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Intellectual outcome in early childhood after neonatal stroke.

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INTELLECTUAL OUTCOME IN EARLY CHILDHOOD AFTER NEONATAL STROKE

by

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Abstract

Pediatric stroke is often associated with long-term neurological deficits, including cognitive and motor impairments. These deficits can adversely affect a child's ability to function in all settings, including home and school. The purpose of the present study was to examine early intellectual outcome for survivors of neonatal arterial ischemic or sinovenous thrombotic stroke (i.e., stroke before 28 days of age). This study was the first of its kind to study intellectual outcome across three years post-stroke in stroke confined to the neonatal period. Children from the Canadian Pediatric Ischemic Stroke Registry were followed at 12, 24, and 36 months post stroke (the number of participants varied across these testing points). The Bayley Scales of Infant Development, the Wechsler Preschool and Primary Scales of Intelligence-Revised, and the Peabody Picture Vocabulary Test-Revised were used to measure intellectual outcome. Scores were compared with standardized normative data of healthy children.

Results revealed that mean scores on measures of intellectual outcome generally fell within the average range. However, children with neonatal stroke obtained significantly lower scores than the normative sample on the Bayley Psychomotor Development Index (PDI) at 12 months and on the Bayley Mental Development Index (MDI) and PDI at 24 months post-stroke. Outcome did not differ based on gender, stroke type, or presence of infarction. However, comparison of intellectual outcome based on hemisphere of infarction revealed performance favouring children with left hemispheric infarction on an absolute basis at all time points. These differences were significant at 24 and 36 months post-stroke. Further research is required to confirm whether the cognitive status of these children improves, remains in the low average range, or declines with development as more complex skills are learned.

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Introduction

This research project details an exploratory study of intellectual outcome after neonatal stroke. The study was archival and used a unique data set from Canadian children who sustained arterial ischemic or sinovenous thrombotic stroke in the neonatal period and underwent intelligence testing at 12, 24, and 36 months of age. The study was the first of its kind to do a three-year follow-up of children with stroke confined to the neonatal period (the first 28 days of life). Before discussing the questions of interest and methodology of this study, a brief definition and description of the nature of stroke in pediatric and neonatal populations ensues. A discussion of theoretical considerations regarding neuroplasticity in the developing brain follows. To conclude, the importance of studying outcome of childhood stroke precedes a summary of the literature on intellectual sequelae of pediatric and neonatal stroke.

What is Stroke?

The current research project utilized a subset of data collected in the Canadian Pediatric Ischemic Stroke Registry (CPISR), created by Dr. Gabrielle deVeber and colleagues, which includes children with arterial ischemic stroke and sinovenous thrombosis (deVeber, MacGregor, Curtis, & Mayank, 2000). Data from children with hemorrhagic stroke were not collected in this registry. Hemorrhagic stroke is typically considered separately in the pediatric stroke literature because it has a different set of etiologies, presentations, and sequelae. Additionally, it has typically been associated with a worse prognosis in children (Schoenberg, Mellinger, & Schoenberg, 1978). Nonetheless, a brief explanation of both ischemic and hemorrhagic stroke will be provided prior to the discussion of ischemic stroke in childhood.

A stroke is defined as a sudden, nonconvulsive, focal neurological deficit that is produced by a change in the brain parenchyma due to cerebrovascular disease. A stroke may result from a thrombus or embolus occluding the lumen of a blood vessel, a vessel rupturing, a change in permeability of a vessel wall, or a change in the viscosity or rate of blood flow (Adams, Victor, & Roper, 1996). Brain tissue that is deprived of oxygen rich blood as a result of any of these pathological changes in brain vasculature undergoes ischemic necrosis or infarction. Infarctions can be characterized as pallid or hemorrhagic. The former term implies an infarct devoid of blood, and the latter denotes more than minimal blood leakage at the site of infarction.

Ischemic stroke occurs secondary to an obstruction of an artery (arterial ischemic stroke) that supplies blood to the brain. Arterial blockage typically results in focal neurological deficits affecting the cortical area supplied by the affected blood vessel and may or may not lead to cerebral infarction (Pavlakis, Kingsley, & Bialer, 2000).

Sinovenous thrombosis occurs when there is an occlusion of one of the cerebral veins or dural sinuses that drains blood from the brain into the internal jugular veins for return into the systemic circulation. In this case neurological deficits arise from mass effects of the blocked blood on adjacent cortical areas. Sinovenous thrombosis is more common in the vessels surrounding rather than within the brain. Cerebral infarction occurs less frequently in sinovenous thrombosis than in arterial ischemic stroke (Adams et al., 1996; deVeber, MacGregor, et al., 2000). A period of hypotension or cessation of circulation due to shock or cardiac failure can also lead to both focal and diffuse ischemic damage (Adams et al., 1996).

Hemorrhagic stroke occurs upon rupture of a vessel or artery within the brain. The ensuing extensive bleeding into the brain parenchyma or subarachnoid space results

in focal or nonfocal neurological deficits, respectively (Pavlakis et al., 2000). Such ruptures typically lead to necrosis confined to surrounding brain tissue (Kolb & Whishaw, 1990). It is also possible for hemorrhage to occur secondary to ischemic stroke, if bleeding occurs into the area of infarction (Adams et al., 1996; deVeber & Roach, 1999).

The clinical presentation of stroke varies in both adults and children, but is more easily identifiable in adults. Presenting symptoms range from very mild neurologic symptoms to severe hemiplegia and coma. The hallmark of this disorder is its temporal profile, with abrupt onset of focal neurologic deficits and then at least partial reversal of the deficit occurring over days, weeks, or months (Adams et al., 1996).

Pediatric Stroke

Epidemiology

Pediatric or childhood stroke refers to stroke that occurs between birth and eighteen years of age, whereas neonatal stroke refers to stroke sustained within the first 28 days of life. Estimates from the CPISR, the source of data for the current study, show that the incidence of stroke between the ages of 0 to 18 years is 3.3 per 100,000 live births per year (deVeber, Roach, Riela, & Wiznitzer, 2000). Seventy-nine percent of nonhemorrhagic pediatric stroke is arterial ischemic, and 21 percent is sinovenous thrombotic (deVeber, Roach, et al., 2000). There is a slightly higher proportion of males (60%) who sustain pediatric stroke (deVeber, 2003a). Thirty-two percent of pediatric arterial ischemic stroke occurs during the neonatal period (deVeber, MacGregor, et al., 2000). Forty-three percent of pediatric sinovenous stroke occurs in the neonatal period (deVeber et al., 2001). Overall estimates of childhood stroke that include hemorrhagic stroke place stroke incidence at 6 per 100,000 live births per year, which is more than double the rate of brain neoplasm in childhood (deVeber, Roach, et al., 2000).

The incidence of pediatric stroke in general appears to be on the rise (Estan & Hope, 1997; Block, Nanson, & Lowry, 1999). Increased rates of stroke in children over the past decade are due to improved recognition of the symptoms of childhood stroke and more sensitive radiographic tests, as well as to a higher survival rate among children with other serious health complications, such as heart disorders, that predispose them to stroke (deVeber, Roach, et al., 2000). However, childhood stroke is not a new problem. One investigation of causes of infant mortality conducted over 20 years ago showed that 17% of infants who underwent autopsy had sustained a stroke. This early study suggested that stroke is a long-standing and important contributor to death in infancy (Barmada, Moossy, & Shuman, 1979).

Symptoms

A common misconception is that stroke in childhood will lead to the same symptomatology as adult stroke. However, it is not possible to extrapolate from studies of adults with stroke to pediatric stroke because the vasculature and neurological systems are so different in children (deVeber, 2003b). Moreover, the mechanism of stroke is much different in adults versus children. Adult stroke is most commonly associated with thickening of the body's blood vessels and arteries, whereas childhood stroke is more frequently associated with cardiac abnormalities and coagulation disorders (Chapman, Max, Gamino, McGlothlin, & Cliff, 2003; deVeber, 2003b; Roach, 2000).

The type and extent of damage resulting from pediatric stroke are widely variable. Children can either be symptom free or neurologically devastated, with varying degrees of sensorimotor and cognitive impairment (Hogan et al., 2000). Often stroke in children is not discovered right away.

Delayed detection of stroke is particularly common in neonates, as classic symptoms of pediatric stroke, such as hemiparesis and seizure activity, may not emerge before six months of age (Golomb et al., 2001). Lethargy, seizures, and hypotonia are the most common presenting symptoms of neonatal stroke (deVeber, MacGregor, et al., 2000; Miller, 2000).

Even if the symptoms of stroke successfully resolve with treatment during the neonatal period, a developmental lag may emerge further along in a child's development as more complex skills are needed (Gil, 2003). This is because disruptions in basic cognitive abilities developing at the time of injury may manifest in impairment of mastery of successive cognitive abilities, creating a snowball effect over time (Gil, 2003). These difficulties may include language (Pitchford, 2000), attention (Max, Fox, Lancaster, Kochunov, Mathews, & Manes, 2002; Max et al., 2003), memory (Lansing et al., 2004), social functioning (Anderson, Damasio, Tranel, & Damasio, 2000), and emotional difficulties (Anderson et al., 2000) that impair the child's functioning at home and at school.

