The Development of Spatial Orientation in Children After Perinatal Stroke

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The Development of Spatial Orientation in Children After Perinatal Stroke

by

Kara Murias

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
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Abstract

To enable investigation of spatial orientation abilities across a range of ages and developmental abilities, we developed a navigation task comprised of a video game in a virtual museum in which subjects were required to find different rooms with distinct themes. We then validated the task by studying a large number of healthy young adults and confirming a strong correlation with self-reported orientation abilities in everyday life (Chapter 2). We also analysed performance on the navigation task as it related to demographics and video game use, verifying previously observed gender differences and demonstrating that individuals with a longer history of video game play, as well as participants who played video games that required navigation, performed better than individuals without experience navigating in video games. Our evidence, therefore, supports the hypothesis that better navigation and orientation skills in individuals playing video games are likely due to the consistent practice of those skills while playing for entertainment (Chapter 2).

Children who have experienced a stroke around the time of birth have been shown to have IQ in the normal or near normal range as a group; however a portion of children has consistently demonstrated cognitive delays. Utilizing both concurrent neuropsychological testing and pre-existing clinical data, we found that the factors that were predictive of initial performance on the spatial orientation task were age, gender, motor dexterity, the presence of Arterial Ischemic Stroke (AIS), and loss of grey matter volume (Chapter 3). Furthermore, the modest deficits in topographical orientation, seen in AIS patients, were ameliorated by further practice and were no longer seen after the second time playing the video game. In contrast, AIS, parental education and involvement of the dorsolateral prefrontal (DLPF) cortex were predictive factors for full-scale intelligence quotient (FSIQ). Loss of tissue volume predicted reduced
verbal comprehension index (VCI) scores (Chapter 3). The relative preservation of spatial orientation, a multifaceted behaviour with a prolonged developmental course, would lend support to the hypothesis that injury within a network allows for better resiliency of that skill and may be an illustration that there is better recovery of an ability if injury occurs before that proficiency has fully matured.
Acknowledgements

Foremost I would like to thank the participants and family that donated their time to contribute to this research. Their ongoing dedication to furthering knowledge is humbling and inspiring.

I would like to extend my warmest appreciation to my supervisor, Giuseppe Iaria, for the support and guidance. I would also like to thank the members of my supervisory committee, Brian Brooks, Susan Graham and Adam Kirton.

Thank you to the members and students of the Neurolab. Collaborating and working with you has provided some of my most enriching professional experiences. You have demonstrated what collaboration and collegiality can achieve.

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Data used for the age, gender-matched hippocampal control volumes were obtained from the NIH Paediatric MRI Data Repository created by the NIH MRI Study of Normal Brain Development. This is a multisite, longitudinal study of typically developing children from ages newborn through young adulthood conducted by the Brain Development Cooperative Group and supported by the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke (Contract #s N01-HD02-3343, N01-MH9-0002, and N01-NS-9-2314, -2315, -2316, -2317, -2319 and -2320). A listing of the participating sites and a complete listing of the study investigators can be found at
http://www.bic.mni.mcgill.ca/nihpd/info/participating_centers.html. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH.
Dedication

This thesis is dedicated to my family - my husband and sons who have provided me with the support and inspiration to pursue my ambitions.
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<tbody>
<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
</tr>
<tr>
<td>ACH</td>
<td>Alberta Children’s Hospital</td>
</tr>
<tr>
<td>AHA</td>
<td>Assisting hand assessment</td>
</tr>
<tr>
<td>AIS</td>
<td>Arterial Ischemic Stroke</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>APPIS</td>
<td>Arterial Presumed Perinatal Ischemic Stroke</td>
</tr>
<tr>
<td>APSP</td>
<td>Alberta Perinatal Stroke Project</td>
</tr>
<tr>
<td>BA</td>
<td>Brodmann area</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood Oxygen Level Dependent</td>
</tr>
<tr>
<td>CCTT</td>
<td>Children Colour Trail Test</td>
</tr>
<tr>
<td>CP</td>
<td>Cerebral Palsy</td>
</tr>
<tr>
<td>c-SBSOD</td>
<td>Child adapted Santa Barbara Sense of Direction scale</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebral Spinal Fluid</td>
</tr>
<tr>
<td>CSVT</td>
<td>Cerebral SinoVenous Thrombosis</td>
</tr>
<tr>
<td>CSWS</td>
<td>Continuous Spike and Wave in Slow wave sleep</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DLPF</td>
<td>Dorsolateral Prefrontal</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
</tr>
<tr>
<td>EEG</td>
<td>ElectroEncephaloGram</td>
</tr>
<tr>
<td>FA</td>
<td>Fractional anisotropy</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid-Attenuated Inversion Recovery</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>FSIQ</td>
<td>Full Scale Intelligence Quotient</td>
</tr>
<tr>
<td>FSPGR</td>
<td>Fast Spoiled Gradient echo</td>
</tr>
<tr>
<td>GFm</td>
<td>Gyrus Frontalis medius; middle frontal gyrus</td>
</tr>
<tr>
<td>GM</td>
<td>Grey Matter</td>
</tr>
<tr>
<td>HICCUP</td>
<td>Healthy Infants and Children’s Clinical Research Program</td>
</tr>
<tr>
<td>Hooper VOT</td>
<td>Hooper Visual Organization Test</td>
</tr>
<tr>
<td>ICH</td>
<td>Intracranial Haemorrhage</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>LL</td>
<td>Left-sided Lesion</td>
</tr>
<tr>
<td>M</td>
<td>Mean</td>
</tr>
<tr>
<td>MEG</td>
<td>MagnetoEncephaloGram</td>
</tr>
<tr>
<td>MCA</td>
<td>Middle Cerebral Artery</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NAIS</td>
<td>Neonatal Arterial Ischemic Stroke</td>
</tr>
<tr>
<td>NHS</td>
<td>Neonatal haemorrhagic stroke</td>
</tr>
<tr>
<td>NIHPD</td>
<td>National Institutes of Health-funded MRI Pediatric Database</td>
</tr>
<tr>
<td>NSAID</td>
<td>NonSteroidal Anti-Inflammatory</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>p-SBSOD</td>
<td>Parent observed Santa Barbara Sense of Direction scale</td>
</tr>
<tr>
<td>PPIS</td>
<td>Presumed Perinatal Ischemic Stroke</td>
</tr>
<tr>
<td>PRI</td>
<td>Perceptual Reasoning Index</td>
</tr>
<tr>
<td>PSOM</td>
<td>Paediatric stroke outcome measure</td>
</tr>
<tr>
<td>PVI</td>
<td>Periventricular Venous Infarction</td>
</tr>
<tr>
<td>PVL</td>
<td>PeriVentricular Leukomalacia</td>
</tr>
<tr>
<td>RL</td>
<td>Right-sided Lesion</td>
</tr>
<tr>
<td>RPS</td>
<td>Research Participation System</td>
</tr>
<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>rs-fMRI</td>
<td>Resting state functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>SBSOD</td>
<td>Santa Barbara Sense of Direction scale</td>
</tr>
<tr>
<td>SES</td>
<td>SocioEconomic Status</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SNAP</td>
<td>Swanson, Nolan and Pelham Rating Scale</td>
</tr>
<tr>
<td>tDCS</td>
<td>transcranial Direct Current Stimulation</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
</tr>
<tr>
<td>VCI</td>
<td>Verbal Comprehension Index</td>
</tr>
<tr>
<td>VG</td>
<td>Video Game</td>
</tr>
<tr>
<td>WAIS</td>
<td>Wechsler Adult Intelligence Scale</td>
</tr>
<tr>
<td>WISC</td>
<td>Wechsler Intelligence Scale for Children</td>
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<tr>
<td>WM</td>
<td>White Matter</td>
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</table>
Chapter One: Introduction

1.1 Summary

Perinatal stroke is an increasingly recognized form of neurological injury affecting young children. With an incidence of 1 in 2300 to 5000 live births for ischemic injury (up to 1 in 1600 when delayed presentations and haemorrhagic strokes are included) (Chabrier, Husson, Dinomais, Landrieu, & Nguyen The Tich, 2011; Laugesaar et al., 2007; Lynch, 2009), perinatal stroke is the leading cause of congenital hemiplegia as well as a significant cause of non-motor delays and epilepsy. Following a perinatal stroke, approximately 60% of children have cerebral palsy (usually presenting as a spastic hemiplegia), 30-60% experience epilepsy, 25% show language delay, and up to 22% manifest behavioural abnormalities (defined as physician diagnosed attention, hyperactivity or behavioural problems) in later childhood (J. Lee, Croen, Lindan et al., 2005). Despite recognition of perinatal stroke as a cause of significant congenital disability, there continues to be uncertainty regarding the prevalence (with reports ranging from 11 to 41% (G. A. deVeber, MacGregor, Curtis, & Mayank, 2000; Golomb, Saha, Garg, Azzouz, & Williams, 2007; Golomb, Garg, Carvalho, Johnson, & Williams, 2007; Hartel, Schilling, Sperner, & Thyen, 2004; Kirton, Deveber, Pontigon, Macgregor, & Shroff, 2008)) and severity of long-term cognitive disorders. The accurate characterization of such complex outcomes is further complicated by the requirement for comprehensive assessments and long-term follow-up.

In the absence of epilepsy, most available information indicates that children with perinatal stroke perform in the normal range, or marginally below the average of healthy controls, on cognitive tasks. Furthermore, most evidence indicates that children with perinatal strokes do not display hemispheric or location specific deficits common to lesions at later ages.
(Ballantyne, Spilkin, & Trauner, 2007; Everts et al., 2008; Muter, Taylor, & Vargha-Khadem, 1997), indicating a potential for plasticity in the developing brain to ameliorate the deleterious effects of early brain injury. However, there are indications that more significant differences can be observed when children are tested with more demanding tasks or more sophisticated measures (Chapman, Max, Gamino, McGlothlin, & Cliff, 2003; Reilly, Wasserman, & Appelbaum, 2013; Stiles, Trauner, Engel, & Nass, 1997).

Topographical orientation is the ability of individuals to orient themselves within, and navigate through, a large-scale environment (Dudchenko, 2010; Wang & Spelke, 2002). This complex activity relies on several cognitive processes such as memory, attention, perception, mental imagery and decision-making skills (Arnold et al., 2013; Burgess, 2008; Palermo, Iaria, & Guariglia, 2008). Consequently, there are indications that spatial navigation is dependent on the integration of many skills, supported by a number of cortical areas, to form and effectively use different cognitive strategies useful for orientation, most importantly the ability to navigate by means of cognitive maps (i.e. mental representations of the surroundings that allow individuals to reach any target location from anywhere within the environment) (Arnold, Protzner, Bray, Levy, & Iaria, 2013; Maguire, 1997). In the adult brain, an injury in one of a number of specific regions results in specific cognitive impairments that can affect these skills and cause “topographical disorientation”, an inability to orient in familiar or unfamiliar surroundings (Barrash, Damasio, Adolphs, & Tranel, 2000a; van Asselen et al., 2006).

In this project I investigate how children with perinatal stroke differ in their abilities to navigate in a virtual environment and perform a spatial orientation task compared to unaffected children. Because topographical orientation utilizes multiple skills and coordination of many
cognitive processes subserved by distributed neural networks, testing spatial orientation in children with perinatal stroke provides the opportunity to investigate the functional outcome of brain plasticity in complex neural networks after early brain injury.

1.2 Spatial Orientation

1.2.1 Development of spatial orientation through a lifetime

Successfully locating yourself and objects within an environment is an important adaptive behaviour from an early age. Whether it is an infant that recognizes a familiar setting or a toddler that directs herself towards her parents, a spatial understanding of the physical environment can shape behavioural reactions in very small children. In fact, children as young as three months old have displayed memory for location of events (Hayne, Rovee-Collier, & Borza, 1991).

Researchers have used a variety of behavioural tests, starting from an early age, to elucidate how large-scale visual memory and orientation abilities emerge in early childhood. Toddlers have demonstrated the ability to encode assessments of length and distance to find hidden objects from different perspectives (Huttenlocher, 2008). When placed in a rectangular enclosure and disoriented by spinning, children aged 18 to 24 months have shown that they can reorient using the geometry of the enclosure (choosing the correct, or rotationally equivalent corner to locate a hidden toy). However, authors Hermer and Spelke found that children at this age do not use other cues or landmarks (such as a coloured wall or other objects in the room) to reorient (Hermer & Spelke, 1994). Based on this experiment, and others in humans and animals, Lee and Spelke (S. A. Lee & Spelke, 2010) have suggested two distinct cognitive processes to
navigate in an environment; one that uses the geometric form of the environment to specify location, and another that utilizes objects (and patterns of objects) available in the environment (landmarks). It was proposed that increased language abilities and the development of a left/right distinction facilitate children’s ability to effectively use landmarks to orient (Hermer-Vazquez, Spelke, & Katsnelson, 1999), although it has been established that a number of non-human animals can also use landmarks to orient (Gouteux, Thinus-Blanc, & Vauclair, 2001; Sovrano, Bisazza, & Vallortigara, 2002).

Despite ongoing research, how orientation abilities arise, and which cognitive process are available to children to locate themselves and other entities in their surroundings, remains controversial. Some experiments demonstrate considerable complexity, with different navigation strategies available to young children in different situations. When the dimensions of the rectangular enclosure were increased, children aged 18 to 24 months were able to reorient to the correct corner using a coloured wall (Learmonth, Newcombe, Sheridan, & Jones, 2008). Furthermore, children were able to reorient in a square enclosure with two brightly coloured walls, or if asymmetric pictures were placed on the wall (Nardini, Atkinson, & Burgess, 2008). A recent study has also shown that, between the ages of three and four years, children are beginning to use multiple sources of spatial information, including more distal non-coincident landmarks (Waismeyer & Jacobs, 2013). Also, in an equilateral triangle (in which corners are geometrically indistinct) four year olds were able to reorient when landmark objects were large and stable, but not when they were small and movable (Newcombe, Ratliff, Shallcross, & Twyman, 2010), indicating that they were able to orient by landmarks and perhaps that they ascribe weighted importance to different features.
As children gain mobility and independence they are increasingly exposed to new and larger environments. In a seminal paper, Seigel and White suggested that children first use landmarks to navigate, then construct routes linking landmarks, and finally integrate routes in an overall framework (or spatial representation) that link smaller portions of the environment together in a cohesive internal model for navigation (Siegel & White, 1975). A stable, internal representation of space that includes distances and directions between locations and allows for flexible navigation through an environment is commonly referred to as a “cognitive map” (O'Keefe & Nadel, 1978). The ability to form and use such cognitive maps for successful navigation and orientation through the environment requires a number of skills, including landmark recognition, path integration (i.e. the ability to process and integrate vestibular, somatosensory and proprioceptive information for navigation), the ability to judge heading orientation and distance, working and spatial memory, mental imagery, and others (Arnold et al., 2013).

The physical space surrounding an individual can be represented in two fundamentally different ways. An egocentric coding of position entails a description of location relative to the individual’s body position. Allocentric coding, on the other hand, describes a location relative to other objects, landmarks, or reference frames in the environment and is, therefore, independent of the individual’s current position in space (Dudchenko, 2010). It was previously thought that the ability to use allocentric reference frames did not develop until school age, but many recent studies have demonstrated the use of allocentric strategies at much earlier ages. Recent studies suggest that the capacity for using allocentric reference frames may be present in children as young as two years old but increases as the child develops (van den Brink & Janzen, 2013). In a room-sized enclosure, children aged 25-39 months were able to locate a single reward position.
among four possible locations in the absence of local or coincident landmarks or cues, and children older than 43 months were capable of discriminating three reward locations among a possible 18, indicating a growth in proficiency in the use of allocentric information over these early ages (Ribordy, Jabel, Banta Lavenex, & Lavenex, 2013).

As in the development of spatial orientation progresses, children increasingly use allocentric reference frames and cognitive maps to locate objects and themselves in space. Using a virtual reality radial arm task in children aged five, seven or ten years of age, Bullens and colleagues found that children at all ages preferentially adopted an egocentric strategy to navigate when both egocentric and allocentric strategies were available. Older children spontaneously used an allocentric strategy more often with increased reliance on environmental landmarks. When an allocentric strategy was forced, all children performed above chance, indicating that the ability to use allocentric reference frames is present early and improves through school age, possibly into adolescence (Bullens, Igloi, Berthoz, Postma, & Rondi-Reig, 2010). In a study of adolescents and adults, participants were asked to perform a task where they navigated within a previously learned environment to find targets. Both age groups located a similar number of targets in the allowed time, but adults had better performance on an allocentric memory task when they were later asked to label locations on a map (Pine et al., 2002).

As children mature and gain navigational experience through school age and into adolescence, they develop the cognitive flexibility to choose the most appropriate or efficient strategy as well as improved ability to access allocentric strategies. This may be due to an increase in working memory, as well as improvements in other executive functions that continue to undergo development into early adulthood. The space around an individual can be divided in a
number of ways but two regions that have been shown to be behaviourally discrete (Belmonti, Berthoz, Cioni, Fiori, & Guzzetta, 2015; Belmonti, Cioni, & Berthoz, 2015) and distinct in their neural representation (Nemmi, Boccia, Piccardi, Galati, & Guariglia, 2013) are near or reaching space, and far or navigational space. It has been shown that working memory for the navigational scale undergoes a protracted development. Two recent cross sectional studies in large groups of school-aged children (Belmonti et al., 2015; Piccardi, Leonzi, D'Amico, Marano, & Guariglia, 2014) showed an increase in spatial working memory on the navigational scale (measured using room-sized adaptations of the Corsi block tapping test; also referred to as the walking Corsi test) across the ages six to 12 years. At 12 years old children had not reached the same span on the walking Corsi test as adults, indicating that there is continued improvement in navigational working memory through adolescence. Verbal memory (as measured by digit span) and reaching working memory (measured by Corsi block tapping test) had nearly reached mature levels by the age of 12 years (Belmonti et al., 2015; Piccardi et al., 2014).

The trend of increased flexibility of navigational strategies and improved use of allocentric reference frames may reverse later in life with age-related declines in memory and attention (Liu, Levy, Barton, & Iaria, 2011). Bohbot and colleagues tested people through a range of ages spanning 8 to 80 years old with a virtual radial arm maze task (Bohbot et al., 2012). They found that 83.3% of children (ages 8 to 18 years) used a spatial strategy that requires learning the spatial relationships between multiple landmarks in the environment and that is dependent on the hippocampus (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003). Only 46.6% of young adults (ages 19 to 40 years) and 39.3% of older adults (> 40 years old) spontaneously used a spatial strategy. Instead, adults favoured a stimulus response strategy that involves learning a set of specific movements from a
given start or landmark location. These data suggest that, through the course of development, individuals use different strategies, underlain by different neuroanatomical basis, for spatial memory, orientation and navigation.

In addition to a significant variation in “normal” ability for topographical orientation (Aguirre & D'Esposito, 1999), a number of different populations have exhibited difficulty orienting or navigating in space. Though people with low IQ have exhibited decreased spatial memory and impaired ability to orient in space (Katz & Ellis, 1991), people both with brain lesions (Iaria et al., 2005) and without (Iaria, Bogod, Fox, & Barton, 2009), have been found to have difficulty with spatial orientation in the absence of decreased IQ or other neuropsychological defects (Nadolne & Stringer, 2001). Literature in children is limited but deficits in spatial orientation have been found in children that have experienced severe traumatic brain injury (Lehnung et al., 2003), intrauterine growth restriction (Leitner, Heldman, Harel, & Pick, 2005), septo-optic dysplasia (Griffiths & Hunt, 1984) and periventricular leukomalacia (PVL) after premature birth (Pavlova, Sokolov, & Krageloh-Mann, 2007).

1.2.2 Neuroanatomy of spatial orientation

Lesion studies in humans and animals, and more recently imaging techniques including functional Magnetic Resonance Imaging (fMRI), have helped determine the neural mechanisms underlying the skills required for successful spatial navigation. In lesion studies, careful testing to determine which component of topographical orientation may be impaired (e.g. recognising landmarks, working memory, judging distance, constructing cognitive maps, etc.) and then correlating deficits to areas of damage, have pointed to important cortical areas. Studies in
animals and the use of non-invasive imaging techniques in humans have helped refine when and how different brain areas contribute to navigation abilities.

The most studied area associated with spatial memory and cognition is the hippocampus. The discovery of “place cells” (specific neurons in the hippocampus that exhibit environmental site selective activity) in animal models (O'Keefe & Nadel, 1978) and later in humans (Ekstrom et al., 2003) brought attention to the hippocampus as a centre for location processing. A number of experiments in humans and animals verified that the hippocampus, particularly the right hippocampus, is involved in allocentric spatial memory (Burgess, Maguire, & O'Keefe, 2002). Lesion studies support that damage to the right hippocampus results in a loss of spatial navigation (Aradillas, Libon, & Schwartzman, 2011). The extent of damage to the right hippocampus was found to correlate with impairments in recognizing landmarks and retracing a newly learned route (van Asselen et al., 2006). Using a virtual radial arm maze and fMRI imaging, Iaria and colleagues demonstrated that participants that used a spatial strategy, utilizing landmarks during initial training, had increased blood oxygen level-dependent (BOLD) signal in the right hippocampus, as opposed to the use of a procedural strategy, which relied on the striatum (Iaria et al., 2003). In addition, Sherrill and colleagues recently demonstrated that there was increased anterior hippocampal (as well as retrosplenial cortex and posterior parietal cortex) recruitment when participants successfully navigated to the goal location in the first or third person (but not map/survey) perspective during a virtual navigation task. In a corollary to increased firing of place cells relative to location seen in rodents (Johnson & Redish, 2007; Pfeiffer & Foster, 2013), increased fMRI signal in the posterior hippocampus was modulated by distance to the goal location when navigating in the first person perspective (Sherrill et al.,
This lends further evidence that the hippocampus is involved in processing allocentric spatial information during navigation.

Closely associated with the hippocampus is the subicular region and entorhinal cortex. Head-direction cells in the postsubiculum of a mammal fire preferentially when the animal is looking in a specific direction (Taube, Muller, & Ranck, 1990a; Taube, Muller, & Ranck, 1990b). In the entorhinal cortex, grid cells fire at specific points along a periodic hexagonal lattice covering the three dimensional area available (Moser, Moser, & Roudi, 2013). Both the subicular region and the entorhinal cortex exist in networks with the hippocampus and are thought to inform the creation of spatial memories (Spiers & Maguire, 2007). Furthermore, fMRI signal in the entorhinal/subicular region was modulated by facing and goal direction when viewing a previously learned route, which authors argued implied that the entorhinal/subicular region may be involved with simulating goal direction during route planning (Chadwick, Jolly, Amos, Hassabis, & Spiers, 2015).

The posterior parahippocampal region has proven to be important for spatial navigation because of its association with the acquisition of landmark information. Takahashi demonstrated that damage to the right posterior parahippocampal gyrus obliterated the ability to acquire novel information about buildings and landscapes in a study of four people with “landmark agnosia”. In addition, damage to that same region, as well as the anterior half of the lingual gyrus and adjacent fusiform gyrus, impaired recognition of familiar landmarks (Takahashi & Kawamura, 2002). In total, this indicates that the inferior medial temporal lobe is a locus for large-scale spatial memory and orientation within the networks that facilitate spatial navigation.
A number of other cortical areas (medial and posterior parietal lobe, occipitotemporal and dorsolateral prefrontal cortex) have been implicated in both lesion and functional neuroimaging studies of navigation (Maguire, 1997). For example, 24 patients with unilateral parietal cortex strokes were studied with two virtual reality tasks, one that measured allocentric memory (navigation in a park environment with landmarks) and another that required egocentric memory (navigation in a brick maze by learned routes). When compared to healthy controls, participants with lesions showed strongly impaired performance on the egocentric memory task but not in the allocentric task (Weniger, Ruhleder, Wolf, Lange, & Irle, 2009). This is consistent with other studies that have implicated the posterior parietal lobe in egocentric orientation (Aguirre, Zarahn, & D'Esposito, 1998). Another study investigated navigation abilities in 127 patients with stable, focal lesions with a “real-life” route-learning task (Barrash, Damasio, Adolphs, & Tranel, 2000b). Impairment was highly associated with damage to the right hippocampus, the right inferotemporal region, or the occipital and posterior parahippocampal cortices in either hemisphere. Impairment was seen in 86% of the individuals with damage to any of these regions, in contrast to impairment in 31% of participants with lesions in other regions (Barrash et al., 2000b).

