LONGITUDINAL NEUROCOGNITIVE TRAJECTORIES IN PERINATAL ARTERIAL ISCHEMIC STROKE

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ABSTRACT

Perinatal stroke occurs between 20 weeks gestation and 28 days postnatally, with arterial ischemic strokes (AIS) the most common subtype. Research regarding neurocognitive outcomes following perinatal AIS has been primarily cross-sectional with contradictory results given methodological variability (small cohorts, varying age at assessment, differing/non-standardized measures, limited follow-up, mixed populations). No research has characterized neurocognitive trajectories across multiple time points spanning critical developmental periods. **Methods:** These studies were the first evaluation of neurocognitive trajectories for individuals followed longitudinally at The Hospital for Sick Children across: 1) infancy and early childhood (Study 1; *N*=40; neonatal AIS), and 2) early and late childhood, adolescence, and early adulthood (Study 2; *N*=208; perinatal AIS). For Study 1, children underwent developmental assessment(s) at 18- and/or 36-months (Bayley) and neuropsychological assessment(s) from ages 4-13 years (WPPSI/WISC/WASI). For Study 2, individuals underwent neuropsychological assessment(s) from ages 2-25 years (WPPSI/WISC/WASI/WAIS). Predictors included sex, lesion volume, lesion laterality, seizure disorder, neurological diagnoses, medical comorbidities, perinatal AIS type, and early screening. Exploratory multilevel growth curve modelling was used to assess longitudinal neurocognitive trajectories, and to examine main or moderating effects of predictors. **Results:** Despite age-appropriate functioning statistically extrapolated at stroke occurrence, neurocognitive decline was found across 1) infancy and early childhood and 2) early and late childhood, adolescence, and early adulthood. For neonatal AIS and perinatal AIS, lesion volume moderated neurocognitive change. For neonatal AIS, medical comorbidities (congenital heart disease, genetic conditions) negatively impacted neurocognition at stroke occurrence (main effect) and early screening in infancy positively impacted neurocognition over time. For perinatal

AIS, seizure disorder status and perinatal AIS type moderated neurocognitive change.

Conclusions: In keeping with the early vulnerability hypothesis, neurocognitive decline was observed across development following perinatal AIS. Lesion volume and seizure disorders had moderating effects on neurocognition whereas medical comorbidities had a main effect; however, differences were apparent for perinatal AIS types. Perinatal AIS type moderated neurocognition such that presumed perinatal AIS involved rapid neurocognitive decline initially followed by improvements relative to neonatal AIS, which demonstrated consistent decline. Understanding neurocognitive trajectories and relevant predictors will inform the early identification of high-risk groups and the implementation of precision-based interventions.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Perinatal strokes are a group of cerebrovascular diseases resulting in injury to the developing brain between 20 weeks gestation and 28 days postnatally (Lynch et al., 2002). The most focused lifetime risk of stroke is the week surrounding birth (Mineyko & Kirton, 2011), with perinatal arterial ischemic stroke (AIS) as the most common subtype of stroke (i.e., approximately two-thirds) presenting during this period (DeVeber & Canadian Paediatric Ischemic Stroke Study Group, 2000). Children with perinatal AIS fall into two categories based on the timing of stroke presentation, including a) children who present acutely in the neonatal period (i.e., acute neonatal AIS), often with symptomatic seizures rather than focal neurological deficits associated with stroke (Kirton & deVeber, 2009), or b) children who do not present until later in the first year of life (i.e., presumed perinatal AIS), often with emerging hemiparesis and retrospective diagnosis by the presence of a chronic infarct on neuroimaging (Kirton & deVeber, 2009). The annual incidence of perinatal AIS is notable and ranges from one per 2500 to 4000 live births (Agrawal et al., 2009).

The purpose of the two present studies was to determine the longitudinal neurocognitive trajectories across infancy, childhood, adolescence, and early adulthood following perinatal AIS for children having received follow-up within the Neonatal Neurodevelopmental Follow-up Clinic and/or the Children's Stroke Program at The Hospital for Sick Children, Toronto, Canada. Predictors of heterogeneity in neurocognitive trajectories were also examined.

Neurodevelopment in Arterial Ischemic Stroke

Although mortality rates are relatively low (3%) in perinatal AIS (Beslow et al., 2018), poor neurological outcomes (i.e., moderate to severe impairment) are present in 37-62% of children with perinatal AIS (DeVeber et al., 2000; Kolk et al., 2011; Pavlovic et al., 2006;

Tuckuviene et al., 2011), whereas approximately one third of children do not exhibit neurological impairments at all (Sreenan et al., 2000). Motor impairments have been widely reported following perinatal AIS (ranging from 9-91%; Boardman et al., 2005; Ferriero, 2005; Golomb, 2009; Golomb et al., 2001; Lee et al., 2005; Nelson & Lynch, 2004), with upwards of 58% of children showing hemiparesis (Boardman et al., 2005; Golomb et al., 2001; Grunt et al., 2015; Laugesaar et al., 2007; Ricci et al., 2008) and approximately 30-70% of children developing cerebral palsy (Golomb et al., 2008; Lee et al., 2005; Moharir & Deveber, 2014), most commonly hemiplegic cerebral palsy (Golomb et al., 2008; Nelson & Lynch, 2004). Approximately 30-60% of children develop epilepsy following perinatal AIS (DeVeber et al., 2000; Golomb, 2009; Golomb et al., 2001; Golomb, Garg, et al., 2007; Kirton et al., 2008; Lee et al., 2005; Moharir & Deveber, 2014; Wanigasinghe et al., 2010; Yang et al., 1995) and 20-60% have sensory impairments (Golomb, 2009; Kirton et al., 2008; Kirton & De Veber, 2013; Thareja et al., 2012).

Following perinatal AIS, many children also live with broad neurodevelopmental deficits, including delays in speech and language (Ballantyne et al., 2007, 2008; Golomb et al., 2001; Lee et al., 2005; Reilly et al., 2013; Trauner et al., 1996), behavioural functioning (Golomb et al., 2001; Kirton et al., 2008; Lee et al., 2005), and learning/academic skills (Chabrier et al., 2016; Trauner & Mannino, 1986). Moreover, children also experience deficits across higher-level capacities post perinatal AIS, including executive functioning (Suppiej & Traverso, 2016), attention (Kolk et al., 2011; Suppiej & Traverso, 2016; Trauner & Mannino, 1986), memory (Kolk et al., 2011), as well as visual-motor integration, visual-spatial, and visual-constructional skills (Kirton & De Veber, 2013; Kolk et al., 2011; van Buuren et al., 2013).

Neurocognitive Development in Arterial Ischemic Stroke

With respect to neurocognitive functioning (i.e., general thinking abilities) after perinatal AIS, cross-sectional research has yielded discrepant results, with some studies suggesting that children fall broadly within age expectations (Cioni et al., 1998; Gonzalez-Monge et al., 2009; Hetherington et al., 2005; Pavlovic et al., 2006; Ricci et al., 2008; Schatz et al., 2000; Trauner et al., 1993; Wulfeck et al., 1991). Notwithstanding, other studies have revealed evidence of neurocognitive deficits post perinatal AIS (Ballantyne et al., 1994; McLinden et al., 2007; Talib et al., 2008; Trauner et al., 2001; Westmacott et al., 2010). There is, however, uncertainty regarding the prevalence of such neurocognitive deficits, with a range in rates from 11-41% (DeVeber et al., 2000; Golomb, 2009; Golomb, Saha, et al., 2007; Härtel et al., 2004; Kirton et al., 2008; Sreenan et al., 2000), and additional uncertainty around the severity of such neurocognitive deficits. The discrepancy in findings is thought to be due to methodological limitations in research on neurocognitive outcomes, and/or neurocognitive deficits varying as a function of age at the time of assessment (Levine et al., 2005), both of which are discussed further below.

Longitudinal Neurocognitive Development in Arterial Ischemic Stroke

To date, very few longitudinal studies have been conducted on neurocognitive outcomes in children following perinatal AIS (Anderson et al., 2020; Ballantyne et al., 2008; Levine et al., 2005; Muter et al., 1997; Westmacott et al., 2009). These studies have produced discrepant results, with some studies indicating that neurocognitive development remains stable over time (Anderson et al., 2020; Ballantyne et al., 2008; Muter et al., 1997), and other studies reporting the emergence of deficits over time (Levine et al., 2005; Westmacott et al., 2009). As such, the research on neurocognitive capacities across development following perinatal AIS is limited and

a key area for ongoing evaluation. Improving knowledge on long-term neurocognitive outcomes following pediatric AIS has been highlighted as a priority for future research by caregivers (Edwards et al., 2015). Improved understanding of neurocognitive outcomes would also inform clinicians in counseling caregivers regarding recovery expectations and intervention planning post stroke.

Predictors of Neurocognitive Outcomes in Pediatric Stroke

Research has highlighted various determinants of neurocognitive outcomes following pediatric stroke. Reports indicate that early stroke (i.e., before 1 year of age) is a risk factor for less optimal neurocognitive outcomes (Allman & Scott, 2013; Chapman et al., 2003; Max et al., 2010; Studer et al., 2014; Westmacott et al., 2010). A non-linear model of age at stroke effects has also been proposed, suggesting that stroke in middle childhood (5 to 10 years) may lead to better neurocognitive outcomes compared to stroke occurring in the perinatal (0 to 5 years) or late childhood (10 to 18 years) periods (Allman & Scott, 2013; Everts et al., 2008; Ganesan et al., 2000; Pavlovic et al., 2006). Emerging evidence has indicated that the impact of younger age at stroke is moderated by lesion location (Allman & Scott, 2013; Everts et al., 2008; Westmacott et al., 2010). Time since stroke is also known to impact neurocognitive outcomes (Ballantyne et al., 2008; Everts et al., 2008; Levine et al., 2005; Westmacott et al., 2009). This impact is likely due to interactive effects with unstudied factors (e.g., cognitive domain, age at stroke, sex, stroke subtype, etiology, etc.; Fuentes et al., 2016). In longitudinal analyses, male relative to female sex has been found to predict poorer neurocognitive performance (Westmacott et al., 2009).

In regard to stroke region, combined cortical and subcortical lesions have been consistently found to have the most detrimental impact on neurocognitive outcomes, whilst cortical strokes have poorer neurocognitive outcomes relative to subcortical strokes alone (Hajek

et al., 2014; Steinlin et al., 2004; Studer et al., 2014; Westmacott et al., 2010). Large lesion volume is a risk factor for negative neurocognitive outcomes (Everts et al., 2008; Hajek et al., 2014; Levine et al., 2005); however, neurological impairment and time since stroke have been noted to be potential moderators of this relationship (Hajek et al., 2014). Inconsistent findings regarding the effects of lesion laterality on neurocognitive functioning (Westmacott et al., 2009, 2010) have resulted in postulation that factors such as age at stroke, age at assessment, time since stroke, and neurocognitive domain are likely moderating influences (Fuentes et al., 2016). Lastly, both seizures (Ballantyne et al., 2008; Studer et al., 2014) and neurological impairments (Allman & Scott, 2013; Hajek et al., 2014; Studer et al., 2014) are additional risk factors for impaired neurocognitive functioning. Moreover, the presence of seizures (Ballantyne et al., 2008), as well as lesion volume (Levine et al., 2005), are thought to interact with time since stroke in their impact on neurocognitive outcomes. Notably, research on predictors of neurocognitive outcomes has largely been cross-sectional rather than longitudinal in nature and has encompassed mixed populations that include children with a history of both perinatal and childhood strokes, rather than perinatal strokes exclusively.

Methodological Limitations of Neurocognitive Research

As previously alluded to, multiple methodological limitations have likely contributed to the inconsistent findings regarding neurocognitive outcomes and predictors of neurocognitive outcomes, both cross-sectionally and longitudinally, post perinatal AIS. These methodological limitations have included retrospective study designs, use of small cohort sizes, varying cohort age ranges, varying ages at time of assessment, use of differential assessment measures (including non-standardized neurocognitive measures), restricted and varied developmental follow-up periods, as well as short and varied test-retest intervals (Ballantyne et al., 2008;

Greenham et al., 2017; McLinden et al., 2007). Many previous studies included participants for whom lesions were inferred from clinical evidence (e.g., hemiparesis or neurological signs), with stroke etiology not adequately documented by neuroimaging techniques (Ballantyne et al., 1994; Murias et al., 2014). Additionally, studies differed in their inclusion/exclusion criteria, as well as in their use of published normative data, healthy controls, or children affected by acute orthopedic injury when quantifying the target cohort's neurocognitive deficits (Ballantyne et al., 2008; Hetherington et al., 2005; Ricci et al., 2008; Westmacott et al., 2009, 2010). Some of the previously studied participants have also had co-existing neurological injury or risk factors for developmental impairments (e.g., hypoxic ischemic encephalopathy, perinatal asphyxia, congenital heart disease, etc.) which may serve as potential confounds (Murias et al., 2014). Moreover, studies differed in their criteria for quantifying neurocognitive deficits, with different terminology and classification systems used to describe level of performance on differing neurocognitive measures (McLinden et al., 2007).

Postnatal brain development is rapid in the first few months of life (Bullins et al., 2016; McCain, 2020); therefore, the impact of perinatal AIS may vary considerably depending on the time of stroke onset and neurological symptom presentation within the first six months. Studies have consistently combined children with acutely diagnosed neonatal AIS and those with presumed perinatal AIS (Ballantyne et al., 2008; Banich et al., 1990; Levine et al., 2005; Muter et al., 1997; Stiles et al., 2003; Trauner et al., 1993). This heterogeneity is problematic methodologically as children with presumed perinatal AIS are typically diagnosed when neurological deficits are severe, and the exact timing of the lesion cannot be confirmed. To date, only one longitudinal study has focused on long-term neurocognitive outcomes after neonatal AIS exclusively (Westmacott et al., 2009), using a two time-point, incremental design. Further

research examining differences in neurocognitive outcomes between acute neonatal and presumed perinatal AIS subgroups is warranted. Additionally, much of the literature on neurocognitive outcomes post pediatric stroke has been conducted with mixed populations that include children with a history of perinatal as well as childhood strokes, other congenital injuries such as hypoxic ischemic encephalopathy, and/or additional risk factors such as prematurity (Chapman et al., 2003; Delsing et al., 2001; Hogan et al., 2000; Lee et al., 2010; Pavlovic et al., 2006; Trauner et al., 1993). There is only one longitudinal study that followed AIS combined samples across neonatal, presumed perinatal, and childhood stroke subtypes with very short follow-up periods (i.e., 12 months post diagnosis; Anderson et al., 2020). Overall, these mixed cohorts further confound results given the varying ages at stroke onset, varying time since stroke occurrence, and potential differences in stroke pathogenesis, lesion characteristics, and mechanisms of neurocognitive risk.

The accurate characterization of neurocognitive trajectories is complicated by the requirement for comprehensive assessments and follow-up from infancy into childhood, adolescence, and early adulthood using longitudinal rather than cross-sectional methods. The inconsistent results that dominate the literature indicate that further research on neurocognitive outcomes in children having experienced perinatal AIS is necessary (Fuentes et al., 2016) to determine whether early deficits resolve, remain stable, or become more pronounced over time, and whether typically developing infants show emerging deficits with maturation (Westmacott et al., 2009).

Theoretical Mechanisms of Brain Recovery

Predicting outcomes post pediatric stroke relies not only on how a stroke affects the structure and function of the brain, but also on the interacting mechanisms of plasticity and brain

recovery post stroke. In addition to discrepant findings in the literature to date regarding longitudinal neurocognitive outcomes following perinatal AIS, there are competing theories in the literature regarding mechanisms of recovery in children having experienced early brain injury. On one hand, there is a longstanding theory that early injury has *less* of an effect on long-term outcomes than injury later in life because of the capacity of the developing brain to "heal" or compensate (i.e., younger brains recover better than older brains; "Kennard principle" or "early plasticity hypothesis"; Ballantyne et al., 2008; Dennis, 2010; Kennard, 1936; Kim et al., 2009). This theory has been supported by investigations on the mechanisms of plasticity through which a child's developing brain is more capable of reorganization after an insult relative to an adult brain. Evidence in animal models has shown that early brain injury induces changes in gene expression, dendritic arborization, and synaptic spine formation and density (Kolb & Teskey, 2012). Evidence in clinical studies has revealed better outcomes (e.g., sensorimotor, speech, cognitive, or behavioural outcomes) in newborns than in older infants and children after early stroke (DeVeber et al., 2000). Clinical studies have also indicated stable neurodevelopment over time in support of this theory (Ballantyne et al., 2008; Muter et al., 1997). Nonetheless, the empirical support for this theory is criticized for being largely due to the confounding effects of good motor and language outcomes, rather than good neurocognitive outcomes specifically (Bates et al., 2001; Dennis, 1998). Additionally, the methodological heterogeneity within the literature on neurodevelopmental outcomes following perinatal AIS may further confound the apparent empirical support.

There are competing theories suggesting that the developing brain is *more* susceptible to injury (i.e., "early vulnerability hypothesis"; Anderson et al., 2011; Chugani et al., 1996). One theory posits that outcomes are worse if early brain injury affects an ability/capacity before it has

been established. It is argued that, when injury occurs later in childhood, the brain can accommodate to "repair" that preexisting ability and harness redundant pathways in the brain which have already been established. In contrast, if injury occurs earlier in childhood, initial development is disrupted, which is thought to be harder to overcome (Westmacott et al., 2010). In this way, although the extent of functional impairments may not be immediately apparent, children may fail to make age-appropriate developmental gains or seemingly "grow into" new deficits over time alongside increasing developmental demands and expectations (Anderson et al., 2011; Gordon et al., 2015; Westmacott et al., 2009). The plasticity of the brain can accommodate early development but, with the increasing demands of more complex skills and the need to process information in a more complex and efficient manner, the biological reserve is no longer thought to be sufficient, and deficits are thought to be revealed with age (Anderson et al., 2005; Dennis, 2000). Therefore, a child with no deficits in their preschool years may manifest deficits when they reach school age and are challenged with tasks of advanced proficiency (i.e., they may grow into deficits over time). This theory is supported by studies indicating worse outcomes following neonatal or perinatal strokes compared to strokes occurring in later infancy, childhood, or adulthood (Ganesan et al., 2000; Goeggel Simonetti et al., 2015; Kolk et al., 2011; Lansing et al., 2004; Westmacott et al., 2010). This theory is also supported by studies indicating the emergence of greater deficits over time as the age at the time of assessment increases (Banich et al., 1990; Levine et al., 2005; Westmacott et al., 2009). Nonetheless, the inconsistent findings surrounding the impact of age at injury on neurodevelopmental outcomes, as well as more nuanced discourse in recent literature, suggest that multiple factors (e.g., size of lesions, type of lesions, location of lesions, cognitive reserve, etc.) interact with the time of focal brain injury to impact neurodevelopment (Malone & Felling, 2020; Taylor & Alden, 1997).

Again, the methodological heterogeneity within the research in this field likely contributes to these inconsistencies.

These competing theoretical perspectives of early plasticity and early vulnerability are thought to represent extremes along a 'recovery continuum' (Anderson et al., 2011). Child-specific outcomes are determined based on injury (e.g., injury severity, nature of injury, age) and environmental (e.g., family, sociodemographic, intervention) factors, and their complex interaction across development (Anderson et al., 2011). It is also apparent that different neurodevelopmental capacities have different critical periods of maximal susceptibility to injury (Kolb et al., 2011). As such, there are also conflicting theories on the interaction of focal brain injury with the development of differentially complex neurodevelopmental skills. Evidence suggests that lower-order skills involving less complex neural networks (e.g., simple language, visual, and sensory-motor skills) often show good functional recovery over time (Anderson et al., 2011). However, more complex skills involving complex or diffuse neural networks (e.g., higher-order cognition), have less complete recovery (Anderson et al., 2011). In contrast, other theories propose that more distributed neurocognitive processes are more likely to be preserved because they have more biological reserve and reorganization potential (Kolb et al., 2011). The effect on neural networks is likely influenced by the time of injury relative to network development. If injury has occurred prior to the integration of large-scale networks, the capacity of those networks may be reduced; alternatively, if injury occurs after the networks are established, the system may have developed redundancy which can allow for stability or functional compensation (Murias et al., 2014). Overall, inconsistent findings regarding longitudinal neurocognitive outcomes, and competing hypotheses surrounding the mechanism of

stroke recovery across development, indicate a pressing need for longitudinal studies that span infancy, childhood, adolescence, and early adulthood with methodological consistency.

Longitudinal Neurocognitive Trajectories

Many studies on outcomes following perinatal strokes have focused on the emergence of neurocognitive challenges cross-sectionally, which does not enable measurement of change over time. Even the few extant longitudinal studies have primarily explored neurocognition across two time points with small sample sizes to conceptualize change as an *increment* (i.e., simple differences between scores on two occasions; Willett, 1989); however, this approach cannot describe individual trajectories of change and confounds true change with measurement error (Rogosa et al., 1982). A neurocognitive trajectory describes the longitudinal patterns and developmental course of an outcome such as neurocognition over age/time. This approach requires that changes in the outcome be evaluated at multiple time points and over a lengthy time interval spanning critical developmental periods.

Growth curve modeling (often implemented using multilevel growth modeling; Bryk & Raudenbush, 1987; Rogosa & Willett, 1985) is a flexible method for the analysis of longitudinal trajectory data. In addition to providing information about how an outcome changes over time with respect to both the rate of change and level (i.e., within-individual change over time; individual growth trajectories), growth curve modeling can provide information about how certain predictors may moderate change for individual participants (i.e., predictors of inter-individual differences in change; Singer & Willett, 2009). Growth curve modeling offers several advantages over traditional methods for analyzing longitudinal data (e.g., repeated-measures ANOVA) in that it accounts for the potential heterogeneity across individuals with respect to change over time rather than assuming that the rate of change is constant across individuals.

Another advantage of growth curve modeling is that it does not require *balanced* data (Singer & Willett, 2003) given that individuals' empirical growth records can contain a unique number of time points/assessments (i.e., generally three or more) collected at unique measurement intervals based on individual need (i.e., *time-unstructured*). A growth curve model can thus be fit to the entire sample without excluding individuals with one or more missing time points and does not impute missing data but rather incorporates all available data into the modelling. Growth curve modeling also offers the possibility of estimating linear and non-linear (e.g., quadratic) change processes. To date, no known studies have utilized growth curve modeling to examine longitudinal neurocognitive outcomes following perinatal AIS. The opportunity to examine predictors of change using this method is relevant to the study of neurocognitive outcomes post perinatal AIS as it can inform the early identification of high-risk children and inform targeted interventions. The two present studies harnessed these statistical techniques to provide analyses of longitudinal neurocognitive trajectories and predictors of heterogeneity in the trajectories across infancy, childhood, adolescence, and early adulthood following perinatal AIS.

STUDY 1:

LOOKING ACROSS DEVELOPMENT – LONGITUDINAL NEUROCOGNITIVE TRAJECTORIES ACROSS INFANCY AND EARLY CHILDHOOD IN NEONATAL ARTERIAL ISCHEMIC STROKE

Introduction

Neonatal strokes are cerebrovascular diseases resulting in injury to the developing brain between 20 weeks gestation and 28 days postnatally (Lynch et al., 2002). Arterial ischemic strokes (AIS) are the most common stroke subtype during this period (DeVeber & Canadian Paediatric Ischemic Stroke Study Group, 2000). Neonatal AIS includes children who are diagnosed acutely in the neonatal period (birth to postnatal day 28), often due to the presentation of symptomatic seizures and detection via neuroradiological or neuropathological investigation (Kirton & deVeber, 2009; Raju et al., 2007). The incidence of neonatal AIS is notable, affecting one in 5000-10,000 live births (deVeber et al., 2017; Grunt et al., 2015; Lynch, 2009; Lynch & Nelson, 2001). Although survival rates post neonatal AIS are high, children are known to experience significant neurological and neurodevelopmental deficits (Kirton & De Veber, 2013). Nonetheless, there have been discrepant results regarding long-term neurocognitive functioning following neonatal AIS (i.e., general thinking abilities). This discrepancy is attributed to numerous methodological limitations, most notably a lack of longitudinal evaluation across homogenous samples and critical development periods. As such, the purpose of the present study was to determine longitudinal neurocognitive trajectories and relevant predictive factors across infancy and early childhood following neonatal AIS.

With respect to neurological functioning after neonatal AIS, children often experience seizures/epilepsy as well as motor (e.g., hemiparesis, cerebral palsy) and sensory impairments

(deVeber et al., 2017; Golomb, 2009; Grunt et al., 2015; Kirton & De Veber, 2013; Lee et al., 2005; Tuckuviene et al., 2011; Wiedemann et al., 2020). Likewise, following neonatal AIS, many children live with broad neurodevelopmental deficits, including delays in speech and language (Ballantyne et al., 2007, 2008; Golomb et al., 2001; Lee et al., 2005; Reilly et al., 2013; Trauner et al., 1996), behavioural functioning (Golomb et al., 2001; Kirton et al., 2008; Lee et al., 2005), learning/academic skills (Chabrier et al., 2016; Trauner & Mannino, 1986), as well as higher-level neuropsychological capacities (Kolk et al., 2011). With respect to neurocognitive functioning/thinking skills post neonatal AIS, current research has been primarily cross-sectional. The findings regarding neurocognitive outcomes following neonatal AIS have been discrepant, with some studies demonstrating age-appropriate functioning (tested mainly as toddlers and preschoolers; Chabrier et al., 2016; Pavlovic et al., 2006; Ricci et al., 2008) and others demonstrating neurocognitive deficits (Grunt et al., 2015; McLinden et al., 2007). Likewise, there is uncertainty regarding the prevalence and severity of the observed neurocognitive deficits. These discrepancies are likely attributable to methodological heterogeneity, including cross-sectional designs, small cohorts, varying age at assessment, differing/non-standardized measures, and limited follow-up (Ballantyne et al., 2008; Greenham et al., 2017; Levine et al., 2005; McLinden et al., 2007). The few longitudinal studies that have been conducted have also yielded discrepant results likely due to limited follow-up periods (e.g., 1-2 years post diagnosis) and evaluation of neurocognition across two time points as an increment rather than as a trajectory across three or more time points across development (Anderson et al., 2020; Ballantyne et al., 2008; Levine et al., 2005; Muter et al., 1997; Westmacott et al., 2009). Most notably, existing outcome studies have included different stroke subtypes, having combined children with acutely diagnosed neonatal AIS and those with retrospectively diagnosed presumed

perinatal AIS (Ballantyne et al., 1994; Banich et al., 1990; Stiles et al., 2003; Trauner et al., 1993). This grouping is problematic methodologically as children with presumed perinatal AIS often present with severe neurological deficits later in the first year of life (≥29 days of life), which results in a retrospective diagnosis based on the presence of a chronic infarct on neuroimaging (Kirton & deVeber, 2009). Because postnatal brain development is so rapid in the first few months of life (Bullins et al., 2016; McCain, 2020), the impact of focal brain injury may vary considerably depending on the time of stroke onset and neurological symptom presentation within the first six months. Preliminary findings and clinical impressions have alluded to differences in outcomes between acute and presumed perinatal AIS subtypes (Lee et al., 2005). Evaluation is thus needed in exclusively neonatal AIS samples.

To date, no research has characterized neurocognitive trajectories and predictors in neonatal AIS wherein comprehensive methodological follow-up across infancy and childhood is required at multiple time points spanning critical developmental periods. This study served to fill this critical gap. Predicting outcomes post neonatal stroke relies not only on how a stroke affects the structure and function of the brain, but also on the interacting mechanisms of plasticity and brain recovery post stroke. As such, inquiry into neurocognitive trajectories exists across a backdrop of competing theoretical perspectives regarding mechanisms of stroke recovery in children having experienced early brain injury. On one hand, there is a longstanding theory that early injury has *less* of an effect on long-term outcomes than injury later in life because of the capacity of the developing brain to "heal" or compensate (i.e., younger brains recover better than older brains; "Kennard principle" or "early plasticity hypothesis"; Ballantyne et al., 2008; Dennis, 2010; Kennard, 1936; Kim et al., 2009). This theory has been supported by

investigations on the mechanisms of plasticity through which a child's developing brain is more capable of reorganization and recovery after an insult relative to an adult brain.

Alternatively, there is a competing theory suggesting that the developing brain is *more* susceptible to injury (i.e., "early vulnerability hypothesis"), positing that outcomes are worse if early brain injury affects an ability/capacity before it has been fully established (Anderson et al., 2011; Chugani et al., 1996). It is argued that, when injury occurs later in childhood, the brain can accommodate to "repair" that preexisting ability and harness redundant pathways in the brain which have already been established. In contrast, if injury occurs earlier in childhood, initial development is disrupted, which is thought to be harder to overcome (Westmacott et al., 2010). In this way, although the extent of functional impairments may not be immediately apparent, children may fail to make age-appropriate developmental gains or seemingly "grow into" new deficits over time (Anderson et al., 2011; Gordon et al., 2015; Westmacott et al., 2009). More specifically, the plasticity of the brain is thought to accommodate early developmental capacities but, with the increasing demands of more complex skills and the need to process information in a more complex and efficient manner, the biological reserve is no longer sufficient, and deficits are thought to be revealed with age (Anderson et al., 2005; Dennis, 2000). Therefore, a child with no deficits in their preschool years may manifest deficits when they reach school age and are challenged with tasks of advanced proficiency, highlighting a need for longitudinal evaluation that considers the effect of age/time at testing. Presenting additional complexity, these competing theoretical perspectives of 'early plasticity' and 'early vulnerability' represent extremes along a 'recovery continuum', with additional influence of injury (e.g., injury severity, nature of injury, age) and environmental (e.g., family, sociodemographic, intervention) factors that warrant

investigation as potential risk and protective factors with nuanced consideration of interacting/moderating effects across development (Anderson et al., 2011).

