EXAMINING THE RELATIONSHIPS AMONG MOTOR, COGNITIVE, AND MENTAL HEALTH OUTCOMES AFTER PEDIATRIC ARTERIAL ISCHEMIC STROKE

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Abstract

Pediatric arterial ischemic stroke (AIS) is an important cause of neurological disability in children with motor, cognitive, and behavioural sequelae. Motor impairments are one of the most common adverse outcomes after pediatric AIS, yet little is known about the impact of motor functioning on neuropsychological functioning. This dissertation consists of three studies examining relationships between motor functioning and neuropsychological outcomes after pediatric AIS. Study 1 examined relationships between motor functioning assessed with the Pediatric Stroke Outcome Measure at two timepoints and intellectual abilities. Results showed that motor functioning assessed during early recovery was associated with aspects of intellectual functioning, whereas later motor functioning was not. Different patterns of associations between motor functioning and intellectual abilities were observed in perinatal and childhood AIS groups. Features associated with poor motor outcome were combined cortical+subcortical lesions, hemiparesis, seizures, and utilizing rehabilitation services. Studies 2 and 3 focused on children with acquired dystonia, a movement disorder characterized by involuntary muscle contractions, after AIS involving subcortical regions. Study 2 compared symptoms of anxiety and depression between children with subcortical AIS, with and without dystonia, as well as associations among motor functioning and cognitive and mental health outcomes. Results supported the presence of greater levels of symptoms of anxiety and depression in children with post-stroke dystonia. There were no significant associations between motor and neuropsychological outcomes in the dystonia group, whereas motor and cognitive outcomes were associated in the no dystonia group. Study 3 examined whether there were differences in infarct characteristics on acute neuroimaging between children with and without dystonia and subcortical AIS. There was a significantly higher proportion of children with dystonia with lesions involving the putamen,

caudate nucleus, and anterior limb of the internal capsule. More children with dystonia had severe cortical involvement and infarct volumes were significantly larger. Regression analyses showed involvement of the putamen significantly predicted dystonia and intellectual outcome. Overall, results support an association between motor and neuropsychological functioning after pediatric AIS that may be related to maladaptive neural reorganization involving cortico-subcortical networks. Clinical implications and suggestions for future research are discussed.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

AIS= arterial ischemic stroke

BASC-2= Behaviour Assessment System for Children, 2nd edition

BRIEF= Behaviour Rating Inventory of Executive Function, 2nd edition

BRI= Behavioural Regulation Index

DWI= diffusion weighted imaging

FSIQ= Full Scale Intellectual Quotient

FRI= Fluid Reasoning Index

GEC= Global Executive Composite

MI= Metacognition Index

MRI= magnetic resonance imaging

PRI= Perceptual Reasoning Index

PSI= Processing Speed Index

PSOM= Pediatric Stroke Outcome Measure

VCI= Verbal Comprehension Index

WD= Wallerian Degeneration

WAIS-IV= Wechsler Adult Intelligence Scale, 4th edition

WISC-IV= Wechsler Intelligence Scale for Children, 4th edition

WISC-V= Wechsler Intelligence Scale for Children, 5th edition

WMI= Working Memory Index

Chapter 1: General Introduction

Pediatric stroke is a significant cause of acquired brain injury in children (deVeber et al., 2000; Krishnamurthi et al., 2013). In the last 20 years there has been an observed 35% increased prevalence of pediatric stroke, in part due to advances in non-invasive neuroimaging methods that allow for earlier detection and increased clinical awareness (Krishnamurthi et al., 2013). There has also been a significant decline in death rates and disability adjusted life years in pediatric stroke, likely related to improvements in post-stroke care (Krishnamurthi et al., 2013). Despite these improvements, pediatric stroke remains an important cause of disability in children, with 50-75% of survivors experiencing long-term neurological impairment, including cognitive, behavioural, and motor challenges (deVeber et al., 2000). Arterial ischemic stroke (AIS) occurs when there is a disruption of normal blood flow to the brain due to a blocked artery, resulting in permanent tissue damage (i.e., infarct) (Festa et al., 2008). Neurological outcomes include motor impairments, sensory loss, dysphasia, and epilepsy (Amlie-Lefond et al., 2008). Motor impairments are one of the most common adverse outcomes affecting approximately half of the survivors of pediatric AIS (Cooper et al., 2018, Kirton et al., 2007; Mercuri et al., 2004; Ganesan et al., 2000), and include hemiparesis and hemiplegia as well as movement disorders such as dystonia (deVeber et al., 2000; Béjot et al., 2012; Cooper et al., 2018; Tibussek et al., 2015). Neuropsychological outcomes include difficulties in cognitive domains (e.g., intellectual functioning, attention, executive functioning) as well as behavioural difficulties and psychiatric diagnoses (e.g., anxiety, depression, adaptive functioning) (Fuentes et al., 2016; O'Keeffe et al., 2014; Max et al., 2002). Insult to the developing brain, such as AIS, can interrupt subsequent development and establishment of critical neural networks (Anderson et al., 2011; Dennis, 2000; Dennis et al., 2013), and a growing body of work suggests that adverse childhood outcomes in cognitive and motor functioning may represent dysfunction in neural networks rather than any

single functional brain region, moving towards a more integrated understanding of how the developing brain reorganizes after injury (Max et al., 2005; Tibussek et al., 2015). Recovery from early brain injury involves neuroplasticity; the capacity of the brain to learn new information, change in response to the environment, and recover from injury (Anderson et al. 2011; Johnston, 2009). The outcomes of plasticity can be adaptive or maladaptive resulting in either resilience in functional outcome or poor outcomes (Dennis et al., 2013; Johnston, 2009); this is seen after pediatric AIS, with some children displaying resilience and others affected by lasting neuropsychological and motor difficulties (Anderson et al., 2020). Therefore, we question whether specific motor impairments (e.g., dystonia) that emerge beyond the acute phase of stroke may be indicative of disruptions in neural networks (i.e., maladaptive outcomes of plasticity) that also affect neuropsychological functioning. This dissertation aims to expand the extant knowledge of relationships among cognitive, mental health, and motor outcomes after pediatric AIS, with an emphasis on understanding potential neural correlates of these maladaptive outcomes in the context of neural reorganization.

Mechanisms and Clinical Presentation of Stroke in Infants and Children

Stroke is a cerebrovascular event that occurs due to a disruption of the normal flow of blood to the brain, which causes neuronal damage (Holtz, 2011). Stroke can be the result of ischemia (i.e., disruption of blood flow to the brain) or hemorrhage (i.e., massive bleeding in the brain caused by the breakage of blood vessels) (Festa et al., 2008; Holtz, 2011). Ischemic stroke is classified in two ways: cerebral sinovenous thrombosis (CSVT) and arterial ischemic stroke (AIS). CSVT refers to a stroke caused by a blood clot in the venous system of the brain (Festa et al., 2008). Arterial ischemic stroke (AIS) occurs when there is a disruption of normal blood flow to the brain due to a blood clot in the artery (Festa et al., 2008). This can occur either though an

embolism (i.e., blood clot travels from one place to another via the bloodstream) or thrombosis (i.e., blood clot is formed locally in the blood vessel). When an ischemic event occurs, the blood supply of the affected brain tissue is interrupted, which leads to deprivation of oxygen and nutrients, which in turn can lead to an infarct (e.g., permanent tissue damage) (Festa et al., 2008). This dissertation will focus on patients with pediatric AIS. Most instances of pediatric AIS involve the middle cerebral artery (MCA) and have a recognizable clinical and imaging pattern (Càrdenas et al., 2011).With respect to location, lesions from AIS can occur at the subcortical level (infarct restricted to the basal ganglia and/or thalamus), cortical level (infarct restricted to the cortex with no subcortical involvement), or combined cortical/subcortical (infarct involving the cortex and the basal ganglia and/or thalamus) (Westmacott et al., 2010). Basal ganglia infarcts occur in approximately one-third of perinatal stroke and half of childhood stroke, often due focal cerebral arteriopathy – inflammatory type, which primarily affect perforator territories (Bernard et al., 2012; deVeber et al., 2017).

Pediatric stroke refers to strokes that occur in the perinatal period (e.g., between 20 weeks gestation and 28 days after birth) or in childhood (e.g., between 29 days of age and 18 years of age) (Cárdenas et al., 2011; Ferriero et al., 2019). The incidence of perinatal stroke is 1 in every 2500 live births (Kirton & deVeber, 2009). However, this figure is higher when considering presumed perinatal strokes. Approximately 50% of perinatal strokes are asymptomatic and diagnosed retrospectively when there is emerging motor asymmetry (e.g., hemiparesis) or seizures at 4-9 months of age, which initiates neuroimaging that demonstrates an old lesion (Cárdenas et al., 2011; Fitzgerald et al., 2007; Kirton & deVeber, 2009). Childhood stroke is less common than perinatal stroke, with an annual incidence of 3-8 out of 100 000 children (deVeber, 2003; Hartel et al., 2004). However, this incidence is on par with other

neurological diseases in children, such as brain tumor, making stroke an important cause of brain injury in children (deVeber, 2002; Fullerton et al., 2003). Although pediatric stroke is a relatively rare condition it can be devastating, and the deficits can last a lifetime resulting in significant burden to the affected child, their family, and society (Cárdenas et al., 2011).

Diagnostic criteria for pediatric AIS are acute neurological deficit (or isolated seizures in infants younger than 6 months of age) and corresponding acute infarcts on brain imaging (deVeber et al., 2017). The highest risk of pediatric stroke is during the newborn period (deVeber et al., 2000). Approximately half of strokes during the perinatal period present acutely (i.e., acute neonatal AIS), most commonly with seizures (Grunt et al., 2015; Kirton, & deVeber, 2013; Ferriero et al., 2019; Nelson & Lynch, 2004). In many cases the seizures associated with AIS are focal and can present in the absence of other signs of neonatal encephalopathy such as abnormalities in tone, feeding, or consiousness (Ferriero et al., 2019); although these signs can be present in some cases (Grunt et al., 2015). The remainder of ischemic strokes occurring during the perinatal period are diagnosed retrospectively, when motor difficulties or seizures are evident in infancy and neuroimaging confirms an old lesion; these are referred to as presumed perinatal strokes (i.e., presumed perinatal arterial ischemic stroke) (Cárdenas et al., 2011). In contrast, the presenting symptoms of childhood stroke are similar to those in adults including sudden focal neurological deficits (e.g., hemiparesis, language and speech difficulties, vision difficulties, and headache) (Kirton, et al., 2007). Neuroimaging is a critical component of diagnosing stroke (Cárdenas et al., 2011; Dlamini et al., 2017; Kirton et al., 2007). Magnetic resonance imaging (MRI) has greater sensitivity to detect early ischemic change and is the preferred neuroimaging modality (Amlie-Lefond et al., 2008). Computed tomography (CT) is used in acute settings and can diagnose large, well-evolved infarcts and exclude hemorrhage, but

is not able to detect ischemic changes within hours of the insult (Kirton et al., 2007; Srinivasan et al., 2009). It is also essential to image the cerebral vascular system. Vascular imaging modalities include magnetic resonance angiography (MRA), CT angiography, arterial wall imaging, and conventional contrast angiography, which is the gold standard (Dlamini et al., 2017; 2018). Other medical investigations for complicating factors such as infection, bleeding disorders, or anemia may be warranted (Càrdenas et al., 2011). Finally, establishing the presence of congenital heart disease should be done via an echocardiography as this carries a risk of recurring stroke (Domi et al., 2008; Rodan et al., 2012). Clinically relevant imaging markers in brain locations remote from the infarct location can be detected using diffusion weighted imaging (DWI) MRI (Dlamini et al., 2017; Kirton et al., 2016). DWI is used to determine the ease of molecular diffusivity of water within tissue (Daniel et al., 2020). In stroke, the presence of restricted diffusion on DWI is seen due to increased intracellular water accumulation and decreased rate of molecular water diffusion within the injured tissue (Daniels et al., 2020) and evolving DWI signal remote from the infarct also carries relevant clinical information (Kirton et al., 2016). Wallerian Degeneration (WD) is an example of an imaging marker of outcome and refers to the anterograde degeneration of axons and their myelin sheaths after proximal axonal or cell body injury (Waller, 1850; Johnson et al., 1950) that is seen as evolving DWI signal down the corticospinal tract (Domi et al., 2009). Diaschisis describes DWI changes (e.g., hyperintense areas with corresponding hyperintensity on apparent diffusion coefficient maps) in brain areas that are structurally remote from the primary focal lesion, but anatomically connected to it via fibre tracts (Carrera & Tononi, 2014; Kirton et al., 2016; Finger et al., 2004).

With respect to risk factors, the known risk factors for adult stroke such as hypertension, diabetes, high cholesterol, atherosclerosis, and smoking are rarely implicated in pediatric stroke

(Cárdenas et al., 2011; Friedman, 2009). Risk factors for perinatal stroke are not well established with respect to their causative role (Cárdenas et al., 2011), however a number have been studied including: maternal risk factors (e.g., infertility, autoimmune disease, drug use, first birth), difficulties during labor and delivery, acute concerns of the infant at birth, and congenital heart disease (Cheong & Cowan, 2009; Kirton & deVeber, 2009; Lynch, 2009). To add further complexity, one-third of cases of pediatric stroke are idiopathic and half present with more than one risk factor (Friedman, 2009; Golomb et al., 2001). In the case of childhood stroke, arteriopathies (i.e., disorders of the arteries such as moyamoya disease, transient cerebral arteriopathy, and cervico-cranial dissection) are the most common risk factors and associated with more than 50% of cases (Amlie-Lefond et al., 2008). Cardiac disease, prothrombotic disorders as well as hematological disorders (e.g., sickle cell disease), and infections (e.g., varicella, encephalitis, meningitis) are also known risk factors of childhood stroke (Askalan et al., 2001; Carvalho & Garg, 2002; Malone & Felling, 2020; Roach et al. 2008). Post-varicella arteriopathy is particularly associated with infarcts in the basal ganglia (Askalan et al., 2001)

Neuropsychological and Motor Outcomes after Pediatric AIS

Neuropsychological Outcomes

Cognitive outcomes. Several cognitive difficulties have been documented after pediatric stroke, which can persist overtime affecting developmental milestones and academic progress (Steinlin et al., 2004). Overall intelligence is typically around the lower end of the average range, but significantly lower than that of the normative group or control group when one is available (Allman & Scott, 2013; Everts et al., 2008; O'Keeffe et al., 2014; Pavlovic et al., 2006; Studer et al., 2014; Westmacott et al., 2009). Multiple studies have reported a large variation in intellectual outcomes within the pediatric stroke population, highlighting the heterogeneity of

this group (Hogan et al., 2000; Long et al., 2011; Steinlin et al., 2004). Additionally, performance on tests of academic achievement has been found to be lower in children with stroke compared to the normative sample (Ballantyne et al., 2008; Deotto et al., 2019; Jacomb et al., 2018; Max et al., 2010; Rodrigues et al., 2011) and learning disabilities are among the most common diagnoses children receive after pediatric stroke (Williams et al., 2017). Attention and executive functioning depend on neural networks that continue to develop into adolescence and are particularly vulnerable to being affected after pediatric stroke (Gogtay et al., 2004; Greenham et al., 2015; Miller & Cohen, 2001). Studies have found deficits in sustained, divided, and selective attention after pediatric AIS (Everts et al., 2008; O'Keeffe et al., 2014) as well as increased attention deficit hyperactivity disorder traits (Max et al., 2002). Executive functioning refers to a set of cognitive skills that enable problem-solving and goal directed behaviour (Lezak, 1995). Survivors of pediatric AIS show difficulties across different domains of executive functioning including inhibition, cognitive flexibility, working memory, and processing speed (Everts et al., 2008; Hajek et al., 2014; Long et al., 2011; O'Keeffe et al., 2014; Studer et al., 2014; Westmacott et al., 2010). Children also showed impairments in executive function in daily life according to a standardized parent-completed questionnaire (O'Keeffe et al., 2014). It is important to note that cognitive outcomes do not manifest uniformly across all survivors of pediatric AIS. In fact, there is notable interindividual variability, which limits our understanding of neuropsychological outcomes as they apply uniquely to individuals (Fuentes et al., 2016). Factors impacting neuropsychological outcome have been identified including neurological impairment, age at stroke, lesion characteristics, and seizures, however findings have been inconsistent and research points to the importance of interactions among factors, rather than any

single factor alone (i.e., age at stroke and lesion location) (Studer et al., 2014; Fuentes et al., 2016).

Psychiatric and behavioural outcomes. A number of studies using standardized parent-report measures found that parents endorsed concerns for their children's behavioural and emotional functioning (Ganesan et al., 2000; O'Keeffe et al., 2013; Pavlovic et al., 2006; Steinlin et al., 2004). Max and colleagues (2002) examined psychiatric diagnoses post-pediatric stroke. When compared to orthopedic controls more children with stroke had post-injury psychiatric diagnoses (59% vs 14%). The most common diagnoses were attention deficit hyperactivity disorder (ADHD; 46%), anxiety disorders (31%), and mood disorders (21%). Furthermore, psychiatric comorbidity was only found in the participants with stroke. Williams et al. (2017) found, out of 126 children, 52.4% received a psychological diagnosis after perinatal or childhood stroke. Intellectual disability, attention deficit hyperactivity disorder, and learning disorder were among the most common diagnoses; however, anxiety and depression were both found at rates of 4%. Westmacott et al. (2018a) investigated outcomes after childhood subcortical stroke and found higher rates of anxiety and depression, 14% and 18% respectively, with these diagnoses more common in those with basal ganglia lesions compared to thalamic lesions, suggesting involvement of these structures may be specifically associated with anxiety and mood difficulties after stroke. A study comparing psychiatric diagnoses in children with stroke and asthma found both groups had similar levels of internalizing symptoms and social problems, suggesting an overall affect of chronic illness on mental health (Greenham et al., 2015). However, the children in the stroke group had additional difficulties with social participation (Greenham et al., 2015). Lower adaptive functioning in pediatric stroke has also been documented in the domains of communication, daily living skills, socialization, and adaptive behaviours (Hurvitz et al., 2004).

Although 40% of participants scores fell the within the “adequate” range, the majority of the remainder fell below, in the “moderately low” to “low” range (Hurvitz et al., 2004). There is evidence that mental health difficulties have been found to emerge over time and persist into adulthood (Elbers et al., 2014). At an average follow-up of 10.8 years, a quarter of young adult survivors of pediatric stroke reported having depression or anxiety (Elbers et al., 2014).

Motor Outcomes

A study with 933 Canadian children found that two-thirds of pediatric AIS survivors showed neurological deficits at long-term follow up (deVeber et al., 2017). Common deficits after pediatric AIS include sensory loss, speech difficulties (e.g., dysphasia), epilepsy, and deficits in motor functioning (e.g., hemiparesis, hemiplegia, spasticity, dystonia, cerebral palsy), (Amlie-Lefond et al., 2008; deVeber et al., 2017; Steinlin et al., 2004; Studer et al., 2014). Motor impairments are the most common adverse outcomes found in 30-60% of children after pediatric AIS and can persist into adulthood. (Cooper et al., 2018; Hartel et al., 2004). Acute hemiparesis presents in 70% to 90% of cases of childhood stroke but is less common in infants (deVeber et al., 2000; Mallick et al., 2014; Boardman et al., 2005; Ganesan et al., 2000; Mercuri et al., 2004; Sreenan et al., 2000; Zimmer et al., 2007). Estimates of chronic hemiparesis (> 6 months duration) in childhood stroke range between 25% to 56% for childhood stroke and 20-28% in neonatal stroke (Boardman et al., 2005; Ganesan et al., 2000; Mercuri et al., 2004, Sreenan et al., 2012). Predictors of poorer motor outcome at 12 months post-stroke were large lesion size, neurological impairment at 1-month, and age at stroke ≥ 5 years (Cooper et al., 2017; Karalok et al., 2019). In terms of lesion location, in neonatal AIS concomitant involvement of the cerebral cortex, basal ganglia, and posterior limb of the internal capsule was found to predict hemiparesis, whereas involvement of only one or two of these structures was not associated with

hemiparesis (Boardman et al. 2005). This association was also seen in childhood-onset AIS; however, in contrast to neonates, children with involvement of only one or two of the structures also displayed hemiparesis, with involvement of only the basal ganglia being the least likely lesion location to be associated with hemiparesis.

Dystonia. Dystonia is a movement disorder characterized by excessive muscle contractions that result in repetitive movements, twisting movements, and/or abnormal posturing (Albanese et al., 2013; Jinnah & Hess, 2006; Mink, 2003, Sanger et al., 2010). It is functionally disruptive, disabling, and often painful (Albanese et al., 2013). Stroke involving the basal ganglia and/or thalamus is one of the commonest causes of childhood dystonia (Soman et al., 2006; Elbers et al., 2010; Mink, 2013). It is the most common post-stroke movement disorder in children and occurs more frequently in children than adults (Béjot et al., 2012). It is unclear why some children with basal ganglia stroke go on to develop acquired dystonia and others do not, but there is some evidence that involvement of multiple basal ganglia structures (as opposed to a single structure), age at stroke before 10 years old, and female sex may place children at higher risk (Soman et al., 2006; Elbers et al., 2010; Goldfarb et al., 2013). In contrast to hemiparesis, which is present during the acute period, dystonia presents after a delay of 6-12 months post-stroke on average (Soman et al., 2006; Tibussek et al., 2015). The delayed presentation of the disorder and its relatively greater prevalence after pediatric stroke contrasted with rarer presentation after adult stroke suggest developmentally determined maladaptive neural reorganization after injury may contribute to its presentation (Marsden et al., 1985; Scott & Jankovic, 1996; Quartarone & Hallett, 2013). Recent findings of additional cognitive difficulties in intellectual, academic, and executive functioning in children with acquired dystonia relative to children with similar patterns of stroke but no dystonia provide further support for the role of

maladaptive outcomes of neuroplasticity in acquired dystonia, which also affects cognition (Westmacott et al., 2018b). Historically, dystonia had been viewed as a disorder primarily of the basal ganglia; however, it is now well documented that the neuroanatomical basis of dystonia is best understood as a network model with abnormal functional connectivity in thalamo–striatal–cortical networks, suggesting that dystonia represents dysfunction in networks rather than any single functional brain region (Jinnah et al., 2017; Lehericy et al., 2013; Stoessl et al., 2014).

Neuroplasticity and Pediatric AIS

Recovery from early brain injury involves neuroplasticity: the capacity of the brain to learn new information, change in response to the environment, and recover from injury (Anderson et al. 2011; Johnston, 2009). The outcomes of plasticity can be adaptive or maladaptive resulting in either resilience in functional outcome or poor outcomes (Dennis et al., 2013; Johnston, 2009), as is seen after pediatric AIS, with some children displaying resilience and others affected by lasting neuropsychological and motor difficulties (Anderson et al., 2020). Basic mechanisms underlying neuroplasticity include neurogenesis, apoptosis, and synaptic plasticity (Johnston, 2009). Brain changes can be observed through neuroimaging as well as through behaviour (Kolb et al., 2010). Historically, some have argued that increased capacity for plasticity in the developing brain leads to more favourable recovery in children than adults after stroke (Villablanca & Hovda, 1999); this is in reference to the “Kennard principle”, based on Margaret A. Kennard’s work on motor impairment after brain injury in monkeys (Kennard, 1936), referring to the greater capacity for recovery after early brain injury. This has been shown to be an oversimplification of Kennard’s work, which focused on a number of factors that predicted functional outcome after brain injury as well as the underlying neural mechanisms (Dennis, 2010). More recently, there is increasing recognition that the developing brain is a

dynamic environment with significant changes in neurobiology occurring throughout childhood (Semple et al., 2013), which have important influence on mechanisms of recovery after injury (Malone & Felling, 2020). There is evidence that developmental stage at the time of injury has an influence on motor recovery and neuropsychological functioning in the instance of childhood brain injuries (Anderson et al., 2011; Lo et al., 2012); because brain development continues throughout childhood, later maturing brain regions rely on the development of early maturing brain regions (Gogtay et al., 2004), and therefore damage to one brain region can disrupt later development in other regions as well as more widespread neural networks, thereby affecting higher-order skills (Greenham et al., 2017; Westmacott et al., 2010). Additionally, Westmacott et al., (2010) found that age at stroke interacted with lesion location in predicting intellectual outcomes in children with pediatric AIS with different peak times of vulnerability for subcortical (perinatal) and cortical lesions (1 month to 5 years old). With respect to motor outcome, a number of studies have found that acute and chronic hemiparesis is more common after stroke in childhood compared to neonatal stroke (Boardman et al., 2005; de Veber, et al., 2000; Ganesan et al., 2000; Husson et al., 2010; Mercuri et al., 2004; Mallick et al., 2014; deVeber et al., 2017). In contrast, Cooper et al., (2017) found similar rates of hemiparesis 12-months post-stroke in neonates, pre-school age children, and school-age children. However, recovery trajectories of motor skills were different between age groups, with neonates showing emerging deficits overtime whereas the pre-school and school-age children showed initial impairment with gradual recovery.

Gaps in the Literature and the Current Dissertation

The existing literature clearly demonstrates the range of adverse motor and neuropsychological outcomes after pediatric stroke. However, understanding of vulnerability to

poor cognitive and mental health outcomes after pediatric stroke continues to need to be elucidated, as interindividual variability is prominent in this population. Lack of knowledge has direct implications for the clinical care of children recovering from stroke, as it is currently difficult to prognosticate about outcomes at the individual level. A growing body of work suggests that difficulties in cognitive and motor functioning after pediatric stroke may represent dysfunction in neural networks rather than any single functional brain region (Max et al., 2005; Tibussek et al., 2015). Further research is required to better understand how changes in the brain following stroke (e.g., post-stroke neural reorganization) affect motor, cognitive, and behavioural outcomes. My dissertation seeks to close this gap by identifying the relationships among cognitive, mental health, and motor functions (e.g., impairment noted on neurological assessment, movement disorder diagnosis) after pediatric AIS. In this dissertation, we propose that observed motor deficits may reflect neural network disruptions or underdevelopment (e.g., damage to white matter or reduced cortical connectivity) in regions implicated in development of motor skills, cognitive functioning, and behavioural regulation, specifically within the cortico-striato-thalamo-cortical circuit and cortical-subcortical connections (Diamond, 2000; Hadders-Algra, 2008; Parent & Hazrati, 1995; Peyton et al., 2020; Oudgenoeg-Paz et al., 2017), whereas appropriate motor functioning may reflect integrity of these regions (Butcher et al., 2009; Bruggink et al., 2010; Murray et al., 2007). Therefore, we question whether motor impairments lasting beyond the acute phase of stroke may be indicative of disruptions in neural networks (i.e., maladaptive outcomes of plasticity) and thus associated with other adverse outcomes in cognitive functioning or mental health. This dissertation is the compilation of three empirical studies:

Study 1: Motor Outcomes in Pediatric Arterial Ischemic Stroke and Associations with Intellectual Outcome

Study 1 examines motor outcomes after pediatric AIS using the Pediatric Stroke Outcome Measure (PSOM; Kitchen et al., 2012). The primary aim is to determine whether motor functioning assessed after the acute phase of stroke is associated with school-age intellectual functioning. We also examined the stability of motor functioning between the first assessment outside of the acute stage and assessment closest to time of neuropsychological testing, as well as associations between current motor functioning and intelligence. Finally, we examined differences in pertinent clinical features of children with good and poor motor outcomes, including age at stroke, lesion size, lesion location, motor presentation, rehabilitation services accessed, and current seizures. It was hypothesized that poorer motor functioning evident early in post-stroke recovery would be associated with school-age intellectual functioning.

Study 2: Mental Health Outcomes in Children with Acquired Dystonia after Basal Ganglia Stroke and Associations with Cognitive and Motor Outcomes

Study 2 had two aims. First, to examine mental health outcomes in children with AIS involving the basal ganglia and/or thalamus with and without-post stroke dystonia, as measured using standardized parent-completed questionnaires and review of clinical neuropsychological reports. We hypothesized that children with post-stroke dystonia would have greater mental health difficulties compared to children with similar patterns of stroke, but no dystonia. Second, to examine associations between mental health, cognitive (intellectual and executive functioning), and motor outcomes in the dystonia and no dystonia groups.

Study 3: Neuroimaging Correlates of Acquired Dystonia and Cognitive Outcome after Pediatric Arterial Ischemic Stroke Involving the Basal Ganglia and/or Thalamus

Study 3 also focused on children with basal ganglia and/or thalamic AIS, with and without dystonia. This study examines whether there are differences in acute neuroimaging features between children who do and do not develop acquired dystonia after stroke. Clinical magnetic resonance imaging scans were reviewed. Volumetric analysis and detailed lesion classification was completed and presence of markers of injury remote from the infarct (i.e., WD, diaschisis) was determined. We hypothesized that involvement of more than one structure of the basal ganglia and cortical and/or internal capsule involvement would be more prevalent in the acquired dystonia group relative to children with stroke and no dystonia, and that children with acquired dystonia would have larger infarct volumes, reflecting more widespread brain involvement. We also hypothesized that markers of remote injury would be more prevalent in the acquired dystonia group relative to children with stroke and no dystonia, reflecting dysfunction in cortical-subcortical networks. We also explored whether neuroimaging features predicted intellectual outcome.

General Methods

Patient Population and Procedure

All three studies utilized data from the Children's Stroke Study Registry, the Toronto site of the Canadian Pediatric Ischemic Stroke Registry (deVeber, 2017). This includes patients and their families seen in the Stroke Clinic at the Hospital for Sick Children who have consented to including their data in the study database. Children seen by the Stroke Clinic are routinely referred for neuropsychological assessment in the Psychology Department at the Hospital for Sick Children. To provide a brief overview of participant selection, for each of the three studies

data extraction occurred in stages. First, all registry participants were reviewed for the inclusion criteria of history of acute AIS diagnosed from birth to 16 years of age as well as study specific lesion characteristics. Second, exclusion criteria of relevant medical comorbidities that could influence cognitive outcomes were applied. Lastly, for each study participants were reviewed to determine whether they had all primary study measures available (i.e., neuropsychological test scores, mental health assessment, motor functioning and/or diagnosis, neuroimaging). Figure 1 provides a summary flow chart of participant selection. Further study specific details are provided in the Methods of each respective chapter.

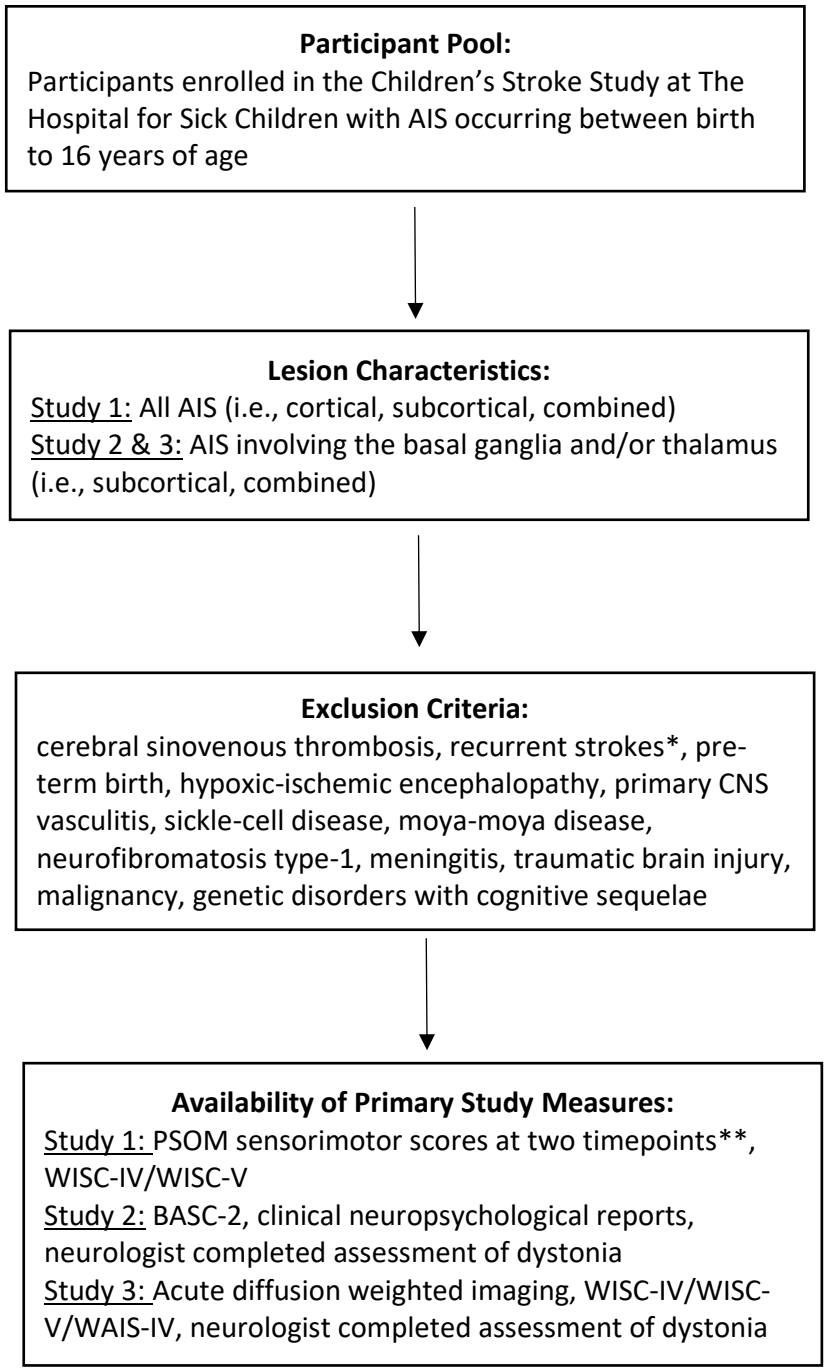

Figure 1. General procedure of participant selection

Note: WISC-IV= Wechsler Intelligence Scale for Children, 4th edition; WISC-V= Wechsler Intelligence Scale for Children, 5th edition; WAIS-IV= Wechsler Adult Intelligence Scale, 4th edition; BASC-2= Behaviour Assessment System for Children, 2nd edition; PSOM= Pediatric Stroke Outcome Measure; CNS= central nervous system. *Only data pertaining to the first

presentation of AIS was included. **Study 1 PSOM timepoints= Time 1: childhood group between 30 days post-stroke to 1 year; perinatal group between 2-5 years of age; Time 2 closest PSOM to neuropsychological testing.

References

Amlie-Lefond, C., Sébire, G., & Fullerton, H. J. (2008). Recent developments in childhood arterial ischaemic stroke. *The Lancet Neurology*, *7*(5), 425-435. 10.1016/S1474-4422(08)70086-3

Albanese, A., Bhatia, K., Bressman, S. B., DeLong, M. R., Fahn, S., Fung, V. S., ... & Lang, A. E. (2013). Phenomenology and classification of dystonia: a consensus update. *Movement Disorders*, *28*(7), 863-873. doi: 10.1002/mds.25475

Allman, C., & Scott, R. B. (2013). Neuropsychological sequelae following pediatric stroke: A nonlinear model of age at lesion effects. *Child Neuropsychology*, *19*(1), 97-107. doi: 10.1080/09297049.2011.639756

Anderson, V., Spencer-Smith, M., & Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*, *134*(8), 2197-2221. doi: 10.1093/brain/awr103

Anderson, V., Darling, S., Mackay, M., Monagle, P., Greenham, M., Cooper, A., ... & Gordon, A. L. (2020). Cognitive resilience following paediatric stroke: Biological and environmental predictors. European Journal of Paediatric Neurology, 25, 52-58. https://doi.org/10.1016/j.ejpn.2019.11.011

Askalan, R., Laughlin, S., Mayank, S., Chan, A., MacGregor, D., Andrew, M., ... & deVeber, G. (2001). Chickenpox and stroke in childhood: a study of frequency and causation. *Stroke*, *32*(6), 1257-1262. https://doi.org/10.1161/01.STR.32.6.1257

Ballantyne, A. O., Spilkin, A. M., Hesselink, J., & Trauner, D. A. (2008). Plasticity in the developing brain: intellectual, language and academic functions in children with ischaemic perinatal stroke. *Brain*, *131*(11), 2975-2985. doi: 10.1093/brain/awn176

Béjot, Y., Giroud, M., Moreau, T., & Benatru, I. (2012). Clinical spectrum of movement disorders after stroke in childhood and adulthood. *European neurology*, *68*(1), 59-64. doi: 10.1159/000336740

Bernard, T. J., Manco-Johnson, M. J., Lo, W., MacKay, M. T., Ganesan, V., DeVeber, G., ... & Ichord, R. (2012). Towards a consensus-based classification of childhood arterial ischemic stroke. *Stroke*, *43*(2), 371-377. https://doi.org/10.1161/STROKEAHA.111.624585

Boardman, J. P., Ganesan, V., Rutherford, M. A., Saunders, D. E., Mercuri, E., & Cowan, F. (2005). Magnetic resonance image correlates of hemiparesis after neonatal and childhood middle cerebral artery stroke. *Pediatrics*, *115*(2), 321-326. doi: 10.1542/peds.2004-0427

Bruggink, J. L., Einspieler, C., Butcher, P. R., Stremmelaar, E. F., Prechtl, H. F., & Bos, A. F. (2009). Quantitative aspects of the early motor repertoire in preterm infants: do they predict minor neurological dysfunction at school age?. *Early human development*, *85*(1), 25-36. https://doi.org/10.1016/j.earlhumdev.2008.05.010

Butcher, P. R., Van Braeckel, K., Bouma, A., Einspieler, C., Stremmelaar, E. F., & Bos, A. F. (2009). The quality of preterm infants' spontaneous movements: an early indicator of intelligence and behaviour at school age. *Journal of Child Psychology and Psychiatry*, *50*(8), 920-930. https://doi.org/10.1111/j.1469-7610.2009.02066.x

Cárdenas, J. F., Rho, J. M., & Kirton, A. (2011). Pediatric stroke. *Child's Nervous System*, *27*(9), 1375-1390. doi: 10.1007/s00381-010-1366-9

Carrera, E., & Tononi, G. (2014). Diaschisis: past, present, future. *Brain*, *137*(9), 2408-2422. https://doi.org/10.1093/brain/awu101

Carvalho, K. S., & Garg, B. P. (2002). Arterial strokes in children. *Neurologic clinics*, *20*(4),

1079-100. doi: 10.1016/s0733-8619(02)00012-9

Cheong, J. L., & Cowan, F. M. (2009, October). Neonatal arterial ischaemic stroke: obstetric issues. In *Seminars in Fetal and Neonatal Medicine* (Vol. 14, No. 5, pp. 267-271). WB Saunders. doi: 10.1016/j.siny.2009.07.009

Cooper, A. N., Anderson, V., Hearps, S., Greenham, M., Ditchfield, M., Coleman, L., ... & Gordon, A. L. (2018). Trajectories of motor recovery in the first year after pediatric arterial ischemic stroke. *Pediatrics, 140*(2), e20163870. doi: 10.1542/peds.2016-3870

Daniel, J., Cho, Y., von Borstel, D., & Summers, K. (2020). Decoding the diffusion: overview of restricted diffusion on brain MRI. J Am Osteopath Coll Radiol, 9, 20-31.