The retrosplenial cortex is believed to be responsible for the conversion of egocentric reference frames, as mediated by the parietal cortex, to and from allocentric reference frames, as processed in the medial temporal regions (Burgess, Maguire, Spiers, & O'Keefe, 2001; Ino et al., 2002). Damage to this area has been associated with a relatively pure topographical disorientation, with patients displaying impairments in learning new routes, navigating in familiar environments and, despite retaining landmark recognition, using landmarks to aid with orientation (Ino et al., 2007; Maguire, 1997; Takahashi, Kawamura, Shiota, Kasahata, &
Hirayama, 1997). Functional imaging studies have also supported the hypothesis that the retrosplenial cortex promotes successful navigation by facilitating incorporation of egocentric information into allocentric representation of space (Iaria, Chen, Guariglia, Ptito, & Petrides, 2007; Wolbers & Buchel, 2005). Increased BOLD signal in the retrosplenial cortex, along with the posterior parietal lobe, provides further evidence that this region is indeed recruited during successful goal directed navigation (Sherrill et al., 2013).

While lesion and fMRI studies have revealed specific areas that are either required or employed during successful navigation, more recent investigations have concentrated on the contribution of networks. As early as the 1960’s, Geschwind outlined the “disconnection hypothesis”; the theory that damage to axonal bundles connecting cortical regions resulted in a range of neurological deficits (Geschwind, 1965a; Geschwind, 1965b). Though not a new proposal, the idea that the coordination between cortical areas is important for cognitive functioning has gained new attention because non-invasive neuroimaging techniques allow for new investigative approaches of this hypothesis. Neuroimaging investigations of networks consist of structural analyses and functional analyses on the scale of millimeters (in high resolution structural MRI) to many centimeters (across the whole brain). Structural network investigations most often involve diffusion tensor imaging (DTI), which is sensitive to the random thermal motion of water molecules. Because cell walls and myelin restrict the motion of water molecules, analysis of DTI can characterize the direction and strength of white matter connections (Clayden, 2013). Functional networks or connectivity in neuroimaging relies on analysis of the time course of neural activity in different areas of the cortex that allows for inference about how these areas activity is dependent (Friston, 1994). Unless otherwise stated, “networks” will refer to functional connectivity for discussion in this document.
The wide variety of functional areas implicated in topographical orientation, and the complexity of when they may or may not be necessary for navigation, hints at the vast underlying functional network of cortical connections (Ekstrom, Arnold, & Iaria, 2014). It has been shown that, during retrieval of temporal spatial details of an environment, there is considerable increase in functional connectivity (temporal correlations across different regions as related to task performance) across multiple lobes (as measured by whole brain graph theory analysis of fMRI BOLD signal). Within this network the hippocampus, prefrontal cortex, precuneus and visual cortex serve as “hubs” of high connectivity during successful memory retrieval (Schedlbauer, Copara, Watrous, & Ekstrom, 2014). Variations in these networks may help explain the wide range of individual variability in navigational ability. Analysis of resting state networks that were composed of brain regions engaged during orientation, indicated that increased levels of global efficiency and increased levels of node centrality in areas associated with higher orientation accuracy (the right supramarginal gyrus, the right primary motor cortex, and the left hippocampus) were indicative of high-performing individuals. This reveals that some of the variation in navigation abilities seen in individuals arises from the properties of the neural networks that are employed for this skill (Arnold et al., 2013).

As progress is made using analysis of functional networks to explain individual variation in healthy individuals, it extends the possibility of measuring network properties to investigate cognitive deficits in people with neurologic injury or illness. While deficits can be traced to injury of specific functional areas in some cases, (a classic example would be aphasia after injury to Broca’s or Wernicke’s area) there are other cases where deficits cannot be explained by, or are not specific to, a particular location (e.g. mild traumatic brain injury (Mayer, Bellgowan, & Hanlon, 2015) or neurodevelopmental diseases such as autism (Plitt, Barnes, Wallace,
Kenworthy, & Martin, 2015)). In cases where dysfunction is diffuse or not easily localized, using functional neuroimaging to interrogate networks may reveal patterns of injury that were not previously evident. By investigating behaviours that are dependent on a distributed network (and later the associated functional network), during childhood can provide a unique view of cognitive development. Furthermore, investigations of these cognitive skills after early injury could provide a window on brain plasticity and accommodation.

1.3 Perinatal Stroke

Recent advances in imaging have led to better understanding of brain injuries in newborns. Magnetic resonance imaging has allowed for increased recognition of perinatal stroke as aetiology for newborn depression, congenital hemiplegia, and symptomatic epilepsy (Lee et al., 2005). Better brain visualization had also allowed for improved classification of perinatal injury and established the basis for investigations into the pathophysiology, prognosis and possible treatment of stroke in neonates. Perinatal stroke includes focal vascular injury thought to have occurred in the period of 20 weeks gestation to 28 days after birth in a baby born at term (Raju, Nelson, Ferriero, Lynch, & NICHD-NINDS Perinatal Stroke Workshop Participants, 2007). For the purpose of this project, this definition would exclude children who have suffered more generalized insults such as hypoxic ischemic injury or congenital brain malformations, as well as preterm children. Stroke diagnosed in the period from birth up to one month is also referred to as neonatal stroke (Kirton et al., 2011). Paediatric or childhood stroke refers to cerebrovascular events in children older than one month of age.
1.3.1 Presentation and pathogenesis of perinatal stroke

1.3.1.1 Acute neonatal presentation

Arterial ischemic strokes (AIS) in newborns can present acutely in the first days or weeks of life with seizures or with a decreased level of activity. Neuroimaging with diffusion weighted MRI shows restricted diffusion consistent with acute ischemia in an arterial territory (Figure 1.1A and B). Lesions most often involve the cortex and underlying white matter in the area of the middle cerebral artery (MCA) (Kirton & deVeber, 2009). For unknown reasons, injuries are more common in the left hemisphere and tend to be larger than those seen in the right hemisphere (Carlsson et al., 1994; Chilosi, Cipriani, Bertuccelli, Pfanner, & Cioni, 2001).
Figure 1.1: Neuroimaging of acute presentations of perinatal stroke

A. Acute axial diffusion weighted MRI indicating bilateral restricted diffusion typical of acute bilateral MCA infarcts in neonatal arterial ischemic stroke (NAIS). B. Acute axial diffusion weighted MRI with restricted diffusion in the left MCA territory indicating acute arterial ischemia. C. Sagittal CT angiogram with filling defect in the superior sagittal and straight sinus in a neonatal cerebral sinovenous thrombosis (CSVT). D. Axial unenhanced CT with acute bleed bilaterally into the lateral ventricles, commonly seen in acute CSVT. E. Axial
gradient echo MRI of an acute intraparenchymal haemorrhage appearing as a dark
“blooming” artefact in the right parietal-occipital area. F. Axial CT of the same patient with
hyperdensity suggestive of acute blood in the occipital parietal area. Figure adapted from
(Murias, Brooks, Kirton, & Iaria, 2014).

A number of risk factors have been associated with perinatal AIS, but definitive causative
mechanisms have not been established and most cases remain idiopathic. There is evidence that a
maternal history of infertility, gestational diabetes, preeclampsia, and placental abnormalities are
independent risk factors (Darmency-Stamboul et al., 2012; Raju et al., 2007). A complicated
delivery history that included foetal heart rate abnormalities, meconium stained liquor or
intervention has been found more commonly in children with perinatal AIS (Darmency-
Stamboul et al., 2012; J. Lee, Croen, Backstrand et al., 2005). In addition, inherited coagulation
abnormalities (particularly factor V Leiden and antiphospholipid antibodies) appear more
common in children with perinatal stroke (Gunther et al., 2000), and their mothers (Simchen et
al., 2009).

Other stroke syndromes that present acutely in the newborn period are cerebral sinovenous
thrombosis (CSVT; Figure 1.1C and D) and haemorrhagic stroke (Figure 1.1E and F). Both of
these syndromes can present in term neonates with seizures, apneic events and encephalopathy
(Brouwer et al., 2010; Kersbergen, Groenendaal, Benders, & de Vries, 2011). Intracranial
haemorrhage (ICH) is classified by location (epidural, subdural, subarachnoid, intraventricular,
or intraparenchymal). Incidence and prognosis of haemorrhages in infants is difficult to
determine because of the range of presentations. Imaging of well, term babies (for research into
normal brain development) has shown that up to 26% can have incidental ICH. Most occur in the subdural region but intraparenchymal haemorrhage was seen in 7% of asymptomatic infants (Looney et al., 2007). However, when presenting acutely, neonatal haemorrhagic stroke carries higher early mortality than other perinatal strokes syndromes, estimated at 10 to 25%. Long-term outcomes include motor deficits in 8 to 38%, and language or cognitive concerns in 16 to 44% (Brouwer et al., 2010; Jhawar, Ranger, Steven, & Del Maestro, 2005; Limperopoulos, Robertson, Sullivan, Bassan, & du Plessis, 2009). Poor outcomes are most often seen in intraparenchymal lesions, particularly when large or involving multiple compartments (Jhawar et al., 2005).

Risk factors for symptomatic sinovenous thrombosis include gestational or delivery complications, comorbid conditions such as dehydration, sepsis, thrombophilia or cardiac defects (G. deVeber et al., 2001; Fitzgerald, Williams, Garg, Carvalho, & Golomb, 2006). Deep venous obstruction is also associated with intraventricular and thalamic haemorrhage (Figure 1.1C and D), in addition to focal ischemia (Kersbergen et al., 2011). The extent of these injuries correlates with poor outcome (Fitzgerald et al., 2006). Mortality ranges from 2 to 20%, with survivors incurring disabilities that include cognitive deficits in 25 to 70%, motor impairment in 10 to 67% and epilepsy in 15 to 40% (Kersbergen et al., 2011; Moharir et al., 2011). Increased recognition and evolving treatments will likely influence these outcomes in the future.

1.3.1.2 Delayed presentation

Many strokes are asymptomatic in the neonatal period. Presentation is typically deferred to late infancy, when delayed motor milestones, early hand preference, or symptomatic epilepsy are recognized (Stiles, Reilly, Levine, Trauner, & Nass, 2012). This has been labeled presumed
perinatal ischemic stroke (PPIS) (Kirton & deVeber, 2009). Delayed presentations occur in both arterial and venous ischemic strokes, which can be well differentiated by MR imaging characteristics (Figure 1.2) (Staudt, 2010a). Focal antenatal venous strokes appear as small lesions of the periventricular white matter and are therefore termed periventricular venous infarctions (PVI) (Kirton et al., 2008). PVI is the result of medullary venous infarction secondary to an in utero germinal matrix haemorrhage prior to 34 weeks gestation (likely 32-34 weeks) (Kirton, Shroff, Pontigon, & deVeber, 2010). Babies are typically born without clinical concern, presenting later in infancy with hemiparesis (Kirton et al., 2008).

Figure 1.2: Chronic neuroimaging in presumed perinatal ischemic stroke
A. Axial T1 weighted MRI of arterial presumed perinatal ischemic stroke (APPIS) with cortical and white matter encephalomalacia in the area of the right MCA. B. Coronal T2
weighted MRI of a left MCA APPIS with both cortical and white matter loss. C. Axial FLAIR MRI with dilatation of the right lateral ventricle from white matter loss due to periventricular venous infarction (PVI). D. Coronal T2 weighted MRI with left PVI indicated by white matter loss next to the lateral ventricle. Figure adapted from Murias et al, 2014)

1.3.2 Pathophysiology and recovery

Studies in mature brains of model organisms have shown that a focal lack of blood flow causes a drop in oxygen and glucose concentrations that result in energy failure and changes in ionic concentrations. What follows is a complex cascade of intracellular changes that include increased pH, increased glutamate, and increased intracellular calcium (Saeed, Shad, Saleem, Javed, & Khan, 2007). The result is cell death, apoptosis or cell oedema. Afterwards changes can be seen distal to the injury with altered metabolism in the injured hemisphere and changes in inhibition or excitation in areas that receive input from the sight of damage (Kolb & Teskey, 2012). This can lead to secondary cell death or loss of function. In developing brains, these processes intersect with the multiple processes of brain maturation such as neuronal maturation, myelination, synaptogenesis and normal neuronal pruning. Therefore the consequence of ischemia and the resulting degeneration, or potential regeneration, can vary depending on the precise stage of development (Kolb & Teskey, 2012; Stiles, 2012). Furthermore, developmental processes change not just with age, but also with brain location and function.

Aside from differences in aetiology and a low risk of recurrence (Fullerton, Wu, Sidney, & Johnston, 2007; Kurnik et al., 2003), perinatal stoke has been shown to have different mechanisms for recovery compared to stroke in older children and adults. Recovery in adult
stroke occurs through diaschisis and its reversal, functional adaptation by augmentation of complimentary undamaged skills and through neuroanatomical reorganization (Nudo, 2011). Neonates have been shown to utilize neuroanatomical reorganization, though likely through different mechanisms. It has been demonstrated in rats that, after early injury, there are epigenetic changes connected to functional adaptation (Kolb, Mychasiuk, Williams, & Gibb, 2011).

1.3.3 Theories of cognition after early brain injury

There is a longstanding and persistent theory that, because of the capacity of the developing brain to “heal” or compensate, an early injury has less of an effect on long-term outcome than an injury occurring later in life (Kim, Han, & Kim, 2009). This is termed the Kennard principle after Margaret Kennard’s work on the functional outcome after early brain lesions in primates (Dennis, 2010). The Kennard principle has been supported by further investigations into the mechanisms of plasticity through which the brain may achieve this healing. The processes that underlie plasticity after early injury are continuing to be elucidated. Through the use of model organisms, it has been shown that changes in gene expression, dendritic arborisation, and synaptic spine formation and density (Kolb & Teskey, 2012) take place on a molecular and cellular level and would be likely to have close correlates in human patients. In the developing brain these processes interact with normal developmental changes such as neurogenesis, neuronal migration, synaptogenesis, apoptosis and myelin formation and change the processes of plasticity and, likely, the consequences. For example, if damage takes place during neurogenesis there is evidence that neurogenesis increases to replace lost neurons.
Neuroimaging has provided evidence for larger scale processes. Functional imaging of language after early injury on the left side has shown transfer of primary language areas to alternative ipsilateral locations and to the homologous locations in the contralateral hemisphere (Booth et al., 2000; Fair et al., 2010; Jacola et al., 2006; Raja Beharelle et al., 2010). See section 1.4.2 for further discussion of functional neuroimaging of language after early injury. There are studies in clinical populations that have found fewer poor outcomes in newborns (measured by sensorimotor, speech and cognitive or behavioural impairments) than in older infants and children after early arterial stroke or sinovenous thrombosis (G. A. deVeber et al., 2000).

There are, however, competing theories suggesting that the developing brain is more susceptible to injury. One theory posits that outcome is worse if damage has potential to affect an ability before it has been established. When injury occurs later in childhood the brain can accommodate to “repair” that pre-existing ability, but if injury occurs earlier the initial development is disrupted, which is harder to overcome (Westmacott, Askalan, MacGregor, Anderson, & Deveber, 2010). This is supported by studies that found worse outcomes in neonatal or perinatal stroke compared to later in childhood (Kolk, Ennok, Laugesaar, Kaldoja, & Talvik, 2011; Lansing et al., 2004; Studer et al., 2014). Yet other studies have found a U-shaped curve relating cognitive deficits with age of stroke. Lesions that occurred in middle childhood (5 years to 10 years old) led to better cognitive outcome than early lesions (0 to 5 years old) or late (10 to 18 years old) (Everts et al., 2008; Ganesan et al., 2000; Pavlovic et al., 2006). It must also be considered that the aetiologies or risk factors for stroke (moya moya, cardiac abnormality, infection, etc.) change through different ages and result in different patterns of injury (Kirton & deVeber, 2012). In a study of ten children with perinatal stroke and 26 children with childhood
stroke where haemoglobinopathies, inborn errors of metabolism, moyamoya disease, stroke during neurosurgery, hypoxic-ischemic encephalopathy, autoimmune vasculitis, trauma and pre-existing conditions had been excluded, the authors found no difference in IQ or measures of executive functioning relative to the age at time of stroke, when measured at school age (Hajek et al., 2013).

In addition, there are conflicting theories on the effect of injury during “critical” or “sensitive” periods of brain development; those times at which an ability undergoes accelerated growth. During these periods, experience (deprivation or enhancement) has been shown to have considerable impact on the emergence of the function as well as the related neural organization (Stiles et al., 2012). Some theorize that these periods have the best possibility for good outcome because of fast development and potential for healing (Kolb et al., 2011). Others present these as periods of vulnerability that may have the worst outcome because, if development is interrupted, there is missed opportunity for optimum learning (Anderson, Spencer-Smith, & Wood, 2011).

There are also conflicting theories on the interaction of injury with development of complex cognitive skills. Evidence suggests that skills maintained by less complex neural networks, such as visual and sensory-motor skills and some language tasks, often show evidence of good functional recovery. However, more complex skills, which are more likely to be subsumed by complex or diffuse neural networks, may have less complete recovery (Anderson et al., 2011). Other theories propose that more distributed cognitive processes are more likely to be preserved because they have more biological reserve and potential to reorganize (Kolb, Muhammad, & Gibb, 2011). The effect on neural networks is likely influenced by the timing of injury relative to the development of those networks. Data from resting state fMRI (i.e. brain
activity detected while participants are not performing any task) has shown that there is a progression from predominantly local connections to incorporation of larger networks through childhood (Fair et al., 2008; Fair et al., 2009). If injury has occurred prior to the integration of large-scale networks, the capacity of those networks may be reduced. On the other hand, if injury occurs after the networks are established, the system may have biological redundancy that allows for stability or compensation of function.

1.4 Cognition in children after perinatal stroke

Multiple studies of cognitive outcomes in stroke or congenital lesions have been undertaken. However, the use of different methodological approaches makes it difficult to interpret the findings available in the literature. Many studies are performed on mixed populations that include perinatal as well as childhood strokes, other congenital injuries such as hypoxic ischemic encephalopathy, or additional risk factors such as prematurity (H. J. Lee et al., 2010). Prior to advances in neuroimaging, investigations of cognition were done in children with clinically diagnosed hemiplegic cerebral palsy. The majority of these cases are perinatal stroke but other aetiologies, such as global insults and congenital malformations, would also be included (Kulak et al., 2007). In addition, a notable minority of patients may have co-existing neurological injury or risk factors for developmental delay. Evidence of hypoxic ischemic encephalopathy was seen in up to 35 to 42% of MR imaging after AIS (Michoulas et al., 2011; van der Aa et al., 2013). In one large multicentre study of symptomatic neonatal AIS, perinatal asphyxia was noted on history in 8% of children (Kirton et al., 2011). That study also found 18% of cases had an associated cardiac issue, 88% of which were complex congenital heart disease.
Congenital heart disease is an independent risk factor for cognitive impairment (Karsdorp, Everaerd, Kindt, & Mulder, 2007; Snookes et al., 2010). All of these considerations complicate the evaluation of outcomes after perinatal stroke.

Studies have also had differences in methods of ascertainment, with the majority of studies collecting cases retrospectively and doing cross sectional measurements across different ages. Studies that have followed children prospectively from diagnosis to determine long-term cognitive outcome have been limited (Ricci et al., 2008; Sreenan, Bhargava, & Robertson, 2000). Furthermore, the tests used to measure cognitive outcomes are complex and have varied widely. The most commonly applied outcome measure was the age-appropriate form of the Wechsler Intelligence scale (used in 34% of studies based on systematic review); the Bayley Scales of Infant and Toddler Development were most commonly used for younger ages. The Pediatric Stroke Outcome Measure (PSOM) consisting of a standardized neurological exam and history has been used in 21% (Engelmann & Jordan, 2012).

Appendix D provides features of the studies that include a measure of full scale IQ or a normalized measure of general development (in children too young for IQ testing) in a population that includes perinatal stroke in term children and has analysis specific to the perinatal group. To gather the literature, MEDLINE was searched for stroke and synonyms (e.g. cerebrovascular disorders, brain infarction) or related childhood presentations (congenital hemiplegia, hemiplegic cerebral palsy) and cognitive outcomes (intelligence, cognition, child behaviour) as well as related measures (e.g. language, quality of life, visuospatial). Articles that included a measure of cognition in children that incurred a stroke in the perinatal period were
included. Articles that included a mixed population, with strokes at different ages, were included if there was analysis that was specific to perinatal stroke.

1.4.1 General intelligence measures

When measured by standardized and age-appropriate IQ tests, many studies have found that groups of children with a history of perinatal stroke have scores in the normal or near normal range (Carlsson, 1997; Cioni, Brizzolara, Ferretti, Bertuccelli, & Fazzi, 1998; Gonzalez-Monge et al., 2009; McLinden, Baird, Westmacott, Anderson, & deVeber, 2007; Ricci et al., 2008; Schatz, Ballantyne, & Trauner, 2000; Trauner, Chase, Walker, & Wulfeck, 1993; Wulfeck, Trauner, & Tallal, 1991). However, when compared to matched controls, children have decreased IQ, likely indicating that early stroke has decreased their cognitive potential (Talib et al., 2008; Trauner, Nass, & Ballantyne, 2001). Though not universal (Ricci et al., 2008), the majority of evidence indicates that verbal IQ is most preserved and perceptual reasoning more affected (Carlsson et al., 1994; Goodman & Yude, 1996; Kolk et al., 2011; Muter et al., 1997).

An important factor in consideration of intellectual deficits is the age of testing; however, it remains unclear how age interacts with ongoing development. There are reports of early improvement in skills at younger ages. In a cross sectional study of 43 children (13 to 46 months of age) with perinatal focal lesions confirmed on neuroimaging (23 with left hemisphere lesions, and 20 with right hemisphere lesions), Vicari and colleagues (2000) found that children had initial delays in language milestones but demonstrated improvement in language ability to reach normal achievement by preschool age (Vicari et al., 2000). In contrast, other studies have reported increasing deficits over time (Banich, Levine, Kim, & Huttenlocher, 1990; McLinden et
al., 2007). Westmacott and co-authors (2009) found IQ measures (using age appropriate Wechsler scales in 26 children with acutely diagnosed unilateral neonatal AIS) did not differ from normative data at preschool but emerging deficits were discovered when children were followed longitudinally to school age (Westmacott, MacGregor, Askalan, & deVeber, 2009). Other longitudinal studies have also found decreasing IQ and slowed language development (Chilosi et al., 2001; Levine, Kraus, Alexander, Surijakham, & Huttenlocher, 2005; van Buuren et al., 2013) but some have demonstrated no change in intelligence measures over time (Ballantyne, Spilkin, Hesselink, & Trauner, 2008; Muter et al., 1997). As with other investigations of cognition after perinatal stroke, comparisons of these divergent findings are complicated by different diagnostic criteria, mixed populations that include asphyxia and other diffuse injury (Levine et al., 2005) as well as different tests (with different normative samples) employed over different ages.

There are at least two theories that might explain an increase in cognitive disability at later ages. The first hypothesis is that children “grow into” their deficits (Anderson et al., 2011). The plasticity of the brain is able to accommodate early development but, with the increased demand of more complex skills, the biological reserve is no longer sufficient and deficits are revealed. A specific developmental function cannot be assessed earlier than it would normally appear. Therefore, a child with no difficulties in their preschool years may only manifest deficits when they reach school age and attempt to initiate a more advanced proficiency.

A second hypothesis refers to the cumulative effects of seizures, which have been shown to be associated with lower IQ in children after perinatal stroke (see section 1.4.5, Predictors of Outcome). Seizures may interfere with ongoing learning and cause secondary functional damage,
resulting in depressed scores as children age. In a longitudinal study of 23 children with perinatal ischemic stroke there was no decrease in full scale IQ at later ages compared to controls. However, when children were divided into groups with and without seizures, there was a significant interaction over time, such that the eight children with seizures had depressed scores relative to children without seizures and to controls (Ballantyne et al., 2008). It should be noted however, that accumulated deficits have been observed in the absence of epilepsy. In a study of 145 children with unilateral AIS occurring at all ages from birth to 16 years of age, none of whom had seizures outside of the acute period, increased deficits (relative to norms) were seen with increased time from stroke (Westmacott et al., 2010).