The neurological status of 161 children in the CPISR was studied approximately two years after ischemic stroke (n = 123) and sinovenous thrombosis (n = 38) (deVeber, MacGregor, et al., 2000). This study included some of the neonates in the current study. Results indicated that 57% of cases exhibited normal status or mild neurological deficits and 42% of cases showed moderate to severe neurological deficits. In particular, children with arterial ischemic stroke showed more residual deficits than children with sinovenous thrombosis, and children with strokes occurring after the first month of life fared worse than children with neonatal stroke.

There were 19 children with neonatal stroke in this study. One third of these children had normal neurological exams on initial testing but subsequently demonstrated developmental abnormalities upon retest 18 months later (deVeber, MacGregor, et al., 2000). Additionally, there was a marked difference in outcome among neonates at 18 months post stroke based on the type of stroke. Neonates with sinovenous thrombosis had the best outcome of all groups of children in the study: 16 of 19 were normal or showed mild deficits when examined at 18 months of age. Therefore, short-term neurological outcome in the 161 children in this study varied according to age at which the stroke occurred, as well as by type of stroke (deVeber, MacGregor, et al., 2000).

Risk Factors for Pediatric Stroke

The risk factors for pediatric stroke as a whole differ greatly from those for adult stroke (Roach, 2000). There are a number of risk factors that have been identified for arterial ischemic stroke in infants and children; in most cases multiple risk factors are present (deVeber & Roach, 1999; Gunther et al., 2001; Kirkham, Prengler, Hewes, & Ganesan, 2000). Congenital factors that can predispose children to having stroke include cardiac disorders (deVeber & Roach, 1999; Kirkham et al., 2000), coagulation disorders (Delsing, Catsman-Berrevoets, & Appel, 2001; deVeber & Roach, 1999; Kurnik, Kosch, Strater, Schobess, Heller, & Nowak-Gottl, 2003), aneurysms (Schoenberg et al., 1978), arteriovenous malformations (Schoenberg et al., 1978), Moya Moya disease (Delsing et al., 2001), collagen tissue abnormalities (Kurnik et al., 2003), maternal diabetes (Gunther et al., 2000), and maternal drug abuse (Kirkham et al., 2000). Dehydration (deVeber & Roach, 1999), trauma leading to arterial dissection (Kirkham et al., 2000), birth asphyxia, and perinatal/postnatal infection (Askalan et al., 2001; deVeber & Roach, 1999; Kirkham et al., 2000) are risk factors that can be acquired from the time of birth onwards.

In another report of children in the CPISR, again including some of the cases in the current study, DeVeber and Roach (1999) reported that a primary risk factor for arterial ischemic stroke was identifiable in 79% of children. Multiple risk factors were typically present. Among children with arterial ischemic stroke, cardiac disorder (19%) was the leading primary risk factor, followed by coagulation disorder (14%), dehydration (11%), infection (6%), vasculitis (7%), dissection (5%), cancer (4%), metabolic disorder (3%), Moya Moya syndrome (2%), sickle cell disease (2%), perinatal complications (2%), and various other identifiable factors (4%).

In the same study, deVeber and Roach (1999) reported that multiple risk factors were also typical for 80 children with sinovenous thrombosis, and were often identifiable. Risk factors included prothrombotic disorders (31%), dehydration (30%), systemic infection (10%), head and neck infection (11%), hematologic disorders (16%), procoagulant drugs (9%), cardiac disease (8%), and perinatal complications (13%). To clarify, prothrombotic disorders, also referred to as prothrombotic / hypercoagulable states, increase the tendency of the blood to form a clot. These disorders can be either congenital or acquired after birth, and often act in concert with other risk factors to precipitate formation of a clot or thrombus within a vein or artery (Chan & deVeber, 2000).

Mechanisms of Neonatal Stroke

It is presumed that in the majority of cases, emboli are the most prevalent mechanism of stroke in neonates. However it is difficult to verify the presence of emboli since symptom onset in neonates is subtle and stroke may not be recognized right away (Miller, 2000). By the time a cerebral embolic stroke is suspected, there is rarely any direct evidence remaining of an embolus or its source.

Miller (2000) clearly delineates a number of physiological factors related to neonatal stroke. These factors include the foramen ovale, congenital heart defects, and placental complications. The foramen ovale is a hole that exists in all fetuses between the right and left atria. It remains open for a brief period after birth, and enables venous clots access to the cerebral arterial circulation (Miller, 2000). Neonates who are catheterized due to an illness are particularly susceptible to stroke caused by emboli formed at the site of catheterization (Miller, 2000). There are also a number of congenital heart disorders that involve an improper closing of the septal wall and allow unrestricted passage of emboli originating from the venous circulation to the blood supply to the brain (Miller, 2000). Two additional sources of emboli that predispose neonates to stroke include placental infection during labour, and the thrombosis of placental blood vessels at the end of pregnancy, particularly upon separation of the placenta at birth (Miller, 2000).

Why Study Outcome of Pediatric Stroke?

Despite the emergence of stroke as an important contributor to death and disability in childhood, there has been relatively little research that speaks to the extent of intellectual recovery that can be expected after childhood stroke, much less neonatal stroke (Hogan, Kirkham, & Isaacs, 2000). Increasing rates of stroke in children highlight the importance of conducting more research into stroke outcome in order to better identify those at risk and to facilitate better treatment interventions. The mortality, morbidity, and economic cost associated with childhood stroke are three important reasons to conduct further research into this area (deVeber, MacGregor, et al., 2000). More specifically, death occurs in 10 percent, recurrence in 20 percent, and neurological deficits in two thirds of survivors of childhood stroke (deVeber, Roach, et al., 2000). A prevalence-based study in Ontario was conducted to measure all direct (medical

treatment, research, community support) and indirect (lost work productivity) disease-related costs in persons with stroke (Chan & Hayes, 1998). The study estimated that $857 million, within a range of $719 to $964 million, was spent on stroke-related costs in a twelve month period beginning in 1994.

Adding to the economic cost is the potential for pediatric stroke to complicate other childhood diseases including cardiac, hematologic, metabolic, infectious, and inflammatory diseases (Chabrier, Husson, Lasjaunias, Landrieu, & Tardieu, 2000). Thus, there is currently an urgent need for research into age-based predictors of outcome from pediatric stroke (deVeber, MacGregor, et al., 2000). The extent of intellectual recovery that can be expected following stroke sustained during the neonatal period is the focus of the current research project.

Theoretical Considerations: Neuroplasticity in the Developing Brain

Neuroplasticity

The study of neuroplasticity after brain injury was made possible by advances in cognitive neuroscience that enabled the mapping of particular cognitive processes, knowledge, and representational elements to modular neural networks that subserve these cognitive phenomena (Grafman, 2000). It is assumed that modular neural networks form functional subcomponent modules that in isolation perform a limited function, but in combination perform a more typical complex human function (Grafman, 2000). Experimental and standardized measures of both limited and more complex functions are commonly used as indicators of extent of recovery after brain injury. The notion of brain/behaviour plasticity is premised upon the idea that the brain is able to change structurally and functionally with maturation, experience, or brain trauma or disease (Kolb, 1995). In relation to brain injury, it is assumed that behavioural change after a

brain insult reflects some change in organization or properties of the neuronal circuits that mediate the behaviour (Kolb, Gibb, & Robinson, 2003).

Grafman (2000) presents a contemporary framework for conceptualizing neuroplasticity that describes the effects of four different types of plastic change on complex human functions. These changes include homologous area adaptation, cross-modal reassignment, map expansion, and compensatory masquerade. Homologous area adaptation and compensatory masquerade are perhaps most relevant to discussions of plasticity of the developing brain and therefore warrant further explanation. In brief, cross-modal reassignment occurs when modular subcomponents switch from processing information from one modality to another when the input for the original modality is destroyed. Map expansion occurs when the area of a functional brain region increases with performance of a function or frequent exposure to a stimulus. However, both increases and decreases in region of activation have been observed with practice, and the meaning of map expansion is not yet clear.

Homologous area adaptation refers to the assumption that compensation for damage to an affected area and its cognitive operation(s) can occur by shifting part or all of the cognitive operation(s), typically to a homologous area in the contralateral hemisphere. Grafman (2000) reviews theory that states that neighbouring and homologous brain areas have primary and secondary functions. In this model, inhibitory inputs normally prevent activation of the secondary functions in a healthy brain. With damage, the inhibitory restraints are removed allowing partial or full transfer of the primary function to the contralateral hemisphere. Negative sequelae of this shift include "crowding" and less brain area dedicated to the primary function in the homologous area, as well as interference when the cognitive functions subserved by the shifted primary

function and the native primary function are activated simultaneously. Connections between maturing brain structures proliferate and solidify with development, and in doing so enable cognitive processes of increased complexity. Thus, the extent of reorganization of neural networks necessitated by homologous area adaptation increases with development, making this type of plastic change less likely to occur with maturation.

