion is used in lieu of mTBI. We hold the opinion that all concussions are classified as mTBI, but that not all mTBIs are concussions. Participants were screened for major medical, neurological and mental health conditions and then categorized as either sedentary controls (n=33, 21 females), athletes without concussion (n=23, 11 females) or athletes with concussion (n=21, 11 females) on the basis of their self-reported levels of activity engagement. Sedentary controls were classified as those who did not engage in regular aerobic physical activity (e.g., running, going to the gym), with exclusion set to no more than 30 minutes of exercise per week. Participants were classified into the athlete groups on the basis of current participation in one or more varsity sports, or sports with equivalent training and competitive levels (recreational athletics were excluded). The group for athletes with concussion was comprised of athletes who had sustained at least one probable concussive event, without

history of moderate to severe TBI. Participants reported a range of 1-5 concussions (median 1.5), with 59% experiencing at least one instance of loss of consciousness. There was an average of 2.1 years (min = 3 months; max = 5 years; SD=1.7) between participants' most recent concussion and their date of testing.

3.3.1. Electroencephalogram Recordings

Electroencephalogram recordings were obtained from a 64-channel system, with 36 scalp electrodes following 10-20 configuration for efficiency, using Brain Vision Recorder software (Version 1.3, Brainproducts, Munich, Germany). During recording, EEG data were referenced to the average voltage across channels (sampled at 250 Hz) and were amplified (Quick Amp, Brain products). Post-processing included bandpass filtering (0.1 - 40 Hz), referencing and ocular correction (0.5 - 35 mV), as well as baseline correction. For the purposes of deriving variability estimates, segmentation of the EEG data was based on 400 msec from the onset of each stimulus.

3.3.3. Measures

Participants were tested individually in a quiet room free of distractions using a fixed battery of tests, presented in a counterbalanced order. For the purposes of this investigation, only the measures of interest are reported. Figure 3.1 depicts a graphic representation of the computerized tasks.

Go/No-Go. This task was designed to measure inhibitory control. Participants were first presented with a block of 50 trials, comprised of individual letters and were asked to respond to each letter as quickly as possible using a keyboard button. Following this, participants were presented with 150 trials and were instructed to respond to each letter as quickly as possible, but to refrain from responding to a target letter (i.e., "j").

Response latency was recorded for each key press. In total, participants were presented with 116 "go" trials and 34 "no-go" trials. Trials consisted of 700 msec of stimulus, followed by 700 msec of interstimulus interval that was jittered to prevent anticipatory responding. Participants can be correct by either accurately responding to the target letters ("hit") or by accurately refraining from responding to letter "j" ("correct rejection"). Similarly, participants can be incorrect by either inaccurately responding to letter "j" ("false alarm") or failing to respond to a target letter ("miss").

Switch Task. This task was designed to measure attention switching. Participants were presented with individual numbers on the screen and were asked to identify as quickly as possible whether the number was odd or even (Logan & Bundesen, 2004). Following two blocks of 50 trials, participants then completed four blocks of 80 trials in which 11 of the trials were presented with a box around them. In these trials, participants are asked to identify as quickly as possible whether the number was greater than or lesser than 5 using the same keyboard buttons. Trials consisted of an unlimited stimulus duration that terminated upon participant response, followed by 1,000 msec of interstimulus interval.

N-Back. This task was designed to measure working memory. Participants were presented with individual letters on the screen and were asked to identify as quickly as possible whether the letter was identical to the letter that was presented 2 or 3 trials ago. Participants were presented with 4 blocks of 75 trials each, grouped into either a 2- or 3-

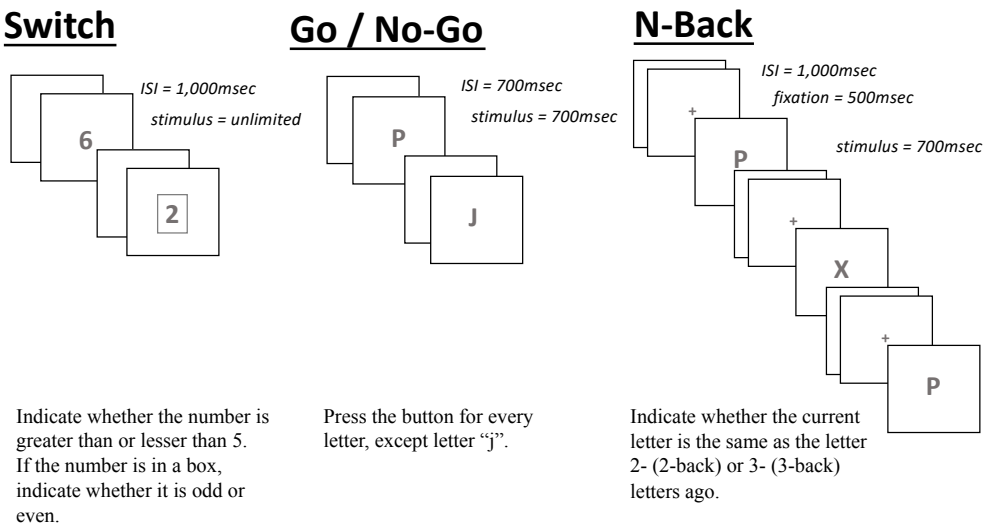

Figure 3.1. Graphical depiction of the Switch, Go/No-Go and N-Back tasks employed in the current study. ISI=inter-stimulus interval.

back condition (4 blocks in total). Trials consisted of 700 msec of stimulus, followed by 1,000 msec of interstimulus interval and then a fixation cross of 500 msec.

Behavior Rating Inventory of Executive Function (BRIEF). The BRIEF questionnaire was completed to measure self-reported difficulties with executive functioning (Gioia, Isquith, Guy & Kenworthy, 2000). The questionnaire provides composite scores of behavioural (e.g., self-monitoring), emotional (e.g., emotional control) and cognitive (e.g., attention shifting) regulation, in addition to individual facets within each domain and shows excellent psychometric properties (e.g., validity, reliability).

The Post-Concussion Symptom Scale (PCSS). The PCSS questionnaire (Lovell & Collins, 1998) was completed by the athletes with concussion to measure cognitive, affective, somatic and sleep related symptoms associated with concussion. Factor analytic research suggests that a 4-factor solution (cognitive-fatigue-migraine, affective, somatic,

and sleep) provides the best model fit in individuals with a sport-related concussion (Kontos, Elbin, Schatz et al., 2012).

3.3.4. EEG Variability Computation

Variability estimates in the electrophysiological recordings (EEG_{SD}) were operationalized using intraindividual standard deviations (ISDs), derived per trial across a 400 msec window following stimulus onset within the tasks, for each electrode site, using bespoke software written in Matlab (2015a). A window of 400 msec was chosen to allow for the event-related potential (ERP) components associated with each of the tasks, which are known to occur within this time frame. Specifically, the N200 component is associated with inhibition and the P300 component is associated with updating working memory and attention switching (George & Coch, 2011; Falkenstein, Hoormann & Hohnsbein, 2002; Sussman, Winkler & Schroger, 2003). The selection of a uniform window of 400 msec therefore offers a liberal window within which to capture the components and allows for a comparison of findings between the constructs of interest. Outliers were identified as values greater than 3 SD from an individual's mean across all channels, with improbable values imputed within-persons, prior to derivation of EEG_{SD}. Outliers were further identified as values greater than 3 SD from the group average, per condition type, which were subsequently deleted listwise. Effects were initially analyzed whole-brain (i.e., averaged across all electrodes), at midline electrode sites, based on previous findings (Karayanidis & Jamadar, 2014) and over frontoparietal electrode sites, given the heavy involvement of the frontoparietal network on executive control (Cisek & Kalaska, 2010).

3.3.5. Behavioural Variability Computation

Intraindividual variability in behavioural performance was operationalized using the residualized intraindividual standard deviation (rISD) approach (Hultsch, MacDonald, Hunter, Levy-Bencheton & Struass, 2000), which partials systematic within- (i.e., trial) and between-subject (e.g., age) sources of variance in mean RT. This was computed for each of the three computerized tasks.

3.4 Results

3.4.1. Group Differences in Self-Reported Executive Functioning and Post-Concussive Symptoms

Between-group differences were observed in self-reported difficulties on BRIEF sub-scales for shifting ($F(2,72)=3.487$, $p<.05$), working memory ($F(2,72)=3.547$, $p<.05$), and organization of materials ($F(2,72)=3.498$, $p<.05$). Post-hoc comparisons using Tukey's HSD confirmed that the athletes with concussion reported more difficulties relative to athletes without concussion in terms of shifting ($p<.05$) and working memory ($p<.05$), and more difficulties with organization relative to sedentary controls ($p<.05$). Figure 3.2 depicts these results. Athletes with concussion reported an average score of 10.0 (± 9.1) on the PCSS. Figure 3.3 depicts the average rating per item. Given the nature of the scale, only the athletes with concussion provided ratings.

3.4.2. Group Differences in Task Performance

Group differences in behavioural performance were examined for measures of accuracy, mean response time and variability in response time (based on rISD) (Table 3.1). Data were initially screened for patterns that would suggest poor understanding of or poor engagement with the tasks, resulting in 2 cases discarded from the Switch task. In

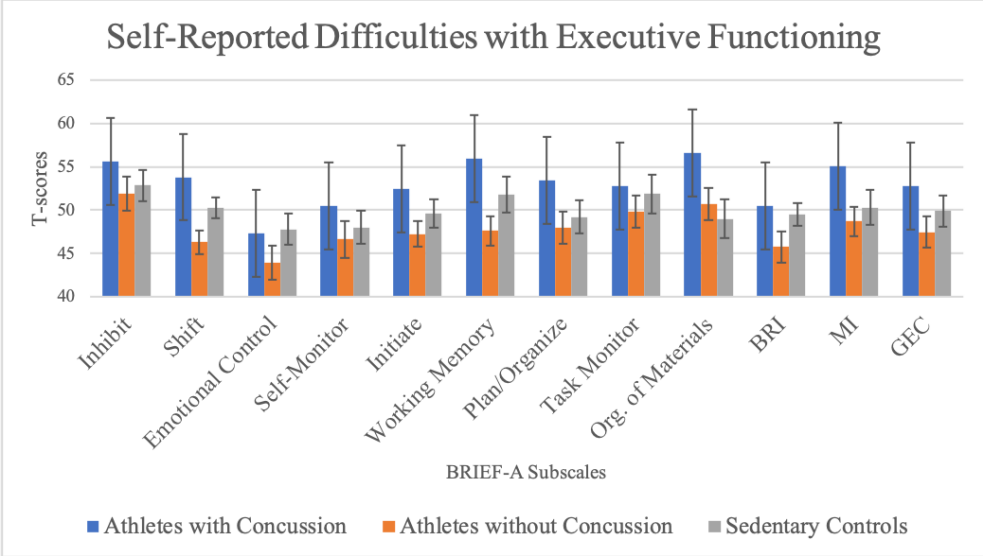

Figure 3.2. Group differences on the Behavior Rating Inventory of Executive Functioning (BRIEF).