As discussed, many studies on outcomes following neonatal strokes have focused on the emergence of neurocognitive challenges cross-sectionally, which does not enable measurement of change over time. Even the few extant longitudinal studies have primarily explored neurocognition across two time points with small sample sizes to conceptualize change as an *increment*; however, this approach cannot describe individual trajectories of change and confounds true change with measurement error (Rogosa et al., 1982). Longitudinal neurocognitive trajectory modelling is needed to understand whether early deficits resolve, remain stable, or become more pronounced over time (Singer & Willett, 2009). Growth curve modeling (Bryk & Raudenbush, 1987; Rogosa & Willett, 1985) is a flexible method for the analysis of longitudinal trajectory data which provides information about 1) how an outcome changes over time with respect to both the rate of change and level (i.e., within-individual change over time), and 2) how certain predictors may moderate change for individual participants (i.e., predictors of inter-individual differences in change; Singer & Willett, 2009). Growth curve modeling offers several advantages over traditional methods for analyzing longitudinal data in that it can accommodate a unique number of time points/assessments per individual (i.e., *imbalanced* data) as well as data collected at unique measurement intervals based on individual need (i.e., *time-unstructured* data; Singer & Willett, 2003). The present study is the first known evaluation to harness these statistical techniques to provide analyses of longitudinal neurocognitive trajectories, and predictors of heterogeneity, across infancy and early childhood after neonatal AIS, and to elucidate recovery mechanisms.

Research Objectives

Throughout this study, the primary objectives were to (1) investigate longitudinal patterns of neurocognitive growth trajectories, and (2) related heterogeneity, for children with neonatal AIS across infancy and early childhood. First, it was hypothesized that children with neonatal AIS would show emerging neurocognitive deficits across development. Second, it was hypothesized that growth trajectories would indicate variability with respect to children's scores and the rate of change over time, which may be predicted by clinically meaningful variables. To further examine potential heterogeneity, the secondary objective was to (3) examine the main and moderating effects of predictor variables on the neurocognitive growth trajectories. Given the paucity of prior longitudinal research on this topic in neonatal AIS samples, there were no specific a priori hypotheses and an exploratory analytical approach was taken. Based on previous research findings in mixed samples using cross-sectional methods, male sex and more extensive neurological (i.e., larger lesions, bilateral infarcts, other neurological diagnoses) and medical (i.e., medical comorbidities) involvement were expected to have a negative impact on the neurocognitive profiles and progressions.

Method

Study Design and Participant Recruitment

The sample for this longitudinal, retrospective cohort study was drawn from the Neonatal Neurodevelopmental Follow-up Registry and the Children's Stroke Outcome Registry at The Hospital for Sick Children in Toronto, Canada. To meet the inclusion criteria for this study, participants had to have: (1) an AIS conforming to established arterial territories with radiological documentation on MRI or CT and confirmed by hospital neurologists in the Stroke Clinic; (2) a history of AIS diagnosed acutely in the neonatal period (<28 days of life); (3)

undergone psychological assessment(s) through the Neonatal Neurodevelopmental Follow-up Clinic at the 18- and/or 36-month visits with available neurocognitive information; (4) undergone neuropsychological assessment(s) through the Children's Stroke Program at age 4 to 13 years with available neurocognitive information; and (5) been born after January 2009, when the Neonatal Neurodevelopmental Follow-up Clinic began routinely conducting psychological assessment for infants who had experienced strokes. Children who were seen in the Neurodevelopmental Follow-up Clinic starting in 2009 could not be older than 13 years at the study end date in June 2022. This calculation informed the upper age limit for inclusion in the study. Given the preliminary and exploratory nature of this study, no children were excluded from analyses.

Procedures

The study was approved by the Research Ethics Boards at The Hospital for Sick Children, Toronto and York University, Toronto. Children and caregivers provided informed assent/consent for use of their health and medical information from standard clinical care appointments as part of their enrollment in the Neonatal Neurodevelopmental Follow-up Study and the Children's Stroke Outcome Study. All neuroimaging was reviewed by hospital neurologists as part of standard clinical care. Psychological and neuropsychological assessment reports and related psychology files were reviewed for specific neurocognitive information. Children who are seen through the Neonatal Neurodevelopmental Follow-up Clinic are routinely referred for psychological assessment at 18- and 36-month time points, regardless of their neurocognitive profile. Children who are seen through the Children's Stroke Program are routinely referred for neuropsychological assessment at school entry (~3-4 years of age) and seen for follow-up assessments across development on a regular basis, regardless of their

neurocognitive profile. This means of follow-up across infancy and early childhood at our centre reduces referral biases and enables long-term neurocognitive outcomes to be evaluated within the pediatric stroke population.

Demographic and Clinical Characteristics

Demographic characteristics of the children included in the study were obtained from the registry databases which included data obtained from standardized review of health records, a structured parent interview, and a medical and neuropsychological history questionnaire completed by parents. This information included biological sex (male/female) and prematurity status (≤36 weeks gestational age). Seizure disorder at the time of the assessment was coded dichotomously (presence/absence of a seizure disorder) and did not include isolated observations of seizures within the neonatal period, which were used as clinical indication for imaging and subsequent acute neonatal AIS diagnoses. Age at psychological and neuropsychological assessment (years) was measured continuously based on the date of neurocognitive testing. Neurological diagnoses and medical comorbidities were also collected to capture other relevant conditions, in addition to acute neonatal AIS. Although the presence of other neurological diagnoses and medical comorbidities may further impact neurocognition beyond the influence of AIS alone, children with other conditions were not excluded from analyses given the preliminary and exploratory nature of this study. Neurological and medical comorbidities were, however, explored as potential predictors of neurocognitive trajectories. For statistical analyses, these variables were collapsed into dichotomous categories (presence/absence of neurological or medical diagnoses) to increase statistical power.

Lesion Characteristics

Determination of lesion location, size, and laterality was made by the study neuropsychologists and neurologists based on systematic reviews of clinically acquired neuroimaging and official radiology and neurology reports. Lesion location was categorized as cortical (infarct with no subcortical involvement), subcortical (infarct with no cortical involvement), combined (infarct with both cortical and subcortical involvement), cerebellar, and/or white matter (not mutually exclusive categories). Lesion volume was coded using the following definitions: Small – involving less than one-third of total volume of a single lobe or major subcortical structure; Medium – involving from one-third to two-thirds of the volume of a single lobe or major subcortical structure OR involving less than half of the volume of two or more lobes/subcortical structures; Large – involving greater than two-thirds of the volume of one lobe or major subcortical structure OR involving greater than half of the volume of two or more lobes/subcortical structures. Lesion laterality was coded categorically as left, right, or bilateral; however, for relevant analyses this was collapsed into dichotomous categories (unilateral/bilateral) to increase statistical power. Other pediatric stroke studies have used similar coding schemes in the past (Westmacott et al., 2010; Williams et al., 2017).

Neurocognitive Functioning

During the psychological assessments that took place through the Neonatal Neurodevelopmental Follow-up Clinic (age 18- and/or 36-month), neurocognitive functioning was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2006). During the neuropsychological assessments that took place through the Children's Stroke Program (age 4 to 13 years), neurocognitive functioning was assessed using Wechsler cognitive tests. Given that this study used retrospective data collected longitudinally

across a wide age span, some children received different versions of the Wechsler tests. As preschoolers, children completed the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV; Wechsler, 2012). As school-age students, children completed the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V; Wechsler, 2014).

The Bayley-III and the Wechsler tests all provide index scores for overall neurocognitive functioning (i.e., Cognitive Composite and Full-Scale IQ, respectively). Overall index scores of neurocognition are known to be the most representative indicator of global intellectual functioning. The index scores are calculated as a standard score with a mean of 100 and a standard deviation of 15. Scores between 90 and 110 fall within the "average range" clinically. To superimpose longitudinal results across the various psychological measures used across differing age ranges, these index scores were considered equivalent, and an overarching neurocognitive domain score was assigned (i.e., Full-Scale IQ). This approach aligns with typical practice in longitudinal clinical neuropsychological research (see Westmacott et al., 2009). All neurocognitive testing across both Clinics/Programs was conducted by experienced psychometrists supervised by clinical psychologists or neuropsychologists. Of note, any declines or improvements reflected over time do not pertain to raw test scores but rather to standardized test scores which enable a more precise and meaningful comparison of scores across individuals in a sample, accounting for age-related developmental changes. As such, declines in standardized test scores do not necessarily reflect an actual loss in individual-level neurocognitive ability over time, rather, a decline could reflect a delay in development compared to typically developing age-matched peers, a plateau in development, or a loss of skills. Similarly, improvements in standardized test scores reflect faster gains over time relative to typically developing age-matched peers diverging positively away from the norm.

Statistical Analyses

Neurocognitive functioning as well as lesion, demographic, and clinical characteristics were analyzed using descriptive statistics. Normally distributed continuous variables were reported as means ± standard deviation (SD); otherwise, medians and interquartile ranges (IQR) were reported. Categorical variables were reported using frequency distributions and proportions. All statistical analyses were conducted in RStudio (RStudio Team, 2019) using two-tailed tests performed at the 0.05 level of significance.

Growth curve models were estimated using the mixed-effects modeling approach implemented with the lme function from the nlme package (Pinheiro et al., 2022). Individual profile trajectories for each child were visualized using empirical growth plots and a linear effect of time was observed; therefore, models with higher-order polynomial terms for non-linear change were not estimated. Unconditional growth models were first estimated to describe within-subjects initial status and rate of change of neurocognitive scores over multiple time points. Conditional models were then estimated for the longitudinal neurocognitive outcomes to assess the impact of covariates on the intercepts and trajectories (i.e., main and moderating effects). The conditional models were compared to the respective unconditional models to examine for potentially improved model fit. Separate conditional models were fit for each of the time-invariant covariates initially (sex, lesion volume, lesion laterality, seizure disorder, other neurological diagnoses, medical comorbidities), with particular focus on whether there was an interaction between time and the covariate (across all levels of the covariate), which would indicate that the covariate moderated change over time (i.e., influenced the trajectories). These models also accounted for potential main effects of the covariates (i.e., influenced the intercepts)

in addition to the potential interaction effects, therefore, main effect and interaction terms were both specified.

Overall, only variables with exclusive categories could be examined as covariates (i.e., not lesion location). Likewise, variables with insufficient sample representation (i.e., prematurity status) were not included to avoid underpowered analyses. Using exploratory methods, any models with significant moderating effects of covariates were expanded upon to examine potential main effects of the remaining covariates. Potentially improved model fit was examined for these expanded conditional models relative to the initial conditional model. For all conditional models, age (in years) was used as the measure of time given that all participants experienced AIS within the neonatal period (acute diagnosis <28 days of life), with comparable durations since stroke upon which to examine potential neurocognitive change. Linear growth curve modelling comprises two main factors: (1) the *"random intercept"*, which represents the initial status, or level, of the neurocognitive outcome at time zero (i.e., time of stroke occurrence/birth), which is statistically extrapolated rather than an objective data point; and (2) the *"random slope"*, which represents the rate of linear change, per year, in neurocognition from the time of stroke occurrence, which is computed across the available growth records/data points. Growth curve modelling can accommodate unbalanced and time-unstructured data without imputing missing data such that growth records can contain a unique number of assessments at unique measurement intervals.

Results

Study Cohort

A total of 435 children with AIS were enrolled in the Children's Stroke Outcome Study. Only 129 had been diagnosed with acute neonatal AIS. Only 44 underwent psychological

assessment(s) through the Neonatal Neurodevelopmental Follow-up Clinic at the 18- and/or 36-month visits with available neurocognitive information. All the children were born after January 2009 and were enrolled in the Neonatal Neurodevelopmental Follow-up Study. Only 40 children also underwent neuropsychological assessment(s) through the Children's Stroke Program at age 4 to 13 years with available neurocognitive information. As such, a total of 40 children met all the inclusion criteria for the present study.

The sample had slightly more representation of male (*n* = 24; 60%) than female children. A small proportion of children were born prematurely (*n* = 3; 7.5%) and had a seizure disorder at the time of assessment (*n* = 6; 15%; Table 1). Lesions were mostly located in white matter (55%), cortical (73.08%), and combined cortical and subcortical (35%) regions (not mutually exclusive), with fewer lesions exclusively in subcortical or cerebellar regions. Lesion volume was primarily in the medium (*n* = 21; 52.50%) to large (*n* = 14; 35%) range, with fewer small volume lesions. Most of the strokes were unilateral (*n* = 31; 77.5%) rather than bilateral in nature, of which, more than double were left-hemispheric (*n* = 11; 52.5%) rather that right-hemispheric. In addition to having experienced an acute neonatal AIS, a small portion of the sample had also been diagnosed with other relevant neurological (*n* = 6; 15%) and medical (*n* = 7; 17.5%) conditions, as specified in Table 1.

Table 1

Demographic, Lesion, and Clinical Characteristics (N = 40)

	n (%)
Sex, male	24 (60.00)
Prematurity (≤36 weeks gestational age)	3 (7.50)
Seizure disorder	6 (15.0)
Lesion location[a]	
Cortical	19 (73.08)
Subcortical	5 (19.23)
Cortical and subcortical[b]	14 (35.00)

Cerebellum	1 (2.50)
White matter	22 (55.00)
Lesion volume	
Small	5 (12.50)
Medium	21 (52.50)
Large	14 (35.00)
Lesion laterality	
Unilateral	31 (77.50)
Right	10 (25.00)
Left	21 (52.50)
Bilateral	9 (22.50)
Other neurological diagnoses	6 (15.00)
Infection	2 (5.00)
Haemorrhage	2 (5.00)
Neonatal hypoxic ischemic encephalopathy	1 (2.50)
Arterial venous malformation	1 (2.50)
Medical comorbidities	7 (17.50)
Congenital heart disease	6 (15.00)
Genetic	1 (2.50)

Note. [a] Not mutually exclusive. [b] Mutually exclusive from individual cortical and subcortical categories.

Of the 40 participants, 5 completed two (M_{age1} = 1.60, *IQR*: 1.52 - 1.71; M_{age2} = 3.07, *IQR*: 2.99 - 3.29), 21 completed three (M_{age3} = 5.18, *IQR*: 4.44 - 5.77), 11 completed four (M_{age4} = 6.95, *IQR*: 6.08 - 8.22), and 3 completed five (M_{age5} = 10.25, *IQR*: 9.44 - 10.66) assessments across the study period (Table 2). Assessment time points one and two primarily involved psychological assessments using the Bayley-III (100% and 82.5% of participants, respectively), consistent with initial testing having occurred through the Neonatal Neurodevelopmental Follow-up Clinic. Of note, although most participants underwent psychological assessment through the Neonatal Neurodevelopmental Follow-up Clinic at both the 18- and 36-month visits (n = 33; 82.5%), seven participants only underwent psychological assessment at one of the two visits. Across the study period, assessment time points three to five exclusively involved neuropsychological assessments using Wechsler cognitive tests, consistent with subsequent

testing having occurred through the Children's Stroke Program. Additional neurocognitive assessment details are shown in Table 2.

Table 2

Neurocognitive Assessment Details

	Assessment Time Points				
	1	2	3	4	5
Proportion of full sample, *n* (%)	40 (100.00)	40 (100.00)	35 (87.50)	14 (35.00)	3 (7.50)
Assessment measure, *n* (%)					
Bayley-III	40 (100.00)	33 (82.50)	–	–	–
WPPSI-IV	–	7 (17.50)	28 (80.00)	3 (21.43)	–
WISC-V	–	–	7 (20.00)	11 (78.57)	3 (100.00)
Median [interquartile range] age at assessment, years	1.60 [1.52, 1.71]	3.07 [2.99, 3.29]	5.18 [4.44, 5.77]	6.95 [6.08, 8.22]	10.25 [9.44, 10.66]
Mean [±standard deviation] Full-Scale IQ at assessment, standard scores	97.88 [±14.76]	100.76 [±15.54]	96.13 [±19.58]	94.36 [±25.45]	80.33 [±30.86]

Visual inspection of individual growth trajectories revealed considerable variability with respect to both individuals' initial scores and how scores changed over time. Some children showed decline, some showed improvement, and others showed a more stable pattern, although the trajectories all showed an approximately linear form. Variability in initial status and rate of change was explicitly modeled by growth curve models.

Objective 1 and 2: Neurocognitive Growth Trajectories and Heterogeneity

Within the unconditional means model, which did not include time as a predictor of change, mean initial neurocognitive status, as determined by the mean of the random intercepts, was 96.86 (standard score; *95% CI*: 92.05, 101.68, $df = 86$, $t = 39.82$, $p < 0.001$). This value indicated that, when baseline neurocognition was statistically extrapolated at stroke occurrence

(i.e., at birth in the neonatal period; time point 0) without consideration of trends over time, neurocognitive performance was within the average clinical range. Relative to the unconditional means model, the unconditional linear growth model had improved model fit when including time as a predictor of change ($\chi^2 = 22.35$, $df = 3$, $p < 0.001$). The results of the unconditional growth model, which provides examination of longitudinal trajectories and within-subject change over time, are summarized in Table 3. Mean initial neurocognitive status (mean of the random intercepts), was 102.48 (standard score). This value indicates that, when baseline neurocognition was statistically extrapolated at stroke occurrence (i.e., at birth in the neonatal period; time point 0), neurocognitive performance was within the average clinical range. Regarding rate of neurocognitive change, a negative effect of time indicated longitudinal neurocognitive decline across follow-up ($\beta = -1.45$, *95% CI*: -2.51, -0.40, $p = 0.008$). Substantial individual differences in the rate of change were apparent ($SD = 1.81$, *95% CI*: 0.77, 4.28), indicating diverse neurocognitive trajectories. This variability suggests that the growth curves may be more accurately predicted by theoretically meaningful variables (e.g., sex, lesion volume, lesion laterality, neurological diagnoses, and medical comorbidities), which was explored in Objective 3.

Table 3

Unconditional Model: Within-Subject Change Over Time

Outcome measure	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
Mean random intercept	102.48	97.70, 107.27	85	42.26	<0.001
Linear slope	-1.45	-2.51, -0.40	85	-2.72	0.008

Objective 3: Predictors of Neurocognitive Trajectories

The results of the conditional growth models which investigated the main and moderating effects of Full-Scale IQ over time by clinical and stroke-related factors are shown in Table 4. These models provide examination of the correlates of within-subject parameters. Of the variables explored, none had a significant effect on the random intercept (i.e., main effect), that is, neurocognitive performance statistically extrapolated at stroke occurrence. More specifically, these extrapolated results indicated that children who differed by sex, lesion volume, lesion laterality, seizure disorder, neurological diagnoses, and medical comorbidities, respectively, demonstrated roughly similar baseline neurocognitive performance. Of the variables explored, only lesion volume had a significant interaction with age such that larger lesion volume was associated with greater neurocognitive decline, indicating that lesion volume moderated the rate of neurocognitive change over time (β = -2.03, *95% CI*: -3.56, -0.51, p = 0.01; Figure 1). More specifically, children with small lesion volumes showed neurocognitive gains over time, whereas children with medium and, most notably, large lesion volumes showed neurocognitive decline. Model fit was improved relative to the unconditional growth model (χ^2 = 7.03, df = 6, p = 0.03).

Table 4

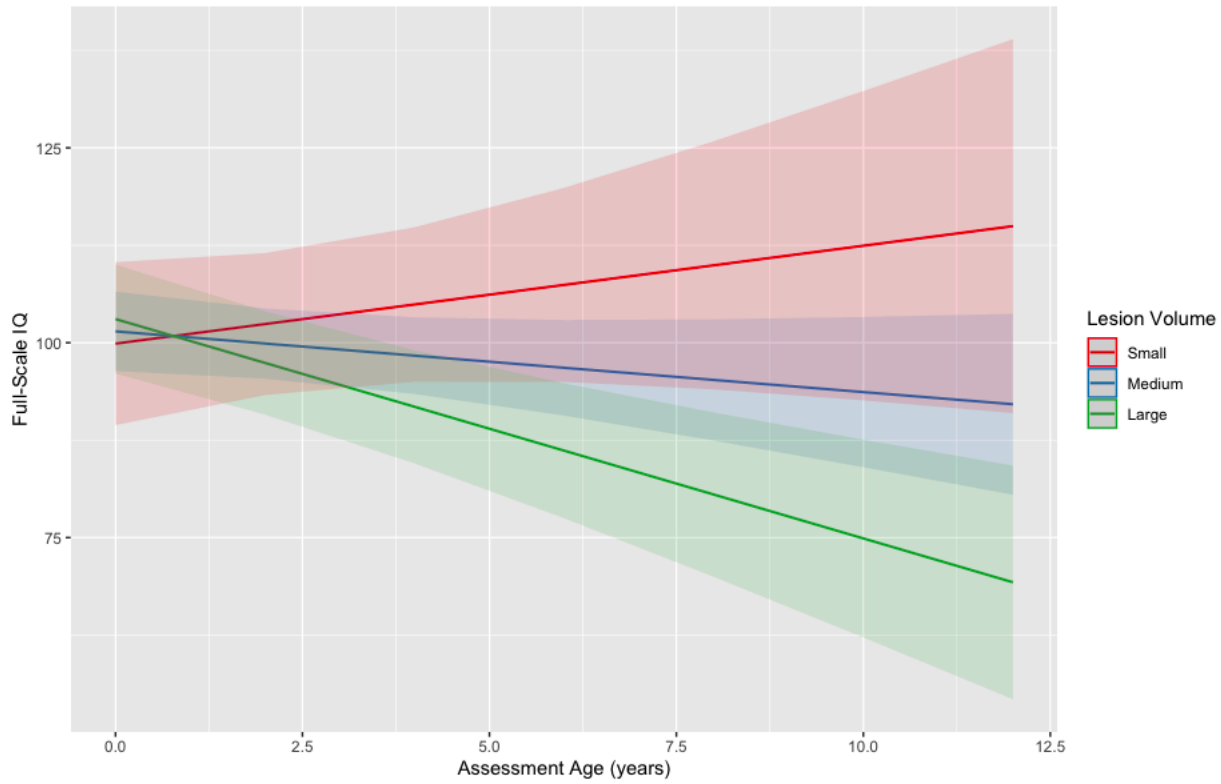
Conditional Models: Main and Moderating Effects on Full-Scale IQ

Clinical and Stroke-Related Factors	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
Sex	-0.04	-9.84, 9.76	38	-0.008	0.99
Sex x age interaction	-0.32	-2.43, 1.79	84	-0.29	0.77
Full-Scale IQ					
Lesion volume	1.58	-5.95, 9.10	38	0.42	0.68
Lesion volume x age interaction	-2.03	-3.56, -0.51	84	-2.60	0.01
Full-Scale IQ					
Lesion laterality	-8.30	-20.64, 4.03	38	-1.34	0.19

Lesion laterality x age interaction	1.76	-1.18, 4.70	84	1.17	0.25
Full-Scale IQ					
Seizure disorder	-6.92	-20.55, 6.71	38	-1.01	0.32
Seizure disorder x age interaction	0.30	-2.71, 3.30	84	0.19	0.85
Full-Scale IQ					
Neurological diagnoses	-5.10	-18.00, 7.81	38	-0.79	0.44
Neurological diagnoses x age interaction	1.39	-1.33, 4.11	84	1.00	0.32
Full-Scale IQ					
Medical comorbidities	-12.03	-24.44, 0.39	38	-1.93	0.06
Medical comorbidities x age interaction	0.44	-2.25, 3.14	84	0.32	0.75

Figure 1:

Lesion Volume as a Moderator of Neurocognitive Decline



In an exploratory manner, the conditional model with the moderating effect of Full-Scale IQ over time by lesion volume was repeated by entering all other variables individually as covariates to examine for potential main effects (i.e., rather than main and moderating effects as before). The results of these expanded conditional growth models are shown in Table 5. In examining for potential main effects of the variables, only medical comorbidities had a significant effect on the random intercept, above and beyond the moderating role of lesion volume. That is, the presence of medical comorbidities contributed to lower baseline neurocognition statistically extrapolated at stroke occurrence (β = -11.97, *95% CI*: -23.27, -0.68, p = 0.04) and thus generally lower performance relative to the absence of medical comorbidities, in addition to larger lesion volume being associated with greater neurocognitive decline (β = -1.98, *95% CI*: -3.50, -0.45, p = 0.01; Figure 2). Again, children with small lesion volumes showed neurocognitive gains over time, whereas children with medium and, most notably, large lesion volumes showed neurocognitive decline, regardless of the presence of medical comorbidities. Model fit was improved relative to the initial conditional model (χ^2 = 4.36, df = 8, p = 0.04). Evaluation of sex, lesion laterality, seizure disorder, and neurological diagnoses yielded non-significant results.

Table 5

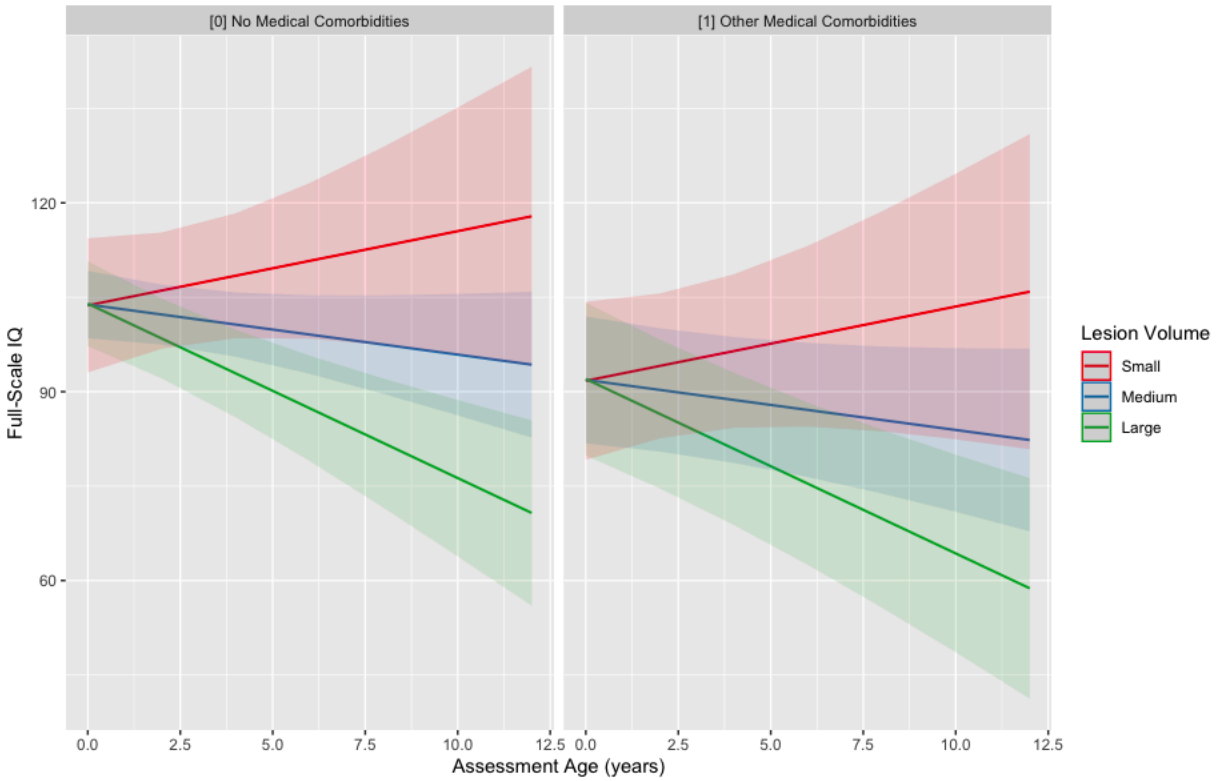
Expanded Conditional Models: Moderation of Full-Scale IQ by Lesion Volume and Potential Main Effects

Clinical and Stroke-Related Factors	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
Sex	-0.18	-9.15, 8.79	37	-0.04	0.97
Lesion volume x age interaction	-2.03	-3.56, -0.50	84	-2.59	0.01
Full-Scale IQ					
Lesion laterality	-4.69	-15.33, 5.95	37	-0.88	0.39

Lesion volume x age interaction	-2.03	-3.57, -0.48	84	-2.56	0.01
Full-Scale IQ					
Seizure disorder	-5.28	-17.61, 7.06	37	-0.85	0.40
Lesion volume x age interaction	-2.02	-3.55, -0.49	84	-2.57	0.01
Full-Scale IQ					
Neurological diagnoses	-2.59	-14.90, 9.73	37	-0.42	0.68
Lesion volume x age interaction	-2.02	-3.55, -0.50	84	-2.58	0.01
Full-Scale IQ					
Medical comorbidities	-11.97	-23.27, -0.68	37	-2.10	0.04
Lesion volume x age interaction	-1.98	-3.50, -0.45	84	-2.53	0.01

Figure 2

Lesion Volume as a Moderator of Neurocognitive Decline and Main Effects of Medical Comorbidities



Discussion

This is the first longitudinal study to examine neurocognitive growth trajectories spanning multiple time points across infancy and early childhood in a cohort of 40 children who experienced exclusively neonatal AIS. From this study, several conclusions can be made about changes in neurocognition (i.e., Full-Scale IQ) as a function of age and the influence of relevant risk factors. First, although neurocognition was statistically extrapolated within the average clinical range at stroke occurrence (i.e., at birth), a negative effect of time was found, indicating significant neurocognitive decline across follow-up. Second, growth curves varied considerably across children, suggesting the potential influence of clinically meaningful risk factors. Third, of the various clinical and stroke-related factors explored as potential predictors of neurocognitive trajectories, a main effect of medical comorbidities was found alongside a moderating role of lesion volume. That is, the presence of medical comorbidities (i.e., congenital heart disease, genetic conditions) contributed to lower neurocognition statistically extrapolated at stroke occurrence and thus generally lower performance across time relative to the absence of medical comorbidities. Larger lesion volume was also associated with greater neurocognitive decline. More specifically, children with small lesion volumes showed neurocognitive gains over time, whereas children with medium and, most notably, large lesion volumes showed neurocognitive decline. Evaluation of sex, lesion laterality, seizure disorder, and neurological diagnoses yielded non-significant results.