1.4.2 Language

In the mature central nervous system, damage to specific areas results in selective and predictable impairments. In children, however, this is not always the case, particularly with very early injuries such as perinatal stroke. Clinical studies have found that observed cognitive deficits after early focal brain injury do not tend to correlate to specific location or lateralization as seen with focal injury in the mature brain (Ballantyne et al., 2007; Everts et al., 2008; Muter et al., 1997). The most striking demonstration of this is language. As measured with verbal comprehension index (VCI), verbal skills tend to be well preserved, even with large left-sided strokes that damage the normal language centers in the mature brain (Carlsson et al., 1994; Goodman & Yude, 1996; Kolk et al., 2011).

Imaging has started to shed light on the underlying brain plasticity that permits retention of language function after early injury (Fiori & Guzzetta, 2015). Functional magnetic resonance
imaging has been used to visualize reorganization of cortical representation. It has been revealed that patterns of fMRI BOLD signal during cognitive tasks (language most commonly) show atypical localization, both to alternative ipsilateral locations and to homologous contralateral regions (Booth et al., 1999; Booth et al., 2000; Heller et al., 2005; Jacola et al., 2006; Lidzba, Staudt, Wilke, & Krageloh-Mann, 2006; Lidzba, Wilke, Staudt, Krageloh-Mann, & Grodd, 2008). The lateralization of neural activity, representing reorganization of language, may be different for each individual patient (Fair et al., 2010) and is not predicted by size of stroke (Tillema et al., 2008), but may be predicted based on the area of white matter that is disrupted (Staudt, Ticini, Grodd, Krageloh-Mann, & Karnath, 2008). Raja and co-authors (2010) used category fluency to study 25 children with left-sided perinatal stroke (AIS or PVI) and 27 sibling controls. It was found that all children had increased fMRI signal in the left inferior frontal region (Broca’s area) while performing the task. However, children with strokes had more bilateral representation of that neural activity. Children with bilateral increased neural activity had better language function than children with more unilateral (left or right) signal (Raja Beharelle et al., 2010).

Imaging is also starting to illuminate different patterns of plasticity after injury at different ages. In a recent fMRI study, the authors investigated laterality of neural activity during verb generation and sentence comprehension tasks in children with a history of left-sided stroke, either in the perinatal period (n = 7) or at a later age (n = 5) as well as a group of healthy controls (n = 12). It was found that children with stroke in the perinatal period had increased bilateral and right-sided BOLD signal and had no difference in expressive and receptive language scores on neuropsychological testing compared to controls. Children who had stroke at later ages had decreased language scores relative to controls and demonstrated left-sided laterality of BOLD
signal at the same rate as controls. This gives some indication that there are differences in the plasticity through development and that they can be investigated with neuroimaging in patients (Ilves et al., 2013).

Despite evidence for neuroplasticity, there are some indications that language acquisition and outcomes are affected by perinatal injury. Thal, Bates and colleagues (1991 and 1997) found that children with left temporal injuries displayed the most severe impairments in initial vocabulary expression. On the other hand, children with right hemisphere injuries had more severe deficits in initial vocabulary comprehension and gesture (Bates et al., 1997; Thal et al., 1991). According to the authors, these site-specific defects, which differed from those observed in adult patients, were no longer detectable by five to seven years of age. A study of children aged five and six years (Lai & Reilly, 2015) also found no difference in language use (including complexity of syntax or morphological errors in a personal narrative) between children with perinatal stroke and typically developing children but did find a paucity of emotional content in children with right sided lesions with reduced affective language use and facial expression.

Tests of specific sophisticated language abilities have revealed that there is likely some reduction in long-term language utilization. Chapman and colleagues (2003) found language generally recovers, with normal vocabulary and grammar (as compared to an orthopaedic control group) within six months to two years after a paediatric stroke that occurred in children ages birth to eight years of age (Chapman et al., 2003). However, older children after paediatric stroke relay fewer details and less information content when retelling a story compared to age matched controls. Reilly and co-authors (2013) had similar findings in children (ages seven to 16 years
old) after perinatal stroke. In their study, the authors found that a group of 35 children with left hemisphere lesions from perinatal stroke made more morphological errors, used less complex syntax, and produced less detailed story settings compared to controls when asked to relay a personal narrative (Reilly et al., 2013). This may indicate that the alternate strategies being employed to acquire language skills impose limitations or delays on language utilization that become more apparent at later ages.

1.4.3 Spatial abilities

Visuospatial skills have not been as extensively investigated as language, but there is evidence for more profound impairments of these abilities after early ischemic damage (Everts et al., 2008). In addition, it has been found that the laterality of visuospatial deficits mirrors more closely the pattern that is seen in adults. Children after perinatal stroke affecting the right hemisphere have difficulty with spatial integration (organizing elements together into a unified whole), whereas left hemisphere lesions result in impairments processing detail (Akshoomoff, Feroleto, Doyle, & Stiles, 2002; Stiles, Stern, Trauner, & Nass, 1996; Stiles et al., 1997). Schatz, Ballantyne and Trauner (2000) grouped children with perinatal stroke into right hemisphere (12 children) and left hemisphere lesions (ten children), and tested them for spatial skills using the block design subtest of the WISC-R. Children in both groups showed similar full scale, verbal and performance IQ’s. However, children with right hemisphere lesions had a significantly higher percentage of global errors (error in the overall outer shape of the design) on the block design task than the group of children with lesions in the left hemisphere. The group with left-hemisphere lesions produced a significantly higher percentage of local errors (errors in the
precise internal pattern). In 2008, Stiles and colleagues found similar results. Sixty two children, 19 with left perinatal focal injury (most presumed to be stroke) and 19 with right lesions, as well as 24 age matched controls, were tested with a task where they recreated geometric and letter stimuli from memory. Children with right hemisphere lesions performed worse on scores for global accuracy and children with left hemisphere lesions showed impairment in local, or detail recall (Stiles et al., 2008). These findings mirror lesion studies in adults that indicate the right hemisphere is dominant for spatial cognition, particularly interpreting parts into a coherent whole and discriminating differences, and the left hemisphere registers details and smaller scale visual information (Delis, Keifner, & Fridlund, 1988; Swindell, Holland, Fromm, & Greenhouse, 1988).

Thareja, Ballantyne, and Trauner (2012) found that children with perinatal stroke (ischemic or haemorrhagic) experienced subtle visual and tactile neglect (Thareja, Ballantyne, & Trauner, 2012). Children that had a left hemisphere stroke showed neglect for stimuli bilaterally when compared to controls, demonstrated by poorer performance bilaterally in both a visual cancellation task and a manual exploration task, with more pronounced deficits on the right. This is unlike in adults, where lesions in the left hemisphere rarely result in neglect and, in the cases where contralateral neglect is observed, deficits resolve within weeks. In the visual cancellation task, children with strokes in the right hemisphere had decreased performance bilaterally compared to controls, with more omissions on the left. However, in the manual exploration task, children with right hemisphere injury had poorer performance only on the left (contralateral) side (Thareja et al., 2012). This does mirror the findings in adults with similar lesions. Authors proposed that the impaired function of the children with strokes in both the left and right hemispheres might be due to poor spatial organization. They also postulated that the difference
in pattern of neglect, with right hemisphere lesions showing a pattern of deficit more similar to what is seen in adult stroke victims, is the result of earlier specialization of cognitive functions in the right hemisphere than the left. Because of earlier development (or some other unrecognized factor) some specified functions, such as visuospatial skills and contralateral visual and tactile attention, might not have the flexibility of reorganization that language has demonstrated.

While interplay between injury and development may explain the differences in outcome between spatial and language skills, other theories have been proposed. One theory is the “crowding hypothesis” (Fiori & Guzzetta, 2015), which proposes that the relocation of language to cortex that typically serves other cognitive functions limits the development of those abilities (Anderson et al., 2011). In support of this hypothesis, Lidzba (2006) studied young adults that had suffered early left hemisphere injury (three AIS in the MCA territory, ten PVI) and showed that increased right hemisphere lateralization of language on fMRI tasks correlated with decreased visuospatial abilities (Lidzba et al., 2006).

Everts and colleagues (2010) found that atypical lateralization of function on fMRI correlated with worse outcome for specific cognitive areas in a group of ten patients with childhood stroke (Everts et al., 2010). Better language and visuospatial performance was seen in patients with left hemisphere language lateralization. It was proposed that recruitment of more brain areas may be due to increased effort for the task, and it may represent utilization of networks that are typically restricted to an earlier stage of development. Immature bilateral networks, however, may not be as effective or efficient for completing tasks. There is some evidence for this hypothesis in a case study of two children with perinatal stroke who were followed longitudinally and were found to retain an immature pattern of increased global neural
activity when presented with spatial tasks (Stiles et al., 2003). This compliments observations that most children with brain lesions solve problems in a suboptimal manner. By utilizing less organized strategies that require more effort, there is less reserve for more advanced challenges (Dennis, Spiegler, & Hetherington, 2000).

Another hypothesis proposed for the preservation of language and relative vulnerability of other brain abilities is rooted in theories of the evolution of higher cognitive function. It is postulated that older functions, such as motor or somatosensory, are based in more localized brain circuitry that develops earlier and is, therefore, more vulnerable to early injury. In contrast newer or higher order cognitive functions arise from older circuits that are redeployed in a more distributed fashion. These broader networks are more flexible and develop over a longer period of time, allowing for resilience of more evolutionarily advanced cognitive functions, such as language (Stiles et al., 2012).

1.4.4 Executive functioning

Executive functioning refers to a group of abilities that allow for behavioural and emotional self-regulation. This includes attention, inhibition, mental flexibility and working memory, as well as metacognitive skills such as planning and problem solving (Hofmann, Schmeichel, & Baddeley, 2012). Studies dedicated to executive function in a well defined perinatal or neonatal stroke population are lacking, but there is increasing recognition of executive functioning as important for future functioning and success. When studied in conjunction with other cognitive functions, Kolk and colleagues (2011) found that executive functioning (as measured by the executive function subtests of the Developmental
Neuropsychological Assessment Battery (NEPSY)) was spared in 21 children with neonatal ischemic or haemorrhagic stroke when compared to controls, even in the presence of other deficits (Kolk et al., 2011). However, attention was more likely to be impaired in children with congenital hemiplegia than in controls (Kolk & Talvik, 2002). Epilepsy (Anderson et al., 2010) and male gender (Kolk & Talvik, 2000) may increase the risk of attention deficits in this population.

Disordered executive functioning is described in paediatric stroke (occurring outside the neonatal period) and other acquired brain injuries in childhood. Studies of paediatric brain tumours (Wolfe, Madan-Swain, & Kana, 2012) and early traumatic brain injuries (Anderson, Godfrey, Rosenfeld, & Catroppa, 2012) have found significant executive function and behavioural control deficits. In paediatric stroke, deficits in attentional control, cognitive flexibility and information processing are described (Long, Anderson et al., 2011; Long, Spencer-Smith et al., 2011). In studies of cerebral palsy, it was found that children with unilateral lesions are less likely to have clinically significant executive functioning impairments compared to children with bilateral brain injury or preterm birth, even when the degree of motor impairment was similar (Pirila, van der Meere, Rantanen, Jokiluoma, & Eriksson, 2011). This is an indication that conclusions regarding executive functioning from other populations that include older children or different types of injuries (particularly more diffuse injury) are likely not generalizable to the perinatal stroke population and further study is required.
1.4.5 Predictors of cognitive outcomes after perinatal stroke

Available studies have found it difficult to predict cognitive outcomes based on neurological signs or symptoms at presentation to clinical care. The most consistent and generalizable correlation is an association between cognitive impairments and symptomatic epilepsy (seizures outside of the neonatal period) e.g. (Ballantyne et al., 2007; Goodman & Yude, 1996; Koelfen et al., 1993; Kolk et al., 2011; Muter et al., 1997; Vargha-Khadem, Isaacs, van der Werf, Robb, & Wilson, 1992). This association has most commonly been made with IQ measurements but has also been seen when more specific skills, such as memory, attention and grammar, were tested. It is difficult to differentiate the possible deleterious effects of antiepileptic medications with risk correlated to seizures or a diagnosis of epilepsy. Small numbers, heterogeneity of seizure pattern and differences in treatment have precluded rigorous analysis, but there are indications that ongoing seizures and EEG abnormalities may impart the greatest risk for poor cognitive outcome regardless of treatment (Ballantyne et al., 2008).

In a retrospective analysis of a population-based registry of children with perinatal and presumed perinatal AIS the presence of continuous spike and wave in slow wave sleep (CSWS; defined as more than 75% of slow wave sleep recording) was highly correlated with abnormal neuropsychological outcomes. All children with CSWS had clinical epilepsy and severely abnormal neuropsychological outcomes (more than two standard deviations below normative mean). In the children without CSWS (including 53% of whom had epilepsy) only 12% had severe intellectual deficits (Mineyko, Brooks, Carlson, Bello-Espinosa & Kirton). Though further work is required, this provides an interesting, and potentially treatable, explanation for long-term cognitive deficits.
Lesion characteristics associated with seizures or EEG abnormalities also result in ambiguity of causation. Lesions that are larger in size (Banich et al., 1990; Lo et al., 2014) or involve more cortex have been associated with a higher risk of symptomatic epilepsy; and both of these features have also been linked to increased cognitive deficits (Wusthoff et al., 2011). Volumetric analysis of anatomical MR images has found that encephalomalacia and atrophy of the affected hemisphere correlated with reduced grey matter in that hemisphere and reduced IQ (Bava, Archibald, & Trauner, 2007). However, most studies have found no correlation between lesion size and cognition when only perinatal strokes were considered (Ballantyne et al., 2007; Hogan, Kirkham, & Isaacs, 2000; J. Lee et al., 2005). It is also possible that the size of the injury is selectively detrimental to some abilities. Booth and colleagues (2000) found that, in a small group of children with perinatal AIS or periventricular haemorrhage (six patients aged nine to twelve years at testing), the size of infarct related to performance only when the tasks involved a large memory component (Booth et al., 2000).

Evidence does suggest that cortical lesions appear to have a larger impact on IQ than those restricted to sub-cortical areas (Cohen & Duffner, 1981; Kirton et al., 2008). The greatest deficits occur when lesions involve both cortical and sub-cortical structures (Westmacott et al., 2010). This finding is consistent when children are grouped according to type of ischemic injury. Term children with PVI (injuries that involve white matter and possibly the thalamus and basal ganglia, but spare the cortical grey matter) show better cognitive outcomes than those who have AIS but also tend to have smaller lesions and less epilepsy (Sauer, Levine, & Goldin-Meadow, 2010).
As noted above, the site or laterality of lesion has only rarely been associated with specific deficits (Ballantyne et al., 2007; Everts et al., 2008; Muter et al., 1997). However, some studies have found that the laterality of the lesion may influence the severity of cognitive outcomes (deficits worse with left-sided lesions (Carlsson et al., 1994; McLinden et al., 2007; Vicari et al., 2000); deficits worse with right-sided lesions (Aram & Ekelman, 1988; Nass, deCoudres Peterson, & Koch, 1989)). In addition to the factors that have been previously noted to confound interpretation (e.g. heterogeneous populations), interpretation of laterality differences is complicated by the use of different measurements of cognitive outcome (IQ measures or different specific cognitive functions) and a preponderance of left-sided strokes. The majority of evidence has found no effect of side on cognitive outcome (Everts et al., 2008; Goodman & Yude, 1996; Ricci et al., 2008; Vargha-Khadem et al., 1992; Westmacott et al., 2009; Westmacott et al., 2010).

There are indications that cognitive deficits are worse when motor outcomes are more severe. However these studies were either restricted to only AIS (Golomb et al., 2007) or did not have a full description of the injuries (Goodman & Yude, 1996), so it is not possible to determine how this would be influenced by stroke location or stroke type (AIS compared to PVI).

With increased interest and investigation into the risk factors for perinatal stroke, some information has emerged connecting these to outcome. In a study of attentional, social and thought problems (as measured using the Achenbach Child Behavior Checklist) no significant correlation could be found with pre and perinatal risk factors for stroke, however, fetal distress and diagnosis in the newborn period was more common in children with clinically relevant scores on parent reported social and attention problems (Harbert, Jett, Appelbaum, Nass, &
Mercuri and colleagues (2001) found that poor neurodevelopmental outcomes (hemiplegia or clinically assessed global developmental delay) were more common in children with prothrombotic risk factors (particularly heterozygosity for Factor V Leiden) in 24 children with perinatal cerebral infarction confirmed on MRI. This association was independent of the extent of lesion on MRI (Mercuri et al., 2001). However, such associations must be considered critically given the relative lack of understanding of perinatal stroke causation itself.

Finally, there have been indications that the outcome after perinatal stroke is more severe in boys than in girls (Kolk & Talvik, 2000; Westmacott et al., 2009). A gender difference in cognitive outcome after isolated unilateral strokes is not well supported by data but remains an important question because there are also indications that there is a male predominance in incidence of paediatric (including perinatal) stroke (Golomb et al., 2004; Golomb, Fullerton, Nowak-Gottl, Deveber, & International Pediatric Stroke Study Group, 2009). Many studies do not report on analysis by gender (e.g. Ballantyne et al., 2008; Ricci et al., 2008) and some finding no difference (Westmacott et al., 2010). However, a gender difference is well established in perinatal hypoxic ischemic injuries (Johnston & Hagberg, 2007) and deserves further investigation.

1.5 Neuroimaging and neural network development in children

Recently, researchers have begun to investigate neurodevelopment through a span of ages utilizing advanced neuroimaging techniques. In both typically developing children, and in a number of different clinical populations, neuroimaging (MRI most commonly) allows for non-
invasive and safe interrogation of brain development, including the development of neural networks, in children.

1.5.1 Neuroimaging investigations of normal development

MR imaging has been used throughout development, from in utero fetal MRI through all ages of childhood. Structural imaging has demonstrated a set, predictable pattern of development after birth. Grey matter volume increases from infancy to the first year of life, plateaus in childhood and then declines after onset of puberty (Blakemore, 2012). A cross sectional study of structural MR images from 325 children ages 4.5 to 18 years-old, demonstrated that age-related decreases in grey matter during this age range is most prominent in parietal and occipital cortex (Brain Development Cooperative Group, 2012). From this same database, images of 203 children, grouped into early childhood, late childhood, early adolescence and late adolescence, was analyzed with graph theory to construct brain networks using interregional correlations in cortical thickness. The result indicated prominent changes in topological properties during the late childhood (8.5-11.3y) period with a reduction in local modularity and an increase in global connections with increased number and span of connector hubs, suggesting a shift from topological to random organization (Khundrakpam et al., 2012).

Maturation of white matter (as seen on MRI) through development is governed by a number of processes including myelination and changes in numbers of axons (Isaacson & Provenzale, 2011). The early progression of myelination follows a pattern that mirrors the developmental milestones (Blakemore, 2012); from motor and optic radiations at birth to some white matter signal apparent in all areas by two years of age (Barkovich, 2005). White matter maturation has
also been investigated with diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI). When analyzed using fractional anisotropy (FA) and apparent diffusion coefficients (ADC), deep white matter (in the genu and splenium of the corpus callosum, and the posterior limb of the internal capsule) appears more mature than peripheral white matter (frontal and parietal semiovale) at birth, with higher FA and ADC values. Both areas increase in FA and ADC after birth, with the peripheral white matter developing faster but remaining significantly lower than in adults in early adolescence (Isaacson & Provenzale, 2011).

Functional magnetic resonance imaging to measure BOLD signal has been used in normal developing children to investigate the functional development of the brain. In developmental studies, fMRI studies often report that a certain brain area has increased activity in adults relative to children or visa versa. Many of these studies also report that children had increased BOLD signal over larger areas than what is expressed in adults (Crone & Ridderinkhof, 2011). This refinement of networks with maturation compliments studies that utilize other imaging methods.

Resting state fMRI (rs-fMRI) has also been employed to help elucidate the development of functional networks in children. Resting-state protocols are short (five to ten minutes) and can be performed when the participant is at rest, asleep or sedated (Kiviniemi et al., 2000). This has advantages in paediatric populations where there may be concerns about compliance, attention or fatigue (de Bie et al., 2012). The history of rs-fMRI studies in children is limited but many, using different techniques, have found a progression of functional connections that compliment the structural development (Hagmann et al., 2010) through childhood. A general theme that emerges is that local regional interactions in children change to longer-distance (also referred to as global
or random) interactions in young adults (Vogel, Power, Petersen, & Schlaggar, 2010). In a study of 238 typically developing children and young adults (ages 7 to 30 years), rs-fMRI networks were found to exhibit a weakening of short-range functional connections and a strengthening of longer-range connections (Dosenbach et al., 2010). Fair and colleagues, using graph theory to analyze rs-fMRI data, similarly found a trend towards segregation (Fair et al., 2008; Fair et al., 2009). This may indicate that children use different strategies (at a neural or network level) than adults to perform the same cognitive tasks (de Bie et al., 2012; Khundrakpam et al., 2012; M. H. Lee, Smyser, & Shimony, 2012).

### 1.5.2 Neuroimaging in perinatal stroke

For clinical proposes, MRI (structural and spectroscopy scans most commonly) has allowed for diagnosis of a broad range of diseases and injuries affecting the brain with more precision and detail (Barkovich, 2005). Furthermore, MRI research in many paediatric conditions are helping improve our understanding of aetiologies, natural history, comorbidities and effects of treatment. Conditions scrutinized by MRI have ranged from learning disorders such as dyslexia (Caylak, 2009), profound developmental conditions such as autism (Lauvin et al., 2012), psychiatric syndromes including depression and schizophrenia (Dichter, Sikich, Song, Voyvodic, & Bodfish, 2012), structural lesions including tumours (M. H. Lee et al., 2012), trauma (Difiori & Giza, 2010), stroke and epilepsy (Pizoli et al., 2011; Stufflebeam et al., 2011).

In perinatal stroke, MRI has improved recognition and diagnosis as well as the delineation of the different perinatal stroke syndromes. In addition, imaging has started to shed light on the underlying mechanisms of brain plasticity after early injury. Anatomical MR images
have been used to characterize extent and location of injury. Though evidence is mixed, volumetric analysis has found that encephalomalacia and atrophy of the affected hemisphere correlated with reduced grey matter in that hemisphere and reduced IQ (Bava et al., 2007). MRI has also begun to reveal secondary injury in networks and areas connected to main sight of injury (Govaert et al., 2008) that may explain differences in IQ between children with perinatal stroke and control groups. For example, Li (2012) found reduced grey matter volume in the ipsilateral cortex after PVI (D. Li, Hodge, Wei, & Kirton, 2012), demonstrating secondary cortical impact of white matter injury.

As stated above, neuroimaging (particularly fMRI) has led to increased understanding of the mechanisms of reorganization and neuroplasticity after early injury. See section 1.4.2 and 1.4.3 for more on language and visual spatial skills after perinatal stroke respectively. Functional MRI studies have demonstrated that, during cognitive tasks (language most commonly), there is atypical representation, with reorganization both to alternative ipsilateral locations and to homologous contralateral regions after early injury (Heller et al., 2005; Jacola et al., 2006; Lidzba et al., 2006; Lidzba et al., 2008). Though these results are limited, with only a few studies in children including limited numbers of participants, it eludes to the potential of MRI for investigating the cognitive underpinnings of neural plasticity and adaption after early life brain injury. Furthermore, investigations into functional networks are just beginning to provide information about how complex networks have been disturbed or have adapted to early injury (Adhikari et al., 2015; Kornfeld et al., 2015). Additional investigations have potential to provide illumination on theories of neuroplasticity and to allow for targeting of emerging therapeutic techniques (Kirton, 2013).
1.6 Conclusion

Studies of cognition after perinatal stroke are important from a clinical perspective. At present we have very few ways of predicting cognitive outcomes in children that have suffered early stroke. A better understanding of the cognitive impact of early stroke is important for providing counselling for families as well as directing rehabilitation programs that must consider motor, sensory and cognitive deficits in the context of the quality of life of the child and the goals of the family (Golomb, 2009). This would also have the potential to elucidate processes of brain development, in addition to providing guidance for prognosis and rehabilitation efforts.

