Location and size of preterm cerebellar hemorrhage and childhood development

by

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Abstract

Cerebellar hemorrhage (CBH) is a common complication of preterm birth but has never been quantitatively mapped. This thesis aimed to (1) measure and spatially define CBH and (2) examine the association between CBH size and location and neurodevelopmental outcomes, hypothesizing that larger anterior CBH would be associated with neuromotor dysfunction whereas posterior CBH would be associated with cognitive and behaviour problems. The MRIs of 221 very preterm neonates were segmented for CBH. CBH occurred mostly in the inferior posterior cerebellar lobes and CBH volume was associated with motor, visuomotor, and externalizing behavioural outcomes at 4.5 years independent of supratentorial brain injury. Moreover, CBH extending deeper into the cerebellum predicted adverse motor, visuomotor, and behavioural outcomes. Therefore, in preterm neonates, CBH size and location were associated with reduced neurodevelopmental function in a dose- and location-dependent fashion. The volumetric quantification and localisation of CBH may promote improved preterm outcomes via targeted intervention.

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Contributions

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Dr. Vann Chau: Contributed to data collection and interpretation of findings

Drs. Ruth E Grunau and Anne Synnes: Contributed to the overall cohort realization and assessments for the follow-up and outcomes

Dr. Jessie Guo: Contributed to image processing and analysis

Mr. Steven Ufkes: Contributed to image storage and segmentation analysis

Dr. Emily WY Tam: Contributed to image segmentation and interpretation of findings

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List of Abbreviations

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CBCL – Child Behaviour Checklist

CBH – Cerebellar hemorrhage

CP – Cerebral palsy

EGL – External granular layer

FSIQ – Full Scale Intelligence Quotient

GA – Gestation age

GMH-IVH – Germinal matrix hemorrhage and intraventricular hemorrhage

IQ – Intelligence quotient

IQR – Interquartile range

IVH – Intraventricular hemorrhage

MABC-2 – Movement Assessment Battery for Children – Second Edition

MAGeT Brain – Multiple automatically generated templates

MRI – Magnetic resonance imaging

NICU – Neonatal intensive care unit

OR – Odds ratio

PICA – Posterior inferior cerebellar artery

SCP – Superior cerebellar peduncle

SD – Standard deviation

SWI – Susceptibility-weighted imaging

TEA – Term-equivalent age

US – Ultrasound

VLSM – Voxel-based lesion-symptom mapping

WMI – White matter injury

WPSI-III – Wechsler Preschool & Primary Scale of Intelligence – Third Edition

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1. Literature Review

1.1 Introduction

Cerebellar hemorrhage (CBH) is a common early complication of preterm birth and affects the youngest born neonates (Tam 2018; Merrill et al. 1998). The hemorrhages likely originate from the germinal matrices of the developing cerebellum, and in particular the sub-pially located external granular layer (EGL) which experiences peak cellular proliferation in a rostral to caudal direction during the early third trimester (Volpe 2009; Haldipur, Dang, and Millen 2018; Machold and Fishell 2005). The earliest reports of CBH in preterm neonates relied on postmortem examinations and cranial ultrasound (US) via the mastoid fontanel and described large hemorrhages that were associated with death and severe neurodevelopmental impairments (Limperopoulos et al. 2007; Merrill et al. 1998).

More recently, large CBH have become less common with improvements in neonatal care and punctate CBH have been increasingly reported in the preterm population with the application of magnetic resonance imaging (MRI) (Senden et al. 2018; Gano et al. 2016; Tam, Rosenbluth, et al. 2011; Steggerda et al. 2009). These punctate CBH are typically defined as those only visualizable on MRI and measuring <4mm in diameter on any given imaging plane (Kidokoro et al. 2014; Boswinkel et al. 2019). A recent systematic review included only 15 subjects with isolated punctate CBH and found that 13-20% of them manifested severe neurodevelopmental impairment, a proportion which may not be different than that of the general very preterm population (Hortensius et al. 2018; Pascal et al. 2018). None of the included studies assessed the children beyond 3 years of age, and as such may not be valid for preschool- and school-age childhood outcomes (Roberts et al. 2010). A separate systematic review was unable to investigate the effect of size and location on outcome due to the small number of studies that described the topography and size of CBH (Villamor-Martinez et al. 2019). In addition, a contemporary case-control study of neonates with punctate CBH reported a higher frequency of abnormalities on neurologic examination at 3-6 years; the study, however, did not systematically evaluate motor function (Tam, Rosenbluth, et al. 2011). Overall, the consequences of CBH on neurodevelopment are unclear.

A recent retrospective, multi-center study of neonates with CBH divided neonates into three qualitative CBH size-based groups (punctate, medium-sized, and massive CBH) but did not find a consistent association between size and outcome. An association between smaller CBH

and neurodevelopmental outcome may nevertheless exist but be undetectable without precise, quantitative evaluation of the size and topography of the hemorrhage. Topographically, the cerebellar hemispheres are divided into the anterior and posterior lobes. Each lobe serves distinct functions in the developed adult brain: damage to the anterior lobe is associated with the classic cerebellar motor syndrome whereas damage to the posterior lobe is associated with the cerebellar cognitive affective syndrome (Ashida et al. 2018; Stoodley et al. 2016). One autopsy study reported that most hemorrhages involved the ventral or inferior aspect of the posterior lobe but the topographic importance of CBH in preterm neonates in largely unknown (Haines, Wang, and Pierson 2013).

Our objectives, therefore, were to (1) precisely measure and spatially define CBH in 3-dimensions and (2) examine the association between CBH *size* and *location* and preschool-age neurodevelopmental outcomes in preterm neonates. We hypothesized that larger, more anterior CBH would be associated with neuromotor dysfunction in preterm neonates whereas posterior CBH would be associated with cognitive and behaviour problems in children born preterm.

1.2 Preterm birth and terminology

The rate of preterm birth, defined as birth before 37 weeks' gestation, remains stagnant in Canada at 8% and is rising worldwide towards 11% (Canada 2016; Chawanpaiboon et al. 2019; Organization 1977). To achieve the United Nations' Sustainable Development Goal 3 to ensure healthy lives and promote well-being for all at all ages, it is therefore important to address the global burden of preterm birth (Chawanpaiboon et al. 2019). Although survival rates of preterm neonates in high income countries have risen in recent decades (Lee et al. 2020; Garfinkle et al. 2019), preterm birth remains a leading cause of childhood and lifelong disability (Olusanya et al. 2018). Even among the most preterm neonates born at <26 weeks, survival has been increasing to the point that neonatal stabilisation may be considered for babies born from 22+0 weeks of gestation in many countries (Lemyre and Moore 2017; Mactier et al. 2020; Norman et al. 2019). In Canada, recent estimates demonstrated that survival increased from 32% for neonates born at 22 weeks to 83% for those born at 25 weeks and 4-6 days (Shah et al. 2020). Preterm birth is estimated to cost the Canadian health care system over $8 billion per year in hospital costs but the additional costs borne by families as a result of childhood disability and modifications to

their everyday activities are inadequately accounted for (Lim et al. 2009; Petrou, Yiu, and Kwon 2019).

Preterm birth is grouped by the World Health Organization into 3 categories based on gestational age (GA) (Organization 1977). Extreme preterm, born at less than 28 weeks' gestation, and very preterm neonates, born at less than 32 weeks' gestation, have a higher risk of poor short-term and long-term outcomes compared to those born moderate to late preterm, at 32-37 weeks' gestation (Pascal et al. 2018; Organization 2018). In Canada, of the 30,000 infants born preterm each year, approximately 4,000 are born very preterm (Canada 2020). Advances in obstetric, perinatal and neonatal care and quality improvement initiatives have reduced mortality and improved short-term outcomes for the most fragile and youngest-born preterm neonates in particular (Stoll et al. 2015; Lee et al. 2020). Worldwide, the number of very preterm births has not significantly decreased, and has even increased in many countries, while mortality rates have decreased in high- and middle-income countries (Yeo et al. 2015). As such, the absolute number of very preterm survivors is increasing and presents a growing public health concern.

Preterm labor may be seemingly unprovoked due to, for instance, spontaneous preterm labor or preterm premature rupture of membranes or medically initiated due to, for instance, acute maternal or fetal indications such as infection, poor fetal growth, or high blood pressure (Villar et al. 2012). Factors that predispose towards spontaneous preterm delivery include sociodemographic (e.g., poverty, race), environmental (e.g., smoking), nutritional (e.g., obesity), lifestyle (e.g., fertility treatment, increasing maternal age), and maternal genetic factors. Nonetheless, the specific cause of preterm labor is unknown in most cases (Muglia and Katz 2010).

With the increasing survival of preterm neonates, the contribution of preterm birth to childhood and adulthood disability remains substantial (Bitta et al. 2017). The reduction in mortality over the last decades due to improvement of neonatal intensive care has not been accompanied by a substantial decrease in the rates of neurodevelopmental disabilities (Cheong et al. 2017). As it stands, there are few neuroprotective interventions available for preterm newborns. One neuroprotective pharmacotherapy, magnesium sulfate, is administered to mothers of fetuses at risk of being born preterm and reduces the risk of cerebral palsy (CP) (Wolf et al. 2020). The mechanism of action of magnesium sulfate is not established but a recent cohort study found that it was associated with reduced CBH (Gano et al. 2016). It is therefore an urgent

priority to investigate preterm brain injury and development in order to improve the brain health and developmental trajectories of these newborns. The vulnerability of the preterm brain can be dichotomized into brain injury and brain dysmaturation, with interactions between them, and will be discussed later.

1.3 Imaging the preterm brain

Neuroimaging of preterm neonates has become part of routine clinical care (de Vries, Benders, and Groenendaal 2013). Cranial US is readily available in the neonatal nursery and has been used extensively to assess the preterm brain. It is a relatively cheap, non-invasive, bedside neuroimaging tool available in nearly every hospital in the developed world. Traditionally, US has been used to detect major abnormalities, such as germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH), periventricular hemorrhagic infarction, post-hemorrhagic ventricular dilatation, and cystic periventricular leukomalacia. More recently, the use of different acoustic windows, such as the mastoid fontanel, allows for recognizing other lesion patterns such as CBH in the posterior fossa (Dudink et al. 2020).

MRI has been a valuable tool for monitoring development and pathology in the preterm brain (Dubois et al. 2020). The clinical application of conventional MRI has become increasingly common in the last 15-20 years (Smyser, Kidokoro, and Inder 2012). Since neuropathologic diagnosis is not available in preterm survivors, conventional MRI provides helpful information about the pattern of injury and dysmaturation within the neonatal brain (Hinojosa-Rodríguez et al. 2017). MRI is useful for assessing numerous pathologies including white matter injury (WMI), GMH-IVH, and CBH, and can help to predict outcome in these infants (Doria, Arichi, and Edwards 2014; de Vries, Benders, and Groenendaal 2013). Additionally, advanced macrostructural and microstructural MRI studies have shown differences between the preterm brain at term-equivalent age (TEA) and term born infants, confirming that the brain develops differently when born preterm (Ment, Hirtz, and Hüppi 2009). These advanced studies have been used to explore multiple neurodevelopmental mechanisms and link everyday neonatal intensive care exposures to vulnerabilities in the developmental trajectories of the preterm neonatal brain and their later neurodevelopmental outcomes (Back and Miller 2014; Dubois et al. 2020).

1.3.1 Overview of cranial ultrasound in preterm brain injury

Cranial US remains the first-line neuroimaging modality to examine the neonatal brain. It is less expensive than MRI and does not require patient transport and for the patient to remain still. As such, cranial US can be performed longitudinally as early as the first day of life and can offer insight into the onset and evolution of brain injuries. Originally, cranial USs were performed to visualize the ventricular system and to diagnose GMH-IVH and cystic periventricular leukomalacia (Pape et al. 1979). In standard neonatal cranial US examination the anterior fontanel is used as the acoustic window. More recently, the use of high-frequency transducers has improved visualization of both superficial and deep areas of the brain and additional acoustic windows, such as the posterior and mastoid fontanels, have extended visualization to areas less accessible via the anterior fontanel (van Wezel-Meijler, Steggerda, and Leijser 2010; Di Salvo 2001). Cerebellar hemispheres, cerebellar vermis, the fourth ventricle, and its plexus can be readily visualized through the mastoid fontanel (Fumagalli et al. 2020). Although it is not yet common, three-dimensional cranial US allows imaging of the entire brain in a single volumetric sweep and offers the capability of reconstructing images in the axial plane and performing volumetric analyses (Kurian et al. 2017).

1.3.2 Overview of MRI and MRI sequences

The primary origin of the MRI signal used to generate almost all clinical images comes from hydrogen nuclei, which consist of a single proton (Currie et al. 2013). The positively charged proton is constantly spinning, creating an electric current that generates its own magnetic field. Each proton's magnetic field is randomly oriented. However, when an external magnetic field is applied the protons align either with (parallel) or against (antiparallel) the external field. The summation of the spinning protons results in a longitudinal magnetic field which parallels the external magnetic field, which lies in the z-axis.

Radiofrequency pulses are switched on and off to disturb the protons so that they fall off their alignment with the external magnet. One result of the radiofrequency pulse activation is transverse magnetisation in which a new magnetisation vector is created in the x–y plane. As the protons eventually start to fall out of phase with each other they relax into their original lower energy state. Relaxation occurs in two different ways: (1) transverse magnetisation begins to

disappear, a process called transverse (or T2) relaxation and the longitudinal magnetisation starts to return to its original value, a process termed longitudinal (or T1) relaxation.

The rate at which longitudinal magnetisation is restored (i.e., T1-relaxtion) is dependent on the tumbling rate of the molecule in which the proton resides (Fullerton 1992). The tumbling generates its own fluctuating magnetic field, and the longitudinal magnetization restoration is more favourable when this fluctuating magnetic field is close to the Larmor frequency. Different molecules have different tumbling rates and thus differ in their efficiency at T1 relaxation. As not all protons return to their original energy state simultaneously, T1 relaxation is a continuous process. Plotting the recovery of longitudinal magnetisation is approximated by an exponential curve, called the T1 curve. T1 is a time constant describing the time taken for longitudinal magnetisation to regrow from 0 to approximately 63% of its final value after it has been tipped into the transverse plane.

Transverse relaxation reflects the process whereby protons fall out of phase in the x–y plane and transverse magnetisation decreases to 0. T2 is a constant describing the time taken for transverse magnetisation to decay to approximately 37% of its initial value. Spin–spin interaction, which denotes the influence of small magnetic fields from neighbouring nuclei on each other, causes a cumulative loss in phase and governs the speed of T2 relaxation for different tissues. Molecules with less spin–spin interaction have slower T2 relaxation times whereas larger molecules or more viscous liquids have more spin-spin and faster T2 relaxation times.

Tissue contrast is determined by differing signal intensities, which are governed by the T1 and T2 relaxation times of tissues within an image. An image in which the difference in signal intensity between tissues is predominantly due to differences in tissue T1 (or T2) relaxation time is referred to as a T1 (or T2)-weighted image.

1.3.3 MRI in preterm brain injury

Imaging the neonatal brain with MRI is both practically and technically challenging (O'Muircheartaigh et al. 2020). Over a matter of weeks, the brain changes in size and shape, tissue contrast changes, and transient developmental structures disappear (Kostović and Jovanov-Milosević 2006). The preterm cortex is seen as high signal intensity on T1 weighted imaging and low signal on T2 weighted imaging, reflecting its high cellular density due to immature neuronal arborization (Counsell et al. 2003). The subependymal germinal matrices are appreciable as a

prominent highly cellular grey-matter structure along the margins of the lateral ventricles. Unmyelinated cerebral white matter appears as high signal intensity on T2 weighted imaging and low signal on T1 weighted imaging due to its high free water content. Myelin is visible as high T1 signal in numerous white matter tracts and grey matter nuclei in the preterm brain due to the water within the myelin sheaths (Counsell et al. 2002; Barkovich 2000). Although the convoluted pattern of the cerebellum is seen from 30 weeks onwards and usually identified beyond 33 weeks, the cerebellar surface appears quite smooth until 31–32 weeks (Fogliarini et al. 2005). The EGL and ventricular zone germinal matrices of the cerebellum, in contrast to the subependymal germinal matrices, are not appreciable on MRI.

Injury to the neonatal brain can take on many forms visible on MRI. Cystic lesions appear as fluid filled areas with signal intensities similar to cerebrospinal fluid. Punctate WMI, which may include some axon necrosis, appears as areas of high T1 signal (Back 2017).

In adults, signal intensity of cerebral hemorrhage on MRI depends on the age of the blood, the type of hemoglobin present, and on whether or not the red blood cell membranes are intact (Bradley 1993). Deoxyhemoglobin has paramagnetic properties and is present in the first few days after intracerebral hemorrhage. It is responsible for early hemorrhage identification on MRI during the acute phase (Macellari et al. 2014). It appears as isointensity or slight hypointensity with a thin hyperintense rim in the periphery on T1 weighted imaging and hypointense with a hyperintense perilesional rim on T2. When the red blood cell is separated from the high oxygen environment of the circulation, deoxyhemoglobin undergoes denaturation to methemoglobin, and the heme iron becomes oxidized to the ferric form. In this early subacute phase, methemoglobin appears hyperintense and hypointense on T1 and T2 weighted imaging, respectively. In the late subacute phase, extracellular methemoglobin appears hyperintense on both T1 and T2 weighted imaging. Microglia then move in from the periphery within a few weeks and remove the iron from the extracellular methemoglobin; this indicates the beginning of the chronic phase when the heme iron is deposited peripherally as a rim of hemosiderin and ferritin, which is hypointense on both T1 and T2 weighted imaging. In practice, the phases are not so well-defined and the stages often coexist (Zyed, Hayman, and Bryan 1991).

Several other factors impact the timing of cerebral hemorrhage MRI signal changes. The location of the cerebral hemorrhage influences the evolution of MRI signal since cerebrospinal fluid has a higher pO_2 than brain parenchyma. As such, the deoxygenation of hemoglobin in

hemorrhages that occur adjacent to cerebrospinal fluid is slower. In preterm neonates, this may result in slower MRI signal changes in GMH-IVH and CBH, which typically occur in the subpial EGL, since both hemorrhages occur adjacent to cerebrospinal fluid. In addition, in newborns, the deoxygenation of oxyhemoglobin is slow because of the high affinity of fetal hemoglobin to oxygen and could theoretically result in delayed appearance of the hemorrhage (Zuerrer, Martin, and Boltshauser 1991). In practical terms, however, MRIs in preterm neonates are not typically undertaken until the neonate is stable from a respiratory standpoint which may only be at several weeks of life. At this point, some of the hemoglobin is degraded to hemosiderin and the hemorrhage appears as a mixture of low and high T1 and T2 signals (Rutherford 2002).