Compensatory masquerade is not a form of neural plasticity, but instead reflects compensation for damage to an operation via substitution of an intact and complementary cognitive process. This type of compensation is often beyond a person's conscious awareness (Grafman, 2000). Grafman uses the example of losing visuospatial navigating ability, and substituting verbal labeling of landmarks to navigate the same path. Often detailed neuropsychological evaluation is required to differentiate this type of plastic change from homologous area adaptation, particularly in children.

Taken together these forms of neuroplastic change may have important implications for prognosis and rehabilitation after brain injury. This model predicts that the likelihood of a cognitive function shifting to a homologous area in the contralateral hemisphere increases as the extent of damage to a functional network increases. Homologous area adaptation is associated with varying degrees of functional recovery, crowding of primary functions, and interference when adjacent functions are activated at the same time. In turn, when partial damage to a functional network does not provoke a shift to the contralateral hemisphere recovery may similarly be variable and incomplete.

Neuroplasticity in the Developing Brain

The degree of neural plasticity present at different stages in the developing brain has yet to be clearly elucidated. It is particularly difficult to parse the effects of normal maturation from functional recovery in children (Gil, 2003). Neuroscientific theory of

recovery after early brain injury is predicated largely upon animal models of stages of neural development associated with age. However, Gil (2003) posits that neurocognitive outcome in human beings is likely to be multi-factorial, and thus can not be ascertained primarily based on the age at injury.

Kolb (1995) has examined brain development and potential for recovery by comparing the embryological state of the nervous system in rats and humans. All mammalian brains follow a similar pattern of several stages of development including cell proliferation, cell differentiation, dendritic and axonal growth, synaptogenesis, cell and synaptic death, and gliogenesis. The mammalian nervous system begins as a hollow tube surrounding a single ventricle. Neurons are generated along the ventricular walls where they migrate to the appropriate destinations predominantly via pathways known as radial glial fibers. Kolb proposes that these glial fibers may also enable transport of cortical neurons in response to damage. The end of cell migration would necessarily limit this form of neuroplasticity, as this is the time at which radial glial fibers disappear. In humans, cell migration terminates at approximately one month of age.

Axonal development that extends to cortical and subcortical areas occurs as cells migrate (Kolb, 1995). Elongation of dendritic branches begins prenatally once axons have reached their destination, and continues after birth for variable periods of time depending on the cortical location. For example, this process is complete by around 18 months in the visual cortex, but is only 50% complete in the frontal cortex at 2 years of age. The most intense period of dendritic growth occurs postnatally, lasting up to 18 months, and is accompanied by a rapid increase in synapse formation. Kolb places overall maximal synaptic density at 12 months in the human, after which cell and synaptic death continues until adult levels are reached. In the visual cortex synaptic density reaches a maximum at

one year, and declines to adult values at approximately 11 years of age. Synaptic density also reaches its peak in the frontal cortex at one year. However, maximum density in the frontal cortex is much higher than in the visual cortex, and the number of synapses does not begin to decline until 5-7 years of age. Adult synaptic density in the frontal cortex is attained at age 16.

Kolb (1995) suggests that the process of synaptic elimination is a critical feature of behavioural development. He posits that the overgrowth of synapses may enable environmental factors to influence brain development whereby only synapses that are used are kept. This mechanism may also be beneficial in that it may allow erroneous and potentially disruptive connections to be discarded.

In sum, Kolb (1995) paints a picture whereby damage at different stages of neuronal development may produce very different sequelae. More specifically, he cites the continuation of cell migration until the end of the 1st month of life and the peak of synaptogenesis at the 12th month of life as two factors that may influence brain plasticity after injury. According to this view, neonatal stroke in particular may result in a better prognosis than stroke later in life because of the availability of radial glial fibers for transport of healthy neurons after damage. However, there are questions about whether the acquisition of brain dysfunction in the neonatal period does indeed result in a better prognosis than stroke later in life. Animal studies have demonstrated that injury during cell migration is more damaging than injury sustained during subsequent dendritic growth, irrespective of site of lesion (Kolb, 1995). However, the literature consistently suggests that the occurrence of damage prior to the time when the bulk of neuronal pruning occurs is one factor that seems to favour a better prognosis in stroke sustained before the age of one.

Kolb (1995) further posits that injury to certain cerebral structures sustained during critical periods of development may hinder future emergence of more complex skills that have their foundation in said structures. Kolb calls this idea the Hebb principle, based on past research by Hebb that showed that frontal lobe injuries could have a worse prognosis if sustained in childhood than in adulthood (Hebb, 1949, as cited in Kolb, 1995).

A recent review of pediatric traumatic brain injury supported the need for a more nuanced view of plasticity that takes into account age at insult, type of insult, and evolution of neurocognitive deficits relative to developmental stage over time (Gil, 2003). More specifically, it is suggested that it is necessary to consider the skills being disrupted at the time of injury and those that are being acquired throughout normal development in order to evaluate the degree to which the brain has effectively compensated for early damage (Gil, 2003). According to this view, older children have to recover old skills and abilities as well as complete their cognitive development, whereas younger children have developed fewer basic cognitive structures upon which to learn newer and more complex skills. Additionally, Chapman and McKinnon (2000) suggest that a greater degree of plasticity is required to recover a previously acquired basic function than to learn a new skill at a later stage in development.

In support of this extension of the Hebb principle, Chapman and McKinnon (2000) reviewed studies that found consistently worse outcomes on measures of word fluency and discourse in children with injury at an earlier age. In one of the studies reviewed it was shown that type of injury interacted with age in predicting recovery in children with diffuse and focal traumatic brain injury (Levin, 2001). A worse prognosis on a word fluency measure over time was observed in younger children who sustained

severe diffuse brain damage, whereas worse prognosis was associated with damage that was focal and localized to the left hemisphere in children who experienced brain injury when they were older. Deficits were subtle and emerged over time in the former group.

Taken together, reviews of recovery after pediatric traumatic brain injury support the use of a more dynamic conceptualization of recovery from early brain damage that considers cognitive developmental stage at injury in addition to neuronal stages of development. Moreover, the emergence of subtle deficits over time in survivors of focal pediatric brain injury is similar to what occurs in pediatric stroke.

Previous Research on Intellectual Outcome after Pediatric Stroke

There is a paucity of research that speaks to intellectual outcome after pediatric stroke compared to the quantity of research that has been conducted with adults. There exists a misconception that children who have a stroke in childhood will necessarily have a much better prognosis than adults who have a stroke due to an unstated assumption regarding the capacity of the developing brain to reorganize and compensate for damage (Hogan et al., 2000). Early studies that showed impressive recovery in language and motor functions after perinatal or infantile focal vascular lesions relative to strokes in adulthood provided support for this idea, which is called the Kennard principle. However, these studies did not compare similar lesions after comparable post-injury intervals in children and adults (Hogan et al., 2000). A recent review of the sequelae of non-penetrating traumatic brain injury noted that more long-lasting and subtle deficits have emerged in studies that are longitudinal and use more discriminating measures (Levin, 2003). Results of studies of intellectual outcome restricted to stroke as an etiology have provided conflicting results regarding brain plasticity in childhood.

Some studies have found evidence that children who sustain a stroke in childhood exhibit significant deficits in cognitive and social functioning (Block et al., 1999; Chapman et al., 2003; Golomb et al., 2001; Trauner, Panyard-Davis, & Ballantyne, 1996), whereas other studies have found little or no evidence of impairment after childhood stroke (Mannino & Trauner, 1983; Trauner et al., 1996; Wulfeck, Trauner, & Tallal, 1991). The basis for the wide variability in results may lie in methodology; most studies are retrospective, use small sample sizes, have different exclusionary criteria, are unconcerned with age at stroke, measure outcome across a restricted period of time, and use unstandardized measures of cognitive functioning (deVeber, MacGregor, et al., 2000). Additionally, MRI and CT have only recently begun to supplement clinical assessments as indicators of stroke type (ischemic or hemorrhagic) and location (e.g., right versus left hemisphere) of stroke. Therefore, it is likely that milder cases of ischemic stroke have been missed in the past, and that children with other disorders have mistakenly received a diagnosis of stroke (deVeber, MacGregor, et al., 2000).

There are also studies that show that children with history of stroke do not experience the same degree of long-term impairment as do adults after stroke. A survey of several recent studies of intelligence after pediatric stroke included research focused on neonates and showed normal intelligence quotients (Trauner, Chase, Walker, & Wulfeck, 1993), scores within the low range of normal but not significantly below age expected scores (Max, 2004; Wulfeck, Trauner, & Tallal, 1991), or scores significantly below those of comparison groups (Hogan et al., 2000). Taken together, these studies suggest that there is a milder and more generalized reduction in intellectual functioning in children who sustain stroke compared to adults who experience stroke. Similar findings

of subtle deficits that evolve over time have been obtained when looking at children with both focal and diffuse traumatic brain injury (Levin, 2003).