By considering the specific patterns of injury and their effect on selective cognitive domains, we can better understand the consequences of perinatal stroke for affected children. Perinatal stroke provides an ideal natural model for studying the effect of injury in early brain development. Perinatal stroke syndromes occur at a defined time period and result in a discrete injury in otherwise healthy brain (Kirton, 2013). The study of cognition in children therefore holds potential to provide insight into the consequences of early injury and mechanisms of neuroplasticity in the developing brain. The ability to form and use cognitive maps is dependent on a number of cognitive abilities including sensory processing, memory, and executive functioning, which undergo prolonged development throughout childhood. By studying spatial orientation in children with perinatal stroke we can help to elucidate the perturbation and recovery of a complex, network-emergent cognitive skill after early brain injury.
Chapter Two: **Spatial orientation in healthy young adults**

2.1 Introduction

Video games have become a significant part of every day life for many people. According to industry information, 80% households in the United States have a device used to play video games (an increase from 69% only five years earlier) and 42% of Americans play video games for three or more hours per week (Entertainment Software Association, 2015). In addition to entertainment, video games and virtual reality presentations have been increasingly utilized in research and neurorehabilitation protocols (Bohil, Alicea, & Biocca, 2011). Advancing technology allows realism and flexibility in task design at a decreasing cost. Progressively naturalistic displays and input devices elicit realistic behavioural responses while also recording detailed information about these responses. In addition, inherently motivating elements of video game (such as points or virtual rewards) can be built into the task, increasing attention and compliance during performance (Gatica-Rojas & Mendez-Rebolledo, 2014; Green, Li, & Bavelier, 2010). Many tasks can be run with little or no manipulation from experimenters, so video games can also be used for automated testing of otherwise inaccessible or unengaged populations (Stanton, Foreman, & Wilson, 1998). However, quickly changing advanced technology introduces the issue of a “digital divide” where individuals with extensive exposure to technology perform differently in virtual environment tasks as compared to those individuals who do not have the same familiarity with video games and computerized tasks (Donohue, Woldorff, & Mitroff, 2010).

Previous investigations have attempted to determine the effect of video game exposure on the underlying cognitive skills that may contribute to improved performance in a virtual
environment task. For example, “action” video games (games that involve fast, high intensity sensory processing) improve the ability to track multiple moving objects (Green & Bavelier, 2006b), heighten visual acuity (Green & Bavelier, 2007), enhance contrast sensitivity (R. Li, Polat, Makous, & Bavelier, 2009), improve abilities to maintain divided attention (Greenfield, deWinstanley, Kilpatrick, & Kaye, 1994), and improve eye-hand motor coordination (Griffith, Voloschin, Gibb, & Bailey, 1983). While improvements in underlying sensory processing and integration (for which there is evidence from both correlational and randomized controlled studies) have been shown to contribute to enhanced performance on other computerized tasks, it remains uncertain if those improvements generalize to other cognitive processes or affect daily life activities.

Topographical orientation is a complex behaviour that depends on a number of cognitive skills, including memory, attention, perception, and sensory processing (Arnold et al., 2013; Burgess, 2008; Palermo et al., 2008), and is an important component of some video games. A recent study by Ventura and colleagues demonstrated a correlation between video game use and performance on a virtual navigation task (Ventura, Shute, Wright, & Zhao, 2013). The authors developed a first-person video game in which participants explored an environment and learned the locations of three different targets (gems). They were then required to find the gems again as quickly as possible. Video game usage was measured using a 7-point ordinal scale (from 1 for no video game experience, to 7 for greater than three hours every day), and participants were asked to report the degree of similarity between the experimental task and the video games they played. Video game use was significantly correlated with performance on the navigation task. Furthermore, when the authors controlled for task-game similarity, the correlation between video game play and task performance persisted but was reduced, indicating that the type of video
games an individual regularly used modulated the relationship between video game play and task execution. Though this provides indications that video game use may have an influence on navigation skills, the issue remains unsolved due to the use of very broad questions regarding video game play and the lack of control for other factors that could contribute to a better performance.

There are a number of reasons that video game use could correlate with performance on a virtual navigation task. First, a pre-existing aptitude for skills that are employed in a virtual task may increase the likelihood that an individual will enjoy and choose to play video games more often (Boot, Kramer, Simons, Fabiani, & Gratton, 2008). As an individual plays more video games they would have improvement in manipulation of controls and inputs, which would result in better performance (Borecki, Tolstych, & Pokorski, 2013). In addition, previous research has shown that video game players have improvement in cognitive tasks specifically related to video games, such as sensory processing, visual attention, and reaction times (Sungur & Boduroglu, 2012). Lastly, video game players may have improvements in their underlying spatial orientation and navigation skills. These reasons are likely interrelated and hard to differentiate. To date, however, no study interrogating the relationship between performance on a navigation task and previous video game play has included detailed information on the amount and type of video games or controlled for improved skill with game controls.

2.2 Hypothesis

In collaboration with Ayogo Health, Inc. (ayogo.com; Vancouver, BC, Canada) and the Human Vision and Eye Movements Laboratory (Departments of Medicine, Ophthalmology and
Visual Science, University of British Columbia, Vancouver, BC, Canada) we developed a video game specifically designed to assess spatial orientation skills. We hypothesized that performance on a navigational task, as measured through our appositely designed video game, would correlate with the Santa Barbara Sense of Direction Scale (SBSOD) (Hegarty, Richardson, Montello, Lovelace, & Subbiah, 2002), a validated measure of subjective navigation abilities. We also hypothesized that people with extensive video game experience would be more proficient at game controls, which would have a positive influence on game performance. Previous video game experience has been shown to enhance sensory processing skills and visual attention (Green & Bavelier, 2006a; Greenfield et al., 1994), and improved performance on a virtual reality navigation tasks correlates with video game use (Ventura et al., 2013). Therefore, we hypothesized that the improvements on navigational tasks in participants with previous video game experience would be most evident in those participants with previous experience playing navigational video games (video games requiring individuals to navigate and orient in the environment), with improved ability performing the game compared to individuals who did not play navigational video games. This would provide supporting evidence that better performance on a virtual navigation task is due to improvement in cognitive processes that are involved in navigation.

2.3 Methods

2.3.1 Participants

One hundred and twenty three participants (68 females, 55 males) were recruited through the University of Calgary Department of Psychology online Research Participation System
(RPS), and volunteers received course credits for their contribution. Participants were required to be fluent in English and could not have a history of significant neurological disease or injury. This study was reviewed and approved by the Conjoint Health Research Ethic Board at the University of Calgary and formal consent was collected from each participant prior to participation in the study.

Questionnaires indicated that all participants were healthy with no significant chronic illness, neurological disease or injury. Two participants reported migraines and one synaesthesia, but their performance was within the normal range and they were not excluded. One female was excluded due to a technical problem during the game and 19 people (15 females and 4 males) were excluded because they felt nauseous or dizzy while performing the task and had to discontinue (a known side effect of virtual first-person tasks (Hettinger, Berbaum, Kennedy, Dunlap, & Nolan, 1990)). The final sample included 103 young adults aged 17 to 28 years; 52 females (mean age 20.8 years; $SD = 2.5$ years) and 51 males ($M = 20.4$ years; $SD = 2.3$ years).

### 2.3.2 Questionnaires

Participants first completed a questionnaire including items on demographics, health status, and video game exposure. The length of exposure to game play was determined by the number of years an individual had played video games of any type: "For how many years have you played video games?" Alternatively, participants could indicate that they do not play video games: “Check here if you do not play". Concurrent frequency of video game play was determined by the question: "How often do you play video games that involve navigation, walking, or driving, in hours per week?" This question specifically asked for frequency of video
game play that involved navigation or active movement through the game environment. From these questions a categorical variable was generated classifying participants into those who currently play video games with a navigational component, and those who do not play navigational video games, in addition to how long in years and how much in hours per week they play.

Participants also completed the Santa Barbara Sense of Direction Scale (SBSOD), a validated measure of real-life orientation and navigation abilities (Hegarty et al., 2002). The SBSOD scale is a 15-item questionnaire evaluating subjective experience of spatial orientation in large-scale ecological (daily life) surroundings (e.g., “I am very good at judging distances”; “I get lost very easily in a new city”). Items were scored on a 1 to 7 scale and were coded and summed such that a high number indicated more orientation proficiency, or a better sense of direction, and a low number indicated less ability. The SBSOD scale has been demonstrated to have a test-retest reliability with an average correlation of $r = 0.91$ and construct validity with significant correlations to direction and distance estimations after learning in a real building environment ($r = 0.43$ and 0.36) (Hegarty et al., 2002).

### 2.3.3 Video game orientation task

The video game consisted of a museum divided into two areas. The introduction area contained an entrance atrium and two rooms; the testing area had five rooms, each with distinct content and theme (Figure 2.1). The first-person perspective game (Figure 2.2) was displayed on a 24" widescreen LED computer monitor, 1920 x 1080 screen resolution, positioned
approximately 50cm from the participant. Movement was controlled using a thumb joystick on an Xbox 360 controller. Audio instructions were given by the game.

Figure 2.1: Layout of virtual reality environment

The left side of the outline shows the area in which participants were introduced to the game and practiced the motor controls (i.e. practice area). The motor task path followed the red line. To the right was the testing area in which the learning phase (tour) and spatial orientation task occurred. The areas shaded yellow in the "testing area" indicated the connections between the rooms that participants did not learn during the tour. The tour started and ended at the blue star, proceeded around the outer perimeter hallway (shown by blue arrows), and entered each room through one door (at the arrow breaks).
Upon starting the game, an audio introduction clearly stated that the objective of the game was to learn the location of different rooms within a museum environment and to navigate as quickly as possible between them. The first activity in the game consisted of a motor task, which ensured that participants met a minimum level of dexterity with game controls before playing the game. In this motor task, participants were instructed to follow a set path (consisting of a trail of dinosaur footprints) located in the practice area (Figure 2.2). Participants were required to complete the path, hitting all of the target footprints in less than 90 seconds, before proceeding to the game. If the task was not completed within the time limit, it was repeated until the criteria was met. We recorded the number of attempts required.
Figure 2.2: Motor control task

A. The figure shows the atrium where participants were introduced to the game and then started practice of the game controls. B. The bottom panel shows the dinosaur room during the control practice. The participant must complete the dinosaur footprint path in less than 1.5 min to move on to the next stage of the game. This zone also included the butterfly room (not displayed).
After successfully completing the motor practice task, there was a learning phase during which participants were conveyed passively on a route around the perimeter of the testing area and into each of the five rooms (Figure 2.3). An introduction to the learning phase advised players to pay attention to the location of rooms and doorways. In each room participants were informed about the content and given salient facts about the theme. The themes of the rooms were trains, crystals, jungle, aquarium and space. All rooms contained distinct wall pictures and statues that were unique to the theme; for example there were pictures of fish and a dolphin statue in the aquarium room. Following the tour, participants were given instructions to play the game and perform the task.

**Figure 2.3: Learning tour**

The figure displays the train room (one of five rooms available in the testing area) during the learning phase (tour).
Instructions during the testing phase were both auditory and visual. In the first trial participants were located in one of the five rooms and asked to “pick up” the letter available in that room (i.e. the starting room). Once they reached the letter, participants were instructed to go to a different room (i.e. target room) as quickly as possible, following the shortest pathway. The trial ended when participants went through any of the doorways of the target room. Upon entering the target room participants were informed of their success and awarded points (to a maximum of 100) based on the length of time it took them to successfully complete the trial (Figure 2.4); the faster they reached the target room the more points they scored. They were then asked to pick up the next letter within the room, which started the next trial to a new target room. The game consisted of 20 unique trials and each participant played twice for a total of 40 trials. For each trial the game output the length of time taken, the distance traveled and the coordinates of the player at 10ms intervals.
**Figure 2.4: Museum Tasks**

A. The figure displays a typical trial in which a participant is instructed to pick up the letter and to proceed to B. the target room. Instructions are given on screen and in audio narration. The target room is the jungle room in this specific trial. C. As the participant entered the target room (jungle room shown) they were awarded points based on how fast they reached the room. The elapsed trial time was displayed in the top left; top middle displayed written instructions for the target location; and the top right showed the amount of points accumulated in the game.

After completion of the 40 trials, participants were asked to describe their strategy for getting to the target rooms (“What were you trying to remember or what strategies did you use to get to the rooms the fastest?”). Open-ended responses were recorded and later coded into one of four categories. Participants that remembered specific objects or features in the environment (most often the paintings or the statues in the hallways) were classified as having a *landmark* strategy. If they commented on remembering specific paths, or described a series of turns, they were given a *route* strategy designation. Individuals were classified as having a *cognitive map* strategy if they described visualizing rooms in a mental map or remembering room locations relative to each other. Participants that commented on having a memory guide that was not spatial in character (such as the order of the rooms on the tour) were classified in the *memory guide* group. Two investigators independently coded answers and disagreement was resolved by discussion (there was agreement in 67% of cases initially and in all cases after discussion). If the participant’s description fell into more than one category they were given up to two different codes with the “primary strategy” being the one used most or offered first. “Secondary
strategies” were those that were identified as less important or were provided after additional prompting. Only primary strategies were used in group analyses.

2.3.4 Analysis

For each trial, a distance “efficiency” score and time “efficiency” score was computed by dividing the participants’ actual distance or time on each trial by the optimal (i.e. shortest) distance or time possible for that trial. A poor performance resulted in an efficiency score far above 1.0; a better performance resulted in a score approaching 1.0. The time and distance efficiency scores for each trial were highly correlated (Pearson’s two-tailed correlation $r = 0.912$ to $0.990$, $p < 0.05$ for 40 trials with Bonferroni correction for multiple comparisons). Therefore only time efficiency was included in further analyses (consistent with participants receiving scores during the game based on time).

The game consisted of 20 unique trials (from each room to all others); so they differed in length and complexity (e.g. number of turns, opportunities to short cut) and were not directly comparable to each other. Therefore the efficiency scores for all 20 trials were averaged to give a single composite time efficiency score over the game play. A mean was also calculated for the second time completing the 20 trials of the game. The first mean time efficiency represented how quickly the environment was learned and the second measured how well the environment was learned after active practice.

Analyses were performed in IBM SPSS version 21. Variables were reported as group means and standard deviations. Between group analyses were performed using two-tailed analysis of variance (ANOVA) with gender, or video game group as independent variables and
the time efficiency for each game play as the dependent variable. Levene’s test was used to ensure equality of variance between groups. Post hoc tests with correction for multiple comparisons were performed where appropriate. Pearson’s correlations were performed to determine relation of continuous variables of interest.

2.4 Results

2.4.1 Self reported measures

Information from questionnaires indicated that the majority of participants (69 out of 103; 25 females, 44 males) played video games with a navigational component at the time of the study. Thirty-four participants (27 females, 7 males) indicated that they did not play navigational video games. This included 11 participants (7 females, 4 males) that had video game experience but did not play any games with a navigational component, and 23 (20 females, 3 males) that reported no video game experience. There was a significant difference ($F_{(1,101)} = 16.85, p < 0.001$) in the number of years of video game experience between males ($M = 10.3$ years, $SD = 5.45$) and females ($M = 5.5$ years, $SD = 6.30$) but not in the number of hours played per week (males $M = 4.42$ hours, $SD = 4.32$; females $M = 3.49$ hours, $SD = 12.8$; $F_{(1,101)} = 0.244 p = 0.623$).

The scores for the SBSOD on the entire sample of participants had a mean of 66.54 ($SD = 15.3$), with a range of 30 to 98. Consistent with previous literature (Hegarty, Montello, Richardson, Ishikawa, & Lovelace, 2006; Ventura et al., 2013), when analyzed by gender, females ($M = 60.38$, $SD = 16.2$) indicated significantly poorer subjective sense of direction ($F_{(1,91.4)} = 20.376, p < 0.001$) than that reported by males ($M = 72.82$, $SD = 11.3$), using the Brown-Forsythe adjustment because Levene’s test indicated a violation of the assumption of
homogeneity of variance ($F_{(1,101)} = 5.50, p = 0.021$). Self-reported orientation abilities were also analyzed based on video game group. Participants who contemporaneously played navigational video games had a significantly higher SBSOD score ($F_{(1,101)} = 5.427, p = 0.022$) with a mean score of 68.96 ($SD = 15.14$) compared to those who do not play video games with a mean of 61.65 ($SD = 14.6$).

### 2.4.2 Performance on navigation video game

The average time efficiency score the first time playing the game was 3.02 ($SD = 1.08$; range of 1.495 to 7.672) and was highly correlated with the performance the second time playing the game ($M = 2.45, SD = 0.83$, range 1.266 to 5.101; Pearson’s $r = 0.785, p < 0.001$). SBSOD scores negatively correlated with time efficiency both the first (Pearson correlation, $r = -0.292, p < 0.001$) and the second ($r = -0.329, p < 0.001$) time through the game. This revealed that participants reporting a subjectively better sense of direction performed better on the game (with time efficiency scores closer to 1.0); indicating that they were able to more quickly learn the room locations and, after the additional practice, navigate to them faster the second time through the game.

As hypothesized, the number of the motor task attempts required to meet criteria correlated with the number of years of video game experience (Pearson $r = 0.336, p < 0.001$), indicating that extensive video game experience increased proficiency at task controls. Due to technical issues, the number of motor task attempts was not recorded in 11 participants. The majority of people (59%) met criteria for the motor task on the first attempt ($M = 1.66, SD = 1.02$). The number of times required to meet criteria for the motor control task correlated with
time efficiency both the first \((r = 0.660, p < 0.001)\) and second \((r = 0.526, p < 0.001)\) time through game play. Therefore the number of motor task attempts was used as a covariate for further analyses between video game groups to control for better fine motor skills affecting performance.

### 2.4.3 Spatial orientation performance and video game experience

The number of years of video game experience correlated significantly with first \((r = -0.334, p = 0.003, \text{ with Bonferroni correction for multiple comparisons})\) and second \((r = -0.413, p < 0.001)\) time efficiency. Self-reported weekly hours of video game use did not reach statistical significant correlation with time efficiency either the first (Pearson \(r = -0.165, p = 0.15\)) or second time \((r = -0.194, p = 0.285)\) through the game. Analysis of variance across video game groups using the number of motor task attempts as a covariate indicated a significant difference across video game groups both the first \((F_{(2,89)} = 8.506, p = 0.004)\) and second time through the game \((F_{(2,89)} = 13.052, p = 0.001); \text{ Figure 2.5B}\) showing that improved navigation performance was in excess of that which could be accounted for by proficiency with game controls.

As seen in previous reports (e.g. (Castelli, Corazzini, & Geminiani, 2008; Lovden et al., 2007), ANOVA across gender groups demonstrated a difference between females \((M = 3.55, SD = 0.929)\) and males \((M = 2.486, SD = 0.948)\) the first \((F_{(1,101)} = 33.2, p < 0.001)\) and the second (female \(M = 2.88, SD = 0.718; \text{ male } M = 2.00, SD = 0.702); \(F_{(1, 101)} = 39.4, p < 0.001)\) time through the game. This persisted when the number of motor task attempts was used as a covariate (first time through game \(F_{(1,98)} = 7.082, p = 0.009); \text{ second time through game } F_{(1, 89)} =\)
17.8, $p < 0.001$) again indicating that better performance on the game by males was more than could be accounted for by better use of game controls (Figure 2.5A).

Figure 2.5: Differences in orientation performance by video game group
A. There was a significant difference in performance by gender with males completing tasks faster both the first and second time through game play. B. There was a difference across the video game groups with those reporting playing navigational video games performed significantly better than those that did not play video games that incorporate navigation. Number of motor tasks required to meet criteria was used as a covariant; adjusted means for 1.67 motor tasks. Error bars indicate 95% confidence interval. * indicates $p < 0.05$, ** indicates $p < 0.001$. VG – video games

2.4.4 Spatial orientation strategy and performance

The self-reported strategies for completing the spatial orientation task were collected from 102 of the 103 participants. The most common primary strategy (40 people; 18 female, 22 male) was a mental map strategy, with people reporting that they remembered “where the rooms were relative to each other”; “the general layout of the rooms”, or that they had “a mental map” of the rooms. Thirty-two people (13 females, 19 males) were classified as having a route primary strategy since they oriented by remembering “the connections between the rooms” or “used the perimeter hallway”. Fifteen participants used another memory guide, most often stating that they remembered the order of the rooms from the tour (13 females, 2 males) and 14 (8 females, 6 males) identified landmarks (paintings on the walls or statues in the hallways) as their primary tool for navigating. One male remained unclassified, stating “[I was] trying to be adventurous” and was excluded from the analysis involving strategy use.

Secondary strategies were offered by 55 people (33 females; 22 males). Nineteen participants used the assistance of landmarks (15 females, 4 males), 13 employed a cognitive
Two-tailed one-way ANOVA was performed across the groups defined by the self-reported primary strategies used to complete the task. There was a difference in the average time efficiency in the first game play ($F_{(4,97)} = 2.90, p = 0.026$) and the second game play ($F_{(4,97)} = 5.64, p < 0.001$) across the different groups (Figure 2.6A). Post hoc tests with Tukey correction for multiple comparisons revealed that people reporting route strategy performed better than those reporting a landmark strategy during the first time through the game’s 20 trials ($p = 0.047$). The difference in performance between those participants using a cognitive map strategy and those using landmarks did not meet statistical significance ($p = 0.062$). The second time through the game there was a significant difference between those reporting use of a memory guide strategy and a cognitive map ($p < 0.001$) or route ($p = 0.001$) strategy (Figure 2.6A).

Despite the difference in game performance, there was no difference in self-reported sense of direction as measured by the SBSOD questionnaire, between the different primary reported strategy groups ($F_{(4,97)} = 1.881, p = 0.120$; Figure 2.6B). People who reported a cognitive map strategy had an average score of 69.23 ($SD = 14.21$); route strategy $M = 68.12$ ($SD = 13.91$); landmark $M = 66.34$ ($SD = 15.82$); and other memory guide $M = 57.33$ ($SD = 18.80$). The one person with an unclassified strategy had a SBSOD score of 58.

More people who played video games with a navigational component endorsed use of a route (25 of 67; 37%) or cognitive map (28 of 67; 42%) as their primary strategy for completing the spatial orientation task (Figure 2.6C). People who did not have video game experience, or
only played video games without a navigational component, were spread more evenly across the different strategy groups.
Figure 2.6: Differences in orientation strategy by video game group

A. There was a significant difference in navigation performance between the groups defined by the participants reported strategy. A route or cognitive map strategy was more efficient than landmarks or memory guide. B. There was no significant difference on self-reported sense of direction between the different strategy groups. C. A large majority of participants that play navigational video game reported using a route or mental map strategy to solve tasks in the orientation game. People that did not play video games that include navigation were more likely to identify a primary landmark or non-spatial memory guide strategy. Error bars indicate 95% confidence interval. * indicates $p < 0.05$, ** indicates $p < 0.001$. VG – video games.
2.5 Discussion

This study aimed to confirm validity of the museum navigation task as a measure of spatial orientation abilities and to investigate how previous experience with video games effects different elements of performance. By collecting detailed information about video game use that included both past experience (years played) and concomitant use (hours per week), as well as details about the games played, we determined some of the elements that contribute to increased efficiency during game play. First, we found that performance on the navigation task correlated significantly with the length of video game experience rather than a measure of the recent exposure. This behavioural finding is complementary to the neurological evidence reported in a previous study (Kuhn & Gallinat, 2014) showing that lifetime amount of video gaming (joystick years) had a significant association with grey matter volume in the entorhinal cortex bilaterally, as well as hippocampal and occipital areas, and that the association with the entorhinal cortex volume was modulated by the type of video games played. Second, we found that participants with higher video game use had better proficiency with game controls, and required fewer attempts at the motor task to reach criteria. However, improved performance on the navigation task persisted in those that play video games with a navigation component when the number of motor task attempts was used as a covariate, indicating that the improved performance was more than what could be attributed to improved motor control. Third, the majority of participants who concurrently played navigational video games reported using a mental map or route strategy to complete the navigation task. This would suggest that better performance on the navigation task involves, at least in part, a difference in the cognitive approach to solving the trials.