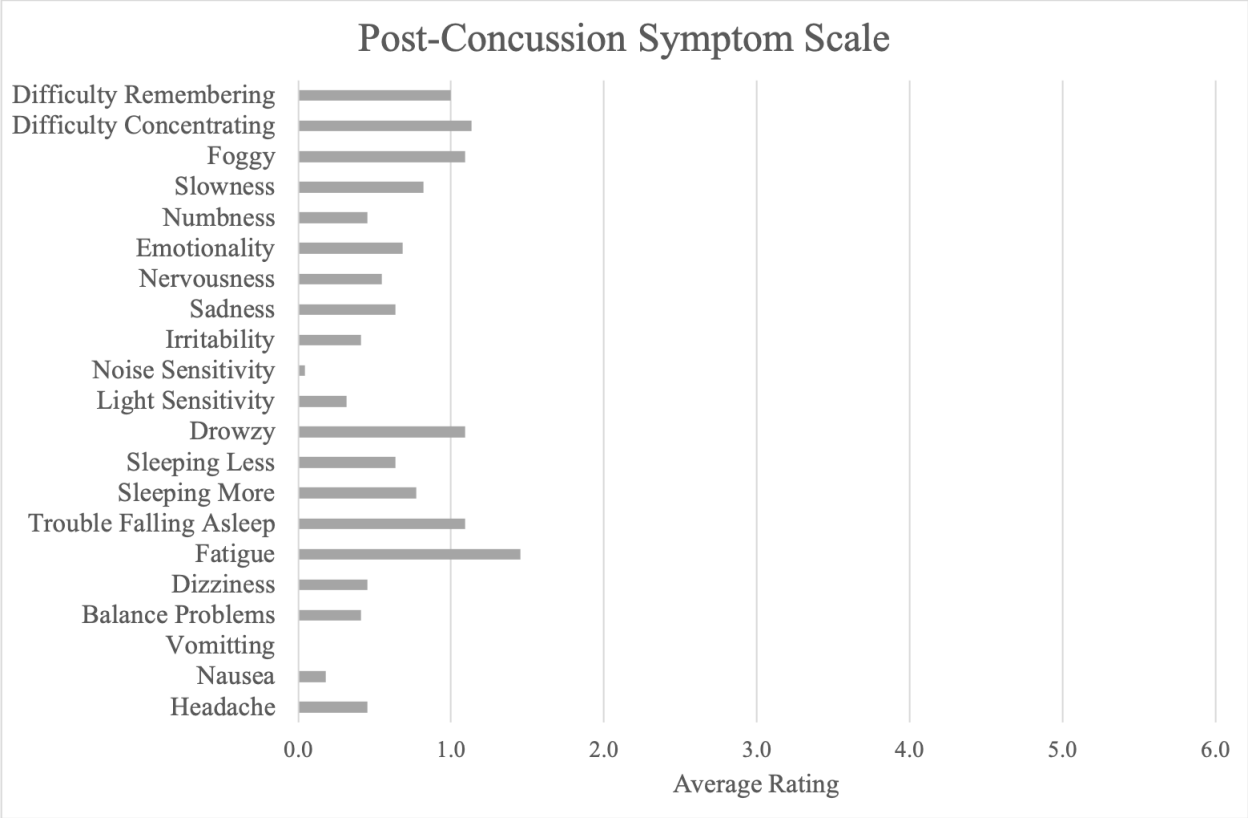

Figure 3.3. Average ratings on the Post-Concussion Symptom Scale (PCSS). Scores were summed across all items.

Table 3.1. Average performance levels across tasks, within each group. RT=response time; rISD=residualized intraindividual standard deviation; GNG=Go/No-Go.

		Athletes with concussion	**Athletes without concussion**	**Sedentary Controls**
Switch Trials	RT rISD	7.80 ±6.92	6.78 ±3.46	7.23 ±5.04
	RT Mean	0.94 ±0.39	0.86 ±0.26	0.89 ±0.33
	Accuracy	0.92 ±0.15	0.95 ±0.14	0.96 ±0.04
Repeat Trials	RT rISD	8.22 ±6.73	7.24 ±3.70	7.39 ±4.50
	RT Mean	0.74 ±0.23	0.70 ±0.16	0.70 ±0.17
	Accuracy	0.92 ±0.13	0.94 ±0.12	0.96 ±0.03
2-Back Trials	RT rISD	9.44 ±1.52	9.36 ±2.14	9.11 ±1.97
	RT Mean	0.47 ±0.05	0.48 ±0.05	0.48 ±0.06
	Hits	31.79 ±10.53	29.06 ±10.49	29.87 ±11.75
	Correct Rej	99.68 ±2.08	99.61 ±3.27	99.67 ±2.29
3-Back Trials	RT rISD	9.53 ±1.22	9.36 ±1.74	9.03 ±1.75
	RT Mean	0.48 ±0.04	0.48 ±0.05	0.48 ±0.06
	Hits	21.00 ±9.81	21.00 ±9.62	24.60 ±9.83
	Correct Rej	96.26 ±3.23	94.11 ±5.60	95.20 ±3.51
GNG	RT rISD	8.60 ±1.72	8.30 ±1.79	9.28 ±2.05
	RT Mean	0.37 ±0.03	0.37 ±0.02	0.38 ±0.03
	Hits	115.48 ±0.87	115.50 ±0.76	114.94 ±2.24
	Correct Rej	28.24 ±2.65	27.20 ±3.21	27.18 ±3.46

deriving the RT estimates (mean, rISD), response times that were improbably fast (<150 msec) were treated as missing. Trials greater than 3 SD above an individual's mean were considered unrepresentative and were also treated as outliers. RT estimates were subsequently computed across correct trials for each condition separately. This method of including correct trials only is commonly employed in IIV methodology in order to circumvent the potential influence of incorrect trials (e.g., Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Halliday et al., 2016). The main effects between group status and cognitive performance were not significant. There were trends in the GNG data

such that the two groups of athletes were slightly less variable than the sedentary controls.

3.4.3. Univariate Analyses

Neural Variability During Inhibition. Given our a priori hypotheses regarding expected directional effects, we employed one-tailed tests for specific, planned comparisons. Effects that were significant one-tailed are specified; otherwise, the reported p-values reflect two-tailed hypotheses. Group differences in EEG_{SD} were observed at the whole brain level during false alarm trials ($F(2,77)=8.099$, $p<.001$), with the athletes with concussion exhibiting less variability than athletes without concussion and sedentary controls (Figure 3.4). No group differences were observed during hits ($F(2,77)=0.639$, $p=.53$) or correct rejections ($F(2,77)=0.509$, $p=.60$). Group differences also failed to emerge in terms of select midline and frontoparietal channels in each of the three response types (i.e., hits, false alarms, correct rejections).

Neural Variability During Working Memory. No group differences were observed during hits (2-back: $F(2,73)=0.477$, $p=.62$; 3-back: $F(2,72)=0.828$, $p=.44$), false alarms (2-back: $F(2,73)=0.621$, $p=.54$; 3-back: $F(2,72)=0.917$, $p=.40$), or correct rejections (2-back: $F(2,72)=0.299$, $p=.74$; 3-back: $F(2,72)=0.748$, $p=.48$). Group differences failed to emerge in terms of select midline and frontoparietal channels during hits and correct rejections; however, there was a main-effect of group status on variability at Cz during false alarms in the 3-back condition ($F(2,73)=2.901$, $p=.06$); however, this effect was only reliable one-tailed. Although post-hoc comparisons using Tukey's test did not pass the threshold for significance, athletes with concussion exhibited a trend for less variability relative to the athletes without concussion and sedentary controls.

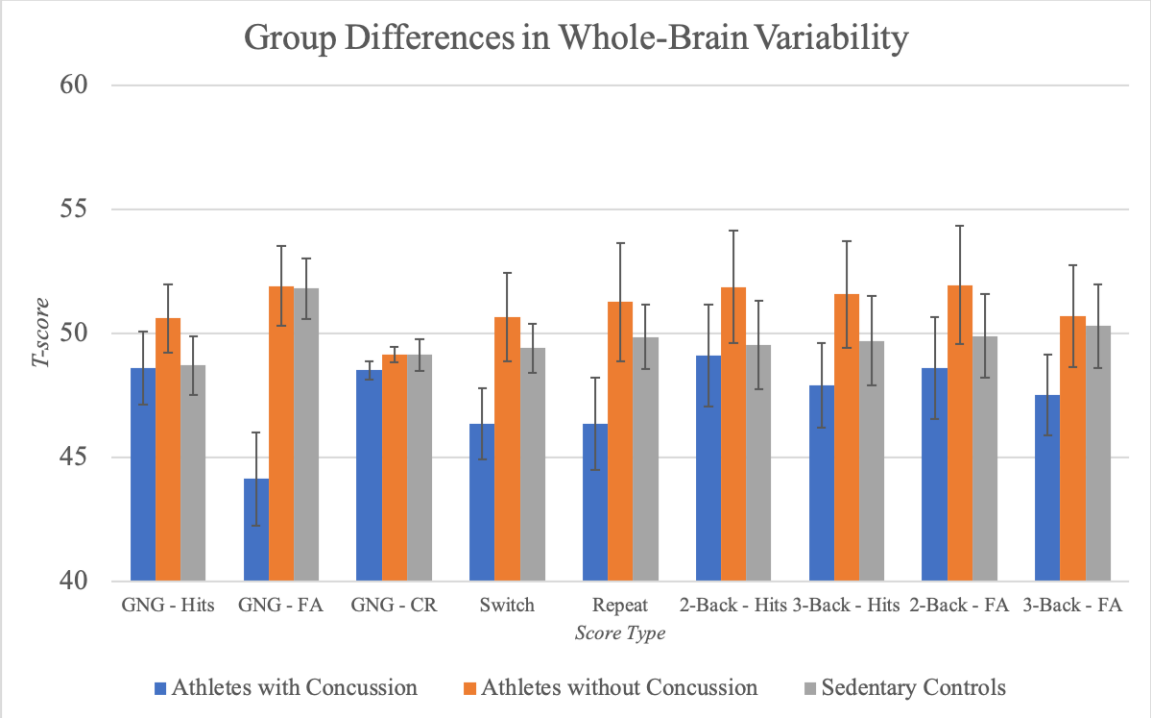

Figure 3.4. Average whole brain variability in electrophysiological recordings across trial types. GNG = Go/No-Go; FA = false alarms; CR = correct rejections.