Dennis, M. (2000). Developmental plasticity in children: the role of biological risk, development, time, and reserve. *Journal of communication disorders*, *33*(4), 321-332. https://doi.org/10.1016/S0021-9924(00)00028-9

Dennis, M. (2010). Margaret Kennard (1899–1975): not a 'principle' of brain plasticity but a founding mother of developmental neuropsychology. *Cortex*, *46*(8), 1043-1059. https://doi.org/10.1016/j.cortex.2009.10.008

Dennis, M., Spiegler, B. J., Juranek, J. J., Bigler, E. D., Snead, O. C., & Fletcher, J. M. (2013). Age, plasticity, and homeostasis in childhood brain disorders. *Neuroscience & Biobehavioral Reviews, 37*(10), 2760-2773. https://doi.org/10.1016/j.neubiorev.2013.09.010

Deotto, A., Westmacott, R., Fuentes, A., deVeber, G., & Desrocher, M. (2019). Does stroke impair academic achievement in children? The role of metacognition in math and spelling outcomes following pediatric stroke. *Journal of clinical and experimental neuropsychology*, *41*(3), 257-269. doi: 10.1080/13803395.2018.1533528

deVeber, G. (2002). Stroke and the child's brain: an overview of epidemiology, syndromes and risk factors. *Current opinion in neurology*, *15*(2), 133-138. Doi: 10.1097/00019052-200204000-00002

deVeber, G. (2003). Risk factors for childhood stroke: little folks have different strokes!. Annals of Neurology: *Official Journal of the American Neurological Association and the Child Neurology Society*, *53*(2), 149-150. doi: 10.1002/ana.10461

deVeber, G. A., MacGregor, D., Curtis, R., & Mayank, S. (2000). Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *Journal of Child Neurology*, *15*(5), 316-324. https://doi.org/10.1177/088307380001500508

deVeber, G. A., Kirton, A., Booth, F. A., Yager, J. Y., Wirrell, E. C., Wood, E., ... & MacGregor, D. (2017). Epidemiology and outcomes of arterial ischemic stroke in children: the Canadian Pediatric Ischemic Stroke Registry. *Pediatric neurology*, *69*, 58-70. doi: 10.1016/j.pediatrneurol.2017.01.006

Diamond, A. (2000). Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child development*, *71*(1), 44-56. https://doi.org/10.1111/1467-8624.00117

Dlamini, N., Wintermark, M., Fullerton, H., Strother, S., Lee, W., Bjornson, B., ... & Linds, A. (2017). Harnessing Neuroimaging Capability in Pediatric Stroke: Proceedings of the Stroke Imaging Laboratory for Children Workshop. doi: 10.1542/peds.2007-1459

Dlamini, N., Yau, I., Muthusami, P., Mikulis, D. J., Elbers, J., Slim, M., ... & Moharir, M. (2018). Arterial wall imaging in pediatric stroke. Stroke, 49(4), 891-898. https://doi.org/10.1161/STROKEAHA.117.019827

Domi, T., Edgell, D. S., McCrindle, B. W., Williams, W. G., Chan, A. K., MacGregor, D. L., ...

& deVeber, G. A. (2008). Frequency, predictors, and neurologic outcomes of vaso-occlusive strokes associated with cardiac surgery in children. *Pediatrics*, *122*(6), 1292-1298.

Domi, T., deveber, G., Shroff, M., Kouzmitcheva, E., MacGregor, D. L., & Kirton, A. (2009). Corticospinal tract pre-wallerian degeneration: a novel outcome predictor for pediatric stroke on acute MRI. Stroke, 40(3), 780-787. https://doi.org/10.1161/STROKEAHA.108.529958

Elbers, J., deVeber, G., Pontigon, A. M., & Moharir, M. (2014). Long-term outcomes of pediatric ischemic stroke in adulthood. *Journal of child neurology*, *29*(6), 782-788. doi: 10.1177/0883073813484358

Elbers, J., Wilkinson, A., DeVeber, G., & Askalan, R. (2010, January). Lesion volume and localization as predictors of dystonia in pediatric basal ganglia stroke. In Annals of Neurology (Vol. 68, No. 4, pp. S98-S98).

Everts, R., Pavlovic, J., Kaufmann, F., Uhlenberg, B., Seidel, U., Nedeltchev, K., ... & Steinlin, M. (2008). Cognitive functioning, behavior, and quality of life after stroke in childhood. *Child Neuropsychology*, *14*(4), 323-338. doi: 10.1080/09297040701792383

Ferriero, D. M., Fullerton, H. J., Bernard, T. J., Billinghurst, L., Daniels, S. R., DeBaun, M. R., deVeber, G., Ichord R.N., Jordan, L.C., Massicotte, P., Meldau, J., Roach, S., Smith, E.R. on behalf of the American Heart Association Stroke Council and Council on Cardiovascular and Stroke Nursing. (2019). Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. Stroke, 50(3), e51-e96. https://doi.org/10.1161/STR.0000000000000183

Festa, J. R., Lazar, R. M., & Marshall, R. S. (2008). Ischemic stroke and aphasic

disorders. *Textbook of clinical neuropsychology*, 363-383.

Finger, S., Koehler, P. J., & Jagella, C. (2004). The Monakow concept of diaschisis: origins and perspectives. *Archives of Neurology, 61*(2), 283-288. doi:10.1001/archneur.61.2.283

Fitzgerald, K. C., Williams, L. S., Garg, B. P., & Golomb, M. R. (2007). Epilepsy in children with delayed presentation of perinatal stroke. Journal of child neurology, 22(11), 1274-1280. https://doi.org/10.1177/0883073807307106

Friedman, N. (2009). Pediatric stroke: past, present and future. *Advances in pediatrics*, *56*(1), 271-299. doi: 10.1016/j.yapd.2009.08.003

Fuentes, A., Deotto, A., Desrocher, M., deVeber, G., & Westmacott, R. (2016). Determinants of cognitive outcomes of perinatal and childhood stroke: A review. *Child Neuropsychology*, *22*(1), 1-38. doi: 10.1080/09297049.2014.969694

Fullerton, H. J., Wu, Y. W., Zhao, S., & Johnston, S. C. (2003). Risk of stroke in children: ethnic and gender disparities. *Neurology*, *61*(2), 189-194. doi: 10.1212/01.WNL.0000078894.79866.95

Ganesan, V., Hogan, A., Shack, N., Gordon, A., Isaacs, E., & Kirkham, F. J. (2000). Outcome after ischaemic stroke in childhood. *Developmental medicine and child neurology*, *42*(7), 455-461. Doi: 10.1017/S0012162200000852

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., ... & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences*, *101*(21), 8174-8179. https://doi.org/10.1073/pnas.0402680101

Goldfarb, J., Askalan, R., Pontigon, A., & deVeber, G. (2013). Lesion Volume and Localization

in Acute Ischemic Basal Ganglia Stroke as Predictors of Dystonia: 151. *Annals of Neurology*, *74*.

Golomb, M. R., MacGregor, D. L., Domi, T., Armstrong, D. C., McCrindle, B. W., Mayank, S., & DeVeber, G. A. (2001). Presumed pre-or perinatal arterial ischemic stroke: risk factors and outcomes. *Annals of neurology*, *50*(2), 163-168. doi: 10.1002/ana.1078

Greenham, M., Hearps, S., Gomes, A., Rinehart, N., Gonzalez, L., Gordon, A., ... & Anderson, V. (2015). Environmental contributions to social and mental health outcomes following pediatric stroke. *Developmental neuropsychology*, *40*(6), 348-362. doi: https://doi.org/10.1080/87565641.2015.1095191

Greenham, M., Anderson, V., & Mackay, M. T. (2017). Improving cognitive outcomes for pediatric stroke. *Current opinion in neurology*, *30*(2), 127-132. doi: 10.1097/WCO.0000000000000422

Grunt, S., Mazenauer, L., Buerki, S. E., Boltshauser, E., Mori, A. C., Datta, A. N., ... & Steinlin, M. (2015). Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. Pediatrics, 135(5), e1220-e1228. https://doi.org/10.1542/peds.2014-1520

Hadders-Algra, M. (2008). Reduced variability in motor behaviour: an indicator of impaired cerebral connectivity?. *Early human development*, *84*(12), 787-789. https://doi.org/10.1016/j.earlhumdev.2008.09.002

Hajek, C. A., Yeates, K. O., Anderson, V., Mackay, M., Greenham, M., Gomes, A., & Lo, W. (2014). Cognitive outcomes following arterial ischemic stroke in infants and children. *Journal of Child Neurology*, *29*(7), 887-894. doi: 10.1177/0883073813491828

Hartman, A. L., Lunney, K. M., & Serena, J. E. (2009). Pediatric stroke: do clinical factors predict delays in presentation?. *The Journal of pediatrics*, *154*(5), 727-732. doi:

10.1016/j.jpeds.2008.11.011

Härtel, C., Schilling, S., Sperner, J., & Thyen, U. (2004). The clinical outcomes of neonatal and childhood stroke: review of the literature and implications for future research. *European Journal of Neurology*, *11*(7), 431-438. doi: 10.1111/j.1468-1331.2004.00861.x

Hogan, A. M., Kirkham, F. J., & Isaacs, E. B. (2000). Intelligence after stroke in childhood: review of the literature and suggestions for future research. *Journal of child neurology*, *15*(5), 325-332. doi: 10.1177/088307380001500509

Holtz, J.L. (2011). Applies Clinical Neuropsychology: An Introduction. *Springer Publishing Company:* New York

Hurvitz, E., Warschausky, S., Berg, M., & Tsai, S. (2004). Long-term functional outcome of pediatric stroke survivors. *Topics in stroke rehabilitation*, *11*(2), 51-59. doi: 10.1310/CL09-U2QA-9M5A-ANG2

Husson, B., Hertz-Pannier, L., Renaud, C., Allard, D., Presles, E., Landrieu, P., & Chabrier, S. (2010). Motor outcomes after neonatal arterial ischemic stroke related to early MRI data in a prospective study. *Pediatrics*, *126*(4), e912-e918. doi: 10.1542/peds.2009-3611

Jacomb, I., Porter, M., Brunsdon, R., Mandalis, A., & Parry, L. (2018). Cognitive outcomes of pediatric stroke. *Child Neuropsychology*, *24*(3), 287-303. doi: 10.1080/09297049.2016.1265102

Jinnah, H. A., & Hess, E. J. (2006). A new twist on the anatomy of dystonia: the basal ganglia and the cerebellum?. doi: 10.1212/01.wnl.0000246112.19504.61

Jinnah, H. A., Neychev, V., & Hess, E. J. (2017). The anatomical basis for dystonia: the motor network model. *Tremor and Other Hyperkinetic Movements*, *7*. doi: 10.7916/D8V69X3S

Johnson, A. C., McNabb, A. R., & Rossiter, R. J. (1950). Chemistry of Wallerian degeneration: a review of recent studies. Archives of Neurology & Psychiatry, 64(1), 105-121. doi:10.1001/archneurpsyc.1950.02310250111010

Johnston, M. V. (2009). Plasticity in the developing brain: implications for rehabilitation. Developmental disabilities research reviews, 15(2), 94-101. doi: 10.1002/ddrr.64

Karalok, Z. S., Genc, H. M., Taskin, B. D., Ceylan, N., Guven, A., & Yarali, N. (2019). Risk factors and motor outcome of paediatric stroke patients. *Brain and Development*, *41*(1), 96-100. https://doi.org/10.1016/j.braindev.2018.07.004

Kennard, M. A. (1936). Age and other factors in motor recovery from precentral lesions in monkeys. *American Journal of Physiology-Legacy Content*, *115*(1), 138-146. https://doi.org/10.1152/ajplegacy.1936.115.1.138

Kirton, A., & deVeber, G. (2009). Advances in perinatal ischemic stroke. *Pediatric Neurology*, *40*(3), 205-214. doi: 10.1016/j.pediatrneurol.2008.09.018

Kirton, A., & deVeber, G. (2013). Life after perinatal stroke. *Stroke*, *44*(11), 3265-3271. doi: 10.1161/STROKEAHA.113.000739

Kirton, A., Westmacott, R., & Deveber, G. (2007). Pediatric stroke: Rehabilitation of focal injury in the developing brain. *NeuroRehabilitation, 22*(5), 371-382. doi: 10.3233/NRE-2007-22504

Kirton, A., Williams, E., Dowling, M., Mah, S., Hodge, J., Carlson, H., ... & PedNIHSS Investigators. (2016). Diffusion imaging of cerebral diaschisis in childhood arterial ischemic stroke. International Journal of Stroke, 11(9), 1028-1035. https://doi.org/10.1177/1747493016666089

Kitchen, L., Westmacott, R., Friefeld, S., MacGregor, D., Curtis, R., Allen, A., Yau, I., Askalan, R., Moharir, M., Domi, T., & deVeber, G. (2012). The pediatric stroke outcome measure: a validation and reliability study. *Stroke*, *43*(6), 1602-1608. doi: 10.1161/strokeaha.111.639583

Kolb, B., Teskey, C., & Gibb, R. (2010). Factors influencing cerebral plasticity in the normal and injured brain. *Frontiers in human neuroscience*, *4*, 204. doi: 10.3389/fnhum.2010.00204

Krishnamurthi, R. V., Feigin, V. L., Forouzanfar, M. H., Mensah, G. A., Connor, M., Bennett, D. A., ... & O'Donnell, M. (2013). Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *The Lancet Global Health*, *1*(5), e259-e281. doi: 10.1016/S2214-109X(13)70089-5

Lehéricy, S., Tijssen, M. A., Vidailhet, M., Kaji, R., & Meunier, S. (2013). The anatomical basis of dystonia: current view using neuroimaging. *Movement Disorders*, *28*(7), 944-957. doi: 10.1002/mds.25527

Lezak, M. D., Howieson, D. B., & Loring, D. W. (1995). Neuropsychological assessment. New York: Oxford University Press

Lo, W., Gordon, A., Greenham, M., Gomes, A., Hajek, C., Mackay, M., ... & Anderson, V. (2012). Pediatric Stroke Outcome Measure Predicts Cognitive And Functional Deficits After Childhood Ischemic Stroke. doi: 10.1161/str.43.suppl_1.A2375

Long, B., Anderson, V., Jacobs, R., Mackay, M., Leventer, R., Barnes, C., & Spencer-Smith, M. (2011). Executive function following child stroke: The impact of lesion size. *Developmental neuropsychology*, *36*(8), 971-987. doi: 10.1080/87565641.2011.581537

Lynch, J. K. (2009, October). Epidemiology and classification of perinatal stroke. In *Seminars in Fetal and Neonatal Medicine* (Vol. 14, No. 5, pp. 245-249). WB Saunders. doi: 10.1016/j.siny.2009.07.001

Mallick, A. A., Ganesan, V., Kirkham, F. J., Fallon, P., Hedderly, T., McShane, T., ... & Edwards, H. B. (2014). Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. *The Lancet Neurology*, *13*(1), 35-43. doi: 10.1016/S1474-4422(13)70290-4

Malone, L. A., & Felling, R. J. (2020). Pediatric stroke: unique implications of the immature brain on injury and recovery. *Pediatric neurology*, *102*, 3-9. https://doi.org/10.1016/j.pediatrneurol.2019.06.016

Marsden, C. D., Obeso, J. A., Lang, A. E., Hill, D., & Se, L. (1985). The anatomical basis of symptomatic hemidystonia. Brain, 108(2), 463–483. doi:10.1093/brain/108.2.463

Max, J. E., Fox, P. T., Lancaster, J. L., Kochunov, P., Mathews, K., Manes, F. F., ... & Lansing, A. E. (2002). Putamen lesions and the development of attention-deficit/hyperactivity symptomatology. *Journal of the American Academy of Child & Adolescent Psychiatry*, *41*(5), 563-571. doi: 10.1097/00004583-200205000-00014

Max, J. E., Schachar, R. J., Levin, H. S., Ewing-Cobbs, L., Chapman, S. B., Dennis, M., ... & Landis, J. (2005). Predictors of attention-deficit/hyperactivity disorder within 6 months after pediatric traumatic brain injury. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*(10), 1032-1040. doi: 10.1097/01.chi.0000173293.05817.b1

Max, J. E., Bruce, M., Keatley, E., & Delis, D. (2010). Pediatric stroke: plasticity, vulnerability, and age of lesion onset. *The Journal of neuropsychiatry and clinical neurosciences*, *22*(1), 30-39. doi: 10.1176/jnp.2010.22.1.30

Mercuri, E., Barnett, A., Rutherford, M., Guzzetta, A., Haataja, L., Cioni, G., ... & Dubowitz, L. (2004). Neonatal cerebral infarction and neuromotor outcome at school age. Pediatrics, 113(1), 95-100. doi: 10.1542/peds.113.1.95

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual review of neuroscience*, *24*(1), 167-202. doi: 10.1146/annurev.neuro.24.1.167

Mink, J. W. (2003). The basal ganglia and involuntary movements: impaired inhibition of competing motor patterns. *Archives of neurology*, *60*(10), 1365-1368. doi: 10.1001/archneur.60.10.1365

Murray, G. K., Jones, P. B., Kuh, D., & Richards, M. (2007). Infant developmental milestones and subsequent cognitive function. *Annals of neurology*, *62*(2), 128-136. https://doi.org/10.1002/ana.21120

Nelson, K. B., & Lynch, J. K. (2004). Stroke in newborn infants. *The Lancet Neurology*, *3*(3), 150-158. doi: 10.1016/S1474-4422(04)00679-9

O'Keeffe, F., Liégeois, F., Eve, M., Ganesan, V., King, J., & Murphy, T. (2014). Neuropsychological and neurobehavioral outcome following childhood arterial ischemic stroke: attention deficits, emotional dysregulation, and executive dysfunction. *Child Neuropsychology*, *20*(5), 557-582. doi: 10.1080/09297049.2013.832740

Oudgenoeg-Paz, O., Mulder, H., Jongmans, M. J., van der Ham, I. J., & Van der Stigchel, S. (2017). The link between motor and cognitive development in children born preterm and/or with low birth weight: A review of current evidence. *Neuroscience & Biobehavioral Reviews, 80,* 382-393. https://doi.org/10.1016/j.neubiorev.2017.06.009

Parent, A., & Hazrati, L. N. (1995). Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain research reviews*, *20*(1), 91-127. https://doi.org/10.1016/0165-0173(94)00007-C

Pavlovic, J., Kaufmann, F., Boltshauser, E., Mori, A. C., Mercati, D. G., Haenggeli, C. A., ... & Perez, E. R. (2006). Neuropsychological problems after paediatric stroke: two year follow-up of Swiss children. *Neuropediatrics*, *37*(01), 13-19. doi: 10.1055/s-2006-923932

Peyton, C., Einspieler, C., Fjørtoft, T., Adde, L., Schreiber, M. D., Drobyshevsky, A., & Marks, J. D. (2020). Correlates of normal and abnormal general movements in infancy and Long-Term neurodevelopment of preterm infants: insights from functional connectivity studies at term equivalence. *Journal of Clinical Medicine*, *9*(3), 834. https://doi.org/10.3390/jcm9030834

Quartarone, A., & Hallett, M. (2013). Emerging concepts in the physiological basis of dystonia. *Movement Disorders*, *28*(7), 958-967. doi: 10.1002/mds.25532

Roach, E. S., Golomb, M. R., Adams, R., Biller, J., Daniels, S., Deveber, G., ... & Smith, E. R. (2008). Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. *Stroke*, *39*(9), 2644-2691. doi: 10.1161/STROKEAHA.108.189696

Rodan, L., McCrindle, B. W., Manlhiot, C., MacGregor, D. L., Askalan, R., Moharir, M., & Deveber, G. (2012). Stroke recurrence in children with congenital heart disease. *Annals of neurology*, *72*(1), 103-111. doi: 10.1002/ana.23574

Rodrigues, S. D. D., Ciasca, S. M., Guimaraes, I. E., Elias, K. M. I. D. F., Oliveira, C. C., &

Moura-Ribeiro, M. V. L. D. (2011). Does stroke impair learning in children?. *Stroke research and treatment*, *2011*. doi: 10.4061/2011/369836

Sanger, T. D., Chen, D., Fehlings, D. L., Hallett, M., Lang, A. E., Mink, J. W., ... & Chen, R. (2010). Definition and classification of hyperkinetic movements in childhood. *Movement Disorders*, *25*(11), 1538-1549. doi: 10.1002/mds.23088

Scott, B. L., & Jankovic, J. (1996). Delayed-onset progressive movement disorders after static brain lesions. *Neurology*, *46*(1), 68-74. https://doi.org/10.1212/WNL.46.1.68

Semple, B. D., Blomgren, K., Gimlin, K., Ferriero, D. M., & Noble-Haeusslein, L. J. (2013). Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. *Progress in neurobiology*, *106*, 1-16. https://doi.org/10.1016/j.pneurobio.2013.04.001

Soman, T., Askalan, R., Martin, M., Allen, A., Zak, M., MacGregor, D., & Logan, W. (2006). Predictors of dystonia in childhood basal ganglia stroke. Neuropediatrics, 37(S1), 121. doi: 10.1055/s-2006-945715

Sreenan, C., Bhargava, R., & Robertson, C. M. (2000). Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *The Journal of pediatrics*, *137*(3), 351-355. doi: 10.1067/mpd.2000.107845

Srinivasan, J., Miller, S. P., Phan, T. G., & Mackay, M. T. (2009). Delayed recognition of initial stroke in children: need for increased awareness. *Pediatrics*, *124*(2), e227-e234. doi: 10.1542/peds.2008-3544

Steinlin, M., Roellin, K., & Schroth, G. (2004). Long-term follow-up after stroke in childhood. *European journal of pediatrics*, *163*(4-5), 245-250. doi: 10.1007/s00431-003-1357-x

Stoessl, A. J., Lehericy, S., & Strafella, A. P. (2014). Imaging insights into basal ganglia function, Parkinson's disease, and dystonia. *The Lancet*, *384*(9942), 532-544. doi: 10.1016/S0140-6736(14)60041-6

Studer, M., Boltshauser, E., Mori, A. C., Datta, A., Fluss, J., Mercati, D., ... & Ramelli, G. P. (2014). Factors affecting cognitive outcome in early pediatric stroke. *Neurology*, *82*(9), 784-792. doi: 10.1212/WNL.0000000000000162

Tibussek, D., Mayatepek, E., Klee, D., & Koy, A. (2015). Post stroke hemi-dystonia in children: a neglected area of research. *Molecular and cellular pediatrics*, *2*(1), 1-5. doi: 10.1186/s40348-015-0026-2

Villablanca, J. R., & Hovda, D. A. (1999). Developmental neuroplasticity in a model of cerebral hemispherectomy and stroke. *Neuroscience*, *95*(3), 625-637. doi: 10.1016/S0306-4522(99)00482-0

Waller, A. V. (1850). XX. Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibres. *Philosophical transactions of the Royal society of London*, (140), 423-429. https://doi.org/10.1098/rstl.1850.0021

Westmacott, R., MacGregor, D., Askalan, R., & deVeber, G. (2009). Late emergence of cognitive deficits after unilateral neonatal stroke. *Stroke*, *40*(6), 2012-2019. doi: 10.1161/STROKEAHA.108.533976

Westmacott, R., Askalan, R., Macgregor, D., Anderson, P., & Deveber, G. (2010). Cognitive outcome following unilateral arterial ischaemic stroke in childhood: effects of age at stroke and lesion location. *Developmental Medicine & Child Neurology*, *52*(4), 386-393. doi: 10.1111/j.1469-8749.2009.03403.x

Westmacott, R., McDonald, K. P., Roberts, S. D., deVeber, G., MacGregor, D., Moharir, M., Dlamini, N., & Williams, T. S. (2018a). Predictors of cognitive and academic outcome following childhood subcortical stroke. *Developmental neuropsychology*, *43*(8), 708-728. https://doi.org/10.1080/87565641.2018.1522538

Westmacott, R., McDonald, K. P., deVeber, G., MacGregor, D., Moharir, M., Dlamini, N., Askalan, R., & Williams, T. S. (2018b). Neurocognitive outcomes in children with unilateral basal ganglia arterial ischemic stroke and secondary hemidystonia. *Child Neuropsychology*, *24*(7), 923-937. doi: 10.1080/09297049.2017.1353073

Williams, T. S., McDonald, K. P., Roberts, S. D., Dlamini, N., deVeber, G., & Westmacott, R. (2017). Prevalence and predictors of learning and psychological diagnoses following pediatric arterial ischemic stroke. *Developmental neuropsychology*, *42*(5), 309-322. doi: 10.1080/87565641.2017.1353093

Zimmer, J. A., Garg, B. P., Williams, L. S., & Golomb, M. R. (2007). Age-related variation in presenting signs of childhood arterial ischemic stroke. *Pediatric neurology*, *37*(3), 171-175. doi: 10.1016/j.pediatrneurol.2007.05.010

Chapter 2: Motor Outcomes in Pediatric Arterial Ischemic Stroke and Associations with Intellectual Outcome

Arterial ischemic stroke (AIS) is a significant cause of acquired neurological disability in children. Between 50-75% of survivors experience long-term neurological impairment, including cognitive, behavioural, and motor challenges (deVeber, et al., 2000). As a group, children with pediatric AIS typically perform toward the lower end of the average range on intellectual batteries, though this is still statistically lower than that of the normative group (Allman & Scott, 2013; Everts et al., 2008; O'Keeffe et al., 2014; Pavlovic et al., 2006; Studer et al., 2014; Westmacott et al., 2009). However, there is notable variability in cognitive outcomes within the pediatric AIS population, with a substantial proportion of children showing below average and impaired performance on tests of intellectual functioning, making it difficult to prognosticate about individual outcome (Fuentes et al. 2016; Hogan et al., 2000; Williams et al., 2017). Improving understanding of cognitive outcomes after stroke is a key priority for caregivers and has important implications for development of rehabilitation and education strategies (Edwards et al., 2015; Greenham et al., 2017). Predictors of intellectual outcome such as age at stroke, lesion characteristics (e.g., location and size), post-stroke seizure disorders, and persistent neurological deficits have been examined, but results across studies have been inconsistent (Fuentes et al., 2016). Motor impairments are one of the most common adverse outcomes after pediatric AIS, affecting approximately half of pediatric stroke survivors (Cooper et al., 2017, Ganesan et al., 2000; Kirton et al., 2007), however there is limited research on the relationship between motor impairment and cognitive outcomes in this population. The development and developmental trajectories of cognitive and motor skills are closely interrelated, and they share common neural substrates, including the prefrontal cortex, cerebellum, and cortico-striatal

connections (Diamond, 2000; Gogtay et al., 2004). Moreover, there is evidence that motor functioning is predictive of intellectual ability in other populations and that brain connectivity, particularly cortical-subcortical pathways, underlies this association (Murray et al., 2007; Oudgenoeg-Paz et al., 2017; Piek et al., 2008). As an insult to the developing brain, such as AIS, can interrupt development of critical neural networks (Anderson et al., 2011; Dennis, 2000; Dennis et al., 2013**)**, we question whether motor impairments after stroke persisting outside of the acute period may reflect maladaptive outcomes in neural reorganization, that may in turn be associated with intellectual functioning. The current study examined whether motor functioning is associated with intellectual outcomes in children with pediatric AIS and explored clinical features associated with motor impairment.

With respect to intellectual functioning, when control groups are available children with AIS have been found to perform significantly lower than healthy siblings, (Schatz & Buzan, 2006), children with orthopedic injuries (Lansing et al., 2004; Max et al., 2010), and children with sickle-cell disease with no history of stroke (Bernaudin et al., 2000; Schatz & Buzan, 2006), There is some evidence that performance (non-verbal) IQ is more affected than verbal IQ, and that children with unilateral injuries do not show the same lateralization of deficits as adults (Everts et al., 2008; Ganesan et al., 2000; Hogan et al., 2000; Pavlovic et al., 2006). Speed of information processing and working memory, which are components of the Wechsler intelligence scales, have also been demonstrated to be lower than expected in pediatric AIS (Everts et al., 2008; Hajek et al., 2014; Long et al., 2011; Studer et al., 2014; Westmacott et al., 2009; 2010; White et al., 2000). However, there is tremendous interindividual variability in cognitive outcomes within the pediatric AIS population (Hogan et al., 2000; Long et al., 2011; Fuentes et al. 2016; Pavlovic et al., 2006; Steinlin et al., 2004). For example, reported ranges of

full-scale IQ (FSIQ) span from impaired to superior performance (e.g., 65-116 [Simma et al., 2007]; 52-132 [Long et al., 2011]).

This heterogeneity within intellectual outcomes is not fully explained by lesion or stroke characteristics (i.e., lesion size, lesion location, age at stroke, neurological impairment), therefore it is important to examine why some children display cognitive resilience whereas other are more severely impacted by AIS. Neurological impairment as assessed by formal rating scales (e.g., the Pediatric Stroke Outcome Measure [PSOM; Kitchen et al., 2012] or modified Rankin Scale [mRS; Bigi et al., 2001]) or detailed neurological examination has been found to be significantly associated with intellectual outcomes, however many scales include subscales that assess cognitive functioning which may account for these associations (Anderson et al., 2020; Hajek et al., 2014; Studer et al., 2014). Younger age at stroke (< 1 year) has been associated with poorer outcomes in intellectual ability (Allman & Scott, 2013; Jacomb et al., 2018; Max et al., 2010; Studer et al., 2014; Westmacott et al., 2010). However, this relationship is moderated by lesion location, with subcortical lesions most detrimental during the perinatal period and cortical lesions most detrimental during early childhood (Westmacott et al., 2010). Emerging deficits after neonatal stroke highlight that while deficits may not be immediately present, they become apparent overtime (Levine et al., 2005; Westmacott et al., 2009). Danguecan et al., (2017) found that, when assessed at early school age, three out of 26 children with neonatal stroke declined by 15 or 16 standard score points from their pre-school testing, such that performance fell below age expectations at follow-up. Of note, all the children whose performance declined had combined cortical-subcortical lesions and hemiparesis providing support that these factors may be moderators of outcome. Larger lesion size has also been associated with poorer intellectual outcome (Hajek et al., 2013; Hetherington et al., 2005; Westmacott et al., 2010) and processing

speed (Everts et al., 2008). However, this finding has not been consistent across studies (e.g., Ballantyne et al., 2008), and the moderating effect of neurological impairment and emerging deficits on this relationship has been highlighted (Hajek et al., 2013; Levine et al., 2005). Combined cortical-subcortical lesions have been shown to be associated with the poorest intellectual outcomes (Studer et al., 2014; Westmacott et al., 2010). In contrast, another study found combined cortical-subcortical lesions impacted attention, but not intellectual ability (Hajek et al., 2013). Additionally, deficits in working memory and processing speed have been documented even in the absence of subcortical involvement (Peterson et al., 2019). Post-stroke seizure disorders affect 15-30% of children with AIS (Fox et al., 2013) and have negative effects on cognitive functioning, especially in language abilities (Avila et al., 2010; Studer et al., 2014; De Schryver et al., 2000). However, the interaction of seizure status with other predictor variables is relevant, for example emerging deficits in neonatal stroke were found regardless of seizure status (Levine et al., 2005) and other studies have found deficits when epilepsy was an exclusion criterion (Westmacott et al., 2010). Taken together, these findings demonstrate the importance of injury and clinical predictors of intellectual outcome in pediatric AIS, but also highlight the complex interactions among them and show that our understanding of predictors of intellectual outcome after pediatric AIS is far from complete.

Motor impairments are one of the most common adverse outcomes after pediatric AIS, affecting 30-60% of children (de Veber et al., 2000; Cooper et al., 2017; Ganesan et al., 2000; Hartel et al., 2004; Kolk et al., 2011). Estimates of chronic hemiparesis (> 6 months duration) in childhood stroke range between 25% to 56% for childhood stroke and 20-28% in neonatal stroke (Boardman et al., 2005; Ganesan et al., 2000; Mercuri et al., 2004, Sreenan et al., 2012). Additionally, post-stroke movement disorders such as dystonia and athetosis present more

commonly in children than in adults (Bejot et al., 2012; Tibussek et al., 2015). Predictors of poorer motor outcome at 12 months include large lesion size, neurological impairment at 1-month, and age at stroke ≥ 5 years (Cooper et al., 2017; Karalok et al., 2019). With respect to the influence of lesion location, concomitant involvement of the cerebral cortex, basal ganglia, and posterior limb of the internal capsule was found to predict hemiparesis in neonatal stroke, whereas involvement of only one or two of these structures was not associated with hemiparesis (Boardman et al. 2005). This association was also seen in childhood-onset stroke; however, in contrast to neonates, children with involvement of only one or two of the structures also displayed hemiparesis, with involvement of only the basal ganglia being the least likely lesion location to be associated with hemiparesis. Additionally, the presence of Wallerian degeneration (WD), the anterograde degeneration of axons and their myelin sheaths after proximal axonal or cell body injury, has been associated with poor motor outcome in neonatal and childhood stroke (De Vries et al., 2005; Domi et al., 2009; Domi et al., 2020; Kirton et al., 2007a). Cooper et al., (2017) found similar rates of hemiparesis 12-months post-AIS in neonates (33%), pre-school age children (21%), and school-age children (33%), however, recovery trajectories of fine and gross motor skills differed. Neonates showed emerging deficits overtime whereas the pre-school and school age children showed initial impairment with gradual recovery. Pre-school and school age children showed a similar magnitude of recovery over time, though pre-school age children had better motor skills at all time points. Motor ability impacts important domains of functioning in children with AIS including adaptive skills, participation in the school and community, fatigue, and quality of life (Cooper et al., 2018; Lo et al., 2012; 2014). A small number of studies have examined associations between current motor functioning and cognitive functioning in pediatric stroke providing some, albeit limited, evidence of an association (Abgottspon et al., 2021; Lo et

al., 2014; Westmacott et al., 2018a). There is also evidence that persistent motor difficulties (e.g., hemiplegia, dystonia) are associated with worse cognitive outcome (Allman & Scott, 2011; Ricci et al., 2007; Westmacott et al., 2018b).

Cognitive and motor skills both display protracted development, continuing into adolescence (Diamond, 2000) as do the neurobiological substrates of these functions (Gogtay et al., 2004). Functional imaging studies demonstrate that the prefrontal cortex and cerebellum are co-activated when completing cognitive and motor tasks (see Diamond, 2000 for a review) and the importance of cortico-striatal connectivity for motor and cognitive skills has been demonstrated (Tekin & Cummings, 2002; Van Schouwenburg et al., 2010; 2013). The capacity of early motor functioning to predict later cognitive skills has been demonstrated in healthy children (Capute et al., 1985; Murray et al., 2007; Piek et al., 2008), whereas associations between concurrent motor and cognitive functioning have shown mixed results (Roebers & Kauer, 2009; Stockel & Hughes, 2016; Wassenberg et al., 2005; van der Fels et al., 2015). In children born preterm, a population at risk for adverse motor and cognitive outcomes, motor functioning assessed early in the post-term period has been associated with later cognitive outcomes (Butcher et al., 2009; Bruggink et al., 2010; Einspieler et al., 2016; Oudgenoeg-Paz et al., 2017; Spittle et al., 2013) and there is some evidence supporting an association between concurrent motor and cognitive functioning in this population (Van Hus et al., 2014). A potential explanation for these associations between motor and cognitive functioning is that the observed motor abnormalities may reflect neural network disruption or underdevelopment (e.g., damage to white matter or reduced cortical connectivity) in regions important for cognitive and motor development such as cortical-subcortical and cortico-cerebellar connectivity (Diamond, 2000; Hadders-Algra, 2008; Murray et al., 2007; Oudgenoeg-Paz et al., 2017; Peyton et al., 2020; Van

Haastert et al., 2012), whereas appropriate motor functioning may reflect integrity of these regions (Bruggink et al., 2010; Butcher et al., 2009; Murray et al., 2007).

Insult to the developing brain, such as AIS, can interrupt subsequent development and establishment of critical neural networks (Anderson et al., 2011; Dennis, 2000; Dennis et al., 2013). There is increasing recognition of the importance of considering the impact of dysfunction on neural networks, rather than focusing on a single functional brain region, when examining cognitive and motor outcomes in pediatric stroke (Govaert et al. 2007; Tibussek et al., 2015; Kirton et al., 2016). Recovery from early brain injury involves neuroplasticity; the capacity of the brain to learn new information, change in response to the environment, and recover from injury (Anderson et al. 2011; Johnston, 2009). The outcomes of plasticity can be adaptive or maladaptive resulting in either resilience in functional outcome or poor outcomes (Dennis et al., 2013; Johnston, 2009), as is seen after pediatric AIS, with some children displaying resilience and others affected by lasting cognitive and motor difficulties (Anderson et al., 2020). Therefore, we question whether motor impairments lasting beyond the acute phase of stroke assessed during early post-stroke recovery may be indicative of disruptions in neural networks (i.e., maladaptive outcomes of plasticity) and therefore associated with poorer intellectual outcomes, which in turn could be used for identification of children who may benefit from early intervention. The primary aim of the current study is to determine whether motor functioning assessed during early recovery is associated with intellectual outcome at school age. We hypothesized that poorer motor functioning during early recovery would be associated with poorer intellectual outcomes. Second, we examined the stability of motor functioning between the first assessment and the assessment closest to the time of neuropsychological testing as well as whether current motor functioning is associated with intellectual outcomes. Finally, we also

examined differences in clinical features of children with good and poor motor outcomes, including previously established predictors of intellectual outcome such as age at stroke, lesion size, lesion location, and current seizures.

Method

Patient Population

Participants were identified upon enrollment in the Children's Stroke Study at the Hospital for Sick Children in Toronto, Ontario, the Toronto site of the Canadian Pediatric Ischemic Stroke Registry (deVeber, 2017). Children were considered for participation if they had a history of arterial ischemic stroke (AIS), diagnosed from birth to 16 years of age; a unilateral or bilateral infarct documented on magnetic resonance imaging (MRI) or computed tomography (CT); and had completed an IQ assessment between 6 to 16 years of age (i.e., WISC-IV or WISC-V). Neuropsychological assessments were all conducted at least one-year post-stroke. This sample included three groups of children: acute neonatal AIS (stroke diagnosed acutely within 28 days of life), acute childhood AIS (stroke diagnosed acutely between 29 days and 18 years of life) and presumed perinatal AIS (retrospective diagnosis of stroke presumed to have occurred in the perinatal period). Exclusion criteria were recurrent stroke, cerebral sinovenous thrombosis, preterm birth, hypoxic-ischemic encephalopathy, CNS vasculitis, sickle cell disease, moyamoya disease, neurofibromatosis type 1, meningitis, traumatic brain injury, malignancy, and genetic disorders with cognitive sequalae. Children were required to have sufficient fluency in English to be able to complete the IQ measure.

Procedure

The study was approved by the Research Ethics Board at the Hospital for Sick Children. Patients seen in the Stroke Clinic at the Hospital for Sick Children and their parents provided

informed consent for use of this information as part of their enrollment in the Children's Stroke Study. Children seen in the Stroke clinic are routinely referred to the Psychology Department for neuropsychological assessment regardless of their neurocognitive functioning. Medical and imaging data were collected between 1994-2013 by pediatric neurologists, the Pediatric Stroke Outcome Measure was completed between 1995-2020 by pediatric neurologists and clinical neuropsychological assessments were conducted between 2005-2019 by clinical neuropsychologists in the Children's Stroke Program.

Measures

Demographic Characteristics

Demographic characteristics were obtained from the registry database of the Children's Stroke Study. Data were collected via a standardized review of health records, structured parental interview, and a medical and neuropsychological history questionnaire completed by parents. Maternal education level was used as an indicator of socioeconomic status rated on a 6-point scale as follows: (1= did not complete elementary school, 2= completed some high school, 3= completed high school, 4= completed some post-secondary education, 5= completed college or university, 6= completed professional or graduate school). Age at stroke was calculated based on the date of clinical presentation and stroke confirmation on neuroimaging. Children with presumed perinatal stroke were assigned 0 as the age of stroke. Children were stratified into two groups based on age at stroke as described above: perinatal AIS including both presumed perinatal and acute neonatal AIS and acute childhood AIS. Age at test was calculated based on the date of the child's neuropsychological assessment.