In general, controversy remains as to whether improvements cultivated by video games persist and generalize to improvements in real-world abilities (H. Lee et al., 2012; Rosenberg,
Landsittel, & Averch, 2005). For example, it has been shown that young adults' experience playing Tetris facilitated performance on mental rotation tasks, but only when Tetris-like shapes were used (Sims & Mayer, 2002). It is also possible that the improvement in navigation skills is limited to navigation within a virtual environment. Richardson and colleagues (A. Richardson, Powers, & Bousquet, 2011) employed real life, desktop and immersive orientation tasks that involved learning an environment and then pointing to the location of landmarks that were out of the field of view. They found that both the amount of current and previous video game use correlated with performance on the virtual tasks, but not with real-life accuracy. However, in our study, a higher subjective reporting of real world orientation skills, and an increased use of cognitive map and route strategies in the navigational video game group, may indicate that they have the potential to transfer skills to the real world. The formation of a cognitive map, an allocentric representation of the environment that allows an individual to flexibly reach any location from any other within an environment (O'Keefe & Nadel, 1978; Palermo et al., 2008), facilitates the use of short cuts and enables the individual to be more successful in solving navigation tasks. Conversely, after discovering an ideal path, route learning (or executing a set of practiced turns) is a fast and efficient, though inflexible, way to solve a navigation problem (Etchamendy & Bohbot, 2007; Hartley, Maguire, Spiers, & Burgess, 2003). This suggests that individuals with experience playing navigational games more commonly employ the optimal techniques to solve navigation tasks, which would have bearing on real world orientation tasks.

Our task was designed to be realistic, consisting of navigation in a museum setting (a circumstance where one might be expected to learn an unfamiliar layout) with a game component that exploits the motivating nature of video games (Revelle, 2013). However, the task remains limited in its ecological validity given the involvement of visual stimuli alone. A
significant correlation with the SBSOD scores (which has previously been validated as a measure of real-life orientation abilities) (Hegarty et al., 2002) substantiates that the museum task is measuring, at least some, of the same skills required to navigate in a real-world environment. In fact, previous research indicates that, while navigating by visual cues alone (without vestibular or kinaesthetic information) may be more difficult (A. E. Richardson & Collaer, 2011), humans can use visual cues alone to solve large-scale spatial problems (A. E. Richardson & Collaer, 2011) and, in rodent studies, that visual information can override internally derived movement cues in a navigation task (Taube, Valerio, & Yoder, 2013).

As with other studies that have found a significant correlation between video game use and superior performance in virtual environment tasks (Ventura et al., 2013), conclusions from our study are confounded by uncertainty regarding direction of causation. It is unclear whether people that play video games with a navigational component improve their navigational abilities or whether people who have better navigation skills self-select video games that utilize navigation skills they already possess. Because performance correlated to years of video game use, and not current amount of video game play, it is less likely that participants would have self-selected for more video game use based on inherent orientation abilities from such an early age. The long duration of video game play may contribute to increased development of spatial abilities because many of those participants with superior performance played video games through early childhood, when there is natural development of these skills (Siegel & White, 1975).

Randomized, controlled intervention studies (which allow stronger conclusions regarding causation) where non-video game players were trained on action video games, have indicated
that increased exposure to virtual environment tasks enhance abilities, supporting the claim that benefits arise from experience and not from pre-existing predilections (De Lisi & Cammarano, 1996; De Lisi & Wolford, 2002; Dorval & Pepin, 1986; Green & Bavelier, 2003; Green & Bavelier, 2006a; Green & Bavelier, 2006b; Green & Bavelier, 2007; Okagaki & Frensch, 1994). A recent extensive review of virtual environment tasks, found that video games led to improved information processing in both the quasi-experimental studies (groups were defined by previous video game exposure) and the true experiments (randomized control studies), but that the effect sizes in the true experiments were much less than in the quasi-experiments (Powers, Brooks, Aldrich, Palladino, & Alfieri, 2013). However, randomized control studies are limited in the amount and duration of video game exposure they can provide to the participants, whereas many native video game players have exposure over many years resulting in thousands of hours of play. Some investigators have found that extensive long-term experience playing action video games results in improvements in multisensory processing (Donohue et al., 2010), better spatial abilities (Quaiser-Pohl, Geiser, & Lehmann, 2010), and improved eye-hand motor coordination (Borecki et al., 2013), which may not be appreciated after the short-term exposure of a research trial. This is consistent with our findings that length of video game exposure correlates with improvements in performance. Furthermore, limitations in dose and length of follow-up after randomized controlled studies of video game exposure may contribute disagreement in the literature about whether cognitive benefits from video game experience can generalize and contribute to improvements in real-world functioning.

Another limitation of our study is the dependence on participant reported measures. Both video game usage and real-world orientation abilities are measured by subjective self-reporting, which can be prone to biases and errors. In addition, we have a restricted population consisting
largely of undergraduate university students. Video game usage would be expected to change over different ages and different social situations, which limits the generalizability of conclusions, particularly to older populations. This study, however, does capture a unique sample where a portion of individuals had extensive exposure to video games for a long period, including during much of the period of cognitive development for spatial orientation (Bavelier, Green, & Dye, 2010). Other participants had very limited exposure. This allows for discrimination between the different exposure groups; a distinction which won’t likely persist in the population as video games are increasingly incorporated in schools and other settings that result in children being exposed to virtual or computer tasks throughout development. Moreover, there is reason to think that exposure to video games during active childhood development may have a unique influence on cognition (Blumberg & Fisch, 2013).

### 2.5.1 Significance

Virtual environments are increasingly available in every-day entertainment and education tasks. They are also being used in research and rehabilitation studies (Bohil et al., 2011; Larson, Feigon, Gagliardo, & Dvorkin, 2014; Turner & Casey, 2014) more frequently. As the pervasiveness of innovative platforms increases, consideration needs to be paid to the sensory and mental processes that are recruited both for the task at hand, as well as in the participants’ previous experience with virtual environments. Whether or not a participant is exposed to video games or virtual environments becomes less a consideration than what the exposure is and how the participant interacts with it. Future investigations should consider, and account for, the variety of experience in their sample population. Furthermore, research into how the maturation
of different cognitive skills (and underlying sensory processing and executive functions) is affected by different video game exposures will lead to better understanding of brain development.
Chapter Three: **Spatial Orientation after Perinatal Stroke**

### 3.1 Introduction

With increased use of MR imaging, perinatal stroke has been recognized as a significant cause of seizures and encephalopathy in neonates (Weeke et al., 2015) and is the leading cause of hemiplegic cerebral palsy (Kirton & deVeber, 2006). Perinatal vascular injury can now be classified into more specific syndromes based on pathophysiology, allowing for more specific investigation into aetiologies (Kirton et al., 2010; Takanashi, Barkovich, Ferriero, Suzuki, & Kohno, 2003) and prognosis (Kirton et al., 2008). Perinatal stroke is a focal vascular injury that occurs, or is presumed to have occurred (Kirton & deVeber, 2009), between 20 weeks gestation and 28 days after birth in a baby born at term (Raju et al., 2007). Injuries can be classified into arterial ischemic stroke (AIS) or periventricular venous infarctions (PVI) by characteristic appearance on magnetic resonance imaging (MRI) and a history that is consistent either with neonatal seizures and decreased level of activity, or delayed early motor milestones and early hand preference (Stiles et al., 2012). See section 1.3.1 for further description of perinatal stroke syndromes.

Previous studies investigating cognitive development after early injury, have most commonly found that, when symptomatic epilepsy is not present, cognitive outcomes are normal or near normal as a group, and many individuals have typical intelligence (Carlsson, 1997; Cioni et al., 1998; Gonzalez-Monge et al., 2009; McLinden et al., 2007; Ricci et al., 2008; Schatz et al., 2000; Trauner et al., 1993; Wulfeck et al., 1991). However, some children do experience intellectual impairment, and have difficulties with attention (Anderson et al., 2010; Kolk & Talvik, 2000; Kolk et al., 2011), behaviour (such as attention problems, social interaction problems and emotional disorders) (Hartel et al., 2004), and adaptive functioning (Hurvitz,
Warschausky, Berg, & Tsai, 2004). See section 1.4 for review of cognition after early injury. Some clinical features or factors have been linked to outcomes but reports are often inconsistent. Most reliably the presence of seizures has been connected to poor cognitive outcomes (Ballantyne et al., 2007; Goodman & Yude, 1996; Koelfen et al., 1993; Kolk et al., 2011; Muter et al., 1997; Vargha-Khadem et al., 1992), but lesions that affect both cortical and subcortical areas (Westmacott et al., 2010), and possibly also size of lesion (Banich et al., 1990), have been suggested as indicators of poor prognosis.

Studies of language development after perinatal stroke have shown that there may be initial delays (Bates et al., 1997; Thal et al., 1991) and, while the majority of children have normal or near normal performance by school age (Chapman et al., 2003), subtle deficits may remain when more advanced or sophisticated measures are used (Reilly et al., 2013). Aside from language, other complex cognitive functions have not been as well characterized in children after early injury. There are, however, some indications that visuospatial skills may have more profound impairments (Everts et al., 2008). For example, children after perinatal stroke affecting the right hemisphere have difficulty with spatial integration (organizing elements together into a unified whole), whereas left hemisphere lesions result in impairments processing internal detail (Schatz et al., 2000; Stiles et al., 1996; Stiles et al., 1997). This has also been demonstrated for visual memory; children with perinatal stroke, particularly those with right-sided lesions, perform worse when recreating patterns from recall (Akshoomoff et al., 2002; Stiles et al., 2008). Taken in total, this would suggest that there is relatively more impairment in visuospatial processing, and possibly memory, in children after early brain injury.
Multiple hypotheses have been proposed to account for relative impairments in the visuospatial domain after early brain injury. Some investigators have implicated the timing of spatial skill development. Damage that occurs during, or shortly after, periods of rapid development in a particular proficiency may have more detrimental impact (Anderson et al., 2011; Westmacott et al., 2010). After finding that children with a history of unilateral perinatal injury had more impairments of face recognition (a “what” or ventral stream task) than on location matching (a “where” or dorsal visuospatial stream task), Paul and colleagues suggested that the early and more rapid development of the ventral pathway, and face processing in particular, may leave it more vulnerable to disruption by early injury. The dorsal pathway may be relatively protected because it undergoes prolonged development from infancy into adolescence (Paul et al., 2014). Alternatively, the “crowding hypothesis” proposes that transfer of language abilities to different cortical areas comes at the cost of other functions (Anderson et al., 2011). This hypothesis has been supported by fMRI imaging studies that have found increased right lateralization of language function is associated with decreased visuospatial abilities after unilateral damage (Everts et al., 2010; Lidzba et al., 2006).

Increasing recognition of the importance of efficient, integrated networks for the development of cognitive skills may also provide insight into the differential effects of injury on different cognitive domains during development (Stiles, 2012). A modular understanding of brain function presupposes that a skill is dependent on a particular brain area, and therefore plasticity after injury is dependent solely on mechanisms that would transfer function to uninjured brain. Moving away from this location-dependent view of cognition and toward a conception of cognition as parallel, recursive processes occurring in distributed networks may allow for different theories of recovery after neurological injury during development (Corbetta, 75
Complex skills supported by diffuse neural networks may have less complete recovery (Anderson et al., 2011) because the intricacies of adjusting complicated systems may put limitations on the efficiency of the network, resulting in immature or suboptimal ways of solving problems or performing tasks (Allman & Scott, 2011; Dennis et al., 2000). Other theories propose that more distributed cognitive processes are more likely to be preserved because they have more biological reserve and potential to reorganize (Kolb et al., 2011). These theories are not to the exclusion of the timing hypothesis or the overcrowding hypothesis, which could, conceptually, work in conjunction with a network hypothesis of impairment or recovery.

Topographical orientation, or the ability to orient within and navigate through a large-scale environment (Wang & Spelke, 2002), is a complex behaviour that relies on the integrity of different brain regions in efficient networks (Aguirre & D'Esposito, 1999; Arnold et al., 2013; Barrash, 1998; Maguire, 1997; Schedlbauer et al., 2014). It is a skill that likely emerges in early childhood (Learmonth et al., 2008; van den Brink & Janzen, 2013) but has a protracted development that extends into adolescence (Bullens et al., 2010; Pine et al., 2002). See section 1.2.1 for further description of the development of topographical orientation. This complex, multi-dimensional behaviour can, therefore, be used as a model for the development of complex cognitive processes in children with perinatal stroke.

There are isolated studies of topographical disorientation after congenital conditions (e.g. septo-optic dysplasia (Griffiths & Hunt, 1984), complex malformation (Iaria et al., 2005), and intrauterine growth restriction (Leitner et al., 2005)) but studies of topographical orientation in children with early brain injury are very limited. In a recent study by Belmonti and colleagues, visuospatial memory was testing in children with cerebral palsy using Corsi Block-tapping test
and the “Magic Carpet test”, a room-sized adaptation of the Corsi block test used to investigate large-scale spatial memory. In a group of children with mixed lesion types, the authors found that children with cerebral palsy performed worse than age-matched controls on both tests (preterm birth, bilateral CP or right-sided lesions were risk factors for poorer performance), but deficits were less severe on the navigational scale (Belmonti et al., 2015). Relative sparing of navigation performance, or large-scale visuospatial memory, may contradict the notion that more advanced or complex skills are more vulnerable to disruption by injury than more basic skills.

3.2 Hypothesis

3.2.1 Hypothesis for behavioural testing

Using a group of children with well-defined unilateral, focal injury, our study investigated the behavioural outcomes on a virtual spatial orientation task to demonstrate the extent and limitations of neuroplasticity of spatial skills in the developing brain. We hypothesized that, consistent with the theory that a complex network would be limited in its plasticity after early injury, children with perinatal stroke would be impaired in spatial orientation. Based on clinical experience and previous reports of general intelligence (which appears to be largely preserved in PVI; (Kirton et al., 2008; Sauer et al., 2010)), we hypothesized that children with AIS would perform worse than children with PVI. However, PVI lesions have potential to disrupt long-range connections or networks that may be more essential for a spatial navigation task. For this reason, we hypothesized that performance on a navigation task would reveal deficits relative to healthy controls in children with PVI as well as in children with AIS.
Demographic information and clinical features were collected to test factors that may be associated with outcomes of cognition and the development of spatial orientation skills after early injury. These included gender (Belmonti et al., 2015; Piccardi et al., 2014) and video game experience (Ventura et al., 2013) because these factors have been shown to have a significant effect on performance of healthy individuals. Seizures (Ballantyne et al., 2008; Muter et al., 1997), socioeconomic status (Hetherington, Tuff, Anderson, Miles, & deVeber, 2005; van Buuren et al., 2013), and lesion laterality (Nass et al., 1989), were also considered because their importance has previously been implicated in cognitive outcomes after early brain injury.

We also performed a selective battery of neuropsychological and neuropsychological testing that includes selective subtests from the age-appropriate Wechsler scale (Wechsler Intelligence Scale for Children (WISC) for six to sixteen years of age, Wechsler Adult Intelligence Scale (WAIS) for over 16 years of age) and selective tests of memory and spatial skills (see Appendix C). These tests allowed for a general measure of cognition to determine if deficits in topographical orientation are commensurate with other cognitive functioning. In addition correlations were performed to uncover to what degree the skills tested by each of the neuropsychological contribute to spatial orientation.

3.2.2 Hypothesis for MRI

The neuroimaging of children with perinatal stroke was also analysed for lesion features and tissue volumes. Tissue volumes were used as an objective substitute for lesion volume and correlated to performance. Some previous studies have found an effect of lesion size (Hajek et al., 2013; Talib et al., 2008), particularly in the AIS group where larger lesions would encompass
larger portions of a combination of cortical and subcortical that has also been shown to be a risk for cognitive impairment (Westmacott et al., 2010). We would not expect to see a difference in performance of topographical orientation based on location of lesion, though some isolated studies have found site-specific deficits in the perinatal stroke group. For example, it has been demonstrated that children with perinatal stroke performed more poorly on a task for facial recognition when their lesion involved the parietal lobe (Ballantyne & Trauner, 1999).

Furthermore, a recent paper performed detailed tracing and analysis of hippocampi volumes in children with perinatal stroke and found that a significant reduction in hippocampal volume (seen largely in those with symptomatic epilepsy) had poorer scores on memory tasks, with left-sided hippocampal reductions linked to decreased verbal memory and right-sided lesions leading to more impaired nonverbal memory (Gold & Trauner, 2014). Because multiple studies have linked topographical orientation to processing in the hippocampus, we hypothesized that reduced hippocampal volumes would also correlate with poorer scores on a navigation task.

3.3 Methods

3.3.1 Participants

Children with perinatal stroke were recruited from the Alberta Perinatal Stroke Project (APSP) based at the Alberta Children’s Hospital (ACH) in Calgary, Canada. The APSP is a population-based database in Alberta with clinical and neuroimaging confirmed perinatal stroke. All children in the APSP have previously consented to be contacted for participation in research studies. Inclusion criteria were children aged six years and over, with confirmed unilateral perinatal stroke and no other significant chronic illness, neurological disease or injury not related
to the stroke. Children were excluded if they were born premature (before 36 weeks gestation) or if they were not fluent in English.

Attempts were made to contact all children within the database that met study criteria and were within traveling distance (approximately less than 3hr drive by car). Because the extent of the stroke population was being approached to participate we did not perform a power analysis prior to recruitment. In the case that results of this study approach significance but may be limited by the sample size, comment is made about the limited power and effect size is noted.

Age and gender matched control children were recruited from siblings of participants, by word of mouth, and from the ACH Health Infants and Children’s Clinical Research Program (HICCUP; a recently established database of healthy children that have consented to be contacted for research studies). As with the patient participants, children needed to be fluent in English and could not have a significant chronic illness, neurological disease or injury. This study was reviewed and approved by the University of Calgary Conjoint Health Research Ethics Board. Written consent was obtained from the parents (or from the participants when of an appropriate age) with assent sought from the children too young to formally consent.

Thirty children with perinatal stroke and 32 control children were tested. Four children with stroke were excluded after testing; one with bilateral stroke and no available MRI, one born premature and two because they felt nauseous or dizzy while carrying out the task (a known side effect of first person virtual reality tasks (Hettinger et al., 1990)). Two controls were also excluded for feeling sick during testing. Included in analysis were 28 children with stroke (17 males, 11 females) age 6 years 2 months to 18 years 9 months old. Thirty control children were included (19 males; 11 females) age 6 years 1 month to 19 years 11 months.
3.3.2 Questionnaires

Through interview with a researcher, participants completed a questionnaire that included detailed inquiries about orientation skills and video game experience. This included how much time they spent playing on different platforms, which games they played frequently, and if they played games that include first person perspective, mazes or other navigational elements. Orientation ability was interrogated using a questionnaire that included items adapted for children from the Santa Barbara Sense of Direction Scale (SBSOD). The SBSOD scale is a standardized, validated measure of subjective navigation abilities (Hegarty et al., 2002) with statements about real-life large-scale memory, orientation, and navigation scores rated on a 1 to 7 scale. Participants were instructed to choose “Unsure” if they had no experience or opinion about the statement. Items were coded and averaged over the remaining answers such that a high number (closer to 7) indicated more orientation proficiency, or a better sense of direction, and a low number (closer to 1) indicated less ability. The child adapted SBSOD (c-SBSOD) scale was initially administered with 20 questions but, after analysis of a large control sample of 112 children, aged six to ten years old, two questions were excluded for not being internally reliable (item did not correlate with the questionnaire average; see Appendix A for details).

Parents completed a questionnaire that included inquiries on demographics, health status, developmental history, orientation abilities, and video game exposure. Parents were also given an attention scale (SNAP-IV) and a version of the SBSOD scale that was modified to be appropriate for a parent observer (p-SBSOD). As with the c-SBSOD, the results from the large control sample were analysed but all had a significant positive correlation with the average score and no questions were excluded (Appendix B). Answers were graded so that a higher score indicated a better sense of direction and averaged for a composite score.
3.3.3 Spatial orientation task

The same museum video game that was used for the young adults was used for the children in this study. See Chapter 2 methods (Section 2.4.3) for further details. In short, the first-person perspective game was displayed on a 24" widescreen LED computer monitor 1920 x 1080 screen resolution positioned approximately 50cm from the participant. Movement was controlled using a thumb joystick on an Xbox 360 controller. Controls were uni-manual and adjusted to the hand (left or right) that was most comfortable for the participant, both for the children with perinatal stroke to accommodate any motor deficits arising from the stroke, and for the control participants. Audio instructions were given by the game.

Children first completed the motor task, repeating the trail of dinosaur footprints until they were able to reach the end of the trail in less than 90 seconds (Figure 2.2). The number of attempts was recorded by the investigator. The player was then taken on the “tour” where they were automatically conveyed to each of the five rooms and introduced to the room’s different themes. After the learning phase, audio instructions were given to the participant to play the game by picking up the letter in each room and then proceeding to the next room as quickly and directly as possible. As the participant entered the target room, they were informed of their success and awarded points (to a maximum of 100) based on the amount of time required to complete the trial. The testing phase consisted of 20 unique trials. Participants were asked to play the game twice for a total of 40 trials but some participants (4 children in stroke group and 4 children in control group), citing either fatigue or disinterest, opted to discontinue after the first 20 trials.
3.3.4 Neuropsychological testing

After completion of the spatial task all children underwent a battery of neuropsychological tests designed to give an overall measure of cognition as well as more detailed measurements of memory and spatial reasoning (see Appendix C for list of tests). For children aged 6 to 16 years of age the battery consisted of six subtests of the Wechsler Intelligence Scale of (WISC-IV): vocabulary, similarities, matrix reasoning, block design, digit span, and cancellation. Vocabulary and similarities were used to calculate an estimated verbal comprehension index (VCI) and matrix reasoning and block design were used to estimate the perceptual reasoning index (PRI). Together with digit span, the scaled scores from these subtests were used to estimate a full scale IQ. Teenagers over the age of 16 were administered the same subtests from the Wechsler Adult Intelligence Scale (WAIS-V). In addition participants did the spatial span block tapping test for spatial memory, the Hooper Visual Organization Test (VOT), the Children’s Colour Trail Test (CCTT) and the Standardized Road Map Test developed by John Money as a table top test for examining direction sense (Vingerhoets, Lannoo, & Bauwens, 1996). When scaled scores were available over all ages tested, results were reported as scaled scores. For measures that did not have appropriate scaled scores the raw score is reported and age was used as a covariate during analysis.

3.3.5 Behavioural analysis

For each trial, a distance “efficiency” score and time “efficiency” score was computed by dividing the participants’ actual distance or time on each task by the optimal (i.e. shortest) distance or time possible for that trial. Therefore a poor performance resulted in an efficiency
score far above 1.0; better performance resulted in a score approaching 1.0. The time and distance efficiency scores for each trial were highly correlated (Pearson’s two-tailed correlation $r = 0.516$ to 0.988, $p < 0.05$ for 40 trials with Bonferroni correction for multiple comparisons). Therefore only time efficiency was included in further analysis (consistent with participants receiving scores during the game based on time).

Analysis was performed in IBM SPSS version 21. Variables were reported as group means and standard deviations. Between group analyses of cognitive tests were performed using two-tailed analysis of variance (ANOVA) with group (stroke group, video game group, etc.) as the independent variable and cognitive test score (for example FSIQ or mean time efficiency over the 20 trials of game play) as the dependent variable. When raw scores (as opposed to scaled scores) were analysed, analysis of covariance (ANCOVA) was done with age as a covariate. Levene’s test was used to ensure equality of variance between groups and, if it indicated that equality of variance could not be assumed, the Brown-Forsyth robust test of equality of means test was used. Post hoc tests, with correction for multiple comparisons, were performed after ANOVA where appropriate. Pearson’s correlations were performed to determine relation of continuous variables of interest. If multiple correlations are done at one time, Bonferroni correction for multiple comparisons was used. Hierarchical multiple mixed model regression were performed to analyze the relative influence of variables that were shown to correlate with key cognitive scores. Diagnostic tests for assumptions of linearity and normality were performed during regression modeling and data was explored to identify outliers.
3.3.6 MRI analysis

During behavioural testing, consent was obtained to access the patients’ existing neuroimaging for this study. The most recent available structural T1 and T2 weighted MRI were obtained through the APSP. In most cases these were research scans completed during participation in other research studies; clinical scans were obtained when research scans were not available. The MRI was viewed for lesion characteristics, processed to obtain tissue volumes, and manual traced for hippocampal volumes.