Neural Variability During Switching. Group differences in EEG_{SD} were observed at the whole brain level during switch trials ($F(2,64)=2.485$, $p=.09$); however, this effect was only reliable one-tailed. Although post-hoc comparisons using Tukey's test did not pass the threshold for significance, athletes with concussion exhibited a trend for less variability relative to the athletes without concussion and sedentary controls (Figure 3.4). No group differences were observed during repeat trials.

In terms of midline channels, group differences were observed exclusively in Fpz ($F(2,66)=3.270$, $p<.05$), with athletes with concussion exhibiting significantly less EEG_{SD} relative to the sedentary controls ($p<.05$) and with a similar trend relative to the athletes without concussion. In frontoparietal channels, significant group differences were observed in F7 during switch trials $F(2,63)=3.260$, $p<.05$), with athletes with concussion

exhibiting significantly less EEG_{SD} relative to the sedentary controls ($p<.05$) and with a similar trend relative to the athletes without concussion that was not significant, based on Tukey's post-hoc comparison. Group differences were also observed in FC5 during switch trials $F(2,64)=2.869$, $p=.06$), with athletes with concussion exhibiting less EEG_{SD} relative to the athletes without concussion; however, this effect was only significant one-tailed. A comparable trend was observed in a similarly positioned electrode over the right frontal scalp region (F4: $F(2,64)=2.456$, $p=.09$), with athletes with concussion exhibiting less EEG_{SD} during switch trials relative to both sedentary controls and athletes without concussion; however, this effect was only significant one-tailed (Figure 3.5). During repeat trials, group differences were observed in FC6 ($F(2,64)=2.457$, $p=.09$), with athletes with concussion exhibiting less EEG_{SD} relative to the athletes without concussion; however, this effect was only significant one-tailed.

3.4.4. Cross-Modality Associations and Model Sensitivity

Correlations Within Constructs. Self-reported difficulties with inhibition (BRIEF-Inhibition subscale) were significantly correlated with GNG Misses ($r=.58$, $p<.01$) based on behavioural performance in the athletes with concussion; however, these effects were not significant in the other groups. Greater levels of subjective difficulties with inhibition corresponded with greater attention lapses, indexed by missing trials. Similarly, EEG_{SD} during hit trials was significantly correlated with rISD during hit trials; however, this effect was only found in the athletes with concussion ($r=-.42$, $p<.05$). This suggests that a greater dynamic range of the electrophysiological response is associated with more consistent performance, but only in the group of athletes with concussion.

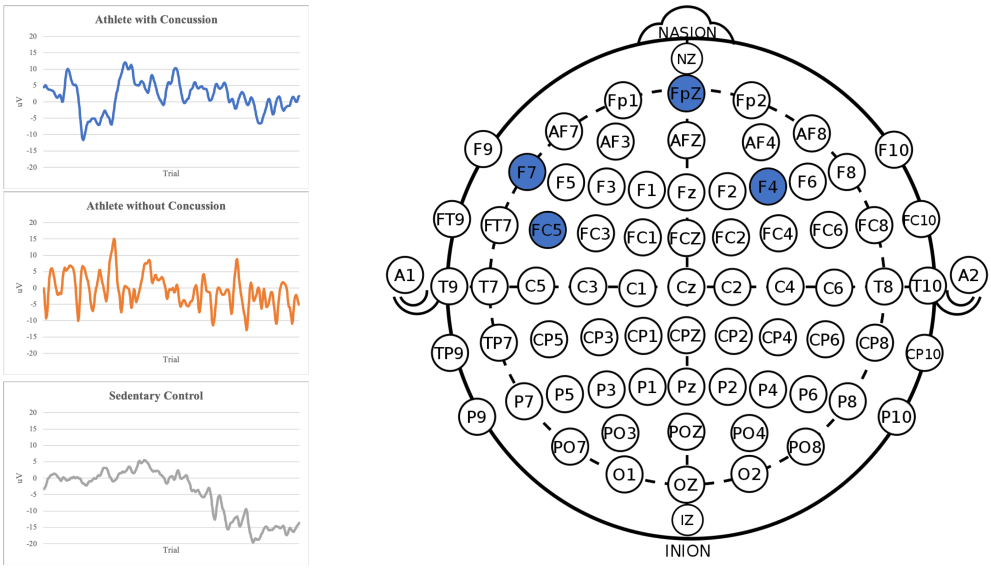

Figure 3.5. Group differences in electrophysiological variability in frontoparietal channels. *Right*: Blue channels represent areas where athletes with concussion exhibited significantly lower variability during switch trials relative to athletes without concussion and/or sedentary controls. *Left*: The fastest correct switch trials are depicted in channel F7 for select exemplars from each group.

Number of concussions was also negatively correlated with EEG_{SD} during FA trials (r=-.48, p<.05), such that more concussions were associated with reduced dynamic range of the electrophysiological response during false alarms.

Self-reported difficulties with working memory (BRIEF-Working Memory subscale) were significantly correlated with 3-Back False Alarms (r=.53, p<.05) and Correct Rejections (r=-.53, p<.05) in the athletes with concussion; however, these effects were not significant in the other groups. Greater levels of subjective difficulties with working memory corresponded with poorer performance in the more demanding working memory task. No significant correlations were observed between EEG_{SD} and the behavioural performance scores. Significant correlations were observed between scores on the BRIEF-Working Memory scale and EEG_{SD} during 2-back false alarms (r=.46, p

<.05) and correct rejection (r=.49, p <.05) in the athletes with concussions only. Contrary to expectation, greater levels of subjective difficulties with working memory corresponded with *greater* dynamic range of the electrophysiological response during false alarm and correct rejection trials. EEG_{SD} during 3-back correct rejection trials was negatively correlated with PCSS ratings of fatigue (r=-.46, p <.05), drowsiness (r=-.51, p <.05) and slowness (r=-.48, p <.05). PCSS drowsiness subscale scores were also negatively correlated with EEG_{SD} during 3-back false alarm trials (r=-.45, p <.05). A greater presence of fatigue-related post-concussive symptoms was reliably associated with a reduce dynamic range of the electrophysiological response during working memory. No reliable cross-modal associations were found in terms of attention switching.

Multinomial Regression. Multinomial regression models were employed to examine the predictive utility of EEG_{SD} magnitude in group classification, separately for each construct (i.e., switching, updating and inhibition). In each model, the whole-brain EEG_{SD} estimate was entered simultaneously with the corresponding BRIEF subscale.

EEG_{SD} during switch trials was not reliably predictive of the athletes without concussion group status (p>.05); however, independent of self-reported difficulties with attention shifting, increased EEG_{SD} during switch trials was associated with *reduced* likelihood of being classified as an athlete without concussion (OR = 0.87, CI = 0.76, 0.99, p < .05, $\chi 2(4) = 10.608$ p < 0.05, Nagelkerke's R-squared = 0.18). For every T-score unit increase in EEG_{SD} (approximately 1/10 of a standard deviation), the likelihood of being classified as an athlete with concussion decreased by 13%. In contrast, BRIEF-Shift subscale scores were not reliably predictive of group status in either athlete group.

EEG_{SD} during GNG false alarm trials was not reliably predictive of the athletes without concussion group status (p>.05); however, independent of self-reported difficulties with inhibition, increased EEG_{SD} during GNG false alarm trials was associated with *reduced* likelihood of being classified as an athlete with concussion (OR = 0.87, CI = 0.79, 0.95, $p < .05$, $\chi 2(4) = 17.803$, $p < 0.001$, Nagelkerke's R-squared = 0.24). For every T-score unit increase in EEG_{SD} (approximately 1/10 of a standard deviation), the likelihood of being classified as an athlete with concussion decreased by 13%. In contrast, BRIEF-Inhibit subscale scores were not reliably predictive of group status in either the concussed or athletes without concussion.

EEG_{SD} during 3-back false alarm trials was not reliably predictive of the athletes without concussion group status (p>.05); however, independent of self-reported difficulties with inhibition, increased EEG_{SD} during 3-back false alarm trials was associated with *reduced* likelihood of being classified as an athlete with concussion (OR = 0.91, CI = 0.84, 0.99, $p < .05$, $\chi 2(4) = 12.979$, $p < 0.05$, Nagelkerke's R-squared = 0.20). For every T-score unit increase in EEG_{SD} (approximately 1/10 of a standard deviation), the likelihood of being classified as an athlete with concussion decreased by 9%. In contrast, BRIEF-Working Memory subscale scores were not reliably predictive of group status in either the athletes with concussion or the athletes without concussion. Similar trends were observed when employing 3-back hits and 3-back correct rejection EEG_{SD} estimates, alongside BRIEF-Working Memory subscale scores. In these models, both predictors were associated with being classified as an athlete with concussion; however, the significance was one-tailed. When employing scores from the 2-back condition, the models failed to reach significance.