The above-mentioned investigations of intellectual outcome after pediatric stroke used global indices of functioning. However, there are also several studies that have looked for differences between verbal and nonverbal functioning associated with side of lesion (Block, Nanson, & Lowry, 1999; Chapman et al., 2003; Lansing et al., 2004; Max, 2004; Schatz, Ballantyne, & Trauner, 2000). Contrasting verbal and nonverbal abilities provides a more detailed picture of the effects of pediatric stroke on intelligence. When such differences are found and are associated with side of stroke, it is commonly assumed that this pattern reflects the development of brain lateralization before the time of the stroke.

Brain lateralization is a concept that traditionally has referred to the biological differences in the organization and functioning of the left and right cerebral hemispheres (Goldberg & Costa, 1981). The concept of brain lateralization first emerged in 1863 when a French country doctor named Marc Dax noted in a paper an association between side of traumatic brain injury in his patients and subsequent loss of speech. Since this time several models of brain lateralization posited to describe left and right hemispheric functioning have emerged, including linguistic-nonlinguistic, sequential-simultaneous, analytic-gestalt, and routinization-acquisition dichotomies (Goldberg & Costa, 1981). The linguistic-nonlinguistic dichotomy posits that tasks mediated by language are based in the left hemisphere, whereas the domain of nonverbal tasks resides in the right hemisphere. In the sequential-simultaneous model, sequential processing is primarily a function of the left hemisphere and requires the ordering of independent stimuli in a linear sequence or temporal order. In contrast, simultaneous processing is associated with

functions of the right hemisphere and requires an individual to synthesize individual pieces of information into a system of relationships (Chow & Skuy, 1999). In the analytic-gestalt model, detail-based cognitive processing is the domain of the left hemisphere, whereas holistic analysis of the "bigger picture" is the domain of the right hemisphere. In the routinization-acquisition dichotomy, the right hemisphere is involved in the acquisition of new skills until they become automatic, at which point the left hemisphere bears primary responsibility for their performance.

The age at which hemispheric lateralization of cognitive functions occurs is an area of current debate in childhood development. Children do not typically show the same lateralization effects as adults, particularly if the lesion was sustained before five years of age (Hogan et al, 2000). Several studies conducted with children with unilateral lesions due to stroke, using standardized measures of intelligence, have revealed equal functioning on measures of verbal and nonverbal ability regardless of the side of lesion (Block et al., 1999; Lansing et al, 2004; Schatz et al., 2000). The age at which children in these three studies experienced stroke ranged from pre/perinatal to 16 years of age, and testing occurred between the ages of 5 and 18 years across studies. Thus evidence for the presence of lateralization according to the linguistic-nonlinguistic model was not found in studies in which the age at stroke and age at testing was widely variable.

In contrast, the study done by Schatz et al. (2000), as well as another recent study (Chapman et al., 2003), found evidence of lateralized performance associated with side of stroke. Schatz et al. (2000) administered the Wechsler Scales of Intelligence-Revised to 22 children between the ages of 6 and 13 who had a hemorrhagic or ischemic stroke with a unilateral lesion before 2 months of age. Additionally, the type of errors that these children made on the Block Design subtest of the WISC-R was recorded. The Verbal,

Performance, and Full Scale IQ did not show significant differences correlated with hemisphere of lesion. However, in line with the analytic-gestalt model of lateralized functioning, analysis of the errors made on Block Design revealed that children with a right hemisphere lesion made significantly more global errors (e.g. broken configuration) than did the left hemisphere lesion group. In turn, the left hemisphere group made more local errors (incorrect details).

In another study, a test of narrative discourse ability was administered to 17 children ranging between 8 and 19 years of age (Chapman et al., 2003). All children had sustained an isolated hemorrhagic or ischemic stroke with a unilateral lesion before the age of 13 years. The results indicated that children who had damage in the left hemisphere had a shorter mean length of utterances than children with damage to the right. It is noteworthy that this study, successful in demonstrating a pattern related to stroke location, involved an experimental measure of a specific ability. The narrative discourse measure was more challenging than tests used in other studies. Moreover, research in narrative discourse shows that this ability typically is dependent more on left than right hemisphere functioning by adulthood (Chapman et al., 2003).

These results (Chapman et al., 2003; Schatz et al., 2000) may suggest that the use of experimental measures or more challenging tests is required to elicit evidence of lateralized deficits associated with lesion location in children, including those who sustain a stroke before the age of five. More research is required to determine whether the results of the above-mentioned studies can be replicated with children who sustained a stroke at an earlier age.

It is also possible that the degree of evidence of lateralization varies with side of injury. Levin (2003) concluded in his review of focal traumatic brain injury due to

various causes that early left hemispheric lesions result in initial delays in language, followed by resolution of deficits by 5 years of age. Overall, early right hemispheric lesions were associated with visuospatial deficits that persisted across childhood but were more subtle than those experienced by adults with similar lesions (Levin, 2003). However, it remained unclear whether early right hemispheric lesions result in a pattern of decreased nonverbal intelligence regardless of age at onset, or whether this pattern emerges only if injury occurs after the age of one. In order to elucidate the early effects of right hemispheric lesions, it may be useful to contrast global scores in children with right versus left hemisphere strokes sustained before the age of one. In doing so, it might be prudent to examine children who sustained stroke within the neonatal period in terms of Goldberg and Costa's (1981) acquisition/routinization model of lateralization.

According to Goldberg and Costa's (1981) acquisition/routinization model of lateralization, the right hemisphere is responsible for the acquisition of new codes and strategies within novel situations. A shift from right to left hemisphere predominance occurs as these codes and strategies become more routinized. Based on this model, children who sustain neonatal stroke in the right cerebral hemisphere might fare more poorly on standardized measures of both verbal and nonverbal abilities, and thus on global indices of intellectual functioning, compared to children with left hemisphere stroke as neonates. Based on Goldberg and Costa's (1981) theory, one might expect that children with neonatal stroke in the right hemisphere might have experienced reduced ability to acquire knowledge and skills of both a linguistic and non-linguistic nature. This model of lateralization may be more suitable to studies of intellectual outcome after neonatal stroke because it enables prediction of patterns of deficits associated with side of stroke even if development of linguistic/non-linguistic functions has not yet occurred.

In sum, it appears that there is wide variability in studies of general cognitive functioning in stroke sustained in childhood (birth to 18 years), ranging from normal abilities, to scores that are significantly below average. Moreover, while it is generally assumed that lateralization of deficits following acquired brain damage emerges later in childhood, two studies using experimental measures have revealed patterns of language (Chapman et al., 2003) and visuospatial functioning (Schatz et al., 2000) that were associated with side of stroke in children who sustained stroke before 6 years of age.

Intellectual outcome data based on a more limited range of ages at time of stroke are needed in order to better understand the relationship between age at injury, lateralization, and recovery. Few studies examining intellectual outcome have been concerned with age at stroke (Hogan et al., 2000). In particular, there is a need for studies that examine full-term neonates as a distinct group across time. Studying stroke during the neonatal period provides an exciting opportunity to study the development of functions at birth prior to the opportunity for considerable post-birth environmental influences/learning. In addition, the use of global standardized measures of cognitive functioning should be supplemented with more refined measures to examine the effects of lateralized lesions on subsequent acquisition of both verbal and nonverbal abilities.

The purpose of the current research project was to examine whether children who are 12, 24, or 36 months after neonatal stroke performed significantly worse on measures of intellectual functioning based on comparisons with standardized scores from a normative sample. This study expanded upon previous research by examining post-stroke outcome across a longer period of time (3 years), using a sample of children who sustained arterial ischemic or sinovenous thrombotic stroke, as defined by CT or MRI studies, exclusively within the neonatal period (within 28 days after birth). It is important

to note that children who were not born full-term (at least 36 weeks gestation) were excluded from the sample, to avoid the confounding variable of the complications associated with premature birth.

The dependent variables in this study were the scores that the participants achieved on standardized measures of intelligence at 12, 24, and 36 months of age. An additional standardized measure of receptive language ability that was administered at 36 months of age was also analysed as a supplemental measure of verbal ability. Exploratory analyses examined whether intellectual outcome within this sample differed based on gender, type of stroke (arterial ischemic or sinovenous thrombotic), and lateralization of stroke (left hemisphere, right hemisphere, or bilateral). The sample is also described carefully on a number of other variables, including neurological outcome, ethnicity, socio-economic status, stroke risk factors, complications, and radiological findings.

Method

Materials

Several measures were administered to children at three different time points. Children at 12 and 24 months of age were administered the Bayley Scales of Infant Development (Bayley, 1969). Children 36 months of age were administered the Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R; Wechsler, 1989), and the Peabody Picture Vocabulary Test – Revised (PPVT-R; Dunn & Dunn, 1981). Age-specific appropriate normative data are available for all of these tests. Twenty-five of 29 children in the current study were also administered the Pediatric Stroke Outcome Measure (PSOM; deVeber, MacGregor, et al., 2000).