Of the 26 children with perinatal stroke that participated in spatial orientation testing, all had MRI available from which to abstract categorical information and tissue volumes. Scans from 22 of the patients were of sufficient quality and resolution to complete hippocampal tracings. Seventeen of the participants had research scans obtained in the 3.0 Tesla GE Discovery MR750w MRI scanner (GE Healthcare, Waukesha, WI) at the Alberta Children’s Hospital (ACH) consisting of a high-resolution T1-weighted fast spoiled gradient echo imaging (FSPGR) sequence (3D acquisition type, 166 slices, voxel size = 1.0 mm isotropic) and a T2-weighted sequence (2D acquisition type, 36 slices, voxel size = 3.6 mm). The remainder of the scans were obtained on 1.5T Signa GE clinical scanner at ACH. The resolution of the T1 weighted clinical scans were 1mm x 1mm x 1mm in 4 cases, 0.43 x 0.43 x 6.0 mm in three cases, 0.35 x 0.35 x 5.5mm in one case, and 0.86 x 0.86 x 7.5 mm in another.

3.3.6.1 Categorical variables in MRI

The MRI was viewed and categorized for a number of variables. The categorical variables were recorded in SPSS 21 and analyzed using one-way ANOVA. Lesion laterality, the
number of lobes affected and which lobes were involved in the lesion were recorded. A number of regions of interest (ROI) for spatial orientation were identified and operationalized for coding. The areas were identified based on previous report of association with cognitive deficits in children with perinatal stroke (basal ganglia; (van Buuren et al., 2013) and hippocampus (Gold & Trauner, 2014)) or based on association with impairment of spatial orientation in study of adult lesions (hippocampus (Aradillas et al., 2011; Barrash et al., 2000b), parahippocampal gyrus (Takahashi & Kawamura, 2002), retrosplenial cortex (Ino et al., 2007; Maguire, 1997; Takahashi et al., 1997), dorsal lateral prefrontal (DLPF) cortex(Bor, Duncan, Lee, Parr, & Owen, 2006; Manes et al., 2002)). Regions of interest were as defined in the Talarich and Tournoux Stereotaxic Atlas (Talarich & Tournoux, 1988). The retrosplenial cortex was defined as Brodmann areas (BA) 29 and 30 and the DLPF cortex was defined as BA 9 and 46, in the dorsal portion of the middle frontal gyrus (GFm). The lesions were relatively homogeneous with PVI affecting only the white matter and all of the AIS affecting the MCA territory; consequently there were no incidences where the hippocampi, the parahippocampal gyri, or the retrosplenial cortex were directly injured by the ischemic infarcts.

3.3.6.2 MRI processing for volumes

Processing of MRI was completed in SPM12. The images were segmented into grey matter, white matter and cerebral spinal fluid (CSF) (Figure 3.1) as well as skull and extracranial space. All segmented volumes were visually inspected to ensure accuracy of tissue designation. The total volume of each tissue was determined using a Matlab script that calculates the total volume of all nonzero voxels in each tissue image. To determine a curve for age indexed volumes T1 structural MRI for age and gender-matched controls were obtained from a large
developmental neuroimaging database (NIH Paediatric MRI Data Repository [NIHPD] created by the NIH MRI Study of Normal Brain Development; (Brain Development Cooperative Group, 2012)). The resolution of the T1 MRIs in the NIH Paediatric MRI Database was 1.0mm on the short axis of the voxel and 1.00mm to 1.60mm (with an average of 1.3mm, $SD = 0.36$) on the long axis. A total of 42 controls (22 males; 20 females) from 6.4 years to 18.3 years of age with an average age of 11.9 years ($SD = 3.24$) also underwent tissue segmentation. For each of the tissue categories, curve estimation was performed for linear and quadratic terms relating volume to age. The predicted tissue volume for each patient was calculated for their age at the time of MRI and subtracted from their actual volume to give an error value that was then correlated with performance measures.
3.3.6.3 Hippocampal volume analysis

MRIs were loaded onto Analyze 10.0 software. Hippocampal tracing was done on each slice of the T1 weighted MRI for all patients with a high resolution (1.0 x 1.0 x 1.0mm voxel) MRI (n = 21; 14 males; 9 females) performed at an average age of 12.03 (SD = 3.78; 3.08 to 18.33). For comparison of hippocampal volumes with healthy children, the hippocampi bilaterally were traced for the T1 structural MRI scans obtained from the NIH Pediatric MRI Data Repository. Unfortunately, the MRI for children below age six years had a resolution of 1.0mm x 1.0mm x 3.00mm and were not of sufficient quality to dependably trace the hippocampi.

Tracings were done according to the protocol reported by Konrad and colleagues (Konrad et al., 2009), which includes the hippocampus proper (Ammon’s horn), dentate gyrus and subiculum, but excludes the alveus, fimbria and fornix. Hippocampus tracings were carried out on each slice in the sagittal view and verified in the axial and coronal views (Figure 3.2). After tracing was completed and verified the volume of the whole hippocampus was calculated by the

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**Figure 3.1: Tissue volumes**

MRI images were segmented in SPM12 and the volumes of each tissue image were calculated.
Analyze 10.0 program. We conducted two-way analysis of covariance (ANCOVA) between groups with age as a covariate, laterality of hippocampus (left, right) and stroke group (control, stroke with epilepsy and stroke without epilepsy) as the predictor variables, and hippocampus volume as the outcome variable. Partial correlations of hippocampal volumes were done with neuropsychological outcomes (FSIQ, digit and spatial span) controlling for age. Because the size of the lesion would influence the intracranial volume (ICV) as well as the whole brain volume (i.e. the brain, and therefore the growth of the entire ICV, would be reduced with larger stroke lesions), these were not considered for use as covariates.
Figure 3.2: Hippocampal tracing
Tracing was done in the sagittal view and then confirmed and adjusted if needed, in the coronal and axial views. A. Tracing in a healthy control from the NIHPD database. B. Hippocampal tracing in a patient with AIS. C. Hippocampal tracing in child with PVI.

3.4 Results

3.4.1 Participant demographics and Questionnaires

The analysis included 26 children with stroke (17 males, 9 females) age 6 years 2 months to 18 years 9 months old (mean age = 12.74 years (SD = 3.67). There were an equal number of right (13) and left hemisphere lesions. Thirty control children were included (19 males; 11
females) age 6 years 1 month to 19 years 11 months ($M = 12.56$ ($SD = 3.92$). All were right handed (Table 3.1). Nine children in the stroke group were taking medication (Table 3.2) at the time of the study. Eight participants in the control group were receiving medications (four inhalers for asthma, one allergy medication, one Adderall and Strattera for attention, one anti-acne medications and one nonsteroidal anti-inflammatory (NSAID) for joint inflammation). Children were asked if they had any mood or behaviour concerns or if anyone else had expressed concerns about their mood or behaviour. Two children in the control group (7%) and 6 children in the stroke group revealed concerns about mood or behaviour with specific concerns including depression, angry outbursts or impulsivity.

Three of the children with stroke (all AIS) had active symptomatic epilepsy and were under treatment with antiepileptic medication. One child with AIS had previously experienced unprovoked seizures outside of the neonatal period but was seizure free and off of medication at the time of testing. Because of previous indications that an EEG with continuous spike and wave in slow wave sleep (rather than epilepsy itself) may be a strong predictor of cognitive deficits in children with AIS (Mineyko et al., 2012), EEG results were sought out for all patients that were tested. Ten children, all with AIS, had an EEG that included sleep. Two children, both with epilepsy, were diagnosed with CSWS based on available EEG (Table 3.2); lack of power in this sample precluded further analysis.
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
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<td>26</td>
</tr>
<tr>
<td>Gender</td>
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</tr>
<tr>
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<td>6.17-18.67 (12.74)</td>
</tr>
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<td>13 right, 13 left</td>
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<td>4 (15%)</td>
</tr>
<tr>
<td>Mood or behavioural concerns</td>
<td>2 (7%)</td>
<td>6 (23%)</td>
</tr>
</tbody>
</table>

Table 3.1: Group details
### Table 3.2: Patient Participant details

- Participant testing was limited by fatigue. AIS – arterial ischemic stroke, PVI – periventricular venous infarction, CSWS – continuous spike and wave in slow wave sleep, VCI – verbal comprehension index, PRI – perceptual reasoning index.
3.4.2 Video game use

Previous experience with video games, particularly video games that include a navigational component, has been shown to correlate with performance on a virtual navigational task (Ventura et al., 2013). Therefore, detailed information was collected on the participant’s video game experience from both the participant and parent (when available). All children except one (in the PVI group) reported some video games use. Seven of the children in the stroke group (27%) and nine of the thirty children in the control group (30%) report playing only games that do not require navigation during play. There was a significant correlation between the video game use reported by parents and by children (Pearson’s $r = 0.411$, $p = 0.005$) but parent reporting ($M = 9.81$ hours per week, $SD = 9.71$) was usually lower than that reported by children ($M = 12.59$ hours per week, $SD = 14.60$). There was no difference between control and stroke groups in the amounts of video game use either reported by parents ($F(1,43) = 1.908$, $p = 0.174$) or by children ($F(1,43) = 1.912$, $p = 0.173$).

3.4.3 Socioeconomic Status of family

To gather information about the groups’ socioeconomic status (SES), parents (or the participants if parents were not available) answered questions regarding household income, parental education and profession. In the stroke group household income ranged from $60 000 to $200 000 with an average of $134 412 ($SD = $43 942); this information was missing in nine cases (declined to answer). In the control group household income was missing in four cases but the range was $70 000 to $600 000 with an average of $221 538 ($SD = $149 363). Table 3.3 contains details of parental education, revealing that the majority of parents in both groups have achieved postsecondary education.
To determine the effect of SES on the sample, correlations were done between mother’s and father’s highest achieved education and composite measures from Wechsler IQ testing. There was a significant linear correlation between mother’s education level and FSIQ ($r = 0.547$, $p < 0.001$), VCI ($r = 0.509$, $p < 0.001$) and PRI ($r = 0.491$, $p < 0.001$) and father’s education (FSIQ ($r = 0.418$, $p = 0.001$), VCI ($r = 0.460$, $p < 0.001$) and PRI ($r = 0.309$, $p = 0.017$), therefore parental education was submitted as a predictor in multiple regression analysis of cognition measures. Pearson’s correlation between household income and FSIQ, VCI and PRI found no significant correlation.

### 3.4.4 Academic performance

Based on parental report, seven (six with AIS and one with PVI) of the 26 children in the stroke group and two of the 30 children in the control group, had received special education services (Figure 3.3A). Because of differing grading systems, academic performance was reported as failing, below average, average or above average as reported on parental
questionnaire. Current academic performance was not available for one participant in the stroke group (with AIS) because they had left formal education. Current academic performance was available for 28 of the participants in the control group; the remaining two were not currently in formal education. The age-matched controls and the PVI group had superior academic performance with almost all children having average or above average performance in core subjects and no one failing in any areas (Figure 3.3B to E). In contrast, the AIS group had significantly poorer academic performance with one or two individuals failing in all areas and, particularly in mathematics, has a substantial proportion of children with below average or failing performance. It should be noted however, that more than half of children with AIS had average or above average performance in core academic subjects (Figure 3.3B to E).

**Figure 3.3: Educational experience**
The percentage of children with PVI have similar uptake of special education services and have similar performance in core academic areas, more children with AIS have used special education services and more have failing or below average performance in school subjects.

3.4.5 Scales from questionnaires

Parent scales for attention and p-SBSOD were available for 46 of the participants (parent’s were not available in the other ten cases). For all children there was a strong correlation between the parent reported SBSOD and the child version (Pearson’s $r = 0.463, p = 0.001$). There was a negative correlation between the attention scale and p-SBSOD Pearson’s $r = -0.471$, $p = 0.001$) indicating that children with more observed inattention and hyperactivity symptoms had poorer observed sense of direction and orientation. There was no significant difference between the stroke groups for SBSOD scales, parent ($F_{(1,44)} = 2.406, p = 0.102$) or child ($F_{(1,53)} = 2.274, p = 0.113$).

3.4.6 Neuropsychological testing

3.4.6.1 Wechsler IQ and subtests

Overall for the stroke group, the average FSIQ was 85.67 ($SD = 19.04$). The average VCI was 91.63 ($SD = 19.56$) and PRI was 88.0 ($SD = 19.71$). This is in keeping with previous reports of near normal performance as a group and relatively preserved language (Carlsson et al., 1994; Goodman & Yude, 1996; Kolk et al., 2011; Muter et al., 1997). There was no correlation between age and FSIQ ($r = -0.002, p = 0.992$), VCI ($r = -0.027, p = 0.895$) or PRI ($r = 0.020, p = 0.920$) within the stroke group. This was performed to determine if there was a change in
cognition through development, which would support the theory that children “grow into”
deficits or diverge from normal cognitive development later in development.

There were robust differences between the stroke groups on all scaled measures of the
subtests of the Wechsler intelligence tests ($F_{(1,54)} = 18.45$ to $22.84$; $p < 0.001$ to $0.022$; using
Brown-Forsyth robust test of means because Levene’s test indicated violation of the assumption
of homogeneity of variance) with the control group significantly better than both stroke groups
on all post hoc tests with Tukey correction for multiple comparison (Figure 3.4). It should be
noted however, that while statistically below the control group, the PVI group had a mean near
10.0 for vocabulary ($M = 9.5$), similarities ($M = 10.3$) and matrix reasoning ($M = 10.14$)
indicating normal performance as a group.
Figure 3.4: IQ subtests

On all subtests of the Wechsler IQ, the stroke groups did significantly worse than the control group. Error bars indicate 95% confidence interval. ** indicates $p < 0.001$, * indicates $p < 0.05$.

To determine the relative contributions of different factors to the cognition measures a hierarchical multiple mixed model regression was done for each of FSIQ, PRI and VCI as outcome measures. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. The predictors entered in all three models were the same. First stroke groups were entered as predictors (as two dichotomous
variables; one indicating the presence of AIS versus no AIS and the other indicating presence of PVI versus no PVI), then epilepsy group, and lastly mother and father’s highest education. Coefficients for AIS group and father’s education were retained in the statistically significant model for FSIQ ($F_{(3,56)} = 49.461, p < 0.001$). Epilepsy and mother’s education was not retained in the model. The model accounted for 64% of variance in participant’s IQ scores ($R^2 = 0.639$). Information about regressor coefficients for the predictor variables in the model is contained in Table 3.4. The coefficients for the AIS group was significant with a negative $\beta$, indicating that membership in this group resulted in lower IQ (by an average of 18.8 points). The coefficient for father’s education was positive and significant indicating a higher paternal education predicted higher IQ.

<table>
<thead>
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<th>Variable</th>
<th>$R^2$</th>
<th>$R^2$ change</th>
<th>B</th>
<th>SE B</th>
<th>$\beta$</th>
<th>p</th>
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<tr>
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Table 3.4 Regression model for FSIQ

B – unstandardized coefficient; SE B – standard error of the coefficient; $\beta$ – standardized coefficient; * indicates coefficient is statistically significant and retained in the model.
The hierarchical regression model for PRI included only AIS groups, and mother’s education as contributory predictors (Table 3.5). Again epilepsy and the PVI group were not retained in the model. The resultant model was significant \( F_{(3,56)} = 22.66, p < 0.001 \) with 45% of the variance explained \( R^2 = 0.447 \). AIS group and father’s education were retained in the model for VCI producing a statistically significant model \( F_{(4, 56)} = 39.470, p < 0.001 \) that accounted for 59% of the variance \( R^2 = 0.585 \) in children’s VCI scores (Table 3.6).

Table 3.5: Regression model for PRI

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<tr>
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<th>( R^2 )</th>
<th>( R^2 ) change</th>
<th>( B )</th>
<th>SE ( B )</th>
<th>( \beta )</th>
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<td>AIS*</td>
<td></td>
<td></td>
<td>-15.726</td>
<td>2.547</td>
<td>-0.633*</td>
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B – unstandardized coefficient; SE \( B \) – standard error of the coefficient; \( \beta \) – standardized coefficient; * indicates coefficient is statistically significant and retained in the model.
Table 3.6: Regression model for VCI

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<th>SE B</th>
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<tr>
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</tbody>
</table>

B – unstandardized coefficient; SE B – standard error of the coefficient; β – standardized coefficient; * indicates coefficient is statistically significant and retained in the model.

3.4.6.2 Measures of visual and spatial skills

ANOVA across stroke groups was done for scaled neuropsychological measures (Table 3.7). For measures that did not have appropriate scaled measures for age, ANCOVA was done with age as the covariate. Pearson correlations between age and unscaled measures were significant in all cases (Spatial span r = 0.527, p < 0.001; Hooper VOT score r = 0.506, p < 0.001; Road Map errors r = -0.692, p < 0.001). Levene’s test of homogeneity of variances indicated that the assumption for equal variances was violated for the SNAP-IV total scores ($F_{(2,46)} = 6.382, p = 0.004$) so the Brown-Forsythe test of means was used in this case.
Table 3.7: Neuropsychological data

There was no significant difference across groups for spatial span. For parent reported scores on the SNAP_ IV there was no difference in hyperactivity scores but children with AIS had a higher average inattention score as a group. There was a significant difference across groups for the Hooper VOT, the number of errors on the road map test, the CCTT and the cancelation subtest of the Wechsler IQ scale. In all cases the AIS group had the poorest performance. The PVI group had performance not significantly different than controls in the case of the CCTT, cancelation, and road map errors but was worse than controls on Hooper VOT. * indicates a significant difference from control group in post hoc pairwise analysis.

Children in the control group were found to have significantly better scores on the Hooper VOT compared to those with AIS ($p < 0.001$) and PVI ($p = 0.042$) after Sidak correction for multiple comparisons. Post hoc tests revealed that control group had significantly fewer errors on the road map test as compared to AIS and PVI. These results suggest that children with AIS and PVI may have difficulties with spatial processing and memory, which may impact their daily functioning and academic performance.
errors in the road map test than the AIS group \((p = 0.014)\) but were not different than the PVI group. Children with AIS had significantly worse scaled scores on the cancelation test than both controls and children with PVI \((p < 0.001\) for both controls and PVI) with no significant difference between PVI and control groups. Similarly for the CCTT the AIS group had significantly worse performance than both controls and the PVI group.

### 3.4.7 Spatial Orientation task

#### 3.4.7.1 Correlation with subjective measures

Parents were asked if they were concerned with their children’s ability to navigate. In three of the 26 children in the stroke group (12%), parents reported spatial orientation concern in their child and none of the parents of children in the control group expressed this as a concern. Considering the possibility that exposure to different complex environments may affect orientation abilities, families were asked if they lived in a rural or urban environment. Five of 26 children in the stroke group and three of thirty in the control group lived in a rural environment.

There was a significant correlation between the p-SBSOD and the time efficiency the first time through the spatial orientation game \((r = -0.356, p = 0.011)\) but not the second \((r = 0.014, p = 0.933)\). There was no correlation between parent reported attention (on the SNAP-IV) and performance on the spatial orientation task (first time efficiency \(r = 0.147, p = 0.334\); second time efficiency \(r = 0.124, p = 0.466\)). There was a significant correlation between the c-SBSOD and performance as measured by time efficiency (first game play \(r = -0.527, p < 0.001\), second game play \(r = -0.443, p = 0.002\)). Unlike IQ measures, there was no significant correlation found between parental education and performance on the video orientation task.
There was no significant correlation between game performance (either the first or second time through the game) and the amount of video game use (in hours per week) reported by parent or child (when controlling for age and motor function). ANCOVA was done comparing children that play video games with a navigational component compared to those who do no play games with navigation (only one participant reported not playing any video games and was included in the group that do not play navigational games). Age and motor tasks were included as covariates. Adjusted means of the first time efficiency (for 12.64 years old and 2.14 motor tasks) of $M = 5.35$ ($SD = 2.50$) for the group that doesn’t play navigational video games and $M = 4.521$ ($SD = 2.45$) for the group that does play navigational video games were not statistically different ($F_{(1,52)} = 1.277, p = 0.264$). There was also no difference in time efficiency between the video game groups the second time playing the navigation task ($F_{(1,44)} = 0.001, p = 0.975$; doesn’t play navigational games $M = 3.495$, $SD = 3.588$; plays navigational video games $M = 3.484$, $SD = 5.88$).

3.4.7.2 Motor controls

To ensure that hemiplegia did not affect performance on the spatial orientation task, time and path efficiency were correlated with Assisting Hand Assessment (AHA) score and Melbourne Assessment of Unilateral Upper Limb Function for the 21 children that had these scores available. AHA consists of 22 separate tasks to assess the practical functionality of the paretic hand done by a paediatric occupational therapist (Gilmore, Sakzewski, & Boyd, 2010; Greaves, Imms, Dodd, & Krumlinde-Sundholm, 2010; Krumlinde-Sundholm, Holmefur, Kottorp, & Eliasson, 2007). The Melbourne assessment is a reliable and validated measure that can detect small changes in motor function in the paretic upper limb (Cusick, Vasquez, Knowles,
& Wallen, 2005). There was no significant correlation between either motor measure and time or distance efficiency scores on the spatial orientation task. There was also no significant correlation between AHA and the Melbourne assessment and FSIQ, PRI, VCI or any individual subtest of the Wechsler IQ test. There was a significant correlation between the number of motor task attempts required to meet criteria and performance on the spatial orientation task. The correlation with the time efficiency \( r = 0.587; p < 0.001 \) the first time through the game was significant and persisted through the second time through the game (time efficiency \( r = 0.352, p = 0.014 \)).

### 3.4.7.3 Regression model of time efficiency

To investigate the influence of different factors, a hierarchical multiple regression was done to model the time efficiency both the first and second time through the spatial orientation task, after tests for normality, linearity, and homoscedasticity were satisfied. First age and gender, then stroke groups were added, and lastly the number of motor task attempts were added as predictors. This produced a significant model \( (F(4,53) = 12.718, p < 0.001) \) that explained 49% of the variance \( (R^2 = 0.490) \) and retained age, gender, AIS group and motor tasks as predictors. PVI group and video game group were determined to not improve the model and were not included. Coefficients for age, and motor tasks were significant (Table 3.8). Interestingly, in the model prior to the addition of number of motor tasks as a predictor (step 2), the coefficients for both gender \( (p = 0.015) \) and AIS group \( (p = 0.0260) \) did reach statistically significance and were therefore retained in the model. This indicated that differences in game performance attributed to gender or membership in the AIS groups were partially due to differences in manual dexterity of
controls as measured by the number of motor control task attempts. The coefficient for AIS group membership was trending toward significance ($p = 0.065$) in the final model.

The second time through the game age and gender were retained as predictors in the hierarchical regression model; stroke groups and number of motor tasks were excluded. The model was significant ($F_{(2,45)} = 38.120$, $p < 0.001$) and accounted for 63% of the variance ($R^2 = 0.629$). Age and gender were the only coefficients that were statistically significant. The details of coefficients in the model are in Table 3.9.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$R^2$</th>
<th>$R^2$ change</th>
<th>$B$</th>
<th>SE $B$</th>
<th>$\beta$</th>
<th>$p$</th>
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<tbody>
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<td><strong>Step 1</strong></td>
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Table 3.8: Regression model for first time efficiency scores
Table 3.9: Regression model for second time efficiency scores

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<td>0.036</td>
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Table 3.9: Regression model for second time efficiency scores

B – unstandardized coefficient; SE B – standard error of the coefficient; $\beta$ – standardized coefficient; * indicates coefficient is statistically significant and retained in the model.

3.4.7.4 Relation to neuropsychological measures

Two-tailed partial correlation was done controlling for age and number of motor tasks to compare the performance on the spatial orientation task with the children’s performance on the neuropsychological battery. After using a Bonferroni corrected alpha value for multiple comparisons ($\alpha = 0.007$) there was a significant correlation between the first time efficiency and FSIQ ($r = -0.432$), PRI ($r = -0.371$), VCI ($r = -0.515$), CCTT scaled ($r = -0.499$), spatial span ($r = -0.459$) and errors on the road map test ($0.411$). In all cases better performance on the neuropsychological test correlated with better performance on the spatial orientation task as indicated by a lower time efficiency score. Hooper VOT ($r = -0.318$) did not reach the significance cut-off for correlation with the time efficiency after correcting for multiple
comparisons. There was no significant correlation, when controlling for age and motor tasks, between with the any of the neuropsychological tests and time efficiency the second time through the game.

3.4.8 MRI analysis

3.4.8.1 Categorical

There were 13 children in the stroke group that had left-sided lesions and 13 with right. The lesions were relatively homogeneous with all AIS occurring in the MCA territory. PVI lesions affect only white matter so the involvement of the ROI was restricted to those children with AIS. There were no incidences where the hippocampi, the parahippocampal gyri, or the retrosplenial cortex directly injured by the ischemic strokes because they fall outside of the MCA vascular territory.