Neurocognitive Growth Trajectories

Longitudinal analyses are essential to better understand the long-term neurocognitive sequalae associated with neonatal AIS, as compared with cross-section analyses. More specifically, cross-sectional studies cannot address whether children who have experienced

neonatal AIS start at a lower level of neurocognition or whether they "grow into deficits". Evaluation of "growing into deficits" requires consideration of whether the child is experiencing a progressive widening of the gap between their performance and age-matched peers, or whether they have experienced a static insult to a neurocognitive trajectory that was impacted early in its maturation, but not necessarily in a progressively deteriorative manner. As such, the negative Full-Scale IQ trajectory that was found indicates a loss of developmental gain over the course of infancy and early childhood, despite age-appropriate functioning extrapolated statistically at stroke occurrence (i.e., birth). The current results thus provide compelling evidence of a greater vulnerability, rather than a greater plasticity/resiliency, of the immature brain that faces early injury. These findings are consistent with prior cross-sectional studies which demonstrated neurocognitive deficits only 2-years post neonatal AIS, including significant deficits compared to a normative sample (McLinden et al., 2007), as well as significant deficits in 31% of a neonatal AIS cohort (Grunt et al., 2015).

In contrast, the robust longitudinal findings from the present study differ from existing cross-sectional studies which have broadly demonstrated age-appropriate functioning following neonatal AIS (Chabrier et al., 2016; Pavlovic et al., 2006; Ricci et al., 2008); however, this discrepancy is likely due to methodological differences. More specifically, Chabrier et al. (2016) found generally age-appropriate median neurocognitive functioning across verbal comprehension, perceptual reasoning, and processing speed indices; however, these findings do not capture the notable variability in scores in their sample (i.e., large IQR as well as significant discrepancies between indices for ~79% of the children), or the low average median scores found in working memory specifically. Likewise, an 8% rate of global intellectual disability (Full-Scale IQ < 70 or verbal comprehension and perceptual reasoning indices < 70) was found 7 years post

neonatal AIS (Chabrier et al., 2016), which was deemed consistent with rates reported in previous neonatal AIS samples (5.8-9.6%; Ricci et al., 2008; Westmacott et al., 2009). Nonetheless, global intellectual disability only affects 1-3% of the general population; therefore, their findings still represent elevated rates of neurocognitive challenge in neonatal AIS relative to typically developing children (Mithyantha et al., 2017). Likewise, Chabrier et al. (2016) only included children born full-term within their sample, with follow-up exclusively at 7-years post stroke. Therefore, they did not capture the known neurocognitive risks associated with prematurity (Johnson et al., 2015) common in neonatal AIS, and failed to follow their sample later into childhood when deficits are most likely to emerge. Similarly, Pavlovic et al. (2006) reported neurocognitive challenges in ~36% children within their neonatal AIS sample, which they largely attributed to comorbid epilepsy. However, deficits were found in over one third of the sample which is notable given that neurocognitive testing occurred at a very young age of 1.8 years on average and, once again, excluded for prematurity. Lastly, Ricci et al. (2008) reported generally typical neurocognitive outcomes in children 5-10 years post neonatal AIS with no other neurological comorbidities (78% of their sample). However, 22% of children in their sample still showed low to exceptionally low neurocognitive functioning (which they associated with seizures and hemiplegia). Of note, their sample only included full-term children with middle cerebral artery infarctions, thus failing to capture the heterogeneity and compounding risks within a typical neonatal AIS sample. In addition, Ricci and colleagues' (2008) results were hampered by heterogenous testing times (spanning 5-10 years), with the majority of their sample being preschoolers at the time of assessment (~5 years); therefore, their follow-up interval may have been too short to detect later-emerging neurocognitive morbidity in a consistent manner.

There has been more evidence of neurocognitive deficits post perinatal AIS in cross-sectional (Ballantyne et al., 1994; McLinden et al., 2007; Talib et al., 2008; Trauner et al., 2001; Westmacott et al., 2010) as well as the limited longitudinal (Anderson et al., 2020; Ballantyne et al., 2008; Levine et al., 2005; Muter et al., 1997) studies within the literature. However, these studies have comprised mixed samples of perinatal AIS (including neonatal and presumed perinatal AIS) which cannot be compared with the exclusively neonatal AIS sample in the present study. In addition to the heterogenous samples, these studies have also been criticized for their methodological heterogeneity (small cohort sizes, varying age at assessment, differing/non-standardized measures, differing definitions of neurocognitive deficits, limited follow-up; Ballantyne et al., 2008; Greenham et al., 2017; Levine et al., 2005; McLinden et al., 2007). This variability may account for some of the discrepancy in neurocognitive findings to date. As such, a longitudinal and methodologically consistent approach was taken within the present study to elucidate neurocognitive functioning following neonatal AIS. Consistent with the findings of the present study, the only other known longitudinal study in an exclusively neonatal AIS sample to date, also revealed a significant decline in neurocognition (Full-Scale IQ, non-verbal reasoning, working memory, and processing speed) from preschool to school-age assessment time points (69.2% of the sample; Westmacott et al., 2009). Neurocognitive performance did not differ from the normative sample at the pre-school assessment time point, rather only at the school-age assessment time point (Westmacott et al., 2009). The rate of neurocognitive deficits may be underestimated in the sample examined by Westmacott et al. (2009), given their exclusion of children with bilateral strokes or other neurological comorbidities which would be expected to pose heightened neurocognitive risks (Fuentes et al., 2016). Nonetheless, similar to the results of the present study, their findings were consistent with emerging deficits over time and an early

vulnerability hypothesis of early brain injury. However, Westmacott et al. (2009) evaluated neurocognition across two time points as an increment (i.e., simple differences between scores on two occasions) rather than as a trajectory over three or more time points (Willett, 1989). An increment approach cannot describe individual trajectories of change and has been criticized for confounding true change with measurement error (Rogosa et al., 1982). Therefore, the neurocognitive trajectory approach taken in the present study was novel in its capacity to describe the longitudinal patterns and developmental course of neurocognition over age/time, including multiple time points (i.e., one to five rather than two) spanning critical developmental periods (i.e., across infancy and early childhood).

Predictors of Neurocognition

Another unique component of the present study was the evaluation of relevant risk factors within an exclusively neonatal AIS sample. There are limitations in the extant research on identified predictors of neurocognition following pediatric stroke (i.e., age at stroke, time since stroke, sex, etiology, lesion characteristics [location, laterality, volume], neurological impairment, seizures), including heterogenous samples spanning various pediatric stroke types (e.g., hemorrhagic, arterial ischemic, cerebral sinovenous thrombosis) and ages at stroke occurrence (e.g., neonatal, perinatal, childhood stroke; Fuentes et al., 2016). As such, existing findings regarding predictors of neurocognition are not generalizable to exclusively perinatal AIS and neonatal AIS samples. In contrast, within this exclusively neonatal AIS sample, a main effect of medical comorbidities (i.e., congenital heart disease, genetic conditions) was identified alongside a moderating role of lesion volume. No work to date has explored long-term trajectories or the interactions between predictive factors and neurocognition.

Existing studies in exclusively neonatal AIS samples, or generalized pediatric stroke samples, have not examined the influence of medical comorbidities on neurocognitive functioning. In the present study, the presence of medical comorbidities, including congenital heart disease and genetic conditions, contributed to lower neurocognition statistically extrapolated at stroke occurrence, and thus generally lower performance across time relative to the absence of medical comorbidities. Congenital heart disease is one of the most common causes of perinatal ischemic stroke (Cárdenas et al., 2011; Friedman, 2009), often secondary to early cardiac procedures (e.g., catheterization, cardiac surgery, or mechanical circulatory support devices; Vázquez López et al., 2017). The strokes experienced by these children are more frequently bilateral, multifocal, affect both anterior and posterior circulation, and show a greater tendency for recurrence and hemorrhagic transformation (Vázquez López et al., 2017). As such, etiologies like congenital heart disease are associated with their own neurocognitive sequelae that can be especially debilitating alongside comorbid stroke. For example, multiple studies show that congenital heart disease alone is a risk factor for deficits in intellectual functioning (Schaefer et al., 2013), visual-spatial processing (Karsdorp et al., 2007; Schaefer et al., 2013), and verbal comprehension (Spijkerboer et al., 2008), and that developmental delays in this group are common (Mussatto et al., 2014). Risk of cognitive sequelae following congenital heart disease has been found to increase with higher disease severity (Limbers et al., 2013). More specifically, children with complex congenital heart disease are at increased risk of neurological sequelae due to the likelihood of hypoxia and chronic cerebral hypoperfusion which often begin in the fetal period (Vázquez López et al., 2017). Cardiac surgery and post-operative hypodynamic instability are other neurological risk factors for these children (Majnemer et al., 2009). A seminal systematic review on predictors of neurocognition following pediatric stroke highlighted the

need for future research to investigate the influence of congenital heart disease within stroke populations (Fuentes et al., 2016). The present study represents the first known research to address this research question with a neurocognitive lens.

To date, preliminary outcome studies in samples of children with AIS (i.e., mixed samples with perinatal and childhood AIS) and heart disease (i.e., mixed samples with congenital and acquired etiologies) have yielded inconsistent results. These studies have not examined neurocognition on standardized measures, but rather clinical outcomes more generally. Cardamone et al. (2015) found neurological deficits in 84% of their sample. Likewise, Vázquez López et al. (2017) reported some degree of impairment in 63% of their sample, primarily across sensorimotor and cognitive-behavioural domains. They also reported poorer outcomes associated with AIS in the neonatal period, larger stroke size, basal ganglia involvement, and epilepsy (Vázquez López et al., 2017). In contrast, Dowling et al. (2013) found no significant difference in clinical outcomes (i.e., death, neurological deficits, status at hospital discharge) when comparing children with AIS and heart disease to those with exclusively AIS. Nonetheless, there appears to be heightened risk associated with comorbid AIS and heart disease, especially in the neonatal period. Further investigation of clinical and neurocognitive outcomes in neonatal AIS populations with heart disease is warranted. Notably, children with congenital heart disease can have a more complex syndromic profile, often genetic in nature with malformations of other organs, including the central nervous system, thus further compounding clinical and neurocognitive risk (Manning et al., 2005).

With respect to genetic conditions more broadly, thrombophilia and genetic factors are associated with AIS in the neonatal period (Lehman & Rivkin, 2014). Prothrombotic risk factors including elevated lipoprotein (a), MTHFR mutation, factor V Leiden, prothrombin gene

mutation, and protein C deficiencies have all been associated with neonatal AIS (Günther et al., 2000; Nowak-Göttl et al., 1997). In a study by Günther et al. (2000), thrombophilia was evident in 68% of infants with neonatal AIS compared with 24% of controls (Odds Ratio: 6.7). Along with prothrombotic genetic risk factors, other genetic risk factors may contribute to neonatal AIS. Gelfand et al. (2013) found that children with neonatal AIS were more likely to have the apolipoprotein E ε4 allele than controls but, because of small sample size, the effect did not reach statistical significance. Apolipoprotein E ε4 is a gene expressed in the central nervous system and involved in lipid transport, the metabolism of which has been associated with cerebral palsy and adult stroke (Gelfand et al., 2013). Although genetic conditions have not been highlighted as a salient predictor of neurocognitive risk following pediatric stroke (Fuentes et al., 2016), genetic disorders, especially alongside central nervous system involvement, are associated with neurocognitive implications (Barnes, 2010). Nonetheless, there has been no known investigation into the neurological and neurocognitive sequalae in neonatal AIS samples of children with genetic conditions to date. Review of the differential neurocognitive mechanisms of impact for various genetic conditions was outside the scope of this study. Moreover, only one child in the present study was classified as having a medical comorbidity due to a genetic condition; therefore, extrapolation of the identified main effect of medical comorbidities to genetic conditions is not justified. Within the present study, the identified main effect of medical comorbidities likely reflects the influence of congenital heart disease on neurocognition.

Given the longitudinal design of the present study, a significant interaction between lesion volume and age in neonatal AIS was identified, indicating that lesion volume moderated the rate of neurocognitive change over time. Lesion volume has been identified as a notable risk factor in the existing mixed pediatric stroke literature (i.e., mixed stroke types and age at stroke

onsets; Fuentes et al., 2016). Many studies have indicated an association between larger lesion volume and poorer neurocognitive functioning (Hajek et al., 2014; Levine et al., 2005; Lo et al., 2014). Other studies have failed to identify an association between lesion volume and neurocognitive functioning (Ballantyne et al., 2008); however, this has been largely attributed to methodological factors such as lesion size classification systems varying across studies, in addition to other methodological inconsistencies (Fuentes et al., 2016). Notably, new evidence has pointed to neurological impairment (Hajek et al., 2014) and time since stroke (Levine et al., 2005) as possible moderators of the relationship between lesion volume and neurocognitive outcomes. More specifically, in a sample of children who experienced neonatal and childhood ischemic strokes (excluded presumed perinatal), Hajek et al. (2014) found that larger lesion volume was associated with poorer neurocognitive functioning on a robust composite score (i.e., Wechsler Abbreviated Scale of Intelligence IQ, Full-Scale IQ). They examined neurological impairment using the Pediatric Stroke Outcome Measure; however, an interaction between lesion volume and neurological impairment was only found for the processing speed sub-domain, and thus did not represent a robust moderation of neurocognition spanning various domains such as Full-Scale IQ (Hajek et al., 2014). Nonetheless, stroke volume and Pediatric Stroke Outcome Measure total scores were significantly negatively correlated, suggesting that larger lesions are associated with poorer neurological functioning (Hajek et al., 2014), although further investigation into the impact on neurocognition is warranted.

In contrast, Levine et al. (2005) examined a small sample ($N = 15$) of children and young adults who presented with infantile hemiparesis and were identified as having unilateral lesions (i.e., mixed stroke sample). Although children with larger lesions fared worse than children with smaller lesions on measures of neurocognition when assessed between the ages of 4 and 6 years,

individuals with smaller lesions evidenced greater declines in neurocognitive functioning when assessed again several years later, thus reflecting an interaction between lesion volume and time since stroke (Levine et al., 2005). Levine and colleagues (2005) proposed that larger lesions are associated with more impairing, immediate, and stable neurocognitive deficits, whereas smaller lesions are associated with milder cognitive deficits that emerge over time. These findings reflect differences in the emergence of deficits over time depending on lesion volume, such that deficits emerge more acutely for those with large lesions whereas they take longer to present for those with smaller lesions. These results from a two-time point, incremental design with a mixed sample cannot be directly compared to the findings from the present exclusively neonatal AIS sample which was tested longitudinally at several time points across infancy and early childhood. Nonetheless, children with medium and, most notably, large lesion volumes showed ongoing neurocognitive decline across follow-up in the present study. In contrast, children with small lesion volumes showed neurocognitive gains over time rather than emerging deficits. Of note, Levine et al. (2005) did not specify their lesion size classification systems and only differentiated between small and large lesions; therefore, their findings for small and large lesion volumes cannot be directly compared to the present findings across small, medium, and large volumes.

Within the studies that have explored exclusively neonatal AIS samples, only one focused on the effects of lesion volume on neurocognition (Ricci et al., 2008). Ricci et al. (2008) reported generally normal neurocognitive outcomes in children 5-10 years post neonatal AIS and no association between neurocognitive impairment and extent of tissue affected within the middle cerebral artery territory. However, their sample did not capture the heterogeneity of a typical neonatal AIS sample (no neurological comorbidities, only full-term children, only middle cerebral artery territory infarctions) and primarily involved neurocognitive testing during the

preschool period (~5 years) prior to the hypothesized emergence of deficits in the literature, which may account for the discrepancy with results from the present study (Ricci et al., 2008). Within the studies that have explored neurocognitive outcomes longitudinally, only one considered the effects of lesion volume on neurocognition (Anderson et al., 2020). Notably Anderson et al., (2020) found that larger lesion volume was associated with poorer neurocognition in a mixed sample of perinatal and childhood AIS, when examined longitudinally over a 12-month follow-up period post-stroke.

Within the present study, evaluation of sex, lesion laterality, seizure disorder, and neurological diagnoses yielded non-significant results. In contrast, existing cross-sectional research in heterogenous pediatric stroke samples (i.e., different stroke types and ages at stroke occurrence) has identified sex, lesion laterality, seizure disorder, and neurological impairment as predictors of neurocognition following pediatric stroke more broadly (Fuentes et al., 2016). Pediatric stroke, including neonatal AIS, is known to be sex dimorphic in terms of prevalence, with males showing a predominance (Fullerton et al., 2003; Golomb et al., 2004, 2009). However, many questions remain concerning the possible sex dimorphism of neurocognitive outcomes following pediatric stroke, with evidence that the effects of sex on neurocognitive outcomes are moderated by lesion laterality (Braun et al., 2001). In neonatal AIS exclusive samples, discrepant results have arisen, with some findings of significant effects of sex (Westmacott et al., 2009) and other non-significant effects (McLinden et al., 2007). Specifically, Westmacott et al. (2009) found that males with neonatal AIS displayed a greater decline than females in non-verbal ability between preschool and school age ($p = .01$); however, they identified non-significant results for overall intellectual functioning, consistent with the findings from the present study as well as those of McLinden et al. (2007).

The cross-sectional literature in heterogenous pediatric stroke samples has yielded discrepant findings concerning the influence of lesion laterality on neurocognitive functioning, including investigations primarily regarding the influence of the hemispheric side of the lesion (i.e., right versus left hemispheric strokes) rather than bilateral versus unilateral infarcts (as was the case in the present study; Fuentes et al., 2016). These discrepancies have led investigators to conclude that the relationship between hemispheric side of the lesion and neurocognitive outcome is moderated by age at injury, age at assessment, and the specific cognitive domain being assessed (Stiles et al., 2010; Westmacott et al., 2009, 2010). In one exclusively neonatal AIS sample, children with bilateral lesions were found to have poorer neurocognitive functioning cross-sectionally 2 years post stroke (Grunt et al., 2015), which is inconsistent with the results of the present study. However, Grunt et al. (2015) had a disproportionate representation of unilateral relative to bilateral lesions in their sample (81% versus 19%) which may have skewed their results. Otherwise, McLinden et al. (2007) and Westmacott et al. (2009) did not find a significant effect of hemispheric side (right versus left), and Ricci et al. (2008) could not assess the impact of hemispheric side given imbalanced numbers (i.e., mainly left hemispheric stroke). Evaluating the impact of hemispheric side on neurocognitive outcomes was beyond the scope of the present study, especially given the higher prevalence of left relative to right hemispheric strokes in the sample, and frequent bilateral infarcts.

Previous studies have indicated that seizure disorders are a risk factor for negative neurocognitive outcomes following pediatric stroke (Fuentes et al., 2016). Specifically, past longitudinal analysis of neurocognitive outcomes in children with unilateral perinatal AIS has demonstrated that those with histories of seizures showed less favourable neurocognitive outcomes than children without histories of seizures (Ballantyne et al., 2008). Nonetheless, these

comparison groups had small and unbalanced sample sizes (n = 10 versus n = 19) and included acute neonatal and presumed perinatal stroke types. Of note, children with histories of seizures also displayed different neurocognitive trajectories than children without seizures, with small improvements apparent in the latter group between preschool and school age (Ballantyne et al., 2008). Anderson et al. (2020) also found that the absence of seizures predicted better neurocognition; however, this work included children with histories of both perinatal and childhood AIS. Similarly, Studer et al. (2014) found that overall neurocognitive outcomes were lower post pediatric AIS in children who experienced both acute and persistent seizures. The limited neonatal AIS specific research to date has also indicated that neurocognitive impairments are significantly associated with seizures/symptomatic epilepsy (Grunt et al., 2015; Pavlovic et al., 2006; Ricci et al., 2008), although ongoing research in homogenous samples is warranted. Therefore, the results of the present study potentially indicate lower compounding risk of seizure disorders in exclusively neonatal AIS samples; however, this hypothesis warrants further longitudinal evaluation in homogenous samples.

The cross-sectional literature in heterogenous pediatric stroke samples has consistently identified neurological impairment as a risk factor for negative neurocognitive outcomes following pediatric stroke (Allman & Scott, 2013; Hajek et al., 2014; Studer et al., 2014). Across studies, the definition of what constituted neurological impairment differed, including hemiplegia/paresis or visual field deficits (Allman & Scott, 2013; Studer et al., 2014) and assessment on the Pediatric Stroke Outcome Measure (Hajek et al., 2014). Once again, these methodological differences may account for discrepant results given that neurological diagnoses within the present study included infection, haemorrhage, neonatal hypoxic ischemic encephalopathy, and arterial venous malformation. In exclusively neonatal AIS samples,

perinatal signs of marked neurological impairment (Pavlovic et al., 2006) and hemiplegia (Ricci et al., 2008) have been associated with neurocognitive impairment. Otherwise, neonatal AIS research has indicated that neurocognitive impairments are significantly associated with cerebral palsy (Grunt et al., 2015); however, evaluation of risk associated with cerebral palsy was outside the scope of the present study and represents an area of future research.

Limitations and Future Directions

The present study represents a sizable sample of children with exclusively neonatal AIS; however, for the multi-level growth curve modelling used in this study, the sample size is relatively small. The sample size hindered the ability to evaluate more complex models (i.e., more compounding moderating and main effects) and non-linear trends with sufficient power. Likewise, this study could have benefited from more assessment time points and a longer follow-up interval. Even though this sample had data spanning across one to five assessment time points and across infancy and early childhood (~18 months to 13 years old), most children (~87%) underwent three assessments. As such, the results generally represent follow-up across infancy (~18 months) into the preschool years (~ age 5 years), with less evaluation into childhood when neurocognitive deficits are thought to emerge after neonatal stroke. Overall, assessment of more children over a longer period spanning into middle and late childhood, with more frequent assessment time points would allow for greater power and precision in determining how neurocognition is affected over the course of stroke recovery. Additionally, given that the longitudinal evaluation across infancy into early childhood occurred using the Bayley-III and the Wechsler measures, neurocognition could only be examined across the overarching neurocognitive domain (i.e., Full-Scale IQ) as it is the only comparable index score across both measures (i.e., Cognitive Composite and Full-Scale IQ, respectively). As such, future research

will be required to examine whether the results of the current study, with respect to both rate and predictors of change, generalize to neurocognitive sub-domains (e.g., verbal comprehension, perceptual reasoning, processing speed, working memory) and other neuropsychological domains (e.g., language, memory). Other potential child-related predictors, including risk and protective factors, should also be investigated. Although future research is warranted to replicate the findings related to neurological/stroke-related factors in neonatal AIS samples followed longitudinally, evaluation of potential demographic and psychosocial factors (e.g., parental education, socioeconomic status, income) that may influence neurocognition is also needed and could directly inform intervention planning. Moreover, these investigations should occur longitudinally to enable consideration of interactions among various factors over time.

An additional limitation of the present study is that it did not include a comparison group. The incorporation of age-matched healthy children could account for potential practice effects, and would provide a reference point of normal neurocognitive developmental trajectories. Performance gains may occur due to familiarity associated with repeated test administration, even when assessments are separated by a minimum of one year, as was the case for the present sample. However, the potential confound of repeated testing would be expected to reduce the likelihood of detecting a negative trajectory over time, as in the present study, because the observed trajectories would be more positively inclined. The use of varying measures across follow-up likewise limited the likelihood of artificial performance gains. Nonetheless, the use of standardized values is a limitation because the derivation of standard scores is dependent on the quality of the normative data, which in turn introduces more variability. Nevertheless, standard scores enable a more precise and meaningful comparison of scores across individuals in a sample, accounting for age-related developmental changes. Despite the limitations noted, this

study comprised a novel and innovative design including comprehensive methodological follow-up across infancy and early childhood at multiple time points spanning critical developmental periods in an exclusively neonatal AIS sample. Therefore, this represents the first longitudinal evaluation of neurocognition and related risk factors in neonatal AIS.

Implications and Conclusions

This is the first study to examine longitudinal neurocognitive trajectories for children who have experienced neonatal AIS. There was evidence of neurocognitive decline across infancy and early childhood, in keeping with an early vulnerability hypothesis of brain recovery. As such, these findings call into question the belief that infancy is a period in which neuroplasticity can offset the potential consequences of central nervous system damage. Moreover, medical comorbidities, including congenital heart disease and genetic conditions, contributed to lower neurocognition statistically extrapolated at stroke occurrence. Larger lesion volume was associated with greater neurocognitive decline. This study highlights the importance of longitudinal follow-up in this population to elucidate stroke recovery mechanisms, and the variability that exists after neonatal AIS. As such, children with neonatal AIS should undergo routine neuropsychological assessments across critical developmental periods, especially as they experience heightened cognitive and academic demands with age. Advanced modelling methods, as those employed in this study, are essential to capture the interplay between brain recovery after early insult and the complex neurodevelopmental course. Trajectory modelling reveals various pathways for recovery and development and helps determine which factors influence alternative pathways. Clinically, improved understanding of predictors of neurocognitive trajectories will inform the early identification of high-risk groups and the development of precision-based interventions.

LAYING THE FOUNDATION FOR STUDY 2

In Study 1, neurocognitive trajectories were examined, including predictors of heterogeneity, across infancy and early childhood post neonatal AIS. Study 2 has similar objectives but expanded upon Study 1 in numerous ways. First, Study 2 captured a larger and more diverse sample relative to Study 1, including 208 children who experienced perinatal AIS, spanning both neonatal AIS and presumed perinatal AIS diagnoses. Additionally, while Study 1 examined trajectories across infancy and early childhood, Study 2 involved more comprehensive longitudinal modelling across early and late childhood, adolescence, and early adulthood. Study 2 is thus the first study to examine neurocognition longitudinally as it emerges across several developmental stages. The sample in Study 2 comprised children who received neuropsychological assessment(s) through the Children's Stroke Program. Although some children also received psychological assessment(s) through the Neonatal Neurodevelopmental Follow-up Clinic at The Hospital for Sick Children, this was not a mandatory inclusion criterion for Study 2, as was the case in Study 1. This extended the cohort from Study 1 to include children seen prior to 2009 when the Neurodevelopmental Follow-up Clinic began routinely conducting psychological assessments for infants who had experienced strokes, and thus represents a more diverse cohort with more assessment time points across a longer period of developmental follow-up (i.e., into late childhood, adolescence, and early adulthood). Given the larger sample and extended follow-up period, more complex models could be examined with heightened statistical power, including quadratic trends and compounding moderating and main effects which are likely more representative of change over time following perinatal AIS.

Given that follow-up in Study 1 spanned infancy and early childhood, different measures were employed, as appropriate for each developmental stage (i.e., Bayley-III and Wechsler

measures). In contrast, follow-up in Study 2 spanned early and late childhood, adolescence, and early adulthood; therefore, only Wechsler tests were utilized. The use of comparable measures enabled more accurate longitudinal evaluation since the measures had various equivalent index scores. A such, rather than being limited to evaluating overall neurocognition exclusively (i.e., Full-Scale IQ), as was the case in Study 1, longitudinal trajectories of overall neurocognition (i.e., Full-Scale IQ), as well as related sub-domains (i.e., Verbal Comprehension Index, Perceptual Reasoning Index, Processing Speed Index, Working Memory Index), were all examined in Study 2. Within Study 1 and Study 2, sex, lesion volume, lesion laterality, neurological diagnoses, and medical comorbidities were examined as potential predictors based on the research to date. Study 2 expanded upon Study 1 in that additional predictors were also explored. Namely, neurocognitive trajectories were compared for children who experienced neonatal relative to presumed perinatal AIS by examining perinatal AIS type as a potential predictor. This represents a novel research question that has not been explored systematically in the literature to date. Of note, all children eligible for inclusion in Study 1 were also eligible for inclusion in Study 2; therefore, Study 1's sample represents a sub-sample of children from Study 2 who had experienced neonatal AIS and received early screening through the Neonatal Neurodevelopmental Follow-up Clinic. The presence of early screening was examined as a potential predictor in Study 2 for children with neonatal AIS. Examining the role of early screening represents emerging research into the role of protective factors, and early intervention specifically, within this population, moving beyond the restricted focus on risk factors to date.

STUDY 2:

A LONGITUDINAL LENS – PREDICTORS OF LONGITUDINAL NEUROCOGNITIVE TRAJECTORIES ACROSS EARLY AND LATE CHILDHOOD, ADOLESCENCE, AND EARLY ADULTHOOD IN PERINATAL ARTERIAL ISCHEMIC STROKE

Introduction

The most focused lifetime risk of stroke is the week surrounding birth (Mineyko & Kirton, 2011), with arterial ischemic stroke (AIS) the most common stroke subtype (i.e., ~two-thirds) during this period (1/2500-4000 live births; Agrawal et al., 2009; DeVeber & Canadian Paediatric Ischemic Stroke Study Group, 2000). Perinatal AIS includes strokes having occurred between 20 weeks gestation and 28 days postnatally (Lynch et al., 2002) and encompasses two categories based on the timing of stroke presentation: A) acute neonatal AIS involves an acute presentation in the neonatal period, often with symptomatic seizures rather than focal neurological deficits (Kirton & deVeber, 2009); and B) presumed perinatal AIS involves a presentation later in the first year, often with hemiparesis and retrospective diagnosis by the presence of a chronic infarct on neuroimaging (Kirton & deVeber, 2009). Although mortality rates are low (3%) in perinatal AIS (Beslow et al., 2018), children are known to experience significant neurological and neurodevelopmental deficits (Kirton & De Veber, 2013). Nonetheless, there have been discrepant results regarding long-term neurocognitive functioning after perinatal AIS (i.e., general thinking abilities). This discrepancy is attributed to numerous methodological limitations, most notably a lack of longitudinal evaluation across homogenous samples and critical development periods. As such, the purpose of the present study was to determine longitudinal neurocognitive trajectories and relevant predictive factors across early to

late childhood, adolescence, and early adulthood following perinatal AIS, including comparison between perinatal AIS types, and consideration of the influence of early screening in infancy.