Bayley Scales of Infant Development (BSID)

The BSID (Bayley, 1969) is used to determine whether children aged 1 to 42 months are developing at an expected rate. It yields three measures: the Mental Development Index (MDI), the Psychomotor Development index (PDI), and the Infant Behavior Rating Scale (IBRS) during testing (Spreen & Strauss, 1998). More specifically, the Mental Development Scale assesses the infant's current level of cognitive, language, and personal-social functioning. The Psychomotor Development Scale assesses fine and gross motor development. The Infant Behavior Rating Scale includes parental and examiner ratings of the child's motor quality, attention and arousal, orientation and engagement, and emotional regulation. The normative sample mean for the BSID is 100, and the standard deviation is 15.

The Wechsler Preschool and Primary Scale of Intelligence - Revised (WPPSI -R)

The WPPSI-R (Wechsler, 1989) is a test of overall level of intellectual functioning, as well as an indicator of the presence of intellectual disability, for children aged 3 to 7 years. Similar to the version of Wechsler tests of intelligence for older children, the WPPSI-R yields an overall IQ score (Full Scale IQ [FSIQ]), an IQ score reflective of ability on verbal subtests (Verbal IQ [VIQ]), and an IQ score tapping ability on non-verbal / performance subtests (Performance IQ [PIQ]). The normative sample mean for the PPVT-R is 100, and the standard deviation is 15.

Peabody Picture Vocabulary Test – Revised (PPVT-R)

The PPVT-R (Dunn & Dunn, 1981) was designed to assess auditory comprehension of picture names, and is often used as a measure of verbal comprehension in clinical populations (Spreen & Strauss, 1998). The PPVT-R has been standardized for use beginning at 2 years, 6 months, until over 90 years of age. It consists of 175 items of

increasing difficulty. Participants are required to identify which of four different pictures matches a word that is orally presented by the examiner. A raw score is calculated and converted to a standard score. The normative sample mean is 100, and the standard deviation is 15.

The Pediatric Stroke Outcome Measure (PSOM)

The PSOM was created by Dr. Gabrielle deVeber at the Hospital for Sick Children (deVeber, MacGregor, et al., 2000). The PSOM is a standardized protocol that is used by neurologists to assess post stroke neurological outcome and collect information on the presence of an extensive list of potential stroke risk factors.

Neurological outcome is assessed using a neurological examination that rates five domains of post-stroke functioning including right sensory-motor functioning (including motor, visual, hearing, and somatosensory functioning), left sensory-motor functioning, language production, language comprehension, and cognitive functioning. A score is assigned for each of these domains ranging from 0 (no deficit) to 2 (severe deficit). Thus the lowest overall score that can be obtained on each domain of the PSOM, and the one denoting the best neurological outcome is 0, and the highest score, indicating the most impairment, is 2.

DeVeber and Roach (1999) reported that a primary risk factor was identifiable in 79% of children with arterial ischemic stroke. Multiple risk factors were typically present and included cardiac disorders, infection, prothrombotic states, hematologic disorders, physical injury, vasculitis, metabolic vasculopathies, and migraine.

DeVeber at al. (2001) reported that four risk factors were identified as occurring most often in children with sinovenous thrombotic stroke from the CPISR: head and neck disorders, acute systemic illness, chronic systemic diseases, and prothrombotic states.

Procedure for Collecting Data

Participants

Data for this study was collected through the CPISR. This registry was established by Dr. Gabrielle deVeber and colleagues to obtain comprehensive prospective epidemiologic data on children who sustained stroke between birth (only after 36 weeks gestation) and 18 years of age (deVeber et al., 2001). Sixteen tertiary care centers in Canada contributed data for each child including demographic information, the clinical symptoms of stroke, risk factors, radiological data, any treatment administered, and neurological outcome.

The present study focused on 29 children who were born full-term (>36 weeks gestation), and who presented with arterial ischemic stroke or sinovenous thrombosis within the first 28 days of life (neonates) to either the Hospital for Sick Children (Toronto, Ontario, Canada) or the Children's Hospital at Chedoke-McMaster (Hamilton, Ontario). Data on all children in this subset of the CPISR were collected either as a result of the child's referral to specialized stroke clinics at these two hospitals, or through annual health record searches of all children seen at these two centers using International Classification of Diseases codes. The data were collected between January 1, 1992 and July 1, 1999 (deVeber, MacGregor, et al., 2000).

Whenever possible, neonates who survived their first stroke were administered a neuropsychological battery at regular intervals. The battery comprised tests specific to the child's age at the time of assessment. Only the 29 children who were administered neuropsychological tests at one or more ages identified for the purposes of the current study (12 months, 24 months, and 36 months of age) were included in the

neuropsychological analyses. Eleven of these 29 children were seen at all three points in time.

Diagnostic Criteria for Ischemic Stroke versus Sinovenous Thrombosis

Neonates with arterial ischemic stroke or sinovenous thrombosis were identified using both strict clinical and neuroimaging criteria.

Clinical criteria.

Neonates with arterial ischemic stroke or sinovenous thrombosis were included based on having presented with seizures, lethargy, or focal neurological deficit. Only neonates who were diagnosed within the neonatal period were included; infants with presumed prenatal or perinatal ischemic strokes were excluded (deVeber, MacGregor, et al., 2000).

Neuroimaging criteria.

The radiographic films and reports of each neonatal patient were reviewed by neurologists at the Hospital for Sick Children prior to entering each patient's data in the CPISR.

To be classified as sinovenous thrombosis, definite evidence of thrombosis in the cerebral veins or sinuses was required through at least one of the following techniques: computer tomography, magnetic resonance imaging with or without magnetic resonance venography, conventional angiography, or transfontanel Doppler ultrasonography (deVeber et al., 2001). Several features of the thrombosis were also noted, including the location, whether it was superficial or deep, and the presence of an infarct. Infarcted tissue was further classified as hemorrhagic or nonhemorrhagic. Hemorrhages located outside of the brain parenchyma were classified as subdural, subarachnoid, or intraventricular (deVeber et al., 2001).

To be classified as an ischemic stroke, evidence of focal infarction in an arterial distribution needed to be seen on the radiographic films (deVeber, MacGregor, et al., 2000). Infarcts were classified according to whether a large vessel (anterior, middle, or posterior cerebral artery) or small vessel (lenticulostriate artery) perfused the infarcted territory. Furthermore, infarcts were classified according to how many occurred (single or multiple concurrent), location (left hemisphere, right hemisphere, or both), presence of hemorrhage (pallid or hemorrhagic), whether the infarct or transient ischemic attack reoccurred, and whether the infarct affected the basal ganglia (deVeber, MacGregor, et al., 2000).

Results

Characteristics of the Sample with Neuropsychological Test Results

Early intellectual outcome was examined in 29 children who sustained stroke during the neonatal period and were followed at least one time with neuropsychological testing at 12, 24, or 36 months post-stroke.

Social Economic Factors

Complete socioeconomic data are not available for all children in the study. Status of parental relationship at the time of stroke is reported for all children, and highest level of education achieved for each parent is reported for the majority of children.

Twenty-seven children lived with parents who were married or who were living common-law. The remaining two children lived in a single parent home. This data was reported at the first neuropsychological assessment, which ranged from 12 months post-stroke to 36 months post-stroke. Follow-up information on status of the parental relationship was not available.

Data on parental education is available for 22 of 29 children and is reported according to the highest level of education achieved. Ten children had two parents who completed post-secondary education. One child from a single-parent family had one parent with a post-secondary education. Four children had one parent who completed high school, and one who completed post-secondary education. For five children, both parents completed high school, and for two children one parent completed high school and the other did not.

Ethnicity information

Information regarding the ethnicity of participants was available for 13 of 29 children. In order of prevalence, 10 participants were Caucasian, 3 were Middle Eastern, 1 was African Canadian, and 1 was East Indian. Three other children were classified as "Canadian."

Radiological findings

Radiological data upon onset of stroke were available for all 29 children in the study. Features of stroke in children with arterial ischemic stroke will be described separately from those with sinovenous stroke.

Nineteen of 29 children sustained an isolated arterial ischemic stroke. Single infarcts were present in 16 of these children, 1 of whom had associated intraventricular hemorrhage. Multiple infarcts were present in three children with arterial ischemic stroke, two of whom also had hemorrhage at the site of infarction. Of the 19 children who sustained arterial ischemic stroke, 9 had infarction in the right hemisphere, 9 had infarction in the left hemisphere, and 1 had bilateral infarction. Large blood vessel territories (full anterior, middle, or posterior cerebral artery territory) were affected in 16 children, small vessel territory (lenticulostriate artery territory) vessels in 1 child, and

both large and small vessel territory in 2 children. The stroke affected what was broadly defined as the anterior circulation alone in 12 of the children, the posterior circulation alone in 5 of the children, and the entire circulation system in 2 children.