There was no difference in time efficiency either the first or second time playing the spatial orientation task, FSIQ, VCI, or PRI based on any of the categorical variables (Table 3.10). Particularly laterality of lesion, which lobes, or involvement of any of the ROI identified for spatial orientation (hippocampus, parahippocampal gyrus, retrosplenial cortex) did not predict performance on the spatial orientation task. Involvement of the DLPF cortex in injury was associated with lower FSIQ \( F_{(1,23)} = 12.91, p = 0.002 \), VCI \( F_{(1,23)} = 8.459, p = 0.008 \), and PRI \( F_{(1,23)} = 12.137, p = 0.002 \).
Table 3.10: Analysis of identified regions of interest

The number of patients with lesions that included areas of interest is shown. In no cases were the hippocampus, the parahippocampal gyrus, or the retrosplenial cortex directly injured by stroke. ANOVA was done with involvement of ROI as factor for each of the tests. p values indicate no significant difference between groups except for involvement of the DLPF cortex for FSIQ and second time efficiency. * indicates $p < 0.05$.

<table>
<thead>
<tr>
<th>Region</th>
<th>Lesioned (n)</th>
<th>Not lesioned (n)</th>
<th>FSIQ 1st time efficiency</th>
<th>2nd time efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>19</td>
<td>7</td>
<td>$p = 0.538$</td>
<td>$p = 0.612$</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>12</td>
<td>14</td>
<td>$p = 0.113$</td>
<td>$p = 0.107$</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>24</td>
<td>2</td>
<td>$p = 0.951$</td>
<td>$p = 0.623$</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>6</td>
<td>20</td>
<td>$p = 0.150$</td>
<td>$p = 0.102$</td>
</tr>
<tr>
<td>DLPF cortex</td>
<td>8</td>
<td>18</td>
<td>$p = 0.002^*$</td>
<td>$p = 0.058$</td>
</tr>
</tbody>
</table>

3.4.8.2 Tissue and lesion volumes

To determine how tissue volumes deviated from the normal growth for age, curve estimation for linear and quadratic trends was done using the segmented volumes from healthy, age-matched controls. For the grey matter (GM) volume, the linear equation alone was the best estimation ($R^2 = 0.078; F_{(1,41)} = 3.463; p = 0.070; \text{coefficient } B = -6.76$, standardized coefficient $\beta = -0.279$). For white matter there was a very strong linear predictive value of age ($R^2 = 0.212; F_{(2,41)} = 5.371, p = 0.009; \text{linear coefficient } B = -31.14; \text{linear standardized coefficient } \beta = 0.642$). For CSF volume both linear and quadratic terms were significant ($R^2 = 0.412; F_{(1,41)} = 28.757, p < 0.001; \text{coefficient } B = 9.875$, standardized coefficient $\beta = -1.970$; quadratic coefficient 1.477; quadratic standardized coefficient $\beta = 2.270$). An error in tissue volumes was calculated from the predicted volume for age of the patients within the stroke group. The average
error in predicted volume for GM was -126.7 cm³ ($SD = 130.8$); WM -105.5 cm³ ($SD = 81.4$) and CSF was 84.8 cm³ ($SD = 110.9$). Correlation was performed between the tissue error and FSIQ, PRI, VCI and time efficiency scores from the spatial orientation task (Figure 3.5). It was found that VCI and correlated with tissue volumes and the GM volume correlated with the performance the first time playing the navigation game.

Figure 3.5: Correlations of tissue volume and cognitive scores

A. Curve estimation for tissue volumes for age yielded a linear curve for GM and WM volume development. Both linear and quadratic terms were retained for tissue prediction for CSF volumes. Using these curve equations the error in predicted tissue volumes was calculated for stroke patients. B. Correlation of tissue errors in patients with performance on age appropriate Wechsler IQ scores and time efficiency scores on the spatial navigation task.
3.4.8.3 Regression analysis

Because a significant correlation was found between tissue volume errors and time efficiency on the spatial orientation task, a regression analysis was done to determine the relative contributions of different predictors. A hierarchical multiple mixed model regression was done entering first age, motor tasks and stroke group as predictors (because of significance or near significance in previous regression analysis), then GM, WM and CSF volume errors in the second stage. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. When modeling the time efficiency scores for first time playing the game the number of motor task attempts and the GM volume were retained in the statistically significant model ($F_{(2,23)} = 15.023, p <0.001$) accounting for 57% of the variance ($R^2 = 0.566$; Table 3.11). The second time through the game only age was retained in the model as a significant predictor of time efficiency ($F_{(1,20)} = 16.071, p = 0.001$). Forty five percent of the variance was explained by the age of the participant ($R^2 = 0.446$; Table 3.12). Stroke group, number of motor tasks, and tissue volumes did not sufficiently improve the model and were not included. While conclusions are limited by the small numbers of observations available for this analysis, these findings suggest that the type and degree of injury becomes less important with more practice in the task.
Table 3.11: Regression model for first time efficiency

Number of motor tasks and grey matter volume were determined to be the best predictors for performance on the first time playing the navigational task.

Table 3.12: Regression model for second time efficiency

Only age was determined to be a significant predictor of performance the second time completing the navigational task. After age was accounted for, no other variable had significant predictive value. B – unstandardized coefficient; SE B – standard error of the coefficient; β – standardized coefficient; * indicates predictors that were retained in the model.
3.4.8.4 Hippocampus volumes

Paired samples T-test found no significant difference between left and right hippocampal volumes within the control group ($t_{(41)} = 1.75, p = 0.087$) and no difference between hippocampal volumes ipsilateral and contralateral to the stroke within the stroke group ($t_{(20)} = 1.641, p = 0.116$). A one-way ANCOVA of hippocampus volumes, using age at the time of scanning as a covariate, across the three groups (control, stroke patients without epilepsy and stroke patients with epilepsy) did find a significant difference in right ($F_{(2,59)} = 7.8, p = 0.001$) and left ($F_{(2,59)} = 5.00, p = 0.010$) hippocampal volumes between groups (Figure 3.6). Post hoc analysis with Sidak correction for multiple comparisons indicated difference between control and patients with epilepsy (right hippocampus $p = 0.001$; left hippocampus $p = 0.008$) and between patients with epilepsy and without (right hippocampus $p = 0.012$; left hippocampus $p = 0.031$).

![Figure 3.6: Hippocampal volumes](image)

Compared to controls and to patients without epilepsy there was a significant reduction in the hippocampus volumes in those patients with epilepsy, on both the left and right side. There
was no other significant difference between left and right hippocampal volumes within groups. Means adjusted for age = 11.86. * indicates \( p < 0.05 \), Error bars indicate 95% confidence interval. LL – left-sided lesion. RL – right-sided lesion

Partial correlation controlling for age found that there was no significant correlation between the volume of the hippocampi and FSIQ (left \( r = 0.233, p = 0.367 \); right \( r = -0.001, p = 0.167 \)), spatial span (left \( r = -0.071, p = 0.786 \); right \( r = -0.132, p = 0.614 \)), digit span (left \( r = 0.368, p = 0.146 \); right \( r = 0.185, p = 0.478 \)), or time efficiency scores on the spatial orientation task for either the first (left \( r = -0.082, p = 0.754 \); right \( r = 0.021, p = 0.935 \)) or second time (left \( r = -0.187, p = 0.472 \); right \( r = -0.112, p = 0.670 \)).

3.5 Discussion

Perinatal stroke provides a unique clinical opportunity to investigate plasticity after injury in the developing brain. As a well-defined and localized lesion in an otherwise healthy brain, studying compensation and ongoing cognitive development after injury, as well as the elements that may contribute to ongoing impairment, has the potential to improve understanding of brain development. By testing topographical orientation, a multifaceted cognitive skill that depends on an extensive neural network for optimal function, in children with a history of perinatal stroke, we investigated how complex neural networks respond to early injury. In addition, the study of cognitive outcomes and the different factors that contribute to good or poor outcomes is important because of the potential impact on the lives of the children with stroke.

Twenty-six children with perinatal stroke who were well characterized demographically and clinically underwent a neuropsychological assessment and were tested using a video game
appositely developed to investigate navigation abilities. As seen in previous literature, based both on neuropsychological testing and on parental report of academic success, children with perinatal ischemic stroke had decreased cognitive functioning relative to healthy age-matched controls but the majority of individuals, and everyone in the PVI group, were within normal functioning. The areas of the neuropsychological testing that were reduced in the PVI group relative to controls were block design, digit span, and Hooper VOT. Block design, because it is a timed bimanual test, could be confounded by hemiplegia. Decreased digit span could point to a reduced working memory, which has been seen in a previous study (Pavlovic et al., 2006). However, spatial span was not similarly affected.

Variables that were found to influence scores on the spatial orientation task were included in a regression analysis to determine their relative importance. Age and gender were found to initially account for 33% of the variance between individuals the first time playing the game, and 63% of variance in time efficiency the second time playing the navigation game. The first time playing the game, the presence of AIS as a predictor accounted for an additional 6% of variance in score, and the addition of the number of motor task attempts accounted for 8% of variance. But the addition of motor tasks to the model also adjusted the significance of the coefficients for gender and AIS suggesting that the contribution of gender and stroke group was less when accounting for differences in motor skills. The regression model contained only age and motor tasks as significant predictors of performance the second time playing the navigation game. This would suggest that the presence of AIS is important for the first time playing the game, or how quickly the children with stroke learned the layout of the rooms and how to navigate to them. However, when playing the game the second time, stroke group made no contribution toward explaining the variation in performance among the children.
There are a number of possible explanations for how increased practice could ameliorate the deficit in spatial orientation attributed to children with AIS. If the problem is isolated to memory formation, increased practice could overcome the deficit in navigation. Previous research has indicated that working memory can be vulnerable in the context of early brain injury (Everts et al., 2008). However, memory did not appear to be preferentially affected in our sample, though this may be limited by power with a limited sample size. It is also possible that the children with AIS had a disorganized approach to learning the layout of the museum or performing the task that increased the time to form a cognitive map or remember routes. However, once memories have formed and a strategy has been established, orientation is as effective as in controls. Lastly, with the number of motor tasks accounting for at least some of the difference attributed to AIS, a portion of the deficit may be due to the patient group’s hemiplegia and associated motor planning difficulties. The PVI group, however, also has hemiplegia, so it would be unlikely that this is the entire explanation for the difference in the AIS group.

Contrary to our hypothesis that dependence on efficient wide spread neural networks would limit the development of topographical orientation after perinatal stroke, there were no deficits in navigation in children with PVI, and modest deficits in children with AIS were largely accounted for by motor proficiency. After further practice, children with AIS had navigation performance that was not different than controls. Instead, these data would support the alternative hypothesis that cognitive skills reliant on distributed networks are less vulnerable to, or more able to accommodate, early injury (Kolb et al., 2011). These findings may also support the hypothesis that skills that undergo late or prolonged development are more resilient to early injury (Paul et al., 2014).
Relative resilience of topographical orientation would suggest that neural networks are able to reorganize or, in some other way accommodate, early focal injury. To date, direct investigation of functional network re-organization has been very limited. In a recent test of language, resting state fMRI was collected to measure functional connectivity in children with perinatal stroke and in typically developing children (Adhikari et al., 2015). Modeling indicated that children with perinatal stroke had functional connectivity, particularly in the damaged area, more closely resembling that of healthy children than what would be expected based on the lesion. Authors suggested that early focal injury is unlikely to have sustained, adverse impact on functional connections, albeit in the resting state, and therefore, the damaged areas could continue to play a role in the development of near normal function of language. However, this data does not provide a mechanism through which connectivity is preserved. A study of individuals with congenital hemiparesis due to large periventricular injury sought to investigate the preservation of somatosensory networks in this population. Using magnetoencephalography and fMRI, the authors determined that the primary somatosensory representation of the paretic hand was still located in the rolandic cortex of the affected hemisphere. Diffusion tensor imaging tractography was used to demonstrate that the afferent sensory pathway deviated from its normal course to bypass the damaged white matter (Staudt et al., 2006), thus providing an illustration of how functional connections may be preserved in a relatively less complicated system.

It is also possible, however, that recovery of a complex skill is achieved through other mechanisms such as behavioural accommodations, or use of different cognitive strategies that result in successful performance through different pathways. This method of recovery would be expected to have limitations that would be revealed if the difficulty of the task was increased or if the situation was changed. In the case of spatial navigation, it may be possible to test, more
directly, the use of different strategies. Previous investigations of spatial navigation have indicated that a “spatial” strategy for navigation is dependent on the right hippocampus but a procedural strategy relied on the striatum (Iaria et al., 2003). It therefore, may be possible to distinguish if children after perinatal stroke favour different cognitive processes and, consequently have different patterns of increased fMRI BOLD signal during spatial navigation.

Regression analysis of identified predictors revealed that the presence of AIS predicted lower intelligence measures, accounting for 54% of variance in FSIQ. While the scores on the subtests of Wechsler IQ testing were statistically lower in the PVI group relative to controls, the presence of PVI was not found to be a statistically significant predictor in the regression model. Parental education (father’s highest education for FSIQ and VCI; mother’s education for PRI) was determined to be a significant predictor in the regression models, accounting for an additional 5% (in the PRI model) to 13% of variance (in the VCI model). This is fitting with previous literature in children with early injury (van Buuren et al., 2013), as well as with animal studies that have shown enhanced environments facilitated increased recovery after early injury (Kolb et al., 2011).

Previous literature would suggest that the presence of epilepsy would be a predictor of lower cognitive functioning but this did not reach statistical significance in the regression models for intelligence measures. This is most likely because the model is underpowered to differentiate epilepsy as a predictor beyond the presence of AIS (because all epilepsy occurred in those patients with AIS).

Analyses of MR imaging was done to determine if any structural elements could predict cognitive outcomes. The only neuroimaging signature found to be predictive of intelligence
(including laterality, which lobes were involved and hippocampal volumes) was involvement of the DLPF cortex in the lesion. This pattern may be a marker of a large AIS and not specifically a location dependent cognitive loss. However, this would also apply to lesions that involve the basal ganglia, which were not found to correspond to increased cognitive deficits. The DLPF cortex is involved with many areas of executive functioning including attentional control, working memory, planning and cognitive flexibility (Abe & Hanakawa, 2009) and undergoes development well into, and even past, adolescence (Eslinger, Flaherty-Craig, & Benton, 2004). Damage in this area was associated with low FSIQ, and also impaired navigation scores, perhaps because it has important regulatory roll in multiple cognitive networks. This is an exploratory finding and investigation in a larger sample size would be appropriate. The prefrontal cortex undergoes prolonged development, which would be incomplete in the children studied. Therefore, the processes that allow for recovery of deficits may also be ongoing and, as seen in early language development, deficits may not be as apparent latter in the course of development (i.e. if participants were tested as adults).

The size of the lesion, as measured by error from predicted tissue volumes, was also correlated to performance within the stroke group. This was further explored with a regression analysis of time efficiency scores the first time playing the navigation game. It was found that, after considering the number of motor tasks, the grey matter volume was a statistically significant predictor accounting for an additional 18% of variance. The second time playing the game only age was found to be predictive of time efficiency. Because perinatal strokes occur early in the growth of the brain and head, getting an accurate measure of the size of lesions is difficult because of the deformation that occurs as structures continue to grow. Previous approaches include assigning categorical sizes (e.g. (Ballantyne et al., 2007; Carlsson et al., 2004).
1994) or segmenting into different anatomically areas to compute volumes (D. Li et al., 2012). These approaches lack sensitivity and ignore the possibility of volume loss (due to degeneration or another developmental process) that may occur distant from the lesion site. In this study, we calculated the “missing” tissue volume from a trend established by values from normally developing children. This approach provides a value that measures the structural consequence over the entire brain for each of grey matter, white matter and CSF. There is however, considerable individual variability in tissue volumes and growth, so this method imposes additional variability in the measure. Other limitations of our MRI study include that this was a cross sectional approach. Longitudinal imaging to follow volumes over time could provide further information on how cognitive development relates to structure. Furthermore, MRIs were collected opportunistically so were at variable lengths of time from testing, which could also increase variability in the correlation between tissue volumes and cognitive outcomes. However, all high resolution scans were within 4 months of testing so likely would not change conclusions.

The volumes of the hippocampi of children with perinatal stroke were reduced, but only for the group with symptomatic epilepsy. This is consistent with previous reports (Gold & Trauner, 2014). Because the hippocampus does not fall within the MCA territory, it would not be reduced in volume because of primary damage from the stroke. Therefore, decrease in hippocampus size is most likely due to progressive damage from epilepsy. There was no correlation between neuropsychological testing, including memory measures and navigation scores, and the size of hippocampi for the children with a perinatal stroke. However, literature suggests that there may be accumulating deficits in children with symptomatic epilepsy (Ballantyne et al., 2008). Increasing deficits could be due to progressive damage in the hippocampus. Following children longitudinally, with repeated neuropsychological testing,
seizure history, neuroimaging and EEG, may help elucidate if hippocampal damage, or some other aspect of epilepsy (such as CSWS), has a roll in contributing to cognitive deficits in children with epilepsy.

Following children longitudinally would also allow for study of other factors that may contribute to development after perinatal stroke. This could include a planned program of intervention. For spatial orientation intervention could consist of either scheduled virtual reality training (which would allow for controlled measurements of exposure and performance) or monitoring of real world exposure to new environments.

This investigation was a behavioural determination of the development of a complex cognitive skill after early injury. However, there are other ways of interrogating network performance and efficiency including resting state fMRI, functional connectivity analysis of fMRI during performance of a task, and with other functional neuroimaging methods such as EEG, magnetoencephalogram (MEG), and transcranial magnetic stimulation (TMS). Furthermore, there are methods such as DTI that are beginning to reveal changes in structure of neural networks after illness or injury (Staudt, 2010b). These methods can have special considerations in paediatric populations (de Bie et al., 2010; Yoon, Fonov, Perusse, Evans, & Brain Development Cooperative Group, 2009) (e.g. pretraining with mock scanner to prevent anxiety and movement or using paediatric templates during processing data). Furthermore, there is added complexity when used in patient populations with physical deficits such as perinatal stroke. However, investigations of functional connectivity, particularly longitudinally, would give additional perspective to plasticity within developing networks. In addition, improved
technologies are making techniques more portable, and able to account for movement and individual behavioural variability, which can be of particular concern in paediatric populations.

As shown in some individuals in our sample (Table 3.2), there can be dissociation of intelligence after early injury, particularly with relatively preserved verbal skills (as measured by VCI). It may be possible that performance on a multifaceted complex skill would be more generalizable to overall cognitive function than interrogation of skills that lie within a specific domain. However, it is important to investigate other complex behaviours to determine how other skills or networks may be affected by damage or plasticity. Likewise, as more is learned about aetiology and pathophysiology of perinatal stroke syndromes, the questions of which factors influence behaviour and how we can predict and ameliorate potential deficits, should be revisited.
Chapter Four: **Discussion and conclusions**

Because perinatal stroke is a well-defined and localized injury in an otherwise healthy brain, it has repeatedly proven itself to be an excellent clinical model in which to study brain plasticity. Children are usually healthy otherwise, and they go on to have many of the experiences and exposures as other growing children, thus providing an opportunity to study compensation and ongoing development after injury. Studies into the mechanisms underlying brain plasticity and recovery, as well as the factors that contribute to impairments (e.g. seizures), have the potential to improve our understanding of brain development as well as have a significant impact in the lives of children with stroke. By studying a complex, network-dependent skill our study focused on investigating the development of neural networks and how its behavioural expression is affected by early injury.

**4.1.1 Spatial orientation in healthy young adults**

To investigate use of a controlled virtual environment task for determining spatial orientation skills we used a unique navigation video game that we developed in collaboration with Ayogo Health, Inc. and the Human Vision and Eye Movements Laboratory at the University of British Columbia. The game was created to be engaging and interactive so that it could be used to test navigational skills in both adults and children. By leveraging motivational aspects of video games, such as rich audio-visuals and performance rewards, the game task is able to bypass limitations of attention to get a controlled and quantified measure of navigation ability across the ages of spatial orientation development.
To confirm validity of the task as a measurement of navigation and orientation abilities, and to further investigate influences on video game task performance, we used the navigation video game to study orientation skills in a large sample of healthy, cognitively intact young adults. We collected participants’ demographics on aspects that have previously been demonstrated or theorized to have an effect on performance of an orientation task in a virtual environment. This included a validated measure of subjective spatial orientation ability, the Santa Barbara Sense of Direction Scale (SBSOD) (Hegarty et al., 2002), and information on current and past video game usage. A strong correlation between performances the first and second time playing the game revealed good internal reliability of the navigation game. We confirmed a strong correlation between subjective navigation abilities and performance on the task as well as a previously reported gender discrepancy between subjective and measured navigation performance (Torok, Nguyen, Kolozsvari, Buchanan, & Nadasdy, 2014; Ventura et al., 2013). As demonstrated previously, there was a wide range of individual variability in orientation skills in health adults (Arnold et al., 2013), as measured both by responses on the SBSOD scale and on performance on the museum navigation task.

Previous studies have indicated a correlation between past video game use and performance on many virtual tasks, including tasks of navigation and orientation. Action video games have been linked to heightened visual perception (Green & Bavelier, 2007; R. Li et al., 2009), increased ability to track multiple objects and maintain divided attention (Green & Bavelier, 2006b; Greenfield et al., 1994), and improved eye-hand motor coordination (Griffith et al., 1983). Video game use, both for entertainment and introduced for an intervention study, has been associated with improved information processing (Powers et al., 2013). There has also been direct correlation between video game use and performance on a virtual navigation task (Ventura
et al., 2013). (See also section 2.1). By characterizing previous video game experience and controlling for increased dexterity with game controls, our study endeavoured to clarify the nature of such improvements in performance. The findings confirmed that individuals with a longer history of video game play, as well as participants who play video games that require virtual navigation, have better performance on a virtual navigation task. Furthermore, young adults who play navigational video games more often reported using more efficient navigational strategies for orientation such as using cognitive maps or adopting procedural approaches through learned routes. The findings reported in our study support the theory that navigation and orientation skills in individuals playing video games are due to the consistent practice of those skills while playing for the purpose of entertainment.

As digital interactions continue to proliferate and transform with the introduction of new technologies, the effects of these different exposures should be considered during the testing of behavioural cognition (Cummings & Bailenson, 2015). Advances in technology provide opportunities to change how we measure and interpret different cognitive processes, but they also have potential to affect the cognitive processes directly, particularly when they have chances to impact the development of these skills (Courage, Bakhtiar, Fitzpatrick, Kenny, & Brandeau, 2015; Duch, Fisher, Ensari, & Harrington, 2013; Ferguson, 2015).

4.1.2 Children with perinatal stroke and spatial orientation

Comparing the performance of topographical orientation in control children and children with perinatal stroke provides a unique opportunity to study the adaptations and accommodations that take place after early focal injury. By correlating with other clinical and demographic
features, we can begin to disentangle how a complex visuospatial behaviour (and its testing) may be affected by different elements through development. Utilizing both concurrent neuropsychological testing and the depth of information available through the Alberta Perinatal Stroke Project (APSP), we found that the factors that were predictive of initial performance on the spatial orientation task were age, gender, motor dexterity, stroke syndrome and decreased grey matter volume for age. Furthermore, the modest deficits in topographical orientation in the AIS group were ameliorated by further practice and were no longer seen after the second time playing the video game. In contrast, stroke syndrome, and parental education were the only significantly predictive factors for full-scale intelligence quotient (FSIQ). Loss of tissue volume also correlated with reduced verbal comprehension index (VCI) scores.

As would be expected, FSIQ correlated with performance on the spatial orientation task but, somewhat surprisingly, the strongest correlation after controlling for age and motor control, came with VCI ($r = -0.515$) and not with perceptual reasoning index (PRI; $r = -0.371$), or spatial span ($r = -0.459$). This may be an indication that, as a group, the children were more successful when dependent on a strategy that can be verbalized, such as a procedural route strategy, rather than a strategy that depends on spatial memory or visualization. However, what little evidence there is would suggest that the majority of children of school age would preferentially use a spatial strategy to solve a navigation problem (Bohbot et al., 2012). The increased correlation of VCI with time efficiency on the navigation task could also be an indication that the relative preservation of language skills in children with perinatal stroke corresponded with an overall plasticity of networks in the developing brain that also allowed for improved spatial orientation performance. Previous investigations in children have shown that the use of language and relational descriptions can help children orient and navigate with the use of landmarks in an
environment (Hermer-Vazquez, Moffet, & Munkholm, 2001; Shusterman, Ah Lee, & Spelke, 2011). However, these studies were done in young children in relatively small areas, so it is uncertain what contribution language has during later development of spatial orientation.