1.3.4 Segmentation of the neonatal brain

Quantitative neuroimaging studies are increasingly being used to assess brain development in the perinatal period. Segmentation of the brain in MRI is required to quantitatively assess regional brain structures (Makropoulos, Counsell, and Rueckert 2018). Quantitative measurements of volume and cortical surface, for instance, are important to characterise normal brain development and can predict neurodevelopmental outcome (Boardman et al. 2010). Manual segmentation of MRI images is extremely time consuming and subject to limitations around reproducibility. As such, there is a need for accurate automatic techniques. Automatic segmentation of the neonatal brain is more challenging than the adult brain due to lower contrast-to-noise ratio, lower signal-to-noise ratio due to the small size of the brain, tremendous variation in brain shape as a result of rapid brain development during this period, and motion artifacts during image acquisition (Makropoulos, Counsell, and Rueckert 2018).

Brain atlases are often used as training data in the automatic segmentation process. Atlases are labelled data that specify the location of different brain structures. There are two types of atlases: single-subject, manually delineated atlases that assign a single tissue label at each voxel and probabilistic atlases that define the structure probability of each tissue at each voxel by averaging automatically derived segmentations. After registering the atlas template and the target image, the atlas labels are propagated to the target image. Label propagation has been extended to multiple atlases to better account for anatomical variability (Cabezas et al. 2011; Pipitone et al. 2014). Brain structures, such as the hippocampus or cerebellum, brain tissues,

such as grey matter or white matter, or brain damage, such as WMI, can then be segmented (O'Muircheartaigh et al. 2020; Guo et al. 2015). Automatic segmentation for CBH in preterm neonates has not been reported.

1.3.5 Lesion-symptom mapping

In a classical lesion analysis, the aim is to infer the function of a region of the human brain by observing the functional consequences of damage to that brain region (de Haan and Karnath 2018). This method of studying the correlation between a behavioural disorder and the location of brain injury was first developed by Paul Broca in 1861. Broca's claim that the third convolution of the inferior frontal gyrus is involved with speech production was supported by the brain of a patient who had been able to produce only one syllable (Rorden and Karnath 2004). Using MRI, there are several methods to draw conclusions about lesion topography and behavioural or functional outcome and these have been applied in adults with cerebellar lesions (Timmann et al. 2013; Stoodley et al. 2016).

Subtraction analysis is the simplest way to quantify group differences based on behavioural cutoffs and is performed on a voxel-wise basis. In subtraction analysis, the lesion overlap map of patients without the deficit of interest is subtracted from the lesion overlap map of patients showing the deficit of interest. Subtraction analyses are superior to simple overlap analyses that focus on only those patients that show the disorder of interest, because overlap analyses might simply highlight regions that are vulnerable to injury but not necessarily functionally important (de Haan and Karnath 2018). The resulting subtraction image specifically highlights regions that are damaged and result in functional impairment. Subtraction analyses are purely descriptive and allow no statistical inference.

Voxel-wise odds ratio maps are more quantitative than subtraction maps in that they reflect the risk of developing an impairment with a lesion at a specific voxel (Sprenger et al. 2012). Odds ratio maps, which are described in more detail below (section 2.6), also suffer from lack of dedicated statistical analysis to distinguish chance findings from findings truly predictive of a deficit.

Voxel-wise statistical lesion-behaviour mapping analysis (VLSM) allows for dedicated statistical analysis that demonstrates whether differences in lesion frequency (for example, between patients who show the deficit of interest and patients who do not) might be due to

chance or might represent a true predictor of behaviour (Rorden and Karnath 2004). In VLSM, a statistical test is performed at each to relate voxel status (injury/no-injury) and behaviour of interest and the VLSM map shows z-scores of lesion voxels for that behaviour (Bates et al. 2003). When the behavioural data is continuous, the behavioural data of the group of patients with damage at a given voxel is compared to the behavioural data of the group of patients without damage at that same voxel (de Haan and Karnath 2018). When the behavioural data is dichotomous, a given voxel's status (injured/non-injured) is statistically related to 'behavioural status' (deficit present vs. deficit not present). During VLSM, the same statistical test is applied to many individual voxels. As such, there is a high probability of observing at least one false positive and correction for multiple comparisons is informative (Rorden, Karnath, and Bonilha 2007).

1.4 Neurodevelopment in preterm newborns

Newborns born very preterm are at risk for both death and neurodevelopmental disability. The importance of evaluating the neurodevelopmental outcomes of preterm survivors was recognized early on. Dr. Julius Hess published the first outcome study of preterm newborns in 1953 and reported that 85% of the survivors were of at least "average" physical and mental development (Hess 1953). As the rates of survival improve (Stoll et al. 2015; Garfinkle et al. 2019), there is little evidence that the neurodevelopmental outcomes for this population have similarly been improving (Cheong et al. 2017; Doyle 2018). In a multicentre longitudinal study over 20 years, Stoll et al. reported only modest reductions in several short term morbidities, including severe GMH-IVH and periventricular leukomalacia (Stoll et al. 2015). Since many trials and cohort studies of preterm populations evaluate *early* outcomes at 18 to 24 months of age, they are limited in their ability to describe the full neurodevelopmental impact of preterm birth (Roberts et al. 2010). Moreover, parents, families, and society are interested in knowing the long-term developmental profile of very preterm children in order to assist with decision making and plan for health care and educational needs (Kilbride et al. 2017).

Compared with the limited repertoire of the infant and toddler, at preschool-age the human brain is capable of a full range of complex tasks that can be evaluated reliably and provide a good estimate of lifelong functioning (Synnes and Hicks 2018). By school age, the researcher has a variety of assessment tools to choose from. Children's abilities and dispositions

can be measured on a continuous or categorical scale for a breadth of domains, including motor, visuomotor, cognitive, language, executive function, behaviour, and vision. In toddlerhood, the Bayley Scales of Infant and Toddler Development, third edition and earlier versions, measures infant development, which has a poor predictive ability for school-age cognitive abilities (Hack et al. 2005). In addition, degree of disability is not static. In the EPICure very preterm cohort assessed at 30 months and 6 years of age, 40% of those with a severe disability at 30 months changed category and 25% initially considered as disability-free were classified as having a moderate to severe disability later on (Marlow et al. 2005). Although studying 2-year outcomes is less resource-intensive, there is general consensus that longer term assessments inform more valid and relevant outcomes (Hintz, Newman, and Vohr 2016).

1.4.1 Motor and visuomotor development

Motor impairments are common in the preterm population. CP, the most severe form of motor impairment, is broadly used to describe a group of movement and posture disorders related to a static insult to the fetal or infant brain that may be accompanied by epilepsy and disorders of sensation, perception, cognition, communication, and behaviour (Rosenbaum et al. 2007). Preterm birth is the most frequent cause of CP (Shevell, Dagenais, and Oskoui 2013). Importantly, approximately two-thirds of preterm children who have CP can be described by a Gross Motor Function Classification System Score of I or II, which denotes children who can ambulate independently (Hafström et al. 2018). The incidence of CP in very preterm newborns, which stands between 10-15%, may be decreasing (Robertson, Watt, and Yasui 2007; Oskoui et al. 2013). An Australian CP registry review from the 1970s to 2004 has shown that since the early 1990s, CP rates have stabilized or decreased (Reid, Carlin, and Reddihough 2011). However, developmental coordination disorder, a disorder of motor coordination not due to CP or other medical conditions that affects daily functioning, is also common in very preterm children (Edwards et al. 2011). In contrast to CP, non-CP motor impairment may be increasing over time. In three consecutive cohorts of extremely preterm newborns born in 1991-1992, 1997, and 2005, the prevalence of non-CP motor-impairment increased from 13%, to 15%, and to 26%, respectively (Spittle et al. 2018).

Motor deficits in coordination, balance, visual spatial, and visual motor integration in preterm children are better evaluated at a later age (Williams, Lee, and Anderson 2010).

Although the motor difficulties associated with developmental coordination disorder are often considered “minor” impairments in comparison to CP, they nonetheless can have significant functional and social impact on the child. Detailed analysis of simple pointing movements has shown that movement programming and execution were slowed in school-age preterm children (Van Braeckel et al. 2008). Preterm children also perform less accurately and less rapidly on visuospatial tasks (PreterButcher et al. 2012).

1.4.2 Cognitive and language development

Cognitive abilities, as measured by intelligence and academic performance, are negatively affected by preterm birth. Cognitive impairment has been reported in young children, adolescents, and adults after preterm birth (Rogers and Hintz 2016; Pyhala et al. 2011). Preterm children show considerable academic difficulties: in a meta-analysis, preterm children were 3 times more likely to receive special educational assistance and scored significantly worse in arithmetic, reading, and spelling (Twilhaar, de Kieviet, et al. 2018). A recent meta-analysis of 71 cohort studies reported that very preterm children had intelligence quotient (IQ) scores 0.86 standard deviations (SD) (95% CI, −0.94 to −0.78) lower than controls at age 5–20 years, which was equal to a 13-point deficit (Twilhaar, Wade, et al. 2018). A direct comparison of intelligence in consecutive cohorts from the same geographical region comes from the Victorian Infant Collaborative Study group for extremely preterm neonates born in 1991–1992, 1997, and 2005. The mean difference in IQ between extremely preterm children and controls was not significantly different for births in 2005 compared with births in the 1990s at age 8 years. Similarly, there was no significant difference in the rate with cognitive impairment (IQ <−2 SD of controls) (Cheong et al. 2017).

A key question is whether cognitive and executive function deficits observed in early childhood persist into adolescence and adulthood or whether very preterm children catch up to their peers as they develop. Meta-analyses have reported that mean differences in IQ do not narrow with age (Allotey et al. 2018; Twilhaar, Wade, et al. 2018). However, the meta-analyses are based on successive cross-sectional cohorts rather than an analysis of individual developmental trajectories across time (Wolke, Johnson, and Mendonça 2019). Studies that have tracked the development of preterm children from birth through adulthood have not detected a developmental catch-up. The EPICure study examined IQ in extremely preterm children at 2, 6,

11, and 19 years of age alongside term controls. Deficits in IQ remained stable over time and an 18-point deficit remained at 19 years of age (Linsell et al. 2018). Significant deficits in executive function have been observed in very preterm cohorts in adulthood (Eryigit Madzwamuse et al. 2015). As such, preterm children do not catch up with their peers, and substantial deficits in achievement are evident throughout schooling.

Intelligence is only one of several determinants of academic success. Academic achievement is often lower than anticipated by the IQ in preterm children and may be explained by frequently identified challenges in executive functioning, attention, visuomotor skills, and verbal memory in preterm children (Synnes and Hicks 2018). Longitudinal school attainment tests have found that preterm children showed improvements between ages 7 and 11, closing the gap slightly with term-born peers, but not at ages 11 and 14 (Odd et al. 2019). Learning difficulties have been reported in 50% to 70% of very low birth weight school-age children. Very preterm birth has a pervasive effect on learning that spans performance in all school subjects (Wolke, Johnson, and Mendonça 2019). The greatest deficits are found in mathematics relative to other subjects (Allotey et al. 2018; Twilhaar, Wade, et al. 2018). The specific mathematics challenges may be due to preterm children's general cognitive deficits, such as impairments in working memory and visuospatial skills, rather than deficits in numerical skills (Simms et al. 2015).

Language is important for social and academic success. Language-impaired children perform more poorly in reading and language scores at school-entry (Botting, Simkin, and Conti-Ramsden 2006). In early language development, expressive language (production) and receptive language (comprehension) are often considered separately. In toddlerhood, both receptive and expressive language abilities are more delayed than motor or cognitive abilities in preterm neonates (Synnes et al. 2017). In later childhood, expressive language, receptive language processing, and articulation deficits are common (Barre et al. 2011). In a longitudinal study, very preterm children displayed language difficulties compared with term controls throughout childhood into early adolescence, with no evidence of developmental "catch-up" (Nguyen et al. 2018). Similarly, there was no significant difference in the rate with cognitive impairment In addition, deficits in phonologic short-term memory are seen (Ortiz-Mantilla et al. 2008).

1.4.3 Behaviour problems

Studies into school age and later childhood have identified challenges with social and behavioural functioning following preterm birth. The term 'behaviour problems' is currently used for a wide spectrum of difficulties in behavioural self-regulation, including hyperactive/aggressive behaviour; attention, sleep, and sensory sensitivity problems; and emotional disorders including anxiety, depression, and somatic symptoms (Arpi and Ferrari 2013). At preschool and early school age, these behaviour problems typically manifest clinically as inattention, hyperactivity, and anxiety (Rogers and Hintz 2016). Extremely preterm infants have a three-fold chance of developing attention deficit and hyperactivity disorder relative to term children (Johnson and Marlow 2011). Importantly, although differences between preterm and term attention capacities may be evident before school age this gap widens over time (van de Weijer-Bergsma, Wijnroks, and Jongmans 2008). Preterm children also have higher rates of screening positive for autism spectrum disorder and of being formally diagnosed with autism spectrum disorder compared with term children (Kuban et al. 2009; Brumbaugh et al. 2020). Autism spectrum disorder refers to a brain-based neurodevelopmental condition characterized by impairments in social interaction and communication in the presence of restricted, repetitive behaviours or interests (Anagnostou et al. 2014).

Preterm children have increased risks of both internalizing and externalizing problems, which can be evaluated on the Child Behaviour Checklist for ages 1.5–5 (CBCL) (Hornman et al. 2016). The CBCL is a frequently used parental questionnaire that detects emotional and behavioural problems (Achenbach and Rescorla 2000). "Externalizing problems" denote aggressive/hyperactive behaviour and attention problems whereas "internalizing problems" include anxious/depressed symptoms, somatic complaints, and withdrawal (Achenbach and Edelbrock 1978). A recent meta-analysis using these measures revealed increased internalizing and externalizing problems in extreme preterm children compared to controls (Mathewson et al. 2017). The incidence of total behaviour problems within the clinical range, which indicate symptoms of psychopathology, has been consistently reported as higher in preterm children (Arpi and Ferrari 2013).

1.5 Brain injury in preterm neonates

The brain of the preterm newborn is in a state of rapid development and is susceptible to three overarching and overlapping forms of brain injury: WMI, GMH-IVH, and CBH (**Figure 1.1**). CBH will be discussed in a subsequent section in more detail.

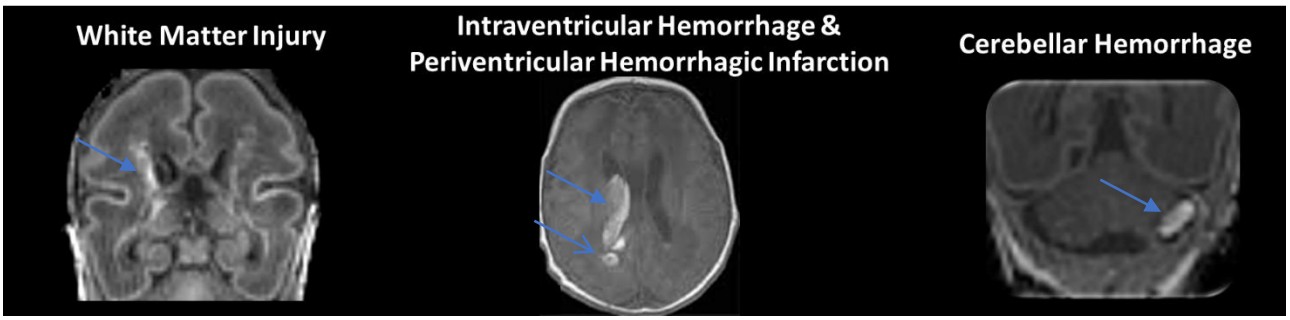

Figure 1.1 Spectrum of preterm brain injury on MRI. Left panel: severe periventricular white matter injury (arrow). Middle panel: severe intraventricular hemorrhage (arrow) and periventricular hemorrhagic infarction (open arrow). Right panel: large cerebellar hemorrhage (arrow).

1.5.1 White matter injury

WMI is one of the commonest forms of brain injury in preterm neonates (Kidokoro, Neil, and Inder 2013). It is linked in experimental models and clinical studies to hypoxia-ischemia, infection, and inflammation (Back and Miller 2014). The preterm brain's vulnerability to WMI is closely tied to the timing of the insult as over the third trimester, certain cell types are selectively more susceptible to injury (Back, Riddle, and McClure 2007). Moreover, a wide array of clinical factors may together sensitize the brain to injury. These factors include antepartum events, nutritional status, systemic illnesses, painful procedures and exposure to glucocorticoids, sedatives, and prenatal exposure to drugs of abuse (Podrebarac et al. 2017).

WMI encompasses two major categories of pathology: focal necrosis, which itself ranges from cystic to microscopic, and diffuse non-necrotic lesions (Back 2017; Guo et al. 2017). Within focal cystic necrosis, the diagnostic category of periventricular leukomalacia is the most severe. Focal cystic necrosis typically occurs in the white matter adjacent to the ventricles and involves degenerative axons and phagocytic macrophages on pathologic examination. The large necrotic lesions of periventricular leukomalacia have become uncommon in contemporary

cohorts of preterm neonates (Gano et al. 2015). Focal microscopic necrosis remains a component of contemporary WMI and is observed in one-third of histopathologic cases (Buser et al. 2012) .

Punctate and diffuse non-necrotic WMI encompass the predominant lesions in most preterm neonates on MRI. Punctate WMI appears as areas of focal high signal changes on T1-weighted images and sometimes low T2 signal (Miller et al. 2005). The burden of punctate WMI is best assessed on early MRI, rather than MRI at TEA, as signal changes tend to resolve over time (Dyet et al. 2006). Punctate WMI has a typical topology, with most lesions occurring in the periventricular regions (Guo et al. 2017). Pathologically, diffuse WMI features selective degeneration and regeneration of pre-oligodendrocytes, a mitotically-active progenitor cell-line that peaks as a cell line between 23 and 32 weeks' gestation (Back et al. 2001). In preterm diffuse WMI, the pre-oligodendrocytes that degenerate then fail to mature to myelin-forming oligodendrocytes; however, axons are spared (Buser et al. 2012). As such, the main cause of myelination failure involves a disrupted cellular response whereby pre-oligodendrocytes fail to differentiate. Over the last two decades, the prevalence of WMI seems to be decreasing. In a cohort of very preterm newborns, the prevalence of moderate/severe focal non-cystic WMI decreased by 11% per year from 1998 to 2011 (Gano et al. 2015). Although the authors could not identify a care practice change responsible for the reduction in WMI over time, they speculated that unmeasured changes in perinatal and neonatal care could account for it.