3.5. Discussion

Mild traumatic brain injuries sustained during sport participation are a deterrent to the otherwise plethora of benefits associated with athleticism, including physical (e.g., strength, agility), health (e.g., cardiovascular) and neurocognitive (e.g., inhibitory control). The likelihood of significant long-term ramifications of mTBI is an area of active investigation and part of this challenge relates to the fact that mTBIs are heterogeneous and multifaceted, and are therefore difficult to study. Objective assessment measures of neurological function that can be translated out of laboratory settings and into clinical practice represent a promising avenue to help address this gap (Conley et al., 2019). Comprehensive neuropsychological testing for individuals with persistent post-concussive symptoms may be useful to disentangle deficits in neurocognitive functioning attributable to an mTBI versus those attributable to (a) the associated psychological trauma (e.g., adjustment disorder), (b) a pre-existing neurodevelopmental (e.g., specific learning disorder) or mood disorder (e.g., generalized anxiety disorder), and/or (c) the overlap and interactions between these various etiologies as it relates to cognitive dysfunction. Given the etiological uncertainty however, it is often difficult to conclude definitively whether an mTBI has caused meaningful and long-lasting changes in neural function (Terry, Mewborn & Miller, 2019). Moreover, there is incomplete understanding as to the ways in which mTBIs can alter neural function in the first place. Intraindividual variability in neural activity is an emerging metric of brain health that has not been directly examined in the context of mTBI, in spite of promising demonstrations thus far. Therefore, this study sought to explore whether neural variability would be sensitive to the impacts of mTBI in varsity-level athletes, and whether it would be sensitive to the

"athletic advantage" of athletes without mTBI, relative to individuals living a more sedentary lifestyle.

Our results reveal differences in EF at multiple levels in athletes with a history of mTBI. In terms of subjective reporting, athletes with a history of mTBI reported greater difficulties with attention switching, working memory and organization of materials, in spite of relatively low levels of post-concussive symptoms. Although no group differences were observed in terms of behavioural performance during measures of shifting, working memory or inhibition, athletes with prior mTBI exhibited less electrophysiological variability during false alarm error trials relative to the other two groups during inhibitory control; however, this difference was only observed at the macro, whole-brain level and was not reliable in terms of select midline or frontoparietal channels. During working memory, this same effect was observed in a centrally positioned electrode, such that Athletes with prior mTBI showed less electrophysiological variability when committing false alarms. During attention switching trials, athletes with prior mTBI exhibited less electrophysiological variability at both the macro, whole-brain level and in terms of select channels, recording from bilateral regions of frontal cortex. These findings are in keeping with research that has demonstrated abnormalities in the electrophysiological response of individuals with mTBI during executive functioning (Broglio et al., 2011; Brush et al., 2018) and resting state paradigms (Conley et al., 2019; Slobounov et al., 2009). This investigation did not reveal reliable differences between athletes without concussions and sedentary controls. Previous investigations that have revealed such differences (i.e., the "athletic advantage") have done so using amplitude and latency measures of the electrophysiological signal in

specific executive processes, in more homogenous groups of athletes (e.g., Bianco et al., 2017). In contrast, our sample spanned a variety of internally- and externally-paced sports, and thus the executive-specific advantages of sport participation may not have been as apparent. These caveats notwithstanding, we did observe consistent trends that would suggest a slight advantage for the athletes without mTBIs, in both the behavioural and electrophysiological markers; however, these effects should be interpreted with caution. Given that the age range of the sample coincided with EF development reaching peak maturity, it is possible that the advantages of athleticism may not have been as apparent relative to different developmental periods (e.g., childhood, late-life).

Several notable associations were observed between electrophysiological variability and other meaningful indicators of neurocognitive function. Greater inconsistency in behavioural performance during sustained attention trials (i.e., hit trials) was associated with a restricted dynamic range of electrophysiological variability in the athletes with mTBI, but not in the other groups. As a proxy for the degree of possible neurological changes associated with mTBI, number of concussions was associated with reduced electrophysiological variability while error monitoring during inhibitory control. Greater self-reported fatigue, drowsiness and slowness was also associated with reduced electrophysiological variability during working memory. In terms of group classification, the whole-brain electrophysiological variability markers for attention switching and error monitoring during inhibitory control and working memory (3-back) were uniquely

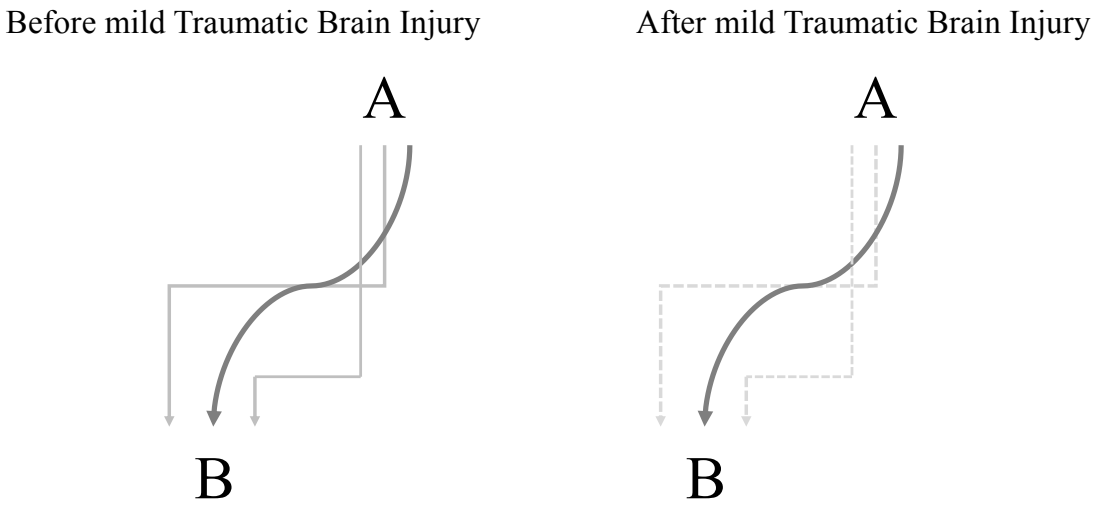

Figure 3.6. Theoretical depiction of a neural network, with inputs from node A to B sent along one of three paths. The thick, dark-grey line represents the strongest and most typically employed path, with the thin, light-grey lines representing alternate paths that may be primed as alternates in a given situation. Prior to a mild traumatic brain injury, these alternate connections may contribute to increased variability in the recording of functional brain activity. After a mild traumatic brain injury, these alternate connections may be damaged and no longer viable.

predictive of status in the athletes with concussion group only, such that greater variability was protective against classification. Importantly, self-reported difficulties in these areas (i.e., BRIEF-Shift, Inhibit and Working Memory subscales scores) were not reliably predictive of group status.

On mass, these findings suggest that mTBI attenuates the dynamic range of the brain's ready state. Whereas evidence exists to suggest that athleticism enhances aspects of executive functioning (Bianco et al., 2017; Muraskin et al., 2015), presumably by way of optimizing synaptic connections, it appears that it may not buffer against the neurocognitive ramifications of mTBI entirely. If long-term engagement in executively demanding athletics increases synaptic connections within and between associated neural networks, then the brain may prime multiple pathways in the context of environmental uncertainty, thereby increasing its dynamic range (Figure 3.6). Diffuse axonal injury may

instead disrupt these alternate connections, thereby attenuating the dynamic range of neural activity recorded from scalp electrodes (Figure 3.6).

3.5.1 Limitations and Future Directions

Although participants were screened for premorbid, neurologically based confounding conditions (e.g., Specific Learning Disorder), this investigation was unable to disentangle other potential confounding variables that may have influenced executive performance (both in terms of the associated electrophysiology and self-reported difficulties), such as subclinical sleep or mood difficulties. Future studies could consider examining the impacts such factors may have on executive functioning, in the context of mTBI, to better assess whether attenuated neural variability is driven by neurological mechanisms (e.g., axonal shearing leading to restricted dynamic range) relative to other factors. To further disentangle the neuroprotective benefits of athleticism from the ramifications of mTBI, future studies might consider including individuals living sedentary lifestyles who have sustained mTBIs alongside those who have not, in addition to athletes who have and have not sustained mTBIs. To retain an emphasis across subcomponents of executive functioning and intraindividual variability in neural and behavioural functioning, this study did not examine additional behavioural score types that may be of relevance (e.g., load effect for the N-Back task, switch costs for the Switch task, d-prime for the Go/No-Go task). Future studies investigating executive functioning with related tasks may benefit from an inclusion of these scores.

This study employed a relatively simple metric of neural variability; however, future studies should consider employing alternate metrics, such as a multiscale entropy or mean square successive differences, in order to assess the sensitivity of these metrics

with respect to mTBI pathophysiology. A comparison across metrics would be especially valuable, as the field of mTBI research and clinical practice continues to search for a more standardized approach within EEG assessment methodology (Conley et al., 2019). Although diffuse axonal injury is a commonly accepted injury mechanism for mTBI, in order to better understand the structural origins behind attenuated neural variability in mTBI and other clinical populations, future studies could consider combining structural (e.g., diffusion tensor imaging) and functional imaging to better address these mechanistic questions.

3.5.2 Conclusion

The post-acute ramifications of mTBI can be multifaceted, with impacts on executive functioning most commonly reported in terms of cognitive and self-regulatory challenges. Neural variability is an emerging metric that captures that brain's dynamic range and readiness to respond to environmental demands. Findings from this study suggest that neural variability captured in the electrophysiological response during performance measures of executive functioning is reduced following mTBI up to 2 years later. Further, neural variability is sensitive to mTBI status in athletes, relative to self-report measures of executive functioning. Neural variability may hold promise as an objective assessment metric in the field of mTBI, spanning any number of applications from assessment of injury severity, tracking of treatment effects, and informing sport policy on matters such as return to play, or contact policy.

Chapter 4

Dispersion Across a Profile of Gait Indicators is Associated with Increased Likelihood of Cognitive Impairment

4.1 Abstract

Background: Declines in gait function occur contemporaneously with cognitive declines in late-life. Variability in both cognitive and gait function are associated with a range of deleterious outcomes, yet the selection of gait parameters and the operationalization of variability within these parameters remains heterogeneous across studies. This study investigated whether dispersion, defined as variability *across* a profile of gait indicators (spatial, temporal, variability), was associated with likelihood of cognitive impairment, and whether any observed association was further buffered by engagement in protective lifestyle activities. Method: Community-dwelling older adults were recruited and classified as healthy controls (n=42), all-cause Mild Cognitive Impairment (MCI: n=35), or all-cause dementia (n=8) on the basis of neuropsychological assessment, including clinical interview. Participants completed single- and dual-tasking gait conditions, in addition to measures of neuropsychological function and lifestyle activities. Results: Greater dispersion across the profile of gait indicators during dual-tasking was associated with increased likelihood of dementia classification, with this association amplified at greater levels of dispersion in neuropsychological test performance. Social activities were protective against dementia classification, while cognitive activities were protective against MCI classification. Conclusions: Indexing dispersion across a profile of diverse indicators may facilitate both a convenient approach for multivariate analysis of the many disparate gait measures commonly reported in the literature, while also providing a sensitive index of cognitive status.