Previous investigations of visuospatial skills in children with perinatal stroke have included a variety of desktop tests. Contrary to studies in language, where no differences with laterality of lesion is seen, studies have found that children with left-sided lesions have difficulties with local or featural processing but children with right-sided lesions have more difficulties with global or configural processing (Akshoomoff et al., 2002; Stiles et al., 1997). These deficits approximate impairments seen in adults and are usually subtle (Stiles et al., 2008). As the children progress in development there is evidence that there is functional recovery of visuospatial memory and processing (Stiles et al., 1997). This recovery may be due to a functional accommodation where the children use compensatory strategies without truly overcoming their deficits. Another possibility is that, over the prolonged development of visuospatial skills (Paul et al., 2014), the processes of brain plasticity could act to ameliorate lesion effects but results in a delay of development over much of childhood. In both cases subtle deficits would likely persist through childhood. Functional neuroimaging studies of visuospatial skills after early injury are very limited, but there are indications that children with deficits have an immature pattern of BOLD activation with diffuse engagement of cortical areas (Stiles et al., 2003). This alone does not distinguish an active process of brain plasticity from a functional accommodation but a longitudinal study following neuroimaging patterns over time could determine if the development of neural networks is delayed or persistently perturbed.
There was also correlation between topographical orientation performance and Children’s Colour Trails Test (CCTT), spatial span and the road map test but, surprisingly, not with Hooper visual organization test (VOT); although the correlation was nearing significance, it did not reach the cut-off for multiple comparisons. It is possible that increased variability during development, which could not be completely accounted for by controlling for age, may have reduced the power to find a significant correlation. There was also no correlation between neuropsychological tests and performance the second time playing the navigation game. This would appear to indicate a disassociation between topographical orientation (after the initial learning phase) and other cognitive processes. It seems unlikely, for the multitude of skills that were tested, that there is a complete disassociation, but there may not be enough power to detect a possible partial association (Hegarty et al., 2006), particularly with the variability seen with a cross section of children at variable ages and developmental stages.

When features of neuroimaging were investigated, the only association with spatial orientation was grey matter volume reduction. This would correspond to larger arterial ischemic stroke (AIS) that have damaged more of the cortical area. This is consistent with previous studies showing that perinatal lesions affecting cortical and subcortical tissue (the majority of which would be AIS) are associated with increased deficits (Westmacott et al., 2010). AIS is also associated with increased risk of symptomatic epilepsy, which may be the reason that increased involvement of the cortex results in cognitive impairment. However, most studies have shown that there is no connection between the size of lesion and the risk of epilepsy; therefore, the presence of seizures would not fully explain the correlation between grey matter loss and deficits.
We confirmed that there was little impact of stroke location on cognition, independent of the type of stroke (PVI vs. AIS) (Anderson et al., 2010; Ballantyne et al., 2007; Everts et al., 2008). As hypothesized, location of stroke also had little effect on spatial orientation functioning. However, the possibility of increased deficits in children with injury to the dorsolateral prefrontal (DLPF) cortex deserves additional attention. While it is possible that the involvement of the prefrontal area is a proxy marker for a large AIS (a known risk factor for impairment), a primary role of the prefrontal area cannot be excluded. Many large AIS in the middle cerebral artery (MCA) territory would also involve the basal ganglia, and no association was found between lesions of the basal ganglia and increased deficits. The prefrontal cortex has been implicated in many different aspects of executive functioning (such response inhibition, conflict monitoring, and switching (Glascher et al., 2012)) that could explain an overall decrease in intelligence measures (Glascher et al., 2009; Petrides, 2005; Robinson, Calamia, Glascher, Bruss, & Tranel, 2013). Among the possible impairments, which could also explain a relative deficit in topographical orientation, is harm to working memory (Klingberg, 2014).

Because of the uniformity of perinatal stroke lesions (all patients in this study have PVI or AIS in the MCA territory) it is not possible to differentiate the contribution of the DLPF cortex independent of the other areas that are damaged concomitantly; in this case other areas of the frontal cortex. To further investigate the possibility that damage to the prefrontal cortex is a particular risk factor for cognitive impairment would require more participants with a variety of lesion locations and sizes. This could be achieved in a study that included other lesion types (e.g. haemorrhagic strokes). However, animal studies have pointed to further complexity after early injury of the frontal lobe. Different areas within the prefrontal cortex respond with different structural and morphological changes after early experiences or exposures, implying that the
exact nature of plastic changes may be dictated by area (Kolb, Gorny, Soderpalm, & Robinson, 2003; Liston et al., 2006).

In analysing the neuroimaging irregularities of children with perinatal stroke, we gave particular attention to the hippocampus, because of its centrality in spatial memory formation and in navigation (Aradillas et al., 2011; Burgess et al., 2002). (See also section 1.2.2.) Furthermore, a recent paper showed that a significant reduction in hippocampal volume in children with a perinatal stroke was linked to decreased performance on memory tasks (Gold & Trauner, 2014). We confirmed that the children with symptomatic epilepsy were at greatest risk for hippocampal volume loss. We did not find a correlation between hippocampal volumes and performance on either spatial navigation or neuropsychological tests for memory. However, there were only four patients with symptomatic epilepsy in our study so additional investigation would be important to determine if differences in the hippocampus are connected to cognitive differences. At present, the cause of decreased hippocampal volume is uncertain. Animal studies have found that a loss of interneurons can be seen after a direct dural injury; later accompanied by enhanced excitability of the hippocampus and eventually spontaneous seizures (Lowenstein, Thomas, Smith, & McIntosh, 1992). However, the most direct evidence in children has found decreased growth of the hippocampi of children after prolonged febrile convulsions (Lewis et al., 2014), indicating direct toxicity to the hippocampal structures by epileptic activity in the brain.

Furthermore, it is important to understand the effect of stroke on the functional networks in which the hippocampi reside (Ding et al., 2014). Changes in the networks could contribute to ongoing hippocampal damage (due to deprivation of input) or explain associated deficits. Knowing the aetiology and consequences of hippocampal structural changes is important because progressive damage to the hippocampal structures with ongoing seizures (Briellmann, 131
Berkovic, Syngeniotis, King, & Jackson, 2002) could contribute to ongoing or progressive deficits through development.

The exploration of different cognitive skills after early injury is critical for addressing different hypotheses of plasticity in the developing brain. This is important for understanding brain plasticity in general, but also for directing rehabilitation efforts and removing potential barriers to recovery. The relative preservation of spatial orientation, a multifaceted behaviour with a prolonged developmental course, would lend support to the hypotheses that injury within a network allows for better resiliency of that skill. It has previously been suggested that there would be better recovery of functions that are more distributed within a network due to flexibility or redundancy within the network (Kolb et al., 2011). In addition, our data may be an illustration of better recovery of a skill if injury occurs before or during the development of that skill. It has been previously theorized that increased flexibility and growth during “critical” periods (time of particularly rapid growth, during which enrichment or deprivation has significant long-term effects) (Berardi, Sale, & Maffei, 2015) may allow for improved recovery of functions that have not yet reached their “critical” period of development. It is therefore possible that the recovery that is facilitated by networks is most effective during the process of development. Additional longitudinal studies that include detailed descriptions of injury, rehabilitation and recovery at all ages, has potential to further the understanding of plasticity within neural networks.

There are theories that children “grow into” their deficits. As children develop, deficits that weren’t evident in early development are revealed (Frielfeld, Westmacott, Macgregor, & Deveber, 2011). This theory could arise because additional impairments are exposed when children reach the age that a skill typically emerges and can be tested. Alternatively, as the
complexity of skills increases, and new skills are built on previously learned skills, brain plasticity is no longer able to compensate for the injury and biological reserve is maximized. Our study does not directly test these theories, but there was no correlation between age and scaled IQ measures within the stroke group. Furthermore, our data do not support a notion that there are increased deficits with age, or with increased complexity of task.

4.2 Limitations

By using an interactive video game designed for investigation of realistic spatial orientation abilities in a short, reproducible task, we endeavour to determine the navigational abilities of individuals across a span of ages. However, by allowing free roaming to solve tasks we allow for the possibility that people are using a number of different strategies, or cognitive processes, to solve the navigation problems. We are therefore, not studying exclusively one cognitive process. This is illustrated by the differences in self-reported strategy described by the young adults studied. Many other studies of navigation have adapted other tasks, particularly from animal research, that are intended to test only one strategy at a time (Overman, Pate, Moore, & Peuster, 1996). For example, using a virtual task that consisted of an adaptation of a radial arm maze, Schwabe and colleagues demonstrated that young adults who had perinatal stress (mother experienced traumatic event during pregnancy) were more likely to employ a response strategy rather than a spatial strategy to choose arms (Schwabe, Bohbot, & Wolf, 2012). Uncertainty in determining the cognitive processes involved is difficult. Individuals have differing insight and were only asked in retrospect to describe their thought process, which has uncertain reliability. Furthermore, different strategies may be more amenable to description than
others. For example if an individual used a verbal or list strategy they might be more capable of describing this strategy than if they used a spatial or visualization strategy that is inherently nonverbal. In children, this particularly becomes a problem because they may be less able to reflect on, or verbalize, their strategy or cognitive process.

Our study employing the video game task in young adults was cross sectional and leveraged a population with an opportunistically advantageous variety of exposure to video games. This allows for discrimination between groups and allows for classification based on long-standing categories; people who regularly play navigational video games (most have played for many years) and those who do not play video games with navigation. The observed dose dependency (people who have played video games for more years have better navigation scores) suggests that there is an effect of improving navigation skills with increased video game exposure; however, it is impossible to definitively assign causation for differences between groups. Differences in navigation abilities could be due to the increased practice gained during game play, or due to a pre-existing aptitude that led them to play and enjoy these games. The only way to establish the link is to independently manipulate exposure to navigational video games; however, it would be very difficult to recreate the exposure of a “gamer” who may have many thousands of hours of exposure over many years. This problem assigning causation extends to the study of children with perinatal stroke.

By using a cross section of children with perinatal stroke across a wide of ages, our study is limited in a number of respects. How different risk factors may affect performance is difficult to determine in a cross sectional sample. Following cognitive growth longitudinally would allow for better ability to draw causal inferences between different possible influences (such as
seizures) and later outcomes. This could also include implementing and evaluating the effect of possible interventions or treatment programs. By following children over time we would be able to investigate how ongoing development of intellectual skills are influenced or limited by brain plasticity. For example, there is a theory that children with early injury “grow into deficits” such that children can develop cognitive skills within a normal range to a point. Beyond a certain age plasticity can no longer accommodate the complexity of development and children diverge from the normal trajectory for skill acquisition (Anderson et al., 2011). Because of the dearth of longitudinal studies, currently there is little evidence to support or refute this hypothesis. Furthermore, following children longitudinally maximizes the limited power of a small sample size and would increase the ability to discriminate real trends from chance occurrences that may have arisen in our sample.

Perinatal stroke is a rare disease and therefore, getting enough patients to ensure sufficient power, particularly for subgroup analysis, can be difficult. For example, to delineate the effect of video game play, when nearly all of the children play at least some video games, or delineating the effect of lesion location when the pattern of lesion is fairly homogeneous, would require very large groups. Furthermore, power may be a particular issue in studies of children because of increased individual variability in performance during development that cannot be completely accounted for by age. The course of development can be affected by genetics (Ehrlich & Josselyn, 2015; Harris & Littleton, 2015), socioeconomic status (SES) (Hackman, Farah, & Meaney, 2010), nutrition (Bolton & Bilbo, 2014; Khan, Raine, Donovan, & Hillman, 2014), and many other factors that may or may not be easily quantified and modelled. This increased variability further decreases power for group analyses. A lack of sufficient power is particularly a problem for the analysis of MRI structure in this investigation. High quality MRIs were
available for 22 patients, all of which had either a PVI lesion or a relatively large MCA ischemic lesion. This limits the ability to discriminate between possible effects based lesion location. While using a continuous variable for volume increases the power to distinguish a correlation with lesion size, we did not have sufficient numbers to do analyses within subgroups (e.g. different lesion types) to better understand these correlations. In particular, the correlation between cognitive measures and decreased grey matter may be due to the relative preservation of abilities in children with PVI, which affects white matter primarily.

A well-established problem with generalizability of research studies that include “normal, healthy” controls is the restricted characteristics of people who are available for research studies. As outlined by Henrich and colleagues the common practice of using university students (often undergraduate students that received course credit for participation such as in our study) leads to limitations on the generalizability of findings in these studies and may lead to erroneous conclusions (Henrich, Heine, & Norenzayan, 2010). Developmental studies are also subject to a similar selection bias, where families that have incentive and availability to participate in research studies are often of higher education and economic status, and are, therefore, over represented (Fernald, 2010). This has been overcome in some studies by investigators travelling into communities to get more population representative samples (Hurtado, Marchman, & Fernald, 2008), which is important for characterizing less available groups, but also for disentangling causation from other group differences. Patient groups have different motivations and, therefore, could have a different demographic makeup than volunteer groups. This would lead to uncertainty in assigning causation for differences between groups. This is illustrated in the control group for our study, which had a higher family income and slightly higher parental education level than the group with perinatal stroke. The children from the control group also
had a higher than expected performance on intelligence measures. As it relates to spatial orientation, differences in resources between the families in the patient group and the control group could mean differences in the number of new environments that the children experienced.

The primary aim of our study was to study topographical orientation in children with perinatal stroke. This has not been studied previously in children with stroke so we wanted to determine if orientation is a particular deficit in this population, and if this is a concern for children or parents. By studying a skill that requires multiple simultaneous cognitive processes across a distributed functional network, we tested the hypothesis that more complex skills may be selectively impaired in children with early injury. For better characterization of the children’s cognitive ability and spatial skills, a selective set of neuropsychological tests was performed (see Appendix C). However, these tests were limited to prevent fatigue of participants and maximize evaluation of relevant memory and spatial skills. As such, the IQ scores were estimates based on a subset of the age-appropriate Wechsler scale and evaluation of some very important cognitive skills, such as language, were limited. Language has been more extensively investigated by other researchers. See section 1.4.2 for review.

4.3 Future Directions

Improved characterization of the different perinatal stroke syndromes has permitted the initiation of more specific investigations into the different aetiologies and risk factors for each of the syndromes (Kirton et al., 2010; Kirton et al., 2011). However, many aspects of perinatal stroke have not yet been thoroughly investigated and further research, leading to potential preventions and acute treatments, would have great clinical relevance. As further advances are
made in perinatal stroke, ongoing work is required to determine how long-term cognitive, behavioural and quality of life outcomes may be affected by changes in treatment and care.

At present, there is little evidence for how treatments and therapies may affect long-term cognitive outcomes. From therapies to ameliorate physical constraints on learning, to early education that targets areas of strength or weakness, there are many possibilities for improving the care for children with early brain injury. With better understanding of how the brain reacts to injury, functional brain imaging may lead to individualized approaches based on the pattern of plastic adaption seen in a particular child’s brain. There is also potential for investigations into direct interventions that change the function of the brain after injury, such as TMS and transcranial direct current stimulation (tDCS). These techniques have been demonstrated to be safe in children (Krishnan, Santos, Peterson, & Ehinger, 2015) but investigations of their effectiveness for neurorehabilitation in children are very recent (Chung & Lo, 2015). With indications that there is more potential for lasting plastic change at an earlier age, these techniques may have more effect if used in children (Kirton, 2013).

For guidance of clinical decision making and counselling, it is necessary that further work include measures of importance to children and families. Topographical orientation can be considered an important adaptive behaviour that facilitates independent functioning. However, we found that there was no difference between the stroke and control groups on parent and child reporting of sense of direction, and getting lost was not reported as a main worry for families. It is important that studies continue to determine which areas of development are of most concern to families. Studies that have concentrated on outcomes that are important to parents and children are limited and most have short follow-up (O'Keeffe, Ganesan, King, & Murphy, 2012).
However, it has been found that impairment in cognitive/behavioural scores were strongly correlated with reduced quality of life in older children (Friefeld et al., 2011).

Though these are largely introductory findings, if families are concerned with their child’s ability to navigate, particularly if it is affecting independence, there are a number of different approaches they may take. It appears that children with stroke may be delayed in development of orientation abilities but most will be able to learn to navigate and should be encouraged to be actively involved in navigating. By pointing out landmarks and describing both the path taken as well as spatial features of the environment (“Notice we are turning at the church and now the store is behind us”), children will learn over time to orient themselves. Safety should always be a consideration but children learn faster when more actively involved in the process of navigation. If concerns persist, further testing, including full neuropsychiatric evaluation if not previously sought, should be considered to determine if deficits are due to a more general process (e.g. attention, memory).

In this investigation, academic performance was used as a measure of everyday functional cognition. It was found that children with PVI had similar outcomes as control children, whereas more children with AIS had below average or failing performance in core academic subjects. However, most children, even in the AIS group had average to above average performance for grade level. This measure is limited as it depends on subjective reporting from parents because of differing reporting standards across school ages and systems. However, it is important that investigations continue to include reporting of “real world” functional outcomes and, when possible, following these outcomes longitudinally. Long-term outcome measures into adulthood would provide essential prognostic information for families (Hurvitz et al., 2004) and could
enrich investigations of cognitive development after injury. To be most relevant these measures should include outcomes in specific cognitive areas that are important to children and families as well as functional outcomes and quality of life and mental health outcomes.

Investigations into long-term outcomes after early brain injury have the potential to help answer questions about the nature and consequence of brain plasticity. Better understanding of the underlying mechanisms of plasticity in the developing brain may also lead to targets that can be leveraged to improve meaningful outcomes for children (Cioni, D'Acunto, & Guzzetta, 2011). In conjunction, ongoing research into factors that limit plasticity after early injury, in particular seizures and EEG changes (Mineyko et al., 2012), will improve long-term cognitive outcomes. Better delineation of the effects of pathological electrographic activity may provide an opportunity for preventative treatment as well as increased understanding into the biology of brain adaption. Our study in children with perinatal stroke supports the hypotheses that injury that occurs before development of a skill that depends on a diffuse neural network would allow for good recovery of that skill. Our data would also support the theory that language has good recovery after early injury and that this may come at the expense of visuospatial skills (as measured by the PRI in the Wechsler IQ score) as proposed by the “crowding” hypothesis (Fiori & Guzzetta, 2015). Further investigations of different cognitive skills, particularly with longitudinal studies that follow developmental trajectory, will be able to reveal what factors could change the course of development in individuals. This will inform the differing hypotheses of brain plasticity after injury. Continuing to pair neuroimaging studies with behavioural outcomes in children with a variety of different neurocognitive disorders can elucidate the structural and functional changes that correspond with deficits and recovery. Taking into account genetic (Ehrlich & Josselyn, 2015) and structural factors (Harris & Littleton, 2015) in human and
animal studies (Kolb et al., 2011) could lead to additional therapeutic targets, as well as improved understanding of brain development.

4.4 Conclusion

Spatial orientation is an interesting adaptive behaviour because of its fascinating neural underpinnings. Place cells, grid cells, and head direction cells (Barry & Burgess, 2014; Burgess, 2008), the networks that they lie in, and how these networks function to produce a variety of behavioural expressions in functioning individuals (Arnold et al., 2013), are all interesting areas of research that can help reveal how the functioning of our brain leads to behaviour. Studying the development of spatial orientation in children allows for better understanding of the development of a complex skill. By investigating both the behavioural and neuroimaging signature of topographical orientation throughout all stages of maturity, we have the opportunity to study how cognitive processes and executive functions undergo integration and regulation through development. Though complex and challenging, this area of study allows for investigation of how different factors during development (including injury, but also different experiences and exposures) affect the growth of this skill.

Literature would tell us that cognitive potential may be limited in children after perinatal stroke (at least in the AIS group) relative to unaffected controls (Talib et al., 2008; Trauner et al., 2001). While there are children within the AIS group that have normal cognitive outcome, all risk factors associated with poor outcome lie within this group. Children with symptomatic epilepsy have the highest risk for poor outcomes in all cognitive domains (Ballantyne et al., 2008) and there are indications that more loss of cortex is associated with deficits in verbal
intelligence and spatial orientation performance. Visuospatial skills may be more affected than language skills but remain understudied despite a presumed importance to functions of daily living and childhood quality of life (Everts et al., 2008).

Studies of cognitive and behavioural outcomes after perinatal stroke are important for clinical treatments, as well as for counselling children and families. Answering questions of prognosis provides a better understanding of the condition for families. By delineating more accurately areas of possible concern, clinical teams can perform appropriate surveillance tests and direct rehabilitation efforts and resources most effectively. Studies into the mechanisms underlying brain plasticity and recovery, as well as the factors that contribute to impairments (e.g. seizures), have the potential to improve understanding of brain development as well as have a significant impact in the lives of children with stroke. Knowledge of natural adaptive strategies gives insight into possibilities for maximizing or augmenting recovery.
References


APPENDIX A: CHILD MODIFIED SBSOD

1. I am very good at giving directions to help people find places or things
   Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

2. I forget where I leave things
   Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure
   [Removed because not reliable in large normative sample.]

3. I am good at guessing how far away things are
   Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

4. I can imagine directions
   Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

5. I like to use north, west, east, south when I find places
   Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

6. I get lost easily
   Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

7. I like to read maps
   Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

8. It is hard for me to follow directions to new places
   Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

9. I am good at reading maps
   Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

10. I don’t usually remember how to get to places
11. I don’t like giving people directions
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

12. I like it when to know where I am and where I’m going
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

13. I can remember how to get somewhere after going there once
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

14. I can imagine where things are in my environment
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

15. I am good at knowing when I’ve been to a place before
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

16. I can tell the difference between left and right
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

17. I get lost in my own neighborhood
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure
[Removed because not reliable in normative sample.]

18. When I am lost, I cannot find my way back
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

19. I like visiting new places
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

20. I visit new places often
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure
APPENDIX B: SBSOD – PARENT VERSION

After reading each statement carefully, circle the number that indicates how well each statement applies to your child. If you are unsure or have not observed these behaviours in your child, circle unsure.

1. My child is very good at giving spatial directions
   Strongly agree  1  2  3  4  5  6  7  Strongly disagree  Unsure

2. My child has poor memory for where he/she left things
   Strongly agree  1  2  3  4  5  6  7  Strongly disagree  Unsure

3. My child is very good at judging distances
   Strongly agree  1  2  3  4  5  6  7  Strongly disagree  Unsure

4. My child’s “sense of direction” is very good
   Strongly agree  1  2  3  4  5  6  7  Strongly disagree  Unsure

5. My child tend to think of environment in terms of cardinal directions (N, E, S, W)
   Strongly agree  1  2  3  4  5  6  7  Strongly disagree  Unsure

6. My child gets lost very easily in a new city
   Strongly agree  1  2  3  4  5  6  7  Strongly disagree  Unsure

7. My child enjoys reading maps
   Strongly agree  1  2  3  4  5  6  7  Strongly disagree  Unsure

8. My child has trouble understanding spatial directions
   Strongly agree  1  2  3  4  5  6  7  Strongly disagree  Unsure
9. My child is very good at reading maps
   Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

10. My child doesn’t remember routes very well while traveling in a car
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

11. My child doesn’t enjoy giving directions
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

12. It is not important to my child to know where he or she is
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

13. My child can usually remember new route after he or she has traveled it only once
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

14. My child doesn’t have a very good “mental map” of his or her environment
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

15. My child is good at recognizing familiar places
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

16. My child is good at discriminating between left and right
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

17. My child gets lost easily in familiar environments that he or she visits at least once a month
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

18. When my child gets lost, it is difficult for him or her to find the way back
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure

19. My child likes to explore new environments
    Strongly agree 1 2 3 4 5 6 7  Strongly disagree  Unsure
20. My child frequently visits new or unfamiliar environments (e.g., a park that he or she has never been to before)
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

APPENDIX C: NEUROPSYCHOLOGICAL BATTERY

For children 6-16yo - WISC-IV:

Vocabulary
Similarities
Matrix reasoning
Block design
Digit span
Cancellation

For ages 17 and over – WAIS-V: same subtests

For all ages:

Spatial span block-tapping test
Children color trail test (CCTT)
Hooper visual organization test (VOT)
Standardized road map test