Neurological and Clinical Factors

Seizure disorder at the time of assessment was coded as present or absent. Time since stroke was calculated as the time between the date of stroke and date of neuropsychological assessment. Information about motor presentation was obtained from a review of medical records. Specifically, the presence of hemiparesis, cerebral palsy, spasticity, and dystonia as diagnosed by neurological assessment completed within one year of neuropsychological testing was recorded. Information about handedness prior to stroke, and a handedness switch was also obtained.

Lesion Characteristics

Lesions were coded for location, size, and laterality by the study neuropsychologist (RW) based on a systematic review of clinically acquired MRI images and official radiology reports using criteria consistent with previous studies (Westmacott et al., 2009; 2010). Lesion location was coded as: cortical – infarct restricted to cortical regions; subcortical – infarct restricted to the basal ganglia and/or thalamus; or combined – infarct involving cortex, plus basal ganglia and/or thalamus. Lesion size was coded as: small – involving 1/3 of total volume of a single lobe or major subcortical structure; medium – involving from 1/3 to 2/3 of the volume of a single lobe or major subcortical structure OR involving less than ½ of the volume of two or more lobes/subcortical structures; large – involving greater than 2/3 of the volume of one lobe or major subcortical structure OR involving greater than ½ of the volume of two or more lobes/subcortical structures. Lesion laterality was coded as right, left, or bilateral.

Motor Functioning

The Pediatric Stroke Outcome measure (PSOM; Kitchen et al, 2012) is a standardized disease-specific, neurologist-completed outcome measure of neurological function and deficit in

survivors of pediatric stroke. It provides information about cognition/behaviour, language comprehension, language production, left sensorimotor function, and right sensorimotor function. Each subscale is rated as 0- no deficit, 0.5- mild deficit, normal function, 1- moderate deficit, decreased function, 2- severe deficit, missing function. The PSOM has demonstrated good construct validity and interrater reliability (Kitchen et al., 2012). In this study we used the right and left sensorimotor subscales. PSOM scores from two time points were obtained for all participants. In the child group the PSOM score after 30 days but within one-year post stroke was used as Time 1. In the perinatal group the earliest PSOM available after 2 years of age was obtained for Time 1, we included children who had PSOMs completed during the preschool period (i.e., between ages 2 to 5 years old). This was done to account for emerging deficits after perinatal stroke that may not be captured by the PSOM administered in infancy (Cooper et al., 2018; Cooper et al., 2020; Kitchen et al., 2012). For both groups, the Time 2 PSOM was the PSOM obtained closest to the time of neuropsychological assessment.

Intellectual Abilities

Intellectual abilities were assessed using either the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV; Wechsler, 2003) or 5th edition (WISC-V; Wechsler, 2014). Index scores common to both measures include measures of overall intellectual ability (Full Scale IQ; FSIQ), verbal knowledge and verbal reasoning (Verbal Comprehension Index; VCI), speed of information processing (Processing Speed Index; PSI), and working memory/mental manipulation (Working Memory Index; WMI). The WISC-IV includes the Perceptual Reasoning Index (PRI) which measures non-verbal reasoning and visual perceptual skills, whereas the WISC-V includes the Fluid Reasoning Index (FRI) to assess non-verbal reasoning and the Visual Spatial Index (VSI) to assess visual perceptual skills. To facilitate consistency across the index

scores between different test versions, we calculated a PRI score for the participants who completed the WISC-V by summing the arithmetic mean of the FRI and VSI, as has been done previously (Slim et al., 2020). We elected to focus on school-age intellectual abilities for the presumed perinatal and acute neonatal stroke groups as there is evidence that cognitive difficulties emerge over time (Westmacott et al., 2009).

Statistical Analysis

All statistical analyses were computed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Released, 2019). The significance level for all research questions was set at the standard $p < .05$. Independent *t* and $\chi 2$ tests were used to examine demographic and clinical differences between the perinatal and childhood AIS groups. The following analyses examined childhood and perinatal AIS groups separately. First, frequencies of PSOM scores were reported for perinatal and childhood AIS groups at Time 1 and Time 2, and group differences were examined using $\chi 2$ tests. McNemar's test was used to examine stability or change of PSOM sensorimotor scores between Time 1 and Time 2 dichotomized as 0-0.5= no/mild deficit and 1-2= moderate/severe deficit (e.g., Cooper et al., 2017; deVeber et al., 2000; Gordon et al., 2015; Kitchen et al., 2012), within the perinatal and childhood AIS groups. Intellectual scores were compared to the normative mean using one-sample *t*-tests. Spearman's correlation between Time 1 and Time 2 PSOM sensorimotor scores and intellectual outcomes were calculated. Independent *t*-tests were used to examine group differences on intellectual outcomes in dichotomized PSOM sensorimotor outcome groups (no/mild deficit vs. moderate/severe deficit). Finally, considering the perinatal and childhood sample together, we examined clinical features including age at stroke, lesion location, lesion size, motor

presentation, rehabilitation services accessed, and current seizure disorder between children in the no/mild deficit and moderate/severe deficit groups.

Missing Data

All children had data for the primary variables of interest: Time 1 and Time 2 PSOM sensorimotor scales and intellectual testing. For the PSOM sensorimotor scales, some children only had either the right or left sensorimotor scale completed. This information is reported under Table 2. Eight parents chose not to report their education level. One child did not have information about current seizures. One child was missing information about handedness and 3 children were missing information about a switch in handedness. Six children were missing information about rehabilitation services accessed. In order to maximize our clinical sample, we included all available data in analyses and did not exclude any participants and report adjusted percentages.

Results

Study Cohort

A total of 64 children met the inclusion criteria for the present study. There were 30 children in the perinatal group (23 acute neonatal, 7 presumed perinatal) and 34 children in the childhood stroke group. The demographic and clinical data for the sample is presented in Table 1. There were no differences in number of males, time since stroke, lesion laterality, motor presentation, handedness, handedness switch, current seizures, or maternal education. The childhood group was older at the time of assessment, as expected. In terms of lesion location, the perinatal group had significantly more children with cortical lesions and the childhood group had significantly more children with subcortical lesions, there were no differences between groups on

combined cortical+subcortical lesions. The perinatal group had a higher proportion of children with large infarcts, there were no group differences for small or medium infarcts.

Table 1. Demographic and clinical characteristics

	Perinatal	Childhood	χ^2/t
Total N	30	34	-
Number of Males	17(56.7%)	16(47.1%)	0.59
Age at Stroke years – M(SD)	-	4.27(3.36)	-
Age at Neuropsychological Assessment yrs – M(SD)	8.75(2.22)	11.90(2.38)	-5.45**
Time since Stroke yrs – M(SD)	8.76(2.21)	7.63(3.42)	1.58
Timing of Stroke			
Presumed Perinatal	7 (23.3%)	-	-
Neonatal	23 (76.7%)	-	-
30 days – 1.9 yrs	-	9(26.5%)	-
2 – 5.9 yrs	-	16(47%)	-
6 – 12.9 yrs	-	9(26.5%)	-
Motor presentation			
Hemiparesis	15(50%)	18(52.9%)	0.06
Dystonia	1 (3.3%)	4(11.8%)	1.57
Cerebral Palsy	0(0%)	0(0%)	-
Spasticity	2 (6.7%)	1(2.9%)	0.02
No motor difficulties	14 (46.7%)	16(47.1%)	0.001
Handedness (Right)	16(55.2%)	26(76.5%)	3.20
Handedness Switch	7(25.9%)	5(14.7%)	1.20
Lesion Laterality			
Right	10(33.3%)	14(41.2%)	0.42
Left	17(56.7%)	13(38.2%)	2.17
Bilateral	3 (10%)	7(20.6%)	1.36
Lesion Location			
Cortical only	17(56.7%)	7(20.6%)	8.85**
Subcortical only	3 (10%)	17(50%)	11.87**
Cortical+Subcortical	10(33.3%)	10(29.4%)	0.11
Lesion Size			
Small	4(13.3%)	11(32.4%)	3.21
Medium	16(53.3%)	21(61.8%)	0.47
Large	10(33.3%)	2(5.9%)	7.88**
Rehabilitation			
Occupational Therapy	17(60.7%)	21(70%)	0.55
Physical Therapy	18(64.3%)	17(56.7%)	0.35
Current Seizure Disorder	7(23.3%)	6(18.2%)	0.26
Maternal Education	4.59(1.00)	4.90(0.77)	-1.27

*$p < .05$; **$p < .01$

Note: All children with NAIS or presumed perinatal stroke were assigned an age of stroke of 0 days.
Maternal Education is rated on a 6-point scale (see text for details)

PSOM Sensorimotor Functioning

Motor functioning was assessed at two points, Time 1 (childhood group between 30 days post-stroke to 1 year; perinatal group between 2-5 years of age) and Time 2 which was the closest PSOM to neuropsychological testing. The average time since stroke to the Time 1 PSOM was *M*= 2.90(1.14) years for the perinatal group and *M*= 0.38(0.22) years for the childhood group. The average time since stroke to Time 2 PSOM was *M*= 7.68(2.07) years for the perinatal group and *M*= 7.20(3.32) years for the childhood group. The average time between Time 2 PSOM and intellectual assessment was *M*= 1.23(1.22) years for the perinatal group and *M*= 0.92(0.98) years for the childhood group. Table 2 shows frequencies of PSOM right and left sensorimotor scores in each group at both time points. Comparing perinatal and childhood stroke groups, at Time 1 the perinatal group had more children with PSOM right sensorimotor scores of 1 (moderate deficit), with a medium effect size, Cramer's V= .316 At Time 2, there were no differences between the perinatal and childhood stroke groups. Regarding bilateral sensorimotor scores, at Time 1 one perinatal and three childhood AIS participants had scores ≥ .05. At Time 2 no participants had bilateral scores ≥ .05.

Table 2. Frequencies of PSOM sensorimotor scores in the perinatal and childhood stroke groups at Time 1 and Time 2

	Time 1			Time 2		
	Perinatal	Childhood	χ^2	Perinatal	Childhood	χ^2
Right						
Sensorimotor						
0	15 (51.7%)	18 (52.9%)	0.01	14 (50%)	24(72.7%)	3.33
0.5	3 (10.3%)	9(26.5%)	2.64	4 (14.3%)	3(9.1%)	0.40
1	10 (34.5%)	3(8.8%)	6.29*	6 (21.4%)	1(3%)	5.05
2	1 (3.4%)	4(11.8%)	1.48	4 (14.3%)	5(15.2%)	0.01
Left						
Sensorimotor						
0	21 (84%)	20(62.5%)	3.21	19(76%)	22(68.8%)	0.37
0.5	1 (4%)	7(21.9%)	3.72	2 (8%)	6(18.8%)	1.34
1	1 (4%)	5(15.6%)	3.21	2(8%)	2(6.3%)	0.66
2	2 (8%)	0(0%)	2.65	2(8%)	2(6.3%)	0.67

*significant at $p < .05$ after applying Bonferroni correction for multiple comparisons

Note: 0- no deficit; 0.5- mild deficit, normal function; 1- moderate deficit, decreased function; 2- severe deficit, missing function
Missing data: Perinatal- Time 1: 1 right sensorimotor, 5 left sensorimotor; Time 2: 2 right sensorimotor, 5 left sensorimotor. Childhood- Time 1: 2 left sensorimotor; Time 2: 1 right sensorimotor, 2 left sensorimotor

Changes in Sensorimotor Functioning from Time 1 to Time 2

Changes in motor functioning on the PSOM were examined with McNemar's test. For this test PSOM data were dichotomized as 0-0.5= no/mild deficit and 1-2= moderate/severe deficit for right and left sensorimotor scores (Kitchen et al., 2012; Slim et al., 2020). Overall, in both the perinatal and childhood groups, there were no significant differences between the distribution of children with no/mild deficit and moderate/severe deficit at Time 1 and Time 2 for either right (perinatal $p = .999$; child $p = .999$) or left sensorimotor scores (perinatal $p = .453$; child $p = .999$).

However, some children did change group membership. In the perinatal stroke group, for the right PSOM, two children declined and two improved between Time 1 and Time 2. For the left PSOM, two children declined and one improved. In the childhood stroke group, for the right PSOM, one child declined and two had improved motor functioning. For the left PSOM, two declined and three improved.

Associations Between Motor and Cognitive Functioning

In the perinatal group 12 (40%) children completed the WISC-IV and 18 (60%) children completed the WISC-V. In the childhood group 27 (79.4%) children completed the WISC-IV and 7 (20.6%) completed the WISC-V. The WISC-V FRI and VSI were averaged to form a PRI to facilitate comparison across children who completed different test versions (e.g., Slim et al., 2020). Table 3 shows the mean and standard deviation of each group and differences from the normative sample. The perinatal group was significantly lower than the normative mean in full scale IQ, verbal comprehension, and processing speed. The childhood group was lower than the normative mean across all WISC indices.

Table 3. Intellectual outcomes compared to the standardization mean for perinatal and childhood stroke groups

	Perinatal				Childhood			
	M(SD)	t	*p*	Cohen's *d*	M(SD)	t	*p*	Cohen's *d*
FSIQ	93.63(19.54)	2.30	.021*	0.37	92.82(15.35)	2.77	.005**	0.47
VCI	96.17(18.08)	1.39	.017*	0.23	97.44(15.71)	0.99	.032*	0.17
PRI	97.65(20.26)	0.84	.397	0.13	94.50(14.01)	2.12	.033*	0.38
WMI	96.83(15.69)	1.15	.251	0.21	92.74(12.59)	2.81	.005**	0.52
PSI	93.23(17.32)	2.45	.014*	0.42	91.50(16.63)	3.27	.001**	0.54

*$p < .05$; **$p < .01$

In the perinatal group (Table 4), PSOM right sensorimotor scores at Time 1 were significantly associated with PSI. There were no significant associations between Time 1 PSOM left sensorimotor scores and intellectual outcomes. There were no significant associations between either right or left PSOM sensorimotor at Time 2 and intellectual outcomes.

In the childhood stroke group (Table 5), PSOM right sensorimotor at Time 1 was significantly associated with PSI. Left sensorimotor was associated with FSIQ, VCI, and WMI. At Time 2 only right sensorimotor PSOM was associated with PSI.

Table 4. Spearman correlations between motor functioning and intellectual outcomes in the perinatal stroke group

	FSIQ	VCI	PRI	WMI	PSI
Time 1					
Right Sensorimotor	-.335	-.160	-.343	-.251	-.391*
Left Sensorimotor	-.218	-.291	-.115	-.207	-.049
Time 2					
Right Sensorimotor	-.076	.098	-.247	.063	-.358
Left Sensorimotor	.111	-.085	.146	.035	.222

*p <.05, *p <.01

Table 5. Spearman correlations between motor functioning and intellectual outcomes in the childhood stroke group

	FSIQ	VCI	PRI	WMI	PSI
Time 1					
Right Sensorimotor	-.170	-.067	-.168	.118	-.351*
Left Sensorimotor	-.414*	-.444*	-.332	-.393*	-.071
Time 2					
Right Sensorimotor	-.139	-.031	-.015	.078	-.525**
Left Sensorimotor	-.053	.006	-.049	-.264	.017

*p <.05

Group Differences in Intellectual Functioning by No/Mild and Moderate Severe Sensorimotor Deficit

To further examine the impact of sensorimotor functioning on intellectual outcomes, we examined whether there were group differences based on no/mild deficits (i.e., PSOM= 0-.5) and moderate/severe deficits (i.e., PSOM= 1-2) motor functioning in the perinatal and childhood stroke groups, at Time 1 and Time 2.

At Time 1, in the perinatal group (Table 6), children with poor motor functioning performed significantly worse on PRI, with a large effect size. Differences in FSIQ, VCI, WMI, and PSI did not reach statistical significance, however effect sizes were medium to large. In the childhood group (Table 7), children with poor motor functioning performed significantly worse on PRI and PSI, with effect sizes in the large range. At Time 2, there were no significant differences between children with good and poor motor functioning in either the perinatal (Table 8) or childhood stroke (Table 9) groups.

Table 6. Group differences in intellectual functioning by no/mild and moderate/severe motor deficit at Time 1 in the perinatal stroke group

	No/Mild (*n*=17) M(SD)	Moderate/Severe (*n*= 13) M(SD)	*t*(28)	*p*	Cohen's *d*
FSIQ	98.71(16.16)	87(22.15)	1.68	.105	0.60
VCI	99.18(17.21)	92.23(19.11)	1.05	.305	0.38
PRI	104.21(20.33)	89.08(17.35)	2.15	.040*	0.80
WMI	101.12(11.80)	91.23(18.71)	1.77	.087	0.63
PSI	97.82(14.01)	87.23(19.87)	1.71	.098	0.61

Table 7. Group differences in intellectual functioning by no/mild and moderate/severe motor deficit at Time 1 in childhood stroke group

	No/Mild (n=22) M(SD)	Moderate/Severe (n= 12) M(SD)	t(32)	p	Cohen's d
FSIQ	96.55(16.63)	86(10.03)	1.99	.054	0.77
VCI	100.68(16.55)	91.5(12.57)	1.67	.104	0.62
PRI	98.41(13.40)	87.33(12.66)	2.35	.025*	0.85
WMI	93.95(11.60)	92.17(14.80)	0.19	.849	0.13
PSI	95.77(17.75)	83.67(11.19)	2.14	.041*	0.82

Table 8. Group differences in intellectual functioning by no/mild and moderate/severe motor deficit at Time 2 in perinatal stroke group

	No/Mild (n=16) M(SD)	Moderate/Severe (n= 14) M(SD)	t(28)	p	Cohen's d
FSIQ	96.94(16.67)	89.86(22.42)	0.99	.331	0.36
VCI	97.44(17.48)	94.71(19.28)	0.41	.688	0.14
PRI	102.66(20.08)	91.93(19.63)	1.48	.151	0.54
WMI	100.63(12.20)	92.50(18.44)	1.44	.161	0.52
PSI	97.94(16.28)	87.86(17.47)	1.64	.113	0.60

Table 9. Group differences in intellectual functioning by no/mild and moderate/severe motor deficit at Time 2 in childhood stroke group

	No/Mild (n=24) M(SD)	Moderate/Severe (n= 10) M(SD)	t(32)	p	Cohen's d
FSIQ	94.54(17.79)	88.70(5.31)	1.46	.155	0.44
VCI	98.63(17.50)	94.60(10.49)	0.68	.504	0.27
PRI	95.15(15.43)	92.95(10.40)	0.41	.684	0.16
WMI	94.13(12.84)	89.40(11.93)	0.99	.326	0.38
PSI	94.75(15.65)	83.70(17.10)	1.83	.077	0.67

Note: the assumption of homogeneity of variance was violated for FSIQ so Welch's t-test is reported (df= 30.35).

Clinical Features of No/Mild and Moderate/Severe Sensorimotor Deficit Groups across the Full Sample

Finally, we examined whether there were differences in clinical features between groups that had no/mild vs moderate/severe sensorimotor deficits according to their Time 1 PSOM across the full sample (Table 10). There was no difference between groups in age at stroke, dichotomized by perinatal and childhood. There was a higher proportion of children in the moderate/severe deficit group with cortical+subcortical lesions (52% vs. 17.9%), whereas there was a higher proportion of subcortical only lesions children in the no/mild deficit group (43.6% vs. 12%). There were no differences between groups in cortical lesions. There was a higher proportion of large lesions in the moderate/severe deficit group (40% vs. 5.1%) and a higher proportion of medium lesions in the no/mild deficit group (71.8% vs 36%). There were no differences between groups on small lesions. In terms of motor presentation at time of neuropsychological assessment there was a higher proportion of children in the moderate/severe

deficit group with hemiparesis (88% vs 28.2%) There was no difference in dystonia or spasticity, however both groups had few children with these presentations. A higher proportion of children in the moderate/severe deficit group accessed occupational therapy (80% vs. 50%) and physical therapy (84% vs. 38.9%). More children in the moderate/severe deficit group had a current seizure disorder (40% vs. 7.7%).

Table 10. Clinical features of participants by no/mild and moderate/severe sensorimotor deficits at Time 1 PSOM

	No/Mild	Moderate/Severe	χ^2	Cramer's *V*
Total N	39	25	-	-
Age at Stroke				
Perinatal	17(43.6%)	13(52%)	0.43	.082
Childhood	22(56.4)	12(48%)		
Lesion Location				
Cortical	15(38.5%)	9(36%)	0.04	.025
Subcortical only	17(43.6%)	3(12%)	7.08**	.333
Cortical+Subcortical	7(17.9%)	13(52%)	8.22**	.358
Lesion Size				
Small	9(23.1%)	6(24%)	0.01	.011
Medium	28(71.8%)	9(36%)	8.00**	.354
Large	2(5.1%)	10(40%)	12.16***	.436
Motor Presentation				
Hemiparesis	11(28.2%)	22(88%)	21.81***	.584
Dystonia	1(2.6%)	4(16%)	3.82	.244
Cerebral Palsy	0(0%)	0(0%)	-	-
Spasticity	1(2.6%)	3(8%)	2.32	.190
No motor difficulties	28(71.8%)	2(7.1%)	24.90***	.624
Rehabilitation				
Occupational Therapy	18(50%)	20(80%)	10.12**	.418
Physical Therapy	14(38.9%)	21(84%)	18.26***	.561
Current Seizure Disorder	3(7.7%)	10(40%)	9.49**	.388

*p <.05; **p <.01; ***p <.001

Discussion

The purpose of this study was to examine whether motor functioning after pediatric AIS is associated with intellectual functioning at school age. We also examined clinical features associated with motor impairment. Overall, results indicated similar levels of sensorimotor

impairment in perinatal and childhood AIS participants, as assessed by the PSOM. In the childhood AIS group, associations were found between overall intellectual functioning, verbal abilities, working memory, and processing speed, and motor functioning during early recovery (i.e., after 30 days but within one-year post AIS) but motor functioning at time of neuropsychological testing was only associated with processing speed. In the perinatal group motor functioning during early recovery (i.e., between 2 to 5 years of age) was associated with processing speed and there were no associations between intellectual outcomes and motor functioning at time of neuropsychological testing. The different patterns of associations between specific intellectual abilities and motor functioning in the perinatal and childhood AIS groups suggest there may be age-dependent effects on this relationship. Considering the AIS cohort together, clinical features associated with moderate/severe motor impairment included combined cortical+subcortical infarcts and large lesion size, whereas subcortical infarcts and medium lesion size were associated with no/mild motor deficits. More children with moderate/severe motor impairment during early recovery had hemiparesis and seizures at time of neuropsychological testing and accessed occupational and physical therapy.

We examined rates of sensorimotor deficit as assessed by the PSOM in perinatal and childhood AIS groups at two time points. Time 1, shortly after stroke (i.e., childhood: 30 days to one-year post-stroke; perinatal: between 2-5 years of age) and at time closest to neuropsychological testing. We found that the perinatal AIS group had significantly more children with scores indicating moderate deficit/decreased function on the right side at Time 1. There were no other significant differences at Time 1 or Time 2. Therefore, in our sample rates of sensorimotor deficits were largely similar across perinatal and childhood AIS. This was also seen in rates of hemiparesis at time of neuropsychological testing, where 50% of perinatal AIS

and 52.9% of childhood AIS participants presented with hemiparesis. Likewise, Cooper et al., (2017) found similar rates of hemiplegia across children with AIS onset as neonates, pre-school age, or school age. However, Boardman et al., (2005) found hemiparesis to be more common after childhood AIS compared to neonatal AIS. The latter study focused on middle cerebral artery strokes only, whereas the former included all arterial territories, which could possibly account for this difference. As our sample was relatively small, we did not examine subgroups of ages within the childhood AIS groups. Our sample had approximately half of childhood AIS in the preschool (2-5.9 years of age), with the other half evenly split between 30 days – 1.9 years and 6 – 12.9 years. Pre-school aged children have been previously found to have better outcomes in motor (Cooper et al., 2017) and cognitive (Allman et al., 2013; Everts et al., 2008) functioning. Future studies with larger sample sizes should examine PSOM sensorimotor outcomes across different age groups within childhood AIS. Additionally, we combined presumed perinatal and acute neonatal AIS into one perinatal group, and future research with larger sample sizes could examine these groups separately, as perinatal stroke has been found to be associated with greater risk of poor outcomes compared to stroke later in infancy (Ganesan et al., 2000; Kolk et al., 2011; Westmacott et al., 2010). Specifically, motor deficits are relatively less common in acute neonatal stroke compared to perinatal stroke (Kirton & deVeber, 2013).

We also examined change in motor functioning between Time 1 and Time 2 in both groups. Although there were no statistically significant differences in the proportion of children with deficits at Time 1 vs Time 2, some children did change group membership. In the perinatal group, four children declined and three improved. In the childhood group, three children had declined motor functioning and five improved. Overall, this finding suggests motor functioning after pediatric AIS was mostly stable in our sample. Previous research examining motor

trajectories after AIS has found emerging deficits after neonatal AIS and gradual recovery after childhood AIS (Cooper et al., 2017). However, this study used standardized assessments of fine and gross motor skills, whereas the current study used motor impairment as identified by the PSOM, a standardized neurological assessment. It is possible that while some children may have shown recovery of some motor skills that may have been captured by a standardized assessment of fine and gross motor skills, the magnitude of recovery was not such that PSOM sensorimotor scores changed. We elected to use the PSOM sensorimotor scores obtained at pre-school age for the perinatal sample in order to account for emerging motor deficits in this population (Cooper et al., 2017), which may account for the relatively few children who declined in this group.

Compared to the normative mean, the perinatal group's performance was significantly lower in full scale IQ, verbal comprehension, and processing speed. The childhood group performed significantly lower than the normative mean across all WISC indices. In the perinatal group, Time 1 right sensorimotor functioning was associated with processing speed. There were no significant associations with motor functioning closest to time of neuropsychological testing and any index of intellectual outcome. In the childhood group, Time 1 right sensorimotor functioning was associated with processing speed and left sensorimotor functioning was associated with overall intellectual functioning, verbal intellectual ability and working memory. At Time 2, right sensorimotor functioning was associated with processing speed. These findings add to a modest body of evidence of associations between motor and cognitive functioning in pediatric stroke (e.g., Abgottspon et al., 2021; Allman & Scott, 2011; Lo et al., 2014; Ricci et al., 2007; Westmacott et al., 2018a; 2018b). Interestingly, Westmacott et al., (2018a) found an association between current sensorimotor PSOM and working memory after childhood subcortical stroke, suggesting that effects of motor functioning on intellectual outcomes may be

moderated by age at stroke and lesion location, as is the case with intellectual outcomes (Westmacott et al., 2010). Relationships between age and cognitive functioning after early brain injury have been found to be non-linear (Anderson et al., 2009; Westmacott et al., 2010), further underscoring the need for larger studies to examine different age groups across childhood. We were limited in our statistical analyses due to sample size, however future studies with larger samples could employ regression analyses to examine the influence of multiple stroke-related variables on the relationship between motor and intellectual functioning. With respect to the perinatal AIS group, we chose to examine the WISC across both age groups for consistency across indices and to account for emerging cognitive deficits after neonatal stroke (Danguecan et al., 2017; Levine et al., 2005; Westmacott et al., 2009). However, it is not clear whether associations would be found between the PSOM sensorimotor scores, and preschool intellectual functioning as assessed by the Wechsler Preschool & Primary Scale of Intelligence. One study with neonatal stroke did not find any associations with current motor functioning and intellectual outcomes (Westmacott et al., 2009). The finding between current motor functioning and processing speed is in line with Lo et al.'s (2014) work in a combined perinatal and childhood AIS sample as well as work in typically developing children (Piek et al., 2008; Wechsler, 2003). Although, interestingly, this association was not seen in a neonatal sample, at either pre-school or school-age assessment (Westmacott et al., 2009) providing further support for the notion that there may be age-related effects on relationships between motor and cognitive functioning in pediatric AIS.

Second, we dichotomized motor functioning into no/mild deficits and moderate/severe deficit and examined group differences in intellectual outcomes. In the perinatal group, children with a moderate/severe deficit at Time 1 had lower non-verbal intellectual abilities. In the

childhood group, children with moderate/severe motor deficits had lower non-verbal abilities and processing speed. Differences in overall intellectual functioning were approaching significance (p= .054). Interestingly, when examining Spearman correlations non-verbal reasoning was not significantly associated with PSOM sensorimotor scores in either group, but there were significant group differences between children with no/mild and moderate severe deficits, suggesting that non-verbal reasoning may be associated with motor functioning when there are deficits, but not in children without motor deficits. There were no group differences between no/mild deficit and moderate/severe deficit at Time 2 in either perinatal AIS or childhood AIS.

Taken together, these findings suggest that motor functioning during early stroke recovery is associated with intellectual outcome at school age, whereas there was no association between motor functioning at time closest to neuropsychological assessment and intelligence. This finding is consistent with findings in typically developing and preterm children showing that early motor functioning predicts later cognitive skills (Bruggink et al., 2010; Butcher et al., 2009; Capute et al., 1985; Einspieler et al., 2016; Murray et al., 2007; Oudgenoeg-Paz et al., 2017; Piek et al., 2008; Spittle et al., 2013), whereas associations between concurrent motor and cognitive functioning are less consistent (Roebers & Kauer, 2009; Stockel & Hughes, 2016; Wassenberg et al., 2005; van der Fels et al., 2015). A potential explanation for this finding is that changes in brain structure and connectivity after injury may affect subsequent development of motor and cognitive outcomes that persist over time, thereby affecting long-term development of cognitive abilities. Additionally, motor functioning closest to time of neuropsychological assessment may be impacted by access to physical and occupational therapy in the interim, which may improve functional outcome even in the presence of a deficit, whereas changes in brain structure and connectivity persist and impact cognitive development, resulting in an

association between early motor functioning and long-term intellectual outcomes, and not concurrent motor functioning and intellectual outcomes. Research in children born very preterm provides some support for this notion. Specifically, children born very preterm with developmental coordination disorder (DCD) showed smaller brain volumes for total brain tissue, cortical grey matter, cerebellum, and basal ganglia, which persisted at long-term follow up (Dewey et al., 2019). Likewise, altered white matter microstructural organization was evident in numerous white matter tracts indicating differences in organization and coherency that could reflect underlying processes including reduced myelination, reduced axon size or density, or less coherent organization of axons (Dewey et al., 2019). Importantly, when comparing children with DCD and without, brain growth of the former was slower in the cerebellum, basal ganglia, and white matter tracts, suggesting these early changes captured at term-equivalent age persisted throughout childhood. Although this study did not examine impact on cognition, subsequent research in the same population found that moderate to severe white matter injury was associated with DCD in children born very preterm, and children with persistent DCD showed lower performance on measures of intellectual and other cognitive (e.g., attention, memory) outcomes compared to children also born very preterm but with typical motor development at 13 years of age (Spittle et al., 2021). Likewise, in typical development, the neural substrates of early motor functioning (i.e., connectivity between the frontal cortex and subcortical structures) are implicated in later cognitive functioning, possibly due to hierarchical maturational processes (Kolb et al., 2010; Sherrard & Bower, 1998). Therefore, in pediatric AIS, motor functioning early in recovery but outside of the acute period may reflect the effects of the primary insult and extent of injury on brain structure and connectivity that has cascading impacts on cognitive development through processes of neuroplasticity and anatomical and functional reorganization

(Anderson et al., 2011), whereas motor functioning assessed closest to time of neuropsychological testing reflects recovery processes that have likely been augmented by intervention.

Finally, we examined clinical features by no/mild and moderate/severe deficit at Time 1 across both perinatal and childhood AIS groups together. We chose to limit our analyses to Time 1 PSOM because Time 1 was associated with cognitive functioning and understanding clinical factors that are associated with early motor outcome may help with early identification of children most at risk. There were no differences in no/mild vs. moderate/severe motor deficit by age group (perinatal vs. childhood). There were more children with subcortical lesions with no/mild deficit, whereas there were more children with cortical+subcortical lesions with moderate/severe motor deficits. A higher proportion of children with no/mild motor deficits had medium lesions, whereas a higher proportion of children with moderate/severe motor deficits had large lesions. Cortical+subcortical involvement as well as larger lesion size have been found to be associated with poorer motor and cognitive outcomes (Cooper et al., 2017; Hajek et al., 2013; Hetherington et al., 2005; Lo et al., 2014; Studer et al., 2014; Wagenaar et al., 2018; Westmacott et al., 2010), suggesting these may be important clinical features to identify, and to provide early multimodal intervention to children who display them. We also examined motor presentation (e.g., hemiparesis, dystonia, spasticity, and cerebral palsy) at time of neuropsychological assessment, as well as use of rehabilitation therapy. Unsurprisingly, more children with moderate/severe motor deficits had a motor presentation of hemiparesis. However, it is notable that 11 (28.2%) of children with no/mild deficits were also indicated as having hemiparesis demonstrating a proportion of children with mild deficit, decreased function. Our sample had very few children with other motor presentations (dystonia, spasticity, cerebral

palsy). This could be due to the multiple assessment points at specific times required in this study, which limited our sample size. Additionally, there were more children with moderate/severe motor deficits who received physical therapy or occupational therapy. However, 20% and 16% of children with moderate/severe motor deficits did not receive physical or occupational therapy, respectively, suggesting a possible barrier to needed services for this group (Vyas et al., 2021), which is problematic as early intervention is considered most beneficial (Kirton et al., 2007b; Kirton & deVeber, 2013; Sakzewski et al., 2009). Finally, there were also more children with moderate/severe deficits with a current seizure disorder. Focal seizures when presenting with stroke has been found to be associated with poorer motor outcomes, but data were not presented for the relationship with current seizures (Karalok et al., 2019).

Limitations to this study must be considered. First, our statistical analyses were constrained by our sample size. Important questions remain to be answered regarding the effects of age at stroke on motor and cognitive functioning and associations between these variables, including examining presumed perinatal and acute neonatal AIS separately as well as different ages of onset within childhood stroke. The lack of childhood AIS onset in ages 13 and up in this sample was unintentional and was likely related to the multiple data points we extracted. While we were able to examine lesion location and size, this study did lack advanced imaging techniques to obtain more detailed classifications of lesion location and size (i.e., volumetrics). Future research should also examine the impact of structural and functional connectivity as well as indications of secondary injury such as Wallerian degeneration and diaschisis (Domi et al., 2009; Domi et al., 2020; Kirton et al., 2007a; Kirton et al., 2016) to better characterize neuroplastic processes underlying motor and cognitive outcome after pediatric stroke (Anderson et al., 2011; Kolb et al., 2010; Kirton et al., 2016).

In conclusion, motor impairment affects a significant number of children with pediatric AIS. Overall, findings from this study suggest that motor functioning during early stroke recovery is associated with intellectual outcome, whereas motor functioning at time closest to neuropsychological assessment is not. We suggest this is related to neuroplastic changes post-injury, likely in fronto-striatal connections that result in observable motor deficits after stroke and affect subsequent development of cognitive outcomes through hierarchal maturational processes (Anderson et al., 2011; Sherrard & Bower, 1998; Spittle et al., 2021). Different patterns of associations between motor functioning and specific intellectual abilities in perinatal and childhood AIS group suggest possible age-mediated effects on this relationship. Combined cortical+subcortical lesions and large lesion size were associated with moderate/severe motor deficit suggesting these features may help with early intervention of children who would benefit from rehabilitation services. Future research with larger samples and advanced imaging methods is needed to better understand age-related neuroplasticity that underlies motor and intellectual outcomes in pediatric AIS.