With respect to neurological functioning post perinatal AIS, 37-62% of children experience neurological deficits, including seizures/epilepsy and motor (e.g., hemiparesis, cerebral palsy) and sensory impairments (DeVeber et al., 2000; Kolk et al., 2011; Pavlovic et al., 2006; Tuckuviene et al., 2011). Likewise, after perinatal AIS, many children live with broad neurodevelopmental deficits, including delays in speech and language (Ballantyne et al., 2007, 2008; Golomb et al., 2001; Lee et al., 2005; Reilly et al., 2013; Trauner et al., 1996), behavioural functioning (Golomb et al., 2001; Kirton et al., 2008; Lee et al., 2005), learning/academic skills (Chabrier et al., 2016; Trauner & Mannino, 1986), as well as higher-level neuropsychological capacities (Kolk et al., 2011). With respect to neurocognitive functioning/thinking skills post perinatal AIS, cross-sectional research has yielded discrepant results. Some studies have suggested age appropriate functioning (Chabrier et al., 2016; Cioni et al., 1998; Hetherington et al., 2005; Pavlovic et al., 2006; Ricci et al., 2008; Schatz et al., 2000; Trauner et al., 1993; Wulfeck et al., 1991), whereas others have revealed neurocognitive deficits (Ballantyne et al., 1994; Grunt et al., 2015; McLinden et al., 2007; Talib et al., 2008; Trauner et al., 2001; Westmacott et al., 2010). There has been additional uncertainty regarding the prevalence (11-41%) and severity of such neurocognitive deficits (DeVeber et al., 2000; Golomb, 2009; Golomb, Saha, et al., 2007; Härtel et al., 2004; Kirton et al., 2008; Sreenan et al., 2000). The few longitudinal studies that have been conducted have also yielded discrepant results (Anderson et al., 2020; Aram & Eisele, 1994; Ballantyne et al., 2008; Gonzalez-Monge et al., 2009; Levine et al., 2005; Muter et al., 1997; Westmacott et al., 2009). These discrepancies are attributed to methodological heterogeneity, including short/varying test-retest intervals, small cohort sizes,

varying ages at assessment, differing/non-standardized measures, limited follow-up, and mixed samples (different stroke subtypes/ages at stroke; Ballantyne et al., 2008; Greenham et al., 2017; Levine et al., 2005; McLinden et al., 2007).

To date, no research has characterized neurocognitive trajectories in perinatal AIS with comprehensive follow-up at several time points across early and late childhood as well as adolescence and emerging adulthood, spanning critical developmental periods. This study served to fill this critical gap. Predicting outcomes after perinatal stroke relies not only on how a stroke affects the structure and function of the brain, but also on the interacting mechanisms of plasticity and brain recovery post stroke. As such, inquiry into neurocognitive trajectories exists across a backdrop of competing theoretical perspectives regarding mechanisms of stroke recovery in individuals having experienced early brain injury. On one hand, there is a longstanding theory that early injury has *less* of an effect on long-term outcomes than injury later in life because of the capacity of the developing brain to "heal" or compensate (i.e., younger brains recover better than older brains; "Kennard principle" or "early plasticity hypothesis"; Ballantyne et al., 2008; Dennis, 2010; Kennard, 1936; Kim et al., 2009). This theory has been supported by investigations into the mechanisms of plasticity through which a child's developing brain is more capable of reorganization and recovery after an insult relative to an adult brain.

There is a competing theory suggesting that the developing brain is *more* susceptible to injury (i.e., "early vulnerability hypothesis"), positing that outcomes are worse if early brain injury affects an ability/capacity before it has been fully established (Anderson et al., 2011; Chugani et al., 1996). It is argued that, when injury occurs later in childhood, the brain can accommodate to "repair" that preexisting ability and harness redundant pathways in the brain which have already been established. In contrast, if injury occurs earlier in childhood, initial

development is disrupted, which is thought to be harder to overcome (Westmacott et al., 2010). In this way, although the extent of functional impairments may not be immediately apparent, children may fail to make age-appropriate developmental gains or seemingly "grow into" new deficits over time (Anderson et al., 2011; Gordon et al., 2015; Westmacott et al., 2009). More specifically, the plasticity of the brain is thought to accommodate early developmental capacities but, with the increasing demands of more complex skills and the need to process information in a more complex and efficient manner, the biological reserve is no longer sufficient, and deficits are thought to be revealed with age (Anderson et al., 2005; Dennis, 2000). Therefore, a child with no deficits in their preschool years may manifest deficits when they reach school age and are challenged with tasks of advanced proficiency, highlighting a need for longitudinal evaluation that considers the effect of age/time at testing. Presenting additional complexity, these competing theoretical perspectives of 'early plasticity' and 'early vulnerability' represent extremes along a 'recovery continuum', with additional influence of injury (e.g., injury severity, nature of injury, age) and environmental (e.g., family, sociodemographic, intervention) factors that warrant investigation as potential risk and protective factors with nuanced consideration of interaction/moderating effects across development (Anderson et al., 2011).

As discussed, many studies on outcomes following perinatal strokes have focused on the emergence of neurocognitive challenges cross-sectionally, which does not enable measurement of change over time. Even the few extant longitudinal studies have primarily explored neurocognition across two time points with small sample sizes to conceptualize change as an *increment*; however, this approach cannot describe individual trajectories of change and confounds true change with measurement error (Rogosa et al., 1982). Longitudinal neurocognitive trajectory modelling is needed to understand whether early deficits resolve,

remain stable, or become more pronounced over time (Singer & Willett, 2009). Growth curve modeling (Bryk & Raudenbush, 1987; Rogosa & Willett, 1985) is a flexible method for the analysis of longitudinal trajectory data which provides information about 1) how an outcome changes over time with respect to both the rate of change and level (i.e., within-individual change over time), and 2) how certain predictors may moderate change for individual participants (i.e., predictors of inter-individual differences in change; Singer & Willett, 2009). Growth curve modeling offers several advantages over traditional methods for analyzing longitudinal data in that it can accommodate a unique number of time points/assessments per individual (i.e., *imbalanced* data) as well as data collected at unique measurement intervals based on individual need (i.e., *time-unstructured* data; Singer & Willett, 2003). The present study is the first known evaluation to harness these statistical techniques to provide analyses of longitudinal neurocognitive trajectories, and predictors of heterogeneity, across early to late childhood, adolescence, and early adulthood following perinatal AIS, and to elucidate recovery mechanisms.

In considering predictors of neurocognitive outcomes having been explored to date, age at stroke, time since stroke, sex, etiology, lesion characteristics (location, laterality, volume), neurological impairment, and seizures have been found to impact neurocognition (uniquely for different domains) post pediatric stroke (Fuentes et al., 2016). Several interaction effects have been found, including between age at stroke and lesion location, lesion characteristics (volume, location) and neurological impairment, lesion volume and time since stroke, sex and lesion laterality, and seizures and time since stroke (Fuentes et al., 2016). Little research has explored the interactions between these factors and neurocognition over long-term trajectories. Likewise, existing literature on predictors of neurocognition has encompassed heterogenous samples spanning various pediatric stroke types (e.g., hemorrhagic, arterial ischemic, cerebral sinovenous

thrombosis) and ages at stroke occurrence (e.g., neonatal, perinatal, childhood stroke); therefore, these findings cannot be generalized to exclusively perinatal AIS samples. Moreover, given that postnatal brain development is rapid in the first few months of life (Bullins et al., 2016; McCain, 2020), the impact of perinatal AIS and relevant predictors may vary considerably depending on the time of stroke onset and neurological symptom presentation within the first six months. Outcome and predictor studies have combined children with neonatal and presumed perinatal AIS (Ballantyne et al., 2008; Banich et al., 1990; Levine et al., 2005; Muter et al., 1997; Stiles et al., 2003; Trauner et al., 1993), which is problematic methodologically as children with presumed perinatal AIS are typically diagnosed when neurological deficits are severe (e.g., hemiparesis). Likewise, preliminary findings, and clinical observations, have alluded to worse outcomes in presumed perinatal relative to neonatal AIS subtypes (Lee et al., 2005). Systematic comparison between neonatal and presumed perinatal AIS samples is warranted, alongside consideration of relevant risk as well as protective factors. More specifically, consideration of the influence of early screening in infancy as a protective factor, especially for individuals who experience brain injury early in infancy, is a notable gap in the literature. Given the rapid early development and neuroplasticity in the infancy and early childhood periods (Galván, 2010; McCain, 2020), screenings and full assessments early in development have the potential to identify high risk groups and inform precision-based interventions that can alter neurodevelopmental trajectories (Anderson et al., 2000; Anderson et al., 2001; Famri et al., 2007; Max et al., 2003; Nass, 1997). Nonetheless, to date, no research has evaluated the influence of early screening in infancy as a protective factor in children who experienced perinatal AIS. This study addressed these critical research gaps.

Research Objectives

Throughout this study, the primary objectives were to (1) investigate longitudinal patterns of neurocognitive growth trajectories, and (2) related heterogeneity, for individuals with perinatal AIS (i.e., neonatal and presumed perinatal diagnoses) across early to late childhood, adolescence, and early adulthood. First, it was hypothesized that individuals with perinatal AIS would show emerging neurocognitive deficits across development. Second, it was hypothesized that growth trajectories would indicate variability with respect to individuals' scores and the rate of change over time, which may be predicted by clinically meaningful variables. To further examine potential heterogeneity, a secondary objective was to (3) examine the main and moderating effects of predictor variables on the neurocognitive growth trajectories. Given the paucity of prior longitudinal research on this topic, there were no specific hypotheses and instead an exploratory analytical approach was taken. Given previous research findings in mixed samples using cross-sectional methods, male sex and more extensive neurological (i.e., larger lesions, bilateral infarcts, other neurological diagnoses) and medical (i.e., medical comorbidities) involvement were expected to have a negative impact on the neurocognitive profiles and progressions.

Additional exploratory analyses were carried out to examine other secondary objectives. Namely, (4) neurocognitive growth trajectories were compared for individuals who experienced neonatal (acute diagnosis) relative to presumed perinatal (retrospective diagnosis) AIS. Again, given limited existing research on this topic, there were no specific hypotheses and an exploratory approach was taken. However, preliminary findings and clinical observations have indicated poorer outcomes for presumed perinatal relative to neonatal AIS. Lastly, (5) among individuals who experienced neonatal AIS, neurocognitive growth trajectories were compared

for those who received early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic relative to those who did not (i.e., seen prior to the commencement of routine psychological assessments in 2009). It was hypothesized that individuals who received early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic would demonstrate superior neurocognitive trajectories given their early identification of neurocognitive needs.

Method

Study Design and Participant Recruitment

The sample for this longitudinal, retrospective cohort study was drawn from the Neonatal Neurodevelopmental Follow-up Registry and the Children's Stroke Outcome Registry at The Hospital for Sick Children in Toronto, Canada. To meet the inclusion criteria for this study, participants had to have: (1) an AIS conforming to established arterial territories with radiological documentation on MRI or CT and confirmed by hospital neurologists in the Stroke Clinic; (2) a history of perinatal AIS including diagnosis acutely in the neonatal period (neonatal AIS: <28 days of life) or retrospectively (presumed perinatal AIS; ≥29 days of life); and (3) undergone neuropsychological assessment(s) through the Children's Stroke Program from age 2.5 years until discharge from programming with available neurocognitive information. Given the preliminary and exploratory nature of this study, no individuals were excluded from analyses.

Procedures

The study was approved by the Research Ethics Board at The Hospital for Sick Children, Toronto and York University, Toronto. Individuals and caregivers provided informed assent/consent for use of their health and medical information from standard clinical care appointments as part of their enrollment in the Neonatal Neurodevelopmental Follow-up Study

and the Children's Stroke Outcome Study. All neuroimaging was reviewed by hospital neurologists as part of standard clinical care. Neuropsychological assessment reports and related psychology files were reviewed for specific neurocognitive information. Individuals who are seen through the Children's Stroke Program are routinely referred for neuropsychological assessment at school entry (~3-4 years of age) and seen for follow-up assessments across development on a regular basis, regardless of their neurocognitive profile. This means of follow-up across early and late childhood, adolescence, and early adulthood at our centre reduces referral biases and enables long-term neurocognitive outcomes to be evaluated within the pediatric stroke population. Although some children with neonatal AIS also received psychological assessment(s) through the Neonatal Neurodevelopmental Follow-up Clinic at The Hospital for Sick Children in infancy, this was not a mandatory inclusion criterion, and these assessments were not included in the longitudinal analyses. Instead, a small sub-sample of the larger cohort underwent early screening which was explored as a predictor variable.

Demographic and Clinical Characteristics

Demographic characteristics of participants included in the study were obtained from the registry databases which included data obtained from standardized review of health records, a structured parent interview, and a medical and neuropsychological history questionnaire completed by parents. This information included biological sex (male/female) and prematurity status (≤36 weeks gestational age). Seizure disorder at the time of the assessment was coded dichotomously (presence/absence of a seizure disorder) and did not include isolated observations of seizures within the neonatal period which were used as clinical indication for imaging and subsequent acute neonatal AIS diagnoses. Perinatal AIS type (neonatal versus presumed perinatal) was distinguished based on timing of AIS diagnosis (acutely versus retrospectively).

Age at neuropsychological assessment (years) was measured continuously based on the date of neurocognitive testing.

Early screening through the Neonatal Neurodevelopmental Follow-up Clinic involved psychological assessment(s) at 18- and/or 36-month visits for children born after January 2009 as that was when the Neonatal Neurodevelopmental Follow-up Clinic began routinely conducting psychological assessment for infants who had experienced strokes. This early screening was only available for a sub-sample of children with neonatal AIS who presented with symptoms acutely at birth. Neurological diagnoses and medical comorbidities were also collected to capture other relevant conditions, in addition to perinatal AIS. Although the presence of other neurological diagnoses and medical comorbidities may further impact neurocognition beyond the influence of AIS alone, individuals with other conditions were not excluded from analyses given the preliminary and exploratory nature of this study. Neurological and medical comorbidities were, however, explored as potential predictors of neurocognitive trajectories. For statistical analyses, these variables were collapsed into dichotomous categories (presence/absence of neurological or medical diagnoses) to increase statistical power.

Lesion Characteristics

Determination of lesion location, size, and laterality was made by the study neuropsychologists and neurologists based on systematic reviews of clinically acquired neuroimaging and official radiology and neurology reports. Lesion location was categorized as cortical (infarct with no subcortical involvement), subcortical (infarct with no cortical involvement), combined (infarct with both cortical and subcortical involvement), cerebellar, brainstem, and/or white matter (not mutually exclusive categories). Lesion volume was coded using the following definitions: Small – involving less than one-third of total volume of a single

lobe or major subcortical structure; Medium – involving from one-third to two-thirds of the volume of a single lobe or major subcortical structure OR involving less than half of the volume of two or more lobes/subcortical structures; Large – involving greater than two-thirds of the volume of one lobe or major subcortical structure OR involving greater than half of the volume of two or more lobes/subcortical structures. Lesion laterality was coded categorically as left, right, or bilateral; however, for relevant analyses these were collapsed into dichotomous categories (unilateral/bilateral) to increase statistical power. Other pediatric stroke studies have used similar coding schemes in the past (Westmacott et al., 2010; Williams et al., 2017).

Neurocognitive Functioning

During the neuropsychological assessments that took place through the Children's Stroke Program, neurocognitive functioning was assessed using Wechsler cognitive tests. Given that this study used retrospective data collected longitudinally across a wide age span, some individuals received different versions of the Wechsler tests. As preschoolers (~age 2.5-6 years), children completed the Wechsler Preschool and Primary Scale of Intelligence, spanning across the Revised Edition (WPPSI-R; Wechsler, 1989), Third Edition (WPPSI-III; Wechsler, 2002), and Fourth Edition (WPPSI-IV; Wechsler, 2012). As school-age students (~age 6-16 years), children completed the Wechsler Intelligence Scale for Children, spanning across the Third Edition (WISC-III; Wechsler, 1991), Fourth Edition (WISC-IV; Wechsler, 2003), and Fifth Edition (WISC-V; Wechsler, 2014), or children completed the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). As adolescents and emerging adults (~age 16+ years), the Wechsler Adult Intelligence Scale was completed, spanning across the Third Edition (WAIS-III; Wechsler, 1997) and Fourth Edition (WAIS-IV; Wechsler, 2008), or the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was completed.

The Wechsler tests all provide index scores for overall neurocognitive functioning (i.e., Full-Scale IQ). Overall index scores of neurocognition are known to be the most representative indicator of global intellectual functioning. Additionally, the Wechsler tests have primary index scores which contribute to the overall neurocognitive score. The index scores are all calculated as standard scores with a mean of 100 and a standard deviation of 15. Scores between 90 and 110 fall within the "average range" clinically. To superimpose longitudinal results across the various psychological measures and editions used across differing age ranges, an overarching neurocognitive domain score (i.e., Full-Scale IQ) and related sub-domain scores (i.e., Verbal Comprehension Index, Perceptual Reasoning Index, Processing Speed Index, Working Memory Index) were assigned based on equivalent index scores (see Table 6 for details); only available results pertaining to these domains were included for analysis. This approach aligns with typical practice in longitudinal clinical neuropsychological research (see Westmacott et al., 2009). All neurocognitive testing was conducted by experienced psychometrists supervised by clinical neuropsychologists. Of note, any declines or improvements reflected over time do not pertain to raw test scores but rather to standardized test scores which enable a more precise and meaningful comparison of scores across individuals in a sample, accounting for age-related developmental changes. As such, declines in standardized test scores do not necessarily reflect an actual loss in individual-level neurocognitive ability over time, rather, a decline could reflect a delayed development compared to typically developing age-matched peers, a plateau in development, or a loss of skills. Similarly, improvements in standardized test scores reflect faster gains over time relative to healthy, age-matched peers diverging positively away from the norm.

Table 6

Overarching Neurocognitive Domains Across Differing Psychological Measures of Varying Editions for Different Ages

Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R/III/IV) Age 2:6-7:7[a]	**Wechsler Intelligence Scale for Children** (WISC-III/IV/V) Age 6-16	**Wechsler Adult Intelligence Scale** (WAIS-III/IV) Age 16-90[a]	**Wechsler Abbreviated Scale of Intelligence** (WASI) Age 6-89	**Neurocognitive Domains and Descriptions**	
Full-Scale IQ	Full-Scale IQ	Full-Scale IQ	Full-Scale IQ	Full-Scale IQ	Overall cognitive ability
Verbal IQ/Verbal Comprehension Index	Verbal IQ/Verbal Comprehension Index	Verbal IQ/Verbal Comprehension Index	Verbal IQ	Verbal Comprehension Index	Verbal reasoning
Performance IQ/Visual Spatial Index/Visual Spatial Index merged with Fluid Reasoning Index[b]	Performance IQ/Perceptual Reasoning Index/ Visual Spatial Index merged with Fluid Reasoning Index[b]	Performance IQ/ Perceptual Organization Index/Perceptual Reasoning Index	Performance IQ	Perceptual Reasoning Index	Abstract and visual-spatial reasoning
Processing Speed Quotient/ Processing Speed Index	Performance Speed/Processing Speed Index	Processing Speed Index	–	Processing Speed Index	Speed of mental processing
Working Memory Index	Freedom from Distraction/Working Memory Index	Working Memory Index	–	Working Memory Index	Mental maintenance and manipulation of information

Note. [a] Age range differs for different editions of this measure, the most comprehensive range is shown. [b] The Visual Spatial Index and Fluid Reasoning Index scores will be merged to contribute to the equivalent Perceptual Reasoning Index overarching score.

Statistical Analyses

Neurocognitive functioning as well as lesion, demographic, and clinical characteristics were analyzed using descriptive statistics. Normally distributed continuous variables were reported as means ± standard deviation (SD); otherwise, medians and interquartile ranges (IQR) were reported. Categorical variables were reported using frequency distributions and proportions. All statistical analyses were conducted in RStudio (RStudio Team, 2019) using two-tailed tests performed at the 0.05 level of significance. Growth curve models were estimated using the mixed-effects modeling approach implemented with the lme function from the nlme package (Pinheiro et al., 2022). Individual profile trajectories for each participant were visualized using empirical growth plots and non-linear effects of time were observed; therefore, quadratic growth models were estimated for the overarching neurocognitive domain and sub-domain scores. Unconditional growth models were first estimated to describe within-subjects initial status and rate of change of the overarching neurocognitive domain and sub-domain scores over multiple time points.

Conditional models were then estimated for the longitudinal overarching neurocognitive outcome (Full-Scale IQ) to assess the impact of covariates on the intercepts as well as the linear and quadratic components of the trajectory (i.e., main and moderating effects). The conditional models were compared to the respective unconditional models to examine for potentially improved model fit. Separate conditional models were fit for each of the time-invariant covariates (sex, lesion volume, lesion laterality, seizure disorder, other neurological diagnoses, medical comorbidities), with particular focus on whether there was an interaction between time and the covariate (including different levels of the covariate), which would indicate that the covariate moderated neurocognitive change over time (i.e., influenced the linear and/or quadratic

components of the Full-Scale IQ trajectory). The interaction terms within these models implicitly included the main effects of the covariates, and thus individual main effect terms were not specified for these covariate-specific quadratic models. Only variables with exclusive categories could be examined as covariates (i.e., not lesion location). Likewise, variables with insufficient sample representation (i.e., prematurity status) were not included to avoid underpowered analyses. Using exploratory methods, any models with significant moderating effects of covariates were expanded upon to examine potential main effects of the remaining covariates on Full-Scale IQ. Potentially improved model fit was examined for these expanded conditional models relative to the initial conditional model. In this way, taking an exploratory approach, a finalized conditional model was established for the robust overarching neurocognitive domain (Full-Scale IQ). That finalized conditional model was then examined directly for the related neurocognitive sub-domains (Verbal Comprehension Index, Perceptual Reasoning Index, Processing Speed Index, Working Memory Index) given known conceptual overlap between the overarching domain and the sub-domains. The conditional models for the sub-domains were compared to the respective unconditional models to examine for potentially improved model fit. This avoided repeated exploratory analyses that would unnecessarily increase Type 1 error rates.

To address the secondary objectives, separate conditional models were estimated for the overarching neurocognitive outcome (Full-Scale IQ) to assess the potentially moderating role of perinatal AIS type as well as access to early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic (in a neonatal AIS specific sub-sample) on the linear and quadratic components of the trajectories. Those results informed whether the covariates would be included as a moderator (if a significant moderation was found) or as a potential main effect (if no significant moderation was found) within the final conditional model that was established for

the robust overarching neurocognitive domain in the previous analyses. Potentially improved model fit was examined for these models relative to the initial conditional models, when possible, for comparable models. These secondary objectives were only examined for the overarching neurocognitive domain (Full-Scale IQ), rather than the neurocognitive sub-domains, given that Full-Scale IQ is most robust and had the most observations available. In this way, repeated exploratory analyses and increased Type 1 error rates were avoided, which would have resulted alongside increased model complexity and reduced sample size for analyses with the neurocognitive sub-domains.

For all conditional models, age (in years) was used as the measure of time given that all participants experienced AIS within the perinatal period, with comparable durations since stroke upon which to examine neurocognitive change. Quadratic growth curve modelling comprises three main factors: (1) the *"random intercept"*, which represents the initial status, or level, of the neurocognitive outcome at time zero (i.e., time of stroke occurrence/birth), which is statistically extrapolated rather than an objective data point; (2) the *"random linear slope"*, which represents the rate of linear change, per year, in neurocognition from the time of stroke occurrence; and (3) the *"random quadratic slope"*, which represents the curvature or deceleration/acceleration in the neurocognitive trajectory over time. Growth curve modelling can accommodate unbalanced and time-unstructured data without imputing missing data such that growth records can contain a unique number of assessments at unique measurement intervals.

Results

Study Cohort

A total of 435 participants with AIS were enrolled in the Children's Stroke Outcome Study. Only 215 had AIS diagnosed in the perinatal period (acute neonatal or presumed perinatal

diagnoses). Only 208 underwent neuropsychological assessment(s) through the Children's Stroke Program at age 2.5 years until discharge from programming with available neurocognitive information. As such, a total of 208 individuals met all the inclusion criteria for the present study.

The sample had generally equal representation of male (*n* = 119; 57.21%) and female individuals. A small proportion of individuals were born prematurely (*n* = 22; 10.58%) and had a seizure disorder at the time of assessment (*n* = 40; 19.23%; Table 7). This sample of individuals with perinatal AIS encompassed slightly more neonatal (59.62%) relative to presumed perinatal (40.38%) diagnoses. Of those with neonatal AIS, approximately one third (32.26%) underwent early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic in infancy. Across the full perinatal AIS sample, lesions were mostly located in cortical (65.07%), white matter (59.90%), combined cortical and subcortical (29.95%), and subcortical (23.45%) regions (not mutually exclusive), with fewer lesions exclusively in cerebellar and brainstem regions. Lesion volume was primarily in the medium (*n* = 93; 46.04%) to large (*n* = 62; 30.69%) range, with fewer small volume lesions. Most of the strokes were unilateral (*n* = 179; 86.06%) rather than bilateral in nature, of which, approximately twice as many were left-hemispheric (*n* = 118; 65.92%) than right-hemispheric. In addition to having experienced a perinatal AIS, a small portion of the sample had also been diagnosed with other relevant neurological (*n* = 18; 8.65%) and medical (*n* = 28; 13.46%) conditions, as specified in Table 7.

Table 7

Demographic, Lesion, and Clinical Characteristics (N = 208)

	n (%)
Sex, male	119 (57.21)
Prematurity (≤36 weeks gestational age)	22 (10.58)
Perinatal AIS type	
Neonatal AIS	124 (59.62)
Early screening[a]	40 (32.26%)

Presumed perinatal AIS	84 (40.38)
Seizure disorder current	40 (19.23)
Lesion location[b]	
Cortical	95 (65.07)
Subcortical	34 (23.45)
Cortical and subcortical[c]	62 (29.95)
Cerebellum	7 (3.38)
Brainstem	2 (0.97)
White matter	124 (59.90)
Lesion volume	
Small	47 (23.27)
Medium	93 (46.04)
Large	62 (30.69)
Lesion laterality	
Unilateral	179 (86.06)
Right	61 (34.08)
Left	118 (65.92)
Bilateral	29 (13.94)
Other neurological diagnoses	18 (8.65)
Haemorrhage	6 (2.88)
Neonatal hypoxic ischemic encephalopathy	4 (1.92)
Infection	2 (0.96)
Periventricular leukomalacia	2 (0.96)
Moya Moya disease	1 (0.48)
Arterial venous malformation	1 (0.48)
Concussion	1 (0.48)
Hematoma	1 (0.48)
Hydrocephalus	1 (0.48)
Microcephaly	1 (0.48)
Craniosynostosis	1 (0.48)
Medical comorbidities	28 (13.46)
Congenital heart disease	23 (11.06)
Genetic	4 (1.92)
Substance exposure	1 (0.48)
Trauma	1 (0.48)
Metabolic	1 (0.48)
Renal failure	1 (0.48)

Note. [a] Only available for those who experienced neonatal AIS; early screening through the Neonatal Neurodevelopmental Follow-up Clinic. [b] Not mutually exclusive. [c] Mutually exclusive from individual cortical and subcortical categories.

Of the 208 participants, 101 completed one (M_{age1} = 5.35, *IQR*: 4.39 - 7.86), 57 completed two (M_{age2} = 8.39, *IQR*: 6.75 - 10.39), 28 completed three (M_{age3} = 11.83, *IQR*: 9.44 - 13.66), 17 completed four (M_{age4} = 13.93, *IQR*: 12.38 - 17.34), 4 completed five (M_{age5} = 17.53, *IQR*: 17.11 - 17.68), and 1 completed six (M_{age6} = 13.90, *IQR*: 13.90 - 13.90) assessments across the study period (Table 8). All assessment time points involved neurocognitive assessments using Wechsler cognitive tests through the Children's Stroke Program. Additional neurocognitive assessment details are shown in Table 8.

Table 8

Neurocognitive Assessment Details

	Assessment Time Points					
	1	2	3	4	5	6
Proportion of full sample, *n* (%)	208 (100)	107 (51.44)	50 (24.04)	22 (10.58)	5 (2.40)	1 (0.48)
Assessment measure, *n* (%)						
WPPSI-R/III/IV[a]	134 (64.42)	15 (14.02)	1 (2.00)	–	–	–
WISC-III/IV/V[b]	69 (33.17)	87 (81.31)	44 (88.00)	13 (59.09)	1 (20.00)	1 (100.00)
WAIS-III/IV[c]	5 (2.40)	4 (3.74)	3 (6.00)	8 (36.36)	4 (80.00)	–
WASI[d]	–	1 (0.93)	2 (4.00)	1 (4.55)	–	–
Median [interquartile range] age at assessment, years	5.35 [4.39, 7.86]	8.39 [6.75, 10.39]	11.83 [9.44, 13.66]	13.93 [12.38, 17.34]	17.53 [17.11, 17.68]	13.90 [13.90, 13.90]
Mean [±standard deviation] Full-Scale IQ at assessment, standard scores	88.40 [±18.94]	84.81 [±20.65]	80.15 [±17.33]	77.67 [±13.27]	76.00 [±9.06]	81.00 [±0.00]
Mean [±standard deviation] Verbal Comprehension Index at assessment, standard scores	90.84 [±18.46]	88.99 [±19.73]	86.57 [±16.05]	85.19 [±13.75]	79.20 [±14.02]	79.00 [±0.00]
Mean [±standard deviation] Perceptual Reasoning Index at	86.89 [±17.41]	86.26 [±19.98]	81.05 [±17.14]	81.55 [±14.56]	85.20 [±11.43]	100.00 [±0.00]

assessment, standard scores						
Mean [±standard deviation] Processing Speed Index at assessment, standard scores	89.74 [±18.41]	84.52 [±19.90]	80.32 [±16.76]	75.60 [±12.76]	81.80 [±11.12]	73.00 [±0.00]
Mean [±standard deviation] Working Memory Index at assessment, standard scores	92.76 [±18.93]	87.46 [±20.53]	82.33 [±16.17]	84.52 [±19.99]	75.60 [±12.44]	86.00 [±0.00]

Note. [a] WPPSI = Wechsler Preschool and Primary Scale of Intelligence. [b] WISC = Wechsler Intelligence Scale for Children. [c] WAIS = Wechsler Adult Intelligence Scale. [d] WASI = Wechsler Abbreviated Scale of Intelligence.

Visual inspection of individual growth trajectories revealed considerable variability with respect to both individuals' initial scores and how scores changed over time. Some individuals showed decline, some showed improvement, and others showed a more stable pattern, although the trajectories all showed a non-linear form. Variability in initial status and rate of change was explicitly modeled by the growth curve analyses.

Objective 1 and 2: Neurocognitive Growth Trajectories and Heterogeneity

Within the unconditional means models (Table 9), which did not include time as a predictor of change, mean initial neurocognitive status, as determined by the means of the random intercepts, ranged from 86.57 to 90.72 (standard scores) across all neurocognitive domains. These values indicated that, when baseline neurocognitive scores (Full-Scale IQ and related sub-domains) were statistically extrapolated at stroke occurrence (i.e., at birth; time point 0) without consideration of trends over time, neurocognitive performance was broadly within the average clinical range (ranging from low average to average).