4.2 Introduction

Greater intraindividual variability (IIV) in late-life has been consistently linked with deleterious health outcomes, spanning a range of measures including response time (Halliday, Stawski & MacDonald, 2016), gait (Rosano, Brach, Studenski, Longstreth Jr. & Newman, 2007), blood pressure (Jennings, Allen, Gianaros, Thayer & Manuck, 2015), neural activity (Garrett et al., 2013) and performance consistency across tests of neuropsychological function (Mella, Fagot & de Ribaupierre, 2016). This has led to the supposition that IIV represents at least a global marker of central nervous system integrity in late-life, and under certain circumstances, a more precise index of pathophysiological processes that may not otherwise surface under conventional assessment parameters. For example, reduced white matter integrity has been uniquely linked to greater response time inconsistency (Nilsson, Thomas, O'Brien & Gallagher, 2014; Walhovd & Fjell, 2007) and to greater inconsistency in performance across neuropsychological tests (Halliday, Gawryluk, Garcia-Barrera & MacDonald, 2019). For assessments of cognitive function, IIV is typically operationalized within-persons across multiple assessments for a single task (e.g., response time inconsistency), with the utility of this approach well-represented in the cognitive aging literature (e.g., Hultsch, Strauss, Hunter & MacDonald, 2008).

Dispersion is a related operationalization of IIV that is derived within-persons across multiple measures at a single time point (Halliday, Stawski, Cerino, DeCarlo, Grewal & MacDonald, 2018). Dispersion has been comparatively understudied, in spite of notable, promising demonstrations of sensitivity to health outcomes in late-life, including accelerated deterioration of memory and speed performance (Christensen,

Mackinnon, Korten, Jorm, Henderson & Jacomb, 1999), incident dementia (Holtzer, Vergehese, Wang, Hall & Lipton, 2008), greater likelihood of Alzheimer's classification (Halliday et al., 2018) reduced microstructural integrity in several, major white matter tracts (Halliday et al., 2019) and individual differences in demographic, health and performance characteristics (Hilborn, Strauss, Hultsch, & Hunter, 2009; Peters, Graf, Hayden & Feldman, 2005). Dispersion can also be comprised of both accuracy and speed metrics simultaneously, rendering it of potential greater ecological validity in applied settings.

4.2.1 Dual Task Cost during Gait

Much of the impetus for exploring assessment techniques sensitive to neurological insults in late-life, including IIV, stems from a growing need to identify those at greatest risk of accelerated cognitive decline in order to facilitate appropriate supports. Gait represents one such potential marker that is sensitive to early decline in late life. Gait is a proxy for multiple bodily systems (e.g., musculoskeletal, nervous, respiratory, circulatory) (Studenski, Perera, Patel et al., 2011) and is therefore sensitive to various insults with increased prevalence in late-life (e.g., white matter alterations, vascular insults), which may be further influenced by neurodegenerative processes. Gait dual-tasking conditions may be particularly useful for elucidating such processes, which involve gait assessment while an individual is engaged in a cognitively demanding task (e.g., spelling words backwards, counting backwards by 7s). Gait speed during single- and dual-tasking conditions appears to evoke separable networks in the brain, with associations to separable domains of cognitive function (Blumen, Brown, Habeck et al., 2018; Tripathi, Verghese & Blumen, 2019). Whereas processing speed and executive

performance appear more associated with cortical activity elicited during single-tasking, memory performance appears to exhibit stronger links to subcortical activity evoked during dual-tasking (Tripathi et al., 2019). Dual-tasking has been shown to elicit more robust gait changes in older adults with greater risk factors (employing both central tendency and IIV metrics), due to cross-domain resource competition (MacDonald, Hundza, Love, et al., 2017; Schaefer, Huxhold & Lindenberger, 2006). Recently, researchers have examined the prevalence of combined cognitive complaints and slowed gait speed in older adults, giving rise to the notion of Motoric Cognitive Risk Syndrome (MCR) (Verghese, Wang, Lipton & Holtzer, 2013; Verghese, Ayers, Barzilai, et al., 2014). MCR is estimated in approximately 6.5-8% of adults 60 years and older, with certain modifiable lifestyle factors associated with greater risk, including depressive symptoms, sedentariness, and obesity (Verghese et al., 2014). On mass, gait dual-tasking has shown promise in identifying older adults at risk for functional impairments in independent daily living, with more recent studies highlighting unique facets of neural functioning that can be ascertained through the methodology.

The impressive array of spatial and temporal gait indicators represented in the literature and the ease of generating over 40 parameters from the standard GAITRite system (GAITRite; CIR Systems, Sparta, NJ) has rendered the parsimonious assessment of gait more challenging. Factor analytic models suggest that five factors reliably index independent aspects, including pace, rhythm, variability, asymmetry and postural control (Lord, Galna, Verghese, Coleman, Burn & Rochester, 2013). These domains have shown further associations with select cognitive domains, including aspects of executive control associated with pace (Inzitari, Newman, Yaffe, et al., 2007; Lord et al., 2013). Further,

recent meta-analytic evidence suggests that decreased pace is highly associated with cognitive decline and dementia in older adults (Quan, Xun, Chen et al., 2017). Although evidence exists for the orthogonality of these gait factors, the sensitivity of *consistency* across these factors (e.g., the magnitude of dispersion across gait indicators) to cognitive status remains unexplored. Recent evidence suggests that mean and variability-based operationalizations of gait parameters are associated with different functional brain networks in older adults (Lo, Halko, Zhou, Harrison, Lipsitz & Manor, 2017); however, as an indicator of variability, gait dispersion currently remains unexplored.

4.2.2. Cognitive Reserve and Lifestyle Activities

Cognitive reserve (CR) refers to an active process in which the brain copes with damage or disruption by using pre-existing cognitive processing approaches, or by employing compensatory strategies (Stern, 2007). CR is typically contrasted against brain reserve, which refers to passive, structural properties that also buffer the brain against damage or disruption (e.g., total size, neural count, synaptic density) (Stern, 2007). A majority of studies have focused on the protective benefits of educational and occupational attainment, as proxies for CR, against deleterious health outcomes in late life (Stern, 2007). More recently, enriching lifestyle activities have also been linked with CR. Maintenance of cognitive health in late-life is supported by healthy lifestyle activities (Small, Hughes, Hultsch & Dixon, 2007), including cognitive, social and physical activity, healthy diet, low-to-moderate alcohol consumption and lack of smoking (Clare, Wu, Teale, et al., 2017). Recent estimates suggest that the prevalence of Alzheimer's disease could be reduced by 8.3% worldwide in 2050 with appropriate intervention of modifiable risk factors (Norton, Matthews, Barnes, Yaffe, & Brayne,

2014), with the World Health Organization having recently offered a more tangible set of risk reduction guidelines, including cognitive, social and physical activity, as well as dietary recommendations (WHO, 2019). Importantly, older adults with greater CR have shown greater protective benefits of EF and episodic memory against gait speed decline (Holtzer, Wang, Lipton & Verghese, 2012). The extent to which healthy lifestyle activities attenuates dispersion in gait function remains unexplored.

4.2.3 The Present Study

Although dispersion in neuropsychological test performance has been linked with advanced age (Christensen et al., 1999; Halliday et al., 2019) and dementia (Halliday et al., 2018; Holtzer et al., 2008), it has not been examined with reference to gait indicators. Multivariate approaches to examining gait indicators are particularly important, given the number of disparate markers that are actively reported in the gait literature (Commandeur, Klimstra, MacDonald et al., 2018) and the fact that multivariate indicators may be more reliable and sensitive to cognitive status and outcome. This study sought to examine what happens in late life as executive and motor control systems become affected by neurodegenerative process. Specifically, primary research questions included (1) whether gait dispersion can be used to reliably differentiate cognitive group status (healthy controls vs. MCI vs. dementia), (2) whether there is an even greater likelihood of cognitive impairment associated with elevated gait dispersion in older adults who also show elevated cognitive dispersion, and (3) whether lifestyle factors moderate any of the observed associations. *A priori* hypotheses included (a) that elevated dispersion during dual-tasking gait conditions would be would be associated with impaired cognitive status, (b) that the likelihood of cognitive impairment classification would increase for

individuals who also demonstrated greater cognitive dispersion, and (c) that increased lifestyle engagement would attenuate the association between dispersion and impaired cognitive status.

4.3 Method

4.3.1. Participants.

Data were collected from community-dwelling older adults from Victoria, BC, Canada participating in The PREVENT Study; a cross-sectional multi-factorial (e.g., biological, physiological, environmental) investigation of risk factors for MCI and probable dementia. Participants were recruited through descriptions of the study in various news outlets and presentations to community groups; individuals aged 65 years and older were sought in an effort to target late-onset pathology. Exclusionary criteria for participation focused on factors that could directly result in cognitive deficits or impairment not reflective of emerging neurodegenerative conditions consistent with dementia or its prodrome. These included (a) newly diagnosed psychiatric disturbance within the past year (e.g., Major Depressive Disorder), (b) history of a chronic neurological condition (e.g., Parkinson's disease, brain tumor), (c) episode(s) of cardio- and/or cerebrovascular disease (e.g., heart attack, stroke, heart surgery) within the past year, and (d) other factors that could contribute to changes in cognitive functioning (e.g., head injury, vitamin deficiency). Severe sensory and/or motor impairment (i.e., unable to read newspaper-sized print with glasses, difficulty writing or pressing keys on a keyboard, or unable to hear a normal spoken conversation adequately with the use of a hearing aid) were also used as exclusionary criteria, given the nature of participation.

Table 4.1 presents the demographic and diagnostic characteristics of the sample, by 5-year age stratification.

4.3.2. Cognitive Status Classification

Participants were classified as either healthy control (HC, *n*=42), having MCI (*n*=35) or having probable dementia (*n*=8), based on a standard and objective classification system involving both neuropsychological test scores and clinical judgement. To meet criteria for the HC group, participants were required to (a) score > than -1.0 S.D. in all cognitive domains, and (b) report no subjective memory complaints or impairment in social, occupational or daily functioning. To meet criteria for the MCI group (Petersen, Smith, Waring, Ivnik, Tangalos & Kokmen, 1999; Petersen, et al., 2009), participants were required to (a) score < than -1.0 S.D. in one or more cognitive domains domain, (b) report at least one associated subjective complaint, and (c) report an absence of impairment in social, occupational or daily functioning. To meet criteria for the probable dementia group, consistent with DSM-5 guidelines (APA, 2013), participants were required to (a) score at least -2.0 S.D. in memory and in one other cognitive domain, (b) have subjective or collateral-reported significant declines from previous levels of functioning in both, with (c) these deficits resulting in impairments in social, occupational and/or daily life functioning. Groups were similar in terms of age and number of years of education, with no reliable differences.