References

Abgottspon, S., Steiner, L., Slavova, N., Steinlin, M., Grunt, S., & Everts, R. (2021). Relationship between motor abilities and executive functions in patients after pediatric stroke. *Applied Neuropsychology: Child*, 1-11. https://doi.org/10.1080/21622965.2021.1919111

Allman, C., & Scott, R. B. (2013). Neuropsychological sequelae following pediatric stroke: A nonlinear model of age at lesion effects. *Child Neuropsychology, 19*(1), 97-107. Doi: 10.1080/09297049.2011.639756

Anderson, V., Spencer-Smith, M., Leventer, R., Coleman, L., Anderson, P., Williams, J., Greenham, M., & Jacobs, R. (2009). Childhood brain insult: can age at insult help us predict outcome?. *Brain, 132*(1), 45-56. https://doi.org/10.1093/brain/awn293

Anderson, V., Spencer-Smith, M., & Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain, 134*(8), 2197-2221. Doi: 10.1093/brain/awr103

Anderson, V., Darling, S., Mackay, M., Monagle, P., Greenham, M., Cooper, A., ... & Gordon, A. L. (2020). Cognitive resilience following paediatric stroke: Biological and environmental predictors. European Journal of Paediatric Neurology, 25, 52-58. https://doi.org/10.1016/j.ejpn.2019.11.011

Avila, L., Riesgo, R., Pedroso, F., Goldani, M., Danesi, M., Ranzan, J., & Sleifer, P. (2010). Language and focal brain lesion in childhood. *Journal of child neurology, 25*(7), 829-833. https://doi.org/10.1177/0883073809350724

Ballantyne, A. O., Spilkin, A. M., Hesselink, J., & Trauner, D. A. (2008). Plasticity in the developing brain: intellectual, language and academic functions in children with

ischaemic perinatal stroke. *Brain*, *131*(11), 2975-2985. Doi: 10.1093/brain/awn176

Béjot, Y., Giroud, M., Moreau, T., & Benatru, I. (2012). Clinical spectrum of movement disorders after stroke in childhood and adulthood. *European neurology*, *68*(1), 59-64. Doi: 10.1159/000336740

Bernaudin, F., Verlhac, S., Freard, F., Roudot-Thoraval, F., Benkerrou, M., Thuret, I., ... & Brugières, P. (2000). Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. *Journal of Child Neurology*, *15*(5), 333-343. https://doi.org/10.1177/088307380001500510

Bigi, S., Fischer, U., Wehrli, E., Mattle, H. P., Boltshauser, E., Bürki, S., ... & Arnold, M. (2010). Differences in risk-factors, aetiology and outcome between children and young adults with acute ischaemic stroke. *Neuropediatrics*, *41*(02), V1255. 10.1055/s-0030-1265517

Boardman, J. P., Ganesan, V., Rutherford, M. A., Saunders, D. E., Mercuri, E., & Cowan, F. (2005). Magnetic resonance image correlates of hemiparesis after neonatal and childhood middle cerebral artery stroke. *Pediatrics*, *115*(2), 321-326. Doi: 10.1542/peds.2004-0427

Bruggink, J. L., Einspieler, C., Butcher, P. R., Stremmelaar, E. F., Prechtl, H. F., & Bos, A. F. (2009). Quantitative aspects of the early motor repertoire in preterm infants: do they predict minor neurological dysfunction at school age?. Early human development, 85(1), 25-36. https://doi.org/10.1016/j.earlhumdev.2008.05.010

Butcher, P. R., Van Braeckel, K., Bouma, A., Einspieler, C., Stremmelaar, E. F., & Bos, A. F. (2009). The quality of preterm infants' spontaneous movements: an early indicator of

intelligence and behaviour at school age. *Journal of Child Psychology and Psychiatry, 50*(8), 920-930. https://doi.org/10.1111/j.1469-7610.2009.02066.x

Capute, A. J., Shapiro, B. K., Palmer, F. B., Ross, A., & Wachtel, R. C. (1985). Cognitive-motor interactions: the relationship of infant gross motor attainment to IQ at 3 years. *Clinical pediatrics*, *24*(12), 671-675. https://doi.org/10.1177/000992288502401201

Cooper, A. N., Anderson, V., Hearps, S., Greenham, M., Ditchfield, M., Coleman, L., Hunt, R.W., Mackay, M.T., Monagle, P., & Gordon, A. L. (2017). Trajectories of motor recovery in the first year after pediatric arterial ischemic stroke. *Pediatrics*, *140*(2), e20163870. Doi: 10.1542/peds.2016-3870

Cooper, A. N., Anderson, V., Greenham, M., Hearps, S., Hunt, R. W., Mackay, M. T., Ditchfield, M., Coleman, L., Monagle, P. & Gordon, A. L. (2018). Motor function daily living skills 5 years after paediatric arterial ischaemic stroke: a prospective longitudinal study. *Developmental Medicine & Child Neurology*, *61*(2), 161-167. https://doi.org/10.1111/dmcn.13915

Danguecan, A., Williams, T., & Westmacott, R. (2017, February) Stability of overall intellectual functioning into early school-age for children with neonatal arterial ischemic stroke. Poster presented at the 45th Annual Meeting of the *International Neuropsychological Society*, New Orleans, USA

Dennis, M. (2000). Developmental plasticity in children: the role of biological risk, development, time, and reserve. *Journal of communication disorders*, *33*(4), 321-332. https://doi.org/10.1016/S0021-9924(00)00028-9

Dennis, M., Spiegler, B. J., Juranek, J. J., Bigler, E. D., Snead, O. C., & Fletcher, J. M. (2013). Age, plasticity, and homeostasis in childhood brain disorders. *Neuroscience &*

Biobehavioral Reviews, *37*(10), 2760-2773. https://doi.org/10.1016/j.neubiorev.2013.09.010

De Schryver, E. L., Kappelle, L. J., Jennekens-Schinkel, A., & Peters, A. B. (2000). Prognosis of ischemic stroke in childhood: a long-term follow-up study. *Developmental Medicine & Child Neurology*, *42*(5), 313-318. https://doi.org/10.1111/j.1469-8749.2000.tb00096.x

deVeber, G., MacGregor, D., Curtis, R., & Mayank, S. (2000). Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *Journal of child neurology*, *15*(5), 316-324. Doi: 10.1177/088307380001500508

deVeber, G. A., Kirton, A., Booth, F. A., Yager, J. Y., Wirrell, E. C., Wood, E., ... & MacGregor, D. (2017). Epidemiology and outcomes of arterial ischemic stroke in children: the Canadian Pediatric Ischemic Stroke Registry. *Pediatric neurology*, *69*, 58-70. doi: 10.1016/j.pediatrneurol.2017.01.006

De Vries, L. S., Van der Grond, J., Van Haastert, I. C., & Groenendaal, F. (2005). Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. *Neuropediatrics*, *36*(01), 12-20. Doi: 10.1055/s-2005-837544

Dewey, D., Thompson, D. K., Kelly, C. E., Spittle, A. J., Cheong, J. L., Doyle, L. W., & Anderson, P. J. (2019). Very preterm children at risk for developmental coordination disorder have brain alterations in motor areas. *Acta Paediatrica*, *108*(9), 1649-1660. https://doi.org/10.1111/apa.14786

Diamond, A. (2000). Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child development*, *71*(1), 44-56. https://doi.org/10.1111/1467-8624.00117

Domi, T., deveber, G., Shroff, M., Kouzmitcheva, E., MacGregor, D. L., & Kirton, A. (2009). Corticospinal tract pre-wallerian degeneration: a novel outcome predictor for pediatric stroke on acute MRI. *Stroke*, *40*(3), 780-787. https://doi.org/10.1161/STROKEAHA.108.529958

Domi, T., deVeber, G., Mikulis, D., & Kassner, A. (2020). Wallerian Degeneration of the Cerebral Peduncle and Association with Motor Outcome in Childhood Stroke. *Pediatric Neurology*, *102*, 67-73. https://doi.org/10.1016/j.pediatrneurol.2019.07.004

Edwards, H., Dunlop, M., Mallick, A., & O'Callaghan, F. (2015). Outcomes following childhood arterial ischaemic stroke: a Delphi Consensus on what parents want from future research. *European journal of paediatric neurology*, *19*(2), 181-187. https://doi.org/10.1016/j.ejpn.2014.12.006

Einspieler, C., Bos, A. F., Libertus, M. E., & Marschik, P. B. (2016). The general movement assessment helps us to identify preterm infants at risk for cognitive dysfunction. *Frontiers in psychology*, *7*, 406. Doi: https://doi.org/10.3389/fpsyg.2016.00406

Everts, R., Pavlovic, J., Kaufmann, F., Uhlenberg, B., Seidel, U., Nedeltchev, K., ... & Steinlin, M. (2008). Cognitive functioning, behavior, and quality of life after stroke in childhood. *Child Neuropsychology*, *14*(4), 323-338. Doi: 10.1080/09297040701792383

Fox, C. K., Glass, H. C., Sidney, S., Lowenstein, D. H., & Fullerton, H. J. (2013). Acute seizures predict epilepsy after childhood stroke. *Annals of neurology*, *74*(2), 249-256. https://doi.org/10.1002/ana.23916

Fuentes, A., Deotto, A., Desrocher, M., deVeber, G., & Westmacott, R. (2016). Determinants of

cognitive outcomes of perinatal and childhood stroke: A review. *Child Neuropsychology*, *22*(1), 1-38. Doi: 10.1080/09297049.2014.969694

Ganesan, V., Hogan, A., Shack, N., Gordon, A., Isaacs, E., & Kirkham, F. J. (2000). Outcome after ischaemic stroke in childhood. *Developmental medicine and child neurology*, *42*(7), 455-461. Doi: 10.1017/S0012162200000852

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., ... & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences*, *101*(21), 8174-8179. https://doi.org/10.1073/pnas.0402680101

Gordon, A. L., Anderson, V., Ditchfield, M., Coleman, L., Mackay, M. T., Greenham, M., Hunt, R.W., & Monagle, P. (2015). Factors associated with six-month outcome of pediatric stroke. *International Journal of Stroke*, *10*(7), 1068-1073. https://doi.org/10.1111/ijs.12489

Govaert, P., Zingman, A., Jung, Y. H., Dudink, J., Swarte, R., Zecic, A., ... & Lequin, M. (2008). Network injury to pulvinar with neonatal arterial ischemic stroke. *Neuroimage*, *39*(4), 1850-1857. https://doi.org/10.1016/j.neuroimage.2007.10.056

Greenham, M., Anderson, V., & Mackay, M. T. (2017). Improving cognitive outcomes for pediatric stroke. *Current opinion in neurology*, *30*(2), 127-132. Doi: 10.1097/WCO.0000000000000422

Hadders-Algra, M. (2008). Reduced variability in motor behaviour: an indicator of impaired cerebral connectivity?. *Early human development*, *84*(12), 787-789. https://doi.org/10.1016/j.earlhumdev.2008.09.002

Hajek, C. A., Yeates, K. O., Anderson, V., Mackay, M., Greenham, M., Gomes, A., & Lo, W. (2014). Cognitive outcomes following arterial ischemic stroke in infants and children. *Journal of Child Neurology*, *29*(7), 887-894. Doi: 10.1177/0883073813491828

Härtel, C., Schilling, S., Sperner, J., & Thyen, U. (2004). The clinical outcomes of neonatal and childhood stroke: review of the literature and implications for future research. *European Journal of Neurology*, *11*(7), 431-438. Doi: 10.1111/j.1468-1331.2004.00861.x

Hetherington, R., Tuff, L., Anderson, P., Miles, B., & deVeber, G. (2005). Short-term intellectual outcome after arterial ischemic stroke and sinovenous thrombosis in childhood and infancy. *Journal of child neurology*, *20*(7), 553-559. https://doi.org/10.1177/08830738050200070201

Hogan, A. M., Kirkham, F. J., & Isaacs, E. B. (2000). Intelligence after stroke in childhood: review of the literature and suggestions for future research. *Journal of child neurology*, *15*(5), 325-332. Doi: 10.1177/088307380001500509

IBM Corp. Released. (2019). IBM SPSS statistics for windows, version 26.0. Armonk, NY: IBM Corp.

Johnston, M. V. (2009). Plasticity in the developing brain: implications for rehabilitation. *Developmental disabilities research reviews*, *15*(2), 94-101. Doi: 10.1002/ddrr.64

Jacomb, I., Porter, M., Brunsdon, R., Mandalis, A., & Parry, L. (2018). Cognitive outcomes of

pediatric stroke. *Child Neuropsychology*, *24*(3), 287-303. Doi: 10.1080/09297049.2016.1265102

Karalok, Z. S., Genc, H. M., Taskin, B. D., Ceylan, N., Guven, A., & Yarali, N. (2019). Risk factors and motor outcome of paediatric stroke patients. *Brain and Development*, *41*(1), 96-100. https://doi.org/10.1016/j.braindev.2018.07.004

Kitchen, L., Westmacott, R., Friefeld, S., MacGregor, D., Curtis, R., Allen, A., Yau, I., Askalan, R., Moharir, M., Domi, T., & deVeber, G. (2012). The pediatric stroke outcome measure: a validation and reliability study. *Stroke*, *43*(6), 1602-1608. Doi: 10.1161/strokeaha.111.639583

Kirton, A., & deVeber, G. (2013). Life after perinatal stroke. *Stroke*, *44*(11), 3265-3271. Doi: 10.1161/STROKEAHA.113.000739

Kirton, A., Shroff, M., Visvanathan, T., & Deveber, G. (2007a). Quantified corticospinal tract diffusion restriction predicts neonatal stroke outcome. *Stroke*, *38*(3), 974-980. https://doi.org/10.1161/01.STR.0000258101.67119.72

Kirton, A., Westmacott, R., & Deveber, G. (2007b). Pediatric stroke: Rehabilitation of focal injury in the developing brain. *NeuroRehabilitation*, *22*(5), 371-382. Doi: 10.3233/NRE-2007-22504

Kirton, A., Williams, E., Dowling, M., Mah, S., Hodge, J., Carlson, H., ... & PedNIHSS Investigators. (2016). Diffusion imaging of cerebral diaschisis in childhood arterial ischemic stroke. *International Journal of Stroke*, *11*(9), 1028-1035. https://doi.org/10.1177/1747493016666089

Kolb, B., Teskey, G. C., & Gibb, R. (2010). Factors influencing cerebral plasticity in the normal and injured brain. *Frontiers in human neuroscience*, *4*, 204. https://doi.org/10.3389/fnhum.2010.00204

Kolk, A., Ennok, M., Laugesaar, R., Kaldoja, M. L., & Talvik, T. (2011). Long-term cognitive outcomes after pediatric stroke. *Pediatric neurology*, *44*(2), 101-109. https://doi.org/10.1016/j.pediatrneurol.2010.08.012

Lansing, A. E., Max, J. E., Delis, D. C., Fox, P. T., Lancaster, J., Manes, F. F., & Schatz, A. (2004). Verbal learning and memory after childhood stroke. *Journal of the International Neuropsychological Society*, *10*(5), 742-752. https://doi.org/10.1017/S1355617704105122

Levine, S. C., Kraus, R., Alexander, E., Suriyakham, L. W., & Huttenlocher, P. R. (2005). IQ decline following early unilateral brain injury: A longitudinal study. Brain and Cognition, 59, 114– 123. Doi:10.1016/j.bandc.2005.05.008

Lo, W., Gordon, A., Greenham, M., Gomes, A., Hajek, C., Mackay, M., ... & Anderson, V. (2012). Pediatric Stroke Outcome Measure Predicts Cognitive And Functional Deficits After Childhood Ischemic Stroke. Doi: 10.1161/str.43.suppl_1.A2375

Lo, W., Gordon, A. L., Hajek, C., Gomes, A., Greenham, M., Anderson, V., ... & Mackay, M. T. (2014). Pediatric stroke outcome measure: predictor of multiple impairments in childhood stroke. *Journal of child neurology*, *29*(11), 1524-1530. Doi: 10.1177/0883073813503186

Long, B., Anderson, V., Jacobs, R., Mackay, M., Leventer, R., Barnes, C., & Spencer-Smith, M. (2011). Executive function following child stroke: The impact of lesion size. *Developmental neuropsychology*, *36*(8), 971-987. Doi:

10.1080/87565641.2011.581537

Max, J. E., Bruce, M., Keatley, E., & Delis, D. (2010). Pediatric stroke: plasticity, vulnerability, and age of lesion onset. *The Journal of neuropsychiatry and clinical neurosciences*, *22*(1), 30-39. Doi: 10.1176/jnp.2010.22.1.30

Murray, G. K., Jones, P. B., Kuh, D., & Richards, M. (2007). Infant developmental milestones and subsequent cognitive function. *Annals of neurology*, *62*(2), 128-136. https://doi.org/10.1002/ana.21120

O'Keeffe, F., Liégeois, F., Eve, M., Ganesan, V., King, J., & Murphy, T. (2014). Neuropsychological and neurobehavioral outcome following childhood arterial ischemic stroke: attention deficits, emotional dysregulation, and executive dysfunction. *Child Neuropsychology*, *20*(5), 557-582. Doi: 10.1080/09297049.2013.832740

Oudgenoeg-Paz, O., Mulder, H., Jongmans, M. J., van der Ham, I. J., & Van der Stigchel, S. (2017). The link between motor and cognitive development in children born preterm and/or with low birth weight: A review of current evidence. *Neuroscience & Biobehavioral Reviews*, *80*, 382-393. https://doi.org/10.1016/j.neubiorev.2017.06.009

Pavlovic, J., Kaufmann, F., Boltshauser, E., Mori, A. C., Mercati, D. G., Haenggeli, C. A., ... & Perez, E. R. (2006). Neuropsychological problems after paediatric stroke: two year follow-up of Swiss children. *Neuropediatrics*, *37*(01), 13-19. Doi: 10.1055/s-2006-923932

Peterson, R. K., Williams, T. S., McDonald, K. P., Dlamini, N., & Westmacott, R. (2019). Cognitive and academic outcomes following childhood cortical stroke. *Journal of child neurology*, *34*(14), 897-906. https://doi.org/10.1177/0883073819866609

Peyton, C., Einspieler, C., Fjørtoft, T., Adde, L., Schreiber, M. D., Drobyshevsky, A., & Marks, J. D. (2020). Correlates of normal and abnormal general movements in infancy and Long-Term neurodevelopment of preterm infants: insights from functional connectivity studies at term equivalence. *Journal of Clinical Medicine*, *9*(3), 834. https://doi.org/10.3390/jcm9030834

Piek, J. P., Dawson, L., Smith, L. M., & Gasson, N. (2008). The role of early fine and gross motor development on later motor and cognitive ability. *Human movement science*, *27*(5), 668-681. https://doi.org/10.1016/j.humov.2007.11.002

Ricci, D., Mercuri, E., Barnett, A., Rathbone, R., Cota, F., Haataja, L., Rutherford, M., Dubowitz, L., & Cowan, F. (2008). Cognitive outcome at early school age in term-born children with perinatally acquired middle cerebral artery territory infarction. *Stroke, 39*(2), 403-410. https://doi.org/10.1161/STROKEAHA.107.489831

Roebers, C. M., & Kauer, M. (2009). Motor and cognitive control in a normative sample of 7-year-olds. *Developmental science, 12*(1), 175-181. https://doi.org/10.1111/j.1467-7687.2008.00755.x

Sakzewski, L., Ziviani, J., & Boyd, R. (2009). Systematic review and meta-analysis of therapeutic management of upper-limb dysfunction in children with congenital hemiplegia. *Pediatrics*, *123*(6), e1111-e1122. https://doi.org/10.1542/peds.2008-3335

Schatz, J., & Buzan, R. (2006). Decreased corpus callosum size in sickle cell disease: relationship with cerebral infarcts and cognitive functioning. *Journal of the International Neuropsychological Society, 12*(1), 24-33. https://doi.org/10.1017/S1355617706060085

Sherrard, R. M., & Bower, A. J. (1998). Role of afferents in the development and cell survival of the vertebrate nervous system. *Clinical and Experimental Pharmacology and Physiology*, *25*(7), 487-495.

Simma, B., Martin, G., Müller, T., & Huemer, M. (2007). Risk factors for pediatric stroke: consequences for therapy and quality of life. *Pediatric neurology*, *37*(2), 121-126. https://doi.org/10.1016/j.pediatrneurol.2007.04.005

Slim, M., Westmacott, R., Toutounji, S., Singh, J., Narang, I., Weiss, S., ... & Dlamini, N. (2020). Obstructive sleep apnea syndrome and neuropsychological function in pediatric stroke. *European Journal of Paediatric Neurology*, *25*, 82-89. https://doi.org/10.1016/j.ejpn.2019.11.006

Spittle, A. J., Spencer-Smith, M. M., Cheong, J. L., Eeles, A. L., Lee, K. J., Anderson, P. J., & Doyle, L. W. (2013). General movements in very preterm children and neurodevelopment at 2 and 4 years. *Pediatrics*, *132*(2), e452-e458. https://doi.org/10.1542/peds.2013-0177

Spittle, A. J., Dewey, D., Ellis, R., Burnett, A., Kwong, A., Lee, K., Cheong, J.L.Y., Doyle, L.W., & Anderson, P. J. (2021). Rates of Developmental Coordination Disorder in Children Born Very Preterm. *The Journal of* Pediatrics, 231, 61-67. https://doi.org/10.1016/j.jpeds.2020.12.022

Sreenan, C., Bhargava, R., & Robertson, C. M. (2000). Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *The Journal of pediatrics*, *137*(3), 351-355. Doi: 10.1067/mpd.2000.107845

Steinlin, M., Roellin, K., & Schroth, G. (2004). Long-term follow-up after stroke in

childhood. *European journal of pediatrics*, *163*(4-5), 245-250. Doi: 10.1007/s00431-003-1357-x

Stöckel, T., & Hughes, C. M. (2016). The relation between measures of cognitive and motor functioning in 5-to 6-year-old children. *Psychological research*, *80*(4), 543-554. Doi: 10.1007/s00426-015-0662-0

Studer, M., Boltshauser, E., Mori, A. C., Datta, A., Fluss, J., Mercati, D., ... & Ramelli, G. P. (2014). Factors affecting cognitive outcome in early pediatric stroke. *Neurology*, *82*(9), 784-792. doi: 10.1212/WNL.0000000000000162

Tekin, S., & Cummings, J. L. (2002). Frontal–subcortical neuronal circuits and clinical neuropsychiatry: an update. *Journal of psychosomatic research*, *53*(2), 647-654. https://doi.org/10.1016/S0022-3999(02)00428-2

Tibussek, D., Mayatepek, E., Klee, D., & Koy, A. (2015). Post stroke hemi-dystonia in children: a neglected area of research. *Molecular and cellular pediatrics*, *2*(1), 1-5. Doi: 10.1186/s40348-015-0026-2

Van der Fels, I. M., Te Wierike, S. C., Hartman, E., Elferink-Gemser, M. T., Smith, J., & Visscher, C. (2015). The relationship between motor skills and cognitive skills in 4–16 year old typically developing children: A systematic review. *Journal of science and medicine in sport*, *18*(6), 697-703. https://doi.org/10.1016/j.jsams.2014.09.007

Van Haastert, I. C., Groenendaal, F., Van De Waarsenburg, M. K., Eijsermans, M. J., Koopman-Esseboom, C., Jongmans, M. J., Helders, P.J.M., & De Vries, L. S. (2012). Active head lifting from supine in early infancy: an indicator for non-optimal cognitive outcome in

late infancy. *Developmental Medicine & Child Neurology*, *54*(6), 538-543. https://doi.org/10.1111/j.1469-8749.2012.04259.x

Van Hus, J. W., Potharst, E. S., Jeukens-Visser, M., Kok, J. H., & Van Wassenaer-Leemhuis, A. G. (2014). Motor impairment in very preterm-born children: links with other developmental deficits at 5 years of age. *Developmental Medicine & Child Neurology*, *56*(6), 587-594. https://doi.org/10.1111/dmcn.12295

van Schouwenburg, M. R., den Ouden, H. E., & Cools, R. (2010). The human basal ganglia modulate frontal-posterior connectivity during attention shifting. *Journal of Neuroscience*, *30*(29), 9910-9918. https://doi.org/10.1523/JNEUROSCI.1111-10.2010

Van Schouwenburg, M. R., Den Ouden, H. M., & Cools, R. (2015). Selective attentional enhancement and inhibition of fronto-posterior connectivity by the basal ganglia during attention switching. Cerebral Cortex, 25(6), 1527–1534. Doi:10.1093/cercor/bht345

Vyas, S. S., Ford, M. K., Tam, E. W., Westmacott, R., Sananes, R., Beck, R., & Williams, T. S. (2021). Intervention experiences among children with congenital and neonatal conditions impacting brain development: patterns of service utilization, barriers and future directions. *The Clinical Neuropsychologist*, *35*(5), 1009-1029. https://doi.org/10.1080/13854046.2020.1871516

Wagenaar, N., Martinez-Biarge, M., van der Aa, N. E., van Haastert, I. C., Groenendaal, F., Benders, M. J., Cowan, F.M., & de Vries, L. S. (2018). Neurodevelopment after perinatal arterial ischemic stroke. *Pediatrics*, *142*(3). https://doi.org/10.1542/peds.2017-4164

Wassenberg, R., Feron, F. J., Kessels, A. G., Hendriksen, J. G., Kalff, A. C., Kroes, M., ... & Vles, J. S. (2005). Relation between cognitive and motor performance in 5-to 6-year-old

children: Results from a large-scale cross-sectional study. *Child development*, *76*(5), 1092-1103. https://doi.org/10.1111/j.1467-8624.2005.00899.x

Wechsler, D. (2003). *WISC-IV: Administration and scoring manual*. Psychological Corporation

Wechsler, D. (2014). *WISC-V: Technical and interpretive manual*. NCS Pearson Incorporated.

Westmacott, R., MacGregor, D., Askalan, R., & deVeber, G. (2009). Late emergence of cognitive deficits after unilateral neonatal stroke. *Stroke*, *40*(6), 2012-2019. Doi: 10.1161/STROKEAHA.108.533976

Westmacott, R., Askalan, R., Macgregor, D., Anderson, P., & Deveber, G. (2010). Cognitive outcome following unilateral arterial ischaemic stroke in childhood: effects of age at stroke and lesion location. *Developmental Medicine & Child Neurology*, *52*(4), 386-393. Doi: 10.1111/j.1469-8749.2009.03403.x

Westmacott, R., McDonald, K. P., Roberts, S. D., deVeber, G., MacGregor, D., Moharir, M., Dlamini, N., & Williams, T. S. (2018a). Predictors of cognitive and academic outcome following childhood subcortical stroke. *Developmental neuropsychology*, *43*(8), 708-728. https://doi.org/10.1080/87565641.2018.1522538

Westmacott, R., McDonald, K. P., deVeber, G., MacGregor, D., Moharir, M., Dlamini, N., Askalan, R., & Williams, T. S. (2018b). Neurocognitive outcomes in children with unilateral basal ganglia arterial ischemic stroke and secondary hemidystonia. *Child Neuropsychology*, *24*(7), 923-937. Doi: 10.1080/09297049.2017.1353073

White, D. A., Salorio, C. F., Schatz, J., & DeBaun, M. (2000). Preliminary study of working memory in children with stroke related to sickle cell disease. *Journal of Clinical and Experimental Neuropsychology*, *22*(2), 257-264. https://doi.org/10.1076/1380-3395(200004)22:2;1-1;FT257

Williams, T. S., McDonald, K. P., Roberts, S. D., Dlamini, N., deVeber, G., & Westmacott, R. (2017). Prevalence and predictors of learning and psychological diagnoses following pediatric arterial ischemic stroke. *Developmental neuropsychology*, *42*(5), 309-322. Doi: 10.1080/87565641.2017.1353093

Chapter 3: Mental Health Outcomes in Children with Acquired Dystonia after Basal Ganglia Stroke and Associations with Cognitive and Motor Outcomes

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Basal ganglia infarcts occur in nearly one third of perinatal strokes and half of all childhood stroke (deVeber et al., 2017). Children who sustain a stroke involving the basal ganglia and/or thalamus are particularly at risk for developing dystonia, a movement disorder that involves excessive and involuntary muscle contractions, twisting or repetitive movements, and abnormal posturing (Albanese et al., 2013, Elbers, Wilkinson, deVeber, & Askalan, 2010; Jinnah & Hess, 2006; Marsden, Obeso, Lang, Hill, & Se, 1985; Mink, 2003, 2013; Sanger et al., 2010; Soman et al., 2006). In a Canadian cohort of pediatric basal ganglia stroke survivors, 21% of children went on to develop hemidystonia (Soman et al., 2006). The reasons why some children develop dystonia after stroke while others do not are not currently well understood, but proposed risk factors include involvement of multiple basal ganglia structures, age at stroke younger than 10, and female sex (Elbers et al., 2010; Goldfarb, Askalan, Pontigon, & deVeber, 2013; Soman et al., 2006). Additionally, in contrast to hemiparesis, which presents during the acute stage, dystonia typically presents after a 6 to12-month delay suggesting different mechanisms underlying these two disorders (Soman et al., 2006). Neurocognitive sequelae have been noted in children with acquired dystonia after stroke in the basal ganglia and/or thalamus, above and beyond those in children with similar patterns of stroke but no dystonia (Westmacott et al., 2018a). Specifically, children with dystonia showed poorer performance on measures of

verbal and non-verbal reasoning, academic achievement, and inhibitory control. These additional cognitive difficulties associated with post-stroke dystonia, as well as the delayed onset of dystonia, suggest the presence of maladaptive post-stroke neural reorganization that contributes to the motor and cognitive challenges in this population (Quartarone & Hallet, 2013; Tibussek, Mayatpek, Klee, & Koy, 2015). Little is currently known about mental health outcomes of children with post-stroke dystonia. The current study examined mental health outcomes via standardized parent-completed questionnaires and clinical neuropsychological reports in children with basal ganglia stroke with and without dystonia in order to determine whether children with post-stroke dystonia showed additional mental health difficulties compared to children with stroke only. Associations between cognitive, motor, and mental health symptoms were also examined.

Stroke has been associated with psychiatric comorbidities in both adults and children (Lo Buono et al., 2017; Max et al., 2002; Max et al., 2010; Neuner et al., 2011). Williams et al. (2017) found, out of 126 children, 52.4% received a psychological diagnosis after perinatal or childhood stroke. Intellectual disability, attention deficit hyperactivity disorder, and learning disorder were among the most common diagnoses; however, anxiety and depression were both found at rates of 4%. Westmacott et al. (2018b) investigated outcomes after childhood subcortical stroke and found higher rates of anxiety and depression, 14% and 18% respectively, with these diagnoses more common in those with basal ganglia lesions compared to thalamic lesions, suggesting involvement of these structures may be associated with anxiety and mood difficulties after stroke. Moreover, the basal ganglia and fronto-striatal circuit have been shown to be involved in mood regulation in healthy adults and implicated in psychiatric disease, including depression, anxiety, and obsessive-compulsive disorder (Stefurak et al., 2003;

Gunaydin & Kreitzer, 2016).

The extant literature on mental health in children with dystonia is very limited. One study reported findings of two boys with dystonia after subcortical stroke who developed tics, attention deficit hyperactivity disorder, and obsessive-compulsive disorder (Kwak & Jankovic, 2002). To our knowledge, no study to date has investigated internalizing symptoms in children with dystonia acquired post-stroke or otherwise. Given the paucity of research of mental health in children with dystonia, relevant literature from adults with dystonia will be reviewed. Research in adults with dystonia has demonstrated the presence of psychiatric comorbidities, with depression and anxiety among the most common (Balas et al., 2006; Conte et al., 2016; Degirmenci, Oyekcin, Bakar, & Kurklu, 2013; Fabbrini et al., 2010; Gundel et al., 2003; Miller et al., 2007; Kleiner-Fisman et al., 2007; Lehn, Mellick, & Boyle, 2014; Lewis, Butler, & Jahanshahi, 2008; Ostrem et al., 2011; van Tricht et al., 2012). According to a systematic review 12-71% of adults with dystonia experience anxiety or depression over their lifetime (Kuyper, Parra, Aerts, Okun, & Kluger, 2011). This incredibly wide range in prevalence varied as a function of study and sample size, with the most frequently reported prevalence rates in the range of 25-50%. Interestingly, one study found that while adults with dystonia showed higher levels of anxiety and depression compared to the healthy control group, there were no differences between adults with isolated and acquired dystonia suggesting that dystonia is associated with mood and anxiety problems regardless of the origin of the condition (Degirmenci et al., 2013).

It is still deliberated whether anxiety and depression are related to the neuropathology of dystonia (Moraru et al., 2002; Heiman et al., 2004; Zurowski, McDonald, Fox, & Marsh, 2013) or if they are a reaction to the functional impact of the disease (Ben-Shlomo, Camfield, Warner, 2002; Degirmenci et al., 2013). The specific neurobiological mechanisms underlying mood and

anxiety disturbances in dystonia are not yet well understood, however the basal ganglia and dopamine system have been implicated (McNeill, 2003; Zurowski et al., 2013). Although the underlying cause of mental health symptomatology in dystonia is not yet clear, the impact of elevated psychiatric symptoms on quality of life is notable. A number of studies have demonstrated that anxiety and depression significantly predict of quality of life in individuals with dystonia, with higher symptom levels predicting lower health related quality of life, and evidence that depression and anxiety were stronger predictors than disease duration and severity. (Ben-Shlomo, Camfield, & Warner, 2002; Soeder et al., 2009; Degirmenci et al., 2013; Kuyper et al., 2011). Although the number of studies in this area are limited, findings indicate the high relevance of mental health symptoms in individuals with dystonia.

Several studies have investigated the associations between mental health, cognitive functioning, and motor symptoms in adults with dystonia, reporting mixed findings. Jahanshahi, Rowe, and Fuller (2003) found that elevated self-report ratings of depression in individuals with idiopathic dystonia were associated with worse performance on a dual performance task of executive function; but no other significant correlations between mental health and cognitive performance were found. In the same sample, motor symptoms were found to be associated with performance on a task of visual conditional associated learning. In contrast, in a sample of individuals myoclonus-dystonia, patients with a history of anxiety disorder performed worse on a test of working memory, but no such effect was found for patients with a history of depressive disorder (Van Tricht et al., 2012). Moreover, correlation analyses revealed no significant associations between mental health and cognitive performance, but motor symptoms were found to be significantly associated with executive functioning. Bugalho, Correa, Guimaraes, and Xavier (2008) found no significant associations between cognition, obsessive-compulsive

symptoms, or motor symptoms in individuals with isolated dystonia. Likewise, Foley, Vinke, Limousin, & Cipolotti (2017) found no associations between cognitive performance and anxiety or depression symptoms, nor motor functioning in patients with cervical and general dystonia. In sum, the current literature shows limited, if any, associations between cognition, mental health, and motor symptoms in patients with dystonia suggesting these features may be independent from one another, and that anxiety and depression may reflect non-motor symptoms of dystonia (Foley et al., 2017).

The current study had two aims. First, we explored mental health outcomes in children with stroke involving the basal ganglia and/or thalamus with and without post-stroke dystonia. Specifically, we aimed to investigate whether the presence of post-stroke dystonia was associated with greater mental health difficulties compared to children with similar patterns of brain injury but no dystonia. We examined mental health outcomes via a parent-completed standardized questionnaire and review of clinical neuropsychological reports. We first examined all scales of the questionnaire as exploratory analyses. We were particularly interested in internalizing symptoms as these have been repeatedly noted in the dystonia literature, and conducted further analyses on these variables, including the Internalizing Index and Anxiety and Depression scales. We hypothesized that children with basal ganglia stroke and post-stroke dystonia would show higher levels of internalizing symptoms relative to children with basal ganglia stroke and no dystonia. Our second aim was to examine the associations between mental health, cognitive, and motor outcomes in the dystonia and no dystonia groups.

Method

Patient Population

Participants were identified upon enrollment in the Children's Stroke Study at the Hospital for Sick Children. This includes patients and their families seen in the Stroke Clinic at the Hospital for Sick Children who have consented to including their data in the study database. Children seen by the Stroke Clinic are stroke are routinely referred for neuropsychological assessment in the Psychology Department at the Hospital for Sick Children. Medical and clinical imaging data were collected between 1991 and 2013 by pediatric neurologists in the Stroke Clinic (GdV, DM, MM, ND). Clinical neuropsychological assessments were conducted by the study neuropsychologists (RW and TW) between 2006-2015. Children were considered for participation if they had a history of arterial ischemic stroke (AIS), diagnosed from birth to 16 years of age, with a single infarct involving the basal ganglia and/or thalamus documented on magnetic resonance imaging (MRI) or computed tomography (CT), and had complete data for the main variable of interest in this study, mental health. This sample included three groups of children: acute neonatal AIS (stroke diagnosed acutely within 28 days of life), acute childhood AIS (stroke diagnosed acutely between 29 days and 18 years of life), and presumed perinatal AIS (retrospective diagnosis of stroke presumed to have occurred during the perinatal period). Neuropsychological assessments were all conducted at least 6 months post-stroke. Exclusion criteria were: multiple lesions, bilateral lesions, recurrent stroke, cerebral sinovenous thrombosis, hypoxic-ischemic encephalopathy, sickle cell disease, moya-moya disease, neurofibromatosis type 1, meningitis, traumatic brain injury, and malignancy. Children who were not fluent in English were also excluded. In cases where children had more than one assessment, we used the most recent assessment in order to give the most up to date measure of their mental health. Our

primary variable of interest was mental health outcomes, specifically anxiety and depression. Cognitive outcomes were included for children who had completed testing within one year of when their mental health measures were obtained. The study was approved by the Research Ethics Board at the Hospital for Sick Children. Patients and their parents provided informed consent for use of this information as part of their enrollment in the Children's Stroke Study.

Determination of Dystonia. Presence and severity of dystonia was diagnosed according to neurological assessment. The Pediatric Stroke Outcome Measure (PSOM; Kitchen, 2012), was completed for each child by pediatric neurologists during routine patient care in the Stroke Clinic (GdV, DM, MM, ND). The PSOM provides information on motor performance including: power, tone, reflexes, and involuntary movements (dystonia, chorea, tics). Increased tone was classified as spasticity, dystonia, or mixed (spasticity and dystonia) patterns. Scores obtained within one year of neuropsychological assessment were used. Children's dystonia or mixed patterns were classified as 'dystonia' and others as 'no dystonia'. Severity of dystonia was coded as subtle/mild or moderate/severe based on the neurological exam completed by the pediatric neurologist.

Imaging Review. Lesion location was coded as outlined in Westmacott et al. (2010): Subcortical – infarct restricted to basal ganglia and/or thalamus; Combined – infarct involving cortex plus basal ganglia and/or thalamus. Lesion size was coded according to the following definitions: Small – involving less than 1/3 of total volume of a single lobe or major subcortical structure; Medium – involving from 1/3 to 2/3 of the volume of a single lobe or major subcortical structure OR involving less than ½ of the volume of two or more lobes/subcortical structures; Large – involving greater than 2/3 of the volume of one lobe or major subcortical structure OR involving greater than ½ of the volume of two or more lobes/subcortical structures.

Determination of lesion location and size was made by the study neuropsychologists (RW and TW) based on a systematic review of clinically acquired MRI images and official radiology reports, using the criteria as specified above.

Demographic Characteristics. Demographic characteristics for the participants included in this study were obtained from the registry database. The database includes data obtained from a standardized review of health records, structured parental interview, and a medical and neuropsychological history questionnaire completed by parents. Maternal education level was used as an indicator of socioeconomic status and rated on a 6-point scale (1= did not complete elementary school, 2= completed some high school, 3= completed high school, 4= some post-secondary training but not a diploma or degree, 5= completed college or university, 6= completed professional or graduate school).

Measures

Mental health

The Behavior Assessment System for Children, 2nd edition Parent Rating Scales (BASC-2 PRS; Reynolds & Kampahus, 2004). The BASC-2 is a parent-completed questionnaire assessing a wide range of behavioral and emotional difficulties in children and adolescents aged 2-25. Parents answer questions on a 4-point scale: 1- Never, 2- Sometimes, 3-Often, and 4- Almost Always. The BASC-2 produces the Hyperactivity, Aggression, Anxiety, Depression, Somatization, Atypical, Withdrawal, Attention Problems, Adaptability, Social Skills, Leadership, Activities of Daily Living, and Functional Communication scales and the Internalizing, Externalizing, Behavioral Symptoms, and Adaptive Skills Indices. Importantly for this study, the Internalizing Index consists of the Anxiety, Depression, and Somatization scales. On the clinical

scales and indices *T*-scores equal to and above 70 are considered clinically significant and *T*-scores equal to and above 60 are considered at-risk. On the adaptive scales and indices *T*-scores equal to or below 30 are considered clinically significant and *T*-scores between 30 and 40 are considered at-risk. The BASC-2 has demonstrated adequate reliability, with internal consistency on Indices and scales ranging from .80-.90, as well as good construct validity and moderate to high correlations with other behavioral rating scales (Tan, 2007).

Review of clinical neuropsychological reports. In addition to the standardized parent-completed questionnaire, clinical neuropsychological assessment reports were reviewed and coded for the presence of concerns pertaining to mental health. Concerns were coded for anxiety and depression, each considered separately, on a three-point scale as 0 – Absent (no concerns), 1 – Mild to moderate concerns, and 2 – Severe concerns by the clinical neuropsychologist who assessed each child. Mild to moderate concerns were indicated when concerns pertaining to symptoms of anxiety or depression were noted in the clinical report and intervention was recommended, but not necessarily urgent. Severe concerns were indicated when the report noted symptoms of anxiety or depression were interfering significantly with daily functioning, and intervention for mental health concerns was the top recommendation.

Cognitive abilities

Intellectual abilities. The Wechsler Intelligence Scale for Children, 4th edition (WISC-IV; Wechsler, 2003) assesses intellectual abilities in children aged 6-16. The WISC-IV provides index scores for overall intellectual ability (Full Scale IQ; FSIQ), verbal knowledge, language development, and verbal reasoning (Verbal Comprehension Index; VCI), non-verbal reasoning (Perceptual Reasoning Index; PRI), speed of information processing (Processing Speed Index; PSI), and working memory (Working Memory Index; WMI). The WISC-IV has demonstrated

good reliability for the Indices, with the average internal consistency and test-retest coefficients ranging from .86 to .97, as well as strong construct validity (Kaufman, Flanagan, Alfonso, & Mascolo, 2006).

Executive functioning. The Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kentworthy, 2000) is a parent-completed behavioral rating measure of executive functioning related behaviors in everyday life. The BRIEF consists of eight clinical scales which are organized into two Indices. These are Inhibit, Shift, and Emotional Control, which make up the Behavioral Regulation Index (BRI) and Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor, which make up the Metacognition Index (MI). An overall Global Executive Composite (GEC) is also derived, which provides an overall measure of executive functioning. Internal consistency on the BRIEF ranges from .80-.90. Test-retest correlations range from .84-.88, and test-retest *T*-score differences showed stability over a 2 to 3-week interval. Convergent and discriminant validity analyses showed expected relationships between other behavioral measures of executive function, attention, and clinical symptomology (Baron, 2000).

Motor outcomes

The PSOM (Kitchen et al., 2012) is a neurologist completed, objective, disease-specific outcome measure of 115 items suitable for use with newborn to adult ages. The PSOM measures neurological deficit and function in survivors of pediatric stroke. There are five subscales right sensorimotor, left sensorimotor, language production, language comprehension, and cognitive/behavioral. Each subscale is rated as 0- no deficit; 0.5- mild deficit, normal function; 1- moderate deficit; decreased function; or 2- severe deficit, missing function, which result in an

overall 10-point deficit score. In this study we used the sensorimotor total (e.g., right plus left). The PSOM has demonstrated good construct validity and interrater reliability (Kitchen et al., 2012).