Table 9

Unconditional Means Models: Within-Subject Initial Status

Outcome measure	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
Mean random intercept	87.44	84.77, 90.10	195	64.70	<0.001
Verbal Comprehension Index					
Mean random intercept	89.93	87.40, 92.45	200	70.13	<0.001
Perceptual Reasoning Index					
Mean random intercept	86.57	84.09, 89.04	191	68.96	<0.001
Processing Speed Index					
Mean random intercept	88.43	85.83, 91.04	183	66.88	<0.001
Working Memory Index					
Mean random intercept	90.72	87.97, 93.47	180	65.03	<0.001

Relative to the unconditional means models, the unconditional quadratic growth models for Full-Scale IQ ($\chi^2 = 41.23$, $df = 5$, $p < 0.001$) as well as the Verbal Comprehension ($\chi^2 = 18.33$, $df = 5$, $p < 0.001$), Perceptual Reasoning ($\chi^2 = 14.25$, $df = 5$, $p < 0.001$), Processing Speed ($\chi^2 = 34.51$, $df = 5$, $p < 0.0001$), and Working Memory ($\chi^2 = 29.80$, $df = 5$, $p < 0.0001$) indices all had improved model fit when including time as a predictor of change. The results of the unconditional quadratic growth models, which provide examination of longitudinal trajectories and within-subject change over time, are summarized in Table 10. Mean initial neurocognitive status, as determined by the mean of the random intercepts, ranged from 92.58 to 112.86 (standard scores) across all neurocognitive domains. These values indicated that, when baseline

neurocognitive scores (Full-Scale IQ and related sub-domains) were statistically extrapolated at stroke occurrence (i.e., at birth; time point 0), neurocognitive performance was broadly within the average clinical range (ranging from average to above average).

Regarding the linear rate of neurocognitive change, a significant negative effect of time was only found for Full-Scale IQ (β = -2.00, *95% CI*: -3.15, -0.85, p = 0.001) as well as Verbal Comprehension (β = -1.36, *95% CI*: -2.68, -0.03, p = 0.046), Processing Speed (β = -2.01, *95% CI*: -3.87, -0.15, p = 0.04), and Working Memory (β = -3.72, *95% CI*: -5.77, -1.67, p = 0.001) indices, indicating longitudinal neurocognitive decline for these capacities. Regarding quadratic neurocognitive change, significant trajectory curvature was only found across time for the Working Memory Index (β = 0.12, *95% CI*: 0.03, 0.21, p = 0.01). Substantial individual differences in the rate of linear (*SD* range: 0.004-0.48) and quadratic (*SD* range: -0.0002-8.91) change were apparent across all domains/sub-domains, indicating diverse neurocognitive trajectories. This variability suggests that the growth curves may be more accurately predicted by theoretically meaningful variables (e.g., sex, lesion volume, lesion laterality, neurological diagnoses, and medical comorbidities), which was explored in Objective 3.

Table 10

Unconditional Models: Within-Subject Change Over Time

Outcome measure	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
Mean random intercept	99.29	93.51, 105.07	194	33.73	<0.001
Linear slope	-2.00	-3.15, -0.85	162	-3.43	0.001
Quadratic slope	0.05	-0.01, 0.10	162	1.76	0.08
Verbal Comprehension Index					
Mean random intercept	98.10	91.78, 104.42	199	30.48	<0.001

Linear slope	-1.36	-2.68, -0.03	166	-2.01	0.046
Quadratic slope	0.03	-0.03, 0.10	166	1.07	0.29
Perceptual Reasoning Index					
Mean random intercept	92.58	85.76, 99.39	190	26.69	<0.001
Linear slope	-0.85	-2.28, 0.58	165	-1.17	0.25
Quadratic slope	0.01	-0.06, 0.08	165	0.30	0.76
Processing Speed Index					
Mean random intercept	101.63	92.68, 110.58	182	22.30	<0.001
Linear slope	-2.01	-3.87, -0.15	127	-2.13	0.04
Quadratic slope	0.03	-0.05, 0.12	127	0.73	0.47
Working Memory Index					
Mean random intercept	112.86	102.33, 123.39	179	21.04	<0.001
Linear slope	-3.72	-5.77, -1.67	111	-3.57	0.001
Quadratic slope	0.12	0.03, 0.21	111	2.57	0.01

Objective 3: Predictors of Neurocognitive Growth

Full-Scale IQ

The results of the conditional growth curve models which investigated the moderation of Full-Scale IQ over time by clinical and stroke-related factors are shown in Table 11. These models provide examination of the correlates of within-subject parameters. Of the variables explored, only lesion volume and seizure disorder status moderated the linear and quadratic components of the neurocognitive trajectory over time. Specifically, there was a significant interaction between lesion volume and age such that large lesion volume was associated with greater neurocognitive decline over time relative to small lesion volume (β = -3.52, *95% CI*: -5.01, -2.03, $p < 0.001$; Figure 3). Likewise, the mean curvature of the neurocognitive trajectory was greater for individuals with large lesion volumes relative to small lesion volumes (β = 0.16, *95% CI*: 0.07, 0.25, $p = 0.001$). No significant differences were found for the linear and quadratic

components of the neurocognitive trajectory when comparing small and medium lesion volumes. Model fit was improved relative to the unconditional growth model ($\chi 2 = 28.27$, $df = 7$, $p < 0.0001$). Upon visual inspection, although individuals with large lesion volumes showed more rapid neurocognitive decline, they showed relative improvement over time compared to individuals with small and medium lesion volumes. As such, similar functioning was apparent at the end of follow-up.

Table 11

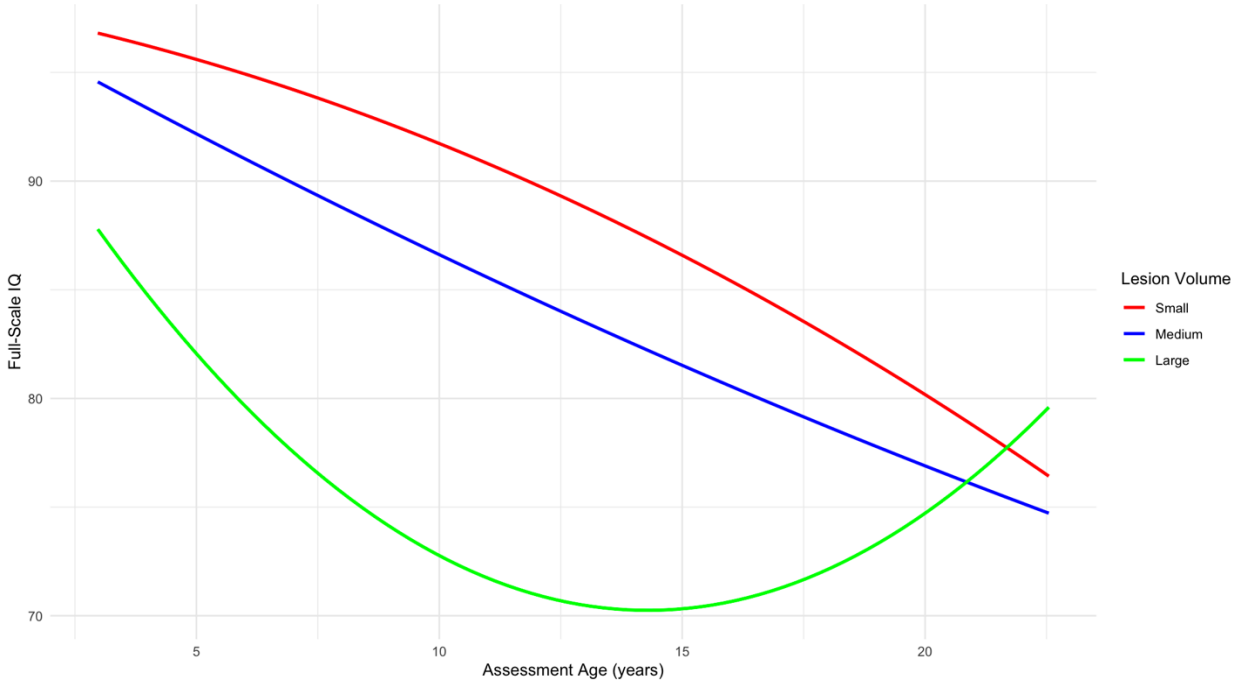
Conditional Models: Moderation of Full-Scale IQ

Clinical and Stroke-Related Factors	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
Sex x age linear interaction	0.82	-0.28, 1.93	160	1.46	0.15
Sex x age quadratic interaction	-0.04	-0.11, 0.02	160	-1.26	0.21
Full-Scale IQ					
Lesion volume x age linear interaction (medium vs. small)	-0.86	-2.29, 0.57	151	-1.18	0.24
Lesion volume x age linear interaction (large vs. small)	-3.52	-5.01, -2.03	151	-4.61	<0.001
Lesion volume x age quadratic interaction (medium vs. small)	0.03	-0.06, 0.12	151	0.76	0.45
Lesion volume x age quadratic interaction (large vs. small)	0.16	0.07, 0.25	151	3.50	0.001
Full-Scale IQ					

Lesion laterality x age linear interaction	-0.14	-1.84, 1.55	160	-0.17	0.87
Lesion laterality x age quadratic interaction	-0.01	-0.12, 0.10	160	-0.18	0.86
Full-Scale IQ					
Seizure disorder x age linear interaction	-2.73	-4.06, -1.40	160	-4.04	0.0001
Seizure disorder x age quadratic interaction	0.12	0.04, 0.20	160	2.94	0.004
Full-Scale IQ					
Neurological diagnoses x age linear interaction	0.11	-1.97, 2.20	160	0.11	0.92
Neurological diagnoses x age quadratic interaction	0.01	-0.12, 0.14	160	0.19	0.85
Full-Scale IQ					
Medical comorbidities x age linear interaction	-0.33	-1.79, 1.12	160	-0.45	0.65
Medical comorbidities x age quadratic interaction	0.05	-0.03, 0.13	160	1.32	0.19

Figure 3:

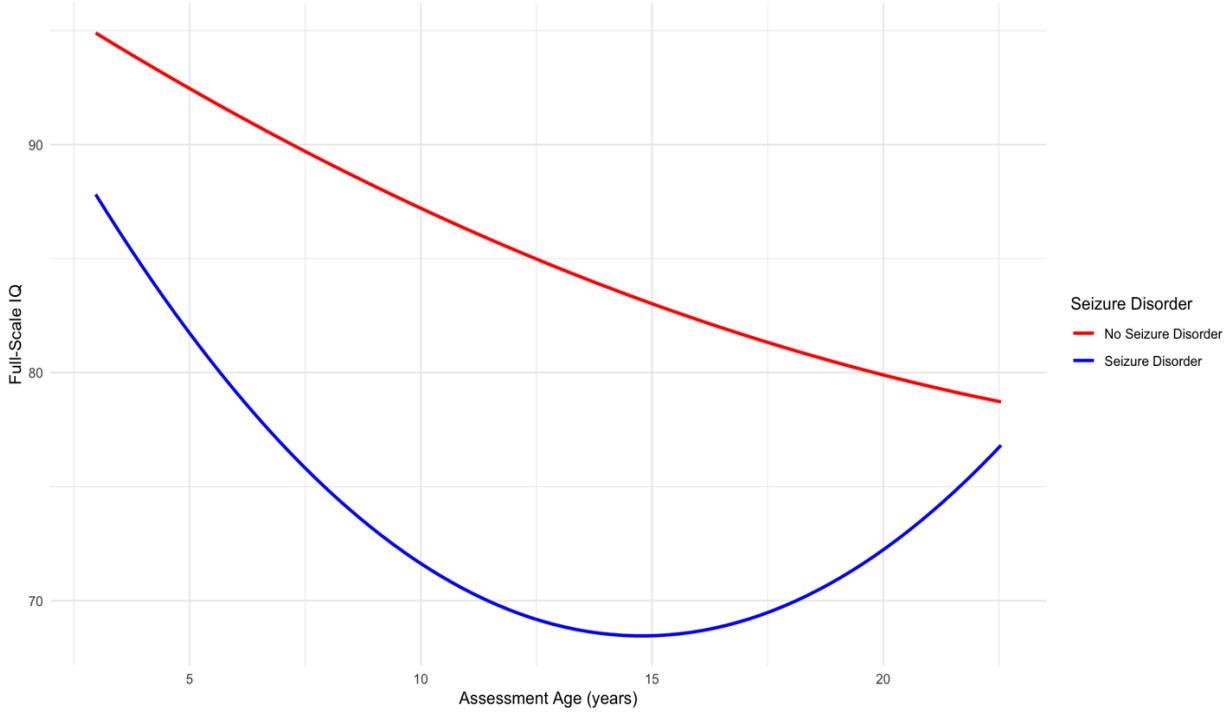
Full-Scale IQ: Lesion Volume as a Moderator of Linear and Quadratic Neurocognitive Decline



There was also a significant interaction between seizure disorder status and age, such that the presence of a seizure disorder was associated with greater neurocognitive decline over time relative to no seizure disorder (β = -2.73, *95% CI*: -4.06, -1.40, p = 0.0001; Figure 4). Likewise, the mean curvature of the neurocognitive trajectory was greater for individuals with seizure disorders relative to no seizure disorders (β = 0.12, *95% CI*: 0.04, 0.20, p = 0.004). Model fit was improved relative to the unconditional growth model ($\chi 2$ = 20.33, df = 7, p < 0.0001). Upon visual inspection, although individuals with seizure disorders showed more rapid neurocognitive decline, they showed relative improvement over time compared to individuals without seizure disorders. As such, similar functioning was apparent at the end of follow-up.

Figure 4:

Full-Scale IQ: Seizure Disorder Status as a Moderator of Linear and Quadratic Neurocognitive Decline

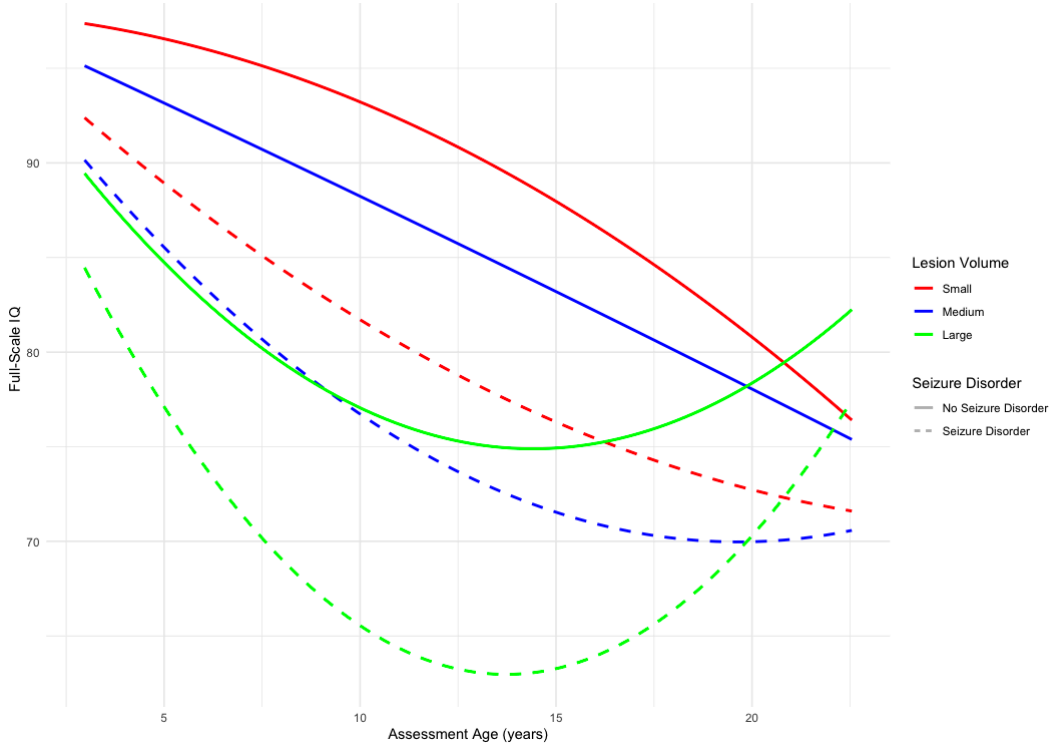


In an exploratory manner, the conditional model was expanded upon to investigate the moderating role of lesion volume and seizure disorder status together (Figure 5). There remained a significant interaction between lesion volume and age such that large lesion volume was associated with greater neurocognitive decline relative to small lesion volume (β = -3.11, *95% CI*: -4.60, -1.63, $p < 0.001$). Likewise, the mean curvature of the neurocognitive trajectory was greater for individuals with large lesion volumes relative to small lesion volumes (β = 0.15, *95% CI*: 0.06, 0.24, $p = 0.002$). Again, no significant difference was found for the linear and quadratic components of the neurocognitive trajectory when comparing small and medium lesion volumes. Upon visual inspection, although individuals with large lesion volumes showed more rapid neurocognitive decline, they showed relative improvement over time compared to individuals

with small and medium lesion volumes. As such, similar functioning was again apparent at the end of follow-up. Additionally, there remained a significant interaction between seizure disorder status and age such that the presence of a seizure disorder was associated with greater neurocognitive decline relative to no seizure disorder (β = -1.90, *95% CI*: -3.21, -0.59, p = 0.005). However, the mean curvature of the neurocognitive trajectory was no longer significantly different for individuals with and without seizure disorders. Model fit was improved relative to the conditional growth model with lesion volume alone ($\chi 2$ = 11.57, df = 11, p = 0.003).

Figure 5:

Full-Scale IQ: Lesion Volume and Seizure Disorder Status as Moderators of Neurocognitive Decline



In an exploratory manner, the conditional model examining the moderation of the linear and quadratic components of Full-Scale IQ over time by lesion volume and seizure disorder status was then expanded upon by entering all other variables individually as covariates to examine for potential main effects. Notably, to simplify the model and heighten power, the non-

significant moderating effect of seizure disorder status on the quadratic component of Full-Scale IQ was excluded from the subsequent models. The results of these expanded conditional growth models are shown in Table 12. In examining potential main effects of the variables, none had a significant effect on the random intercept, above and beyond the moderating role of lesion volume and seizure disorder status. Specifically, evaluation of sex, lesion laterality, neurological diagnoses, and medical comorbidities all yielded non-significant results. Likewise, inclusion of these variables as potential main effects did not lead to improved model fit.

Table 12:

Expanded Conditional Models: Moderation of Full-Scale IQ by Lesion Volume and Seizure Disorder Status, Alongside Potential Main Effects

Clinical and Stroke-Related Factors	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
Sex	4.57	-0.07, 9.22	188	1.92	0.06
Lesion volume x age linear interaction (medium vs. small)	-0.86	-2.25, 0.53	150	-1.20	0.23
Lesion volume x age linear interaction (large vs. small)	-3.38	-4.84, -1.92	150	-4.52	<0.001
Lesion volume x age quadratic interaction (medium vs. small)	0.04	-0.05, 0.13	150	0.85	0.40
Lesion volume x age quadratic interaction (large vs. small)	0.17	0.08, 0.26	150	3.63	<0.001
Seizure disorder x age linear interaction	-0.68	-1.16, -0.20	150	-2.77	0.006
Full-Scale IQ					
Lesion laterality	-2.03	-5.64, 1.58	188	-1.10	0.27

Lesion volume x age linear interaction (medium vs. small)	-0.93	-2.33, 0.47	150	-1.29	0.20
Lesion volume x age linear interaction (large vs. small)	-3.39	-4.86, -1.93	150	-4.52	<0.001
Lesion volume x age quadratic interaction (medium vs. small)	0.04	-0.05, 0.13	150	0.93	0.35
Lesion volume x age quadratic interaction (large vs. small)	0.17	0.08, 0.26	150	3.65	<0.001
Seizure disorder x age linear interaction	-0.71	-1.19, -0.23	150	-2.87	0.005
Full-Scale IQ					
Neurological diagnoses	-6.61	-15.04, 1.81	188	-1.53	0.13
Lesion volume x age linear interaction (medium vs. small)	-0.70	-2.13, 0.73	150	-0.96	0.34
Lesion volume x age linear interaction (large vs. small)	-3.34	-4.80, -1.88	150	-4.45	<0.001
Lesion volume x age quadratic interaction (medium vs. small)	0.03	-0.06, 0.12	150	0.70	0.48
Lesion volume x age quadratic interaction (large vs. small)	0.17	0.08, 0.25	150	3.59	<0.001
Seizure disorder x age linear interaction	-0.70	-1.19, -0.22	150	-2.85	0.005
Full-Scale IQ					

Medical comorbidities	-2.31	-9.29, 4.67	188	-0.64	0.52
Lesion volume x age linear interaction (medium vs. small)	-0.97	-2.37 – 0.44	150	-1.34	0.18
Lesion volume x age linear interaction (large vs. small)	-3.44	-4.91, -1.96	150	-4.53	<0.001
Lesion volume x age quadratic interaction (medium vs. small)	0.04	-0.04, 0.13	150	0.97	0.33
Lesion volume x age quadratic interaction (large vs. small)	0.17	0.08, 0.26	150	3.68	<0.001
Seizure disorder x age linear interaction	-0.70	-1.18, -0.22	150	-2.83	0.005

Neurocognitive Sub-Domains

Given the conceptual overlap between the overarching domain and the sub-domains, the finalized model established for the robust overarching neurocognitive domain (Full-Scale IQ; moderation of lesion volume and seizure disorder status) was directly examined for the related neurocognitive sub-domains (Verbal Comprehension Index, Perceptual Reasoning Index, Processing Speed Index, Working Memory Index). Once again, the previously non-significant moderating effect of seizure disorder status on the quadratic component of Full-Scale IQ was excluded from these subsequent models to simplify the models and heighten power. The results of the finalized conditional growth model for each neurocognitive sub-domain are shown in Table 13.

Table 13

Conditional Models for Neurocognitive Sub-Domains: Moderation by Lesion Volume and Seizure Disorder Status

Clinical and Stroke-Related Factors	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Verbal Comprehension Index					
Lesion volume x age linear interaction (medium vs. small)	-0.80	-2.30, 0.70	154	-1.04	0.30
Lesion volume x age linear interaction (large vs. small)	-2.68	-4.27, -1.10	154	-3.31	0.001
Lesion volume x age quadratic interaction (medium vs. small)	0.04	-0.07, 0.14	155	0.70	0.49
Lesion volume x age quadratic interaction (large vs. small)	0.13	0.02, 0.24	154	2.42	0.02
Seizure disorder x age linear interaction	-0.67	-1.19, -0.15	154	-2.50	0.01
Perceptual Reasoning Index					
Lesion volume x age linear interaction (medium vs. small)	-0.19	-1.67, 1.28	154	-0.25	0.80
Lesion volume x age linear interaction (large vs. small)	-3.00	-4.56, -1.44	154	-3.76	<0.001
Lesion volume x age quadratic interaction	-0.01	-0.11, 0.08	154	-0.29	0.77

(medium vs. small)					
Lesion volume x age quadratic interaction (large vs. small)	0.15	0.05, 0.25	154	2.84	0.005
Seizure disorder x age linear interaction	-0.64	-1.16, -0.13	154	-2.44	0.02
Processing Speed Index					
Lesion volume x age linear interaction (medium vs. small)	-1.91	-3.42, -0.41	116	-2.49	0.01
Lesion volume x age linear interaction (large vs. small)	-3.41	-5.01, -1.81	116	-4.17	<0.001
Lesion volume x age quadratic interaction (medium vs. small)	0.15	0.04, 0.25	116	2.72	0.007
Lesion volume x age quadratic interaction (large vs. small)	0.18	0.07, 0.30	116	3.25	0.002
Seizure disorder x age linear interaction	-0.58	-1.12, -0.04	116	-2.10	0.04
Working Memory Index					
Lesion volume x age linear interaction (medium vs. small)	-0.80	-2.40, 0.79	102	-0.98	0.33
Lesion volume x age linear interaction (large vs. small)	-2.82	-4.50, -1.13	102	-3.26	0.002
Lesion volume x age quadratic interaction	0.01	-0.10, 0.13	102	0.26	0.80

(medium vs. small)					
Lesion volume x age quadratic interaction (large vs. small)	0.12	0.01, 0.24	102	2.04	0.04
Seizure disorder x age linear interaction	-0.90	-1.44, -0.37	102	-3.29	0.001

For the Verbal Comprehension Index, lesion volume and seizure disorder status moderated the verbal comprehension trajectory over time. Specifically, there was a significant interaction between lesion volume and age such that large lesion volume was associated with greater decline in verbal comprehension over time relative to small lesion volume (β = -2.68, *95% CI*: -4.27, -1.10, p = 0.001; Figure 6.A). Likewise, the mean curvature of the verbal comprehension trajectory was greater for individuals with large lesion volumes relative to small lesion volumes (β = 0.13, *95% CI*: 0.02, 0.24, p = 0.02). No significant difference was found for the linear and quadratic components of the verbal comprehension trajectory when comparing small and medium lesion volumes. Although individuals with large lesion volumes showed a more rapid decline in verbal comprehension, they showed relative improvement over time compared to individuals with small and medium lesion volumes who showed a stable decline. As such, the three groups experienced similar functioning at the end of follow-up. Additionally, there was a significant interaction between seizure disorder status and age such that the presence of a seizure disorder was associated with a greater decline in verbal comprehension over time relative to no seizure disorder (β = -0.67, *95% CI*: -1.19, -0.15, p = 0.01). Lower verbal comprehension was consistent across time for individuals with seizure disorders. Model fit was improved relative to the unconditional growth model without any moderating effects ($\chi 2$ = 24.47, df = 7, p = 0.0002).

For the Perceptual Reasoning Index, both lesion volume and seizure disorder status moderated the perceptual reasoning trajectory over time. Specifically, there was a significant interaction between lesion volume and age such that large lesion volume was associated with a greater decline in perceptual reasoning over time relative to small lesion volume (β = -3.00, *95% CI*: -4.56, -1.44, $p < 0.001$; Figure 6.B). Likewise, the mean curvature of the perceptual reasoning trajectory was greater for individuals with large lesion volumes relative to small lesion volumes (β = 0.15, *95% CI*: 0.05, 0.25, $p = 0.005$). No significant difference was found for the linear and quadratic components of the perceptual reasoning trajectory when comparing small and medium lesion volumes. Although individuals with large lesion volumes showed a more rapid decline in perceptual reasoning, they showed greater relative improvement over time compared to individuals with small and medium lesion volumes who showed a stable decline. As such, the three groups experienced similar functioning at the end of follow-up. Additionally, there was a significant interaction between seizure disorder status and age such that the presence of a seizure disorder was associated with a greater decline in perceptual reasoning over time relative to no seizure disorder (β = -0.64, *95% CI*: -1.16, -0.13, $p = 0.02$). Lower perceptual reasoning was consistent across time for individuals with seizure disorders. Model fit was improved relative to the unconditional growth model without any moderating effects ($\chi 2 = 32.70$, $df = 7$, $p < 0.0001$).

For the Processing Speed Index, lesion volume and seizure disorder status moderated the processing speed trajectory over time. Specifically, there was a significant interaction between lesion volume and age such that medium (β = -1.91, *95% CI*: -3.42, -0.41, $p = 0.01$) and large (β = -3.41, *95% CI*: -5.01, -1.81, $p < 0.001$) lesion volumes were associated with a greater decline in processing speed over time relative to small lesion volume (Figure 6.C). Likewise, the mean

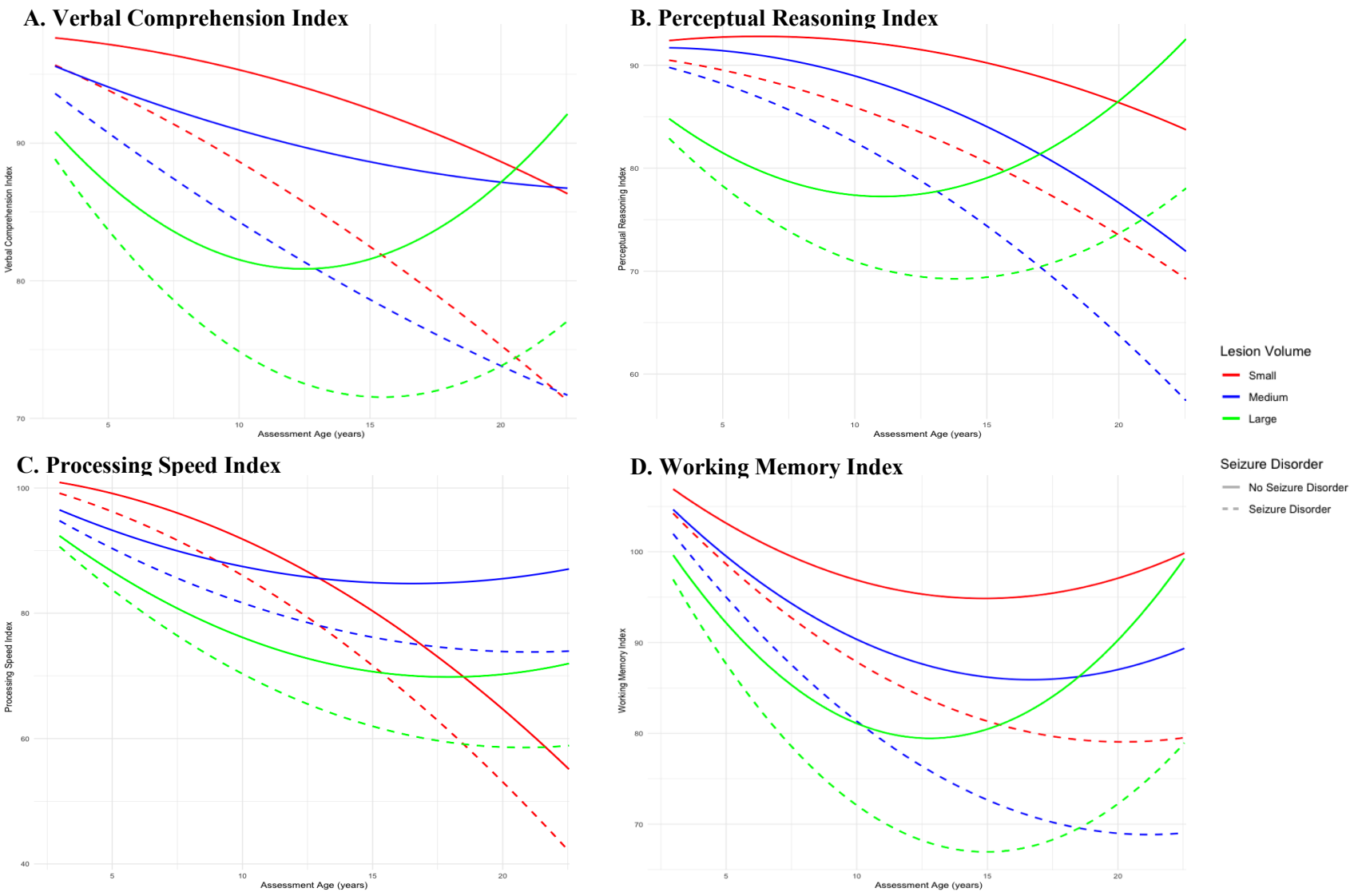
curvature of the processing speed trajectory was greater for individuals with medium (β = 0.15, *95% CI*: 0.04, 0.25, p = 0.007) and large (β = 0.18, *95% CI*: 0.07, 0.30, p = 0.002) lesion volumes relative to small lesion volumes. Although individuals with medium and large lesion volumes initially showed a more rapid decline in processing speed, this decline appeared to plateau over time. In contrast, individuals with small lesion volumes initially showed a less steep decline, but escalation was visible in their decline over time. Additionally, there was a significant interaction between seizure disorder status and age such that the presence of a seizure disorder was associated with a greater decline in processing speed over time relative to no seizure disorder (β = -0.58, *95% CI*: -1.12, -0.04, p = 0.04). Lower processing speed was consistent across time for individuals with seizure disorders. Model fit was improved relative to the unconditional growth model without any moderating effects ($\chi 2$ = 35.06, df = 7, p < 0.0001).