WMI has been associated with motor, cognitive, and language impairments in early childhood (Shah et al. 2008). The presence of cystic WMI and the number of lesions is predictive of early neurodevelopment. In particular, lesions affecting the corticospinal tracts are associated with CP (Martinez-Biarge et al. 2019). Preterm children with adverse early motor outcome, but not cognitive or language outcomes, have a larger burden of WMI volume. In addition, quantitative maps of preterm WMI suggest that frontal lesions are most predictive of adverse outcomes (Guo et al. 2017). At preschool age, WMI anterior to the midventricle line predicted an adverse motor outcome (Cayam-Rand et al. 2019).

1.5.2 Germinal matrix hemorrhage and intraventricular hemorrhage

Subependymal GMH-IVH is common and its incidence is inversely proportional to GA. The bleeding originates in the subependymal germinal matrix, from which cortical neuronal and glial cell precursors develop during the late second and early third trimesters (Del Bigio 2011).

The pathogenesis of GMH-IVH, although incompletely understood, is thought to share some aspects with that of CBH and is most often considered to arise from the thin-walled veins (Ghazi-Birry et al. 1997; Volpe 2009). The vasculature within the germinal matrix is described as an "immature vascular rete" as the vessels are primitive and cannot be classified as arterioles, venules, or capillaries. When cell division and migration are complete, the germinal matrix progressively involutes and almost completely regresses by TEA (Inder, Perlman, and Volpe 2018).

The predisposition of the very preterm neonate to germinal matrix hemorrhage is due to several factors: arterioles lack autoregulation and exist in a pressure-passive state; capillaries lack a supporting basement membrane; and extravascular tissue pressure in the first few days of extrauterine life is low (Ment, Stewart, et al. 1995). Thus, elevated venous pressure or fluctuations in cerebral blood flow emanating from cardiorespiratory disturbances may trigger GMH-IVH (**Figure 1.2**). Ment et al. have suggested that the germinal matrix vessels change significantly over the first days after birth with an increase in the basement membrane integrity. The rapid ex-utero maturation of the germinal matrix vessels may be one of the reasons that GMH-IVH occur during the first few days after preterm birth.

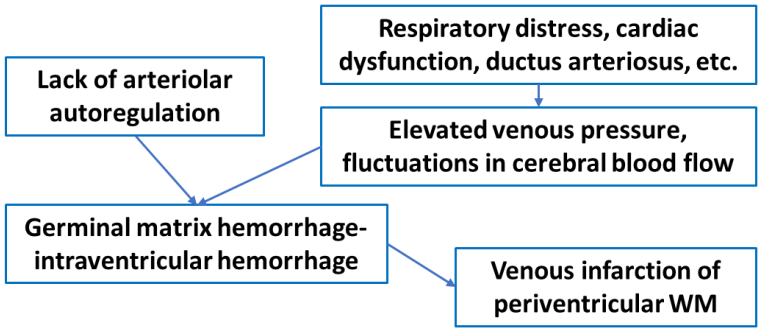

Figure 1.2 Pathophysiology of germinal matrix hemorrhage-intraventricular hemorrhage

The risk period for GMH-IVH is highest in the first 3 or 4 days of life (Paneth et al. 1993). Studies with serial US describe the onset of GMH-IVH at a mean of 24–48h after delivery. Cranial US examinations are typically performed in the first week of life to detect GMH-IVH and the images are used to classify GMH-IVH according to the algorithm adapted by Papile et al. in 1978 (Papile et al. 1978). Grade I GMH-IVH is limited to the subependymal region and is truly an isolated germinal matrix hemorrhage; grade II GMH-IVH contains blood

in the ventricles without ventricular distension; and grade III GMH-IVH shows enlargement of the ventricles secondary to distension. The classic grade IV GMH-IVH arises from venous infarction of the periventricular white matter rather than from a direct extension of the GMH-IVH into the parenchyma. Some small GMH-IVH in the posterior horns of the lateral ventricles may be absent on US but detectable on MRI (Maalouf et al. 2001).

Although there was a reduction in the incidence of GMH-IVH in the 1990s, over the last decade, the incidence of GMH-IVH seems to have remained stable (Heuchan et al. 2002; Inder, Perlman, and Volpe 2018). The incidence of GMH-IVH is inversely related to GA and birth weight (Thorp et al. 2001). Some of the clinical factors associated with GMH-IVH include respiratory distress, pneumothorax, asphyxia, left ventricular dysfunction, patent ductus arteriosus, hypotension, hypothermia, and hyperosmolarity (Ballabh 2014). Prenatal administration of steroids and maternal transfer to a tertiary level hospital are the best means of preventing GMH-IVH (Ment, Oh, et al. 1995; Thorp et al. 2001). Currently, studies have focused on gentle resuscitation and gentle care and handling and positioning in the first few days of life as a means of preventing GMH-IVH (de Bijl-Marcus et al. 2019). Delayed cord clamping, in which clamping of the umbilical cord is delayed by 60 seconds after birth rather than immediately clamped, may also reduce the incidence of GMH-IVH (Backes et al. 2014). At birth, neonates undergo a dramatic physiological transition driven by the shift in respiratory function from the placenta to the lungs; delayed cord clamping may reduce GMH-IVH by improving dynamic cerebral autoregulatory function during the transition (Vesoulis, Liao, and Mathur 2019). Recent, large randomized controlled trials, however, have not detected a neuroprotective effect in delayed cord clamping (Tarnow-Mordi et al. 2017).

Grade I and II GMH-IVH are associated with a statistically higher likelihood of later moderate or severe impairment, but the vast majority of neonates with mild GMH-IVH do not have such impairments (Mukerji, Shah, and Shah 2015). Neonates with Grade III GMH-IVH, and especially those with associated periventricular hemorrhagic infarction or posthemorrhagic ventricular dilatation, are at higher risk for poor neurodevelopmental outcome (Leijser et al. 2018).

In contrast to WMI and GMH-IVH, which have been frequent targets of investigation and experiments, CBH has been less often studied in the preterm population.

1.6 Cerebellar development, organization, functional topography, and injury

An understanding of the developmental processes that occur in the immature cerebellum and its ultimate anatomic and functional organization is essential to contextualize CBH in the preterm neonate. The cerebellum is vulnerable during the preterm period because the cerebellum is in a state of rapid development in the third trimester (Volpe 2009). During the third trimester, cerebellar volume increases fivefold and the cerebellar surface area increases 20-fold (Chang et al. 2000; Volpe 2009). Cerebellar proliferation continues into the second postnatal year, by which point the cerebellum contains the majority of all neurons in the central nervous system (Azevedo et al. 2009). To accommodate such a vast number of cells in a confined space, the cerebellar cortex is folded into multiple lobes and lobules.

1.6.1 Cerebellar development and vasculogenesis

There are two primary progenitor zones in the developing cerebellum for cerebellar neurons: the rhombic lip, which forms adjacent to the fourth ventricle in the dorsolateral part of the alar plate, and the ventricular zone, which forms along the lining of the fourth ventricle on the ventral surface of the alar plate (ten Donkelaar et al. 2003; Haldipur, Dang, and Millen 2018). Cells from the rostral aspect of the rhombic lip migrate to the superficial aspect of the cerebellum, beneath the pial membrane, to form the EGL (Martinez et al. 2013). The EGL, therefore, constitutes a secondary germinal zone, or transit amplifying center. Neurogenesis in the ventricular zone peaks in the first trimester whereas neurogenesis in the EGL appears at the end of the embryonic period and persists for several months to two years after birth (**Figure 1.3**). The Purkinje cells, GABAergic projection neurons, and later the Golgi, stellate and basket interneurons and Bergmann glia arise from the ventricular zone whereas the granule cells, glutaminergic projection neurons, and unipolar brush cells arise from the EGL (Carletti and Rossi 2007).

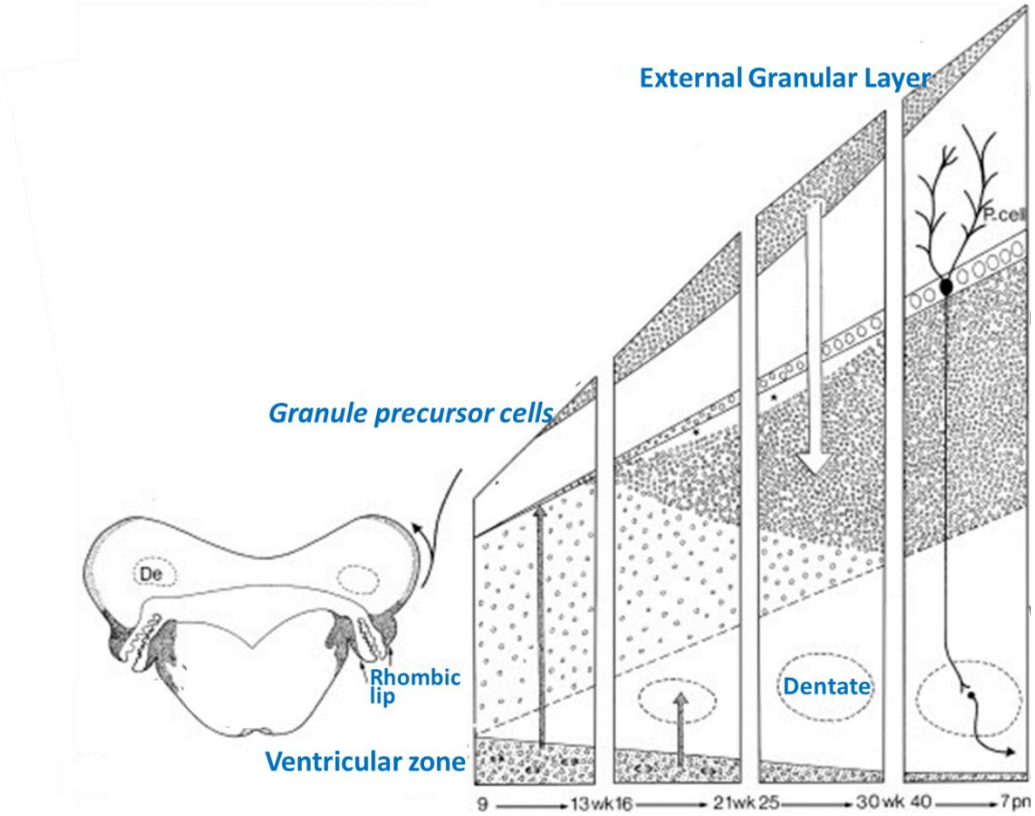

Figure 1.3 Overview of histogenesis of the cerebellum. Left panel: transverse section demonstrating the rhombic lip at the level of the fourth ventricle. Right panel: formation of the several layers of the cerebellum from the early fetal period till 7 weeks postnatally. Figure was adapted from ten Donkelaar *et al*. (2003) in *J Neurol*; reproduced with permission from SpringerLink.

The EGL comprises two sublayers: an external proliferating zone and an inner differentiating zone (Haldipur, Dang, and Millen 2018). Neuronal precursor proliferation peaks in magnitude during the third trimester in the EGL, induced by Sonic hedgehog secreted by differentiating Purkinje cells (De Luca et al. 2015). As a result, the EGL is susceptible to myriad insults during the preterm period. In mice, peak EGL proliferation occurs around postnatal day 7 in mice, which approximately corresponds to the first half of the third trimester in humans. Math-1 is a transcription factor maintained throughout proliferation of the EGL. Temporal fate mapping of rhombic lip progenitors with Math-1 demonstrated that granule cell precursors generated the earliest tend to populate the anterior lobes of the cerebellum while those exiting the rhombic lip later populate more posterior regions (Machold and Fishell 2005). As precursor

neurons exit the cell cycle, they exit the EGL by migrating radially inward to settle beneath the developing Purkinje cell layer to form the internal granule layer, resulting in the final laminar arrangement of the mature cerebellum.

The ontogeny of the cerebellar vasculature may also play an important role in the topography of preterm CBH and as such is worth describing. Early in embryogenesis, only the superior cerebellar arteries supply the cerebellar rudiment (Padget 1948). The posterior inferior cerebellar artery (PICA) is only visualizable in the human embryo several weeks later (Macchi et al. 2005). In addition, the ultimate course of the PICA is the most highly variable among the cerebellar arteries. Macchi et al. speculated that for these reasons, the PICA may represent an acquired source of vascularization via angiotrophic vasculogenesis (Macchi et al. 2005). In adults, the superior cerebellar artery perfuses the anterior lobe while the PICA perfuses the posterior lobe (**Figure 1.4)** (Amarenco 1991). It is possible that as an acquired source of vasculogenesis the is more susceptible to the hemodynamic perturbations typical of prematurity, although there is currently little experimental evidence to support this hypothesis (Haines, Wang, and Pierson 2013).

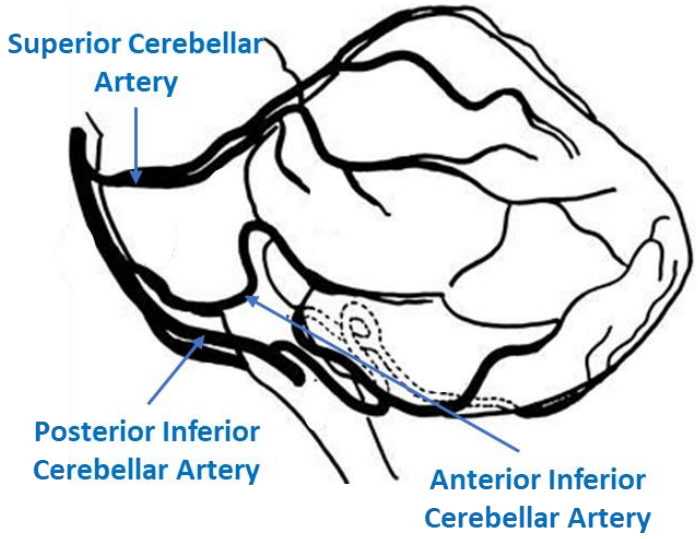

Figure 1.4 Arterial supply of the adult cerebellum. Figure was adapted from Amarenco (1991) in Neurology; reproduced with permission from Wolters Kluwer Health, Inc.

The posterior cerebellum not only has a distinct arterial supply, it also has a separate venous return. The superior cortical surface of the cerebellum is drained by the superior vermian veins and the superior hemispheric veins, which empty into the great vein of Galen in the

midline (Delion, Dinomais, and Mercier 2017; Rhoton 2000). The posterior inferior cortical surface of the cerebellum is drained by the inferior hemispheric veins, which empty into the transtentorial sinuses, and the inferior vermian veins, which empty into the straight sinus directly or via the medial transtentorial sinuses.

1.6.2 Cerebellar organization

The cerebellar cortex is organized into three rostrocaudally oriented compartments: the midline vermis, paravermis, and lateral hemispheres. The cerebellar cortex connects to the brainstem via three paired cerebellar peduncles, by way of the cerebellar deep nuclei. The cerebellar deep nuclei are embedded in the white matter of the cerebellum. These nuclei include, medially to laterally, the fastigial, interpositus (globose and emboliform), and dentate nuclei. The cerebellar cortex projects to the deep nuclei in a medial to lateral pattern: the midline vermis projects to the medial fastigial nuclei; the paravermal regions project to the interpositus nuclei; and the lateral hemispheres project to the dentate nuclei. The final cerebellar output arises from these deep cerebellar nuclei via the superior and inferior peduncles. The cerebellum projects to specific cerebral destinations and receives input back from these same regions, and thus forms reciprocal and functional circuits, or closed loops (Strick, Dum, and Fiez 2009).

The primary fissure divides the cerebellar hemispheres into the anterior and posterior lobes and the posterolateral fissure divides it into the flocculonodular lobe. The cerebellar hemispheres are further folded into multiple lobules which are in turn subdivided into folia (Ashida et al. 2018). There are 10 lobules in the cerebellar cortex: lobules I–V represent the anterior lobe; lobules VI–IX the posterior lobe; and lobule X the flocculonodular lobe (Stoodley and Schmahmann 2010). Lobule VII comprises almost 50% of the cerebellar cortex in humans and is subdivided into crus I, crus II, and VIIB (**Figure 1.5**) (Diedrichsen et al. 2009; Park et al. 2014).

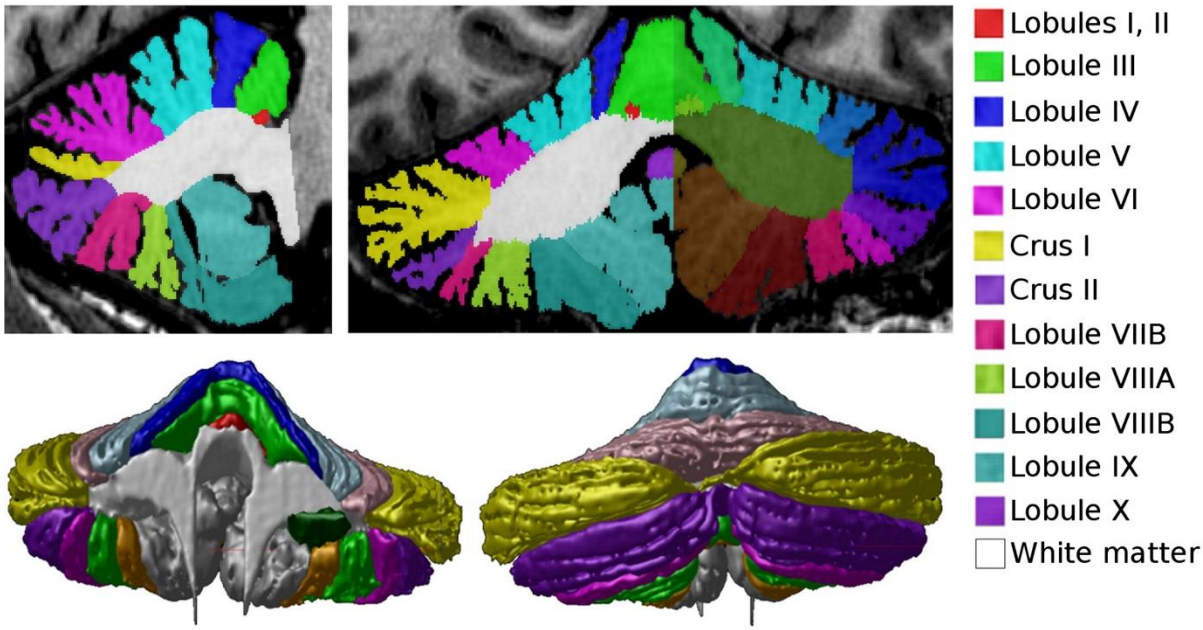

Figure 1.5 Segmented MRI T1-weighted images of the adult cerebellum. Top panel: cerebellar lobules defined according to fissures with the left and right hemispheres containing a different set of labels in a sagittal (left) and coronal (right) section. Bottom panel: 3D surface representation of the cerebellar lobules. Figure was adapted from Park et al. (2014) in NeuroImage; reproduced with permission from Elsevier.