4.3.4. Measures.

Neuropsychological Battery. The neuropsychological battery was administered by graduate students in the Neuropsychology stream of the Clinical Psychology program

Table 4.1. Demographic characteristics as a function of age strata.

Age	n	Education (years)	% Dementia	% MCI
65-69	22	16.6	4.5	27.3
70-74	22	16.4	4.5	54.5
75-79	16	13.8	18.8	25.0
80-84	12	14.1	16.7	41.7
85-89	8	15.0	12.5	37.5
90+	5	14.3	0.0	80.0

at the University of Victoria, under the supervision of a registered psychologist. The measures included spanned the following cognitive domains; global cognitive functioning (Modified Mini-Mental State Test (3MS)), auditory attention (WAIS-R Digit Span (Total score)), auditory working memory (WAIS-R Digit Span Backwards), visual memory (Benton Visual Retention Task-BVRT), auditory immediate and delayed memory (Rey Auditory Verbal Learning Task (RAVLT; Total, A6 (short delay), A7 (long delay), executive functioning (WAIS-R Similarities, Trail Making Test B-TMT-B, Mental Alternation Test-MAT), language (Controlled Oral Word Associations Test-COWAT, Animal Naming), visuospatial ability (WAIS-R Block Design), and processing speed (Trail Making Test A-TMT-A, WAIS-R Digit Symbol, Serial Response Time-SRT, Lexical Decision Task). Table 4.2 displays the corresponding test measures. Normative data from the Canadian Study of Health and Aging (CSHA) were used to derive T-scores for the WAIS-R short-form subtests, RAVLT interference (A6) and long-delay (A7), BVRT, COWAT (using CFL) and Animal Naming. Normative data from the Mayo's Older Americans Normative Studies (MOANS) were used to derive T-scores for

Table 4.2. List of Neuropsychological tasks

Cognitive Domain	Test	Scores
Global Cognition	3MS	Total
Attention	WAIS-R Digit Span Forwards	Total
Working Memory	WAIS-R Digit Span Backwards	Total
Memory	Benton Visual Retention Task (BVRT) Rey Auditory Verbal Learning Task (RAVLT)	BVRT - Total RAVLT - A1-5 total, A6, A7
Executive Function	WAIS-R Similarities Trail Making Test B (TMT-B) Mental Alternation Test (MAT)	Similarities - Total TMT-B - Total MAT - Total
Visuo-construction	WAIS-R Block Design	Total
Language	Controlled Oral Word Association Test (COWAT) Animal Naming	COWAT - Total Animal - Total
Processing Speed	WAIS-R Digit Symbol (DS) Trail Making Test A (TMT-A) Serial Response Time (SRT) Lexical Decision Task (LDT)	DS - Total TMT-A - Total SRT - Average RT LDT - average accuracy, average RT

TMT-A, TMT-B, and the immediate recall trials of RAVLT (A1-5), due to the lack of available normative data for these tests in the CSHA study. Individuals over the age of 90 (n=1; age 93, a-MCI group) were compared to 90-year olds in the CSHA reference sample. In addition to the neuropsychological tests administered, a structured interview (Appendix A) with the participant and/or their family member was conducted to obtain self-report or collateral-report information pertaining to the participant's social, occupational, or daily life functioning.

Lifestyle Activities. The revised Activity Lifestyle Questionnaire (ALQ) (Jopp & Hertzog, 2010), a self-report activity questionnaire of adult leisure activities, was

initially developed and administered for the Victoria Longitudinal Study (VLS). The revised version of the VLS-ALQ employed in this study enhanced the content validity of the scale by including supplemental items on physical and social activities. The structure of this revised ALQ was validated using confirmatory factor analyses in independent samples. Good psychometric properties (reliability, convergent and discriminant validity) for the ALQ support the use of its subscales as indicators of leisure activities across the lifespan (Jopp & Hertzog, 2010). For each of the items, individuals self-reported the frequency of participation for a given activity within the past year on a 9-point scale (0=never, 1=less than once a year, 2=about once a year, 3=2 or 3 times a year, 4=about once a month, 5=2 or 3 times a month, 6=about once a week, 7=2 or 3 times a week, 8=daily). Individual scores from cognitive, physical and social subscales were computed (see Halliday, et al., 2018 for a full description).

Gait. Gait patterns were measured using a 6.4m instrumented walkway with embedded 1cm^2 pressure sensors (GAITRite; CIR Systems, Sparta, NJ). Sensors are activated under pressure of heel strike and deactivated upon toe-off, enabling the detection of footfalls as a function of time. Additionally, spatial information between two subsequent footfalls is captured, allowing for an analysis of both spatial and temporal properties of gait. Partial footfalls at the beginning and end of the mat were removed, and each pass of the mat was visually inspected for abnormalities. To avoid the influence of initiation and termination gait, participants walked for an additional 1.5 meters before and after a given pass of the walkway. Participants completed six passes for each of the three conditions; walk-only, walk while spelling words backwards, and walk while serially subtracting 7s from a starting number. Target words were seven letters in length with

difficulty determined between Grade 7 - 9 level, based on the Fry readability score (Fry, 1968). Target starting numbers were 3-digits.

Dispersion Computation. Dispersion was operationalized using a regression technique, which computes ISD scores from standardized scores (Christensen et al., 1999; Hultsch et al., 2002). Gait and neuropsychological test scores of interest were regressed separately on linear and quadratic age trends to control for group differences in mean performance, with the resulting residuals standardized as T-scores, and ISDs then subsequently computed from these residualized test scores. Multinomial regression models were employed to examine the utility of gait and neuropsychological test dispersion in predicting cognitive group classification (MCI or dementia). Gait dispersion was computed across the 16 commonly employed gait indicators identified by Lord and colleagues (2013). Neuropsychological dispersion was computed across the 15 neuropsychological test measures not employed in cognitive status classification.

4.4 Results

4.4.1 Between-Group Differences

There were significant differences between groups in terms of mean levels of dispersion based on neuropsychological test performance ($F(2,82)=19.442$, $p<.001$) and during the walk + numbers gait dual-tasking condition $F(2,73)=12.717$, $p<.001$) (Figure 4.1). No differences were observed in the walk only, or walk + words gait conditions. In terms of self-reported activity levels on the ALQ, there were significant between group differences in terms of social ($F(2,79)=4.560$, $p<.05$) and cognitive $F(2,79)=7.608$, $p<.001$) activity levels, and a similar trend in terms of physical activity levels ($F(2,79)=2.875$, $p=.06$). In each instance, HC participants demonstrated the greatest

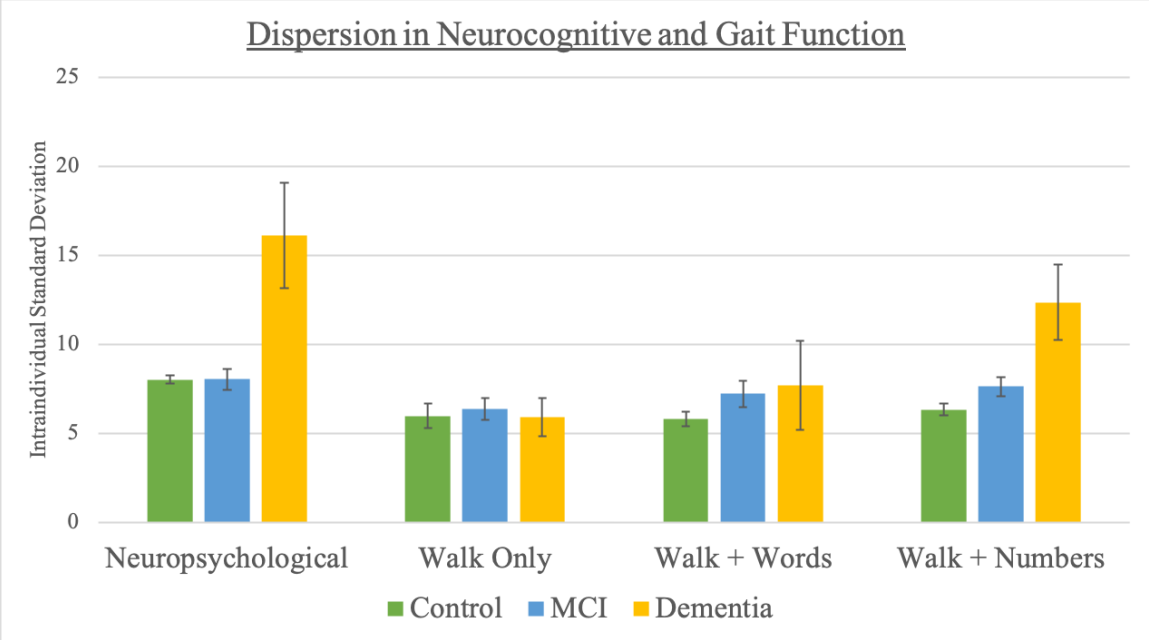

Figure 4.1. Between-group differences in neuropsychological test performance and gait performance, based on walk-only, walk + spell words backwards, and walk + count backwards by 7s.

levels of functioning (i.e., lowest amounts of dispersion and highest amounts of self-reported activity levels) and the participants with dementia demonstrated the lowest (i.e., highest amounts of dispersion and lowest amounts of self-reported activity levels).

4.4.2 Risk Associated with Dispersion in Neuropsychological and Gait Dual-Task Performance

Multinomial logistic regression models were used to examine the likelihood of being classified as having MCI or dementia, based on neuropsychological and gait dispersion. Increased dispersion in neuropsychological test performance was associated with a greater likelihood of being classified as having dementia (OR = 1.33, CI = 1.11 1.61, $p<.01$) $\chi2(2) = 16.824$ $p<.001$, Nagelkerke's R-squared = 0.21, but not MCI (OR = 1.00, CI = 0.84 1.19, $p>.05$). Increased dispersion during the dual-tasking walk +

numbers condition was associated with greater likelihood of being classified as having dementia (OR = 1.65, CI = 1.24 2.19, $p<.01$) $\chi 2(2) = 17.12$ $p<.001$, Nagelkerke's R-squared = 0.24), with a trend in the hypothesized direction observed for MCI classification (OR = 1.20, CI = 0.99 1.46, $p=.06$).