For the Working Memory Index, lesion volume and seizure disorder status moderated the working memory trajectory over time. Specifically, there was a significant interaction between lesion volume and age such that large lesion volume was associated with a greater decline in working memory over time relative to small lesion volume (β = -2.82, *95% CI*: -4.50, -1.13, p = 0.002; Figure 6.D). The mean curvature of the working memory trajectory was greater for individuals with large lesion volumes relative to small lesion volumes (β = 0.12, *95% CI*: 0.01, 0.24, p = 0.04). No significant difference was found for the linear and quadratic components of the working memory trajectory when comparing small and medium lesion volumes. Although individuals with large lesion volumes showed a more rapid decline in working memory, they showed relative improvement over time (similar to medium volume at end of follow-up). In contrast, for individuals with small and medium lesion volumes, relative gains in working memory were also apparent, although to a lesser extent. There was also a

significant interaction between seizure disorder status and age such that the presence of a seizure disorder was associated with a greater decline in working memory over time relative to no seizure disorder (β = -0.90, *95% CI*: -1.44, -0.37, p = 0.001). Lower working memory was consistent across time for individuals with seizure disorders. Model fit was improved relative to the unconditional growth model without any moderating effects ($\chi 2$ = 34.16, df = 7, $p < 0.0001$).

Figure 6

Neurocognitive Sub-Domains: Moderation by Lesion Volume and Seizure Disorder Status

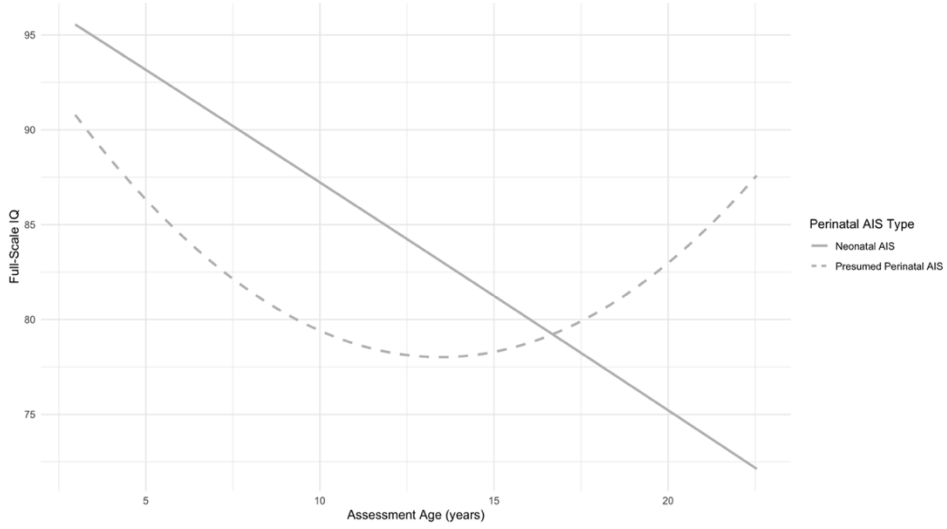


Objective 4: Neonatal Relative to Presumed Perinatal AIS

Perinatal AIS type (neonatal versus presumed perinatal) was examined as a potential moderator of the linear and quadratic components of the neurocognitive trajectory over time. Significant moderations were found for the linear (β = -1.95, *95% CI*: -3.02, -0.88, $p < 0.001$) and quadratic (β = 0.12, *95% CI*: 0.06, 0.18, $p < 0.001$) components of the neurocognitive trajectory (Figure 7). Model fit was improved relative to the unconditional growth model without any moderating effects ($\chi 2 = 6.58$, $df = 7$, $p = 0.04$).

Figure 7

Full-Scale IQ: Moderation by Perinatal AIS Type



The finalized model that was established for the robust overarching neurocognitive domain (Full-Scale IQ; moderation of lesion volume and seizure disorder status) was expanded upon to include the moderating role of perinatal AIS type on Full-Scale IQ. Given the inclusion of a new moderating variable, and the preliminary nature of these analyses, a moderating effect of seizure disorder status on the linear and quadratic components of Full-Scale IQ were both included, despite previous non-significant findings for the quadratic component. The results of the finalized conditional growth model are shown in Table 14.

Table 14

Conditional Model: Moderation by Lesion Volume, Seizure Disorder Status, and Perinatal AIS Type

Clinical and Stroke-Related Factors	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
AIS type x age linear interaction (presumed perinatal vs. neonatal)	-1.32	-2.38, -0.25	147	-2.45	0.02
AIS type x age quadratic interaction (presumed perinatal vs. neonatal)	0.09	0.03, 0.15	147	2.84	0.005
Lesion volume x age linear interaction (medium vs. small)	-1.04	-2.44, 0.37	147	-1.46	0.15
Lesion volume x age linear interaction (large vs. small)	-3.05	-4.54, -1.56	147	-4.05	<0.001
Lesion volume x age quadratic interaction (medium vs. small)	0.05	-0.04, 0.14	147	1.10	0.27
Lesion volume x age quadratic interaction (large vs. small)	0.14	0.05, 0.23	147	3.10	0.002
Seizure disorder x age linear interaction	-1.84	-3.18, -0.51	147	-2.74	0.007
Seizure disorder x age quadratic interaction	0.08	0.00, 0.15	147	2.00	0.047

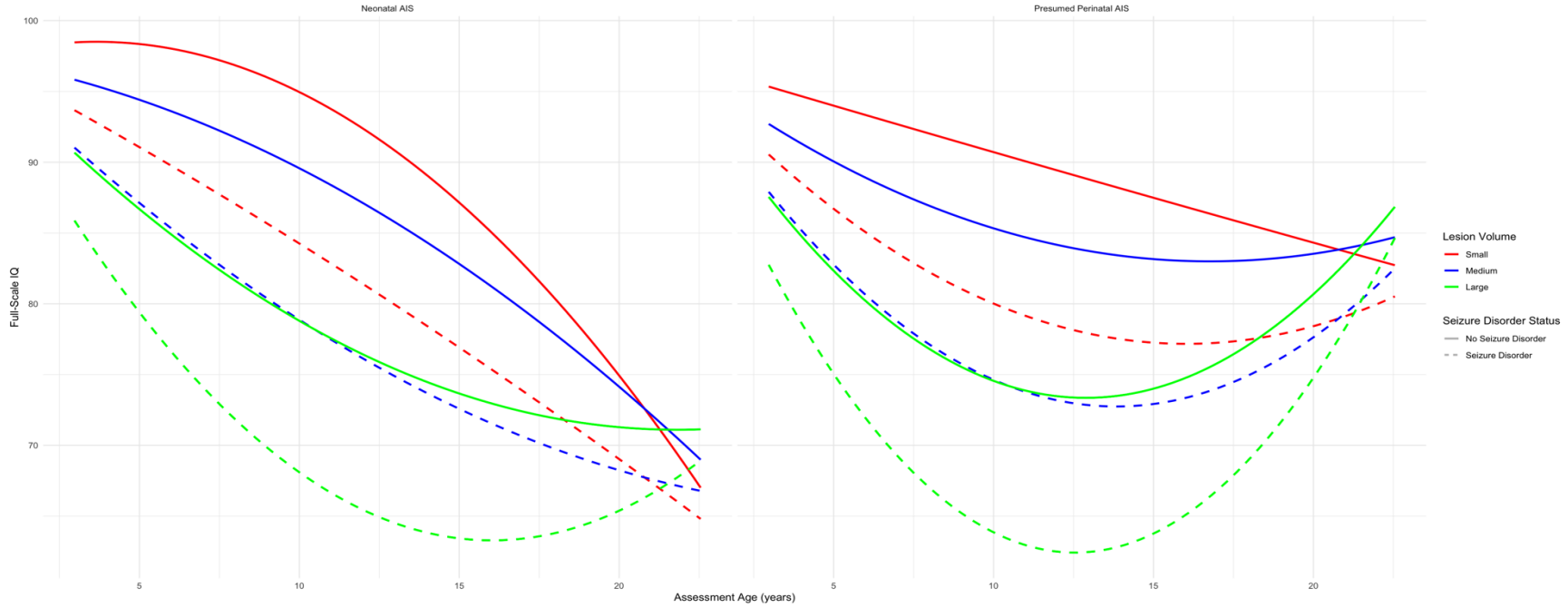
Perinatal AIS type, lesion volume, and seizure disorder status all moderated the linear and quadratic components of the neurocognitive trajectory (Figure 8). There was a significant interaction between perinatal AIS type and age such that presumed perinatal AIS was associated

with a greater neurocognitive decline over time relative to neonatal AIS (β = -1.32, *95% CI*: -2.38, -0.25, p = 0.02). Likewise, the mean curvature of the neurocognitive trajectory was greater for those with presumed perinatal AIS relative to neonatal AIS (β = 0.09, *95% CI*: 0.03, 0.15, p = 0.005). Although individuals with presumed perinatal AIS had a more rapid neurocognitive decline initially, they showed relative improvement over time compared to those with neonatal AIS who showed a consistent decline. Individuals with neonatal relative to presumed perinatal AIS thus demonstrated worse neurocognitive functioning at the end of follow-up.

Additionally, there was a significant interaction between lesion volume and age such that large lesion volume was associated with a greater neurocognitive decline over time relative to small lesion volume (β = -3.05, *95% CI*: -4.54, -1.56, $p < 0.001$). The mean curvature of the neurocognitive trajectory was also greater for individuals with large relative to small lesion volumes (β = 0.14, *95% CI*: 0.05, 0.23, p = 0.002). No significant difference was found for the linear and quadratic components of the neurocognitive trajectory when comparing small and medium lesion volumes. Likewise, there was a significant interaction between seizure disorder status and age, such that the presence of a seizure disorder was associated with a greater neurocognitive decline over time relative to no seizure disorder (β = -1.84, *95% CI*: -3.18, -0.51, p = 0.007). The mean curvature of the neurocognitive trajectory was also greater for individuals with seizure disorders relative to no seizure disorders (β = 0.08, *95% CI*: 0.00, 0.15, p = 0.047). Lower neurocognitive abilities were consistently apparent for those with seizure disorders across time. Model fit was improved relative to the initial model with only a moderating effect of perinatal AIS type ($\chi 2$ = 18.70, df = 9, p = 0.005).

Figure 8

Full-Scale IQ: Moderation by Lesion Volume, Seizure Disorder Status, and Perinatal AIS Type



Objective 5: Early Screening in a Neonatal AIS Sub-Sample

Early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic was examined as a potential moderator of the linear and quadratic components of the neurocognitive trajectory over time among children who experienced only neonatal AIS. Non-significant moderations for the linear (β = 1.63, *95% CI*: - -0.88, 4.13, p = 0.20) and quadratic (β = -0.15, *95% CI*: -0.39, 0.10, p = 0.24) components of the neurocognitive trajectory were found. Model fit was not compared to the initial unconditional growth model given that this analysis involved a sub-group of the larger sample, thus the samples were not equivalent in nature to facilitate comparison. As such, the finalized model that was established for the robust overarching neurocognitive domain (Full-Scale IQ; moderation of lesion volume and seizure disorder status) was expanded to include a potential main effect of early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic. Given the inclusion of a new main effect, and the preliminary nature of these analyses, a moderating effect of seizure disorder status on the linear and quadratic components of Full-Scale IQ were both included despite previous non-significant findings for the quadratic component. The results of the finalized conditional growth model are shown in Table 15.

Table 15

Conditional Model: Moderation by Lesion Volume and Seizure Disorder Status, Adjusting for Early Screening

Clinical and Stroke-Related Factors	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
Early Screening	5.99	-1.07, 13.04	109	1.68	0.09
Lesion volume x age linear interaction (medium vs. small)	-0.93	-2.91, 1.05	86	-0.93	0.35

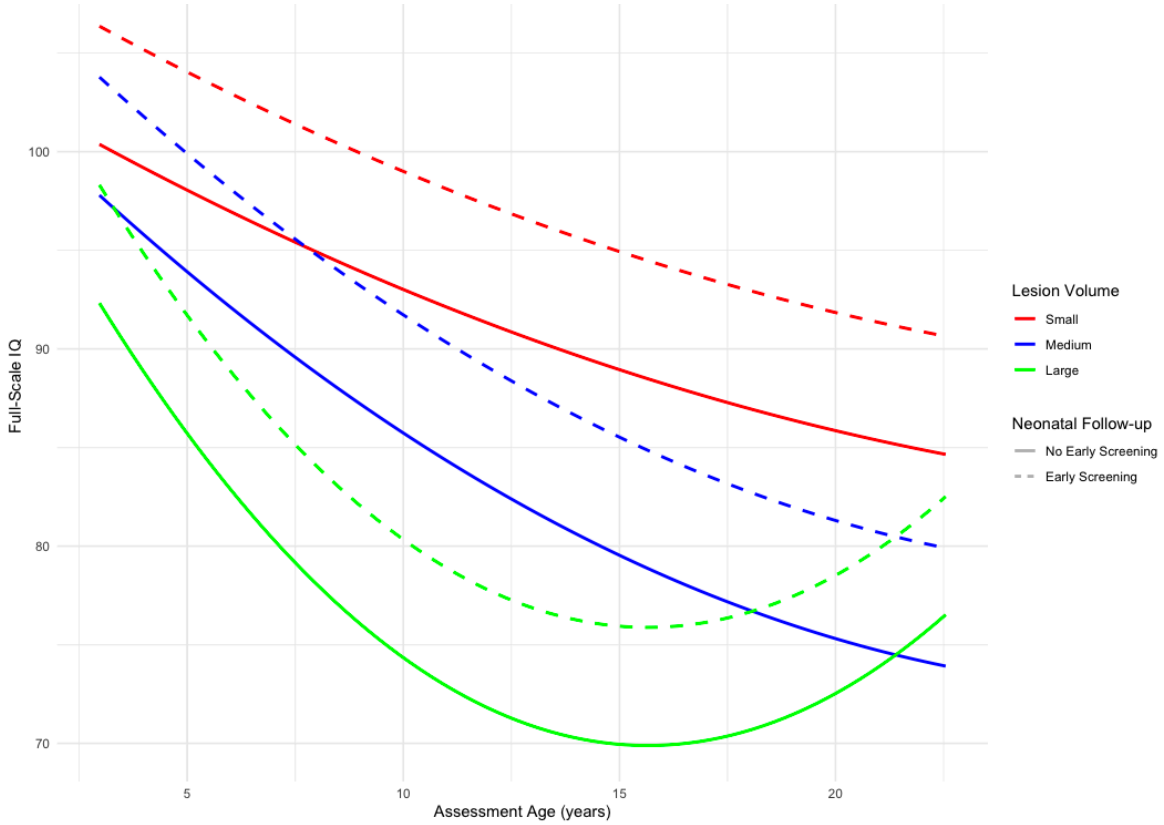
Lesion volume x age linear interaction (large vs. small)	-3.07	-5.31, -0.83	86	-2.72	0.008
Lesion volume x age quadratic interaction (medium vs. small)	0.02	-0.11, 0.15	86	0.31	0.76
Lesion volume x age quadratic interaction (large vs. small)	0.12	-0.02, 0.26	86	1.65	0.10
Seizure disorder x age linear interaction	0.08	-2.03, 2.20	86	0.08	0.94
Seizure disorder x age quadratic interaction	-0.01	-0.12, 0.11	86	-0.09	0.93

Early screening through the Neonatal Neurodevelopmental Follow-up Clinic did not have a significant main effect on the random intercept (Full-Scale IQ at stroke occurrence). As such, extrapolated results indicated that individuals who differed by early screening status demonstrated roughly similar statistically extrapolated baseline neurocognitive performance. Although the effect of early screening was not significant, visual inspection revealed that individuals who did not receive early screening showed consistently lower Full-Scale IQ than those who did receive early screening across all lesion volumes (Figure 9). As such, there was notable value in adjusting for early screening status. Additionally, lesion volume moderated the linear component of the neurocognitive trajectory over time. Specifically, there was a significant interaction between lesion volume and age such that large lesion volume was associated with greater neurocognitive decline over time relative to small lesion volume (β = -3.07, *95% CI*: -5.31, -0.83, p = 0.008). No significant difference was found for the linear component of the neurocognitive trajectory when comparing small and medium lesion volumes. No significant

difference was found for the quadratic components of the neurocognitive trajectory when comparing small and medium, as well as small and large lesion volumes. Although individuals with large lesion volumes initially showed a more rapid neurocognitive decline, they showed relative improvement over time (similar to medium volume at end of follow-up). In contrast, those with small and medium lesion volumes showed a consistent neurocognitive decline. Seizure disorder status did not significantly moderate the linear or quadratic components of the neurocognitive trajectory. Model fit was not improved relative to the initial model with only the effect of early screening ($\chi 2 = 6.43$, $df = 9$, $p = 0.27$).

Figure 9

Full-Scale IQ: Moderation by Lesion Volume and Seizure Disorder Status (not shown as non-significant), Adjusting for Early Screening



Given the deterioration in model fit, the model was re-run to examine a moderating effect of lesion volume on the linear and quadratic components of Full-Scale IQ, adjusting for early screening status. The results of this finalized conditional growth model, excluding the previously non-significant effects of seizure disorder status, are shown in Table 16. Early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic again did not have a significant main effect on the random intercept (Full-Scale IQ at stroke occurrence). As such, the statistically extrapolated results indicated that individuals who differed by early screening status demonstrated roughly similar baseline neurocognitive performance. Although the effect of early screening was not significant, visual inspection revealed that individuals who did not receive early screening showed a consistently lower Full-Scale IQ than those who did receive early screening across all lesion volumes (Figure 10). As such, there was notable value in adjusting for early screening status nonetheless.

Lesion volume moderated the linear component of the neurocognitive trajectory over time. Specifically, there was a significant interaction between lesion volume and age such that large lesion volume was associated with a greater neurocognitive decline over time relative to small lesion volume (β = -3.05, *95% CI*: -5.22, -0.87, p = 0.007). No significant difference was found for the linear component of the neurocognitive trajectory when comparing small and medium lesion volumes. No significant difference was found for the quadratic components of the neurocognitive trajectory when comparing small and medium as well as small and large lesion volumes. Although individuals with large lesion volumes initially showed a more rapid neurocognitive decline, they showed relative improvement over time (similar to medium volume at end of follow-up). In contrast, those with small and medium lesion volumes showed a consistent neurocognitive decline. Despite similar results to the prior model, model fit for this

finalized model was improved relative to the initial conditional model with only the effect of early screening ($\chi 2 = 10.34$, $df = 9$, $p = 0.02$).

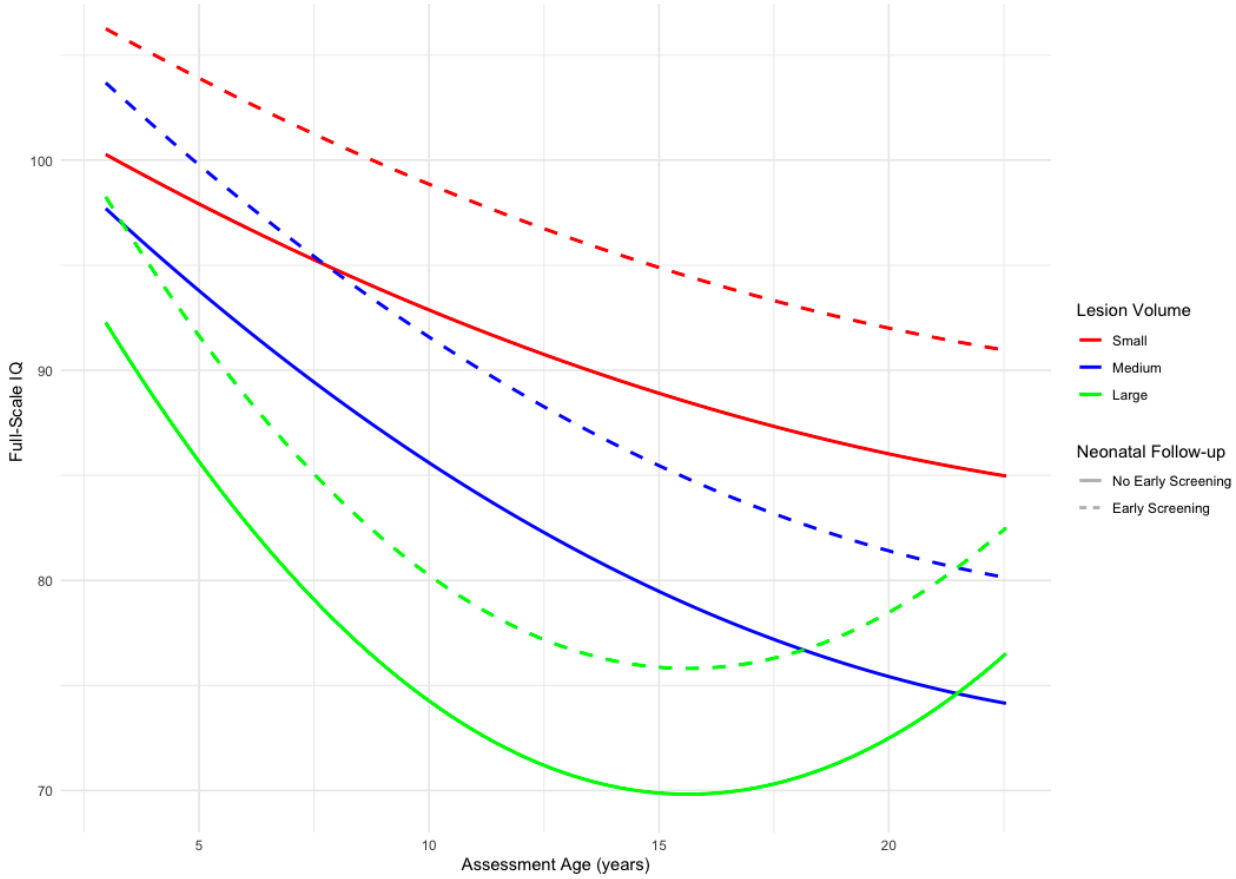
Table 16

Conditional Model: Moderation by Lesion Volume, Adjusting for Early Screening

Clinical and Stroke-Related Factors	Estimated parameter	95% *CI*	*df*	*t*-Value	*p*-Value
Full-Scale IQ					
Early Screening	5.99	-1.03, 13.00	109	1.69	0.09
Lesion volume x age linear interaction (medium vs. small)	-0.92	-2.89, 1.04	88	-0.94	0.35
Lesion volume x age linear interaction (large vs. small)	-3.05	-5.22, -0.87	88	-2.79	0.007
Lesion volume x age quadratic interaction (medium vs. small)	0.02	-0.11, 0.15	88	0.30	0.76
Lesion volume x age quadratic interaction (large vs. small)	0.12	-0.02, 0.26	88	1.70	0.09

Figure 10

Full-Scale IQ: Moderation by Lesion Volume, Adjusting for Early Screening



Discussion

This is the first longitudinal study to examine neurocognitive growth trajectories spanning multiple time points across early and late childhood, adolescence, and early adulthood in a diverse cohort of 208 children who had experienced perinatal AIS, including acute and presumed perinatal diagnoses. From this study, several conclusions can be made about changes in neurocognition as a function of age, as well as the influence of risk and protective factors. First, although neurocognition was statistically extrapolated within the broadly average clinical range at stroke occurrence (i.e., at birth), a negative effect of time was found across most domains of neurocognition (Full-Scale IQ, Verbal Comprehension, Processing Speed, Working

Memory), indicating significant neurocognitive declines across follow-up. Second, growth curves varied across individuals, suggesting the potential influence of clinically meaningful risk and protective factors. Third, of the various factors explored as potential predictors, lesion volume and seizure disorder status moderated the linear and quadratic components of the Full-Scale IQ trajectory. Evaluation of sex, lesion laterality, neurological diagnoses, and medical comorbidities all yielded non-significant results for both main and moderating effects. Fourth, the moderating role of lesion volume and seizure disorder status differed across neurocognitive sub-domains, indicating the need for specific investigation into distinct neurocognitive abilities. Fifth, in addition to moderating roles of lesion volume and seizure disorder status, perinatal AIS type (acute versus presumed perinatal AIS) moderated the linear and quadratic components of the Full-Scale IQ trajectory. Sixth, in a neonatal AIS sub-sample, lesion volume moderated the linear component of the Full-Scale IQ trajectory despite non-significant effects of seizure disorder status. Adjustment for early screening in infancy was relevant, with consistently lower functioning observed for those who did not receive early screening.

Neurocognitive Growth Trajectories

Longitudinal analyses are essential to understand the long-term neurocognitive sequalae associated with perinatal AIS. Specifically, longitudinal studies are more informative than cross-sectional studies because they can identify whether individuals who have experienced perinatal AIS start at a lower level of neurocognition or whether they "grow into deficits". Evaluation of "growing into deficits" requires consideration of whether individuals are experiencing a progressive widening of the gap between their performance and age-matched peers, or whether they have experienced a static insult to a neurocognitive trajectory that was impacted early in its maturation, but not necessarily in a progressively deteriorative manner. As such, the negative

trajectory for Full-Scale IQ and the relevant neurocognitive sub-domains (i.e., Verbal Comprehension, Processing Speed, Working Memory) indicate a loss of developmental gain over the course of early and late childhood, adolescence, and early adulthood, despite broadly age-appropriate functioning statistically extrapolated at stroke occurrence (i.e., birth). The current results thus provide compelling evidence of a greater vulnerability, rather than a greater plasticity/resiliency, of the immature brain that faces early injury.

Findings with respect to emergent deficits are consistent with prior cross-sectional studies which demonstrated neurocognitive deficits post perinatal AIS (Ballantyne et al., 1994; Grunt et al., 2015; McLinden et al., 2007; Talib et al., 2008; Trauner et al., 2001; Westmacott et al., 2010). Notably, two of these studies involved exclusively neonatal AIS samples examined 2-years post-stroke, with significant overall neurocognitive deficits demonstrated compared to a normative sample (McLinden et al., 2007) and in 31% of a neonatal AIS cohort (Grunt et al., 2015). Within perinatal AIS samples, lower Full-Scale IQ (Ballantyne et al., 1994; Talib et al., 2008; Trauner et al., 2001; Westmacott et al., 2010), Verbal Comprehension (Ballantyne et al., 1994; Talib et al., 2008; Westmacott et al., 2010), Perceptual Reasoning (Ballantyne et al., 1994; Talib et al., 2008; Westmacott et al., 2010), Working Memory (Westmacott et al., 2010), and Processing Speed (Westmacott et al., 2010) have been indicated across different studies relative to healthy comparison groups (i.e., control group, healthy co-twin, normative sample).

Conversely, the robust longitudinal findings of the present study differ from existing cross-sectional studies which have demonstrated broadly age-appropriate neurocognitive functioning following perinatal AIS (Chabrier et al., 2016; Cioni et al., 1998; Hetherington et al., 2005; Pavlovic et al., 2006; Ricci et al., 2008; Schatz et al., 2000; Trauner et al., 1993; Wulfeck et al., 1991). This discrepancy is likely due to methodological differences given that none of

these cross-sectional studies included an exclusively perinatal AIS sample. More specifically, many of these studies included mixed stroke subtypes within the perinatal period, with either non-specified or ischemic and hemorrhagic stroke histories (Cioni et al., 1998; Schatz et al., 2000; Trauner et al., 1993; Wulfeck et al., 1991). Hence, these existing findings cannot be directly compared to findings from the perinatal AIS sample included in the present study. Similarly, the one study that did have an exclusively AIS sample included those who experienced both perinatal and childhood AIS (Hetherington et al., 2005). The remaining studies were exclusively neonatal AIS samples (Chabrier et al., 2016; Pavlovic et al., 2006; Ricci et al., 2008). Notably, almost all of these studies involved testing in infancy or early childhood (Chabrier et al., 2016; Cioni et al., 1998; Hetherington et al., 2005; Pavlovic et al., 2006; Ricci et al., 2008; Trauner et al., 1993; Wulfeck et al., 1991), and thus did not examine neurocognition into later childhood as well as adolescence and adulthood when deficits are most likely to emerge alongside increasing developmental demands and expectations. In addition to small cohort sizes, these samples frequently excluded individuals born prematurely (Chabrier et al., 2016; Pavlovic et al., 2006; Ricci et al., 2008) and those with bilateral/multifocal lesions (Cioni et al., 1998; Schatz et al., 2000; Trauner et al., 1993; Wulfeck et al., 1991), thus failing to capture the diversity and compounding neurocognitive risks typical in perinatal AIS.