Ten of 29 children sustained sinovenous thrombosis. Hemorrhage was detected in 3 children with sinovenous thrombosis; two hemorrhages were extraparenchymal and one occurred in the thalamus. Infarction occurred in 1 of 2 children with sinovenous thrombosis who had more than one stroke.

Information regarding the presence of seizures, one of the hallmarks of stroke in infancy, was available for all 29 children. Seizures occurred in 26 children at the onset of stroke. Seizures did not occur in 2 children with arterial ischemic stroke, and in 1 child with sinovenous thrombotic stroke. Recurrent seizures were reported in a child with sinovenous thrombosis at two subsequent follow up neurological assessments. Recurrent seizures were also reported in a child with arterial ischemic stroke at one subsequent follow up assessment attended. Seizures were not reported at any of the follow-ups for the remaining 24 children who presented with seizures with the onset of stroke.

Of the 11 children who were tested at all time points, there were 4 males and 7 females, 7 children with arterial ischemic stroke and 4 with sinovenous thrombotic stroke. All 7 children with arterial ischemic stroke and 1 child with sinovenous thrombotic stroke sustained infarction. Three of these children had infarctions lateralized to the right hemisphere, 4 to the left, and 1 to both hemispheres.

Risk Factors

Of the 19 neonates with arterial ischemic stroke in the current study, at least one of the common identifiable risk factors identified by deVeber & Roach (1999) was found in 17 children. Six children had cardiac disorders; 4 had patent foramen ovale, and 2 had

cardiac disease. Sepsis was present in 1 child, and dehydration in another. The presence of a prothrombotic state was identified in 5 children. One child had a hematological disease, namely thrombocytopenia. Two children suffered head trauma and 1 had an arteriovascular malformation. Hypoglycemia was listed as a metabolic risk factor in one child. Perinatal illness/complications were present in 13 children.

One or more of the four common risk factors listed by deVeber et al. (2001) was noted for 7 of the 10 children with sinovenous thrombotic stroke. There was no head and neck pathology or arteriopathy present in any of the 10 children with sinovenous thrombosis included in the present study. Acute systemic illness was present within 7 days of stroke in three children. One child with sinovenous thrombosis had dehydration, fever, and apnea. Dehydration and a prothrombotic state were found in a second child. A third child had meningitis, shock, dehydration, and sepsis, along with the presence of a risk factor for a prothrombotic state. Of the remaining 7 children, 1 had an unidentified acute systemic illness, 1 had lung disease, a prothrombotic state was detected in 2, and 3 had no risk factors that fell within these four categories.

Statistical Analyses

Preliminary Analyses

An analysis of whether the 29 children who attended neuropsychological testing at 12, 24, or 36 months are different from those who did not was conducted by comparing scores obtained on the PSOM neurological examination before 36 months of age. Scores from each of the five domains were added to create an overall outcome score. An average overall outcome score was calculated for children who were administered more than one PSOM within this time frame.

Only children with scores on all five indices of the PSOM were included in the comparison of overall scores (n = 125). PSOM data was available for 25 of 29 children with neonatal stroke with neuropsychological testing included in the current study (86.2%), as well as for 8 children with neonatal stroke with neuropsychological testing at other time points. Data was available for 92 children with neonatal stroke with PSOM testing alone.

Preliminary analyses revealed that children who attended neuropsychological testing by the age of 36 months obtained significantly better overall outcome scores (M = .53, SD = .61) on the neurological examination of the PSOM than did children who did not participate in neuropsychological testing (M = 1.26, SD = 1.66), t (122.85) = 3.60, $p < .01$ (two-tailed), d = 0.81.

Main Analyses

The main question in the current study asks whether children with neonatal stroke obtain significantly lower scores on measures of intellectual ability administered at 12, 24, and 36 months post-stroke than an age-matched normative sample. Because not all children had all measures at each time of study, this question was addressed using a cross-sectional design. Of the whole sample of 29, some children were tested at more than one time point, and 11 children were tested on all measures at all time points. Participant and stroke characteristics for the whole sample of 29 are listed in Table 1.

One-tailed z-tests were conducted using an alpha of .05 to compare the mean of the clinical sample with the mean of the normative sample at each time of testing. Mean scores were significantly lower than those found in the normative sample on the Bayley (1969) PDI at 12 months post stroke (z = -1.93), and the Bayley MDI (z = -2.23) and PDI (z = -1.87) at 24 months post-stroke. Post-hoc tests revealed that the mean score on the

WPPSI-R PIQ at 36 months post stroke was significantly superior to the normative sample mean ($z = 2.24$) All other findings were nonsignificant. Means, standard deviations, and z scores for each time at testing are displayed in Table 2.

Table 1.

Participant gender, stroke type, and hemisphere of infarction if present

Measure	Gender		Type of Stroke		Hemisphere of infarction		
	Male	Female	AIS	SVT	Left	Right	Bilat
BSID-II	Twelve months post-stroke						
	12	12	15	9	8	7	1
	Twenty-four months post-stroke						
	10	11	13	8	6	6	2
	Thirty-six months post-stroke						
WPPSI-R	6	8	8	6	4	4	1
PPVT-R	7	8	9	6	4	5	1

Note. BSID-II = Bayley Scales of Infant Development Mental Development-II; WPPSI-R = Wechsler Preschool and Primary Scales of Intelligence–Revised; PPVT-R = Peabody Picture Vocabulary Test-Revised; AIS = arterial ischemic stroke; SVT = sinovenous thrombotic stroke; Bilateral = Infarction sustained in both cerebral hemispheres.

Table 2.

Neonatal Mean Scores Compared with the Normative Sample Mean on Measures of Intellectual Functioning

Measure	*M*	Range	*SD*	*Z*	*p*	*d*
BSID-II	Twelve months post-stroke ($n = 24$)					
MDI	98.58	84-113	6.80	-0.46	0.32	0.09
PDI	93.71	62-117	14.18	-2.05*	0.02	0.42
BSID-II	Twenty-four months post-stroke ($n = 21$)[a]					
MDI	92.19	53-122	15.64	-2.39*	0.01	0.52
PDI	93.48	50-119	14.92	-1.99*	0.02	0.43
WPPSI-R	Thirty-six months post-stroke ($n = 14$)[b]					
VIQ	101.79	90-118	9.07	0.45	0.33	0.12
PIQ	109.00	95-130	10.01	2.24[t]	--	--
FSIQ	106.36	91-126	9.26	1.59	0.06	0.42
PPVT-R	Thirty-six months post-stroke ($n = 15$)[c]					
SS	104.07	76 - 119	13.42	1.05	0.15	0.27

Note. All *z* tests were one-tailed except where noted.

MDI = Mental Development Index; PDI = Psychomotor Development Index; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; SS = Standard Score. [a]Nineteen of these participants were seen at 12 months. [b]One was seen before only at 12 months. One was seen before only at 24 months. Twelve were seen on both previous time points. [c] Two were seen only for this measure. One was seen before at 12 months and 36 months (WPPSI-R). One was seen before at 24 months and 36 months (WPPSI). Eleven were seen for all three previous tests. [t] While none of the test scores for neonates were different from the normative sample in the expected direction at 36 months, post hoc analyses revealed that

the WPPSI-R PIQ was different from the normative sample in the unexpected direction ($p < .05$, two-tailed).

* $p < .05$.

Auxiliary Analyses

Gender, type of stroke (arterial ischemic or sinovenous thrombosis), presence of an infarct, and laterality of infarction (right, left, or bilateral) were entered as variables in two-tailed independent samples *t* tests, using an alpha =.10 with scores obtained on measures of intellectual functioning at 12, 24, and 36 months of age as the dependent variables. There was no difference by gender, type of stroke, or presence of an infarct at any time point in any of the dependent variables.

Children with a right hemisphere infarct scored significantly lower than children with a left hemisphere infarct on the Bayley PDI at 24 months, the WPPSI-R PIQ at 36 months, and the WPPSI-R FSIQ at 36 months. Although there were no other statistically significant differences, comparison of all other dependent variables at all time points revealed that scores in the left hemisphere infarct group were consistently superior to those in the right hemisphere infarct group. See Table 3 for a list of means, *t* test values, and effect sizes.

Table 3.

Comparison of Intellectual Outcome after Neonatal Stroke with Infarction

Measure	MPS	Side of Stroke	*n*	*M*	Range	*SD*	*t*	*p*	*d*
BSID-II MDI	12	Left	8	99.63	93-105	4.10	.20	.85	0.15
		Right	7	99.00	88-113	7.77			
BSID-II PDI	12	Left	8	95.88	64-117	15.76	.72	.48	0.35
		Right	7	90.43	65-106	13.14			
BSID-II MDI	24	Left	6	95.67	64-122	19.20	.52	.62	0.23
		Right	6	91.33	82-100	7.12			
BSID-II PDI	24	Left	6	102.76	88-115	9.42	2.57*	.03	1.28
		Right	6	90.67	84-100	6.53			
WPPSI-R VIQ	36	Left	4	104.50	94-118	11.90	.92	.39	.57
		Right	4	97.75	90-107	8.54			
WPPSI-R PIQ	36	Left	4	111.50	109-115	2.52	5.10***	.00	4.56
		Right	4	100.00	95-104	3.74			
WPPSI-R FSIQ	36	Left	4	109.00	101-117	7.30	1.96*	.10	1.27
		Right	4	99.75	91-104	5.97			
PPVT-R SS	36	Left	4	109.75	101-119	8.62	1.33	.23	1.27
		Right	5	98.80	76-116	14.41			

Note. MPS = months post-stroke. All t tests are two-tailed. Pooled variances were not used in the calculation of Cohen's D because the variances of left and right hemisphere were homogeneous at each time point for all measures.