Statistical Analysis

All statistical analyses were computed using the Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corporation, 2015). The significance level for all research questions was set at the standard $p < .05$. Independent *t* and χ^2 tests were used to examine demographic and neurological characteristics (Table 1). To examine the first aim, frequencies of T-scores in the at-risk and clinically significant range on the BASC-2 scales and indices were examined in the whole sample, and group differences between dystonia and no dystonia groups were examined using χ^2 tests. Normality of the variables was examined using the Shapiro-Wilk test of normality as well as visual inspection of histograms and Q-Q plots. The distributions of the BASC-2 variables were not normal and due to this reason as well as unequal group sizes, Independent Samples Mann-Whitney U Tests were used to examine group differences in the mental health variables of interest, the Anxiety and Depression scales and Internalizing Index. Group differences of anxiety and depression concerns indicated on clinical neuropsychological reports were examined with χ^2 tests. Group differences in cognitive abilities (intellectual ability and executive functioning) were examined with *t*-tests. To examine the second aim, Pearson correlations between mental health, cognitive, and motor outcomes were calculated for the dystonia and no dystonia groups separately.

Missing data. No data were missing for the primary variable of interest, mental health outcomes (BASC-2 or clinical neuropsychological reports) or for the WISC-IV (for the subset

that had cognitive testing completed). One child did not have a BRIEF completed. Several parents chose not to report their education level and results include only those with available data. Seizure data was not available for 2 children. Data on handedness and switch in handedness was not available for 7 children. In order to maximize our clinical sample, we included all available data in analyses and did not exclude any participants.

Results

Study Cohort

A total of 75 children (dystonia n= 24, 14 females, no dystonia n= 51, 12 females) from the Children's Stroke Study at the Hospital for Sick Children in Toronto, Canada met the inclusion criteria for the present study. There were 14 with acute neonatal stroke, 47 with acute childhood stroke, and 14 with presumed perinatal stroke. All children in the dystonia group were exhibiting symptoms of dystonia at the time of data collection. All children had data for the primary variable of interest, mental health from the BASC-2 and neuropsychological reports as well as motor outcomes data from the PSOM sensorimotor subscale. Cognitive data (WISC-IV, BRIEF) that was collected at the same time as the mental health data were available for 68 participants (24 dystonia, 44 no dystonia).

Group analyses using independent *t*-tests and χ^2 were conducted to compare dystonia and non-dystonia groups on demographic and neurological variables (Table 1). There were no significant differences between dystonia and non-dystonia groups on maternal education, age at stroke, age at assessment, time since stroke, lesion size, lesion laterality, or timing of stroke. The proportion of children with current seizures did not significantly differ between the groups. The dystonia group had a smaller proportion of children with subcortical lesions only, and a larger proportion of children with additional small/medium cortical lesions. There were no differences

between groups with respect to additional large cortical lesions. There was a larger proportion of males in the no-dystonia group, which is consistent with past findings indicating post-stroke dystonia may be more common in females (Soman et al., 2006). There were also differences between groups on the PSOM sensorimotor subscale, with the dystonia group showing higher impairment scores. The dystonia group also had significantly more children with hemiparesis as well as children who switched handedness. Four of the 24 children with dystonia were reported to be taking medication to treat dystonia at time of the study, one was taking Artane, two were taking Baclofen, and one child was taking both Artane and Baclofen. All children in the dystonia group were confirmed as exhibiting symptoms of dystonia at the time of data collection.

Table 1. Demographic and neurological characteristics of patient group, by dystonia status

	All Patients	Dystonia	No Dystonia	Statistic χ^2 /*t*	*p* value
Total N	75	24	51		
Number of Males	49(65.3%)	10(41.7%)	39(76.5%)	8.73	.003*
Maternal Education – Mean (SD)	4.48(1.01)	4.25(1.16)	4.59(.92)	1.22	.226
Age at Stroke yrs – Mean (SD)	3.53(4.16)	3.13(3.20)	3.72(4.56)	.57	.572
Age at Test yrs – Mean (SD)	11.90(3.32)	12.09(2.88)	11.82(3.53)	-.32	.750
Time since Stroke yrs- Mean (SD)	8.37(4.52)	8.96(4.31)	8.11(4.63)	-.759	.450
Lesion Location					
Subcortical only	37(49.3%)	6(25%)	31(60.8%)	8.36	.004*
Subcortical+Cortical (sm/med)	17(22.7%)	11(45.8%)	6(11.8%)	10.81	.001*
Subcortical+Cortical (lg)	21(28%)	7(29.2%)	14(27.5%)	.02	.877
Lesion Size					
Small	28(37.3%)	10(41.7%)	18(35.3%)	.28	.595
Medium	21(28%)	6(25%)	15(29.4%)	.16	.691
Large	26(34.7%)	8(33.3%)	18(35.3%)	.03	.868
Lesion Laterality					
Right	33(44%)	13(54.2%)	20(39.2%)	1.48	.224
Left	42(56%)	11(45.8%)	31(60.8%)	1.48	.224

Timing of Stroke					
Presumed Perinatal	14(18.7%)	4(16.7%)	10(19.6%)	.09	.760
Neonatal	14(18.7%)	3(12.5%)	11(21.6%)	.88	.347
30 days – 5.9 yrs	30(40%)	12(50%)	18(35.3%)	1.47	.225
6-16	17(22.7%)	5(20.8%)	12(23.5%)	.07	.795
Current Seizure Disorder	14(14.6%)	2(8.3%)	7(14.6%)	.57	.450
PSOM	.93(.77)	1.42(.64)	.71(.73)	-4.09	< .001*
Hemiparesis	32(42.7%)	15(62.5%)	17(33.3%)	5.68	.024
Cerebral Palsy	3(4%)	1(4.2%)	2(3.9%)	.003	.999
Spasticity	3(4%)	2(8.3%)	1(2%)	1.73	.238
Handedness (Right)	41(60.3%)	15(68.2%)	26(56.5%)	2.73	.255
Handedness Switch	8(11.7%)	6(27.3%)	2(4.4%)	7.54	.012

Maternal Education is rated on a 6-point scale (see text for details)
PSOM= Pediatric Stroke Outcome Measure: 0= normal, 0.5= mild deficit, 1= moderate deficit, 2= severe deficit

Frequencies of at-risk and clinically significant ratings on the BASC-2 across the entire sample and dystonia and no dystonia groups. Table 2 shows frequencies of at-risk and clinically significant ratings on the BASC-2 across all stroke patients and dystonia and no dystonia groups. After correcting for multiple comparisons using the Bonferroni correction, only the at-risk ratings on the Internalizing Index were statistically significant difference with a greater proportion of children represented in the dystonia group compared to the no dystonia group.

Table 2. Frequencies of At-Risk and Clinically Significant Scores on the BASC-2 for subjects with dystonia, subjects without dystonia, and the entire patient group

	All patients (n= 75) n(%)	Dystonia (n= 24) n(%)	No dystonia (n= 51) n(%)	χ^2	*p*	*V*
BASC-2 Scale/Index						
Hyperactivity						
At-risk	12(16.0%)	4(16.7%)	8(15.7%)	.01	.914	.012
Clinically significant	9(12.0%)	2(8.3%)	7(13.7%)	.45	.503	.077
Aggression						
At-risk	5(6.7%)	3(12.5%)	2(3.9%)	1.93	.165	.160
Clinically significant	6(8.0%)	0(0%)	6(11.8%)	3.07	.080	.202
Anxiety						
At-risk	12(16.0%)	6(25%)	6(11.8%)	2.13	.145	.168
Clinically significant	6(8.0%)	3(12.5%)	3(5.9%)	.97	.324	.114
Depression						
At-risk	11(14.7%)	6(25%)	5(9.8%)	3.01	.083	.200
Clinically significant	8(10.7%)	3(12.5%)	5(9.8%)	.12	.724	.041
Somatization						
At-risk	12(16.0%)	5(20.8%)	7(13.7%)	.61	.433	.090
Clinically significant	7(9.3%)	5(20.8%)	2(3.9%)	5.52	.019	.271
Atypicality						
At-risk	6(8.0%)	0(0%)	6(11.8%)	3.07	.080	.202
Clinically significant	8(10.7%)	1(4.2%)	7(13.7%)	1.57	.211	.144
Withdrawal						
At-risk	21(28.0%)	8(33.3%)	13(25.5%)	.50	.480	.081
Clinically significant	7(9.3%)	4(16.7%)	3(5.9%)	2.24	.134	.173
Attention Problems						
At-risk	24(32.0%)	7(29.2%)	17(33.3%)	.130	.718	.042
Clinically significant	7(9.3%)	2(8.3%)	5(9.8%)	.04	.838	.024
Adaptability						
At-risk	16(21.3%)	7(29.2%)	9(17.6%)	1.29	.256	.131
Clinically significant	3(4.0%)	0(0%)	3(5.9%)	1.47	.225	.140
Social Skills						
At-risk	12(16.0%)	4(16.7%)	8(15.7%)	.01	.914	.012
Clinically significant	3(5.3%)	1(4.2%)	3(5.9%)	.09	.758	.036
Leadership						
At-risk	26(34.7%)	11(45.8%)	15(29.4%)	1.94	.163	.161
Clinically significant	6(8.0%)	1(4.2%)	5(9.8%)	.71	.401	.097
Activities of Daily Living						
At-risk	14(18.7%)	3(12.5%)	11(21.6%)	.884	.347	.109
Clinically Significant	12(16.0%)	3(12.5%)	9(17.6%)	.32	.571	.065

Functional Communication						
At-risk	24(32.0%)	4(16.7%)	20(39.2%)	3.81	.051	.225
Clinically Significant	3(4.0%)	1(4.2%)	2(3.9%)	.003	.960	.006
Externalizing Index						
At-risk	10(13.3%)	2(8.3%)	8(15.7%)	.764	.382	.101
Clinically significant	5(6.7%)	0(0%)	5(9.8%)	2.52	.112	.183
Internalizing Index						
At-risk	10(13.3%)	8(33.3%)	2(3.9%)	12.22	.001*	.404
Clinically significant	8(10.7%)	3(12.5%)	5(9.8%)	.12	.724	.041
Behavioral Symptoms Index						
At-risk	13(17.3%)	5(20.8%)	8(15.7%)	.30	.583	.063
Clinically significant	8(10.7%)	2(8.3%)	6(11.8%)	.20	.653	.052
Adaptive Skills Index						
At-risk	22(29.3%)	5(20.8%)	17(33.3%)	1.23	.267	.128
Clinically significant	5(6.7%)	1(4.2%)	4(7.8%)	.36	.552	.069

*$p \leq .003$, adjusted for multiple comparisons using the Bonferroni correction

Note: BASC-2 Clinically significant= $T \geq 70$, At-risk= $T \geq 60$;
Adaptability, Social Skills, Leadership, Activities of Daily Living, Functional Communication Scales and Adaptive Skills Index Clinically Significant= $T \leq 30$, At-risk= T 30 – 40

Group differences between dystonia and no dystonia groups on distribution of BASC-2 internalizing symptoms. Independent Mann-Whitney U tests were used to compare BASC-2 Anxiety, Depression and Somatization scales and the Internalizing Index between the dystonia and no dystonia groups (Table 3). Distributions were significantly different on the Anxiety and Depression scales, indicating that a greater number of children in the dystonia group had elevated ratings on these scales, with effect sizes in the small range. Groups were not significantly different on the Somatization scale. The distributions were also significantly different on the Internalizing Index, again with a small effect size.

Table 3. BASC-2 Anxiety and Depression Scales and Internalizing Index for subjects with and without dystonia

	Dystonia (n= 24) Median(range)	No dystonia (n= 51) Median(range)	*U*	*z*	*p*	*r*
Anxiety	58.5(61)	50(63)	818.5	2.35	.019*	.27
Depression	56(78)	49(68)	815.5	2.32	.021*	.27
Somatization	53.5(65)	48(42)	770	1.80	.072	.21
Internalizing Index	58.5(83)	47(62)	804.0	2.18	.029*	.25

* $p < .05$

Frequencies of mild-moderate and severe mental health concerns indicated on clinical reports across the entire sample and dystonia and no dystonia groups. Table 4 shows the frequencies of concerns of depression and anxiety indicated on clinical neuropsychological reports. X^2 tests were used to compare dystonia and no dystonia groups. Overall, the no dystonia group had a significantly greater proportion of children with no concerns (absent) indicated for both depression and anxiety. With respect to depression concerns, a significantly greater proportion of children were indicated to have severe concerns in the

dystonia group and mild-moderate concerns pertaining to depression. Likewise, there was a greater proportion of children with severe anxiety concerns indicated in the dystonia group. There were no significant differences for proportion of children indicated as having mild-moderate concerns pertaining to anxiety. Effect sizes for significant differences were in the medium range.

Table 4. Frequencies and group differences of mental health concerns indicated on clinical neuropsychological reports for subjects with dystonia, subjects without dystonia, and the entire patient group

	All patients (*n*= 75) n(%)	Dystonia (*n*= 24) n(%)	No dystonia (*n*= 51) n(%)	χ^2	*p*	*V*
Depression						
Absent	54(72.0%)	10(41.7%)	44(86.3%)	16.11	<.001***	.463
Mild-Moderate	15(20.0%)	8(33.3%)	7(13.7%)	3.92	.048*	.229
Severe	6(8.0%)	6(25%)	0(0%)	13.86	<.001***	.430
Anxiety						
Absent	49(65.3%)	10(41.7%)	39(76.5%)	8.73	.003*	.341
Mild-Moderate	17(22.7%)	7(29.2%)	10(19.6%)	.85	.356	.107
Severe	9(12.0%)	7(29.2%)	2(3.9%)	9.85	.002*	.362

Note: Concerns were coded for anxiety and depression, each considered separately, on a three-point scale as 0 – Absent (no concerns), 1 – Mild to moderate concerns, and 2 – Severe concerns. See text for further details

Group differences between mild and severe dystonia groups on mental health outcomes. Dystonia status was classified as mild or severe. In terms of the BASC-2 (Table 5), distributions were significantly different on the Somatization scales, indicating that a greater number of children in the severe dystonia group had elevated ratings on this scale, with effect sizes in the small range. There were no differences on the Anxiety or Depression scales. The distributions were also significantly different on the Internalizing Index, with a medium effect size.

Table 5. BASC-2 Internalizing Index and Scales for patients with mild and severe dystonia

	Mild (n= 13) Median(range)	Severe (n= 11) Median(range)	*U*	*z*	*p*	*r*
Anxiety	58(30)	66(54)	104.0	1.88	.063	.38
Depression	55(27)	57(67)	91.5	1.17	.252	.23
Somatization	48(39)	60(56)	106.5	2.03	.041*	.42
Internalizing Index	48(33)	62(71)	116.0	2.58	.009*	.53

* $p < .05$

As presented in Table 6, there were no differences between mild and severe dystonia groups on mental health concerns on clinical neuropsychological reports with the exception of anxiety concerns. There was a significantly greater proportion of children with mild dystonia with "Absent" concerns. There were no differences between groups on mild-moderate or severe concerns.

Table 6. Mental health concerns indicated on clinical neuropsychological reports for patients with mild and severe dystonia

	All patients (*n*= 24) n(%)	Mild (*n*= 13) n(%)	Severe (*n*= 11) n(%)	χ^2	*p*	*V*
Depression						
Absent	10(41.7%)	6(46.2%)	4(36.4%)	.235	.697	.099
Mild-Moderate	8(33.3%)	5(38.5%)	3(27.3%)	.336	.679	.118
Severe	6(25%)	2(15.4%)	4(36.4%)	1.40	.357	.241
Anxiety						
Absent	10(41.7%)	8(61.5%)	2(18.2%)	4.61	.047*	.438
Mild-Moderate	7(29.2%)	3(23.1%)	4(36.4%)	.509	.659	.146
Severe	7(29.2%)	2(15.4%)	5(45.5%)	2.61	.182	.330

Note: Concerns were coded for anxiety and depression, each considered separately, on a three-point scale as 0 – Absent (no concerns), 1 – Mild to moderate concerns, and 2 – Severe concerns. See text for further details

Group differences on cognitive abilities. Group differences between the dystonia and no dystonia group on measures of intellectual abilities and executive functioning are presented in

Table 7. The dystonia group performed significantly poorer on measures of intellectual abilities including Full Scale IQ, verbal abilities, and perceptual reasoning. There were no significant differences on any of the BRIEF rating indices. Effect sizes for significant differences were in the medium range.

Table 7. Cognitive test scores for subjects with and without dystonia

	Dystonia (*n*= 24) M(SD)	No dystonia (*n*= 44) M(SD)	*t*	*P*	Cohen's *d*
Intellectual ability (WISC-IV)					
FSIQ	79.96(9.64)	90.25(21.68)	2.20	.009*	0.61
VIQ	84.13(11.73)	93.50(20.13)	2.09	.018*	0.57
PRI	84.63(10.07)	93.73(20.45)	2.04	.017*	0.56
WMI	84.42(10.85)	88.66(18.44)	1.03	.237	0.28
PSI	82.96(15.57)	88.84(19.81)	1.26	.183	0.30
Executive Functions (BRIEF)					
BRI	56.50(11.73)	54.74(15.54)	-0.48	.632	0.13
MCI	60.74(14.09)	58.79(12.62)	-0.57	.568	0.15
GEC	63.04(24.75)	57.84(13.84)	-1.10	.276	0.26

Note: WISC-IV data is presented with standard scores (M= 100, SD= 15), BRIEF data is presented with T-scores (M= 50, SD= 10).

Associations between mental health, cognitive, and motor outcomes. In the dystonia group (Table 8), the only significant association was between the BASC-2 depression scale and the BRIEF behavioral regulation index (BRI). In the no dystonia group (Table 9) significant associations emerged between the BASC-2 Anxiety scale and the BRIEF BRI, metacognition index (MI), and general executive composite (GEC), the BASC-2 depression scale and BRI, MI, and GEC, and the BASC-2 Internalizing Index and BRI, MI, and GEC.. Significant associations were also found between the PSOM sensorimotor total and FSIQ, VCI, PRI, WMI, and PSI in the no dystonia group.

Table 8. Correlations in dystonia group

	1	2	3	4	5	6	7	8	9	10	11	12
Mental Health (BASC-2)												
1. Anxiety	-											
2. Depression	.64**	-										
3. Internalizing	.83***	.84***	-									
Intellectual Abilities (WISC-IV)												
4. FSIQ	-.12	.01	-.19	-								
5. VCI	-.10	.06	-.13	.81***	-							
6. PRI	-.06	.13	.02	.75***	.66***	-						
7. WMI	-.06	-.17	-.13	.68***	.57**	.32	-					
8. PSI	-.24	-.06	-.30	.58***	.09	.24	.19	-				
Executive Functioning (BRIEF)												
9. BRI	.40	.48*	.40	-.01	.07	.05	-.09	-.11	-			
10. MI	.33	.37	.27	-.08	.14	-.17	.09	-.28	.68***	-		
11. GEC	.27	.22	.17	.05	.20	-.15	.18	-.11	.55**	.89***	-	
Motor												
12. PSOM	.18	.30	.25	.18	.20	.11	.18	.02	-.11	.02	.11	-

***p ≤ .001, **p ≤ .01 *p ≤ .05

Table 9. Correlations in no dystonia group

	1	2	3	4	5	6	7	8	9	10	11	12
Mental Health (BASC-2)												
1. Anxiety	-											
2. Depression	.77*	-										
3. Internalizing	.89***	.89***	-									
Intellectual Abilities (WISC-IV)												
4. FSIQ	-.15	.20	-.23	-								
5. VCI	-.10	-.16	-.18	.92***	-							
6. PRI	-.13	-.24	.27	.90***	.77***	-						
7. WMI	-.13	-.17	-.16	.87***	.81**	.73***	-					
8. PSI	-.03	-.01	-.06	.82***	.67***	.67***	.65***	-				
Executive Functioning (BRIEF)												
9. BRI	.63***	.84***	.72***	-.16	-.14	-.23	-.20	-.03	-			
10. MI	.42**	.56***	.44**	-.21	.13	-.28	.22	-.09	.75***	-		
11. GEC	.54***	.72***	.59***	.19	-.13	-.27	.22	-.06	.92**	.95***	-	
Motor												
12. PSOM	-.02	-.01	-.04	-.53***	-.42**	-.49*	-.40*	-.53***	.09	.12	.10	-

***p ≤ .001, **p ≤ .01 *p ≤ .05

Discussion

The purpose of this study was to explore mental health outcomes in children with stroke involving the basal ganglia and/or thalamus with and without post-stroke dystonia and to determine whether children with post-stroke dystonia experienced greater mental health difficulties. Overall, results indicated that there was a larger proportion of children with dystonia in the at-risk range on the Internalizing Index, children with dystonia had higher levels of depression and anxiety symptoms on the BASC-2, and a greater proportion of children with dystonia had concerns relating to anxiety and depression on clinical neuropsychological reports. Therefore, results supported the presence of greater levels of anxiety and depression symptoms in children with post-stroke dystonia after stroke relative to those with similar patterns of stroke, but no dystonia.

There were no significant differences between the proportion of dystonia and no dystonia groups with either at-risk or clinically significant ratings on any of the clinical scales on the BASC-2. However, it is important to note that the proportion of children in the at-risk and clinically significant range was higher in children with dystonia, in some cases nearly twice as high compared to children with stroke only (e.g., clinically significant Anxiety dystonia 12.5% vs no dystonia 5.9%, at-risk Depression dystonia 25% vs no dystonia 9.8%). It is possible that with larger and more even sample sizes these differences would reach significance. The at-risk ratings on the Internalizing Index were significantly different, with a greater number of children with post-stroke dystonia showing elevations on this index. We also examined the distributions of the ratings to account for the observation that many children with stroke show subclinical symptoms and do not necessarily meet full criteria for a psychological diagnosis, and therefore examining only cut-off rates may underestimate the psychological needs of children (Westmacott

et al., 2018b). We focused on the Anxiety and Depression scales and Internalizing Index as these are most frequent psychological symptoms in adults with dystonia (Balas et al., 2006; Conte et al., 2016; Degirmenci et al., 2013; Fabbrini et al., 2010; Gundel et al., 2003; Miller et al., 2007; Kleiner-Fisman et al., 2007; Lehn et al., 2014; Lewis et al., 2008; Ostrem et al., 2011; van Tricht et al., 2012). Indeed, children with dystonia showed higher levels of symptoms on the Anxiety and Depression scales, and the Internalizing Index, with effect sizes in the small range. On clinical neuropsychological reports, there was a higher proportion of children with dystonia with mild-moderate concerns as well as the severe concerns for depression, compared to children with stroke only. There was also a higher proportion of children with dystonia in the severe anxiety group than children with no dystonia, however there were no group differences on mild-moderate anxiety.

Overall, our study demonstrates the presence of anxiety and depression concerns in children with basal ganglia stroke, with additional challenges associated with post-stroke dystonia. The rates of anxiety and depression in our sample were more frequent than those found by Williams et al. (2017) who investigated psychological outcomes in AIS, finding 4% of their overall sample had diagnoses of anxiety as well as depression. The rates in our sample were more similar to those found by Westmacott et al., (2018b) who focused on mental health diagnoses in subcortical stroke but did not examine the role of post-stroke dystonia, which is consistent with the observation that involvement of subcortical structures may be specifically associated with anxiety and mood difficulties after stroke. Importantly, our results suggest that children who develop secondary dystonia after a stroke involving the basal ganglia and/or thalamus are at risk for poorer mental health outcomes relative to children with a similar pattern of brain injury but no dystonia.

We also examined associations between mental health, cognitive, and motor outcomes in the dystonia and stroke only groups separately. There were no significant associations between motor and cognitive or mental health outcomes in children with post-stroke dystonia aside from one association depression and behavioral regulation. Motor and cognitive outcome were significantly associated in the stroke only group. Significant associations were also found between anxiety, depression, and somatization scales as well as the internalizing index and executive functioning in the stroke only group. Given the small sample sizes, these results should be considered preliminary, however the lack of associations in the dystonia group suggest these features are independent of one another in this population consistent with findings in adult dystonia (Foley et al. 2017). This is in contrast to the idea proposed by Stamelou and colleagues (2012) that mood and motor symptoms may have a distracting effect that contributes to the cognitive difficulties observed in individuals with dystonia. However, the relationship between mental health and cognitive performance should be further studied in children with post-stroke dystonia as this was the first study to do so, and our sample was relatively small.

With respect to demographic and neurological characteristics, the dystonia and no dystonia groups were not significantly different in terms of mean lesion size, age at stroke, age at assessment, time since stroke, and maternal education level. The dystonia group had more females, which is consistent with what has been demonstrated in the literature (Elbers et al., 2010; Goldfarb et al., 2013; Soman et al., 2006). Additionally, the dystonia group was more likely to have cortical involvement whereas the stroke only group was more likely to have strokes involving subcortical regions only. Finally, the PSOM scores were significantly different between groups, which is expected given the dystonia and no dystonia groups differ in terms of level of motor impairment.

Limitations to this study must be considered. First, a formal dystonia rating scale (e.g., Hypertonia Assessment Tool; Jethwa et al., 2010) was not systematically implemented in this retrospective cohort, and diagnosis was made on the basis of a neurologist's judgement. Additionally, the diagnosis of dystonia is based on a unique assessment. However, it is important to note that all children in the dystonia group were exhibiting symptoms at the time of the neuropsychological assessment. We are currently implementing regular use of the Hypertonia Assessment Tool (Jewtha et al., 2010) in this clinic. This tool will also be used in future, prospective studies in order to provide more information about the manifestation of dystonia that is important to outcomes (e.g., affected limb, severity, and functional impairment). We also did not have sufficient data available in this cohort for performance-based measures of executive functioning and had to rely solely on parent report. Interestingly, in our group's previous research, found significant differences between dystonia and no dystonia groups on a performance-based measure of executive functioning, the Delis Kaplan Color-Word Interference test, but not on parent-completed questionnaires (Westmacott et al., 2018a). Therefore, including a performance-based measure of executive functioning when investigating associations with mental health and motor outcomes would be beneficial. Additionally, we were limited by our sample size. Larger sample sizes would allow us to explore the effects of different potential risk factors such as time of stroke (e.g., perinatal versus childhood), length of living with dystonia, the relative contribution of other present movement disorders (e.g., hemiparesis and spasticity), current age, and family history on mental health and cognitive outcomes. Importantly, Williams et al., (2017) note that mental health issues are not always apparent during the initial presentation for neuropsychological assessment and tend emerge over time. This is demonstrated in a study by Elbers, deVeber, Pontigon, and Moharir (2014) that found a quarter of the young adult

survivors of pediatric stroke in their sample self-reported having a mental illness (e.g., depression or anxiety) and points to the importance of longitudinal examinations of mental health.

The cause of the higher symptoms of anxiety and depression in children with post-stroke dystonia is not yet clear. Research has found mental health outcomes to be related to the neuropathology of dystonia, including the dopamine and monoamine systems and basal ganglia dysfunction along with disruptions in frontal-striatal networks (Moraru et al., 2002; McNeill, 2003; Heiman et al., 2004; Zurowski et al., 2013) as well as a reaction to the functional impact of the disease including pain, disability, and occupational and social stress (Ben-Shlomo, et al., 2002; McNeill, 2003; Degirmenci et al., 2013). A number of studies have found that, in adults, onset of psychiatric symptoms preceded the onset of motor symptoms, suggesting the mental health changes could not be simply a reaction to the dystonia (Wenzel et al., 1998, Moraru et al., 2003, Lencer et al., 2009). However, it has also been demonstrated that pain, lack of control over movement, disability in activities of daily living, negative body image, and stigma contribute to negative quality of life and psychiatric symptoms (Jahanshahi, 1991; Papathanasiou, MacDonald, Whurr, & Jahanshahi, 2001; Ben-Shlomo et al., 2002; Slawek et al., 2007; Queiroz, Chien, & Barbosa, 2011). With respect to children, Westmacott et al., (2018a) note that in their clinical observations post-stroke dystonia affects self-esteem and peer relationships. It is possible that low self-esteem and difficulties with peers contribute to depression and anxiety. McNeill (2003) proposed adapting a biopsychosocial model in order to integrate the neurobiological and psychosocial influences on mental health outcomes in dystonia.

Our group has recently demonstrated that children with post-stroke dystonia showed additional cognitive difficulties in the domains of intelligence, inhibitory control, and academics

compared to children with the same pattern of stroke but no dystonia, which provides support for the hypothesis that that maladaptive reorganization after stroke in the frontal-striatal circuits may contribute to the development of post-stroke dystonia and suggests this reorganization also contributes to cognitive outcomes (Lehericy et al., 2013; Quartarone & Hallet, 2013, Tibussek et al., 2015; Westmacott et al., 2018a). Our group is currently collecting neuroimaging data in order to examine the structural and functional neural correlates of cognitive, mental health, and motor outcomes in this population. Specifically, we aim to determine whether key neural networks differ between survivors of pediatric stroke with and without dystonia and how these relate to pertinent cognitive and mental health outcomes. This future research will further elucidate the neural basis of cognitive and mental health difficulties present in children with post-stroke dystonia. Additionally, we are collecting self and parent-reported measures of child participation at in school, home, and social situations as well as measures of pain and disability. This will allow for the investigation of the relative contributions of functional disability and altered neural networks on mental health outcomes in children with post-stroke dystonia.

In conclusion, the results of this study suggest that children who go on to develop secondary dystonia after a stroke involving the basal ganglia and/or thalamus are at risk for poorer mental health outcomes relative to children with a similar pattern of brain injury but no dystonia. Additionally, our examination of the parent ratings on standardized questionnaires of mental health, as well as clinical impressions captured in neuropsychological reports underscores the importance of not focusing solely on questionnaire data and cut-off points but ensuring to document subclinical symptoms of depression and anxiety in the context of a full neuropsychological assessment. Results suggest that cognitive, mental health, and motor outcomes are independent in dystonia, however this is an area for further study. The results point

to the importance of clinical assessment, close monitoring, and providing intervention for mental health in children with basal ganglia stroke and dystonia.

References

Albanese, A., Bhatia, K., Bressman, S. B., DeLong, M. R., Fahn, S., Fung, V. S., ... & Lang, AE. (2013). Phenomenology and classification of dystonia: a consensus update. *Movement Disorders*, *28*(7), 863-873. doi:10.1002/mds.25475

Balas, M., Peretz, C., Badarny, S., Scott, R. B., & Giladi, N. (2006). Neuropsychological profile of DYT1 dystonia. *Movement disorders: official journal of the Movement Disorder Society*, *21*(12), 2073-2077. doi: 10.1002/mds.21070

Baron. I.S (2000). Test review: Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2004). Behavior rating inventory of executive function. *Child Neuropsychology*, *6*(3), 235-238. doi: 10.1076/chin.6.3.235.3152

Ben-Shlomo, Y., Camfield, L., & Warner, T. (2002). What are the determinants of quality of life in people with cervical dystonia?. *Journal of Neurology, Neurosurgery & Psychiatry*, *72*(5), 608-614. doi: 10.1136/jnnp.72.5.608

Bugalho, P., Corrêa, B., Guimarães, J., & Xavier, M. (2008). Set-shifting and behavioral dysfunction in primary focal dystonia. *Movement Disorders*, *23*(2), 200-206. doi: 10.1002/mds.21784

Conte, A., Berardelli, I., Ferrazzano, G., Pasquini, M., Berardelli, A., & Fabbrini, G. (2016). Non-motor symptoms in patients with adult-onset focal dystonia: sensory and psychiatric disturbances. *Parkinsonism & related disorders*, *22*, S111-S114. doi: 10.1016/j.parkreldis.2015.09.001

Degirmenci, Y., Oyekcin, D. G., Bakar, C., & Kurklu, N. (2013). Anxiety and depression in primary and secondary dystonia: a burden on health related quality of life. *Neurology, Psychiatry and Brain Research*, *19*(2), 80-85. doi: 10.1016/j.npbr.2013.01.002

deVeber, G. A., Kirton, A., Booth, F. A., Yager, J. Y., Wirrell, E. C., Wood, E., ... & MacGregor, D. (2017). Epidemiology and outcomes of arterial ischemic stroke in children: the Canadian Pediatric Ischemic Stroke Registry. *Pediatric neurology*, *69*, 58-70. doi: 10.1016/j.pediatrneurol.2017.01.016

Elbers, J., Wilkinson, A., DeVeber, G., & Askalan, R. (2010). Lesion volume and localization as predictors of dystonia in pediatric basal ganglia stroke. Annals of Neurology, 68(4), S98–S98.

Elbers, J., deVeber, G., Pontigon, A. M., & Moharir, M. (2014). Long-term outcomes of pediatric ischemic stroke in adulthood. *Journal of Child Neurology*, *29*(6), 782-788. doi: 10.1177/0883073813484358

Fabbrini, G., Berardelli, I., Moretti, G., Pasquini, M., Bloise, M., Colosimo, C., ... & Berardelli, A. (2010). Psychiatric disorders in adult-onset focal dystonia: a case-control study. *Movement Disorders*, *25*(4), 459-465. doi: 10.1002/mds.22983

Foley, J. A., Vinke, R. S., Limousin, P., & Cipolotti, L. (2017). Relationship of cognitive function to motor symptoms and mood disorders in patients with isolated dystonia. *Cognitive and Behavioral Neurology*, *30*(1), 16-22**.** doi: 10.1097/WNN.0000000000000117

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). Behavior rating inventory of executive function. Child Neuropsychology, 6(3), 235–238. doi:10.1076/chin.6.3.235.3152

Goldfarb, J., Askalan, R., Pontigon, A. M., & DeVeber, G. (2013). Lesion volume and localization in acute ischemic basal ganglia. *Abstract Presented at the Annual Conference of the Child Neurology Society, October 2013.*

Gunaydin, L. A., & Kreitzer, A. C. (2016). Cortico–basal ganglia circuit function in psychiatric disease. *Annual review of physiology*, *78*, 327-350. doi: 10.1146/annurev-physiol-021115-105355

Gundel, H., Wolf, A., Xidara, V., Busch, R., Ladwig, K. H., Jacobi, F., ... & Ceballos-Baumann, A. O. (2003). High psychiatric comorbidity in spasmodic torticollis: a controlled study. *The Journal of nervous and mental disease*, *191*(7), 465-473. doi: 10.1097/01.NMD.0000081667.02656.21

Heiman, G. A., Ottman, R., Saunders-Pullman, R. J., Ozelius, L. J., Risch, N. J., & Bressman, S. B. (2004). Increased risk for recurrent major depression in DYT1 dystonia mutation carriers. *Neurology*, *63*(4), 631-637. doi: 10.1212/01.WNL.0000137113.39225.FA

IBM Corp. Released. (2015). IBM SPSS statistics for windows, version 23.0. Armonk, NY: IBM Corp.

Jahanshahi, M. (1991). Psychosocial factors and depression in torticollis. *Journal of Psychosomatic Research*, *35*(4-5), 493-507. doi: 10.1016/0022-3999(91)90044-O

Jahanshahi, M., Rowe, J., & Fuller, R. (2003). Cognitive executive function in dystonia. *Movement disorders: official journal of the Movement Disorder Society*, *18*(12), 1470-1481. doi: 10.1002/mds.10595

Jethwa, A., Mink, J., Macarthur, C., Knights, S., Fehlings, T., & Fehlings, D. (2010). Development of the Hypertonia Assessment Tool (HAT): a discriminative tool for hypertonia in children. Developmental Medicine & Child Neurology, 52(5), e83-e87. doi: 10.1111/j.1469-8749.2009.03483.x

Jinnah, H. A., & Hess, E. J. (2006). A new twist on the anatomy of dystonia: the basal ganglia and the cerebellum?. *Neurology*, 67(10), 1740–1741.

doi:10.1212/01.wnl.0000246112.19504.61

Kaufman, A. S., Flanagan, D. P., Alfonso, V. C., & Mascolo, J. T. (2006). Test review: Wechsler intelligence scale for children, (WISC-IV). *Journal of Psychoeducational Assessment*, *24*(3), 278-295. doi: 10.1177/0734282906288389

Kitchen, L., Westmacott, R., Friefeld, S., MacGregor, D., Curtis, R., Allen, A., ... & deVeber, G. (2012). The pediatric stroke outcome measure: a validation and reliability study. *Stroke*, *43*(6), 1602-1608. doi: 10.1161/STROKEAHA.111.639583

Kleiner-Fisman, G., Liang, G. S. L., Moberg, P. J., Ruocco, A. C., Hurtig, H. I., Baltuch, G. H., ... & Stern, M. B. (2007). Subthalamic nucleus deep brain stimulation for severe idiopathic dystonia: impact on severity, neuropsychological status, and quality of life. *Journal of neurosurgery*, 107(1), 29-36. doi: 10.3171/JNS-07/07/0029

Kuyper, D. J., Parra, V., Aerts, S., Okun, M. S., & Kluger, B. M. (2011). Nonmotor manifestations of dystonia: a systematic review. *Movement Disorders*, *26*(7), 1206-1217. doi: 10.1002/mds.23709

Kwak, C. H., & Jankovic, J. (2002). Tourettism and dystonia after subcortical stroke. *Movement disorders*, *17*(4), 821-825. doi: 10.1002/mds.10207

Lehericy, S., Tijssen, M. A., Vidailhet, M., Kaji, R., & Meunier, S. (2013). The anatomical basis of dystonia: current view using neuroimaging. *Movement Disorders*, 28(7), 944-957. doi: 10.1002/mds.25527

Lehn, A., Mellick, G., & Boyle, R. (2014). Psychiatric disorders in idiopathic-isolated focal dystonia. *Journal of neurology*, *261*(4), 668-674. doi: 10.1007/s00415-014-7244-8

Lencer, R., Steinlechner, S., Stahlberg, J., Rehling, H., Orth, M., Baeumer, T., ... & Hagenah, J.

(2009). Primary focal dystonia: evidence for distinct neuropsychiatric and personality profiles. Journal of Neurology, Neurosurgery & Psychiatry, 80(10), 1176-1179. doi: 10.1136/jnnp.2008.170191

Lewis, L., Butler, A., & Jahanshahi, M. (2008). Depression in focal, segmental and generalized dystonia. *Journal of neurology*, *255*(11), 1750. doi: 10.1007/s00415-014-7244-8

Lo Buono, V., Corallo, F., Bramanti, P., & Marino, S. (2017). Coping strategies and health-related quality of life after stroke. *Journal of health psychology*, *22*(1), 16-28. doi: 10.1177/1359105315595117

Marsden, C. D., Obeso, J. A., Lang, A. E., Hill, D., & Se, L. (1985). The anatomical basis of symptomatic hemidystonia. *Brain*, 108(2), 463–483. doi:10.1093/brain/108.2.463

Max, J. E., Mathews, K., Lansing, A. E., Robertson, B. A., Fox, P. T., Lancaster, J. L., ... & Smith, J. (2002). Psychiatric disorders after childhood stroke. *Journal of the American Academy of Child & Adolescent Psychiatry*, *41*(5), 555-562. doi: 10.1097/00004583-200205000-00013

Max, J. E., Bruce, M., Keatley, E., & Delis, D. (2010). Pediatric stroke: plasticity, vulnerability, and age of lesion onset. *The Journal of neuropsychiatry and clinical neurosciences*, *22*(1), 30-39. doi: 10.1176/jnp.2010.22.1.30

McNeill, A. (2003). Aetiology of co-morbid psychiatric disorders in dystonia: a biopsychosocial hypothesis. *Internet Journal of Neurology*, *2*(2), 5.