Next, we computed a model specifying the main effects of both domains of dispersion (neuropsychological and walk + numbers gait), as well as their interaction, in order to evaluate the cumulative risk associated with multi-domain inconsistency. The likelihood of dementia classification based on increased gait dispersion became progressively higher at greater levels of neuropsychological test dispersion. Specifically, for every unit increase in gait dispersion while counting backwards by 7s, individuals who were in the highest tertile in neuropsychological test dispersion were almost twice as likely to be classified as having dementia (OR = 1.98, CI = 1.16 3.37, $p<.05$), relative to individuals who were lowest in neuropsychological test dispersion (OR = 1.55, CI = 1.07 2.25, $p<.05$) (Figure 4.2).

4.4.3 Protective Benefits of Retrospective Lifestyle Factors

To examine the protective benefits of lifestyle factors, we employed multinomial logistic regression models to examine the decrease in likelihood of dementia and MCI classification associated with participation in physical, social and cognitive activities (Table 4.3 displays the associated odds ratios, confidence intervals and p values). Engagement in cognitive activities was protective against MCI classification at low, medium and high levels of both loaded gait and neuropsychological test dispersion. Engagement in social activity was protective against dementia classification at low,

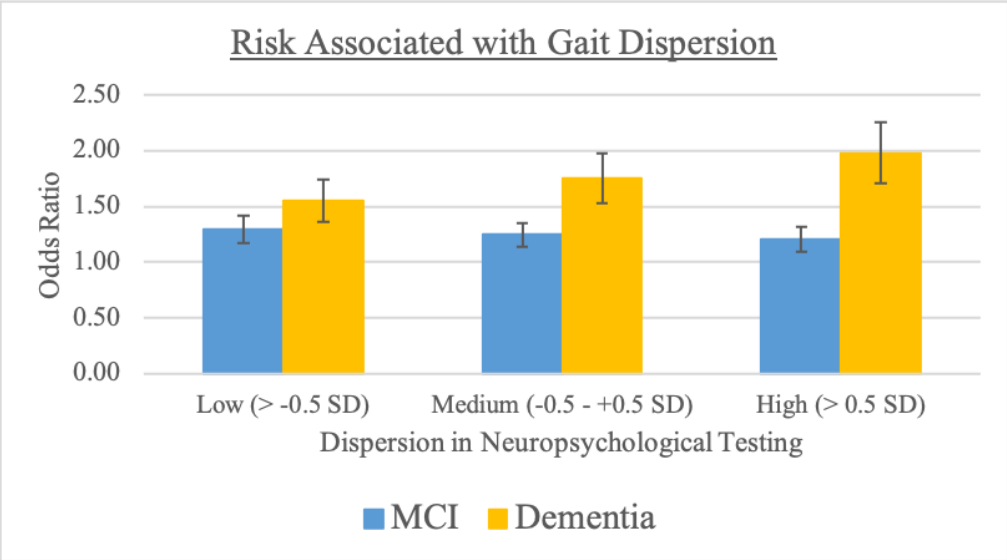

Figure 4.2. Cumulative risk associated with dispersion in the walk + numbers gait dual-tasking condition, based on low (0.5 standard deviations below the sample mean), medium (within 0.5 standard deviations of the sample mean) and high (0.5 standard deviations above the sample mean) dispersion in neuropsychological test performance. Error bars are based on standard errors.

medium and high levels of neuropsychological test dispersion only. Engagement in social activity also approached significance as protective against MCI classification at high levels of loaded gait dispersion. Engagement in physical activity was not reliably protective against MCI or dementia at low, medium or high levels of either loaded gait or neuropsychological test dispersion.

Table 4.3. Summary of multinomial logistic regression models, depicting the odds ratios, 95% confidence intervals (CI) and p-values for classification as either MCI (left panels) or Dementia group status (right panels), based on physical (top) social (middle) and cognitive (bottom) lifestyle activities at low, medium and high levels of loaded gait (walk + numbers backwards) and neuropsychological test dispersion.

	Physical Activities					
	MCI			**Dementia**		
Loaded Gait	*Odds Ratio*	*CI*	*p-value*	*Odds Ratio*	*CI*	*p-value*
Low (> -0.5 SD)	0.976	0.933 - 1.021	0.282	0.963	0.883 - 1.049	0.387
Medium (-0.5 - +0.5 SD)	0.970	0.932 - 1.009	0.134	0.972	0.883 - 1.070	0.561
High (> 0.5 SD)	0.965	0.921 - 1.011	0.130	0.981	0.873 - 1.104	0.755
Neuropsychological	*Odds Ratio*	*CI*	*p-value*	*Odds Ratio*	*CI*	*p-value*
Low (> -0.5 SD)	0.955	0.905 - 1.007	0.090	0.997	0.920 - 1.081	0.947
Medium (-0.5 - +0.5 SD)	0.962	0.924 - 1.001	0.055	0.995	0.915 - 1.082	0.903
High (> 0.5 SD)	0.969	0.930 - 1.009	0.130	0.992	0.897 - 1.097	0.881

	Social Activities					
	MCI			**Dementia**		
Loaded Gait	*Odds Ratio*	*CI*	*p-value*	*Odds Ratio*	*CI*	*p-value*
Low (> -0.5 SD)	0.980	0.939 - 1.023	0.363	0.939	0.849 - 1.037	0.213
Medium (-0.5 - +0.5 SD)	0.968	0.930 - 1.007	0.110	0.928	0.818 - 1.052	0.243
High (> 0.5 SD)	0.955	0.911 - 1.002	0.060	0.917	0.782 - 1.075	0.284
Neuropsychological	*Odds Ratio*	*CI*	*p-value*	*Odds Ratio*	*CI*	*p-value*
Low (> -0.5 SD)	0.963	0.913 - 1.016	0.170	0.851	0.738 - 0.981	0.026
Medium (-0.5 - +0.5 SD)	0.974	0.938 - 1.011	0.167	0.810	0.682 - 0.961	0.015
High (> 0.5 SD)	0.985	0.950 - 1.021	0.403	0.770	0.625 - 0.949	0.014

	Cognitive Activities					
	MCI			**Dementia**		
Loaded Gait	*Odds Ratio*	*CI*	*p-value*	*Odds Ratio*	*CI*	*p-value*
Low (> -0.5 SD)	0.957	0.923 - 0.991	0.015	0.975	0.917 - 1.036	0.407
Medium (-0.5 - +0.5 SD)	0.959	0.932 - 0.986	0.004	0.999	0.945 - 1.056	0.969
High (> 0.5 SD)	0.961	0.933 - 0.990	0.009	1.024	0.966 - 1.084	0.425
Neuropsychological	*Odds Ratio*	*CI*	*p-value*	*Odds Ratio*	*CI*	*p-value*

Low (> -0.5 SD)	0.964	0.940 - 0.990	0.006	0.967	0.927 - 1.010	0.129
Medium (-0.5 - +0.5 SD)	0.962	0.938 - 0.986	0.003	0.959	0.911 - 1.010	0.110
High (> 0.5 SD)	0.959	0.932 - 0.988	0.005	0.950	0.893 - 1.011	0.107

4.5 Discussion

As a proxy for multiple bodily systems (Studenski et al., 2011), gait function confers important prognostic implications for late-life neurocognitive health. Gait assessment using computerized walkways affords a multitude of spatial and temporal parameters, which has rendered the parsimonious assessment of gait challenging, resulting in heterogeneity across studies. Intraindividual variability in select gait parameters has been linked to deleterious health outcomes (e.g., Montero-Odasso et al., 2018; Rosano et al., 2007) and is reflective of neural systems that are separable from mean-based computations of gait function (Lo et al., 2017); however, intraindividual variability *across* gait parameters (i.e., gait dispersion) has yet to be investigated. This study examined whether gait dispersion was sensitive to MCI and dementia status, and further examined the protective benefits of retrospectively reported physical, social and cognitive activities as indicators of cognitive reserve.

Increased gait dispersion while dual tasking (walking while counting backwards by 7s) was associated with greater risk of dementia classification, with a similar trend observed for MCI risk. Risk of dementia classification increased incrementally with increased dispersion in neuropsychological test performance, with increased inconsistency across gait parameters during dual tasking (i.e., increased loaded gait dispersion) associated with nearly twice the risk of dementia classification, relative to individuals with low levels of neuropsychological test dispersion. Taken together, these

results suggest that dispersion computed across a broad profile of gait parameters during dual-tasking conditions may offer a metric of intraindividual variability that is robust across (a) selection of gait parameters, and (b) operationalizations of intraindividual variability within any given parameter.

In terms of the protective benefits of retrospectively self-reported lifestyle activities, physical activity was not reliably protective against MCI or dementia classification; however, social and cognitive activity were. Specifically, engagement in cognitive activities was protective against MCI classification, even in individuals with the highest levels of gait and neuropsychological test dispersion. Engagement in cognitive activities was not protective against dementia classification, however. In contrast, engagement in social activities was protective against dementia classification in individuals with low, medium and high levels of neuropsychological test dispersion; however, social activity was not protective in the context of gait dispersion or in terms of MCI. The lack of significant effects associated with physical activity may be driven by several factors. Although robust effects have been reported in physical exercise intervention studies (e.g., Hillman et al., 2008), the threshold of physiological duress (e.g., in terms of intensity, frequency and duration) needed to achieve the associated health benefits is perhaps beyond that reflected by the ALQ measure, which includes physical activities of relatively low demand (e.g., walking).