Cytoarchitecturally, the cerebellar cortex is arranged into three layers: from superficial to deep these are known as the molecular layer, the Purkinje cell layer, and the granular layer. These three cortical layers contain five main cell types, among others: Purkinje, stellate, basket, Golgi, and granule cells. Granule cells are glutaminergic/excitatory while the others are GABAergic/inhibitory (Geurts, De Schutter, and Dieudonné 2003). Purkinje cells provide the sole outflow from the cerebellar cortex in the form of an inhibitory projection to the cerebellar nuclei.

1.6.3 Functional topography

Accumulating evidence indicates that the role of the human cerebellum extends considerably beyond motor control to include nonmotor behaviours. This conclusion emanates principally from neuroimaging studies showing cerebellar involvement during a range of nonmotor tasks and clinical populations in whom cerebellar damage produces nonmotor deficits in cognition and behaviour (Schmahmann 2019).

The cerebellum is reciprocally connected with sensorimotor and association regions of the cerebral cortex via the feedforward cortico-ponto-cerebellar pathway and the feedback cerebello-thalamo-cortical pathway. Sensory and motor projections to the cerebellum reveal body maps in the anterior lobe and lobule VIII of the posterior lobe. The remaining lobules of the posterior lobe of the cerebellum are linked with the parietal and prefrontal cortices (Stoodley and Schmahmann 2009). Much of our knowledge around the functional organization of the human cerebellum originates from task-based and resting state functional MRI (fMRI) studies. In task-based fMRI studies, activations related to cognitive processes are usually observed in the lateral posterior lobe, spanning lobule VI and Crus I/II of lobule VII. Studies of affective processing demonstrate cerebellar activation in more medial regions of the lateral posterior lobe (Argyropoulos et al. 2020; Buckner et al. 2011). In order to understand the contribution of the cerebellum to the visual guidance of movement, Glickstein et al. injected a label into the pontine visual cells of monkeys. They discovered antegrade labeled cells in lobule IX of the posterior lobe of the cerebellum, suggesting that this region is important for visuomotor coordination (Glickstein et al. 1994).

Projections from the cerebellar hemispheres to the dentate nuclei are also organized according to their destinations in the cerebral cortex. The dorsal dentate projects to supplementary and primary motor cortices while the ventral dentate projects to prefrontal cortices (Dum and Strick 2003; Clower, Dum, and Strick 2005). In other words, the dorsal dentate nucleus is involved with motor function whereas the ventral dentate nucleus is involved with higher-order processing (Bernard et al. 2014). On task-based fMRI, ventral regions of the dentate nucleus were activated for performance of cognitive tasks whereas dorsal regions of the dentate were predominantly activated by finger tapping (Küper et al. 2011). On resting state fMRI, there were two distinct motor and cognitive networks within the dentate nucleus (Bernard, Orr, and Mittal 2016).

Functional and structural imaging studies have revealed regional differences in neonatal and childhood development within the cerebellum. Recently, Herzmann et al. demonstrated via resting state fMRI that cortico-cerebellar functional connectivity is well-established by term (Herzmann et al. 2019). Preterm birth was associated with reduced correlation magnitudes, but no alterations in cortico-cerebellar functional connectivity topography. One important difference between functional organization of the cerebellum during the neonatal period relative to that of

the adult was discovered in the somatomotor network. In the adult, the cerebellar sensorimotor network is located in lobules I–V of the anterior lobe and lobule VIII of the posterior lobe (Buckner et al. 2011). In contrast to adult studies, the study by Herzmann et al. revealed the inferior posterior cerebellum to be positively correlated with the somatomotor cortex in neonates but they did not find evidence for somatomotor representation in the anterior lobe of the cerebellum. The authors speculated that the somatomotor network and with it the anterior lobe of the cerebellum matures over the first years of life. This discrepancy between the neonatal and adult somatomotor representation in the cerebellum may herald discrepant deficits from similarly located injuries between the two groups. In a longitudinal study of children and adolescents, Tiemeier et al. demonstrated that the posterior cerebellum maturation peaks later than that of the anterior cerebellum (Tiemeier et al. 2010). Indeed, cerebello-frontal networks show continued development into young adulthood whereas cerebello-motor networks do not show further changes over time in adolescence (Bernard, Orr, and Mittal 2016).

1.6.4 Adult cerebellar infarct

In the adult, cerebellar functional topography is readily examined when the effects of cerebellar injury or disease are studied in clinical populations. Infarcts impacting the superior cerebellar artery, which implicate the anterior cerebellar lobe, are more likely to cause limb and gait ataxia. In contrast, infarcts impacting the PICA, which perfuses most of the posterior lobe of the cerebellum, are more likely to result in the cerebellar cognitive affective syndrome (CCAS) (Tedesco et al. 2011; Amarenco 1991). The anterior inferior cerebellar artery perfuses the ventral surface of the cerebellum and the lower pons and occlusion of this artery results in a vestibular syndrome termed the lateral pontine syndrome (Kumral, Bayülkem, and Evyapan 2002). In adults, posterior lobe infarcts occur more often than anterior lobe infarcts (De Cocker et al. 2015).

The CCAS is characterized by deficits in language, visual spatial function, executive function, and affective dysregulation following cerebellar damage. A recent voxel-based lesion symptom-mapping study reported that patients with cerebellar motor syndrome but no cognitive deficits had damage to the anterior lobe with spared posterolateral hemispheres; the inverse pattern was seen in patients with CCAS but normal motor function (Stoodley et al. 2016). Patients with both the cerebellar motor syndrome and CCAS had lesions that covered anterior

sensorimotor regions and posterior cognitive cerebellar lobules, including damage to the deep cerebellar nuclei. These findings suggest good agreement between functional connectivity and lesion-deficit studies of the adult cerebellum.

1.7 Preterm cerebellar hemorrhage

1.7.1 Epidemiology and diagnosis with imaging

CBH is an increasingly recognized complication of preterm birth and ranges in size from punctate lesions to larger hemispheric and vermian hemorrhages (Tam 2018). The original reports of CBH were driven by post-mortem studies (Perlman et al. 1983; Pape, Armstrong, and Fitzhardinge 1976). In the mid-1990s, routine posterior fossa imaging through the mastoid fontanel became more commonly instituted to improve the ultrasonographic visualization of the posterior fossa in neonates (Merrill et al. 1998). These CBH visualized on US have typically been associated with adverse neurodevelopmental outcomes as only larger CBH can be visualized on cranial US (**Figure 1.6**).

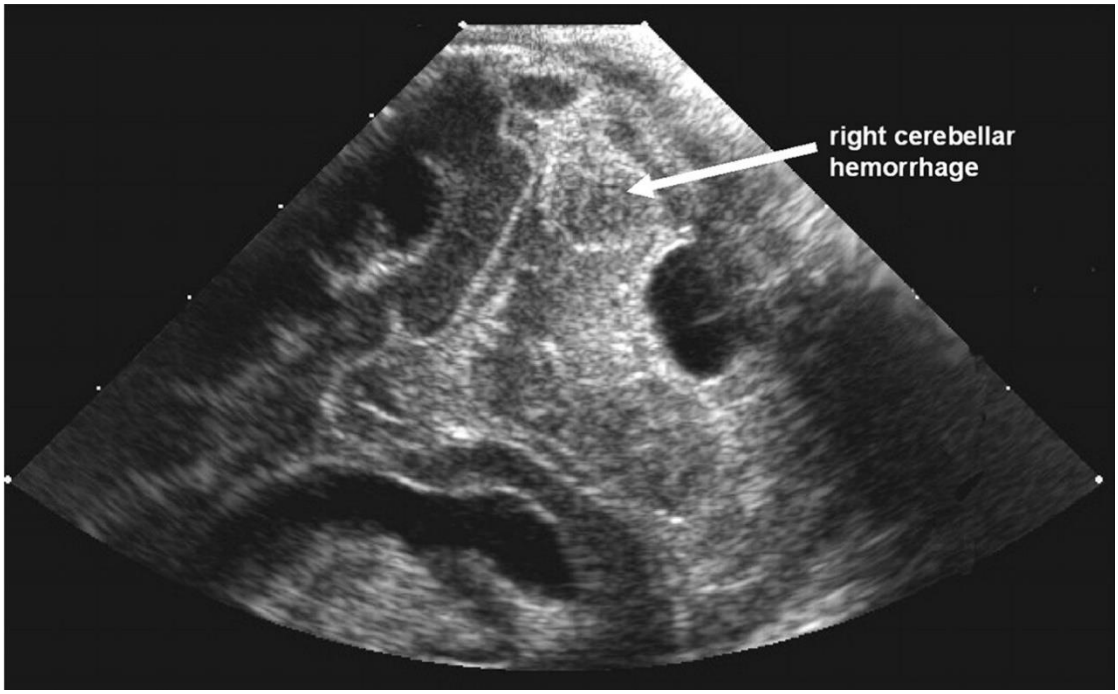

Figure 1.6 Ultrasound image of the posterior fossa obtained through the right mastoid fontanel depicting a large right CBH. Figure was reproduced from Limperopoulos et al. (2005) in Pediatrics; reproduced with permission from the American Academy of Pediatrics.

The reported frequency of CBH in preterm neonates in contemporary studies varies and depends on whether diagnosis was made by cranial US or MRI. Cranial US is only capable of detecting relatively large CBH that are at least 4mm in diameter; as such, reported rates of CBH diagnosed by cranial US are lower than those reported by brain MRI. For example, one prospective cohort study scanning preterm neonates with both serial cranial US and MRI reported that 7/140 (5%) had CBH on cranial US but 28/140 (20%) had CBH on MRI with susceptibility-weighted imaging (SWI) (Parodi et al. 2015). The reported rates of CBH range from 14-37% in recent cohort studies of very preterm neonates using MRI with different sequences (Gano et al. 2016; Steggerda et al. 2009; Parodi et al. 2015; Senden et al. 2018). The specific MRI imaging protocol is also important, with SWI sequences possibly identifying more hemorrhages (Gano et al. 2016; Merrill et al. 1998; Steggerda et al. 2013; Steggerda et al. 2009). SWI identifies iron deposition from degraded hemoglobin, and as such is highly sensitive for hemorrhage. However, SWI would not be an ideal sequence to measure volume of hemorrhage as it overestimates hemorrhage due to the "blooming" effect (Sun et al. 2018).

Massive CBH can be diagnosed on cranial US through the anterior fontanel though imaging via the mastoid fontanel is more sensitive (Merrill et al. 1998; Parodi et al. 2015; Perlman et al. 1983). Different US features of large CBH can be observed according to timing. In the acute phase, a globular and ill-defined area of increased echogenicity is seen within the cerebellar parenchyma; in the subacute phase, less echogenic and some echolucent lesions are observed; weeks later, atrophy of the cerebellum is appreciated (Fumagalli et al. 2020). Punctate hemorrhages, which are typically classified as those less than 4mm in diameter, can by definition only be diagnosed on MRI (Kidokoro et al. 2014). Studies comparing the diagnostic accuracy of US against the gold-standard of MRI for non-punctate CBH have found that US via the mastoid fontanel is capable of detecting the majority, but not all, of these CBH (Parodi et al. 2015; Steggerda et al. 2009).

1.7.2 Pathogenesis and risk factors

Volpe proposed that cerebellar hemispheric hemorrhages originate in the germinal matrix of the EGL while cerebellar vermian hemorrhages originate in the residual germinal matrix of the ventricular zone in the roof of the fourth ventricle (Volpe 2009). The co-occurrence of CBH and GMH-IVH further supports the hypothesis that CBH, like GMH-IVH, originate in the

germinal matrices (Steggerda et al. 2013; Steggerda et al. 2009). The richly vascularized EGL germinal matrix, like the subependymal germinal matrices adjacent to the lateral ventricles, are more vulnerable to rupture in the perinatal period. Circulatory factors related to impaired cerebrovascular autoregulation and shunts via a large patent ductus arteriosus may be important in the pathogenesis, as in supratentorial GMH-IVH (Limperopoulos, Benson, et al. 2005). US studies of CBH indicate detection in the first days of life, similar to GMH-IVH (Steggerda et al. 2009; Zayek et al. 2012). In punctate CBH, in which the diagnosis is made by MRI, the precise timing of CBH occurrence is undeterminable as the MRIs are performed weeks or months into postnatal life.

Preterm neonates born at <28 weeks' gestation are at highest risk for CBH (Gano et al. 2016; Steggerda et al. 2013). Other documented risk factors for preterm CBH include birth weight <750g, hypotension, inotrope exposure, intubation during resuscitation, and mechanical ventilation (Gano et al. 2016; Limperopoulos, Benson, et al. 2005; Steggerda et al. 2013; Steggerda et al. 2009; Vesoulis et al. 2019). There is no consistent relationship between mode of delivery and CBH with conflicting results from several studies (Villamor-Martinez et al. 2019). One cohort study reported a reduced risk of CBH in preterm neonates exposed to antenatal magnesium sulfate for an obstetric or neuroprotective indication (Gano et al. 2016). The relationship between delayed cord clamping and CBH has not been evaluated.

The association between magnesium sulfate and CBH was of particular interest because it was novel and represents the only known pharmacologic intervention (Gano et al. 2016). In the late 1990s reports of preterm neonates born to mothers given magnesium sulfate to prevent eclamptic seizures or as tocolysis showed a remarkable association with reduced CP (Schendel et al. 1996). In those babies born preterm and exposed to magnesium sulfate the odds ratio (OR) for CP was 0.11 (95% CI 0.02-0.81). Since then, at least six randomized controlled trials and subsequent meta-analyses have demonstrated that magnesium sulfate administered to women at imminent risk for preterm delivery decreases the offspring's risk of CP; the relative risk in a recent meta-analysis was 0.68 (95% CI 0.54-0.85) (Wolf et al. 2020; Magee et al. 2011). However, antenatal magnesium sulfate has not been associated with a reduction in brain injuries known to cause CP, such as severe GMH-IVH or cystic periventricular leukomalacia, in randomized trials that used US imaging to diagnose brain injury (Marret et al. 2007; Rouse et al. 2008; Crowther et al. 2003). It is therefore possible that the association between antenatal

magnesium sulfate and reduced CP may be mediated through a reduction in CBH (Gano et al. 2016).

Although the exact mechanisms of action of magnesium as a neuroprotective agent are unknown, it has several biologically plausible actions which may contribute to its neuroprotective effect on the preterm brain. Magnesium may reverse the harmful effects of brain injury by blocking NMDA receptors, thus reducing calcium influx and excitotoxic calcium-induced injury (Nowak et al. 1984). Magnesium also reduces oxidative stress, reduces the production of pro-inflammatory cytokines interleukin-6 and tumor necrosis factor-α, and prevents depletion of high-energy phosphates under hypoxic-ischemic conditions (Burd et al. 2010; Koning et al. 2019). In addition, magnesium has a vasodilatory effect in the cerebral microcirculation, thus playing an important role in the regulation of the cerebral circulation by maintaining normal blood flow and pressure (Murata et al. 2016). In preterm fetal sheep exposed to asphyxia, magnesium increased systemic perfusion after umbilical cord occlusion without impairing arterial blood pressure to cerebral blood flow (Galinsky et al. 2016). As such, magnesium may stabilize against rapid fluctuation in cerebral blood flow.

1.7.3 Pathology

One of the original descriptions of CBH involved 20 neonates born at <1500g admitted to the NICU at The Hospital for Sick Children between 1973-1974 (Pape, Armstrong, and Fitzhardinge 1976). They reported, “The smaller hemorrhages were often multiple and occurred in various locations: subpial in the external granular cell layer; subependymal in the germinal plate region of the fourth ventricle, in the region of the dentate nucleus, or in the superior cerebellar peduncle.” Several of these cases involved destruction of a complete cerebellar hemisphere or complete encasement of the cerebellum in blood.

A large recent autopsy cohort of 19 preterm neonates born at <37 weeks between 1999-2010 with CBH reported that in all cases, a destructive hematoma occupied the inferior aspect of the posterior lobe of the cerebellum in a distribution that roughly corresponded to the territory supplied by the PICA (Haines, Wang, and Pierson 2013). The hematomas typically involved the superficial cortex and the adjacent white matter and most of the specimens demonstrated multifocal hemorrhages, with satellite hemorrhages appearing near the larger ones. Other authors have speculated that larger hemorrhages could have occurred due to the coalescence of multiple

smaller hemorrhages (Pierson and Al Sufiani 2016). In addition, histopathology of the lesions show acute hemorrhages admixed with subacute or chronic changes, suggesting that at least some hemorrhages may evolve over time and are due to repeated episodes of bleeding rather than a single hemorrhagic event.

In the recent cohort, there was often significant associated pathology in the inferior olivary and dentate nuclei and supratentorially, with a high frequency of GMH-IVH and WMI. The damage sustained by these adjacent and interconnected structures is important because it has the potential to compound cerebellar hemispheric injury. In particular, injury to the dentate nucleus, which supplies the output from the cerebellar hemispheres to the cerebrum, may be critical. Importantly, autopsy cohorts may not be completely representative of the brain pathology of premature neonates with CBH who survive beyond the perinatal period.

1.7.4 Experimental models

Yoo et al. developed an animal model of preterm CBH in neonatal mouse pups (Yoo, Mak, and Goldowitz 2014). They used pups at postnatal day 2, which corresponds developmentally to the third trimester in humans (Haldipur, Dang, and Millen 2018), to examine the anatomical features of CBH and the associated behavioural phenotype. They injected bacterial collagenase, which disrupts the basal lamina of blood vessels, into the cerebral aqueduct, which is rostral to the cerebellum. On histopathology, the area of EGL in the CBH mice was reduced on postnatal day 7. Behaviourally, mice with CBH spent more time in the center of an open field, which is considered to be maladaptive and may be associated with decreased anxiety and increased risk-taking. In addition, mice with CBH displayed deficits in motor coordination and balance on the rotarod and horizontal ladder rung walking test.