* $p < .10$. ** $p < .05$. *** $p < .01$

Next the scores of children with unilateral infarction were compared with the normative sample by side of infarction (right or left hemisphere) using two-tailed *z* tests, and an alpha=.10. When compared with the normative sample separately by side of infarction, children with right hemisphere infarcts scored significantly lower than the normative sample on the Bayley PDI at 12 months ($M = 90.43$, $SD = 13.14$), $z\ (7) = 1.69$, $p = .05$ (two-tailed). All other comparisons were nonsignificant.

Separate analyses were conducted using only the children who were tested at all time points ($n = 11$). Analyses of these children using two-tailed *z* tests and a $p = .10$ revealed scores that were not significantly lower than the mean of the normative population at any time point, unlike results for the larger sample of 29.

However, similar to results for the whole sample, a comparison of performance of 7 children tested at all time points by side of infarction revealed that children with right hemisphere infarction obtained significantly lower mean scores than children with left hemisphere infarction on the Bayley PDI at 24 months, and on the WPPSI-R PIQ and FSIQ at 36 months (See Table 4 for a list of means, *t* values, and effect sizes). None of the other differences were significant at any other time point. However, on an absolute basis there was a trend for children with right hemisphere lesions to have lower scores at seven of eight testing points.

It should be noted that 7 of these 11 children had infarcts lateralized to one of the cerebral hemispheres. Therefore, these children make up the majority of the larger sample with lateralized infarcts, especially at the 36 month follow up. The only 4 children with left hemispheric infarction in the sample of children who were tested at all time points were also the only 4 children included in the analysis of the sample of children with left hemispheric infarction from the whole group of 29 children. Similarly,

the 3 children with right hemisphere infarction who were tested at all time points were 3 of the 4 children with right hemisphere infarctions at 36 months included in the analyses of the larger group at this time-point. Thus the analysis for the 11 children and the analysis for the whole sample is largely redundant because children who were seen at all time points made up the majority of the total sample of children with lateralized infarction.

Table 4.

Comparison of Intellectual Outcome after Neonatal Stroke with Infarction in Seven Children Tested at all Time points

Measure	MPS	Side of Stroke	*n*	*M*	*Range*	*SD*	*t*	*p*	*d*
BSID-II PDI	24	Left	4	106	96-122	.79	4.36**	.01	2.65
		Right	3	85.33	84-88	2.31			
WPPSI-R PIQ	36	Left	4	111.50	109-115	2.52	4.49**	.01	4.69
		Right	3	99.67	95-104	4.51			
WPPSI-R FSIQ	36	Left	4	109	101-117	7.30	2.01*	.10	1.46
		Right	3	98.33	91-103	6.43			

Note. MPS = Months post-stroke. All t tests are two-tailed. Pooled variances were not used in the calculation of Cohen's D because variances of left and right hemisphere were homogeneous at each time point for all measures. Only comparisons that were significant are included in this table.

* $p < .10$. ** $p < .01$.

Additional Follow-up Information of Three Children with Neonatal Stroke

Additional follow up assessments will be described for three children with neonatal stroke included in the present study. These children were referred for further follow-up by neurologists for research or clinical purposes or by parents who expressed concern over persistent deficits.

Follow up on one child with neonatal stroke (male, sinovenous thrombosis) without infarction revealed a pattern of performance at 10 years of age that was very similar to that obtained at 36 months of age (WPPSI-R VIQ = 90, PIQ = 100; FSIQ = 94). At follow up this child continued to demonstrate low average verbal skills and average non-verbal intellectual abilities on the Wechsler Intelligence Scales for Children for Children – Revised (WISC-R; Verbal Comprehension Index [VCI] = 91, Working Memory Index [Working Memory Index] = 77, Perceptual Organization Index [POI] = 104, Processing Speed Index [PSI] = 97; FSIQ = 90). Furthermore, a discrepancy between intellectual skills and academic achievement in the presence of poor phonological skills indicated the emergence of a language-based learning disability. Thus, a learning disability emerged in the presence of a persistent discrepancy between Verbal and Performance IQ.

Follow up of another child with neonatal stroke (female, sinovenous thrombosis) without infarction revealed a severe decline in performance on measures of intellectual functioning from 36 months to nine years of age. This child's stroke at birth was complicated by the presence of meningitis and the development of epilepsy. This child's performance at 36 months on the WPPSI-R was characterized by scores that were average (VIQ = 100, PIQ = 101, FSIQ = 102). However, she was described as being developmentally delayed by 5 years of age. Her scores at 9 years of age on the WISC-R

were globally depressed, and three of four intelligence quotient indices fell below the 5th percentile (VCI = 87, WMI = 62, POI = 63, PSI = 59; FSIQ = 62). Marked difficulties were noted with attention, behavioural regulation, and emotional lability.

Follow up of a third child with neonatal stroke (female, arterial ischemic stroke) with left hemispheric infarction revealed the presence of a learning disability at 10 years of age. This child demonstrated normal functioning on the Bayley MDI at 12 months (MDI=103), with worse functioning on the Bayley PDI (PDI=86). No neuropsychological testing data were available for her at 24 or 36 months of age. Records indicated that this child spoke her first words at 7 months of age, but that her parents first noticed difficulties with speech production and word-finding at 2 years of age. At her most recent assessment, at approximately 10 years of age, this child was described as having pervasive, long-standing difficulties with language that stood in contrast to strengths in non-verbal domains. This child met the diagnostic criteria for a Specific Language Impairment at this assessment. Significant and widespread impairments were also noted in attention, working memory, executive functioning, and understanding of social norms.

Discussion

The primary purpose of the current study was to examine intellectual outcome in children with neonatal stroke by comparing their mean scores on standardized measures of intellectual functioning at 12, 24, and 36 months post-stroke with normative data. The 29 neonates included in the present study demonstrated poorer psychomotor functioning than the normative sample at 12 months and poorer psychomotor and mental functioning at 24 months. However, as a group, children with neonatal stroke did not show

significantly lower scores than the normative sample at 36 months of age on the WPPSI-R FSIQ, PIQ, or VIQ or on the PPVT-R.

Thus overall evidence was found suggesting initial deficits with apparent recovery by 3 years post-stroke. The implication of these findings is that on average at least subtle impaired performance is present on measures of psychomotor and cognitive development within the first two years following neonatal stroke. Moreover, since neurological outcome for the children who underwent testing was significantly better than those who did not, the present results may underestimate the effects of neonatal stroke on intellectual outcome.

In the present study, at 36 months of age children with neonatal stroke did not have significantly lower WPPSI-R VIQ and FSIQ scores than the normative sample. In fact, this small sample had significantly higher PIQ scores than the sample on which the WPPSI-R was standardized. Other studies of early childhood stroke have found that intelligence quotients were not significantly below normal. Trauner et al. (1993) found that children with pre or perinatal stroke did not differ from the normative sample by two years of age. Max (2004) found that children with early stroke demonstrated normal scores when tested after 5 years of age. Scores that were low average but were not significantly poorer than the normative sample were also found in a study that measured post-stroke intellectual outcome between 6 and 24 months of age in children who sustained stroke within the first 2 months of life (Wulfeck, et al., 1991). It is possible that a similar pattern of early impairment occurred in the children included in the study by Wulfeck et al. (1991), but was masked by the use of such a broad range of ages at testing, a common practice in studies of childhood post-stroke outcome.

There are several potential explanations for the finding that scores of the children in the present sample did not obtain VIQ and FSIQ scores that were significantly lower than the normative sample at 36 months post-stroke and obtained significantly higher PIQ scores. The presence of a floor effect has been noted for the WPPSI-R, meaning that it does not clearly differentiate among children who perform in the lower range of the test (Sattler, 2001). In fact, it is only possible to reach the lower limit of the WPPSI-R (IQ=40) at 5 ¼ years of age. Thus it is possible that the WPPSI-R scores over-estimated intelligence scores in this sample at 36 months of age.

An alternate explanation for the apparent recovery in the children in the current study is that the children represented a unique group whose parents were more diligent about attending physiotherapy and occupational therapy. This explanation is supported by the finding that the 11 children who attended all times of neuropsychological testing did not perform worse than the normative sample at any time point. It is possible that parents who bring their children in for neuropsychological assessment are more likely to follow up with other forms of intervention. Children who were tested at 36 months of age achieved a WPPSI-R PIQ that was significantly higher than the normative sample. The presence of this anomalous finding supports the possibility that some form of intervention affected intellectual functioning at this time point.