Miller, K. M., Okun, M. S., Fernandez, H. F., Jacobson IV, C. E., Rodriguez, R. L., & Bowers, D. (2007). Depression symptoms in movement disorders: comparing Parkinson's disease, dystonia, and essential tremor. *Movement Disorders*, *22*(5), 666-672. doi: 10.1002/mds.21376

Mink, J. W. (2003). The basal ganglia and involuntary movements: Impaired inhibition of competing motor patterns. *Neurological Review*, 60(10), 1365–1368. doi:10.1001/archneur.60.10.1365

Mink, J. W. (2013). Special concerns in defining, studying, and treating dystonia in children. *Movement Disorders*, 28(7), 921–925. doi:10.1002/mds.25548

Moraru, E., Schnider, P., Wimmer, A., Wenzel, T., Birner, P., Griengl, H., & Auff, E. (2002). Relation between depression and anxiety in dystonic patients: implications for clinical management. *Depression and anxiety*, *16*(3), 100-103. doi: 10.1002/da.10039

Neuner, B., von Mackensen, S., Krümpel, A., Manner, D., Friefeld, S., Nixdorf, S., ... & Nowak-Göttl, U. (2011). Health-related quality of life in children and adolescents with stroke, self-reports, and parent/proxies reports: cross-sectional investigation. *Annals of neurology*, *70*(1), 70-78. doi: 10.1002/ana.22381

Ostrem, J. L., Racine, C. A., Glass, G. A., Grace, J. K., Volz, M. M., Heath, S. L., & Starr, P. A. (2011). Subthalamic nucleus deep brain stimulation in primary cervical dystonia. *Neurology*, *76*(10), 870-878. doi: 10.1212/WNL.0b013e31820f2e4f

Papathanasiou, I., MacDonald, L., Whurr, R., & Jahanshahi, M. (2001). Perceived stigma in Spasmodic Torticollis. *Movement Disorders*. 16(2), 280-285. doi: 10.1002/mds.1055

Quartarone, A., & Hallett, M. (2013). Emerging concepts in the physiological basis of dystonia. *Movement Disorders*, 28(7), 958–967. doi:10.1002/mds.25532

Queiroz, M. A. R., Chien, H. F., Sekeff-Sallem, F. A., & Barbosa, E. R. (2012). Physical therapy program for cervical dystonia: a study of 20 cases. *Functional neurology*, *27*(3), 187.

Reynolds, C. R., & Kamphaus, R. W. (2004). Behavior Assessment System for Children (2nd ed.). Circle Pine, MN: American Guidance Service

Sanger, T. D., Chen, D., Fehlings, D. L., Hallett, M., Lang, A. E., Mink, J. W., . . . Valero-Cuevas, F. (2010). Definition and classification of hyperkinetic movements in childhood. Movement Disorders, 25(11), 1538–1549. doi:10.1002/mds.23088

Slawek, J., Friedman, A., Potulska, A., & Krystkowiak, P. (2007). Factors affecting the health-related quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections. *Functional neurology*, *22*(2), 95.

Soeder, A., Kluger, B. M., Okun, M. S., Garvan, C. W., Soeder, T., Jacobson, C. E., ... & Fernandez, H. H. (2009). Mood and energy determinants of quality of life in dystonia. *Journal of neurology*, *256*(6), 996. doi: 10.1007/s00415-009-5060-3

Soman, T., Askalan, R., Martin, M., Allen, A., Zak, M., MacGregor, D., & Logan, W. (2006). Predictors of dystonia in childhood basal ganglia stroke. *Neuropediatrics*, 37(S1), 121. doi:10.1055/s-2006-945715

Stamelou, M., Edwards, M. J., Hallett, M., & Bhatia, K. P. (2011). The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. *Brain*, *135*(6), 1668-1681. doi: 10.1093/brain/awr224

Stefurak, T., Mikulis, D., Mayberg, H., Lang, A. E., Hevenor, S., Pahapill, P., ... & Lozano, A. (2003). Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: a functional MRI case study. *Movement disorders: official journal of the Movement Disorder Society*, *18*(12), 1508-1516. doi: 10.1002/mds.10593

Tan, C. S. (2007). Test Review: Reynolds, CR, & Kamphaus, RW (2004). Behavior assessment system for children. Circle Pines, MN: American Guidance Service. *Assessment for Effective Intervention*, *32*(2), 121-124. doi: 10.1177/15345084070320020301

Tibussek, D., Mayatepek, E., Klee, D., & Koy, A. (2015). Post stroke hemi-dystonia in children:

A neglected area of research. *Molecular and Cellular Pediatrics*, 2(1), 14. doi:10.1186/s40348-015-0026-2

van Tricht, M. J., Dreissen, Y. E., Cath, D., Dijk, J. M., Contarino, M. F., van der Salm, S. M., ... & Tijssen, M. A. (2012). Cognition and psychopathology in myoclonus-dystonia. *J Neurol Neurosurg Psychiatry*, *83*(8), 814-820. doi: 10.1136/jnnp-2011-301386

Wenzel, T., Schnider, P., Wimmer, A., Steinhoff, N., Moraru, E., & Auff, E. (1998). Psychiatric comorbidity in patients with spasmodic torticollis. *Journal of Psychosomatic Research*, *44*(6), 687-690. doi: 10.1016/S0022-3999(97)00229-8

Wechsler, D. (2003). Wechsler intelligence scale for children–Fourth Edition (WISC-IV). San Antonio, TX: The Psychological Corporation.

Westmacott, R., Askalan, R., Macgregor, D., Anderson, P., & Deveber, G. (2010). Cognitive outcome following unilateral arterial ischaemic stroke in childhood: Effects of age at stroke and lesion location. Developmental Medicine and Child Neurology, 52(4), 386–393. doi:10.1111/j.1469-8749.2009.03403.x

Westmacott, R., McDonald, K. P., deVeber, G., MacGregor, D., Moharir, M., Dlamini, N., ... & Williams, T. S. (2018a). Neurocognitive outcomes in children with unilateral basal ganglia arterial ischemic stroke and secondary hemidystonia. *Child Neuropsychology*, *24*(7), 923-937. doi: 10.1080/09297049.2017.1353073

Westmacott, R., McDonald, K. P., Roberts, S. D., deVeber, G., MacGregor, D., Moharir, M., ... & Williams, T. S. (2018b). Predictors of cognitive and academic outcome following childhood subcortical stroke. *Developmental neuropsychology*, *43*(8), 708-728. doi: 10.1080/87565641.2018.1522538

Williams, T. S., McDonald, K. P., Roberts, S. D., Dlamini, N., deVeber, G., & Westmacott, R.

(2017). Prevalence and predictors of learning and psychological diagnoses following pediatric arterial ischemic stroke. *Developmental neuropsychology*, *42*(5), 309-322. doi: 10.1080/87565641.2017.1353093

Zurowski, M., McDonald, W. M., Fox, S., & Marsh, L. (2013). Psychiatric comorbidities in dystonia: emerging concepts. *Movement Disorders*, *28*(7), 914-920. doi: 10.1002/mds.25501

Chapter 4: Neuroimaging Correlates of Acquired Dystonia and Cognitive Outcome after Pediatric Arterial Ischemic Stroke Involving the Basal Ganglia and/or Thalamus

Dystonia is a disabling and often painful movement disorder that is characterized by involuntary, repetitive muscle contractions, twisting movements, and abnormal posturing (Albanese et al., 2013). The involuntary movements and muscle contractions can be functionally disruptive, painful, and disabling, and tend to be unresponsive to pharmacotherapy (Mink, 2013). One of the most common causes of acquired dystonia in childhood is arterial ischemic stroke (AIS) involving the basal ganglia and/or thalamus (Elbers et al., 2010; Soman et al., 2006; Mink, 2003; 2013); yet not all children with an infarct in the basal ganglia and/or thalamus will develop dystonia (Soman et al., 2006). Although there is some evidence that lesion location, younger age, and female sex may be associated with greater risk, consistent predictors of post-stroke dystonia have not yet been identified (Tibussek et al., 2015). The delayed presentation of the disorder and its relatively greater prevalence after pediatric stroke contrasted with rarer presentation after adult stroke suggest developmentally determined maladaptive neural reorganization after injury may contribute to its presentation (Marsden et al., 1985; Scott & Jankovic, 1996; Quartarone & Hallett, 2013). Moreover, recent findings of additional cognitive difficulties in children with acquired dystonia relative to children with similar patterns of stroke but no dystonia provide further support for the presence of maladaptive reorganization in acquired dystonia, which also affects cognitive functioning (Westmacott et al., 2018a). Diffusion weighted imaging (DWI) magnetic resonance imaging (MRI) has been effectively used to identify clinically relevant markers remote from the primary infarct location predicting motor and cognitive outcomes in pediatric stroke (Dlamini et al., 2017; Domi et al., 2020; Kirton et al., 2016). In order to further elucidate the hypothesis of maladaptive response to injury in post-stroke dystonia volumetric

analysis, detailed lesion classification, and presence of secondary injury is needed. The current study examined whether there were differences in neuroimaging features in children who developed acquired dystonia compared to those who did not as well as whether these were associated with intellectual functioning.

Basal ganglia infarcts occur in approximately one-third of perinatal stroke and half of childhood stroke, often due focal cerebral arteriopathy which primarily affects perforator territories (Bernard et al., 2012; deVeber et al., 2017). The basal ganglia are an interconnected network of deep nuclei which integrate all cortical activity into one output (Herrero et al., 2002; Ide et al., 2015). They represent a series of parallel circuits, mediated by excitatory and inhibitory neurotransmitters and are responsible for the integration of motor output, cognition, and emotion (Alexander et al., 1991; Gunaydin & Kreitzer, 2016). There is limited data on the prevalence of acquired dystonia after pediatric stroke, however one study reported 21% of their sample developed dystonia (Soman et al., 2006). It is not clear why some children develop acquired dystonia and others do not. Findings from studies examining predictors of acquired dystonia in children have been inconsistent (Tibussek et al., 2015), but there is some evidence that left hemisphere lesions, involvement of multiple basal ganglia structures (as opposed to a single structure), age at stroke before 10 years old, and female sex may place children at higher risk (Soman et al., 2006; Elbers et al., 2010; Goldfarb et al., 2013). In adults, lesions involving the putamen were more frequently associated with dystonia (Mehanna & Jankovic, 2013).

In contrast to hemiparesis and spasticity, which present during the acute period, dystonia presents after a delay of 6-12 months post-stroke on average, suggesting that different neurobiological mechanisms underlie these motor presentations (Boardman et al., 2005; Béjot et al., 2012; Ganesan et al., 2000; Mercuri et al., 2004, Pettigrew & Jankovic, 1985; Scott &

Jankovic, 1996; Sreenan et al., 2012; Tibussek et al., 2015). Historically, dystonia was viewed as primarily a disorder of the basal ganglia; however, it is now well documented that the neuroanatomical basis of dystonia is best understood as a network model, with involvement of the cerebral cortex, cerebellum, thalamus, and brainstem (Berman & Jinnah, 2015; Jinnah & Hess, 2018; Quartarone & Hallet, 2013). Recent studies in adults with primary dystonia have found abnormal functional connectivity in thalamo-striatal-cortical networks, suggesting that dystonia represents a dysfunction in networks rather than any single functional brain region (Lehericy et al., 2013; Stoessl et al., 2014). Furthermore, dystonia is one of the most common post-stroke movement disorders after pediatric stroke, however it rarely occurs in adults (Béjot et al., 2012; Tibussek et al., 2015). These observations suggest that developmentally determined maladaptive neuroplasticity and reorganization following basal ganglia stroke likely contribute to the manifestation of dystonia (Quartarone & Hallet, 2013; Scott & Jankovic, 1996; Tibussek et al., 2015) Conversely, children who do not develop dystonia after stroke may be displaying compensatory or adaptive plasticity, which results in an absence of observable movement difficulties (Dennis et al., 2013; Johnston, 2009; Marsden et al., 1985).

Neurocognitive outcomes after basal ganglia stroke differ by age of stroke in that basal ganglia lesions acquired in the perinatal period have been associated with poor intellectual outcome, whereas similar lesions later in childhood have been associated with specific deficits in attention and executive function (Long et al., 2011; Max et al., 2002; 2003; 2005; Westmacott et al., 2010). Recent work from our group has demonstrated that children with post-stroke dystonia showed additional cognitive difficulties when compared to children with similar lesions who did not develop dystonia (Westmacott et al., 2018a). As a group, children with basal ganglia stroke performed lower than expected on measures of intelligence, cognitive inhibition, set-shifting, and

executive function in daily life. Notably, children with post-stroke dystonia showed additional deficits in overall intellectual ability, verbal ability, visual-perceptual reasoning, working memory, academic ability, inhibitory control, and set-shifting, above and beyond those associated with the stroke (Westmacott et al., 2018a). Importantly, dystonia and no dystonia groups were matched on factors that could influence cognitive outcomes including lesion location, lesion size, age at stroke, age at test, and severity of hemiparesis. Furthermore, preliminary data demonstrated white matter microstructure alterations in children with post-stroke dystonia compared to typically developing controls, and that white matter integrity was significantly associated with intellectual functioning and inhibitory control (Ledochowski et al., 2022). Taken together, these findings support and extend the hypothesis that maladaptive post-stroke reorganization may be the underlying pathology of acquired dystonia after pediatric stroke, and also impact cognitive outcomes.

Clinically relevant imaging markers in brain locations remote from the infarct location can be detected using diffusion weighted imaging (DWI) magnetic resonance imaging (MRI) (Dlamini et al., 2017). Wallerian Degeneration (WD) refers to the anterograde degeneration of axons and their myelin sheaths after proximal axonal or cell body injury (Waller, 1850; Johnson et al., 1950). Ipsilesional acute WD (also termed “pre-Wallerian degeneration” [Dlamini et al., 2017]), which appears as restricted DWI signal within descending corticospinal tracts, has been associated with poor motor outcome (e.g., hemiparesis) in neonatal and childhood stroke (De Vries et al., 2005; Domi et al., 2009; Domi et al., 2020; Kirton et al., 2007), however whether WD may predict cognitive outcomes has not yet been examined. Diaschisis describes changes in brain areas that are structurally remote from the primary focal lesion, but anatomically connected to it via fibre tracts (Carrera & Tononi, 2014; Finger et al., 2004). It appears on DWI as restricted

diffusion, hyperintense areas with corresponding hyperintensity on apparent diffusion coefficient maps (Kirton et al., 2016). Diaschisis has been identified in neonatal and childhood AIS and found to be associated with motor and neurological outcomes (Govaert et al., 2008; Kirton et al., 2016). Recent work has extended these findings to cognitive outcomes, demonstrating significant associations between diaschisis and expressive and receptive language as well as cognitive and behavioural deficits (Kirton et al., 2016). These findings suggest that DWI diaschisis provides a marker of location and severity of disrupted connectivity, or "network injury" with high clinical relevance for predicting outcome and planning rehabilitation (Govaert et al., 2008; Kirton et al., 2016).

The current study explored whether there are differences apparent on neuroimaging in children with basal ganglia stroke who go on to develop dystonia compared to those who do not. Specifically, we completed volumetric analysis and detailed lesion classification for all participants and determined whether markers of remote injury, WD and diaschisis, were present. We hypothesized that involvement of more than one structure of the basal ganglia and cortical and/or internal capsule involvement would be more prevalent in the acquired dystonia group relative to children with stroke and no dystonia, and that children with acquired dystonia would have larger infarct volumes, reflecting more widespread brain involvement. We also hypothesized that markers of remote injury would be more prevalent in the acquired dystonia group relative to children with stroke and no dystonia, reflecting dysfunction in cortical-subcortical networks. Moreover, we endeavoured to examine the relative contribution of each of these variables in predicting dystonia in order to expand on and consolidate current understanding of neuroimaging features differentiating children who develop dystonia from those who do not. We elected to focus our analysis on acute scans as this would be most relevant

for early identification of children who would benefit from monitoring for development of dystonia. We also explored whether these neuroimaging predictors were associated with intellectual outcomes.

Method

Patient Population

Patients who were previously enrolled in the Children's Stroke Study Registry, the Toronto site of the Canadian Pediatric Ischemic Stroke Registry, were considered for eligibility within the present study (deVeber, 2017). Inclusion criteria consisted of history of acute arterial ischemic stroke (AIS) diagnosed from birth to 16 years of age, with unilateral or bilateral infarct identified on magnetic resonance imaging (MRI) or computed tomography (CT), availability of acute (at diagnosis) diffusion weighted imaging (DWI); and IQ scores (e.g., WISC-IV, WISC-V, or WAIS-IV) from neuropsychological assessment completed between 6 to 16 years of age. Exclusion criteria consisted of presumed perinatal stroke, recurrent stroke, cerebral sinovenous thrombosis, pre-term birth, hypoxic-ischemic encephalopathy, primary CNS vasculitis, sickle-cell disease, moya-moya disease, neurofibromatosis type-1, meningitis, traumatic brain injury, malignancy, and genetic disorders with cognitive sequelae. All neuropsychological assessments were completed at least one-year post-stroke and children were required to have sufficient fluency in English to complete the IQ measure.

Procedure

The study was approved by the Research Ethics Board at the Hospital for Sick Children. Patients seen the in the Stroke Clinic at the Hospital for Sick Children and their parents provided assent and informed consent for use of this information as part of their enrollment in the

Children's Stroke Study. Children seen in the Stroke Clinic are routinely referred to the Psychology Department for neuropsychological assessment.

Measures

Demographic Characteristics

Demographic characteristics were derived from the Children's Stroke Study registry database. Data obtained from the registry was collected through a standardized review of medical records, structured parent interviews, and a parent-report questionnaire of medical and neuropsychological history. Socioeconomic status was defined by the highest level of maternal education achieved and was rated on a 6-point scale as follows: (1= did not complete elementary school, 2= completed some high school, 3= completed high school, 4= completed some post-secondary education, 5= completed college or university, 6= completed professional or graduate school). Age at stroke was calculated based on the date of stroke confirmation on neuroimaging. The sample included acute neonatal AIS (stroke diagnosed within first 28 days of life) and acute childhood AIS (stroke diagnosed within 29 days to 18 years if life). Age at the test was calculated based on the date of the child's neuropsychological assessment.

Neurological and Clinical Factors

Time since stroke was calculated as the time between the date of stroke and the date of neuropsychological assessment. Seizure disorder was indicated as either present or absent. Information about post-stroke motor functioning was documented via the Pediatric Stroke Outcome Measure (PSOM; Kitchen et al., 2012) and neuropsychological history and included chronic hemiparesis, spasticity, cerebral palsy, handedness, handedness switch after stroke (or presumed switch based on family history for neonatal AIS), and the PSOM sensorimotor score

(0= no deficit; 0.5= mild deficit; normal function; 1= moderate deficit, decreased function; 2= severe deficit, missing function).

Determination of Dystonia

Presence of dystonia was diagnosed according to neurological assessment. The PSOM was completed for each child by pediatric neurologists during routine patient care in the Stroke Clinic. The PSOM provides information on motor performance including: power, tone, reflexes, and involuntary movements (i.e., dystonia, chorea, tics). Increased tone was classified as spasticity, dystonia, or mixed (spasticity and dystonia) patterns. Dystonia or mixed patterns were classified as "dystonia" and others as "no dystonia".

Neuropsychological Testing

Intellectual abilities were assessed using either the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV; Wechsler, 2003) Wechsler Intelligence Scale for Children, 5th edition (WISC-V; Wechsler, 2005), or Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV; Wechsler, 2008). In order to maximize our sample, we considered participants between 6 and 20 years of age. As a result, they received different age-appropriate versions of intelligence tests (i.e., WISC for under 17 years vs. WAIS for 17-20 years).

Index scores common to all measures include measures of overall intellectual ability (Full Scale IQ; FSIQ), verbal knowledge and verbal reasoning (Verbal Comprehension Index; VCI), speed of information processing (Processing Speed Index; PSI), and working memory/mental manipulation (Working Memory Index; WMI). The WISC-IV and WAIS-IV include the Perceptual Reasoning Index (PRI) which measures non-verbal reasoning and visual perceptual skills, whereas the WISC-V includes the Fluid Reasoning Index (FRI) to assess non-verbal reasoning and the Visual Spatial Index (VSI) to assess visual perceptual skills. To facilitate

consistency across the index scores between different test versions, we calculated a PRI score for the participants who completed the WISC-V by summing the arithmetic mean of the FRI and VSI, as has been done previously (Slim et al., 2020).

Neuroimaging

DWI Acquisition

All MRI scans were obtained on 3.0T Siemens PrismaFit with a 48-channel head coil. The protocol included a DWI scan with a b-value of 100 s/mm, 1 b=0 image which was performed during initial presentation to the emergency department within the Hospital for Sick Children.

Lesion Volume Quantification

DWI images were imported into 3D slicer (version 4.10.2), using the 'multivolume importer' tool where necessary (Kikinis et al., 2014). Lesion volumes were manually traced by a trained neuroradiologist (N.R. & B.E-W.) around the region of acute infarction using the 'segment editor' tool within the segmentations module in 3D Slicer (Pinter et al., 2019). Volumetric information was extracted for the region of acute infarction (ROI) using the 'radiomics' plug-in (Harvard Medical School: Computational Imaging & Bioinformatics Lab, Boston, MA) and output was expressed in cubic centimetres.

Detailed Lesion Classification

DWI images were reviewed by a trained neuroradiologist (N.R. & B.-EW.) using RadiAnt DICOM imaging viewer (Poznan, Poland). Individual scans were visually inspected slice-by-slice to determine areas of involvement including subcortical structures (i.e., putamen, globus pallidus, caudate putamen, and thalamus), anterior limb of the internal capsule, posterior limb of the internal capsule, and cortical (i.e., frontal, parietal, temporal, occipital) structures.

Location of cortical infarcts were described as per the on-site clinical standards utilized for quantifying scans and severity was rated as: 0-none, 1-mild, 2-mild-moderate, 3-moderate, and 4-severe. Presence of pre-Wallerian degeneration and diaschisis was determined and location of diaschisis was described by two trained neuroradiologists.

Statistical Analyses

All statistical analyses were computed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., released, 2019). The significance level for all research questions was set at the standard $p < .05$. Independent t and χ^2 tests were used to examine demographic and clinical characteristics (Table 1). Infarct characteristics including areas of involvement and presence of pre-Wallerian degeneration or diaschisis were compared between no dystonia and dystonia groups using χ^2 or Fisher's exact test. Lesion volume (mm^3) was compared between no dystonia and dystonia groups using non-parametric tests. Locations of cortical involvement and diaschisis were described qualitatively. Standardized scores on the measures of intellectual functioning were compared to the standardization mean in the no dystonia and dystonia groups separately. In order to determine the relative variance accounted for, neuroimaging variables that were significantly different between no dystonia and dystonia groups were further examined as predictors of dystonia and intellectual functioning across the whole sample using regression analyses.

Missing Data

All children had DWI imaging and intellectual testing. One child in the no dystonia group was missing the PRI score and one child in the dystonia group was missing the WMI score. Analyses were adjusted for these particular indices. Some demographic and clinical features were not available. One child was missing information about current seizures, 4 children were

missing information about handedness and handedness switch, and 10 parents chose not to report their education level. In order to maximize our sample, we included all available data in analyses and therefore report adjusted percentages for these variables.

Results

Study Cohort

A total of 41 children (22 no dystonia, 19 with dystonia) from the Children's Stroke Study met inclusion criteria for the present study. Demographic and clinical characteristics are presented in Table 1. All children with dystonia were exhibiting symptoms of dystonia at time of neuropsychological testing. Group analyses using independent *t*-tests and χ^2 were conducted to compare dystonia and no dystonia groups on demographic and clinical characteristics (Welch's *t*-test and Fisher's exact are reported where appropriate). There were no significant differences between no dystonia and dystonia groups on age at stroke, age at neuropsychological assessment, time since stroke, timing of stroke, or maternal education. The analyses for age at stroke and sex were repeated excluding the neonatal AIS and found no differences for age at stroke (t[31]= 0.85, p= .402) or sex (χ^2 = 1.34, p= .304). Children in the dystonia group had a significantly higher proportion of children with hemiparesis, right-handed children, and children who switched handedness as well as higher PSOM motor scores. There were more children in the dystonia group with current seizures. No children in either group presented with cerebral palsy or spasticity at time of neuropsychological testing.

Table 1. Demographic and clinical characteristics

	All Patients *n*= 41	No dystonia *n*= 22	Dystonia *n*= 19	χ^2/t
Males	23(56.1%)	14(63.6%)	9(47.4%)	1.09
Age at stroke (years; M[SD])	5.89(4.58)	6.43(4.68)	5.26(4.50)	0.81
Age at neuropsychological assessment (years; M[SD])	11.71(4.01)	11.89(3.81)	11.67(4.12)	0.17
Time since stroke (years; M[SD])	5.84(3.93)	5.49(3.97)	6.24(3.93)	-0.60
Timing of Stroke				
Neonatal	8(19.5%)	4(18.2%)	4(21.1%)	0.05
30 days – 1.9 years	1(2.4%)	0(0%)	1(5.3%)	1.19
2 – 5.9 years	16(39%)	8(36.4%)	8(42.1%)	0.14
6 – 12.9 years	10(24.4%)	6(27.3%)	4(21.1%)	0.21
13 – 16.9 years	6(14.6%)	4(18.2%)	2(10.5%)	0.48
Hemiparesis	26(63.4%)	9(40.9%)	17(89.5%)	10.36***
Handedness (Right)	27(71.1%)	18(90%)	9(47.4%)	7.37**
Handedness Switch	8(24.2%)	1(5.6%)	7(36.8%)	7.53**
PSOM Motor Score	0.78(0.74)	0.43(0.60)	1.18(0.69)	-3.72***
Seizures	5(12.5%)	0(0%)	5(26.3%)	6.98**
Mother's education	4.52(1.03)	4.75(0.77)	4.26(1.22)	1.31

***$p \leq .001$, ** $p \leq .01$

Note: PSOM= Pediatric Stroke Outcome Measure; 0 = no deficit, 0.5 = mild deficit, 1 = moderate deficit, 2 = severe deficit; Maternal Education is rated on a 6-point scale (see text for details)

Infarct Analysis

Differences in lesion characteristics between no dystonia and dystonia groups are presented in Table 2. There were no differences between dystonia and no dystonia groups in lesion laterality or bilateral lesions. Isolated thalamic infarcts were not associated with the development of dystonia, and no children with dystonia had subcortical lesions involving only the thalamus. Comparing basal ganglia structures, involvement of the putamen and caudate nucleus was associated with dystonia, whereas involvement of the globus pallidus was not

significant. There was no association between the number of basal ganglia structures involved and dystonia. A greater proportion of subjects in the dystonia group had involvement of the ALIC, whereas involvement of the PLIC was not significantly different between groups. There was a significantly higher proportion of subjects with dystonia with severe cortical involvement; however, differences between other severity levels were not significant. There was no difference between groups in proportion of subjects with pre-Wallerian degeneration or diaschisis. Infarct volume was significantly larger in subjects with dystonia.

The locations of diaschisis and cortical infarcts are presented in Tables 3 and 4. Due to the sample size no statistical comparisons were made between groups and data are presented qualitatively.

Table 2. Lesion characteristics by dystonia status

	No dystonia *n*= 22	Dystonia *n*= 19	χ^2/U	V/ r
Lesion Laterality				
Right	10(45.5%)	6(31.6%)	0.83	.142
Left	6(27.3%)	9(47.4%)	1.78	.208
Bilateral	6(27.3%)	4(21.1%)	0.21	.072
Subcortical structures				
BG+Thalamus	2(9.1%)	5(26.3%)	2.14	.228
BG only	13(59.1%)	14(73.7%)	0.97	.153
Thalamus only	7(31.8%)	0(0%)	7.92**	.422
BG Structures				
Putamen	12(54.5%)	18(94.7%)	8.39**	.452
Globus Pallidus	11(50%)	15(78.9%)	3.68	.300
Caudate Nucleus	12(54.5%)	16(84.2%)	4.14*	.318
# of BG structures				
One	4(26.7.%)	3(15.8%)	0.61	.134
Two	2(13.3%)	2(10.5%)	0.06	.043
Three	9(60%)	14(73.7%)	0.72	.145
ALIC	3(13.6%)	10(52.6%)	7.16*	.418
PLIC	10(45.5%)	11(57.9%)	0.63	.124
Cortical Involvement				
None	12(54.5%)	6(31.6%)	2.18	.231
Mild	4(18.2%)	5(26.3%)	0.39	.098
Moderate	6(27.3%)	4(21.1%)	0.21	.072
Severe	0(0%)	4(21.1%)	.513*	.354
Pre-Wallerian Degeneration	6(27.3%)	4(21.1%)	0.21	.072
Diaschisis	5(22.7%)	7(36.8%)	0.98	.155
Lesion Volume ($mm^{3;}$ Median[IQR])	3020.89(13022.89)	17449.99(68296.56)	302*	.380

***$p \leq .001$, ** $p \leq .01$, * $p \leq .05$

Note: BG= basal ganglia; ALIC= anterior limb of internal capsule; PLIC= posterior limb of interior capsule. Due to small cell sizes mild-moderate and moderate cortical severity categories were combined for statistical analysis. Analysis for # of basal ganglia structures excludes children with isolated thalamic infarcts as those were in the no dystonia group only; adjusted percentages are reported for the no dystonia group.

Table 3. Cortical lesion location

Study ID	Cortical Infarct Description (Severity rating)
No Dystonia	
ND13	Insula (mild)
ND14	PFC; insula (mild)
ND15	Mesial temporal lobe, occipital lobe, precuneus (mild)
ND16	BL superior parietal lobes (mild)
ND17	PFC; both inferior parietal lobules, left occipital lobe (mild-moderate)
ND18	angular, supramarginal, superior, middle and inferior temporal gyri (mild-moderate)
ND19	L PFC; R post-central gyrus; R superior parietal lobule (mild-moderate)
ND20	PFC; insula; precentral, postcentral, angular, supramarginal, superior temporal, middle temporal, inferior temporal, parahippocampal gyri; mesial temporal lobe (moderate)
ND21	BL PFC; BL precentral gyrus; R postcentral gyrus (moderate)
ND22	Insula; precentral, postcentral, angular, supramarginal, superior temporal, middle temporal gyri (moderate)
Dystonia	
D7	Insula (mild)
D8	Insula (mild)
D9	Insula (mild)
D10	Insula; postcentral, angular, superior temporal gyri (mild)
D11	Insula; temporal pole (mild)
D12	PFC; insula; postcentral, superior temporal, middle temporal gyri (moderate)
D13	PFC; insula; postcentral, angular, supramarginal, superior temporal, middle temporal, inferior temporal gyri (moderate)
D14	PFC; insula; postcentral gyrus; temporal lobe; inferior parietal lobule; (moderate)
D15	Medial temporal lobe; occipital lobe (moderate)
D16	BL PFC, BL precentral and postcentral gyri; BL superior parietal lobule; R occipital pole; L precuneus; L cuneus; L occipital pole; L superior temporal, middle temporal, inferior temporal, and parahippocampal gyri; L hippocampus; posterior insula (severe)
D17	R PFC; R precentral and postcentral gyri; R superior parietal lobule; R posterior temporal lobe; R mesial temporal lobe; BL occipital pole (severe)
D18	PFC; precentral and postcentral gyri; superior and inferior parietal lobules; temporal lobe; occipital lobe (severe)
D19	BL PFC; R precentral and postcentral gyri; BL occipital lobes; R superior parietal lobule (severe)

Note: PFC= prefrontal cortex; R= right; L=left; BL= bilateral

Table 4. Location of diaschisis

Study ID	Diaschisis Location
No Dystonia	
ND8	Corpus callosum
ND14	Thalamus
ND17	Thalamus
ND20	Thalamus
ND22	Thalamus; corpus callosum
Dystonia	
D7	Thalamus
D12	Corpus callosum
D13	Corticospinal tract
D16	Cerebellum; central pons
D17	Cerebellum
D18	Thalamus; corpus callosum corticospinal tract
D19	Thalamus; corticospinal tract

Intellectual Functioning Compared to Normative Mean

In the no dystonia group 9 subjects completed the WISC-IV, 7 completed the WISC-V, and 6 completed the WAIS-IV. In the dystonia group 8 subjects completed the WISC-IV, 7 completed the WISC-V, and 4 completed the WAIS-IV. The WISC-V FRI and VSI were averaged to form a PRI to facilitate comparison across children who completed different test versions (Slim et al., 2020). Standard scores of the no dystonia and dystonia groups were each compared to the normative mean (Table 5). In the no dystonia group FSIQ, WMI, and PSI were significantly lower than that of the normative mean, with medium effect sizes. In the dystonia group all indices (FSIQ, VCI, PRI, WMI, and PSI) were significantly lower than the normative mean, with large effect sizes.

Table 5. Intellectual functioning compared to the standardization mean for no dystonia and dystonia groups

		No Dystonia			Dystonia			
	M(SD)	t	*p*	Cohen's *d*	M(SD)	t	*p*	Cohen's *d*
FSIQ	91.50(17.41)	2.33	.020*	0.52	84.47(11.64)	4.50	<.001***	1.16
VCI	94.91(15.79)	1.58	.011	0.33	88.47(11.67)	3.34	<.001***	0.85
PRI	94.14(16.24)	1.78	.075	0.37	88.66(11.18)	3.29	.001**	0.86
WMI	93.00(16.94)	2.17	.030*	0.43	86.72(15.85)	3.74	<.001***	0.86
PSI	88.63(15.65)	2.45	<.001***	0.74	86.84(12.13)	3.71	<.001***	0.96

Note: Intellectual ability presented in standard scores (M=100, SD= 15)

*p < .05; **p <.01; ***p< .001

Neuroimaging Predictors of Dystonia and Intellectual Functioning

Regression analyses were used to further examine the amount of variance explained by the infarct features that were significantly different between groups. Specifically, the putamen, ALIC, lesion volume, and caudate nucleus were entered in the order of largest to smallest effect size in one model to predict dystonia and one model to predict FSIQ. Although involvement of the thalamus only and severe cortical lesions were significantly different between groups these were not included in the models as no children with dystonia had subcortical lesions restricted to the thalamus only (all had basal ganglia involvement). Additionally, no children in the no dystonia group had severe cortical lesions.

Dystonia

Table 6 presents the nested logistic regression to examine whether the putamen, ALIC, caudate nucleus, and lesion volume predict group membership (no dystonia vs. dystonia). The first model, with the putamen only, was significant and correctly classified 68.3% of cases with 94.7% sensitivity and 45.5% specificity). The second model, with the putamen and ALIC, was significant, however neither of the predictors significantly contributed. The model correctly classified 70.7% of cases, with 52.6% sensitivity and 86.4% specificity. The third model, with the putamen, ALIC, and lesion volume was significant overall, but none of the predictors were significant. The model correctly classified 70.7% of cases, with 57.9% sensitivity and 81.8% specificity. The final model, with the putamen, ALIC, volume, and caudate nucleus was significant, but none of the predictors were significant. The model correctly classified 70.7% of cases, with 57.9% sensitivity and 81.8% specificity.

Table 6. Nested logistic regression predicting dystonia

	B(SE)	Wald	Odds ratio [95% CI]
Model 1			
Putamen	2.71(1.11)	5.92*	15.00 [1.69, 132.90]
Nagelkerke R^2= .28			
$\chi^2(1)$= 9.56, *p*= .002			
Model 2			
Putamen	2.18(1.16)	3.57	8.89 [0.92, 85.66]
ALIC	1.32(0.82)	2.61	3.75 [0.75, 18.64]
Nagelkerke R^2= .35			
$\chi^2(2)$= 12.36, *p*= .002			
Model 3			
Putamen	2.33(1.20)	3.81	10.33 [0.99, 107.66]
ALIC	0.69(0.90)	0.59	2.00 [0.34, 11.76]
Lesion Volume	0(0)	1.53	1.00 [1.00, 1.00]
Nagelkerke R^2= .41			
$\chi^2(3)$= 14.84, *p*= .002			
Model 4			
Putamen	2.35(1.28)	3.37	10.44 [0.85, 127.67]
ALIC	0.70(0.94)	0.55	2.02 [0.32, 12.87]
Lesion Volume	0(0)	1.53	1.00 [1.00, 1.00]
Caudate Nucleus	-0.02(.99)	0.001	0.98 [0.14, 6.76]
Nagelkerke R^2= .41			
$\chi^2(4)$= 14.84, *p*= .005			

*p <.05

Intellectual Outcomes

Table 7 presents hierarchal linear regression examining whether the putamen, ALIC, lesion volume, and caudate nucleus predict FSIQ. Only the first model, with the putamen only as a predictor was significant, $F(1, 39)= 9.34$, $p= .004$. Across models, the putamen was consistently a significant predictor of FSIQ (p <.05), and none of the ALIC, lesion volume, or caudate nucleus were significant predictors of FSIQ in any model.

Table 7. Hierarchal linear regression predicting FSIQ across the whole sample

Predictors	Model 1	Model 2	Model 3	Model 4
Putamen	-.44*	-.42*	-.42*	-.43*
ALIC		-.05	.01	.002
Lesion Volume			-.11	-.11
Caudate Nucleus				.01
Adjusted R^2	.17	.15	.14	.12
R^2 change		.002	.01	.00
F change	9.34**	0.08	0.44	0.01

*p <.05; **p <.01

Discussion

The purpose of this study was to examine whether there were differences on acute neuroimaging in children with stroke involving the basal ganglia and/or thalamus who develop dystonia, compared to those with stroke in the same regions who do not develop dystonia. We also examined intellectual outcomes in both groups, as well as the relative contribution of neuroimaging features in predicting dystonia and intellectual functioning.

Neuroimaging features were coded via systematic, detailed lesion classification completed by the study neuroradiologists (N.R. & B.E-W.). We found that infarcts involving only the thalamus (i.e., no basal ganglia involvement) were only present in the no dystonia group, and that all children with dystonia had strokes with basal ganglia involvement. Post-thalamic stroke movement disorders involving involuntary movements, including dystonia, have been well-documented (Ghika-Schmid et al., 1997; Gupta & Pandey, 2018; Handley et al., 2009; Kim et al., 2001; Kojovic et al., 2013; Krystkowiak et al., 1998) and, therefore, this finding may be an artifact of our smaller sample. Alternatively, it is possible that thalamic vs. basal ganglia (with or without thalamic involvement) lesions implicate different neural pathways resulting in

different motor presentations such as tremor and spasticity (Mehanna & Jankovic, 2013; Miwa et al., 1996; Gupta & Pandey, 2018). It is also important to note that the aforementioned studies refer primarily to stroke during adulthood, so it is critical to consider how age-related differences in neuroplasticity and brain development may also impact or mediate the relationship between subcortical lesion location and motor outcome (Scott & Jankovic, 1996; Tibussek et al., 2015). Further research with larger sample sizes is needed to delineate the role of the basal ganglia and thalamus in acquired dystonia after pediatric stroke.

In our study, there was a significantly higher proportion of children with dystonia relative to children with no dystonia with lesions involving the putamen, caudate nucleus, and anterior limb of the internal capsule. Notably, 18/19 children who developed dystonia in our sample had a lesion involving the putamen. The role of the caudate nucleus and putamen in dystonia is well-documented (Burton et al., 1984; Ghika-Schmid et al., 1997; Marsden et al., 1985; Mink, 2003; 2013) and there is emerging evidence that lesions in the putamen are predictive of dystonia (Mehanna & Jankovic, 2013). The extant literature on the role of the anterior limb of the internal capsule is limited, though cases of dystonia after injury affecting the caudate, putamen, and anterior limb of the internal capsule have been documented (Demierre & Prondot, 1983). Interestingly, the anterior limb of the internal capsule has been implicated in psychiatric disease, including major depressive disorder, generalized anxiety disorder, obsessive-compulsive disorder, and Tourette syndrome (Mithani et al., 2020). Additionally, psychiatric comorbidities have been documented in dystonia, including work by our research group (Conte et al. 2016; Foley et al., 2017; Ledochowski et al., 2020; Stamelou et al., 2012). Furthermore, it has been well established that dystonia should be considered a “network disorder”, with abnormal functional and structural connectivity in brain networks responsible for interhemispheric

information transfer, sensorimotor processing, and executive control of motor commands including subcortical (e.g., basal ganglia, thalamus) and cortical regions (e.g., frontoparietal, supplementary motor and primary sensorimotor areas). The anterior limb of the internal capsule is a key component of the cortico-striatal-thalamo-cortical loop (Parent & Hazrati, 1995). Therefore, injuries to a part of this network could have cascading effects, resulting in clinical presentation of dystonia. Alternatively, a combination of different subcortical and cortical areas of injury could result in the same motor phenotype of acquired dystonia. Further research is needed to examine these hypotheses in dystonia acquired after pediatric stroke. We also found that children with dystonia were more likely to have severe cortical involvement, as indicated by neuroradiologist review, and infarct volumes were significantly larger in children with dystonia. The greater proportion of children with severe cortical involvement and larger infarct size likely reflects greater interruption to the networks in children with dystonia due to involvement of multiple brain regions and is consistent with previous work (Elbers et al., 2010).