In a second experiment by the same authors, bacterial collagenase was injected directly in the cerebellar hemisphere rather than adjacent to it (Tremblay et al. 2017). They found that cerebellar volume at postnatal day 15 was affected only when the CBH was inflicted in conjunction with systemic inflammation. CBH-alone did not significantly affect cerebellar volume. On neurosensory and behavioural assessments, they reported deficits in long-term memory but no significant changes in motor behaviour. Overall, their findings demonstrate that inflammation, which is associated with preterm birth, neonatal infections, and chronic lung disease, may amplify the damage and consequences of CBH.

In a recent juvenile model of targeted cerebellar injury, Designer Receptors Exclusively Activated by Designer Drugs were applied to achieve reversible, anatomically-localized perturbation of the molecular layer interneurons in freely moving mice (Badura et al. 2018). Using this approach, they were able to reversibly perturb neural function in juvenile mice in individual lobules for minutes to days and test adult behavioural outcomes. These experiments allowed for a precise interrogation of lobule-specific behavioural consequences and distal anatomical targets of cerebellar influence. They found that activity of posterior regions in juvenile life modulates adult expression of eyeblink conditioning (lobule VI and crus I), reversal learning (lobule VI), persistent behaviour and novelty-seeking (lobule VII), and social preference (crus I/II). When the same perturbations were applied to adult mice, the behavioural phenotypes were less affected. These findings provided anatomical evidence that posterior lobular injury can impact later social behaviour.

1.7.4 Outcomes

The large CBH diagnosed in the 1990s and early 2000s were associated with mortality and severe neurodevelopmental impairment across multiple domains. In one stark example, children with isolated CBH had a 66% rate of neurodevelopmental impairment relative to 5% in matched controls at mean age of 32 months (Limperopoulos et al. 2007). The deficits spanned gross and fine motor, expressive and receptive language, cognition, and behaviour. Behaviourally, there was a higher frequency internalizing behaviour problems and abnormal autism spectrum disorder screening results. This cohort, however, included children born between 1998-2003 who had larger hemorrhages (**Figure 1.5**).

Two systematic reviews published recently concluded that CBH is associated with motor and cognitive outcomes (Villamor-Martinez et al. 2019; Hortensius et al. 2018). However, one of the reviews included only 15 patients with punctate CBH and found that neonates with isolated punctate CBH had a frequency of neurodevelopmental impairment (13-20%) that is similar to that of the general very preterm population (Hortensius et al. 2018; Pascal et al. 2018) while the other review was unable to evaluate the effect of CBH size on outcome due to the small number of patients (Villamor-Martinez et al. 2019). In addition, most of the studies included in the systematic reviews began enrolling their cohorts in the 1990s and the mean age at follow-up in all the studies was less than 3 years of age (Hortensius et al. 2018).

Motor outcomes

Motor outcome in preterm neonates with large CBH is more likely to be impaired compared to preterm infants without cerebellar injury (Limperopoulos et al. 2007; Limperopoulos et al. 2014; Zayek et al. 2012). CP has been described in preterm children with CBH (Johnsen, Bodensteiner, and Lotze 2005; Zayek et al. 2012). However, the causal attribution of CBH to CP is unclear given the frequent co-occurrence of severe WMI. In one retrospective cohort study, 79 of 1120 children born between 1998-2008 had CBH diagnosed on US. The rate of CP was higher in those with CBH compared to those without, but after adjusting for confounders, there was no significant difference between the groups. Of note, cerebellar vermian hemorrhage, but not hemispheric hemorrhage, was associated with CP after adjustment for confounders (Zayek et al. 2012). Unfortunately, cohort studies of CBH have not described the subtype of CP. Children with hypotonic or ataxic CP are often found to have injuries or malformations to the cerebellum, so it would be worthwhile to classify the type of CP identified in preterm children with CBH.

Contemporary cohort studies that have examined preterm children with punctate CBH have not identified an independent association with motor outcomes at 2 years (Senden et al. 2018; Steggerda et al. 2013). Senden et al. examined 24 very preterm children with punctate CBH born between 2008-2013 at 2 years of age in a case-control study. They found no statistically significant differences on gross or fine motor assessment even when comparing children with bilateral, unilateral, and no punctate CBH. Steggerda et al. examined a cohort of 108 very preterm children born between 2006-2007 at 2 years of age as well, of whom 16 had punctate CBH. There was no association between punctate CBH and mildly or severely abnormal fine or gross motor developmental outcome at 2 years of age. One small cohort study with standardized examinations at 4 years found a higher rate of neurologic abnormalities spanning tone, strength, and reflexes on blinded neurologic exams (Tam, Rosenbluth, et al. 2011). This study, however, did not assess functional neuromotor outcomes.

The reduced motor function reported after large CBH may be mediated by interruption of trans-synaptic trophic interactions between the cerebellum and cerebrum (Limperopoulos et al. 2014). In the Limperopulos cohort described above, preterm children were re-imaged at mean 34 months of age and cortical grey matter volume was measured. They reported an association between the volume of the sensorimotor cortex contralateral to isolated CBH and motor scores,

thus linking secondary impairment in cerebral cortical growth and motor function in survivors of CBH.

Cognitive and language outcomes

Preterm children with large CBH have a higher frequency of cognitive and language impairment relative to those without (Limperopoulos et al. 2007; Limperopoulos et al. 2014; Zayek et al. 2012). Bilateral, large CBH may have the highest odds of cognitive dysfunction. In a retrospective cohort of extreme preterm neonates who underwent cranial US, CBH was associated with a higher odds of mental impairment at 18 months (Zayek et al. 2012). In contrast, punctate CBH have not been associated with early cognition, even when there are multiple punctate bleeds (Senden et al. 2018; Steggerda et al. 2013). Tam et al. evaluated cognition using the WPPSI-III at 4 years of age (Tam, Rosenbluth, et al. 2011). Mean Full Scale IQ (FSIQ) was nearly identical between children with and without CBH after accounting for GMH-IVH and WMI (98 ± 6 and 99 ± 2, respectively).

Behavioural outcomes

Few studies have examined childhood behaviour in survivors of preterm CBH (Hortensius et al. 2018). The Limperopoulos cohort identified a high burden of internalizing but not externalizing problems in preterm children with CBH (Limperopoulos et al. 2007). Neonates with CBH also scored significantly higher on the autism screening test (M-CHAT). Children with bilateral CBH and vermian involvement had the highest odds of an abnormal M-CHAT score. A contemporary cohort study, on the other hand, did not find an association between CBH and behavioural outcomes on the CBCL at 2 years (Steggerda et al. 2013).

1.8 Brain dysmaturation in preterm neonates

Until recently, the extensive brain abnormalities in preterm neonates were thought to be related mostly to destructive processes that lead to degeneration of axons, glia, and neurons in the developing brain. However, advances in neonatal care have coincided with evidence that the preterm brain often sustains less severe insults, in which tissue injury is not the critical component. Rather, these milder insults involve aberrant responses to injury that disrupt the maturation of glial progenitors and neurons (Back and Miller 2014).

1.8.1 White matter maturation

While WMI is the most commonly observed abnormality in preterm neonates on diagnostic MRI, it does not fully account for the burden of neurodevelopmental disability in this population (Chau et al. 2013). Impaired *maturation* of the white matter contributes more to neurodevelopmental disability following preterm birth. In other words, white matter dysmaturation is the primary brain abnormality in contemporary cohorts of preterm neonates (Back and Miller 2014).

The underlying tenet of preterm white matter dysmaturation is that glial cells fail to fully mature after less severe insults that are not characterized by tissue destruction or necrosis (Back 2017; Back and Miller 2014). In contrast to WMI, white matter dysmaturation is thought to be secondary to developmental arrest rather than degeneration of the pre-oligodendrocytes. The temporal and causal relationship between brain injury and dysmaturation remains uncertain (Schneider and Miller 2019). However, the proposed events leading to white matter dysmaturation are as follows. First, in response to pre-oligodendrocyte death, early oligodendrocyte progenitors proliferate extensively at the site of injury. To make up for the cell loss, these oligodendrocytes partially differentiate. Second, there is a disruption in the typical differentiation of newly regenerated OL cells. The repopulated cells fail to mature into myelinating oligodendrocytes, and therefore lead to a failure in myelination.

Advanced neuroimaging studies now provide more insight in assessing dysmaturation of white matter. Diffuse excessive high signal intensity within periventricular white matter detected on T2-weighted imaging has been frequently described at TEA (Dyet et al. 2006). These hyperintense areas have corresponding increased diffusivity in downstream, myelinated white matter tracts, indicative of delayed myelination (Counsell et al. 2006). However, this diffuse white matter abnormality has not been consistently associated with functional neurodevelopment (Broström et al. 2016). Serial imaging with diffusion tractography has demonstrated an increase in fractional anisotropy of the white matter, which is a measure of directionality (Drobyshevsky et al. 2005). The absence of the normal increase of fractional anisotropy has been associated with abnormal later neurodevelopment in preterm newborns (Chau et al. 2013).

1.8.2 Regional brain growth and cerebellar growth

Neuroimaging studies have established that the growth of other brain structures, including the thalami, basal ganglia, and cerebellum, have important implications for neurodevelopment in preterm children. Imaging at TEA in extremely low birth weight preterm neonates has demonstrated that abnormal signal and reduced volume in the deep cerebral grey matter was associated with reduced intelligence and motor function at 7 years (Anderson et al. 2017). Delayed growth of the thalami and basal ganglia during childhood was similarly associated with reduced academic achievement and motor function at 7 years in the same cohort of preterm children (Loh et al. 2019).

Cerebellar hypoplasia is a relatively common finding in preterm newborns. Cerebellar hypoplasia is thought to occur from primary injury like CBH and from more remote, secondary factors including supratentorial brain injury and glucocorticoid and morphine exposure (Limperopoulos, Soul, et al. 2005; Zwicker et al. 2016; Ranger et al. 2015). The preterm cerebellum is particularly at risk during the preterm period as it undergoes rapid growth. When assessed in the fetus by 3-dimensional volumetric US, the cerebellar volume increases 5-fold from 24 weeks to 40 weeks gestation (Chang et al. 2000). When assessed in the fetus by 3-dimensional volumetric MRI, cerebellar volume increases 3.5-fold from 27 weeks to 40 weeks gestation (Bouyssi-Kobar et al. 2016). On fetal brain MRI, the cerebellum grows disproportionately relative to the rest of the brain during the last 20 weeks of gestation (Andescavage et al. 2017). On histologic examination, the surface area of the cerebellar cortex increases more than 30-fold from 24 weeks of gestation to term (Rakic and Sidman 1970; Volpe 2009).

Crossed cerebellar diaschisis or atrophy of the cerebellum contralateral to unilateral supratentorial lesions has been well recognized in adults. In an early positron tomography study, the majority of adults with large unilateral strokes had reduced oxygen consumption in the contralateral cerebellum (Pantano et al. 1986). The cerebellar hemispheric oxygen consumption was especially depressed when the contralateral cortex or internal capsule was affected, suggesting destruction of the cortico-ponto-cerebellar tracts. A series of seven preterm children with periventricular hemorrhagic infarction who later developed contralateral cerebellar atrophy confirmed the phenomenon of crossed cerebellar diaschisis in preterm children (Rollins, Wen, and Dominguez 1995). Supratentorial WMI encompassing periventricular leukomalacia,

ventricular dilation, and periventricular hemorrhagic infarctions have since been associated with reduced cerebellar volume (Limperopoulos, Soul, et al. 2005; Srinivasan et al. 2006). Tam et al. demonstrated that severe GMH-IVH was associated with altered fractional anisotropy measured in the cerebellar cortex and middle cerebellar peduncles and that the severity of GMH-IVH was associated with cerebellar volume (Tam et al. 2009; Tam, Miller, et al. 2011). These results were replicated in a separate study using a surface-based mapping approach to segment the cerebellum: Kim et al. reported that severe GMH-IVH was associated with slower cerebellar growth in preterm neonates (Kim et al. 2016). In contrast to CBH, which was associated with slower growth in the *inferior* posterior lobe of the cerebellum, GMH-IVH-associated cerebellar volume reduction was most pronounced in the *superior* posterior cerebellar lobe. The distinct pattern of impaired cerebellar growth in patients with GMH-IVH suggests a different pathway than that related to CBH. The authors of the study speculated that in GMH-IVH, intraventricular blood deposition in the fourth ventricle may have a neurotoxic effect on the underlying cerebellar tissue.

Medications, nutrition, and infection have all been associated with cerebellar hypoplasia in preterm newborns. Postnatal glucocorticoid exposure has been associated with selectively reduced cerebellar volume at TEA (Tam, Chau, et al. 2011). In a mouse model, a single postnatal injection of glucocorticoid resulted in selective apoptosis of granule precursor cells in the EGL. (Noguchi et al. 2008). Follow-up of preterm children has also shown an association between postnatal glucocorticoid exposure and reduced cerebellar volume on MRI at school-age (Ranger et al. 2015). Animal models have also shown Purkinje cell death and impaired cerebellar development following morphine exposure (Bekheet et al. 2010). Prospective cohort studies have demonstrated an association between morphine exposure and cerebellar volume at TEA and in later childhood (Ranger et al. 2015; Zwicker et al. 2016). However, neonatal painful procedures were associated with cerebellar volume; as such, it remains unclear if procedural pain its treatment, or both contributes to cerebellar growth impairment (Ranger et al. 2015).

Impaired cerebellar maturation in preterm children has been linked to several neurodevelopmental outcomes. Cerebellar hypoplasia has been associated with poor visuospatial and visuomotor functioning in preterm children (Van Braeckel and Taylor 2013). Lower verbal comprehension and visual perception/perceptual reasoning at age 7 years were also related to smaller cerebellar volumes in the cerebellar hemispheres (Ranger et al. 2015).

1.9 Hypothesis and aims

1.9.1 Hypothesis

We hypothesized that larger, more anterior CBH would be associated with neuromotor dysfunction whereas larger, posterior CBH would be associated with cognitive and behaviour problems in children born very preterm.

1.9.1 Aims

Aim 1: To precisely measure and spatially define CBH in three- and two-dimensions.

Aim 2: To examine the association between CBH size and location and preschool-age neurodevelopmental outcomes in preterm neonates.

2. Methods

2.1 Study population and clinical data collection

A total of 234 neonates born at 24-32 weeks' gestation (median 27.7 weeks, interquartile range [IQR] 26.0-29.6) and admitted to the neonatal intensive care unit (NICU) at BC Women's Hospital, Vancouver, Canada, were recruited into this prospective longitudinal cohort study from 2006-2012. Neonates were excluded if they had a congenital malformation or syndrome, congenital infection, or large parenchymal hemorrhagic infarction (>2 cm) on US, as these conditions are strongly predictive of neurodevelopmental impairments or early mortality. This cohort has been described previously to address different hypotheses (Guo et al. 2017). The study was approved by the University of British Columbia/BC Children's and Women's Health Centre Clinical Research Ethics Board and informed consent was obtained from parent(s)/guardian(s).

Clinical characteristics about the pregnancy, delivery, and perinatal course were collected via prospective systematic chart review. Antenatal steroids were defined as at least a single dose of either betamethasone or dexamethasone; magnesium sulfate as intravenous magnesium sulfate for neuroprotection or preeclampsia; and early onset infection as any culture-proven infection in the first 72 hours of life. Maternal level of education was classified as "primary/secondary school," defined as education including the completion of high school, and "undergraduate/postgraduate," defined as at least 1 year of college or university studies. Cranial US reports were reviewed for data on highest grade of GMH-IVH, but severity of GMH-IVH was determined by the preterm MRI in order to be contemporaneous with the measurement of CBH (see below).

2.2 Magnetic resonance imaging

MRI was performed twice without pharmacologic sedation: first in early-life when the neonate was clinically stable and again at TEA. A total of 221 neonates underwent preterm MRI (median post-menstrual age 32.0 weeks, IQR 30.4-33.6) and 185 underwent a TEA MRI at median postmenstrual age 40.3 weeks (IQR 38.9-41.9) (**Figure 2.1**). MRIs were carried out on a Siemens 1.5 Tesla Avanto scanner using an MR-compatible isolette (Lammers Medical Technology, Luebeck, Germany) with a specialized neonatal head coil (Advanced Imaging Research, Cleveland, Ohio). Three-dimensional coronal volumetric T1-weighted (TR, 36; TE,

9.2; FOV, 200mm; slice thickness, 1mm; no gap) and axial fast-spin echo T2-weighted images (TR, 4610; TE, 107; FOV, 160mm; slice thickness, 4mm; gap, 0.2mm) were used to examine CBH. An experienced pediatric neuroradiologist blinded to the participant's medical history reviewed the images and recorded the presence of CBH and severity of GMH-IVH, as previously described (Miller et al. 2005). WMI was previously quantified by a member of our team (Guo et al. 2017).

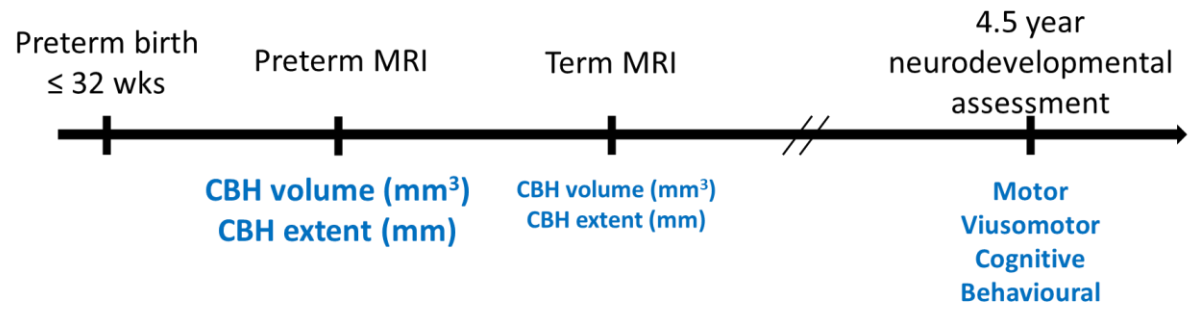

Figure 2.1 Overview of the study procedure.