The potential confounding influence of time at testing on discrepant results in cross-section studies (i.e., testing in infancy/preschool versus school-age) has highlighted the need for longitudinal evaluations. The limited longitudinal evaluations of neurocognitive abilities following pediatric stroke have likewise demonstrated discrepant results and methodological variability (Anderson et al., 2020; Aram & Eisele, 1994; Ballantyne et al., 2008; Gonzalez-Monge et al., 2009; Levine et al., 2005; Muter et al., 1997; Westmacott et al., 2009). Across

these studies, there has been evidence for stable neurocognition (Anderson et al., 2020; Aram & Eisele, 1994; Ballantyne et al., 2008; Gonzalez-Monge et al., 2009; Muter et al., 1997) as well as emerging neurocognitive deficits (Levine et al., 2005; Westmacott et al., 2009). Although these studies have typically comprised samples of individuals who experienced strokes in the perinatal period, the majority of these longitudinal studies included mixed/non-specified stroke subtypes which were not specific to AIS (Aram & Eisele, 1994; Gonzalez-Monge et al., 2009; Levine et al., 2005; Muter et al., 1997). As such, many of these studies do not offer relevant comparisons for the perinatal AIS cohort of the current study given known differences in outcomes between AIS and other stroke subtypes (Kirton & De Veber, 2013).

Of the existing longitudinal studies with AIS samples, Westmacott et al. (2009) evaluated a neonatal AIS cohort and found significant decline in neurocognition (69.2% of the sample) spanning various sub-domains (i.e., Full-Scale IQ, Perceptual Reasoning, Working Memory, and Processing Speed) from preschool to school-age assessments. Neurocognitive performance did not differ from the normative sample at the pre-school assessment time point, rather only at the school-age assessment time point (Westmacott et al., 2009). The rate of neurocognitive deficits may be underestimated in the sample examined by Westmacott et al. (2009), given their exclusion of children with bilateral strokes or other neurological comorbidities which would be expected to pose heightened neurocognitive risks (Fuentes et al., 2016). Nonetheless, similar to the results of the present study, their findings were consistent with emerging deficits over time for Full-Scale IQ, Working Memory, and Processing Speed, supporting an early vulnerability hypothesis of early brain injury. Ballantyne et al. (2008) also evaluated neurocognition longitudinally within a perinatal AIS sample; however, their findings contrasted with those of both the present study and Westmacott et al. (2009). Specifically, their findings were in support

of the early plasticity hypothesis given stable neurocognition when assessed across two time points in the pre-school and school-age periods (Ballantyne et al., 2008). A notable difference in their study was the small sample sizes and testing having occurred across two time points from age 4-10 years (n = 23; different test versions) and 7-11 years (n = 15; same test versions; Ballantyne et al., 2008). Therefore, they were unable to capture the full spectrum of early development across infancy into early and late childhood as well as adolescence and early adulthood, which is likely needed to elucidate emerging deficits across follow-up. Likewise, neurocognition was consistently lower in the perinatal AIS group relative to controls, indicating significant neurocognitive challenges post perinatal AIS which are inconsistent with their proposed support for the early plasticity hypothesis (Ballantyne et al., 2008). The study also only included individuals who experienced unilateral strokes, thus failing to capture compounding risk due to bilateral strokes (Ballantyne et al., 2008).

Finally, Anderson et al. (2020) evaluated neurocognition across four time points (i.e., baseline, 1-, 6-, 12-months post stroke) in a pediatric AIS sample including perinatal and childhood AIS. They demonstrated stable neurocognition 12-months post-stroke and indicated support for neurocognitive resilience (Anderson et al., 2020). However, their follow-up interval (i.e., 12-months post-stroke) was likely too short to detect later-emerging neurocognitive morbidity, especially in the perinatal AIS subset of their sample given that emerging deficits are likely present in childhood rather than in infancy when they underwent testing. In comparing perinatal AIS to preschool/childhood AIS, they found that the former group had poorer neurocognition over the 12 months post-stroke. This difference highlights potential variability in recovery expectations for the perinatal AIS subgroup starting as early as in infancy, which aligns with the findings of the present study and the early vulnerability hypothesis. Notably, unlike the

novel trajectory approach to analyses undertaken in the preset study, these existing longitudinal studies all evaluated neurocognition across various time points as an average increment (i.e., simple differences between average scores on various occasions; Willett, 1989), which cannot highlight diverse trajectories of change and confounds true change with measurement error (Rogosa et al., 1982). As such, the discrepancies in the extant research highlight the need for longitudinal evaluation with homogenous populations (i.e., consistent stroke type and time of stroke), systematic comparison between stroke subtypes, evaluation beyond full-scale IQ to include neurocognitive sub-domains, and a more nuanced trajectory analytical approach.

Predictors of Neurocognition

Another unique component of the present study was the evaluation of relevant risk factors within a diverse and longitudinal perinatal AIS sample. There are limitations in the extant research on identified predictors of neurocognition following pediatric stroke (i.e., age at stroke, time since stroke, sex, etiology, lesion characteristics [location, laterality, volume], neurological impairment, seizures), including heterogenous samples spanning various pediatric stroke types (e.g., hemorrhagic, arterial ischemic, cerebral sinovenous thrombosis) and ages at stroke occurrence (e.g., neonatal, perinatal, childhood stroke; Fuentes et al., 2016). As such, these findings are not generalizable to exclusively perinatal AIS samples. In contrast, within the exclusively perinatal AIS sample of the current study, a moderating role of lesion volume and seizure disorder status was identified. Limited research to date has explored long-term trajectories or the interactions between these factors and neurocognition.

Given the longitudinal design of the present study, a significant interaction between lesion volume and age in perinatal AIS was identified, which indicates that lesion volume moderated neurocognitive change. To date, lesion volume has been identified as a notable risk

factor in the cross-sectional and mixed pediatric stroke research (i.e., mixed stroke types and age at stroke onsets; Fuentes et al., 2016). Some studies have reported an association between larger lesion volume and poorer neurocognitive functioning (Hajek et al., 2014; Levine et al., 2005; Lo et al., 2014). In contrast, other studies have failed to detect an association between lesion volume and neurocognitive functioning (Ballantyne et al., 2008; Ricci et al., 2008). This discrepancy has been attributed to methodological factors such as lesion size classification systems that varied across studies, in addition to other methodological inconsistencies (Fuentes et al., 2016). Emerging evidence points to neurological impairment (Hajek et al., 2014) and time since stroke as possible moderators of the relationship between lesion volume and neurocognitive outcomes (Levine et al., 2005). For example, in a sample of children who experienced neonatal and childhood ischemic strokes (excluded presumed perinatal), Hajek et al. (2014) found that larger lesion volume was associated with poorer neurocognitive functioning on a robust composite score (i.e., Wechsler Abbreviated Scale of Intelligence IQ, Full-Scale IQ). They examined neurological impairment using the Pediatric Stroke Outcome Measure; however, the interaction between lesion volume and neurological impairment was only found for the Processing Speed sub-domain, and thus did not represent a robust moderation of neurocognition spanning a broad range of domains (Hajek et al., 2014). Nonetheless, stroke volume and Pediatric Stroke Outcome Measure total scores were significantly negatively correlated, suggesting that larger lesions are associated with poorer neurological functioning (Hajek et al., 2014), although further investigation into the impact on neurocognition is warranted.

In contrast, Levine et al. (2005) examined a small sample ($N = 15$) of children and young adults who presented with infantile hemiparesis and were identified as having unilateral lesions (i.e., mixed stroke sample). Although children with larger lesions fared worse than children with

smaller lesions on measures of neurocognition when assessed between the ages of 4 and 6 years, individuals with smaller lesions evidenced greater declines in neurocognitive functioning when assessed again several years later, thus reflecting an interaction between lesion volume and time since stroke (Levine et al., 2005). Levine and colleagues (2005) proposed that larger lesions are associated with more impairing, immediate, and stable neurocognitive deficits, whereas smaller lesions are associated with milder cognitive deficits that emerge over time. These findings reflect differences in the emergence of deficits over time depending on lesion volume, such that deficits emerge more acutely for those with large lesions whereas they take longer to present for those with smaller lesions. These results from a two-time point, incremental design with a mixed sample cannot be directly compared to the findings from the current exclusively perinatal AIS sample which was tested longitudinally at several time points across early and late childhood, adolescence, and early adulthood. Nonetheless, in the current study, individuals with large lesion volumes initially showed a rapid neurocognitive decline; however, they showed relative improvement over time compared to individuals with small and medium lesion volumes who showed less extreme but more stable challenges across follow-up. Of note, Levine et al. (2005) did not specify their lesion size classification systems and only differentiated between small and large lesions; therefore, their findings for small and large lesion volumes cannot be directly compared to the present findings across small, medium, and large volumes. Within the studies that have explored neurocognitive outcomes longitudinally, only one considered the effects of lesion volume on neurocognition (Anderson et al., 2020). Notably Anderson et al., (2020) found that larger lesion volume was associated with poorer neurocognition in a sample of perinatal and childhood AIS, when examined longitudinally over a 12-month follow-up period post-stroke.

In the present study, a significant interaction was found between seizure disorder status and age in perinatal AIS, indicating that seizure disorder status moderated the rate of neurocognitive change over time. To date, cross-sectional research with heterogenous pediatric stroke samples (i.e., different stroke types and ages at stroke occurrence) has identified seizure disorder status to be a predictor of neurocognition following pediatric stroke more broadly (Fuentes et al., 2016). Studer et al. (2014) found that overall neurocognitive outcomes were lower post pediatric AIS in children who experienced both acute and persistent seizures. Likewise, in neonatal AIS specific samples, neurocognitive impairments have been found to be significantly associated with seizures/symptomatic epilepsy (Grunt et al., 2015; Pavlovic et al., 2006; Ricci et al., 2008). The limited longitudinal studies to date have also demonstrated consistent negative effects of seizure disorder status on neurocognition. Both Anderson et al. (2020) and Ballantyne et al. (2008) demonstrated negative effects of seizure disorder status on neurocognition. Anderson et al. (2020) showed that the absence of seizures predicted better neurocognition, whereas Ballantyne et al. (2008) showed that seizures limited the capacity for early plasticity in their sample across development such that children with histories of seizures showed less favourable neurocognitive outcomes than children without histories of seizures. Children with histories of seizures experienced different neurocognitive trajectories than children without seizures, with small improvements apparent in the latter group between preschool and school age time points (Ballantyne et al., 2008). Similar findings have been reported from other longitudinal studies with mixed/non-specified stroke subtypes which were not specific to AIS. Namely, the presence of seizures/epilepsy has been found to have deleterious effects on verbal (Muter et al., 1997) and non-verbal (Gonzalez-Monge et al., 2009; Muter et al., 1997) aspects of neurocognition. In contrast, Levine et al. (2005) did not find effects of seizure history on

neurocognition, which they attributed to their small sample size and exclusion of children who experienced more than mild seizure disorders from the cohort.

Within the present study, analyses of the main and moderating effects of sex, lesion laterality, medical comorbidities, and neurological diagnoses yielded non-significant results. In contrast, existing cross-sectional research in heterogenous pediatric stroke samples (i.e., different stroke types and ages at stroke occurrence) has identified sex, lesion laterality, medical comorbidities, and neurological diagnoses as predictors of neurocognition following pediatric stroke more broadly (Fuentes et al., 2016). Many questions remain concerning the possible sex dimorphism of neurocognitive outcomes following pediatric stroke, with evidence that the effects of sex on neurocognitive outcomes are moderated by lesion laterality (Braun et al., 2001). Likewise, research has yielded discrepant findings concerning the influence of lesion laterality on neurocognitive functioning, including investigations primarily into the influence of the hemispheric side of the lesion (i.e., right versus left hemispheric strokes) rather than bilateral versus unilateral infarcts (as was the case in the present study; Fuentes et al., 2016). These discrepancies have led investigators to conclude that the relationship between hemispheric side of the lesion and neurocognitive outcome is moderated by age at injury, age at assessment, and the specific cognitive domain being assessed (Stiles et al., 2010; Westmacott et al., 2009, 2010). Existing studies in generalized and specific pediatric stroke samples have not examined the influence of medical comorbidities on neurocognitive functioning. Nonetheless various specific medical comorbidities common alongside perinatal AIS, including congenital heart disease (Schaefer et al., 2013; Vázquez López et al., 2017), are associated with specific neurocognitive sequelae that can be devastating alongside comorbid stroke. In contrast, neurological impairment has been consistently identified as a risk factor for negative neurocognitive outcomes following

pediatric stroke (Allman & Scott, 2013; Hajek et al., 2014; Studer et al., 2014). However, the definition of what constituted neurological impairment has differed across studies, including hemiplegia/paresis or visual field deficits (Allman & Scott, 2013; Studer et al., 2014) and assessment on the Pediatric Stroke Outcome Measure (Hajek et al., 2014). Neurological diagnoses encompassed differing neurological conditions within the present study; therefore, this methodological variability may account for the discrepancy in results. Nonetheless, sex, lesion laterality, medical comorbidities, and neurological diagnoses have not been found to negatively influence neurocognition in the limited longitudinal studies having occurred to date; however, this may be due to the lack of evaluation of these variables. The lack of attention to these potential risk factors highlights the need for ongoing investigation of relevant risk factors within homogenous samples using longitudinal designs to account for the high degree of interactions apparent across predictors post pediatric stroke (Fuentes et al., 2016).

Effect of Perinatal AIS Type (Neonatal Versus Presumed Perinatal AIS)

This study was novel in that it represents the first known comparison of neurocognitive outcomes between acute neonatal and presumed perinatal AIS types. In addition to the moderating roles of lesion volume and seizure disorder status, perinatal AIS type moderated the linear and quadratic components of the Full-Scale IQ trajectory. Specifically, although individuals with presumed perinatal AIS diagnoses showed a more rapid neurocognitive decline initially, they appeared to show relative improvement over time compared to individuals with neonatal AIS diagnoses who showed a consistent decline. As such, individuals with neonatal relative to presumed perinatal AIS demonstrated worse neurocognitive functioning at the end of follow-up.

The acute presentation of perinatal AIS refers to neurological symptoms occurring before 28 days of life, often in the form of symptomatic seizures (Kirton & deVeber, 2009). Individuals with a delayed presentation appear asymptomatic in the neonatal period, with presentation delayed until late infancy or toddlerhood when delayed motor milestones, early hand preference/hemiparesis, or symptomatic epilepsy are recognized and a retrospective diagnosis is provided due to the presence of a chronic infarct on neuroimaging (Golomb et al., 2001; Kirton & deVeber, 2009). Whether the age at presentation depends on differences in radiological appearance, severity of stroke, environmental, or other factors is largely unknown. It has been posited that certain patterns of injury, such as involvement of deep structures, may be more difficult to diagnose in the newborn period because the infants are less likely to exhibit resulting neonatal seizures (Lee et al., 2005). Additionally, chorioamnionitis in the mother has been associated with perinatal AIS diagnosis in the newborn period (i.e., acute neonatal AIS) but not with perinatal AIS diagnosis later in infancy (i.e., presumed perinatal AIS; Lee, Croen, Backstrand, et al., 2005). As such, the presence of inflammation may increase the likelihood of neonatal symptoms, thus prompting an earlier diagnosis of perinatal AIS. Alternatively, the pathogenesis of perinatal AIS may differ for infants with earlier versus later presentations. Nonetheless, the underlying mechanisms distinguishing acute neonatal and presumed perinatal AIS diagnoses remain unknown, with only theoretical speculation to date.

Broadly, acute neonatal and presumed perinatal AIS are thought to represent the same disease, differing only in the timing of presentation (Kirton & De Veber, 2013). Attributable in part to a strong identification bias (i.e., only late symptomatic infants will present and be diagnosed), presumed perinatal AIS has been found to involve relatively severe outcomes compared with other perinatal stroke disease states (Kirton & De Veber, 2013). Hemiparetic

cerebral palsy is the most frequently identified morbidity following presumed perinatal AIS, present in greater than 70-90% of children (Golomb et al., 2001; Kirton et al., 2008; Lee et al., 2005; Trauner et al., 1993), with motor outcomes predicted by basal ganglia involvement (Miller et al., 2007). Presumed perinatal AIS also commonly includes cortical involvement, which creates additional late clinical presentations and long-term outcomes including non-motor developmental delays such as language, cognitive, and behavioural morbidities as well as seizures/epilepsy (Fitzgerald et al., 2007; Golomb et al., 2001; Kirton et al., 2008, 2010; Lee, Croen, Lindan, et al., 2005; Miller et al., 2007). These non-motor outcomes have been less widely studied to date. These non-motor findings cannot be directly compared to the results of the present study which included formal neurocognitive testing and perinatal AIS type comparison groups. However, these existing findings align with the general demonstration in the present study that individuals with presumed perinatal AIS initially show a more rapid neurocognitive decline relative to acute neonatal AIS. That said, the need for longitudinal research is highlighted given that individuals with presumed perinatal AIS showed improvement over time compared to individuals with neonatal AIS in the present study. Likewise, individuals with neonatal AIS showed a consistent decline, resulting in worse neurocognitive functioning near the end of follow-up. As such, the comparison between acute neonatal and presumed perinatal AIS may be more nuanced, with differing recovery mechanism and neurocognitive trajectories changing over time.

To date, there has been more research on neurocognitive outcomes for individuals with acute neonatal AIS than for those with presumed perinatal AIS (Kirton & De Veber, 2013), with little to no systematic comparisons of neurocognitive outcomes between the two groups. However, Lee et al., (2005) found increased risk for cerebral palsy in children with a delayed

presentation (i.e., presumed perinatal AIS) relative to acute neonatal AIS (relative risk: 2.2). Lee and colleagues (2005) found no significant differences between the two groups for epilepsy, language, and behavioural outcomes; however, they did not assess formal language and cognitive abilities. Other studies have also indicated that infants with presumed perinatal AIS tend to have worse motor outcomes relative to acute neonatal AIS (Wu et al., 2004), as consistent with the typical motor impairments found in presumed perinatal AIS outcome research. Lee et al., (2005) found that infants who present with motor-related stroke indicators later in infancy were more likely to have sustained injury to the internal capsule, which they posited as the potential mechanism for poor prognoses in the presumed perinatal AIS group. Nonetheless, posits of factors differentiating between acute neonatal and presumed perinatal AIS remain largely theoretical in nature and require investigation in homogenous samples using longitudinal methods, as in the present study. There is a need for investigations into neurocognitive and non-motor outcomes specifically, to extend beyond the understanding of heightened motor risk alone.

Effect of Early Screening in Acute Neonatal AIS

In the present study, predictors of neurocognitive functioning were examined within a homogenous neonatal AIS sub-sample of the larger mixed perinatal AIS cohort. Despite non-significant effects of seizure disorder status, lesion volume moderated the linear component of the Full-Scale IQ trajectory for the neonatal AIS sub-sample. This moderation helps elucidate risk posed by larger lesion volume even in individuals who experienced exclusively neonatal AIS. Within the studies that have included exclusively neonatal AIS samples, only Ricci et al. (2008) considered the effects of lesion volume on neurocognition and reported no association between extent of tissue affected within the middle cerebral artery territory and neurocognitive impairment in children 5-10 years post neonatal AIS. However, their sample did not capture the

diversity and compounding neurocognitive risks present within a typical neonatal AIS sample (no neurological comorbidities, only full-term children, only middle cerebral artery territory infarctions; Ricci et al., 2008). Likewise, their study primarily involved neurocognitive testing during the preschool period (~5 years) prior to the hypothesized emergence of deficits in later childhood (Ricci et al., 2008), which may explain the discrepancies with the results of the present study. Nonetheless, the findings from the present study in an exclusively neonatal AIS sub-sample are consistent with those of Study 1, wherein lesion volume moderated Full-Scale IQ within a neonatal AIS sample. More broadly, it appears that larger lesion volume is consistently associated with poorer neurocognitive functioning in the majority of the cross-sectional and mixed pediatric stroke literature to date (i.e., mixed stroke types and age at stroke onsets; Fuentes et al., 2016; Hajek et al., 2014; Levine et al., 2005; Lo et al., 2014). Although these findings cannot be directly compared to an exclusively neonatal AIS sub-sample, they do provide evidence that lesion volume is a consistent risk factor following perinatal AIS, as consistent with the results from the present study in both a mixed perinatal AIS (neonatal and presumed perinatal) sample and an exclusively neonatal AIS sub-sample. In a mixed stroke sample, there was evidence that time since stroke was a possible moderator of the relationship between lesion volume and neurocognitive outcomes (Levine et al., 2005). There was also evidence that lesion volume was a neurocognitive risk factor in longitudinal evaluation (Anderson et al., 2020), highlighting the importance of longitudinal research to elucidate relevant risk factors, and moderators, that may underly potential differences, or lack thereof, between stroke subtypes.

In the present study, seizure disorder status did not moderate the Full-Scale IQ trajectory within the neonatal AIS sub-sample of the larger cohort. This finding was consistent with the findings from Study 1 wherein seizure disorder status was not a predictor of neurocognition in a

neonatal AIS sample. These findings highlight a potentially different risk of seizure disorder status across stroke subtypes such that seizure disorder status poses heightened risk in perinatal AIS more broadly (and potentially the presumed perinatal AIS sub-group), but not in an exclusively neonatal AIS sub-sample. In contrast, the limited neonatal AIS specific research to date has indicated that neurocognitive impairments are significantly associated with seizures/symptomatic epilepsy (Grunt et al., 2015; Pavlovic et al., 2006; Ricci et al., 2008). The discrepancy between existing findings and those of the present study may be attributable to methodological differences, including limited representation of compounding neurocognitive risks in a typical neonatal AIS sample (e.g., exclusion for pre-term birth, exclusion of different infarction locations, etc.), heterogenous testing times, and limited follow-up into later childhood. Existing longitudinal studies in mixed stroke samples have demonstrated consistent negative effects of seizure disorder status on neurocognition (Anderson et al., 2020; Ballantyne et al., 2008); however, these findings may be attributable to the negative effects of seizure disorder in perinatal AIS more broadly, as consistent with the present findings within a mixed neonatal and presumed perinatal AIS sample. Taken together, these findings highlight the need for ongoing investigation with homogenous samples using longitudinal evaluation methods.

The present study was novel in its evaluation of the role of protective factors, namely early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic. Notably, adjustment for early screening in infancy was relevant in this group (i.e., resulting in improved model fit), with consistently lower functioning observed for those who did not receive early screening in infancy, despite overall non-significant main and moderating effects. These findings are consistent with the vast literature regarding early identification and subsequent intervention facilitated through early screening (Arruda et al., 2023; Guilfoyle et al., 2012; Newman, 2012).

The early developmental period can be seen as a window of opportunity in which early screening/assessments can facilitate early identification. Early identification can then inform prevention and early interventions which, together, can harness the neuroplasticity and dynamic development that is unique to the early developmental period to maximize neurodevelopmental trajectories across the lifespan. As such, given the rapid early development and neuroplasticity in the infancy and early childhood periods (Galván, 2010; McCain, 2020), screenings and full assessments early in development have the potential to identify high risk groups and inform precision-based interventions that can alter neurodevelopmental trajectories (Anderson et al., 2000; Anderson et al., 2001; Famri et al., 2007; Max et al., 2003; Nass, 1997). Nonetheless, the results of the current study are preliminary in nature and highlight a critical gap in the literature regarding the influence of protective factors on neurocognitive outcomes following perinatal AIS. There is a critical need to begin evaluating the protective role of early screening/assessments to support the early identification of neurocognitive challenges and inform interventions for this high-risk group of children who experience early neurocognitive risks that appear to worsen across development.

Limitations and Future Directions

Although this study represents a sizable sample of individuals with perinatal AIS, larger sample sizes with adequate and comparable sub-groups would enable more robust comparisons between individuals with acute neonatal and presumed perinatal AIS. Larger sample sizes would also support analyses of more complex models (i.e., compounding moderating and main effects) to elucidate the interconnections among predictor variables over time. Although this study was novel in capturing anywhere from one to six assessment time points spanning an extensive follow-up interval across early and late childhood, adolescence, and early adulthood (~2.5 to 25

years), most individuals underwent one to three assessments (~24-100%), with fewer receiving four to six assessments (~0.5-11%). As such, the results generally represented follow-up across childhood (~ age 2.5-5 years) into early adolescence (~ age 12 years), with less evaluation into adulthood. Overall, assessment of more individuals over a longer period with more frequent assessment time points would allow for greater power and precision in determining how neurocognition is affected over the course of stroke recovery across the developmental period. Given that this study included robust longitudinal evaluation across comparable Wechsler measures, neurocognition, and the impact of relevant predictors, could be examined across the overarching neurocognitive domain (i.e., Full-Scale IQ) and related sub-domains (i.e., Verbal Comprehension Index, Perceptual Reasoning Index, Processing Speed Index, Working Memory Index). However, given the preliminary and exploratory nature of the secondary objectives regarding the influence of perinatal AIS type and growth trajectories of those who received early screening in a neonatal AIS sub-sample, these evaluations only focused on the overarching neurocognitive domain (i.e., Full-Scale IQ). As such, future research is needed to determine whether these results generalize to neurocognitive sub-domains. More broadly, future investigations are needed to examine whether all the results from the present study generalize to other neuropsychological domains (e.g., language, memory). Other individual-related predictors, including risk and protective factors, should also be investigated. Future research is needed to both replicate and extend the present findings related to neurological/stroke-related risk factors and the protective role of early screening in perinatal AIS. Specifically, evaluation into potential demographic and psychosocial factors (e.g., parental education, socioeconomic status, income) that may influence neurocognition is highly needed and could directly inform intervention planning. These investigations should occur in homogenous samples (i.e., neonatal versus

presumed perinatal AIS) and longitudinally to elucidate high-risk groups in unique stroke subtypes and to enable consideration of interactions among various factors.

An additional limitation of the present study was the lack of a comparison group. The incorporation of age-matched healthy individuals could account for potential practice effects, and would provide a reference point of normal neurocognitive developmental trajectories. Performance gains may occur due to familiarity associated with repeated test administration, even when assessments are separated by a minimum of one year, as was the case for the present sample. However, the potential confound of repeated testing would be expected to reduce the likelihood of detecting a negative trajectory over time, as was found in the present study, because the observed trajectories would be more positively inclined. Nonetheless, the use of standardized values is a limitation in longitudinal research because the derivation of standard scores is dependent on the quality of the normative data, which in turn introduces more variability. Nevertheless, standard scores enable a more precise and meaningful comparison of scores across individuals in a sample, accounting for age-related developmental changes.

Despite these limitations, the present study employed a novel and innovative design including comprehensive follow-up across early and late childhood, adolescence, and early adulthood at multiple time points spanning critical developmental periods in a diverse perinatal AIS sample. Therefore, this study represents the first longitudinal evaluation of neurocognition and related risk and protective factors in perinatal AIS across development. Likewise, this study represents the first known investigation into differences in neurocognitive trajectories between neonatal and presumed perinatal AIS subtypes.

Implications and Conclusions

This is the first study to examine longitudinal neurocognitive trajectories across several developmental periods for individuals who experienced perinatal AIS. There was evidence of neurocognitive decline across several neurocognitive capacities spanning early and late childhood, adolescence, and early adulthood, in keeping with an early vulnerability hypothesis of brain recovery. As such, these findings call into question the belief that infancy is a period in which neuroplasticity can offset the potential consequences of central nervous system damage. Moreover, larger lesion volume and seizure disorder status were associated with greater neurocognitive decline in perinatal AIS. Likewise, perinatal AIS type moderated the overall neurocognitive trajectory, such that individuals with presumed perinatal AIS diagnoses showed a more rapid neurocognitive decline initially and relative improvement over time, whereas individuals with neonatal AIS diagnoses showed a consistent decline. In contrast, in a neonatal AIS sub-sample, only larger lesion volume was associated with greater neurocognitive decline, as well as consistently lower functioning for individuals who did not receive early screening in infancy. This study highlights the importance of longitudinal follow-up in this population to elucidate stroke recovery mechanisms and the variability that exists after perinatal AIS. As such, individuals with perinatal AIS should undergo routine neuropsychological assessments across critical developmental periods, especially as they experience heightened cognitive and academic demands with age. Advanced modelling methods, as those employed in this study, are essential to capture the interplay between brain recovery after early brain insult and the complex neurodevelopmental course. Trajectory modelling reveals various pathways for recovery and development and helps determine which factors influence alternative pathways. Clinically, improved understanding of predictors of neurocognitive trajectories and unique recovery

expectations for specific stroke subtypes will inform the early identification of high-risk groups and the development of precision-based interventions.

GENERAL DISCUSSION

Neurocognitive Growth Trajectories

To date, evaluations of neurocognitive functioning following perinatal AIS have comprised cross-sectional or increment-based (i.e., simple differences between scores on two occasions) designs. These designs are limited in that they do not enable measurement of change over time and have the potential to confound true change with measurement error (Rogosa et al., 1982). With cross-sectional or increment-based designs, preliminary research on predictors of neurocognitive functioning post perinatal AIS has identified age at stroke and time since stroke as influencing factors. Reports indicate that early stroke (i.e., before 1 year of age) is a risk factor for less optimal neurocognitive outcomes (Allman & Scott, 2013; Chapman et al., 2003; Max et al., 2010; Studer et al., 2014; Westmacott et al., 2010). Hence, a non-linear model of age at stroke effects has been proposed, suggesting that stroke in middle childhood (5 to 10 years) may lead to better neurocognitive outcomes compared to stroke occurring in the perinatal (0 to 5 years) or late childhood (10 to 18 years) periods (Allman & Scott, 2013; Everts et al., 2008; Ganesan et al., 2000; Pavlovic et al., 2006). Time since stroke has also been shown to impact neurocognitive outcomes after perinatal AIS (Ballantyne et al., 2008; Everts et al., 2008; Levine et al., 2005; Westmacott et al., 2009). Moreover, moderating effects of age at stroke and/or time since stroke have been found when considering the influence of other stroke-related predictors (i.e., lesion volume, lesion laterality, seizures) on neurocognition post perinatal AIS (Ballantyne et al., 2008; Fuentes et al., 2016; Hajek et al., 2014; Levine et al., 2005).