It was unexpected that we did not find any group differences with respect to infarcts in the globus pallidus (Elbers et al., 2010; Simonyan, 2018; Valeriani & Simonyan, 2020). Previous work comparing randomly selected children with basal ganglia stroke with and without dystonia from the Canadian Pediatric Stroke Registry found more lesions involving the globus pallidus in the dystonia group, however the sample size for this study was relatively small with five children in each group (Elbers et al., 2010). Interestingly, pallidotomy and deep brain stimulation (DBS) of the internal segment of the globus pallidus have been shown to be effective in improving dystonia however, the degree of improvement was stronger in patients with inherited forms of dystonia (i.e., DYT1 and DYT6) and less robust in patients with cervical dystonia (Barow et al., 2014; Fox et al., 2015; Ostrem et al., 2011; Vidailhet et al., 2005; Volkmann et al., 2012).

Notably, patients with acquired dystonia have been found to show poor response to globus pallidus DBS (Andrews et al., 2010; Speelman et al., 2010) and outcomes after globus pallidus DBS for childhood dystonia show great variability (Lumsden et al., 2017). The reason for this heterogeneity in response to DBS it not yet clear but highlights the role of other structures in the basal ganglia-thalamo-cortical circuit, widespread effects across the whole motor network connected to nuclei targeted in surgery, and points to different neuropathological processes underlying genetic, idiopathic, and acquired dystonia (Conte et al., 2019; Lumsden et al., 2016; Wichmann & DeLong, 2016).

In order to examine the relative contribution of these variables in predicting dystonia we entered the putamen, anterior limb of the internal capsule, infarct volume, and caudate nucleus as predictors in regressions predicting dystonia and intellectual outcome. In predicting dystonia, only involvement of the putamen was a significant predictor, and remained significant when other predictors were entered in the model. The model with the putamen only had 94.7% sensitivity and 45.5% specificity. When other predictors were added, the model remained significant, though sensitivity was reduced (52.6% - 57.9%) and specificity increased (81.8% - 86.4%). Although these findings point to the importance of the putamen, it is unlikely that only one lesion location will predict dystonia given the complex interactions across parallel neural pathways in the manifestation of dystonia (Lumsden et al., 2016; Mehanna & Jankovic, 2013; Valeriani & Simonyan, 2020). The changes in specificity with the addition of more lesion locations underscores the need to consider multiple variables as well as their interactions in any models predicting dystonia. However, it is also notable that post-stroke movement disorders are relatively rare, which highlights individual brain plasticity and resilience, potentially including parallel processing of cortical-subcortical networks and compensatory mechanisms that result in

an absence of clinically evident movement disorders (Bhatia & Marsden, 1994; Conte et al., 2019; Mehanna & Jankovic, 2013; Tibbusek et al., 2015). Lesion volume was not found to be a significant predictor, despite being significantly larger in the dystonia group. However, this is in line with studies examining lesion volume in predicting motor (i.e., hemiparesis; cerebral palsy) and neurological outcomes, pointing to mediating factors including secondary injury and interactions with lesion location (Domi et al., 2009; 2020; Ganesan et al., 1999; Wagenaar et al., 2018; Wiedemann et al., 2019).

Comparing intellectual outcomes of both groups to the normative mean revealed that children with dystonia had lower scores across all indices of the Wechsler scales with large effect sizes, whereas the no dystonia group had significantly lower working memory and processing speed as well as full scale IQ with medium effect sizes. These findings are consistent with our group's previous work demonstrating additional cognitive difficulties in children with post-stroke dystonia relative to children with the same pattern of stroke and no dystonia (Westmacott et al., 2018a), as well as weaker working memory, but age-appropriate verbal and non-verbal abilities in children with basal ganglia stroke (Westmacott et al., 2018b). The greater difficulties observed in children with stroke and dystonia, relative to stroke point to maladaptive reorganization after injury leading to observable cognitive and motor difficulties, likely involving neural connections between the basal ganglia and prefrontal cortex, which are involved in the regulation of cognition and behaviour (Gunaydin & Kreitzer, 2016; McNab & Klingberg, 2008; Stoessl et al., 2014; Tibussek et al., 2015). Hierarchical linear regression demonstrated that involvement of the putamen was the only significant predictor of intellectual outcome. Taken together with the regression predicting dystonia this points towards the putamen as a structure that likely mediates an underlying neurobiological mechanism important for the clinical

manifestation of dystonia after subcortical AIS, with implications on cognitive outcomes as well. Moreover, the putamen has been associated with intelligence as well as stereotypic movements in children and it has been proposed that the neural circuitry between the putamen and prefrontal cortex underlie these associations (Burgaleta et al., 2013; Mahone et al., 2016; Sandman et al., 2014). Taken together, with the findings of the current study, this provides further support for disruptions to the cortico-striato-thalamo-cortical circuits as the underlying neuropathological mechanism of acquired dystonia after pediatric stroke. Preliminary work from our group found associations between the cingulum and superior longitudinal fasciculus and cognitive outcomes (Ledochowski et al., 2022). Further studies of structural and functional connectivity are needed to elucidate the specific pathways affected in children with dystonia acquired post-stroke and relations to functional outcomes (i.e., motor, cognitive, behaviour). As with predicting dystonia, lesion volume was not significant, highlighting the importance of other mediators of cognitive function after stroke and the need for a more granular analysis of lesion location and network connectivity (Everts et al., 2008; Westmacott et al., 2010).

In contrast to our hypotheses, there were no differences between groups in the number of basal ganglia structures involved or markers of remote injury (e.g., WD or diaschisis). Involvement of multiple deep gray matter structures has been previously identified as a potential risk factor for dystonia (Goldfarb et al., 2013), however this study used a different classification scheme (i.e., caudate head, caudate body, caudate tail, putamen, globus pallidus externa, globus pallidus interna, and thalamus) which may explain the discrepant findings. Furthermore, both Goldfarb et al., (2013) and the current study have relatively limited sample sizes, which points to the need for multi-site investigations to obtain larger sample sizes for this relatively rare, but important, population. It was unexpected that markers of remote injury (e.g., WD, diaschisis)

were similar between no dystonia and dystonia groups. WD within corticospinal tracts on acute DWI has been associated with poor motor outcome including hemiparesis (Domi et al., 2009; Domi et al., 2020; Kirton et al., 2007) and hemiplegic cerebral palsy (De Vries et al., 2009; Groenendaal et al., 2006; Wagenaar et al., 2018), however literature on WD and dystonia is much more limited and has not been examined in pediatric populations (Dietl et al., 1982; Karşidağ et al., 1998). It is possible this may reflect different neuropathological mechanisms underlying different motor presentations after stroke (Mehanna & Jankovic, 2013; Tibussek et al., 2015), however, further examination of WD in this population is needed to make a conclusion. With respect to diaschisis, it has been associated with both motor and cognitive outcomes after pediatric stroke (Govaert et al., 2008; Kirton et al., 2016), however it is notable that diaschisis was found to evolve over time. Specifically, out of 19 children, one showed diaschisis on acute imaging, but eight showed diaschisis on follow up imaging (Kirton et al., 2016). We chose to focus on acute imaging for the current study in order to capture potential markers for early identification of children who would benefit from close monitoring or intervention, however examining markers of remote injury on follow up scans is warranted, especially because dystonia has also been demonstrated to emerge over time (Béjot et al., 2012; Tibussek et al., 2015). The locations of diaschisis in our sample were similar to those found by Kirton et al., (2016), with mostly instances of thalamic or callosal diaschisis in both dystonia and no dystonia groups. In addition to the thalamus and corpus callosum, in the dystonia group, three children had diaschisis in the corticospinal tract, two in the cerebellum, and one in the central pons, whereas diaschisis was primarily found in the thalamus or corpus callosum in the no dystonia group. Future studies should examine longitudinal scans to determine whether

diaschisis is seen on follow up imaging as well as whether there are specific regions affected in acquired dystonia.

As is common in research in populations with relatively rare patterns of injury, our analyses were constrained by sample size. In particular, we had relatively few children with neonatal stroke in our sample and this precluded comparisons between stroke sustained at different ages. Additionally, a formal dystonia rating scale was not systematically implemented in this retrospective cohort, we are currently implementing regular use of the Hypertonia Assessment Tool (Jewtha et al., 2010) in this clinic. The majority of the MRI scans in the current study were not able to be processed via semiautomated methods and required manual segmentation, and as such we were not able to obtain whole brain volumes and calculate infarct volume, which is important as children's brain volumes change with age (Jiang et al., 2021). However, lesion volume was not a primary variable of interest in the current study. We are expanding on the current work with longitudinal scans that have been processed using automated methods and can re-examine whether infarct volume expressed as a percentage is associated with outcomes.

The current study focused on dystonia acquired after pediatric AIS involving subcortical structures. In our clinical experience, dystonia also often presents in the context of periventricular venous infarction. There is also evidence for recurrent dystonia in childhood and adult moya-moya disease (Kumar et al., 2016; Lyoo et al., 2000). Examining other vascular causes of acquired dystonia is important to inform the clinical profile of these patients and gain better understanding of the underlying neuropathological mechanisms of dystonia acquired secondary to vascular causes. Additionally, it will be important to examine other cognitive outcomes, especially cognitive inhibition and attention, in relation to lesion characteristics and

neural network connectivity in order to understand the underlying pathology of the cognitive and motor difficulties in this population (Max et al., 2002; Middleton & Strick, 2000; Van Shouwenburg et al., 2010; 2013; Westmacott et al., 2018a). The role of environmental stressors in dystonia is an emerging area of research (Simonyan, 2019) and recent work has demonstrated the importance of environment in neurodevelopmental outcomes after early brain injury, pointing to potential modifiable risk and protective factors (Williams, 2021). The impact of these variables such as therapies, enriched environments, and psychosocial factors and their role in brain plasticity and resilience should be considered in future research. Finally, inherited forms of dystonia highlight the contribution of genetics to its pathophysiology (Lohmann & Klein, 2017). The current study focused on acquired dystonia after ischemic stroke, however it is possible that genetic factors mediate dystonia outcome after stroke or other brain insult.

In conclusion, the current study adds to our understanding of the role lesion characteristics in children with subcortical stroke, with and without dystonia. We found that children with dystonia were more likely to have involvement of the putamen, caudate nucleus, and anterior limb of the internal capsule as well as larger infarct sizes and severe cortical involvement. Regression analyses demonstrated that putamen involvement was a significant predictor of dystonia as well as intellectual outcome, suggesting a common neurobiological mechanism of these outcomes. Further research with larger sample sizes is needed to confirm these findings. Future directions include investigating secondary network disruptions after focal injury in order to determine whether post-stroke dystonia is a manifestation of maladaptive reorganization that has an impact on motor and cognitive presentation, and to elucidate the specific neurobiological substrates of acquired dystonia after pediatric stroke to inform biomarkers of risk for poor outcome. Our group is currently using multimodal neuroimaging to

characterize structural and functional network connectivity in this population as well as examining this in relation to cognitive and behavioural outcomes in order to determine the specific mechanism underlying the multifaceted deficits in acquired dystonia after pediatric stroke.

References

Albanese, A., Bhatia, K., Bressman, S. B., DeLong, M. R., Fahn, S., Fung, V. S., ... & Lang, A. E. (2013). Phenomenology and classification of dystonia: a consensus update. *Movement Disorders*, *28*(7), 863-873. doi: 10.1002/mds.25475

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1991). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Progress in brain research*, *85*, 119-146. https://doi.org/10.1016/S0079-6123(08)62678-3

Andrews, C., Aviles-Olmos, I., Hariz, M., & Foltynie, T. (2010). Which patients with dystonia benefit from deep brain stimulation? A metaregression of individual patient outcomes. *Journal of Neurology, Neurosurgery & Psychiatry*, *81*(12), 1383-1389. http://dx.doi.org/10.1136/jnnp.2010.207993

Barow, E., Neumann, W. J., Brücke, C., Huebl, J., Horn, A., Brown, P., ... & Kühn, A. A. (2014). Deep brain stimulation suppresses pallidal low frequency activity in patients with phasic dystonic movements. *Brain*, *137*(11), 3012-3024. https://doi.org/10.1093/brain/awu258

Béjot, Y., Giroud, M., Moreau, T., & Benatru, I. (2012). Clinical spectrum of movement disorders after stroke in childhood and adulthood. *European neurology*, *68*(1), 59-64. doi: 10.1159/000336740

Berman, B. D., & Jinnah, H. A. (2015). Dystonia: five new things. *Neurology: Clinical Practice*, *5*(3), 232-240. https://doi.org/10.1212/CPJ.0000000000000128

Bernard, T. J., Manco-Johnson, M. J., Lo, W., MacKay, M. T., Ganesan, V., DeVeber, G., ... & Ichord, R. (2012). Towards a consensus-based classification of childhood arterial

ischemic stroke. *Stroke*, *43*(2), 371-377. https://doi.org/10.1161/STROKEAHA.111.624585

Bhatia, K. P., & Marsden, C. D. (1994). The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain*, *117*(4), 859-876. doi: https://doi.org/10.1093/brain/117.4.859

Boardman, J. P., Ganesan, V., Rutherford, M. A., Saunders, D. E., Mercuri, E., & Cowan, F. (2005). Magnetic resonance image correlates of hemiparesis after neonatal and childhood middle cerebral artery stroke. *Pediatrics*, *115*(2), 321-326. doi: 10.1542/peds.2004-0427

Burgaleta, M., MacDonald, P. A., Martínez, K., Roman, F. J., Álvarez-Linera, J., González, A. R., ... & Colom, R. (2014). Subcortical regional morphology correlates with fluid and spatial intelligence. *Human brain mapping*, *35*(5), 1957-1968. https://doi.org/10.1002/hbm.22305

Burton, K., Farrell, K., Li, D., & Calne, D. B. (1984). Lesions of the putamen and dystonia: CT and magnetic resonance imaging. *Neurology*, *34*(7), 962-962. https://doi.org/10.1212/WNL.34.7.962

Carrera, E., & Tononi, G. (2014). Diaschisis: past, present, future. *Brain*, *137*(9), 2408-2422. https://doi.org/10.1093/brain/awu101

Conte, A., Berardelli, I., Ferrazzano, G., Pasquini, M., Berardelli, A., & Fabbrini, G. (2016). Nonmotor symptoms in patients with adult-onset focal dystonia: Sensory and psychiatric disturbances. Parkinsonism and Related Disorders, 22, S111–S114. doi:10.1016/j. parkreldis.2015.09.001

Demierre, B., & Rondot, P. (1983). Dystonia caused by putamino-capsulo-caudate vascular lesions. *Journal of Neurology, Neurosurgery & Psychiatry, 46*(5), 404-409. http://dx.doi.org/10.1136/jnnp.46.5.404

Dennis, M., Spiegler, B. J., Juranek, J. J., Bigler, E. D., Snead, O. C., & Fletcher, J. M. (2013). Age, plasticity, and homeostasis in childhood brain disorders. *Neuroscience & Biobehavioral Reviews, 37*(10), 2760-2773. https://doi.org/10.1016/j.neubiorev.2013.09.010

Dietl, H. W., Pulst, S. M., Engelhardt, P., & Mehraein, P. (1982). Paraneoplastic brainstem encephalitis with acute dystonia and central hypoventilation. *Journal of Neurology, 227*(4), 229-238. doi: 10.1007/BF00313390

deVeber, G. A., Kirton, A., Booth, F. A., Yager, J. Y., Wirrell, E. C., Wood, E., ... & MacGregor, D. (2017). Epidemiology and outcomes of arterial ischemic stroke in children: the Canadian Pediatric Ischemic Stroke Registry. *Pediatric neurology, 69*, 58-70. doi: 10.1016/j.pediatrneurol.2017.01.006

De Vries, L. S., Van der Grond, J., Van Haastert, I. C., & Groenendaal, F. (2005). Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. *Neuropediatrics, 36*(01), 12-20. doi: 10.1055/s-2005-837544

Dlamini, N., Wintermark, M., Fullerton, H., Strother, S., Lee, W., Bjornson, B., ... & Linds, A. (2017). Harnessing Neuroimaging Capability in Pediatric Stroke: Proceedings of the Stroke Imaging Laboratory for Children Workshop. doi: 10.1542/peds.2007-1459

Domi, T., deveber, G., Shroff, M., Kouzmitcheva, E., MacGregor, D. L., & Kirton, A. (2009). Corticospinal tract pre-wallerian degeneration: a novel outcome predictor for pediatric

stroke on acute MRI. *Stroke*, *40*(3), 780-787. https://doi.org/10.1161/STROKEAHA.108.529958

Domi, T., deVeber, G., Mikulis, D., & Kassner, A. (2020). Wallerian Degeneration of the Cerebral Peduncle and Association with Motor Outcome in Childhood Stroke. *Pediatric Neurology*, *102*, 67-73. https://doi.org/10.1016/j.pediatrneurol.2019.07.004

Elbers, J., Wilkinson, A., DeVeber, G., & Askalan, R. (2010, January). Lesion volume and localization as predictors of dystonia in pediatric basal ganglia stroke. In Annals of Neurology (Vol. 68, No. 4, pp. S98-S98).

Finger, S., Koehler, P. J., & Jagella, C. (2004). The Monakow concept of diaschisis: origins and perspectives. *Archives of Neurology, 61*(2), 283-288. doi:10.1001/archneur.61.2.283

Foley, J. A., Vinke, R. S., Limousin, P., & Cipolotti, L. (2017). Relationship of cognitive function to motor symptoms and mood disorders in patients with isolated dystonia. *Cognitive and Behavioral Neurology*, *30*(1), 16-22. https://doi.org/10.1097/WNN.0000000000000117

Fox, M. D., & Alterman, R. L. (2015). Brain stimulation for torsion dystonia. *JAMA neurology*, *72*(6), 713-719. doi: 10.1001/jamaneurol.2015.51

Ganesan, V., Hogan, A., Shack, N., Gordon, A., Isaacs, E., & Kirkham, F. J. (2000). Outcome after ischaemic stroke in childhood. *Developmental medicine and child neurology*, *42*(7), 455-461. Doi: 10.1017/S0012162200000852

Ghika-Schmid, F., Ghika, J., Regli, F., & Bogousslavsky, J. (1997). Hyperkinetic movement disorders during and after acute stroke: the Lausanne Stroke Registry. *Journal of the neurological sciences*, *146*(2), 109-116. https://doi.org/10.1016/S0022-510X(96)00290-0

Goldfarb, J., Askalan, R., Pontigon, A., & deVeber, G. (2013). Lesion Volume and Localization in Acute Ischemic Basal Ganglia Stroke as Predictors of Dystonia: 151. *Annals of Neurology*, *74*.

Govaert, P., Zingman, A., Jung, Y. H., Dudink, J., Swarte, R., Zecic, A., ... & Lequin, M. (2008). Network injury to pulvinar with neonatal arterial ischemic stroke. *Neuroimage*, *39*(4), 1850-1857. https://doi.org/10.1016/j.neuroimage.2007.10.056

Groenendaal, F., Benders, M. J., & De Vries, L. S. (2006, June). Pre-wallerian degeneration in the neonatal brain following perinatal cerebral hypoxia–ischemia demonstrated with MRI. In *Seminars in perinatology* (Vol. 30, No. 3, pp. 146-150). WB Saunders. https://doi.org/10.1053/j.semperi.2006.04.005

Gunaydin, L. A., & Kreitzer, A. C. (2016). Cortico–basal ganglia circuit function in psychiatric disease. *Annual review of physiology*, *78*, 327-350. https://doi.org/10.1146/annurev-physiol-021115-105355

Gupta, N., & Pandey, S. (2018). Post-thalamic stroke movement disorders: A systematic review. *European Neurology*, *79*(5-6), 303-314. https://doi.org/10.1159/000490070

Handley, A., Medcalf, P., Hellier, K., & Dutta, D. (2009). Movement disorders after stroke. *Age and ageing*, *38*(3), 260-266. https://doi.org/10.1093/ageing/afp020

Herrero, M. T., Barcia, C., & Navarro, J. (2002). Functional anatomy of thalamus and basal ganglia. *Child's Nervous System*, *18*(8), 386-404. doi: 10.1007/s00381-002-0604-1

IBM Corp. Released. (2019). IBM SPSS statistics for windows, version 26.0. Armonk, NY: IBM Corp.

Ide, S., Kakeda, S., & Korogi, Y. (2015). Anatomy of the thalamus. *Brain and Nerve= Shinkei Kenkyu No Shinpo*, *67*(12), 1459-1469. doi: 10.11477/mf.1416200323

Jethwa, A., Mink, J., Macarthur, C., Knights, S., Fehlings, T., & Fehlings, D. (2010). Development of the Hypertonia Assessment Tool (HAT): a discriminative tool for hypertonia in children. Developmental Medicine & Child Neurology, 52(5), e83-e87. doi: 10.1111/j.1469-8749.2009.03483.x

Jiang, B., Hills, N. K., Forsyth, R., Jordan, L. C., Slim, M., Pavlakis, S. G., ... & Lo, W. D. (2021). Imaging predictors of neurologic outcome after pediatric arterial ischemic stroke. *Stroke*, *52*(1), 152-161. https://doi.org/10.1161/STROKEAHA.120.030965

Jinnah, H. A., & Hess, E. J. (2018). Evolving concepts in the pathogenesis of dystonia. *Parkinsonism & related disorders*, *46*, S62-S65. https://doi.org/10.1016/j.parkreldis.2017.08.001

Johnson, A. C., McNabb, A. R., & Rossiter, R. J. (1950). Chemistry of Wallerian degeneration: a review of recent studies. Archives of Neurology & Psychiatry, 64(1), 105-121. doi:10.1001/archneurpsyc.1950.02310250111010

Johnston, M. V. (2009). Plasticity in the developing brain: implications for rehabilitation. *Developmental disabilities research reviews*, *15*(2), 94-101. doi: 10.1002/ddrr.64

Karşidağ, S., Özer, F., Şen, A., & Arpacı, B. (1998). Lesion localization in developing poststroke hand dystonia. *European neurology*, *40*(2), 99-104. https://doi.org/10.1159/000007965

Kikinis, R., Pieper, S. D., & Vosburgh, K. G. (2014). 3D Slicer: a platform for subject-specific image analysis, visualization, and clinical support. In *Intraoperative imaging and image-guided therapy* (pp. 277-289). Springer, New York, NY.

Kim, J. S. (2001). Delayed onset mixed involuntary movements after thalamic stroke: clinical, radiological and pathophysiological findings. *Brain*, *124*(2), 299-309. https://doi.org/10.1093/brain/124.2.299

Kirton, A., Shroff, M., Visvanathan, T., & Deveber, G. (2007). Quantified corticospinal tract diffusion restriction predicts neonatal stroke outcome. *Stroke*, *38*(3), 974-980. https://doi.org/10.1161/01.STR.0000258101.67119.72

Kirton, A., Williams, E., Dowling, M., Mah, S., Hodge, J., Carlson, H., ... & PedNIHSS Investigators. (2016). Diffusion imaging of cerebral diaschisis in childhood arterial ischemic stroke. *International Journal of Stroke*, *11*(9), 1028-1035. https://doi.org/10.1177/1747493016666089

Kitchen, L., Westmacott, R., Friefeld, S., MacGregor, D., Curtis, R., Allen, A., Yau, I., Askalan, R., Moharir, M., Domi, T., & deVeber, G. (2012). The pediatric stroke outcome measure: a validation and reliability study. *Stroke*, *43*(6), 1602-1608. doi: 10.1161/strokeaha.111.639583

Kojovic, M., Pareés, I., Kassavetis, P., Palomar, F. J., Mir, P., Teo, J. T., ... & Edwards, M. J. (2013). Secondary and primary dystonia: pathophysiological differences. *Brain*, *136*(7), 2038-2049. https://doi.org/10.1093/brain/awt150

Krystkowiak, P., Martinat, P., Defebvre, L., Pruvo, J. P., Leys, D., & Destee, A. (1998). Dystonia after striatopallidal and thalamic stroke: clinicoradiological correlations and pathophysiological mechanisms. *Journal of Neurology, Neurosurgery & Psychiatry*, *65*(5), 703-708. http://dx.doi.org/10.1136/jnnp.65.5.703

Kumar, S., Sharma, S., Jhobta, A., & Sood, R. G. (2016). Dystonia an unusual presentation in pediatric moyamoya disease: Imaging findings of a case. *Journal of Pediatric Neurosciences*, *11*(2), 115. doi: PMC4991150

Ledochowski, J., Feldman, S., Walker, K., Domi, T., Robertson, A., Jobst, C., Cheyne, D., Westmacott, R., Desrocher, M., & Dlamini, N. (2022, February). Maladaptive Plasticity In Dystonia Following Pediatric Basal Ganglia Stroke: Associations Between Structural Connectivity And Cognitive Functioning. *Stroke,* 53. https://doi.org/10.1161/str.53.suppl_1.TMP96

Lehéricy, S., Tijssen, M. A., Vidailhet, M., Kaji, R., & Meunier, S. (2013). The anatomical basis of dystonia: current view using neuroimaging. *Movement Disorders*, *28*(7), 944-957. https://doi.org/10.1002/mds.25527

Lohmann, K., & Klein, C. (2017). Update on the genetics of dystonia. *Current neurology and neuroscience reports*, *17*(3), 1-12. doi: 10.1007/s11910-017-0735-0

Long, B., Spencer-Smith, M. M., Jacobs, R., Mackay, M., Leventer, R., Barnes, C., & Anderson, V. (2011). Executive function following child stroke: The impact of lesion location. Journal of Child Neurology, 26(3), 279–287. doi:10.1177/0883073810380049

Lumsden, D. E., Kaminska, M., Ashkan, K., Selway, R., & Lin, J. P. (2017). Deep brain stimulation for childhood dystonia: is ‘where’as important as in ‘whom’?. *European Journal of Paediatric Neurology*, *21*(1), 176-184. https://doi.org/10.1016/j.ejpn.2016.10.002

Lyoo, C. H., Oh, S. H., Joo, J. Y., Chung, T. S., & Lee, M. S. (2000). Hemidystonia and hemichoreoathetosis as an initial manifestation of moyamoya disease. *Archives of neurology*, *57*(10), 1510-1512. doi:10.1001/archneur.57.10.1510

Mahone, E. M., Crocetti, D., Tochen, L., Kline, T., Mostofsky, S. H., & Singer, H. S. (2016). Anomalous putamen volume in children with complex motor stereotypies. *Pediatric neurology*, *65*, 59-63. https://doi.org/10.1016/j.pediatrneurol.2016.08.023

Marsden, C. D., Obeso, J. A., Lang, A. E., Hill, D., & Se, L. (1985). The anatomical basis of symptomatic hemidystonia. Brain, 108(2), 463–483. doi:10.1093/brain/108.2.463

Max, J. E., Fox, P. T., Lancaster, J. L., Kochunov, P., Matthews, K., Manes, F. F., . . . Lansing, A. E. (2002). Putamen lesions and the development of attention-deficit/hyperactivity symptomatology. Journal of the American Academy of Child & Adolescent Psychiatry, 41(5), 563–571. doi:10.1097/00004583-200205000-00014

Max, J. E., Mathews, K., Manes, F. F., Robertson, B. A. M., Fox, P. T., Lancaster, J. L., . . . Collings, N. (2003). Attention deficit hyperactivity disorder and neurocognitive correlates after childhood stroke. Journal of the International Neuropsychological Society, 9(6), 815–829. doi:10.1017/S1355617703960012

Max, J. E., Manes, F. F., Robertson, B. A. M., Mathews, K., Fox, P. T., & Lancaster, J. (2005). Prefrontal and executive attention network lesions and the development of attention-deficit/ hyperactivity symptomatology. Journal of the American Academy of Child and Adolescent Psychiatry, 44(5), 443–450. doi:10.1097/01.chi.0000156661.38576.0f

McNab, F., & Klingberg, T. (2008). Prefrontal cortex and basal ganglia control access to working memory. Nature Neuroscience, 11(1), 103–107. doi:10.1038/nn2024

Mehanna, R., & Jankovic, J. (2013). Movement disorders in cerebrovascular disease. The Lancet Neurology, 12(6), 597–608. doi:10.1016/S1474-4422(13)70057-7

Middleton, F. A., & Strick, P. L. (2000). Basal ganglia output and cognition: Evidence from

anatomical, behavioral, and clinical studies. Brain and Cognition, 42(2), 183–200. doi:10.1006/brcg.1999.1099

Mercuri, E., Barnett, A., Rutherford, M., Guzzetta, A., Haataja, L., Cioni, G., ... & Dubowitz, L. (2004). Neonatal cerebral infarction and neuromotor outcome at school age. Pediatrics, 113(1), 95-100. doi: 10.1542/peds.113.1.95

Mink, J. W. (2003). The basal ganglia and involuntary movements: impaired inhibition of competing motor patterns. *Archives of neurology*, *60*(10), 1365-1368. doi: 10.1001/archneur.60.10.1365

Mink, J. W. (2013). Special concerns in defining, studying, and treating dystonia in children. Movement Disorders, 28(7), 921–925. doi:10.1002/mds.25548

Mithani, K., Davison, B., Meng, Y., & Lipsman, N. (2020). The anterior limb of the internal capsule: Anatomy, function, and dysfunction. *Behavioural Brain Research*, *387,* 112588. https://doi.org/10.1016/j.bbr.2020.112588

Miwa, H., Hatori, K., Kondo, T., Imai, H., & Mizuno, Y. (1996). Thalamic tremor: case reports and implications of the tremor-generating mechanism. *Neurology*, *46*(1), 75-79. https://doi.org/10.1212/WNL.46.1.75

Ostrem, J. L., Racine, C. A., Glass, G. A., Grace, J. K., Volz, M. M., Heath, S. L., & Starr, P. A. (2011). Subthalamic nucleus deep brain stimulation in primary cervical dystonia. *Neurology*, *76*(10), 870-878. https://doi.org/10.1212/WNL.0b013e31820f2e4f

Parent, A., & Hazrati, L. N. (1995). Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain research reviews*, *20*(1), 91-127. https://doi.org/10.1016/0165-0173(94)00007-C

Pettigrew, L. C., & Jankovic, J. (1985). Hemidystonia: a report of 22 patients and a review of the literature. *Journal of Neurology, Neurosurgery & Psychiatry*, *48*(7), 650-657. http://dx.doi.org/10.1136/jnnp.48.7.650

Pinter, C., Lasso, A., & Fichtinger, G. (2019). Polymorph segmentation representation for medical image computing. *Computer methods and programs in biomedicine*, *171*, 19-26. https://doi.org/10.1016/j.cmpb.2019.02.011

Quartarone, A., & Hallett, M. (2013). Emerging concepts in the physiological basis of dystonia. *Movement Disorders*, *28*(7), 958-967. doi: 10.1002/mds.25532

Sandman, C. A., Head, K., Muftuler, L. T., Su, L., Buss, C., & Davis, E. P. (2014). Shape of the basal ganglia in preadolescent children is associated with cognitive performance. *Neuroimage*, *99*, 93-102. https://doi.org/10.1016/j.neuroimage.2014.05.020

Scott, B. L., & Jankovic, J. (1996). Delayed-onset progressive movement disorders after static brain lesions. *Neurology*, *46*(1), 68-74. https://doi.org/10.1212/WNL.46.1.68

Simonyan, K. (2018). Neuroimaging applications in dystonia. *International review of neurobiology*, *143*, 1-30. https://doi.org/10.1016/bs.irn.2018.09.007

Slim, M., Westmacott, R., Toutounji, S., Singh, J., Narang, I., Weiss, S., ... & Dlamini, N. (2020). Obstructive sleep apnea syndrome and neuropsychological function in pediatric stroke. *European Journal of Paediatric Neurology*, *25*, 82-89. https://doi.org/10.1016/j.ejpn.2019.11.006

Speelman, J. D., Contarino, M. F., Schuurman, P. R., Tijssen, M. A. J., & De Bie, R. M. A. (2010). Deep brain stimulation for dystonia: patient selection and outcomes. *European Journal of Neurology*, *17*, 102-106. https://doi.org/10.1111/j.1468-1331.2010.03060.x

Soman, T., Askalan, R., Martin, M., Allen, A., Zak, M., MacGregor, D., & Logan, W. (2006).

Predictors of dystonia in childhood basal ganglia stroke. Neuropediatrics, 37(S1), 121. doi: 10.1055/s-2006-945715

Sreenan, C., Bhargava, R., & Robertson, C. M. (2000). Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *The Journal of pediatrics*, *137*(3), 351-355. doi: 10.1067/mpd.2000.107845

Stamelou, M., Alonso-Canovas, A., & Bhatia, K. P. (2012). Dystonia in corticobasal degeneration: a review of the literature on 404 pathologically proven cases. *Movement disorders*, *27*(6), 696-702. https://doi.org/10.1093/brain/awr224

Stoessl, A. J., Lehericy, S., & Strafella, A. P. (2014). Imaging insights into basal ganglia function, Parkinson's disease, and dystonia. *The Lancet*, *384*(9942), 532-544. https://doi.org/10.1016/S0140-6736(14)60041-6

Tibussek, D., Mayatepek, E., Klee, D., & Koy, A. (2015). Post stroke hemi-dystonia in children: a neglected area of research. *Molecular and cellular pediatrics*, *2*(1), 1-5. doi: 10.1186/s40348-015-0026-2

Valeriani, D., & Simonyan, K. (2020). A microstructural neural network biomarker for dystonia diagnosis identified by a DystoniaNet deep learning platform. *Proceedings of the National Academy of Sciences, 117*(42), 26398-26405. https://doi.org/10.1073/pnas.200916511

van Schouwenburg, M. R., den Ouden, H. E., & Cools, R. (2010). The human basal ganglia modulate frontal-posterior connectivity during attention shifting. *Journal of Neuroscience*, *30*(29), 9910-9918. https://doi.org/10.1523/JNEUROSCI.1111-10.2010

Van Schouwenburg, M. R., Den Ouden, H. M., & Cools, R. (2015). Selective attentional enhancement and inhibition of fronto-posterior connectivity by the basal ganglia during

attention switching. Cerebral Cortex, 25(6), 1527–1534. doi:10.1093/cercor/bht345

Vidailhet, M., Vercueil, L., Houeto, J. L., Krystkowiak, P., Benabid, A. L., Cornu, P., ... & Pollak, P. (2005). Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *New England Journal of Medicine*, *352*(5), 459-467. doi: 10.1056/NEJMoa042187

Volkmann, J., Wolters, A., Kupsch, A., Müller, J., Kühn, A. A., Schneider, G. H., ... & DBS Study Group for Dystonia. (2012). Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. *The Lancet Neurology*, *11*(12), 1029-1038. https://doi.org/10.1016/S1474-4422(12)70257-0

Wagenaar, N., Martinez-Biarge, M., van der Aa, N. E., van Haastert, I. C., Groenendaal, F., Benders, M. J., Cowan, F.M., & de Vries, L. S. (2018). Neurodevelopment after perinatal arterial ischemic stroke. *Pediatrics, 142*(3). https://doi.org/10.1542/peds.2017-4164

Waller, A. V. (1850). XX. Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibres. *Philosophical transactions of the Royal society of London*, (140), 423-429. https://doi.org/10.1098/rstl.1850.0021

Wechsler, D. (2003). *WISC-IV: Administration and scoring manual*. San Antonio, TX: Psychological Corporation

Wechsler, D. (2008). *Wechsler adult intelligence scale–Fourth Edition (WISC-IV*). San Antonio, TX: Psychological Corporation.

Wechsler, D. (2014). *WISC-V: Technical and interpretive manual*. NCS Pearson Incorporated.

Westmacott, R., Askalan, R., Macgregor, D., Anderson, P., & Deveber, G. (2010). Cognitive outcome following unilateral arterial ischaemic stroke in childhood: effects of age at

stroke and lesion location. *Developmental Medicine & Child Neurology*, *52*(4), 386-393. doi: 10.1111/j.1469-8749.2009.03403.x

Westmacott, R., McDonald, K. P., deVeber, G., MacGregor, D., Moharir, M., Dlamini, N., Askalan, R., & Williams, T. S. (2018a). Neurocognitive outcomes in children with unilateral basal ganglia arterial ischemic stroke and secondary hemidystonia. *Child Neuropsychology*, *24*(7), 923-937. doi: 10.1080/09297049.2017.1353073

Westmacott, R., McDonald, K. P., Roberts, S. D., deVeber, G., MacGregor, D., Moharir, M., Dlamini, N., & Williams, T. S. (2018b). Predictors of cognitive and academic outcome following childhood subcortical stroke. *Developmental Neuropsychology*, *43*(8), 708-728. https://doi.org/10.1080/87565641.2018.1522538

Wichmann, T., & DeLong, M. R. (2016). Deep brain stimulation for movement disorders of basal ganglia origin: restoring function or functionality?. *Neurotherapeutics*, *13*(2), 264-283. doi: 10.1007/s13311-016-0426-6

Wiedemann, A., Pastore-Wapp, M., Slavova, N., Steiner, L., Weisstanner, C., Regényi, M., Steinlin, M., & Grunt, S. (2020). Impact of stroke volume on motor outcome in neonatal arterial ischemic stroke. *European journal of paediatric neurology*, *25*, 97-105. https://doi.org/10.1016/j.ejpn.2019.10.006

Williams, T. S. (2021). Introduction to the special issue: Transdiagnostic approaches to early brain injury: Harnessing neuroprotection through parents and families. *The Clinical Neuropsychologist*, *35*(5), 841-845. https://doi.org/10.1080/13854046.2021.1927192

Chapter 5: General Discussion

Motor impairments are one of the most common adverse outcomes after pediatric AIS, yet little is known about the impact motor functioning has on other domains of neuropsychological functioning. This dissertation consists of three studies examining relationships between motor functioning and neuropsychological outcomes after pediatric AIS. Study 1 examined the relationships between motor functioning as assessed by the PSOM and intellectual abilities after pediatric AIS with cortical, subcortical, or combined infarcts. Studies 2 and 3 focused on children with AIS involving subcortical regions (i.e., basal ganglia and/or thalamus) with and without acquired dystonia, examining mental health and neuroimaging features, respectively. The general discussion begins with a brief summary of the main findings of each study. A number of themes emerged across the three component studies of this dissertation, which will be reviewed and synthesized across studies. Finally, clinical implications, limitations, and directions for future research will be discussed.