It is also possible that a decrement in IQ was not detected at 36 months in the present study due to the influence of socioeconomic status (SES). A separate study examined the relation of socioeconomic status to post-stroke outcome in 47 children who sustained stroke before the age of four, and included children from the present study (Hetherington, Tuff, Anderson, Miles, & deVeber, 2005). A weak association was noted between parental occupational status and IQ at the first post-stroke assessment, with mean

IQ five points higher in the group of children of professionals. Children from higher SES families may have parents who are able to personally provide or pay for better post stroke care for their child. Children with parents with higher SES may also have higher innate premorbid intelligence, which may serve as a neuroprotective factor in brain injury. If the SES of parents of children seen at 36 months in the present study was high overall, then one or both of these factors may have resulted in WPPSI-R IQ scores that were equivalent to or better than the mean score in the normative group.

Based on a study by Ballantyne, Scarvie, and Trauner (1994), it is also conceivable that using a control group matched for socioeconomic status, among other variables, may have revealed that the average scores obtained at 36 months post-stroke in the present study represented impaired performance. Ballantyne et al. (1994) demonstrated the importance of using a well-matched control group in discerning impairment in children who perform within the average range. They found IQ scores that were normal but were significantly poorer than children with peri or prenatal stroke matched according to age, sex, and socioeconomic status. This difference in IQ was evident even though the age at testing ranged from 4 to 20 years of age. In line with the results of this study (Ballantyne et al., 1994), three of the children included in the present study demonstrated notable impairment at follow-up approximately 10 years post-stroke.

Taken together, numerous factors preclude clear interpretation of the WPPSI-R scores including the small sample size, and lack of socioeconomic data or a control group. Nonetheless, the results of the follow-up cases highlight the importance of monitoring the progression of intellectual functioning for many years after neonatal stroke, regardless of whether impairment is noted within the first three years post-stroke.

Theoretical Considerations

It is important to consider the findings of the current study in terms of models of neuroplasticity and lateralization. When considered as one group, the children included in the current study did not obtain scores that were significantly lower than the normative sample at 36 months of age on the indices of the WPPSI-R or on the PPVT-R. According to Kolb (1995), two factors promoting adaptive neuroplastic change in neonatal stroke include the availability of radial glial fibers for transporting healthy neurons to damaged areas in the 1st month of life, and the occurrence of stroke prior to the elimination of disruptive connections during peak synaptogenesis at the 12th month of life. Thus it is possible that these two characteristics of neuronal development underlie the apparent recovery seen at 36 months. However, Kolb (1995) predicts poorer outcome after injury sustained during cell migration despite the presence of radial glial fibers. Kolb et al. (2003) further posits that damage to certain cerebral structures during critical developmental periods could hinder the emergence of more complex skills later in development. Therefore it is possible that a shift of simple functions to an undamaged area (homologous area adaptation) occurred post-stroke. It is further possible that this shift may have become more evident after 36 months of age as competing and neighbouring regions were activated with learning of more complex skills. The follow-up description of deficits that persisted and worsened in three children with neonatal stroke at follow-up at approximately 10 years of age supports this possibility.

There were no differences in scores obtained on measures of psychomotor or intellectual functioning based on gender, type of stroke, or presence of infarction. However, several differences were noted dependent upon hemisphere of infarction when comparing the performance of 20 children with unilateral infarctions, of whom 19 had

sustained arterial ischemic stroke. Children with right hemisphere infarcts performed more poorly than the normative population on the Bayley PDI at 12 months, and performed more poorly than children with left hemisphere infarcts on the Bayley PDI at 24 months post-stroke, and on the WPPSI-R PIQ and FSIQ at 36 months post-stroke.

The pattern of lateralized performance that emerged was variable, but did lend some support to the Goldberg and Costa (1981) model of lateralization of functioning, which predicts poorer global cognitive functioning in children with right hemisphere infarction. There was a significant difference favouring children with a left hemisphere infarction on the Bayley PDI at 24 months post-stroke in the whole sample of 29 children. Morever, a qualitative comparison of scores demonstrates that scores for children with right hemisphere infarcts were lower on all measures at all time-points. Wulfeck et al. (1991) similarly found mean MDI and PDI scores in the first 24 months following prenatal or perinatal stroke that were lower on an absolute basis in 4 children with right hemisphere infarction (MDI = 78, PDI = 66) than 10 children with left hemisphere infarction (MDI = 102, PDI = 87). Taken together, in support of the Goldberg and Costa model, the findings of the current study and of Wulfeck et al. (1991) demonstrate reduced functioning with early right hemispheric infarction.

At 36 months post-stroke all scores were in the average range, and it was not possible to discriminate children with neonatal stroke from the normative sample except for the unexpected superiority of the children with stroke on the WPPSI-R PIQ. However, the sample size at this time point was small (n = 14), and it is possible that significant differences may have been found with a larger sample size.

A comparison of children by side of infarction at this time point did evidence a significant difference favouring children with left hemisphere infarction on the WPPSI-

PIQ and FSIQ. Additionally, on an absolute basis, children with left hemispheric infarction obtained higher scores on the WPPSI-R VIQ and on the PPVT-R. Thus evidence of subtle lateralized differences in functioning was still present at 36 months post-stroke.

The Goldberg and Costa (1981) model predicts that children with right hemispheric lesions are more likely to have global cognitive deficits than children with left hemispheric lesions sustained at the same age. The results of the present study support this model, but are not supported by the results of several other studies of long-term functioning after early stroke. Ballantyne et al. (1994) studied children with prenatal or perinatal unilateral focal brain infarctions up to 20 years of age and found that nonverbal abilities were more markedly affected than verbal abilities in children with infarctions confined to the right hemisphere. In contrast, children with left hemispheric infarctions exhibited the same degree of impairment in verbal and nonverbal abilities. Levin (2003) reviewed several studies of neuroplasticity following traumatic brain injury, and did not find evidence of global cognitive deficits in children with right hemispheric lesions. Instead, subtle and persistent visuospatial deficits were associated with right hemisphere lesions sustained after the age of one, whereas language deficits that were subtle, transient, and variable were associated with early left frontal lesions.

Further research following a larger sample across a more extended time period is required to determine whether subtle indications of deficits in children with right hemisphere infarcts persist or evolve with further development, and if so whether they continue to manifest as global deficits or become more lateralized in nature.

Implications for Clinical Practice

Findings of the current study can inform clinical treatment of patients with neonatal stroke in several ways. Because the presence of a floor effect has been noted for the WPPSI-R before approximately 5 years of age, it is recommended that the Bayley be used to assess intellectual outcome as long as is possible (can be used until 42 months of age). In addition, in light of the presence of persistent deficits in three children with neonatal stroke approximately 10 years post-stroke, it is recommended that clinicians use measures of intellectual functioning within the first 3 years of life as indicators of current but not future functioning. It is suggested that clinicians make parents aware that normal neurological and neuropsychological functioning within the first 3 years following neonatal stroke does not preclude the emergence of future deficits. Moreover, clinicians should explain how and when these deficits might present in their child, as well as recommend regular follow-up through childhood and adolescence. Finally, because intellectual testing within this time period does not seem to be predictive of future intellectual functioning, it should not be used to determine the need for continuing occupational or physical therapy.

Limitations

There are several important limitations to the study including absence of a comparison group and socioeconomic data, and the presence of various risk factors that differed among children included in the sample. Additional limitations include a small sample size and multiple comparisons. Even though no difference by type of stroke, or presence of an infarct was found, it is important to note that only 1 of the 20 children from the whole sample of 29 who had lateralized infarctions sustained sinovenous thrombosis. In addition, children were not matched for location of infarction and stroke

etiology. A further limitation includes the use of a different test of cognitive functioning at 36 months post-stroke than at 12 and 24 months of post-stroke, rendering it difficult to directly compare performance on the Bayley and WPPSI-R.

Only a small percentage of children with neonatal stroke at the Hospital for Sick Children and the Children's Hospital at McMaster-Chedoke had neuropsychological testing, and there is good reason to believe that the children who were tested were less impaired than those who were not. Furthermore, less than half of the children who had testing had it on all three occasions. Typically, other conditions putting a child at risk for cognitive impairment were present in the neonatal period. For example, at least one seizure occurred in most children during the neonatal period. Lastly, the use of IQ scores rather than scores on measures of specific abilities may mask patterns related to the site and type of neonatal stroke.

Future Directions

The possibility of the emergence of less subtle lateralized findings and / or specific learning disabilities with development remains, as evidenced by follow up of three children in the current study who presented with intelligence scores that were within the average range in the first three years of life but later showed marked specific learning disorders. Follow up of intellectual outcome using a large sample of children with neonatal stroke matched for age, sex, and socioeconomic status is required across a longer follow-up period. Furthermore, it would be helpful to use more refined and discriminating measures (e.g., analysis of types of errors made on a particular subtest of the WISC) that can detect subtle differences.

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