2.3 Manual segmentation of lesions

Without knowledge of neurodevelopmental outcomes, CBH was independently identified as areas of abnormal T1 signal by 2 trained raters (Jarred Garfinkle and Ting Guo). To avoid mislabeling normal cerebellum as hemorrhage, all CBH identified on volumetric T1-weighted images were cross-referenced with the axial T2-weighted images. CBH segmentation was performed on the volumetric T1-weighted images with simultaneous coronal, sagittal, and axial views of the brain via Display software (Montreal Neurology Institute and Hospital, Montreal, Canada; http://www.bic.mni.mcgill.ca/software/Display) (**Figure 2.2**). Tricubic interpolation was applied as it permitted accurate segregation of the hemorrhage from the surrounding cerebellar tissue. Images were inspected to ensure that voxels with ambiguous signal intensity were not erroneously considered within the CBH segmentation. An experienced neonatal neurologist (Steven P. Miller) reviewed the segmented CBH for quality control.

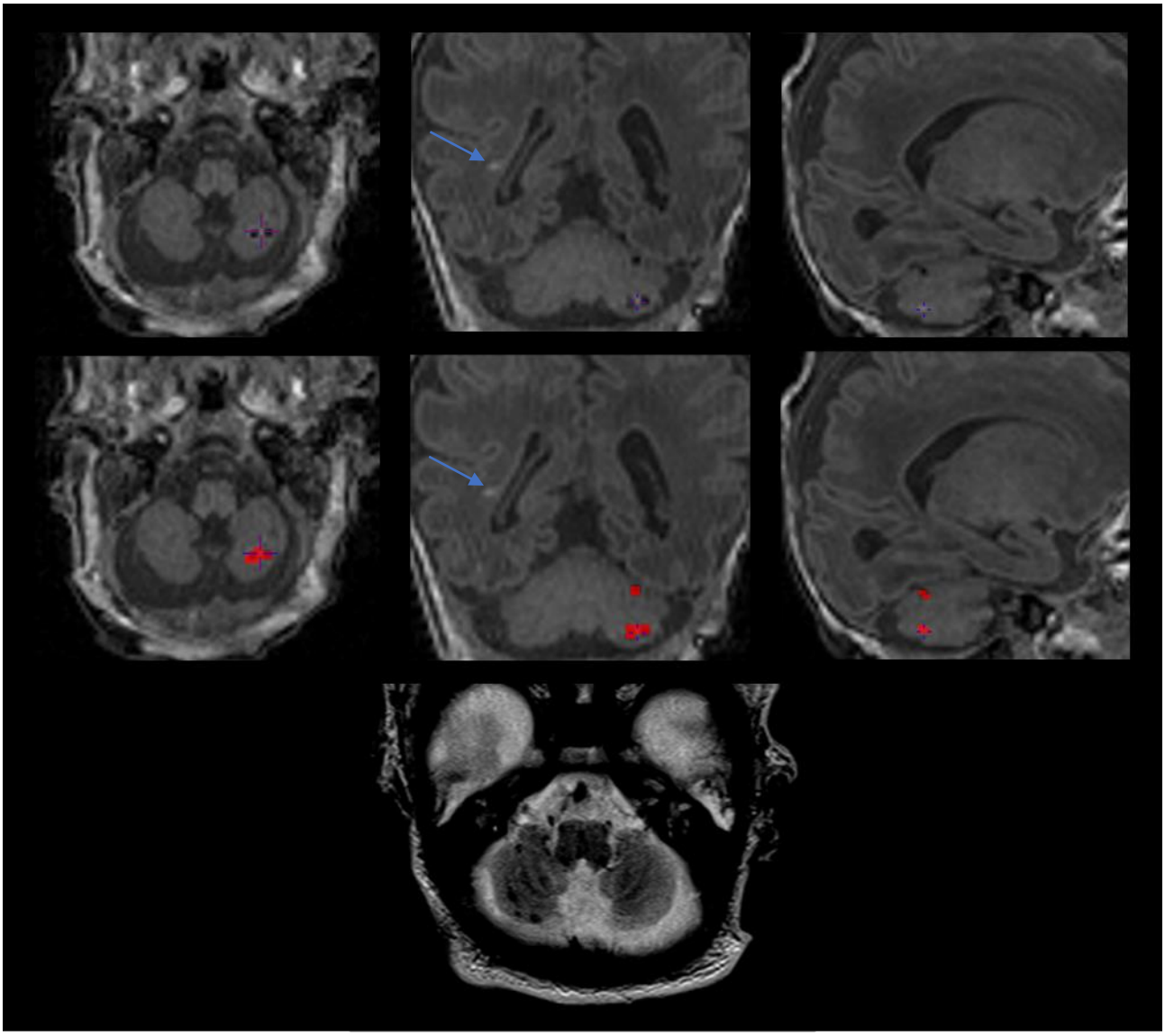

Figure 2.2 Neonatal brain MRI demonstrating several CBHs at 34+0 weeks' gestation. The purple cursor is placed over the largest CBH in the top two panels. Top panel: T1-weighted images in axial, coronal, and sagittal views (from left to right). Middle panel: T1-weighted images with manual segmentation in red. Bottom panel: T2-weighted axial image. Note that this subject also manifests punctate white matter injury in the left periventricular region (arrow), which is visible in the coronal image.

CBH total volume and volume of the single largest CBH (hereafter referred to as CBH greatest volume) were calculated based on the manual segmentation. In order to provide a more clinically applicable measure, the extent of the CBH was calculated as the distance between the two points in the lesion that are furthest apart, measured from the edges of the voxels.

2.4 Segmentation of the cerebellum

Automated cerebellar segmentations were performed with the multiple automatically generated templates (MAGeT Brain), which has been adapted for neonates (Chakravarty et al. 2013; Guo et al. 2015; Pipitone et al. 2014). Blinded with respect to GA and functional outcome measures, an expert (Emily Tam) in manual segmentation of the cerebellum delineated the cerebellum on both the preterm and TEA images in 21 subjects evenly distributed in terms of sex (Tam, Miller, et al. 2011; Tam et al. 2019). Automated cerebellar segmentations were performed with an adapted version of the MAGeT Brain pipeline previously validated in the context of neonatal and adult cerebellar segmentation (Guo et al. 2015; Park et al. 2014). The pipeline uses the manual segmentations as inputs and uses the total population under study to refine the segmentations via an intermediate dataset, which is called the template library (Pipitone et al. 2014). MAGeT Brain propagates each of the labeled atlases to all the template images to generate the template library. The purpose of this intermediate stage is to use the variability of the population under study to improve the final segmentation output. Subsequently, the templates are each warped to match each of the subjects via nonlinear registration, and all labels are propagated and then fused using a majority vote. The generated cerebellar segmentations were reviewed (Jarred Garfinkle) and manually corrected where needed (**Figure 2.3**). All image processing took place in the minc environment (http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC).

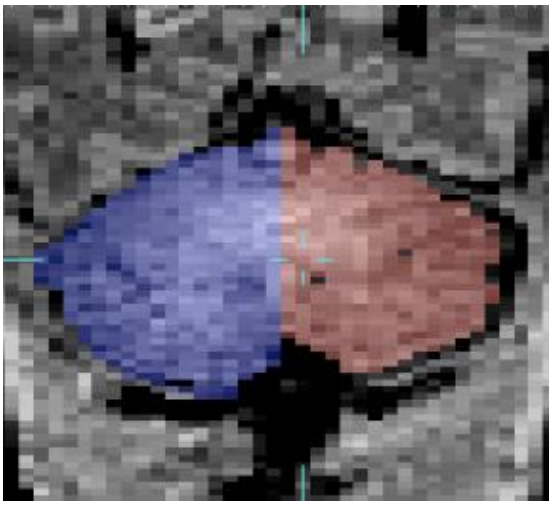

Figure 2.3 Segmentation of the left (blue) and right (red) cerebellum in the coronal plane.

2.5 Neurodevelopmental outcome assessment

Children were assessed in the Neonatal Follow-up Program at BC Women's Hospital by experienced clinical staff, blinded to the imaging findings, at chronologic age 4.5 years. The Movement Assessment Battery for Children Second Edition (MABC-2) (Henderson, Sugden, and Barnett 2007), administered by an occupational therapist, was used to assess motor competence in manual dexterity, aiming and catching, and balance domains. The MABC-2 is designed to identify and describe impairments in motor performance of children and adolescents 3 through 16 years of age (Brown and Lalor 2009). Motor impairment was defined as a total MABC-2 score of <5th percentile (Griffiths et al. 2017). Psychology personnel administered the Beery-Buktenica Developmental Test of Visual-Motor Integration 6th Edition (Beery VMI-6) (Beery, Buktenica, and Beery 2010), and the Wechsler Primary and Preschool Scale of Intelligence Fourth Edition (WPPSI-III) (Wechsler 2002). The Beery VMI-6 test consists of 30 geometrical shapes that the child is asked to copy with a pen and paper, and it is terminated when three figures in a row have been incorrectly copied. The drawings are examined, and acceptable approximations of the model drawings are each given one point. The raw score is the total number of correct drawings and this is then transformed to an age-corrected standard score. Overall indices of the Beery VMI-6 and WPPSI-III FSIQ are standard scores with mean (SD) of 100 (15) and impairment was defined as a score of <1 SD below the mean. Impairment was defined in this study as -1 SD due to the general high performance of this cohort.

Parents completed the CBCL, which detects emotional and behavioural problems in children (Achenbach and Rescorla 2000). The CBCL consists of 100 behaviour-related questions for which the primary caregiver rates each problem behaviour on a 3-point scale that produces a T-score as its standard score. The CBCL produces an Internalizing Problem score (composed of 4 syndrome scales: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn Behaviour) and an Externalizing Problem score (composed of 2 syndrome scales: Attention Problems, Aggressive Behaviour), which are commonly used. A T-score of 50 represents the mean with a standard deviation of 10; for the Internalizing and Externalizing Problem scales, a T-score ≥60 is considered subclinical/clinical. CP was defined as a confirmed diagnosis made by an experienced pediatrician (Rosenbaum et al. 2007). Our protocol did not include a formal diagnostic assessment for autism spectrum disorder.

2.6 Probabilistic maps

The manually labeled CBH on each brain image was mapped to the common space of the early preterm template using a nonlinear transformation, which accommodates the anatomical variability between the patient and the template images (Guo et al. 2017; Avants et al. 2011). The probabilistic CBH map was then generated based on the cumulative number of CBH that occurred in homologous brain regions across participants in the standard template. The map permits the identification of vulnerable regions in the cerebellum, and whether the hemorrhages occur in a characteristic spatial distribution.

We employed similar techniques to develop CBH maps for neurodevelopmental outcomes. The CBH voxels that are unique to the neonates with typical outcomes, unique to neonates with adverse outcomes, and common to both groups were labeled in 3 distinguishable colors. These outcome-based maps allowed us to visually assess the differences in CBH location between typical and adverse outcome groups.

2.7 Statistical analyses examining the association of CBH and neurodevelopmental outcomes

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS, v20; IBM, Armonk, NY). Except where otherwise specified, the analyses were performed using the preterm MRI (rather than the MRI at TEA) as CBH occurs early in the preterm period. After the initial hemorrhage, the blood is slowly resorbed; as such, TEA imaging may underestimate the burden of CBH compared to preterm imaging. The cohort was divided into 3 groups: no CBH, punctate CBH only, and at least one larger CBH (≥4mm) (Kidokoro et al. 2014). Clinical characteristics and demographic variables were compared by CBH group using the χ^2 or Fisher exact tests for categorical data and the Jonckheere-Terpstra test for trends in continuous data variables across ordered groups.

To assess whether CBH total volume was associated with childhood motor function, visuomotor function, cognition, and behaviour (internalising and externalizing), we applied multivariable linear regression models for each of the outcomes controlling for GA, sex, and supratentorial brain injury, which we operationalized as WMI volume and the presence of GMH-IVH grades 2 or 3. The multivariable models were also extended to include adjustment for factors associated with CBH and maternal education. In addition, we assessed the association

between two secondary predictors, CBH greatest volume and CBH greatest extent, and neurodevelopmental outcomes. Significant univariate regression analyses are presented only where the multivariable analyses were non-significant. We considered p-values <0.05 as significant and adjusted p-values according to the Benjamini–Hochberg method for the 10 models assessing the two secondary predictor variables.

2.8 Lesion odds ratio mapping and voxel-based lesion-symptom mapping

We created voxelwise OR maps to further demonstrate the importance of lesion location for neurodevelopmental outcomes which were associated with CBH in multivariable linear regression models. The OR maps quantify the levels of risk that CBH occurring at different anatomical regions pose for adverse outcomes (Sprenger et al. 2012; Guo et al. 2017). The OR of having adverse developmental outcomes at each voxel can be derived using the following formula:

$$OR = (I_a/N_a) \,/\, (I_t/N_t) = (I_a N_t) \,/\, (I_t N_a)$$

Where I_a is the number of neonates with adverse outcome who have CBH at a specific voxel, I_t is the number of neonates with typical outcome who have CBH at a specific voxel, N_a is the number of neonates with adverse outcome who do not have CBH at a specific voxel, and N_t is the number of neonates with typical outcome who do not have CBH at a specific voxel. To prevent divisions by zero, we set the voxels that exhibited lesions in the adverse outcome group but with no lesions in the typical outcome group to a value of 1.

To quantify the voxel-wise statistical association between CBH and neurodevelopment, we also performed VLSM (Bates et al. 2003). The continuous neurodevelopmental data of neonates with CBH at a given voxel were statistically compared to those of neonates without CBH at the same voxel using the assumption-free rank order test proposed by Brunner and Munzel (Rorden, Karnath, and Bonilha 2007). The CBH and neurodevelopmental outcome association for the binomial outcome data were statistically assessed at each voxel using the quasi-exact test proposed by Liebermeister (Rorden, Karnath, and Bonilha 2007). We reported voxels as predictive of outcome using a criterion of z-score ≥2.00 ($p < 0.05$) due to the small number of voxels with CBH (Frenkel-Toledo et al. 2019). We also performed permutation thresholding (1000 permutations) to control the family-wise error rate, thresholded at $p(FWE) < 0.05$ (Rorden, Karnath, and Bonilha 2007).

2.9 Validation of CBH detection on MRI

Susceptibility-weighted imaging (SWI) was not routinely acquired in this cohort. In order to evaluate if any CBH could have been missed in the absence of SWI, we examined a separate prospective cohort which included SWI. This separate cohort included 48 neonates born at 24-32 weeks' gestation (median 26.8 weeks, interquartile range [IQR] 25.0-28.1) admitted to Mount Sinai Hospital or Hospital for Sick Children, Toronto, Canada from 2014-2016, as previously reported (Duerden et al. 2019). Forty-six of them underwent preterm imaging (median post-menstrual age 33.2 weeks, IQR 31.4-35.1) on a Siemens 3 Tesla Tim Trio MRI scanner. Two trained raters (J.G. and T.G.) identified CBH as areas of abnormal T1 or T2 signal. To ascertain if any CBH were undetected on T1 and T2 images, SWI images were subsequently reviewed.

3. Results

3.1 Clinical characteristics

Of the 221 neonates with preterm imaging, 14 (6%) had punctate CBH only, 22 (10%) had at least one larger CBH, and 185 (84%) did not have CBH (**Figure 3.1**). Demographic and clinical factors are compared between the three groups in **Table 3.1**. Administration of antenatal steroids and antenatal magnesium sulfate were both more common in neonates without CBH; in fact, none of the neonates with CBH received antenatal magnesium sulfate. Preeclampsia was also more common in neonates without CBH. In the 196 neonates who received antenatal steroids, and in the 166 neonates born without preceding preeclampsia, the receipt of antenatal magnesium sulfate was still more common in neonates without CBH (p=0.007 and 0.043, respectively). In addition, antenatal magnesium sulfate was not associated with the presence of WMI (p=0.375) nor with the total volume of WMI (p=0.411; Mann-Whitney U test).

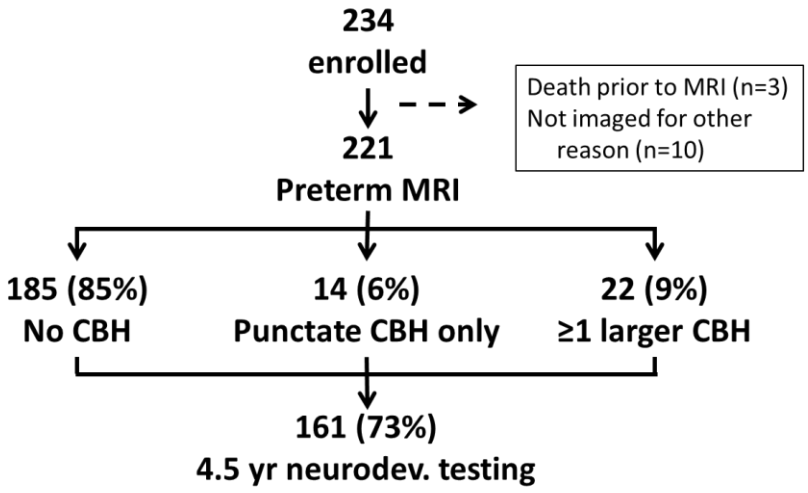

Figure 3.1 Flow chart of study enrollment, MRI scans and follow-up.

GMH-IVH grades 2 and 3 were associated with CBH (p=0.004). The highest grade of GMH-IVH on US corresponded to the MRI findings in 82% of neonates. Neither the presence of WMI (p=0.85) nor WMI volume (p=0.53) were associated with CBH. In addition, WMI volume was not associated with CBH total volume (β=0.149, 95% CI [-1.35, 1.65]).

	No CBH (n=185)	**Only punct. CBH** (n=14)	**≥1 larger CBH** (n=22)	**P value**
Female sex (n, [%])	89 (48)	5 (36)	13 (59)	0.38
Gestational age (weeks, median, IQR)	28 (25,28)	26 (25,28)	25 (25,26)	<0.001
Antenatal steroids (n, [%])	169 (92)	13 (93)	14 (64)	<0.001
Magnesium sulfate (n, [%])	47 (25)	0 (0)	0 (0)	0.003
Preeclampsia (n, [%])	52 (28)	2 (14)	1 (5)	0.034
Cesarean (n, [%])	115 (62)	11 (79)	13 (59)	0.44
5-min Apgar (median, IQR)	8 (6,9)	7 (6,8)	5 (2,7)	<0.001
Early onset infection (n, [%])	43 (23)	1 (7)	8 (36)	0.13
Intraventricular hemorrhage grades 2 or 3 (n, [%])	54 (29)	6 (43)	14 (64)	0.004
White matter injury (n, [%])	56 (27)	5 (29)	7 (32)	0.85
White matter injury volume (mm^3, median, IQR)	0 (0, 8)	0 (0, 15)	0 (0, 54)	0.53
Maternal undergraduate or postgraduate education (n, [%])	135 (87) (n=158)	11 (92) (n=12)	15 (79) (n=19)	0.62

Table 3.1 Early clinical characteristics for neonates without CBH, with only punctate CBH, and with ≥1 larger CBH.