To the extent that inconsistency across neuropsychological test performance and across spatial and temporal gait parameters under dual-tasking represent risk factors associated with dementia and/or MCI classification, these results suggest that the protective benefits of lifestyle factors may differ, depending on the severity of the

neurodegenerative process, and whether an individual shows impairment in gait and/or cognitive function. Engagement in cognitively stimulating activities may be more protective for individuals with MCI, relative to social or physical engagement. In contrast, social engagement may be more protective for individuals who have progressed to dementia, relative to physical or cognitive engagement. Fratiglioni and colleagues (2004) argue that social networks affect health through behavioural (e.g., adopting others' healthy lifestyle habits), psychological (e.g., stress reduction, reduced isolation and depressive symptoms) and physiological (e.g., reduced vascular burden) pathways and that these pathways may have more utility in buffering against the impacts of dementia on cognitive function. Indeed, social isolation has been linked to a host of risk factors for mortality (e.g., inflammatory processes) (Holt-Lunstad, Smith, Baker, Harris & Stephenson, 2015; Umberson & Montez, 2010). Cognitive activity, by way of the "use it or lose it principal", is purported to increased cognitive reserve and create more efficient neural networks (Fratiglioni et al., 2004; Stern, 2007). For individuals with MCI, cognitive engagement may preserve the neural networks underpinning gait control during executive demand. This is in keeping with longitudinal observations of healthy older adults (Holtzer et al., 2012) and suggests that cognitive engagement continues to buffer against declines in cognitive and gait function into the dementia prodrome.

4.5.1 Limitations and Future Directions

Replication of the reported findings will be necessary to improve our understanding of gait variability and the role of gait dispersion in late-life cognitive function and decline. Similarly, further examination of the extent to which gait dispersion demonstrates construct validity as a proxy of executive motor control would contribute to

our understanding of both the theoretical construct, as well as what gait dispersion is uniquely capturing. Given evidence that mean and variability-based operationalizations of gait are associated with different brain networks in older adults (Lo et al., 2017), in conjunction with evidence for separable brain networks evoked during single- versus dual-tasking gait conditions (Blumen et al., 2018; Tripathi et al., 2019), further research will be essential for titrating the specificity of various assessment and operationalization parameters.

The reported measures of lifestyle activities are somewhat limited due to self-report, which can be unreliable. Future work examining the protective benefits of cognitive reserve in late-life should consider examining multimodal indicators to leverage the synergistic and potentially additive effects of combined lifestyle factors (e.g., enriching lifestyle activities, dietary choices, stress management practices). The findings are also limited given the nature of retrospectively reporting on activities over the 12 months prior to participation. Accordingly, it is not feasible to make particularly strong claims regarding whether and to what extent the lifestyle activities reported on are truly protective against the neurodegenerative processes underpinning dementia or its prodrome.

4.5.2 Conclusion

Gait function is a proxy for multiple systems that are impacted in late-life. Gait function while dual-tasking shows particular promise in identifying older adults with early stages of cognitive decline in the absence of functional impairment (e.g., instrumental activities of daily living). As a complex and multi-faceted construct, multivariate approaches to analyzing gait data represent an important line of

investigation, particularly when considering the multitude of gait indicators that are available to researchers and clinicians. Our results demonstrate that dispersion across a set of parsimonious gait indicators (a) is sensitive to having dementia, (b) is buffered by protective lifestyle factors, and (c) represents a convenient multivariate approach to operationalizing the numerous gait indicators that are actively in use.

Chapter 5

Summary and Conclusions

Executive and motor control overlap in terms of neural substrates and cognitive processes, and appear to develop and change in tandem across the lifespan. Numerous developmental and acquired conditions impacting brain function routinely disrupt executive and motor control, with ADHD, mTBI and MCI representing some of the most common. The goal of this dissertation was to better understand (a) the concept of executive motor control in the context of these developmental relationships, (b) the influence of neurological impairment from ADHD, mTBI and MCI, and (c) how modifiable lifestyle factors might influence executive motor control. Although assessments of executive and motor control are often conducted separately, they interact constantly in day-to-day activities over the course of a given moment (cf. affordance competition hypothesis; Cisek, 2007). Cisek and Kalaska (2010), suggesting that early activity that is elicited by initially ambiguous stimuli and that evokes multiple representations, "does not encode the stimuli themselves, but rather the set of potential actions that are most strongly associated with those stimuli, such as actions with high stimulus-response compatibility" (p. 281). In the context of ADHD and motor dysregulation, this means that inhibitory control must initially repress the most compatible stimulus-response, with attention switching subsequently employed to select a less automatically evoked motor plan. In the context of gait control in late-life, this means that older adults need to do similar; first inhibit an automatic walking plan (e.g., "put next foot forward") when walking goes awry (e.g., due to a cognitive distraction) to avoid aversive events, such as a fall. Competitive athletes routinely practice these skills in

pressured environments that demand rapid execution of executive motor control; for example, when an original motor plan must be modified due to a change in environmental circumstances during play.

Across mid- to late-childhood, findings in chapter 2 demonstrate that multiple aspects of motor and cognitive function improve, but that relative to typically developing children, children with ADHD show greater gains in cognitive interference control with age (Figure 2.1), while maintaining lower motor performance. Motor variability and response time inconsistency during executive performance appear to be predictive of hyperactive/impulsive ADHD symptoms and may be well-suited to capturing motor regulation difficulties. Taken together, these results suggest that difficulties with basic motor regulation may detract from executive control resources in children with ADHD and that they may compensate in different ways relative to typically developing children from mid- to late-childhood.

Findings from chapter 4 suggest that in late-life, gait stability under cognitive load is predictive of dementia risk, especially for individuals who also demonstrate inconsistent functioning across cognitive domains (Figure 4.2). Enriching lifestyle activities that contribute to cognitive reserve seem to buffer against this risk, although the modality may differ depending on the degree of neuropathology; individuals with dementia may benefit from more social engagement, whereas individuals with MCI may benefit from more cognitive engagement (Table 4.2).

In reality, the pathways through which protective lifestyle activities (e.g., social, cognitive, physical) benefit neurocognitive health likely overlap (Fratiglioni et al., 2004) and these overlapping pathways offer hope in the sense that individuals facing barriers in

one domain (e.g., social isolation) may reap the benefits from engagement in another (e.g., vascular benefits from exercise). Ultimately, cognitive reserve can be conceptualized as "the sum of its lifetime input" (Richards & Deary, 2005) and the earlier such protective lifestyle habits can be implemented, the better.

Research has demonstrated that cognitive reserve in late-life that results from healthy lifestyle behaviours is particularly impactful when implemented in early-life (Fritsch, McClendon, Smyth, Lerner, Friedland, & Larson, 2007), and that cognitive activities in early-life set an important precedent for late-life cognitive function (Wilson, Barnes, & Bennett, 2003). Over the course of early-life development, experience strengthens the connections within and between core components subserving cognitive control, and thus these experiences seem to set the foundation for executive motor control and cognitive reserve (Luna et al., 2015). Sports participation appears to strengthen aspects of executive motor control (e.g., Marchetti, et al., 2015; Muraskin, et al., 2015; Verburgh, et al., 2016), presumably by optimizing the underlying connections during play. This is especially the case in novel and engaging situations that employ multiple aspects of EF (e.g., goal-directed thinking, executive motor control, physiological changes), relative to simple aerobic exercise only. Similarly, related activities involving the practice of executive motor control such as dance and performance art also confer cognitive benefits (Tomporowsiki & Pesce, 2019). Adolescence may be a particularly important time period in which to prioritize such activities, based on the unique role of dopaminergic reward processing during this developmental period and the potential for athletics to increase the signal-to-noise ratio of the neural synchrony underlying executive motor control (Luna et al., 2015).

Although findings from chapter 3 did not replicate those of previous studies demonstrating an "athletic advantage" in executive behavioural performance or the associated electrophysiological signal, they offer an important cautionary tale. Mild traumatic brain injuries are more common during contact sports and may result in altered neural dynamics in executive motor areas up to two years post-injury (Figures 3.5 and 3.6), with associations to subjective experiences of executive dysfunction. Although it has been implied here that physical activity, especially when it exercises executive motor control, may improve motor regulation in ADHD and gait control in late-life, mTBI may just as easily result in increased risk of ADHD (Stojanovski, Felsky, Viviano, et al., 2019) and MCI (Guskiewicz, Marshall, Bailes, et al., 2005; Lehman, Hein, Baron, & Gersic, 2012). The cost-benefit ratio of physical activity that has a higher risk of sustaining an mTBI should ultimately be evaluated on an individual basis, so as to maximize the potential benefits and reduce the potential costs.

Closing Statement

Executive and motor control interact to facilitate self-regulation and meaningful, goal-directed behaviours across the lifespan. In spite of the influences of normative development and neurological conditions on executive and motor control, there are multiple avenues through which to set a robust foundation for reserve in these areas, and similarly, to improve or optimize a developmental trajectory that has been steered off course. The process of skill acquisition appears to be one common means through which activities that activate executive motor control generalize more broadly to benefits seen in cognition (Tomporowski & Pesce, 2019). Acquiring these skills in novel and engaging circumstances also impacts cognitive control via additional pathways (e.g., goal-directed

thinking, executive motor control, physiological changes), relative to simple and familiar circumstances (Best, 2010). The benefits of physical exercise and enriching cognitive activities extend to cognitive and self-regulatory processes, and have synergistic effects with subsequent protective lifestyle behaviours.

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Appendix A

PREVENT Classification: Clinical Interview

Background / Qualitative Information

1. Age of participant at time of diagnosis from medical doctor: _____
2. Individual's / proxy's perception of when symptoms first appeared: _____

   _____
3. Description of Disease Course from participant / proxy (gradual and continual vs. fast): _____
4. Participants biological family history of cognitive impairment (if any): _____

   _____
5. Does the participant have a complaint about memory? Yes ____ No ____

   Description: _____
6. Does the proxy have a complaint of participant's memory difficulties?

   Yes ____ No ____ Description: _____
7. Does the participant / proxy believe **memory impairments** cause significant impairment in social or occupational functioning? Yes ___ No ___ Who _____

   Description: _____
8. Does the participant / proxy believe **"other" impairments** (executive, language, constructional) cause significant impairment in social or occupational functioning?

   Yes ___ No ___ Who _____ Description: _____
9. Does the participant / proxy believe **memory impairments** represent significant declines from previous levels? Yes ___ No ___ Who _____

   Description: _____

10. Does the participant / proxy believe **"other" impairments** (executive, language, constructional) represent significant declines from previous levels?

    Yes ___ No ___ Who _____ Description: _____

11. Is general cognitive functioning essentially preserved (clinician's judgment)?

    Yes ___ No ___

12. Are functional activities largely intact? (i.e., no impairments in social or occupational functioning **AND** no declines from previous levels). Yes ___ No ___