Summary of Main Findings of Each Study

Study 1 found that motor functioning was associated with intellectual outcomes, with different patterns of association in childhood and perinatal AIS groups. Specifically, early motor functioning was associated with overall intellectual functioning, verbal abilities, working memory, and processing speed in the childhood group, but only with processing speed in the perinatal group. Motor functioning closest to time of neuropsychological assessment was not associated with intellectual abilities in the perinatal group, and only with processing speed in the childhood group. The different patterns of associations between motor functioning and specific intellectual abilities point to possible age-dependent effects on this relationship. Considering the full AIS sample, clinical features associated with moderate/severe motor impairment were

combined cortical+subcortical infarcts, hemiparesis, and seizures as well as accessing occupational therapy and physical therapy.

Study 2 demonstrated the presence of anxiety and depression concerns in children with subcortical stroke, with additional challenges associated with acquired dystonia. Specifically, a greater proportion of children with acquired dystonia had ratings in the at-risk range for internalizing behaviours on a standardized parent-completed questionnaire, as well as higher levels of depression and anxiety symptoms. Also, a greater proportion of children with dystonia had concerns related to anxiety and depression indicated on clinical neuropsychological reports. These results suggest that children who develop dystonia after subcortical AIS are at elevated risk for poor mental health outcomes. This study also examined associations between motor, cognitive, and mental health outcomes separately in the dystonia and no dystonia groups. There were no significant associations between motor functioning and neuropsychological outcomes in the dystonia group. Motor and cognitive outcomes were associated in the no dystonia group.

Study 3 examined neuroimaging features in children with subcortical stroke, with and without dystonia as well as intellectual outcomes. Results show that infarcts involving only the thalamus were only present in the no dystonia group and all children with dystonia in the sample had involvement of the basal ganglia. There was a significantly higher proportion of children with dystonia with lesions involving the putamen, caudate nucleus, and anterior limb of the internal capsule. More children with dystonia had severe cortical involvement and infarct volumes were significantly larger. Children with dystonia had significantly lower performance on measures of intellectual abilities relative to the normative mean across all domains, whereas the scores of children with no dystonia were significantly lower only on working memory, processing speed, and overall intellectual functioning. Regression analyses across the full sample

demonstrated involvement of the putamen was the sole significant predictor of dystonia as well as intellectual outcomes.

Synthesis Across Studies

Associations Between Motor and Neuropsychological Outcomes in Pediatric AIS

Overall, the dissertation findings support a relationship between motor and neuropsychological outcomes in pediatric AIS. This is consistent with an existing, but limited, literature (Abgottspon et al., 2021; Lo et al., 2014; Westmacott et al., 2018a). Interestingly, Abgottspon et al., (2021) found an association between upper limb performance and executive functioning. Examining other domains of cognition is an important future direction, as well as other measures of motor functioning such as performance-based measures. Additionally, we dichotomized motor functioning as no/mild deficits and moderate/severe deficits and examined group differences on intellectual outcomes. In the perinatal group, children with moderate/severe deficits performed significantly worse on measures of non-verbal reasoning, and in the childhood group children with moderate/severe deficits performed significantly worse on non-verbal reasoning and processing speed. Notably, correlation analyses did not show significant associations between non-verbal reasoning and motor functioning in either group, suggesting that non-verbal reasoning may be associated with motor functioning only when there are motor deficits.

Study 2 found that children with dystonia after stroke had poorer mental health outcomes in anxiety and depression, relative to children without dystonia. It is unclear whether this finding is explained by maladaptive neural reorganization involving the basal ganglia and/or dopamine system (Moraru et al., 2002; McNeill, 2003; Heiman et al., 2004; Zurowski et al., 2013), a reaction to the functional impact of disability, pain, and stress (Ben-Shlomo, et al., 2002;

McNeill, 2003; Degirmenci et al., 2013), or a combination of both factors (McNeill, 2003). Future research adapting a biopsychosocial model is needed to further elucidate the cause of this presentation (McNeill 2003).

Interestingly, in a subset of children that had cognitive data available, motor functioning was not associated with mental health or cognitive outcomes in the dystonia group; but there were significant associations in the no dystonia group between motor and neuropsychological outcomes. An association between motor symptoms and executive functioning was found in adults with myoclonus-dystonia using performance-based measures of executive functioning (Van Tricht et al., 2012). Additionally, Westmacott et al., (2018b) found that children with dystonia had poorer performance on a measure of cognitive inhibition, but parent rating indicated similar levels of executive dysfunction in daily life among all children with subcortical stroke. This highlights the importance of examining performance-based measures of executive functioning in addition to rating scales. Alternatively, the findings of Study 2 might point to different associations between continuous motor functioning vs. discrete movement disorder diagnosis. The literature is limited, but there is some evidence to suggest the three components are independent from one another in dystonia (Foley et al., 2017). However, another study found that dystonia severity (mild vs. moderate/severe) had an effect on measures of working memory, math problem-solving and calculations, word reading, and spelling, suggesting that there may be an association between more severe motor deficits and neuropsychological outcomes in dystonia acquired after stroke (Westmacott et al., 2018b).

In Study 3 regression analyses demonstrated that involvement of the putamen was a significant predictor of both dystonia and overall intellectual functioning. This suggests the putamen is a structure that may mediate the underlying neurobiological mechanism that is

important for both the manifestation of dystonia as well as adverse intellectual outcomes. Future research with advanced imaging techniques can help determine whether there are similar or distinct neurobiological substrates for cognitive and motor outcomes. Further work can also examine neuroimaging characteristics associated with other measures of motor functioning or movement presentations after stroke (e.g., cerebral palsy).

Consideration of Influence of Age

Across studies, results pointed to consideration of age of stroke on findings. Study 1 found a different pattern of associations between PSOM sensorimotor scores and intellectual outcomes. Specifically, in the perinatal AIS group early motor functioning was associated with processing speed, and there were no associations between concurrent motor and intellectual functioning. In the childhood AIS group, there were associations between early motor functioning and overall intellectual functioning, verbal intellectual ability, working memory, and processing speed, and only processing speed with concurrent motor functioning. A previous study with neonatal stroke did not find any associations with concurrent motor functioning and intellectual outcomes at either pre-school or school-age (Westmacott et al., 2009), providing further support there be age-related effects on relationships between motor and cognitive outcomes in pediatric AIS.

Motor and cognitive development are both protracted and continue to change over childhood and adolescence (Diamond, 2000), along with the neurobiological substrates of these skills (Gogtay et al., 2004), therefore it would not be surprising that relationships between them would differ based on developmental stage. Indeed, work examining intellectual outcomes (Allman et al., 2013; Everts et al., 2008) and motor outcomes (Cooper et al., 2017) separately has found effects of age, with pre-school age children showing better outcomes and perinatal and

childhood stroke associated with poorest outcomes (Ganesan et al., 2000; Kirton & de Veber, 2013; Kolk et al., 2011; Westmacott et al., 2010). The current study also did not have a sufficient sample size to examine different age groups within childhood (e.g., preschool, school age, adolescence). There is also evidence for different outcomes for presumed perinatal and acute neonatal groups (Kirton & de Veber, 2013). Future work with larger samples would help elucidate the effects of age at stroke on the relationship between motor and cognitive outcomes.

In Study 2, there were no significant differences in the dystonia and no dystonia groups for timing for AIS (presumed perinatal, acute neonatal, or acute childhood), age at stroke, or age at test. However, that does not preclude influence of these variables on mental health outcomes. Importantly, Williams et al., (2017) note that mental health difficulties are not always apparent during initial neuropsychological assessment and emerge over time. This is supported by Elbers et al.'s (2014) work, which found that a quarter of young adults who had pediatric stroke self-reported mental illness. Additionally, in adults the functional impact of dystonia including pain, disability, negative body image, stigma, and occupational and social stress were associated were with psychiatric symptoms (Ben-Shlomo et al., 2002; Degermenci et al., 2013; McNeill 2003; Queiroz, Chien, & Barbosa, 2011). The impact of these domains may increase as children get older and have increased responsibilities and independence.

As Study 3 examined infarct characteristics on acute MRI, we excluded presumed perinatal AIS since this diagnosis is given retrospectively after a delay of months to years as initial signs are not always indicative of a need for brain imaging (Gacio et al., 2015) and children are typically identified once they begin showing signs of hemiparesis or early hand preference (Cárdenas et al., 2011). However, dystonia can occur after presumed perinatal stroke, as is demonstrated in Study 2 and by Westmacott et al., (2018b). Additionally, the sample in

Study 3 had relatively few participants with neonatal stroke. Therefore, we were not able to examine whether lesion characteristics predictive of dystonia are different between categories of age at stroke in the current study. As brain maturation is an ongoing, dynamic process (Gogtay et al., 2004; Toga et al., 2006), infarcts sustained at different developmental stages may lead to different outcomes. With respect to subcortical stroke, this is supported by different neurocognitive outcomes after basal ganglia infarcts in the perinatal and childhood periods. Specifically, basal ganglia infarcts during the perinatal period are associated with poor intellectual outcome (Westmacott et al., 2010), whereas basal ganglia later in childhood are associated with specific deficits in attention and executive functioning (Long et al., 2011; Max et al., 2005; Westmacott et al., 2018). It remains to be determined whether lesion characteristics associated with dystonia differ based on age at stroke.

Lesion Characteristics

The primary objective of Study 3 was to examine neuroimaging features in children with subcortical AIS, and whether there were differences in children who developed dystonia. Overall, more children with dystonia had involvement of the putamen, caudate nucleus, and anterior limb of the internal capsule as well as severe cortical involvement and larger infarct volumes. Furthermore, although analyses were not possible due to sample size, it was observed that among children with diaschisis, the no dystonia group had the most instances of diaschisis in the thalamus (four) and two in the corpus callosum, whereas location of diaschisis was more heterogenous in the dystonia group involving the thalamus (3), corpus callosum (2) as well as the corticospinal tract (3), cerebellum (2), and central pons (1). Overall, these findings point to both specific subcortical structures and related white matter that may be key factors in predicting dystonia, as well as the potential impact of more diffuse brain injury (i.e., cortical involvement,

lesion size, more areas of diaschisis). This is in line with the conceptualization of dystonia as a network disorder (Lehericy et al., 2013; Stoessl et al., 2014), and suggests that specific regions as well as overall network integrity must be considered in the prediction of dystonia.

Although not a direct aim of Study 2, examination of neurological characteristics showed that fewer children in the dystonia group had subcortical only lesions. Significantly more children with dystonia had additional small/medium cortical lesions. These findings are discrepant across studies (i.e., severe cortical involvement vs. small/medium cortical lesions), however each study used different classification methods for describing lesion size. Nevertheless, the additional presence of cortical involvement in the dystonia group was present. This also points to the importance of completing quantitative volumetric lesion analysis of each of the involved structures, subcortical and cortical, which our research team is currently completing.

In Study 1 examination of clinical features between groups with no/mild motor deficits and moderate/severe motor deficits showed that there was a higher proportion of children with moderate/severe motor deficits with combined cortical+subcortical lesions, and a higher proportion of children with no/mild motor deficits had subcortical only lesions. There were no differences with respect to cortical lesions. While this study did not focus on dystonia, rather motor impairment, the findings are similar to the other two studies with respect to the influence of subcortical+cortical lesions on poor motor outcome and are consistent with previous research (Boardman et al., 2005). Combined cortical+subcortical lesions have also been associated with adverse cognitive outcomes (Danguecan et al., 2017; Lo et al., 2014; Studer et al., 2014; Westmacott et al., 2010). By examining associations between these motor and intellectual outcomes, the findings of this dissertation contribute to the literature by suggesting that changes

within fronto-striatal connections after AIS affect both motor and cognitive development, leading to presence of deficits in both domains (Anderson et al., 2011).

The Impact of Developmentally Mediated Neuroplasticity on Motor and Cognitive Outcomes in Pediatric AIS

Neuroplasticity refers to the capacity of the central nervous system to respond to both normal (e.g., learning) or abnormal (e.g., injury) changes in the internal and external environment (Dennis et al., 2013). Pediatric AIS presents a unique opportunity to examine the effects of a focal, well-defined lesion with documented onset on the remaining healthy brain. Specifically, adverse motor and cognitive outcomes after pediatric AIS may reflect suboptimal neural reorganization as well as the effects of interruption to the typical development of critical neural networks, even outside of the infarct itself (Anderson et al., 2011; Dennis, 2000; Dennis et al., 2013; Kolb et al., 2011).

In Study 1 the association between motor functioning during early recovery and later intellectual outcome suggests that changes in brain structure and connectivity after injury are first apparent via the presentation of motor deficits and have cascading effects that impact long-term intellectual outcome due to dynamic developmental processes of brain maturation (Gogtay et al., 2004), whereas the lack of association of concurrent motor and intellectual functioning implicates recovery processes that have likely been augmented by intervention. Critically, the impact of AIS likely extends beyond impact of the lesion itself and affects ongoing brain development, with the infarct interrupting hierarchal brain maturational processes that are needed to support development of higher order skills (Gogtay et al., 2004; Greenham et al., 2017). This is consistent with work in typically developing children and children born preterm, which shows associations with early motor functioning and later cognitive outcome (Bruggink et al., 2010;

Butcher et al., 2009; Capute et al., 1985; Einspieler et al., 2016; Murray et al., 2007; Oudgenoeg-Paz et al., 2017; Piek et al., 2008; Spittle et al., 2013). Further understanding of these processes needs to be informed via longitudinal neuroimaging and assessments of motor and cognitive function.

With respect to dystonia acquired after pediatric stroke, the potential role of maladaptive neural reorganization within fronto-striatal circuits after injury has been proposed (Tibussek et al., 2015). This is further supported by evidence of additional cognitive deficits in children with post-stroke dystonia relative to those with stroke only (Westmacott et al., 2018b). Moreover, the relatively greater prevalence after pediatric AIS compared to adult suggests developmentally mediated maladaptive plasticity may contribute to the presentation of dystonia (Tibussek et al., 2015; Quaratone & Hallett, 2013). The basal ganglia and fronto-striatal circuit have also been shown to be involved in mood regulation and implicated in depression and anxiety (Stefurak et al., 2003; Gunaydin & Kreitzer, 2016). The findings from Study 2 are consistent with this, finding greater mental health difficulties in children with dystonia compared to stroke, however further research is needed to delineate the contribution of disrupted neural networks vs. a reaction to the functional impact of dystonia (McNeill, 2003). In Study 3, contrary to our hypothesis, markers of remote injury (e.g., WD, diaschisis) were not significantly different between dystonia and no dystonia groups. However, we only examined acute scans and diaschisis after pediatric AIS has been shown to evolve over time (Kirton et al., 2016). Examination of longitudinal neuroimaging is needed to determine whether rates of diaschisis differ between children with and without post-stroke dystonia. However, the greater proportion of children with severe cortical involvement as well as larger infarct size likely reflects greater

interruption to the networks in children with dystonia due to involvement of multiple brain regions and is consistent with previous work (Elbers et al., 2010).

Clinical Implications

A number of clinical implications arise out of this dissertation. In Study 1, the association between early motor functioning and intellectual outcome at school age suggests that persistent motor deficits may be an indicator of children at greater risk for adverse cognitive outcome. Moreover, clinical features of the moderate/severe motor deficit group included combined cortical+subcortical infarcts, large lesions, and current seizures, suggesting these are important risk factors to consider for motor and cognitive outcome (Cooper et al., 2017; Hajek et al., 2013; Lo et al., 2014; Studer et al., 2014; Wagenaar et al., 2018). In Study 3, differences in neuroimaging features were found between children with and without dystonia. Specifically, more children with dystonia had involvement of the putamen, caudate nucleus, and anterior limb of the internal capsule, as well as severe cortical involvement and larger infarct size. Furthermore, involvement of the putamen was found to predict both dystonia and intellectual outcome, suggesting this may be a critical structure to consider for risk of adverse motor and cognitive outcome. Early identification of children who are at risk of adverse outcome is critical (Kirton et al., 2007; Kirton & de Veber, 2013; Sakzewski et al., 2009), especially as not all children who could benefit from rehabilitation services are accessing them due to barriers preventing families from utilizing interventions (Vyas et al., 2021). In fact, in our sample in Study 1, 20% and 16% of children with moderate/severe motor deficits did not receive physical or occupational therapy, respectively. Improved understanding of the neurobiological substrates of dystonia acquired after pediatric stroke could also inform targeted surgical interventions such as DBS, especially given the variability in response to the globus pallidus as a target in DBS for

childhood and acquired dystonia (Lumsden et al., 2017). Study 2 also highlighted the importance of avoiding overreliance of cut-off scores on standardized measures of mental health, as many children may show subclinical and "at-risk" symptoms, yet not meet full criteria for a psychological diagnosis (Westmacott et al., 2018a). Nevertheless, dystonia may have negative impact on mood, peer relationships, and self-esteem (Westmacott et al., 2018b). Clinical assessment, ongoing monitoring, and access to mental health interventions are critical to promote mental health in this population (Elbers et al., 2014).

Limitations

One limitation across studies was that statistical analyses were constrained by sample size. This is not uncommon in research with populations with relatively rare patterns of injury, such as pediatric stroke and points to the importance of multi-site collaboration to further advance the field. Larger sample sizes would allow for statistical exploration of the contribution of and interaction among various risk factors (e.g., age at stroke, dystonia onset, lesion location, impact of other movement disorders such as spasticity). Across studies, the samples included relatively few presumed perinatal and acute neonatal AIS. Examination of AIS at different developmental stages would allow for further comparison across examination of true neural reorganization after injury (which implies some organization must have taken place) vs. interruption to ongoing development of neural networks.

Regarding dystonia diagnosis in Study 2 and 3, a standardized assessment of dystonia (e.g., Hypertonia Assessment Tool; Jewtha et al., 2010) had not been systematically implemented in the retrospective cohort. However, dystonia diagnoses were made by pediatric neurologists with multiple years of expertise at the Hospital for Sick Children. Additionally, diagnoses were reviewed upon study inclusion. Consistent use of the Hypertonia Assessment

Tool is being implemented in clinical practice as well as prospective studies in recent years. This tool will also provide more information about the manifestation of dystonia including the affected limb(s), severity, and functional impairment. Furthermore, in Study 2 mental health was examined via parent-completed questionnaires, as this was the most common source of data available across participants, however the perspectives of children and young people of their own mental health must also be taken into consideration (Bates et al., 2021).

Future Directions

Future research with advanced neuroimaging methods assessing structural and functional connectivity, such as diffusion tensor imaging (DTI) MRI, functional MRI, and magnetoencephalography (MEG) are needed to further characterize neuroplastic processes underlying motor and cognitive outcome after pediatric stroke (Anderson et al., 2011; Kolb et al., 2010; Kirton et al., 2016). Furthermore, analysis of imaging in the chronic phase of stroke, as well as longitudinal scans over time will further inform the understanding of the development of secondary injury such as WD and diaschisis as well as critical timepoints in recovery when these may emerge and have impact on motor and neuropsychological outcome. Finally, future research should also examine connectivity between structures in the cerebrum and the cerebellum. Functional neuroimaging implicates cortico-cerebellar connections in cognitive and motor functioning (Diamond, 2000; Stoodley et al., 2012) as well as dystonia (Berman & Jinnah, 2015; Jinnah & Hess, 2006; Quartarone & Hallett, 2013). Improving understanding of the underlying neurobiological substrates of adverse outcomes after pediatric AIS is important to identify clinically relevant biomarkers of risk and to improve interventions and outcomes after pediatric AIS (Mirkowski et al., 2019). Additionally, examination of other neuropsychological domains, particularly executive functioning and attention are much needed as difficulties in these domains

are prevalent in AIS and are especially relevant to cortico-subcortical circuity and the basal ganglia (Greenham et al., 2015; Miller & Cohen, 2001; van Schouwenburg et al., 2010; 2013). Finally, the focus of this dissertation was to identify features of children who were most at risk for adverse outcomes after AIS in the areas of motor functioning, cognition, and mental health. However, it is critically important to understand factors that account for *resilience* in functional outcome. Namely, children who do not show motor deficits or neuropsychological morbidities may be showing compensatory or adaptive plasticity, resulting in optimal outcome. Identifying factors associated with resilience after AIS, especially modifiable factors such as the parent-child relationship and home environment is an important area of further research (Dennis, 2000; Kirton et al., 2007; Williams et al., 2021).

Conclusion

The aim of this dissertation was to examine the associations between motor functioning and cognitive and mental health outcomes after pediatric AIS. Overall, the results of the three component studies support an association between motor functioning and neuropsychological outcome after pediatric AIS, such that poorer motor functioning or diagnosis of dystonia was associated with poorer intellectual and mental health outcomes. We suggest these are related to maladaptive neural reorganization, likely in fronto-striatal networks, that result in observable motor deficits and affect the ongoing development of cognitive skills due to interruption of typical hierarchical brain maturational processes. Further research is needed to delineate the impact of age at stroke and lesion characteristics on these associations, as well as characterization of structural and functional neural networks. Improving understanding of risk factors of adverse outcomes after pediatric AIS is critical for optimizing recovery and ongoing development of affected children.

References

Abgottspon, S., Steiner, L., Slavova, N., Steinlin, M., Grunt, S., & Everts, R. (2021). Relationship between motor abilities and executive functions in patients after pediatric stroke. Applied Neuropsychology: Child, 1-11. https://doi.org/10.1080/21622965.2021.1919111

Allman, C., & Scott, R. B. (2013). Neuropsychological sequelae following pediatric stroke: A nonlinear model of age at lesion effects. *Child Neuropsychology, 19*(1), 97-107. doi: 10.1080/09297049.2011.639756

Anderson, V., Spencer-Smith, M., & Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain, 134*(8), 2197-2221. doi: 10.1093/brain/awr103

Bates, L., Taylor, M., Lin, J. P., Gimeno, H., Kingston, J., & Rudebeck, S. R. (2021). Mental health and behaviour in children with dystonia: Anxiety, challenging behaviour and the relationship to pain and self-esteem. *European Journal of Paediatric Neurology, 35*, 40-48. https://doi.org/10.1016/j.ejpn.2021.09.002

Ben-Shlomo, Y., Camfield, L., & Warner, T. (2002). What are the determinants of quality of life in people with cervical dystonia?. *Journal of Neurology, Neurosurgery & Psychiatry, 72*(5), 608-614. doi: 10.1136/jnnp.72.5.608

Berman, B. D., & Jinnah, H. A. (2015). Dystonia: five new things. *Neurology: Clinical Practice, 5*(3), 232-240. https://doi.org/10.1212/CPJ.0000000000000128

Boardman, J. P., Ganesan, V., Rutherford, M. A., Saunders, D. E., Mercuri, E., & Cowan, F. (2005). Magnetic resonance image correlates of hemiparesis after neonatal and childhood middle cerebral artery stroke. *Pediatrics, 115*(2), 321-326. doi: 10.1542/peds.2004-0427

Bruggink, J. L., Einspieler, C., Butcher, P. R., Stremmelaar, E. F., Prechtl, H. F., & Bos, A. F. (2009). Quantitative aspects of the early motor repertoire in preterm infants: do they predict minor neurological dysfunction at school age?. Early human development, 85(1), 25-36. https://doi.org/10.1016/j.earlhumdev.2008.05.010

Butcher, P. R., Van Braeckel, K., Bouma, A., Einspieler, C., Stremmelaar, E. F., & Bos, A. F. (2009). The quality of preterm infants' spontaneous movements: an early indicator of intelligence and behaviour at school age. *Journal of Child Psychology and Psychiatry*, *50*(8), 920-930. https://doi.org/10.1111/j.1469-7610.2009.02066.x

Capute, A. J., Shapiro, B. K., Palmer, F. B., Ross, A., & Wachtel, R. C. (1985). Cognitive-motor interactions: the relationship of infant gross motor attainment to IQ at 3 years. *Clinical pediatrics*, *24*(12), 671-675. https://doi.org/10.1177/000992288502401201

Cárdenas, J. F., Rho, J. M., & Kirton, A. (2011). Pediatric stroke. *Child's Nervous System*, *27*(9), 1375-1390. doi: 10.1007/s00381-010-1366-9

Cooper, A. N., Anderson, V., Hearps, S., Greenham, M., Ditchfield, M., Coleman, L., Hunt, R.W., Mackay, M.T., Monagle, P., & Gordon, A. L. (2017). Trajectories of motor recovery in the first year after pediatric arterial ischemic stroke. *Pediatrics*, *140*(2), e20163870. doi: 10.1542/peds.2016-3870

Danguecan, A., Williams, T., & Westmacott, R. (2017, February) Stability of overall intellectual functioning into early school-age for children with neonatal arterial ischemic stroke. Poster presented at the 45th Annual Meeting of the *International Neuropsychological Society*, New Orleans, USA

Diamond, A. (2000). Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child development, 71*(1), 44-56. https://doi.org/10.1111/1467-8624.00117

Degirmenci, Y., Oyekcin, D. G., Bakar, C., & Kurklu, N. (2013). Anxiety and depression in primary and secondary dystonia: a burden on health related quality of life. *Neurology, Psychiatry and Brain Research, 19*(2), 80-85. doi: 10.1016/j.npbr.2013.01.002

Dennis, M. (2000). Developmental plasticity in children: the role of biological risk, development, time, and reserve. *Journal of communication disorders, 33*(4), 321-332. https://doi.org/10.1016/S0021-9924(00)00028-9

Dennis, M., Spiegler, B. J., Juranek, J. J., Bigler, E. D., Snead, O. C., & Fletcher, J. M. (2013). Age, plasticity, and homeostasis in childhood brain disorders. *Neuroscience & Biobehavioral Reviews, 37*(10), 2760-2773. https://doi.org/10.1016/j.neubiorev.2013.09.010

Elbers, J., Wilkinson, A., DeVeber, G., & Askalan, R. (2010, January). Lesion volume and localization as predictors of dystonia in pediatric basal ganglia stroke. In Annals of Neurology (Vol. 68, No. 4, pp. S98-S98).

Elbers, J., deVeber, G., Pontigon, A. M., & Moharir, M. (2014). Long-term outcomes of pediatric ischemic stroke in adulthood. *Journal of Child Neurology, 29*(6), 782-788. doi: 10.1177/0883073813484358

Einspieler, C., Bos, A. F., Libertus, M. E., & Marschik, P. B. (2016). The general movement assessment helps us to identify preterm infants at risk for cognitive dysfunction. *Frontiers in psychology, 7*, 406. doi: https://doi.org/10.3389/fpsyg.2016.00406

Everts, R., Pavlovic, J., Kaufmann, F., Uhlenberg, B., Seidel, U., Nedeltchev, K., ... & Steinlin, M. (2008). Cognitive functioning, behavior, and quality of life after stroke in childhood. *Child Neuropsychology, 14*(4), 323-338. doi: 10.1080/09297040701792383

Foley, J. A., Vinke, R. S., Limousin, P., & Cipolotti, L. (2017). Relationship of cognitive function to motor symptoms and mood disorders in patients with isolated dystonia. *Cognitive and Behavioral Neurology, 30*(1), 16-22**.** doi: 10.1097/WNN.0000000000000117

Gacio, S., Munoz Giacomelli, F., & Klein, F. (2015). Presumed perinatal ischemic stroke: a review. *Arch Argent Pediatr, 113*(5), 449-55. http://dx.doi.org/10.5546/aap.2015.eng.449

Ganesan, V., Hogan, A., Shack, N., Gordon, A., Isaacs, E., & Kirkham, F. J. (2000). Outcome after ischaemic stroke in childhood. *Developmental medicine and child neurology, 42*(7), 455-461. Doi: 10.1017/S0012162200000852

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., ... & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences, 101*(21), 8174-8179. https://doi.org/10.1073/pnas.0402680101

Greenham, M., Anderson, V., & Mackay, M. T. (2017). Improving cognitive outcomes for pediatric stroke. *Current opinion in neurology*, *30*(2), 127-132. doi: 10.1097/WCO.0000000000000422

Gunaydin, L. A., & Kreitzer, A. C. (2016). Cortico–basal ganglia circuit function in psychiatric disease. *Annual review of physiology, 78*, 327-350. https://doi.org/10.1146/annurev-physiol-021115-105355

Hajek, C. A., Yeates, K. O., Anderson, V., Mackay, M., Greenham, M., Gomes, A., & Lo, W. (2014). Cognitive outcomes following arterial ischemic stroke in infants and children. *Journal of Child Neurology*, *29*(7), 887-894. doi: 10.1177/0883073813491828

Heiman, G. A., Ottman, R., Saunders-Pullman, R. J., Ozelius, L. J., Risch, N. J., & Bressman, S. B. (2004). Increased risk for recurrent major depression in DYT1 dystonia mutation carriers. *Neurology*, *63*(4), 631-637. doi: 10.1212/01.WNL.0000137113.39225.FA

Jethwa, A., Mink, J., Macarthur, C., Knights, S., Fehlings, T., & Fehlings, D. (2010). Development of the Hypertonia Assessment Tool (HAT): a discriminative tool for hypertonia in children. Developmental Medicine & Child Neurology, 52(5), e83-e87. doi: 10.1111/j.1469-8749.2009.03483.x

Jinnah, H. A., & Hess, E. J. (2006). A new twist on the anatomy of dystonia: the basal ganglia and the cerebellum?. *Neurology*, 67(10), 1740–1741. doi:10.1212/01.wnl.0000246112.19504.61

Kirton, A., & deVeber, G. (2013). Life after perinatal stroke. *Stroke*, *44*(11), 3265-3271. doi: 10.1161/STROKEAHA.113.000739

Kirton, A., Westmacott, R., & Deveber, G. (2007). Pediatric stroke: Rehabilitation of focal injury in the developing brain. *NeuroRehabilitation*, *22*(5), 371-382. doi: 10.3233/NRE-2007-22504

Kirton, A., Williams, E., Dowling, M., Mah, S., Hodge, J., Carlson, H., ... & PedNIHSS Investigators. (2016). Diffusion imaging of cerebral diaschisis in childhood arterial ischemic stroke. *International Journal of Stroke*, *11*(9), 1028-1035. https://doi.org/10.1177/1747493016666089

Kolb, B., Teskey, C., & Gibb, R. (2010). Factors influencing cerebral plasticity in the normal and

injured brain. *Frontiers in human neuroscience*, *4*, 204. doi: 10.3389/fnhum.2010.00204

Kolk, A., Ennok, M., Laugesaar, R., Kaldoja, M. L., & Talvik, T. (2011). Long-term cognitive outcomes after pediatric stroke. *Pediatric neurology*, *44*(2), 101-109. https://doi.org/10.1016/j.pediatrneurol.2010.08.012

Lehéricy, S., Tijssen, M. A., Vidailhet, M., Kaji, R., & Meunier, S. (2013). The anatomical basis of dystonia: current view using neuroimaging. *Movement Disorders*, *28*(7), 944-957. https://doi.org/10.1002/mds.25527

Lo, W., Gordon, A. L., Hajek, C., Gomes, A., Greenham, M., Anderson, V., ... & Mackay, M. T. (2014). Pediatric stroke outcome measure: predictor of multiple impairments in childhood stroke. *Journal of child neurology*, *29*(11), 1524-1530. doi: 10.1177/0883073813503186

Long, B., Spencer-Smith, M. M., Jacobs, R., Mackay, M., Leventer, R., Barnes, C., & Anderson, V. (2011). Executive function following child stroke: The impact of lesion location. Journal of Child Neurology, 26(3), 279–287. doi:10.1177/0883073810380049

Lumsden, D. E., Kaminska, M., Ashkan, K., Selway, R., & Lin, J. P. (2017). Deep brain stimulation for childhood dystonia: is ‘where’as important as in ‘whom’?. European Journal of Paediatric Neurology, 21(1), 176-184. https://doi.org/10.1016/j.ejpn.2016.10.002

Max, J. E., Manes, F. F., Robertson, B. A. M., Mathews, K., Fox, P. T., & Lancaster, J. (2005). Prefrontal and executive attention network lesions and the development of attention-deficit/ hyperactivity symptomatology. Journal of the American Academy of Child and Adolescent Psychiatry, 44(5), 443–450. doi:10.1097/01.chi.0000156661.38576.0f

McNeill, A. (2003). Aetiology of co-morbid psychiatric disorders in dystonia: a biopsychosocial

hypothesis. *Internet Journal of Neurology*, *2*(2), 5. doi: 10.5580/299e

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual review of neuroscience*, *24*(1), 167-202. Doi: 0147-006X/01/0301-0167

Mirkowski, M., McIntyre, A., Faltynek, P., Sequeira, N., Cassidy, C., & Teasell, R. (2019). Nonpharmacological rehabilitation interventions for motor and cognitive outcomes following pediatric stroke: a systematic review. *European Journal of Pediatrics*, *178*(4), 433-454. Doi: 10.1007/s00431-019-03350-7

Moraru, E., Schnider, P., Wimmer, A., Wenzel, T., Birner, P., Griengl, H., & Auff, E. (2002). Relation between depression and anxiety in dystonic patients: implications for clinical management. *Depression and anxiety*, *16*(3), 100-103. doi: 10.1002/da.10039

Murray, G. K., Jones, P. B., Kuh, D., & Richards, M. (2007). Infant developmental milestones and subsequent cognitive function. *Annals of neurology*, *62*(2), 128-136. https://doi.org/10.1002/ana.21120

Oudgenoeg-Paz, O., Mulder, H., Jongmans, M. J., van der Ham, I. J., & Van der Stigchel, S. (2017). The link between motor and cognitive development in children born preterm and/or with low birth weight: A review of current evidence. *Neuroscience & Biobehavioral Reviews*, *80*, 382-393. https://doi.org/10.1016/j.neubiorev.2017.06.009

Piek, J. P., Dawson, L., Smith, L. M., & Gasson, N. (2008). The role of early fine and gross motor development on later motor and cognitive ability. *Human movement science*, *27*(5), 668-681. https://doi.org/10.1016/j.humov.2007.11.002

Quartarone, A., & Hallett, M. (2013). Emerging concepts in the physiological basis of dystonia. *Movement Disorders*, *28*(7), 958-967. doi: 10.1002/mds.25532

Queiroz, M. A. R., Chien, H. F., Sekeff-Sallem, F. A., & Barbosa, E. R. (2012). Physical therapy

program for cervical dystonia: a study of 20 cases. *Functional neurology*, *27*(3), 187.

Sakzewski, L., Ziviani, J., & Boyd, R. (2009). Systematic review and meta-analysis of therapeutic management of upper-limb dysfunction in children with congenital hemiplegia. *Pediatrics*, *123*(6), e1111-e1122. https://doi.org/10.1542/peds.2008-3335

Spittle, A. J., Spencer-Smith, M. M., Cheong, J. L., Eeles, A. L., Lee, K. J., Anderson, P. J., & Doyle, L. W. (2013). General movements in very preterm children and neurodevelopment at 2 and 4 years. *Pediatrics*, *132*(2), e452-e458. https://doi.org/10.1542/peds.2013-0177

Stefurak, T. L., & Mayberg, H. S. (2003). Cortical-limbic-striatal dysfunction in depression. In *Mental and behavioral dysfunction in movement disorders* (pp. 321-338). Humana Press, Totowa, NJ.

Stoessl, A. J., Lehericy, S., & Strafella, A. P. (2014). Imaging insights into basal ganglia function, Parkinson's disease, and dystonia. *The Lancet*, *384*(9942), 532-544. https://doi.org/10.1016/S0140-6736(14)60041-6

Stoodley, C. J., Valera, E. M., & Schmahmann, J. D. (2012). Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *Neuroimage*, *59*(2), 1560-1570. https://doi.org/10.1016/j.neuroimage.2011.08.065

Studer, M., Boltshauser, E., Mori, A. C., Datta, A., Fluss, J., Mercati, D., ... & Ramelli, G. P. (2014). Factors affecting cognitive outcome in early pediatric stroke. *Neurology*, *82*(9), 784-792. doi: 10.1212/WNL.0000000000000162

Tibussek, D., Mayatepek, E., Klee, D., & Koy, A. (2015). Post stroke hemi-dystonia in children: a neglected area of research. *Molecular and cellular pediatrics*, *2*(1), 1-5. doi: 10.1186/s40348-015-0026-2

Toga, A. W., Thompson, P. M., & Sowell, E. R. (2006). Mapping brain maturation. *Focus*, *29*(3), 148-390. https://doi.org/10.1176/foc.4.3.378

van Schouwenburg, M. R., den Ouden, H. E., & Cools, R. (2010). The human basal ganglia modulate frontal-posterior connectivity during attention shifting. *Journal of Neuroscience*, *30*(29), 9910-9918. https://doi.org/10.1523/JNEUROSCI.1111-10.2010

Van Schouwenburg, M. R., Den Ouden, H. M., & Cools, R. (2015). Selective attentional enhancement and inhibition of fronto-posterior connectivity by the basal ganglia during attention switching. Cerebral Cortex, 25(6), 1527–1534. doi:10.1093/cercor/bht345

van Tricht, M. J., Dreissen, Y. E., Cath, D., Dijk, J. M., Contarino, M. F., van der Salm, S. M., ... & Tijssen, M. A. (2012). Cognition and psychopathology in myoclonus-dystonia. *J Neurol Neurosurg Psychiatry*, *83*(8), 814-820. doi: 10.1136/jnnp-2011-301386

Vyas, S. S., Ford, M. K., Tam, E. W., Westmacott, R., Sananes, R., Beck, R., & Williams, T. S. (2021). Intervention experiences among children with congenital and neonatal conditions impacting brain development: patterns of service utilization, barriers and future directions. *The Clinical Neuropsychologist*, *35*(5), 1009-1029. https://doi.org/10.1080/13854046.2020.1871516

Wagenaar, N., Martinez-Biarge, M., van der Aa, N. E., van Haastert, I. C., Groenendaal, F., Benders, M. J., Cowan, F.M., & de Vries, L. S. (2018). Neurodevelopment after perinatal arterial ischemic stroke. *Pediatrics*, *142*(3). https://doi.org/10.1542/peds.2017-4164

Westmacott, R., MacGregor, D., Askalan, R., & deVeber, G. (2009). Late emergence of cognitive deficits after unilateral neonatal stroke. *Stroke*, *40*(6), 2012-2019. doi: 10.1161/STROKEAHA.108.533976

Westmacott, R., Askalan, R., Macgregor, D., Anderson, P., & Deveber, G. (2010). Cognitive

outcome following unilateral arterial ischaemic stroke in childhood: effects of age at stroke and lesion location. *Developmental Medicine & Child Neurology*, *52*(4), 386-393. doi: 10.1111/j.1469-8749.2009.03403.x

Westmacott, R., McDonald, K. P., Roberts, S. D., deVeber, G., MacGregor, D., Moharir, M., ... & Williams, T. S. (2018a). Predictors of cognitive and academic outcome following childhood subcortical stroke. *Developmental neuropsychology*, *43*(8), 708-728. https://doi.org/10.1080/87565641.2018.1522538

Westmacott, R., McDonald, K. P., deVeber, G., MacGregor, D., Moharir, M., Dlamini, N., ... & Williams, T. S. (2018b). Neurocognitive outcomes in children with unilateral basal ganglia arterial ischemic stroke and secondary hemidystonia. *Child Neuropsychology*, *24*(7), 923-937. doi: 10.1080/09297049.2017.1353073

Williams, T. S., McDonald, K. P., Roberts, S. D., Dlamini, N., deVeber, G., & Westmacott, R. (2017). Prevalence and predictors of learning and psychological diagnoses following pediatric arterial ischemic stroke. *Developmental neuropsychology*, *42*(5), 309-322. doi: 10.1080/87565641.2017.1353093

Williams, T. S. (2021). Introduction to the special issue: Transdiagnostic approaches to early brain injury: Harnessing neuroprotection through parents and families. *The Clinical Neuropsychologist*, *35*(5), 841-845. https://doi.org/10.1080/13854046.2021.1927192

Zurowski, M., McDonald, W. M., Fox, S., & Marsh, L. (2013). Psychiatric comorbidities in dystonia: emerging concepts. *Movement Disorders*, *28*(7), 914-920. doi: 10.1002/mds.25501