Taken together, there is longstanding evidence that age at stroke and time since stroke impact neurocognition after perinatal AIS; however, these effects cannot be fully elucidated without longitudinal designs that evaluate neurocognitive trajectories across multiple time points

and over a lengthy time interval spanning critical developmental periods. More specifically, cross-sectional and increment-based designs cannot address whether children who have experienced perinatal AIS start at a lower level of neurocognition or whether they "grow into deficits". Evaluation of "growing into deficits" requires consideration of whether the child is experiencing a progressive widening of the gap between their performance and age-matched peers, or whether they have experienced a static insult to a neurocognitive trajectory that was impacted early in its maturation, but not necessarily in a progressively deteriorative manner. Evaluations of "growing into deficits" also exist across a backdrop of competing theoretical perspectives regarding mechanisms of stroke recovery in children who experience early brain injury, including models of increased potential for recovery (Ballantyne et al., 2008; Dennis, 2010; Kennard, 1936; Kim et al., 2009), as well as heightened vulnerability (Anderson et al., 2011; Chugani et al., 1996). Caregivers have identified improved knowledge on long-term neurocognitive outcomes following pediatric AIS as a key research priority (Edwards et al., 2015), further highlighting the critical nature of this research gap.

The present studies harnessed growth curve modelling to provide the first analyses of longitudinal neurocognitive trajectories and predictors of heterogeneity in trajectories across the developmental course post perinatal AIS, including 1) infancy and early childhood (Study 1) and 2) early and late childhood, adolescence, and early adulthood (Study 2). Across both studies, declining Full-Scale IQ trajectories were found, indicating a loss of developmental gain over both developmental periods, despite age-appropriate functioning consistently extrapolated statistically at stroke occurrence (i.e., birth). The current results are notable in that they provide compelling evidence of a greater vulnerability, rather than a greater plasticity/resiliency, of the immature brain that faces early injury, as consistent with the "early vulnerability hypothesis"

(Anderson et al., 2011; Chugani et al., 1996). The broadly age-appropriate neurocognitive functioning apparent at stroke occurrence (i.e., birth) based on statistical extrapolation in both samples supports the conceptual understanding that the extent of functional impairment due to early injury may not be immediately apparent. Instead, children affected by stroke may fail to make age-appropriate developmental gains or seemingly "grow into" new deficits over time alongside increasing developmental demands and expectations (Anderson et al., 2011; Gordon et al., 2015; Westmacott et al., 2009). Within the present studies evaluating two different developmental time courses, including infancy and early childhood as well as early and late childhood, adolescence, and early adulthood, it is notable that the emergence of deficits, when examined longitudinally, were identified as early as in the infancy and early childhood period, as in Study 1. Consistent with the emergence of deficits over time (i.e., growing into deficits), the plasticity of the brain is thought to accommodate early developmental capacities but, with the increasing demands of more complex skills and the need to process information in a more complex and efficient manner, the biological reserve is no longer thought to be sufficient, and deficits are thought to be revealed with age (Anderson et al., 2005; Dennis, 2000). The emergence of deficits is thus thought to be demonstrated in middle/late childhood; however, the results of the present studies highlight that, in children who experience perinatal AIS, the capacity for accommodation may be more limited. As such, emerging deficits can be seen as early as during the transition from infancy into early childhood, with more apparent demonstration into late childhood, adolescence, and adulthood.

Taken together, the results from the present studies shed light on recovery expectations following perinatal AIS. To date, there have been discrepant results regarding long-term neurocognitive functioning following perinatal AIS. Some studies have suggested age

appropriate neurocognitive functioning post perinatal AIS (Chabrier et al., 2016; Cioni et al., 1998; Hetherington et al., 2005; Pavlovic et al., 2006; Ricci et al., 2008; Schatz et al., 2000; Trauner et al., 1993; Wulfeck et al., 1991), whereas others have revealed neurocognitive deficits (Ballantyne et al., 1994; Grunt et al., 2015; McLinden et al., 2007; Talib et al., 2008; Trauner et al., 2001; Westmacott et al., 2010). These discrepancies are attributed to numerous methodological limitations. Although the most notable limitation has been a lack of longitudinal evaluation across critical developmental periods, existing research has also been limited by other methodological heterogeneities, including short/varying test-retest intervals, small cohort sizes, varying ages at assessment, differing/non-standardized measures, limited follow-up, and mixed samples (different stroke subtypes/ages at stroke; Ballantyne et al., 2008; Greenham et al., 2017; Levine et al., 2005; McLinden et al., 2007). Therefore, the current results are also notable in that they involved homogenous samples of children who experienced perinatal AIS (rather than including other stroke subtypes/ages at stroke) with methodological consistency. Comparison of the results between the two studies also allowed examination into more homogenous samples such that similar patterns of neurocognitive decline were apparent in both an exclusively neonatal AIS sample (Study 1) as well as a more diverse perinatal AIS sample including children with both acute neonatal and presumed perinatal AIS diagnoses (Study 2). These findings point to similar recovery expectations for perinatal AIS more broadly and highlight the importance of examining neurocognitive trajectories in homogenous stroke samples as different mechanisms of recovery may exist when timing of stroke occurrence differs more dramatically (e.g., perinatal AIS versus childhood AIS). As such, future research is warranted using similar longitudinal and methodologically consistent designs in homogenous stroke samples given the complexities

related to the intersection of brain recovery post stroke and the dynamic early neurodevelopmental course.

The current results are notable in that longitudinal neurocognitive decline was apparent across follow-up for most sub-domains evaluated in Study 2, in addition to the negative Full-Scale IQ trajectories found across Studies 1 and 2. Once again, this neurocognitive decline across specific sub-domains occurred despite age-appropriate functioning statistically extrapolated at stroke occurrence (i.e., birth), as consistent with the "early vulnerability hypothesis" (Anderson et al., 2011; Chugani et al., 1996). Emerging deficits were specifically apparent for Verbal Comprehension, Processing Speed, and Working Memory; however, there was no evidence of a significant decline for the Perceptual Reasoning Index. Significant trajectory curvature over time was only indicated for the Working Memory Index. Overall, this preliminary investigation beyond Full-Scale IQ alone highlights the need for specific evaluation of distinct neurocognitive abilities to better understand whether neurocognitive sub-domains show differences in recovery, and overall vulnerability versus resilience, after perinatal AIS. As such, the discrepancies in the extant research alongside the strengths of the current study designs highlight the need for longitudinal evaluation with homogenous populations (i.e., consistent stroke type and time of stroke), systematic comparison among stroke subtypes, evaluation beyond full-scale IQ to include neurocognitive sub-domains, and a more advanced trajectory analytical approach.

Predictors of Neurocognition

There are limitations in the extant research on identified predictors of neurocognition following pediatric stroke (i.e., age at stroke, time since stroke, sex, etiology, lesion characteristics [location, laterality, volume], neurological impairment, seizures), including heterogenous samples spanning various pediatric stroke types (e.g., hemorrhagic, arterial

ischemic, cerebral sinovenous thrombosis) and ages at stroke occurrence (e.g., neonatal, perinatal, childhood stroke; Fuentes et al., 2016). As such, existing findings are not generalizable to exclusively perinatal AIS samples. Likewise, there is a paucity of longitudinal research exploring the interactions between previously identified risk factors and neurocognition using longitudinal designs. As such, the present studies were unique in their longitudinal evaluation of relevant risk factors in homogenous neonatal AIS and more diverse perinatal AIS samples, thus allowing both main and moderating effects to be examined across time. In comparing the findings between Study 1 and Study 2 with respect to predictors of neurocognitive trajectories, similarities and differences were also identified between the neonatal AIS and more diverse perinatal AIS samples.

In both the neonatal AIS and the more diverse perinatal AIS sample, a significant interaction between lesion volume and age was identified, thus indicating that lesion volume moderated the rate of neurocognitive change for Full-Scale IQ over time. Likewise, these results held within an exclusively neonatal AIS sub-sample in Study 2. To date, lesion volume has been identified as a notable risk factor in the cross-sectional and mixed pediatric stroke research (i.e., mixed stroke types and age at stroke onsets; Fuentes et al., 2016). Nonetheless, there have been discrepancies in findings across studies, with some studies reporting an association between larger lesion volume and poorer neurocognitive functioning (Hajek et al., 2014; Levine et al., 2005; Lo et al., 2014) and others failing to detect an association (Ballantyne et al., 2008; Ricci et al., 2008). These discrepancies have been largely attributed to methodological factors such as lesion size classification systems that varied across studies, in addition to other methodological inconsistencies such as heterogenous stroke types included in evaluation (Fuentes et al., 2016). As such, the present studies, which utilized consistent designs (e.g., same lesion volume

classification system), confirmed that lesion volume is a notable moderator of neurocognitive trajectories in perinatal AIS more broadly, as well as in neonatal AIS more specifically. Although lesion volume was a significant moderator in both samples, the interaction effects differed over time. In the exclusively neonatal AIS sample using a simplistic linear change model (Study 1), children with small lesion volumes showed neurocognitive gains over time, whereas children with medium and, most notably, large lesion volumes showed neurocognitive declines. In contrast, in the more diverse perinatal AIS sample using a more robust quadratic change model (Study 2), individuals with large lesion volumes showed more rapid neurocognitive decline; however, they showed relative improvement over time compared to individuals with small and medium lesion volumes. As such, similar functioning was apparent at the end of follow-up for all groups. That said, although lesion volume appears to be a consistent moderator across both samples, the nature of its interactive effect on trajectories may differ for stroke subtypes within perinatal AIS. Future research offering systematic comparisons between these perinatal AIS subtypes is thus warranted.

There were also differences in the results pertaining to relevant predictors between the two studies. For the exclusively neonatal AIS sample in Study 1, a main effect of medical comorbidities was found. That is, the presence of medical comorbidities (i.e., congenital heart disease, genetic conditions) contributed to lower neurocognition statistically extrapolated at stroke occurrence and thus generally lower performance across time relative to the absence of medical comorbidities. These findings were not replicated within the broader perinatal AIS sample encompassing neonatal AIS and presumed perinatal AIS diagnoses in Study 2. Notably, the present studies represent the first known research to investigate the influence of congenital heart disease, as well as genetic conditions, within stroke populations with a neurocognitive lens,

as previously highlighted as a key area for future research by Fuentes et al. (2016). Results from Study 1 indicate heightened risk associated with medical comorbidities as differences in neurocognition were statistically extrapolated at stroke occurrence (i.e., birth), likely related to comorbid congenital heart disease and neonatal AIS. Given that a significant main effect was found rather than a moderation, children with congenital heart disease and neonatal AIS likely present with a different mechanism of early brain injury relative to children who experience neonatal AIS alone. This hypothesis is consistent with previous research which has indicated that children with congenital heart disease experience increased risk of neurological sequelae due to the likelihood of hypoxia and chronic cerebral hypoperfusion that often begins in the fetal period (Vázquez López et al., 2017). Cardiac surgery and post-operative hypodynamic instability are other neurological risk factors for these children which often occur early in infancy (Majnemer et al., 2009). Congenital heart disease has been identified as one of the most common causes of perinatal ischemic stroke (Cárdenas et al., 2011; Friedman, 2009), often secondary to early cardiac procedures (e.g., catheterization, cardiac surgery, or mechanical circulatory support devices; Vázquez López et al., 2017). Given that these procedures typically occur acutely in the neonatal period, the present findings may reveal preliminary evidence of unique risk related to congenital heart disease in neonatal AIS samples as compared to presumed perinatal AIS; however, systematic comparison between the perinatal AIS subtypes is warranted to further investigate this hypothesis. Nonetheless, strokes in children who have congenital heart disease are more frequently bilateral, multifocal, affect both anterior and posterior circulation, and show a greater tendency for recurrence and hemorrhagic transformation (Vázquez López et al., 2017). As such, stroke etiologies like congenital heart disease are associated with their own neurocognitive sequelae that can be especially debilitating alongside comorbid stroke, thus

impacting neurocognition early in development, potentially as early as at stroke occurrence, as suggested in Study 1.

For the diverse presumed perinatal AIS sample in Study 2, a significant interaction between seizure disorder and age was identified. That is, seizure disorder status moderated the rate of neurocognitive change and was associated with greater neurocognitive decline and trajectory curvature for Full-Scale IQ. Findings did not replicate within the exclusively neonatal AIS sample in Study 1 when followed across infancy and early childhood, nor did they hold in the exclusively neonatal AIS sub-sample of Study 2 when followed across early and late childhood, adolescence, and early adulthood. As such, these results highlight a potentially different risk of seizure disorder status across perinatal AIS subtypes such that seizure disorder status poses heightened risk for perinatal AIS more broadly (and potentially the presumed perinatal AIS sub-group), but not for neonatal AIS. In contrast, the limited research to date in exclusively neonatal AIS samples has indicated that neurocognitive impairments are significantly associated with seizures/symptomatic epilepsy (Grunt et al., 2015; Pavlovic et al., 2006; Ricci et al., 2008). The discrepancy between existing findings and those of the present studies may be attributable to methodological differences, including limited representation of compounding neurocognitive risks in a typical neonatal AIS sample (e.g., exclusion for pre-term birth, exclusion of different infarction locations, etc.), heterogenous testing times, and limited follow-up into later childhood. More broadly, cross-sectional research with heterogenous pediatric stroke samples (i.e., different stroke types and ages at stroke occurrence) has identified seizure disorder status to be a predictor of neurocognition following pediatric stroke (Fuentes et al., 2016). Existing longitudinal studies in mixed stroke samples have also demonstrated consistent negative effects of seizure disorder status on neurocognition (Anderson et al., 2020; Ballantyne

et al., 2008). However, these past findings may be attributable to the negative effects of seizure disorder status in perinatal AIS more broadly, as consistent with the present findings within a mixed neonatal and presumed perinatal AIS sample. Taken together, these discrepancies highlight the need for ongoing investigation with homogenous samples using longitudinal evaluation methods, including systematic comparison between the perinatal AIS subtypes.

Overall, the similarities and differences highlighted with respect to predictors of neurocognitive trajectories (i.e., main and moderating effects) between the present studies indicate a critical need for systematic comparisons among stroke types. With preliminary evidence of differences between perinatal AIS subtypes (i.e., neonatal AIS versus presumed perinatal AIS) in the present studies, more robust differences may exist when large-scale comparisons occur among different pediatric stroke types (e.g., hemorrhagic, arterial ischemic, cerebral sinovenous thrombosis) with more vast differences in ages at stroke occurrence (e.g., neonatal, perinatal, childhood stroke) across development. Notably, within Study 2, the moderating role of lesion volume and seizure disorder status differed slightly when evaluated across neurocognitive sub-domains, indicating the need for specific investigation into predictors of distinct neurocognitive capacities as well. Moreover, it remains essential that future studies explore various neurocognitive outcomes, investigate differences among stroke types, and utilize longitudinal designs with methodological consistency to account for potential interactive effects across time.

Effect of Perinatal AIS Type (Neonatal Versus Presumed Perinatal AIS)

Perinatal AIS encompasses acute neonatal and presumed perinatal AIS, which are thought to represent the same disease, differing only in the timing of symptom presentation and stroke diagnosis (i.e., before 28 days of life versus retrospectively later in the first year of life; Kirton &

De Veber, 2013). Nonetheless, the underlying mechanisms distinguishing the timing of presentation and acute neonatal and presumed perinatal AIS diagnoses remain unknown, with only theoretical speculation to date. Given that postnatal brain development is rapid in the first few months of life (Bullins et al., 2016; McCain, 2020), the impact of perinatal AIS and relevant predictors may vary considerably depending on the time of stroke onset and neurological symptom presentation within the first six months of life. Neurocognitive outcome and predictor studies have consistently combined children with neonatal and presumed perinatal AIS (Ballantyne et al., 2008; Banich et al., 1990; Levine et al., 2005; Muter et al., 1997; Stiles et al., 2003; Trauner et al., 1993), which is problematic methodologically as children with presumed perinatal AIS are typically diagnosed when neurological deficits are severe (e.g., hemiparesis). Preliminary findings and clinical observations have alluded to worse outcomes in presumed perinatal relative to neonatal AIS subtypes (Lee et al., 2005). Study 2 was novel in that it represents the first known systematic comparison of neurocognitive outcomes between acute neonatal and presumed perinatal AIS subtypes. Comparison of results between the two study cohorts also allowed informal comparison of predictors of neurocognitive trajectories for differing perinatal AIS subtypes, as discussed in the prior section. Through systematic evaluation in Study 2, perinatal AIS type was found to moderate the linear and quadratic components of the Full-Scale IQ trajectory. Although children with presumed perinatal AIS diagnoses showed a more rapid neurocognitive decline initially, they appeared to show relative improvement over time compared to those with neonatal AIS diagnoses, who showed a consistent decline. As such, individuals with neonatal relative to presumed perinatal AIS demonstrated worse neurocognitive functioning at the end of follow-up.

Attributable in part to a strong identification bias (i.e., only late symptomatic infants will present and be diagnosed), presumed perinatal AIS has been found to involve relatively severe outcomes compared with other perinatal stroke disease states (Kirton & De Veber, 2013). Presumed perinatal AIS often includes basal ganglia involvement, which is thought to contribute to motor difficulties (Miller et al., 2007), as well as cortical involvement, which is thought to contribute to late clinical presentations and long-term outcomes including non-motor developmental delays such as language, cognitive, and behavioural morbidities as well as seizures/epilepsy (Fitzgerald et al., 2007; Golomb et al., 2001; Kirton et al., 2008, 2010; Lee, Croen, Lindan, et al., 2005; Miller et al., 2007). To date, non-motor outcomes have been less widely studied. Existing non-motor findings cannot be directly compared to the results of Study 2, which included formal neurocognitive testing and perinatal AIS type comparison groups. However, existing findings of poorer outcomes in presumed perinatal AIS align with the current demonstration that individuals with presumed perinatal AIS diagnoses initially show a more rapid neurocognitive decline relative to acute neonatal AIS. That said, the need for longitudinal research is highlighted given that individuals with presumed perinatal AIS showed improvement over time compared to individuals with neonatal AIS diagnoses. Likewise, children with neonatal AIS showed a consistent decline, resulting in worse neurocognitive functioning near the end of follow-up. As such, the comparison between acute neonatal and presumed perinatal AIS may be more nuanced with recovery mechanisms and neurocognitive trajectories changing over time.

To date, there has been more research on neurocognitive outcomes for individuals with acute neonatal AIS than for those with presumed perinatal AIS (Kirton & De Veber, 2013), with little to no systematic comparisons of neurocognitive outcomes between the two groups. Instead, existing research has primarily demonstrated increased risk for motor deficits (e.g., cerebral

palsy) in children with presumed perinatal AIS relative to acute neonatal AIS (Lee, Croen, Lindan, et al., 2005; Wu et al., 2004), as consistent with the motor impairments found in presumed perinatal AIS outcome research. Lee et al. (2005) found that children who present with motor-related stroke indicators later in infancy were more likely to have sustained injury to the internal capsule, which they posited as the potential mechanism for poor prognoses in the presumed perinatal AIS group. In contrast, no significant differences were found between the two groups for epilepsy, language, and behavioural outcomes (Lee et al., 2005); however, these evaluations did not include formal assessment of language and cognitive abilities. There is a pressing need for investigations into neurocognitive and non-motor outcomes, to extend beyond the understanding of motor risk alone. Moreover, posits of factors differentiating acute neonatal and presumed perinatal AIS remain largely theoretical in nature and require investigation in homogenous samples using longitudinal methods, as well as systematic comparisons between perinatal AIS groups.

Effect of Early Screening in Acute Neonatal AIS

The early developmental period can be seen as a window of opportunity in which early screening/assessments can facilitate early identification. Given the rapid early development and neuroplasticity in the infancy and early childhood periods (Galván, 2010; McCain, 2020), screenings and full assessments early in development have the potential to identify children who may be at heightened neurocognitive risk. Early identification can then inform prevention and precision-based early interventions which, together, can harness the neuroplasticity and dynamic development that is unique to the early developmental period to maximize neurodevelopmental trajectories across the lifespan (Anderson et al., 2000; Anderson et al., 2001; Famri et al., 2007; Max et al., 2003; Nass, 1997). To date, no research has evaluated the influence of early screening

in infancy as a protective factor for children who experienced perinatal AIS. The majority of research on predictors of neurocognitive outcomes after perinatal AIS has focused on stroke-related risk factors, with limited consideration of protective factors more broadly (Fuentes et al., 2016). Study 2 was novel in its focus on the role of protective factors, namely early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic, for children with neonatal AIS. Notably, adjustment for early screening in infancy was relevant in this group (i.e., resulting in improved model fit), with consistently lower functioning observed for those who did not receive early screening in infancy, despite overall non-significant main and moderating effects. These findings are consistent with the understanding that early identification and subsequent intervention are facilitated through early screening (Arruda et al., 2023; Guilfoyle et al., 2012; Newman, 2012), although this understanding has not been applied in the field of perinatal AIS to date. Nonetheless, the present results are preliminary in nature and highlight a critical gap in the literature regarding the influence of protective factors on neurocognitive outcomes following perinatal AIS. There is a need to begin evaluating the protective role of early screening/assessments to support the early identification of neurocognitive challenges and to inform interventions for this high-risk group of children who experience early neurocognitive risks that appear to worsen across development. Future research should also evaluate the potentially differential effectiveness of early screening between neonatal AIS and presumed perinatal AIS groups, in addition to other pediatric stroke types.

Having evaluated two different developmental time courses in the present studies, including 1) infancy and early childhood and 2) early and late childhood, adolescence, and early adulthood, it is notable that the emergence of deficits, when examined longitudinally, was identified as early as in the infancy and early childhood period in Study 1. Typically, the

emergence of deficits after early injury is thought to occur in middle/late childhood. The results of the present studies highlight that, in children who experience perinatal AIS, the capacity for accommodation may be limited and emerging deficits can be seen as early as during the transition from infancy into early childhood, with more apparent demonstration into late childhood, adolescence, and adulthood. These results related to early emerging deficits, alongside a preliminary indication of the protective role of early screening, highlight a need for early screening/assessments in infancy and early childhood, rather than waiting until later childhood or adolescence. The greatest period of neuroplasticity is within the first few years of life when more than a million new neural connections form every second (Centre on the Developing Child, 2008). In recognizing the dynamic and complex nature of early brain development, early screening/assessments have many functional applications, including: determining the early neurodevelopmental status of infants and young children, identifying children who would benefit from early intervention supports, evaluating outcomes post medical procedures/interventions, documenting change in neurodevelopmental status over time, predicting later levels of functioning and prognoses, and yielding information about early brain-behaviour relationships (Aylward, 1988, 1997). In contrast, waiting to receive assessments until school-age has less efficacy in altering neurodevelopmental trajectories given the reduced potential for neuroplasticity (Anderson et al., 2000; Anderson et al., 2001; Famri et al., 2007; Max et al., 2003; Nass, 1997).

Taken together, the lack of access to routine early screening can be seen as a health equity issue, given that early screening in infancy can contribute toward improved outcomes across development. This equity issue is most notable in populations of children who have experienced heightened adversity, namely environmental and biological risks, specifically central nervous

system injury (i.e., perinatal stroke), who are known to manifest neurocognitive deficits with time. Nonetheless, there is stagnancy in the field of early neurodevelopmental assessments more broadly, with criticism of the sparse attention and limited resources allocated to advance early assessment methods (Baron & Anderson, 2012; Baron & Leonberger, 2012; Bondi et al., 2024; Brito et al., 2019). The present studies also highlight a unique component of service delivery at The Hospital for Sick Children, namely the availability of early screening in infancy for children who experience acute central nervous systems risks in the neonatal period. However, these services are currently limited to children who experience acute neonatal AIS (i.e., are seen in the Neonatal Intensive Care Unit in infancy) and are not available for children who experience presumed perinatal AIS. Given the evidence from Study 2 that children with presumed perinatal AIS may show worse neurocognitive outcomes relative to neonatal AIS, there is justification for implementing early screening in infancy for both groups.

IMPLICATIONS AND CONCLUSIONS ACROSS STUDIES

The present studies are the first to examine longitudinal neurocognitive trajectories across several developmental periods for children who experienced perinatal AIS. These studies provide evidence of neurocognitive decline across the developmental course following perinatal AIS, despite age-appropriate functioning statistically extrapolated at stroke occurrence/birth. This decline spanned across 1) infancy and early childhood and 2) early and late childhood, adolescence, and early adulthood, in keeping with an early vulnerability hypothesis of brain recovery. As such, these findings call into question the belief that infancy is a period in which neuroplasticity can offset the potential consequences of central nervous system damage. Likewise, these studies highlight the importance of longitudinal follow-up and routine neuropsychological testing across critical developmental periods, starting early in infancy and

early childhood after perinatal AIS. To better elucidate recovery pathways following perinatal AIS, longitudinal trajectory modelling must be harnessed to capture the interplay between brain recovery mechanisms after early insult and dynamic developmental mechanisms, including the influence and interaction of predictor variables.

Moreover, the present studies were unique in their evaluation of relevant risk factors in homogenous neonatal AIS and more diverse perinatal AIS samples using longitudinal designs, thus allowing both main and moderating effects to be examined over time. In both neonatal AIS and perinatal AIS samples/sub-samples, lesion volume moderated the rate of neurocognitive change over time for Full-Scale IQ. In an exclusively neonatal AIS sample, medical comorbidities (i.e., congenital heart disease, genetic conditions) had a main effect on neurocognition. This finding highlighted that children with congenital heart disease and neonatal AIS likely present with a different mechanism of early brain injury relative to children who experience neonatal AIS alone, as differences in neurocognition were statistically extrapolated at stroke occurrence (i.e., birth), rather than emerging differently over time. In a diverse perinatal AIS sample (including neonatal AIS and presumed perinatal AIS), seizure disorder status (in addition to lesion volume) moderated the rate of neurocognitive change and was associated with greater neurocognitive decline and trajectory curvature. Notably, the moderating role of lesion volume and seizure disorder status in perinatal AIS differed across neurocognitive sub-domains beyond Full-Scale IQ alone, indicating the need for specific investigation into distinct neurocognitive abilities. Moreover, the similarities and differences highlighted across the present studies with respect to predictors of neurocognition relevant for different perinatal AIS subtypes indicate the need for systematic comparisons between subtypes with homogenous samples using longitudinal evaluation methods with methodological consistency, including exploration of

various neurocognitive outcomes. Clinically, improved understanding of predictors of neurocognitive trajectories will inform the early identification of high-risk groups and the development and implementation of precision-based interventions.

In addition to striving to address the discrepancies that exist within past research on neurocognitive outcomes and relevant predictors post perinatal AIS, the current studies offered novel insights into the effects of perinatal AIS type and early screening in infancy. Study 2 represents the first known comparison of neurocognitive outcomes between acute neonatal and presumed perinatal AIS subtypes. Perinatal AIS type moderated the overall neurocognitive trajectory such that children with presumed perinatal AIS diagnoses showed a more rapid neurocognitive decline initially and relative improvement over time. In contrast, children with neonatal AIS diagnoses showed a consistent decline over time. These findings highlight the importance of comparisons of neurocognitive trajectories (and relevant predictors) between different perinatal AIS subtypes, as well as more broadly between other pediatric stroke types. Thus, there is a need for longitudinal research with homogenous samples and systematic comparison methods across extended follow-up periods. Lastly, in the exclusively neonatal AIS sub-sample, consistently lower neurocognitive functioning was identified for children who did not receive early screening in infancy through the Neonatal Neurodevelopmental Follow-up Clinic relative to those who did. These preliminary results highlighted the importance of screening/assessments commencing early in infancy following perinatal AIS, especially given that neurocognitive decline was apparent as early as across the transition from infancy to early childhood in Study 1, not just when follow-up spanned across childhood, adolescence, and early adulthood in Study 2.

Taken together, the present studies inform clinical recommendations in pediatric stroke. Overall, improved understanding of predictors of neurocognitive trajectories and unique recovery expectations for specific stroke subtypes will inform recovery expectations, the early identification of high-risk groups, and the implementation of precision-based interventions. Individuals with perinatal AIS should undergo routine neuropsychological assessments across critical developmental periods, especially as they experience heightened cognitive and academic demands with age. More specifically, these early assessments should commence as early as possible, with benefits of screening in the infancy period, in addition to routine follow-up assessments across the full developmental course. These novel findings highlight the need for early screening/assessments to support the early identification of neurocognitive challenges for all perinatal AIS subtypes, including presumed perinatal AIS groups who were seen to be at heightened risk for neurocognitive challenges relative to neonatal AIS groups, for whom early screening services are currently limited at The Hospital for Sick Children. Early screening has the potential to directly inform interventions for these high-risk groups of children who experience early neurocognitive risks that appear to worsen starting in infancy and early childhood. A lack of access to routine early screening can be seen as a health equity issue given the understanding that early screening in infancy can contribute to improved outcomes across development.

To date, studies investigating neuropsychological recovery following pediatric stroke have yielded inconsistent findings, largely due to variations in research methods and assessment approaches. The cutting-edge methods harnessed within the present studies, including longitudinal designs, growth curve modeling, methodological consistency, and homogenous samples, help advance the field of pediatric stroke research design. Advanced modelling

methods, as those employed in these studies, are essential to capture the interplay between brain recovery after early brain insult and the complex neurodevelopmental course. Trajectory modelling reveals various pathways for recovery and development and helps determine which factors influence alternative pathways. In the broader pediatric stroke literature, there is a pressing need for refinement regarding when, how, and whom to assess in neuropsychological practice to advance understanding of neuropsychological abilities across development post-stroke. In offering a clearer understanding of which methods to employ, neuropsychological outcomes can be elucidated more comprehensively for unique populations within pediatric stroke, thereby optimizing clinical care, establishing recovery expectations, and formulating effective intervention strategies post-stroke. Additionally, the current studies begin to disentangle competing theoretical perspectives of recovery mechanisms (i.e., 'early plasticity' vs. 'early vulnerability'), alongside relevant risk and protective influences. Taken together, in addition to advancing clinical practice, understanding of recovery theories, and research methods in pediatric stroke specifically, the current findings and methodologies can be extrapolated to advance the field of pediatric neuropsychology more broadly.

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