3.2 Quantitative measurements of CBH and location.

Among the 36 neonates with CBH on the preterm MRI, 35 CBH were quantifiable and one was not due to excessive motion artifact. The median CBH total volume was 31.5mm^3 (IQR 15.2-103.1); the median CBH greatest volume was 19.5mm^3 (IQR 6.5-61.8); and the median CBH greatest extent was 5.5mm (IQR 3.3-11.9) (**Figure 3.2**).

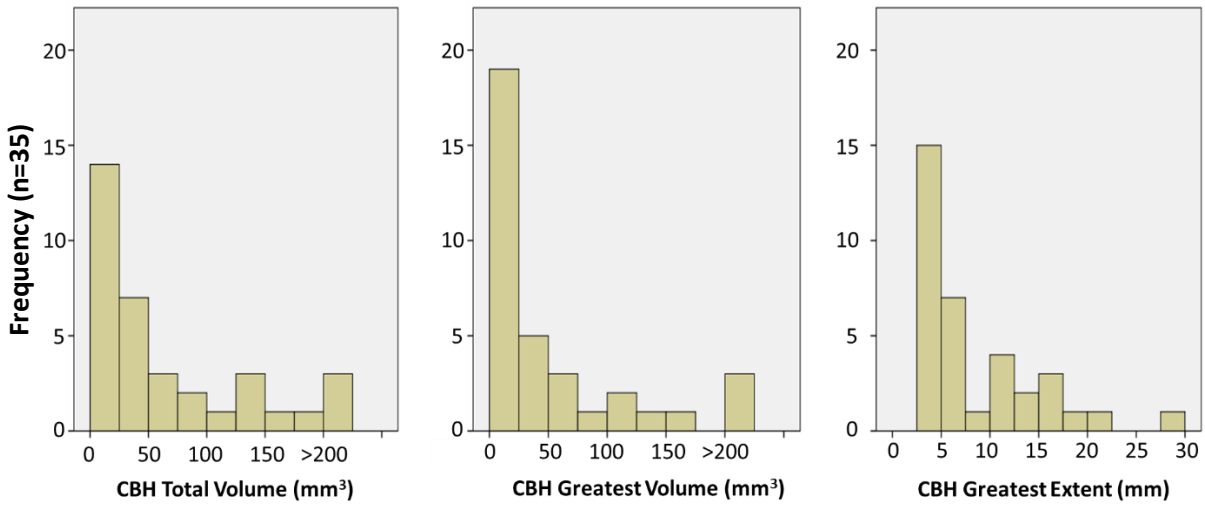

Figure 3.2 Histograms representing the CBH total volume, CBH greatest volume, and CBH greatest extent in the 35 neonates with quantifiable CBH.

Only three neonates had very large CBH with total volumes that exceeded 5% of the total cerebellar volume (CBH total volumes: 400, 441, and 3496mm^3). These three were *a priori* assigned values of 200mm^3 for CBH total and CBH greatest volumes for multivariable regression models so as not to skew the results.

The CBH probabilistic map indicated that CBH occurs at homologous brain regions across participants and that the inferior aspect of the posterior lobes were more prone to CBH (**Figure 3.3**).

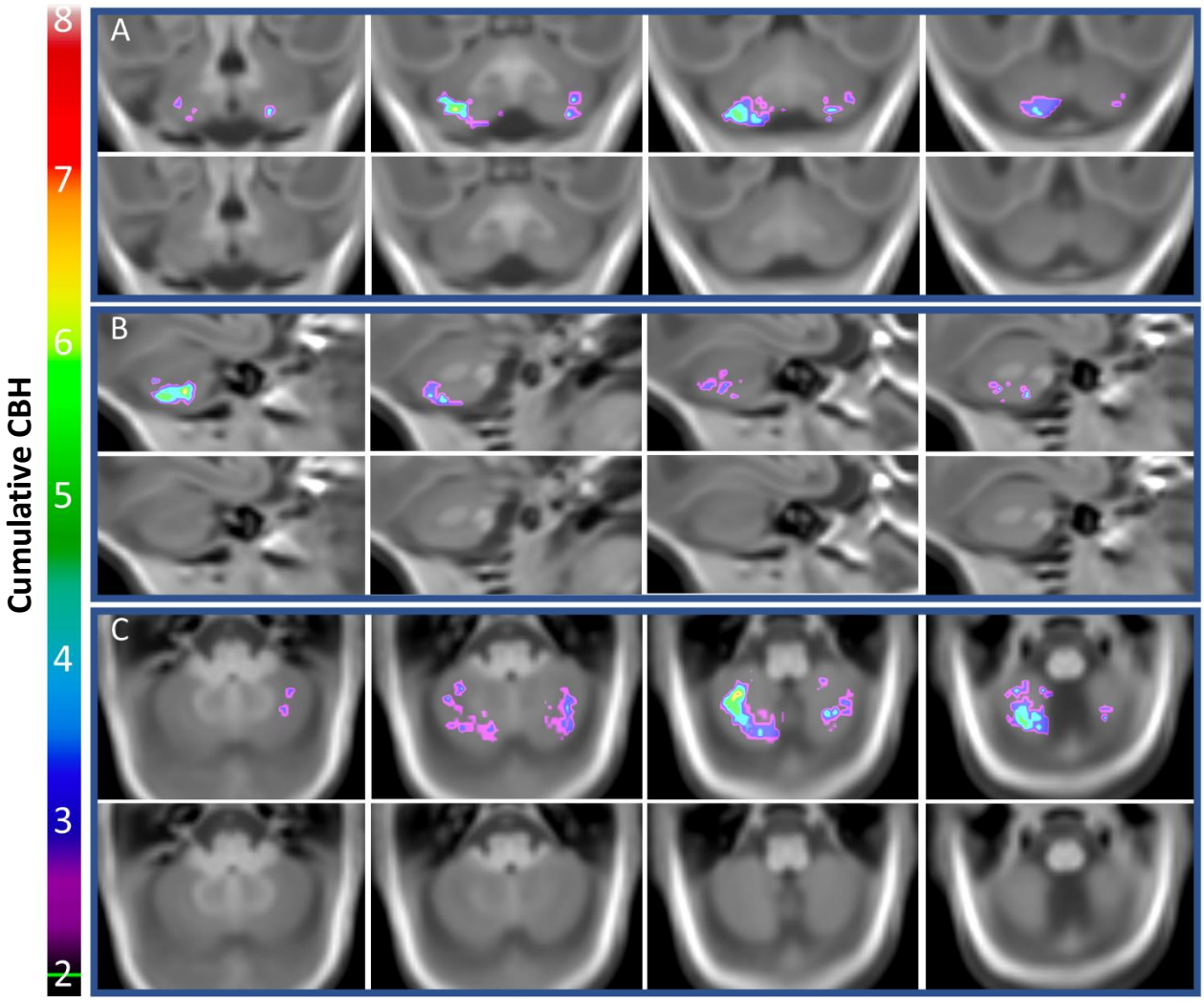

Figure 3.3 Probabilistic CBH map of 35 very preterm neonates overlaid on a T1-weighted early preterm brain template. CBH that occurred at a homologous region in 2 or more very preterm neonates are displayed. CBH seen only in a single neonate are omitted. The cumulative (summed) CBH map is overlaid on the neonatal brain template in (a) coronal (left to right: anterior to posterior), (b) sagittal (left to right: left to right), and (c) axial (left to right: superior to inferior) planes. The color bar on the left indicates the color coding of the CBH summation. The maximum value on the map is 8.

3.3 CBH at term-equivalent age and cerebellar growth

Of the 185 neonates who underwent a subsequent TEA MRI, 23 had CBH. In these 23 neonates, CBH total volume diminished by median -5.6mm^3 (IQR -25.5, 3.8) between the two MRIs. The median cerebellar volume at the preterm MRI in these 185 neonates was 7280mm^3

(IQR 5724, 9334) and at TEA 20977mm^3 (IQR 17262, 24817). At TEA, newborns with CBH had reduced median cerebellar volumes relative to those without CBH (21271mm^3 vs. 18351mm^3, p=0.007 Mann-Whitney U test).

The cerebellum grew by median 1637mm^3/week (IQR 1461, 1778) over this period. In a model adjusting for sex, birth GA, and postmenstrual age at preterm scan, CBH total volume was negatively associated with cerebellar growth (β=-1.87, 95% CI [-3.28, -0.47]). After additional adjustment for total brain growth, CBH total volume remained negatively associated with cerebellar growth (β=-1.67, 95% CI [-2.71, -0.63]). In addition, the cerebellar hemisphere with a greater burden of CBH grew less than the one other hemisphere: the difference between right and left CBH total volume was negatively associated with the difference between right and left cerebellar hemispheric weekly growth (β=-1.32, 95% CI [-1.56, -1.08]).

3.4 Association of CBH with outcome

A total of 165 children (75%) underwent motor, 163 (74%) visuomotor, 162 (74%) cognitive, and 170 (77%) behavioural assessment at age 4.5 years (median 4.8 years, IQR 4.8-4.9). Six neonates died and the remainder were lost to 4.5 year follow-up. Children with 4.5 year assessments had similar early clinical and imaging characteristics compared to those who did not undergo the assessments (**Table 3.2**).

	MABC-2 assessment (n=165)	**No MBC-2 assessment** (n=56)	**P value**
Female sex (n, [%])	77 (47)	26 (46)	0.44
Gestational age (med, IQR)	28 (26,30)	28 (26,29)	0.25
Antenatal steroids (n, [%])	147 (89)	49 (88)	0.74
Magnesium sulfate (n, [%])	34 (21)	13 (23)	0.69
Preeclampsia (n, [%])	41 (25)	14 (25)	0.89
Cesarean (n, [%])	108 (66)	31 (55)	0.22
5-min Apgar (med, IQR)	8 (6,9)	7 (5,8)	0.014
Early onset infection (n, [%])	35 (21)	17 (30)	0.20
Intraventricular hemorrhage grades 2 or 3 (n, [%])	54 (33)	20 (37)	0.62
White matter injury (n, [%])	46 (28)	22 (41)	0.09
Cerebellar hemorrhage (n, [%])	26 (16)	10 (18)	0.71

Table 3.2 Early clinical and imaging characteristics for children with and without 4.5 year MABC-2 assessments.

Neonates with CBH were more likely to have adverse MABC-2, Beery VMI-6, and WPPSI-III FSIQ scores (**Table 3.3**). Eighteen children had CP, of whom 4 (22%) had ≥1 larger CBH. Of the four children with CBH who developed CP, two had mixed CP with predominant hypotonia (both of whom had WMI but no GMH-IVH) and two had spastic hemiplegia (both of whom had severe GMH-IVH in the hemisphere contralateral to the deficit).

	No CBH	Only punct. CBH	≥1 larger CBH	P value
MABC-2 score <5th percentile (n/165, [%])	28/139 (20)	5/11 (46)	6/15 (40)	0.048
Beery VMI-6 score <85 (n/163, [%])	10/137 (7)	3/10 (30)	3/16 (19)	0.03
WPPSI-III FSIQ scores <85 (n/162, [%])	7/137 (5)	3/10 (30)	2/15 (13)	0.01
CBCL internalizing T-score ≥60 (n/170, [%])	28/142 (20)	3/10 (30)	7/18 (40)	0.15
CBCL externalizing score ≥60 (n/170, [%])	12/142 (9)	1/10 (10)	4/18 (22)	0.19

Table 3.3: Comparison of performance on the MABC-2, Beery VMI-6, WPPSI-III FSIQ, and CBCL between children without CBH, with only punctate CBH, and with ≥1 larger CBH.

In multivariable regression models accounting for sex, GA, GMH-IVH grades 2 and 3, and WMI volume, CBH total volume, CBH greatest volume, and CBH greatest extent were all associated with the MABC-2 score (β=-0.095, -0.14, and -1.01, respectively; **Table 3.4**). Only CBH greatest volume was independently associated with the Beery VMI-6 score (β=-0.073; Table 4) while CBH total volume and CBH greatest extent were only associated with the Beery VMI-6 score on univariate analysis (β=-0.056, 95% CI [-0.10, -0.012] and β=-0.53, 95% CI [-0.93, -0.12], respectively). Standardized β coefficients demonstrated that the effect size of CBH total volume on MABC-2 score (standardized β=-0.16) was similar to that of WMI volume (standardized β=-0.22). There were no significant associations between CBH size and the WPPSI-III FSIQ. In a supplemental analysis we examined the models with WPPSI-III Verbal IQ and Performance IQ and the results remained non-significant.

Factor*	β Coefficient (95% CI)	Standardized β	P value (adjusted p-value**)
4.5 year MABC-2 scores			
CBH total volume			
CBH total volume (mm^3)	-0.095 (-0.184, -0.005)	-0.16	0.038
Female sex	1.87 (-4.37, 9.10)		0.56
GA	2.58 (1.21, 3.95)	0.28	<0.001
IVH Grade 2 or 3	-0.12 (-6.76, 6.73)		0.99
WMI volume (mm^3)	-0.018 (0.031, -0.006)	-0.22	0.003
CBH greatest volume			
CBH greatest volume (mm^3)	-0.14 (-0.247, -0.037)	-0.20	0.008 (0.03)
Female sex	2.17 (-4.03, 8.36)		0.49
GA	2.54 (1.18, 3.89)	0.28	<0.001
IVH Grade 2 or 3	0.20 (-6.48, 6.89)		0.95
WMI volume (mm^3)	-0.019 (-0.031, -0.006)	-0.22	0.003
CBH greatest extent			
CBH greatest extent (mm)	-1.01 (-1.85, -0.17)	-0.18	0.019 (0.038)
Female sex	2.03 (-4.19, 8.24)		0.52
GA	2.54 (1.18, 3.90)	0.28	<0.001
IVH Grade 2 or 3	-0.24 (-6.97, 6.50)		0.95
WMI volume (mm^3)	-0.019 (-0.031, -0.006)	-0.22	0.003
4.5 year Beery VMI-6 scores			
CBH total volume			
CBH total volume (mm^3)	-0.042 (-0.086, 0.001)		0.058
Female sex	0.27 (-2.81, 2.35)		0.87
GA	0.90 (0.22, 1.58)	0.19	0.009
IVH Grade 2 or 3	-1.44 (-4.79, 1.90)		0.40
WMI volume (mm^3)	-0.006 (-0.010, -0.003)	-0.28	<0.001
CBH greatest volume			
CBH greatest volume (mm^3)	-0.073 (-0.124, -0.021)	-0.21	0.006 (0.025)
Female sex	0.44 (-2.61, 3.49)		0.78
GA	0.86 (0.19, 1.53)	0.19	0.012
IVH Grade 2 or 3	-1.35 (-4.65, 1.95)		0.42
WMI volume (mm^3)	-0.006 (-0.010, -0.003)	-0.28	<0.001
CBH greatest extent			
CBH greatest extent (mm)	-0.42 (-0.82, -0.020)	-0.16	0.040 (0.057)
Female sex	0.34 (-2.74, 3.42)		0.83
GA	0.89 (0.210, 1.57)	0.20	0.010
IVH Grade 2 or 3	-1.58 (-4.93, 1.77)		0.36
WMI volume (mm^3)	-0.006 (-0.010, -0.003)	-0.28	<0.001
4.5 year WPPSI-III FSIQ			
CBH total volume			
CBH total volume (mm^3)	0.010 (-0.052, 0.073)		0.75
Female sex	1.69 (-2.28, 5.65)		0.41
GA	1.30 (0.41, 2.19)		0.004
IVH Grade 2 or 3	-1.37 (-5.72, 2.97)		0.54

WMI volume (mm^3)	0.000 (-0.008, 0.008)		0.944
CBH greatest volume			
CBH greatest volume (mm^3)	0.006 (-0.074, .085)		0.89
Female sex	1.68 (-2.29, 5.65)		0.41
GA	1.27 (0.38, 2.16)		0.005
IVH Grade 2 or 3	-1.43 (-5.76, 2.90)		0.52
WMI volume (mm^3)	0.000 (-0.008, 0.008)		0.95
CBH greatest extent			
CBH greatest extent (mm)	0.093 (-0.54, 0.73)		0.77
Female sex	1.68 (-2.29, 5.65)		0.41
GA	1.30 (0.40, 2.20)		0.005
IVH Grade 2 or 3	-1.34 (-5.72, 3.05)		0.55
WMI volume (mm^3)	0.000 (-0.008, 0.008)		0.95
*Addition of either antenatal steroids, magnesium sulfate, preeclampsia, 5-min Apgar, or maternal education to the model did not change the above results **P-values for CBH greatest volume and CBH greatest extent adjusted according to the Benjamini–Hochberg method			

Table 3.4: Association between CBH total volume, CBH greatest volume, and CBH greatest extent and 4.5 year MABC-2, Beery VMI-6, and WPPSI-III FSIQ scores in multivariable regression models.

CBH greatest extent was independently associated with CBCL internalizing behaviour (β=0.49; Table 5) while CBH total volume and CBH greatest volume were only associated with internalizing behaviour on univariate analysis (β=0.051, 95% CI [0.005, 0.097] and β=0.060, 95% CI [0.007, 0.11]). CBH total volume, CBH greatest volume, and CBH greatest extent were all independently associated with externalizing behaviour (β=0.058, 0.076, and 0.55, respectively; **Table 3.5**). The addition of antenatal steroids, magnesium sulfate, preeclampsia, 5-min Apgar, or maternal education to the models did not meaningfully change the above results.

Factor*	β Coefficient (95% CI)	P value (adjusted p-value**)
4.5 year Internalizing score		
CBH total volume		
CBH total volume (mm^3)	0.043 (-0.004, 0.090)	0.076
Female sex	1.09 (-2.44, 4.62)	0.54
GA	-0.75 (-1.54, 0.045)	0.065
IVH Grade 2 or 3	2.17 (-1.64, 5.97)	0.264
WMI volume (mm^3)	0.001 (-0.003, 0.005)	0.661
CBH greatest volume		
CBH greatest volume (mm^3)	0.051 (-0.004, 0.105)	0.068 (0.085)
Female sex	1.034 (-2.50, 4.56)	0.57

GA	-0.76 (-1.55, 0.023)	0.057
IVH Grade 2 or 3	2.06 (-1.73, 5.85)	0.29
WMI volume (mm^3)	0.001 (-0.03, 0.005)	0.65
CBH greatest extent		
CBH greatest extent (mm)	0.49 (0.051, 0.94)	0.029 (0.048)
Female sex	0.98 (-2.53, 4.94)	0.59
GA	-0.71 (-1.49, 0.082)	0.079
IVH Grade 2 or 3	2.40 (-1.41, 6.20)	0.22
WMI volume (mm^3)	0.001 (-0.003, 0.005)	0.63
4.5 year Externalizing score		
CBH total volume		
CBH total volume (mm^3)	0.058 (0.017, 0.10)	0.006
Female sex	-2.84 (-5.96, 0.27)	0.074
GA	-0.20 (-0.90, 0.50)	0.57
IVH Grade 2 or 3	0.63 (-2.73, 3.99)	0.71
WMI volume (mm^3)	0.002 (-0.002, 0.006)	0.28
CBH greatest volume		
CBH greatest volume (mm^3)	0.076 (0.028, 0.123)	0.002 (0.02)
Female sex	-2.93 (-6.03, 0.163)	0.063
GA	-0.20 (-0.89, 0.49)	0.56
IVH Grade 2 or 3	0.52 (-2.80, 3.85)	0.76
WMI volume (mm^3)	0.002 (-0.002, 0.006)	0.27
CBH greatest extent		
CBH greatest extent (mm)	0.55 (0.16, 0.94)	0.006 (0.025)
Female sex	-2.96 (-6.08, 0.15)	0.062
GA	-0.20 (-0.90, 0.50)	0.65
IVH Grade 2 or 3	0.78 (-2.59, 4.15)	0.65
WMI volume (mm^3)	0.002 (-0.001, 0.006)	0.256
*Addition of either antenatal steroids, magnesium sulfate, preeclampsia, 5-min Apgar, or maternal education to the model did not change the above results		

Table 3.5 Association between CBH total volume, CBH greatest volume, and CBH greatest extent and 4.5 year internalizing and externalizing CBCL scores in multivariable regression models.

There were no significant associations between CBH size at TEA and any of the outcomes. In addition, when accounting for the maximum severity of GMH-IVH detected on US rather than MRI the results were not meaningfully changed.

3.5 Association between CBH location and outcome

In labeling CBH relative to outcome, lesions common to both typical and adverse outcome groups were in the inferior regions and more superficial (**Figure 3.4**). Lesions only identified in neonates with adverse outcomes extended more superiorly and deeper into the cerebellum.

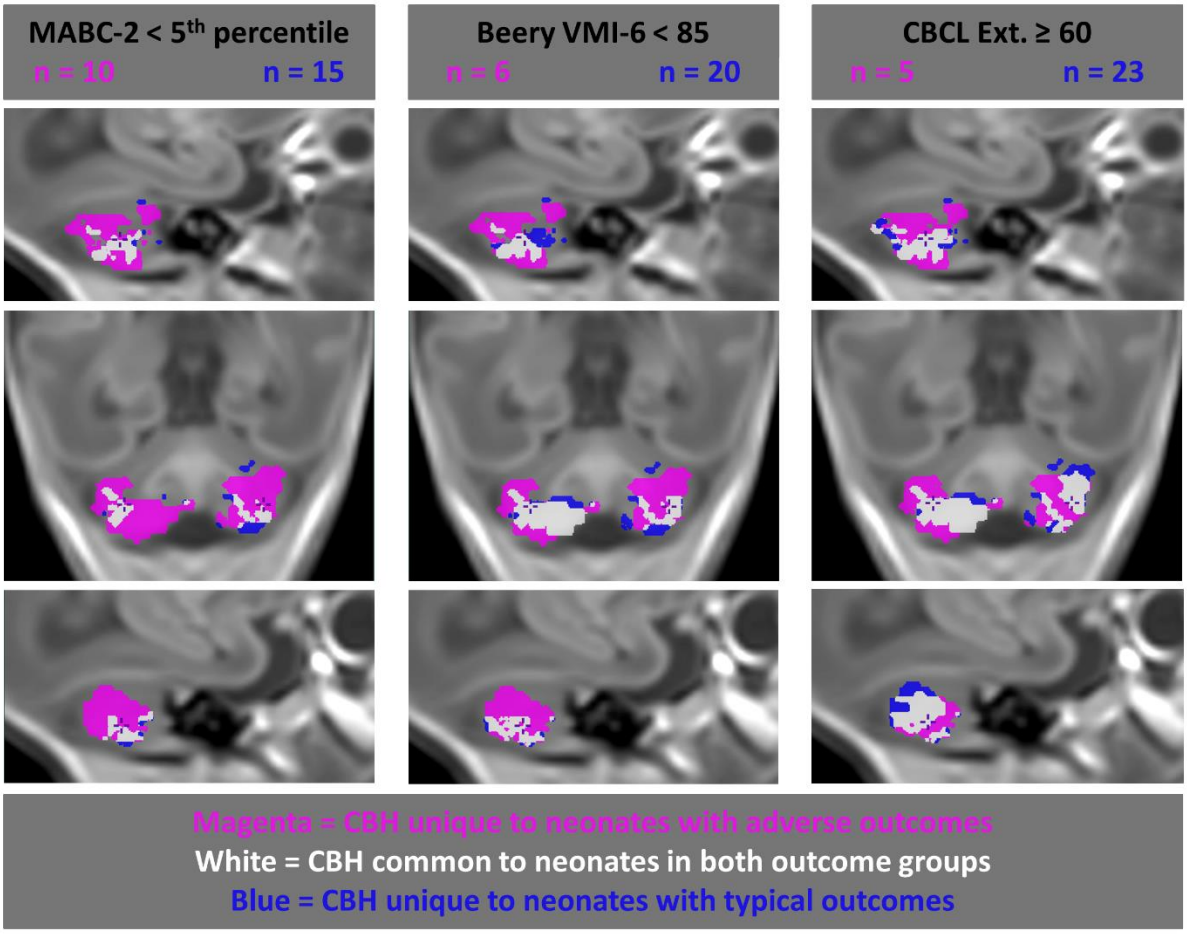

Figure 3.4 Probabilistic CBH map of very preterm neonates based on the 4.5 year MABC-2 (n=25), Beery VMI-6 (n=26) and CBCL externalizing (n=28) scores. Voxels in blue: CBH that are unique to the neonates who had typical outcomes (percentile score ≥5 for MABC-2 or ≥85 for Beery VMI-6); voxels in magenta: CBH that are unique to the neonates who had adverse outcomes (percentile score <5 for MABC-2, <85 for Beery VMI-6 and ≥60 for CBCL externalizing); voxels in white: CBH common to neonates in both typical and adverse outcome groups. The top column represents a sagittal section of the left cerebellar hemisphere and the bottom column the right hemisphere. The cross indicates the intersecting point; 2 crosses were

placed for each coronal section corresponding to left and right cerebellar hemispheric sagittal sections.

OR maps demonstrate the odds of developing an adverse outcome if CBH occurs in a specific voxel while VLSM compares the neurodevelopmental scores between neonates with and without CBH on a voxel-wise basis (**Figure 3.5**). The inferior cerebellum was the region with the highest odds of developing adverse outcomes, and in particular, the deeper areas of the inferior cerebellum. The voxels which were associated with outcomes on the VLSM maps coincided with those with the highest ORs on the OR maps. The OR maps and VLSM illustrated that CBH at different locations pose different risks for adverse outcomes. The number of voxels that were significant in the three VLSM maps (z-score ≥2.00) was 18 for MABC-2; 355 for Beery VMI-6; and 367 for externalizing behaviour. The z-score required to survive the correction for multiple comparisons by permutation thresholding for MABC-2, Beery VMI-6 and externalizing behaviour was 2.95, 3.03, and 3.17, respectively. VLSM for externalizing behaviour (maximum z-score=3.93) survived the FWE correction for multiple comparisons but VLSM for MABC-2 (maximum z-score=2.34) and Beery VMI-6 (maximum z-score=2.73) did not.

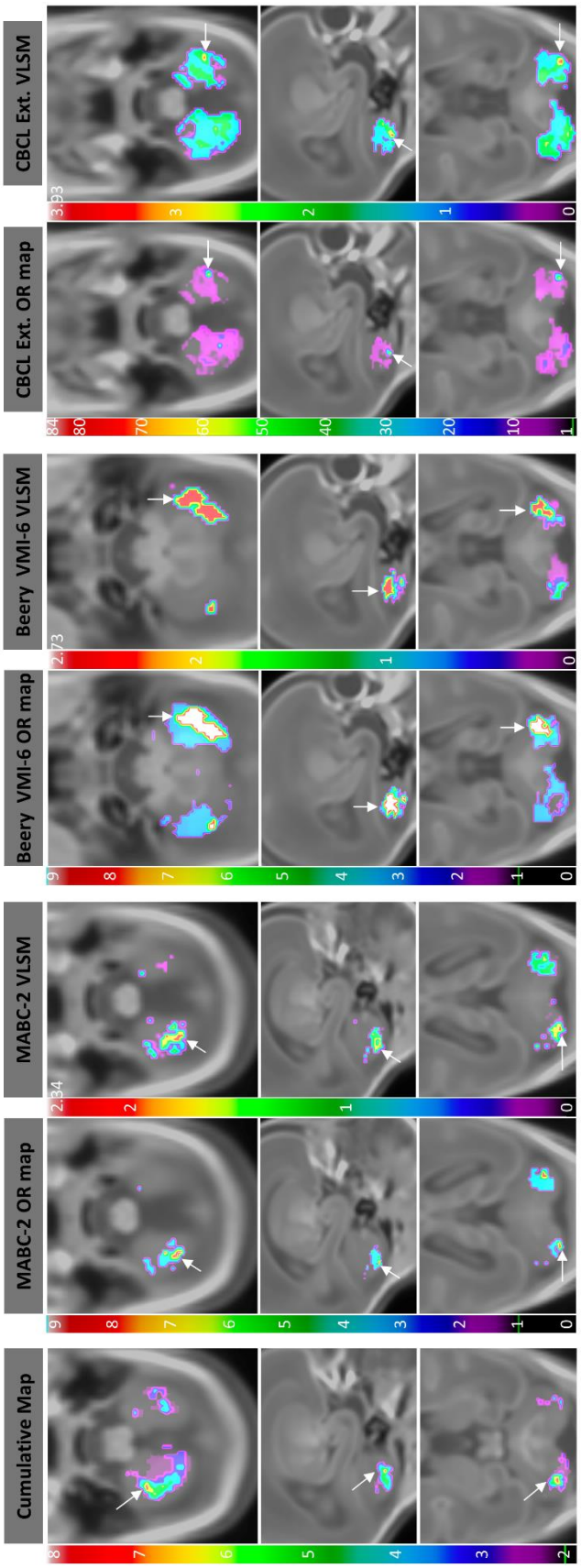

Figure 3.5: OR maps and VLSM of CBH for 4.5 year MABC-2 (n=25, second and third columns), Beery VMI-6 (n=26, fourth and fifth columns), and CBCL externalizing (n=28, sixth and seventh columns) outcomes overlaid on the T1-weighted neonatal brain template. The first column shows the spatial cumulative CBH map for the 35 very preterm neonates. Note the different scaling of the OR maps/VSLM in each column as indicated by each color bar. The white arrow points to the region with the highest cumulative number/OR/z-score in each respective map. The MABC-2 & Beery VMI-6 VLSM were calculated using the Brunner Munzel test while the externalizing behaviour VLSM was calculated using the Liebermeister test.

3.6 Validation of CBH detection on MRI

Of the 46 neonates with preterm imaging in the validation cohort, 10 (22%) had CBH identified on T1 and T2 weighted imaging. No additional CBH were detected on subsequent review of the SWI images.

4. Discussion

4.1 Summary and interpretation

In our contemporary prospective cohort of very preterm neonates, we demonstrated that CBH occurred in a particular spatial distribution and that the localization and quantification of CBH were important and independent determinants of later motor, visuomotor, and behavioural outcomes but not cognitive outcome. Contrary to our hypothesis, more anteriorly located CBH were uncommon and those located in the deeper aspects of the posterior lobe had higher odds of both motor and visuomotor dysfunction and externalizing behaviour problems. Our findings suggest that there is a dose- and location-dependent relationship between CBH and specific developmental outcomes and provides some clarity on the relationship between preterm CBH and outcome. Interestingly, the strength of the association between CBH size and motor outcomes approached that of WMI volume and motor outcomes whereas CBH size, but not WMI volume, was associated with externalizing behaviour problems.

Preterm CBH occurred most commonly in the inferior region of the posterior lobe, consistent with an autopsy series and a separate preterm cohort that underwent imaging (Haines, Wang, and Pierson 2013; Kim et al. 2016). The CBH were mainly distributed within the surface layers of the inferior posterior lobe. This area likely corresponds to the EGL, which is the germinal matrix for granule cells that proliferates during the third trimester and into the second postnatal year (Haldipur, Dang, and Millen 2018). The human fetal EGL achieves its maximum thickness between the 20th and 32nd gestational week and therefore requires a substantial blood supply during this period (Rakic and Sidman 1970). The vulnerability of the inferior aspect of the posterior lobe of the preterm cerebellum to hemorrhage remains unexplained but may relate to the anterior to posterior development of the EGL. Math-1, a transcription factor maintained throughout proliferation of the EGL, is expressed on granule cell precursors that populate the posterior lobe of the cerebellum later in development than those that populate the anterior lobe (Machold and Fishell 2005). In addition, the inferior aspect of the posterior lobe is supplied by the PICA. The PICA appears later during the ontogenic process and could be more susceptible to the hemodynamic perturbations typical of prematurity (Haines, Wang, and Pierson 2013; Macchi et al. 2005). The predilection of the posterior lobe for acquired injury extends to the adult, in whom posterior lobe infarcts occur more often than anterior lobe infarcts (De Cocker et al. 2015).

CBH size was independently associated with motor, visuomotor, and behavioural outcomes, but not cognitive outcome. Early reports of CBH detected by US had shown an association between CBH and early neurodevelopmental impairment implicating multiple domains. In one stark example, children with isolated CBH had a 66% rate of neurodevelopmental impairment relative to 5% in matched controls (Limperopoulos et al. 2007). This cohort, however, included children born between 1998-2003 who had larger hemorrhages. More recent cohort studies of neonates with mostly punctate CBH have not detected a higher rate of neurodevelopmental impairment in those with CBH (Senden et al. 2018; Steggerda et al. 2013; Tam, Rosenbluth, et al. 2011). In quantifying the size of the CBH, we were able to demonstrate that the precise dose of CBH is important. Given that volumetric quantification of CBH is not practical on routine clinical imaging, we also measured the 2-dimensional imprint of CBH and found that the CBH greatest extent was similarly associated with childhood neurodevelopment.

Functional topographic evidence points to a critical role for the human cerebellum in both motor and nonmotor behaviours (Stoodley and Schmahmann 2010). In adults, lesions to the anterior lobe can result in the cerebellar motor syndrome of dysmetria, dysarthria, and ataxia, while lesions to the posterior lobe can result in the cerebellar cognitive affective syndrome of executive, visual spatial, and linguistic impairments and affective dysregulation (Stoodley et al. 2016; Tedesco et al. 2011). Our results suggest that preterm CBH predicts motor, visuomotor and behavioural function, but not cognitive function, despite predominantly affecting the posterior lobes. Several explanations may be offered for this unexpected observation. First, the developing cerebellum may not have the same functional topography as the mature cerebellum. The cerebellar hemispheres are in state of rapid development during the preterm period and cell migration from the EGL persists into the second postnatal year (Rakic and Sidman 1970). Moreover, a neonatal resting state fMRI study revealed differences between the neonatal and adult functional cerebellar topography (Herzmann et al. 2019). Second, motor processing is represented twice in the cerebellar hemispheres: in the anterior lobe and lobule VIII of the inferior posterior lobe (Guell and Schmahmann 2020). Third, closer attention to the tasks involved in the MABC-2 and Beery VMI-6 reveal that visual spatial skills are critical to their performance (Beery, Buktenica, and Beery 2010; Henderson, Sugden, and Barnett 2007). In adults, lobule IX of the inferior posterior lobe is considered essential for the visual guidance of

movement (Glickstein et al. 1994). Although our probabilistic and OR maps were not of sufficient resolution to differentiate the lobules, the vulnerable posterior cerebellar regions could include lobules VIII and IX. Fourth, the lack of association between CBH and cognition may be attributable to the evolving concept of "cerebellar reserve," which expounds the existence of cerebellar cognitive resilience and recovery in cerebellar disorders (Mitoma et al. 2020). Impaired cerebellar cognitive functions, which include language, verbal working memory, and executive functions, may be compensated for by other cerebellar or extracerebellar areas not directly affected by the lesion.

More deeply seated voxels with CBH had higher odds for and were statistically associated with motor, visuomotor, and behavioural dysfunction. Many of these deep voxels were uniformly associated with an adverse outcome in our 3-color maps of CBH. These observations suggest that larger CBH, which may originate in the superficial EGL but permeate more deeply, may have a greater neurodevelopmental impact than smaller ones that are restricted to the EGL. Embedded in the cerebellar hemispheric white matter are the dentate nuclei, which receive Purkinje projections from the cerebellar cortex and project to the contralateral cerebral cortex via the cerebello-thalamo-cortical tracts (Bernard et al. 2014). It is possible that larger CBH that permeate more deeply implicate the dentate nuclei and their supratentorial projections. Indeed, in a cohort of preterm-born children with large CBH, childhood cortical volumes were linked to functional disabilities (Limperopoulos et al. 2014). In adults, involvement of the cerebellar deep nuclei is a predictor of deficits (Tedesco et al. 2011). Due to lack of grey-white differentiation in the context of weak myelination in the preterm brain (Hernandez-Castillo, Limperopoulos, and Diedrichsen 2019), we were unable to accurately distinguish hemorrhage within the deep nuclei from that within the adjacent white matter, and thus this remains a question for further study in the preterm population.

Consistent with a prior report, antenatal magnesium sulfate administration was associated with a lower frequency of CBH but not WMI (Gano et al. 2016). Magnesium sulfate for neuroprotection was first recommended by the Society for Obstetricians and Gynecologists of Canada in 2011, which corresponds to the midway point of enrollment in our cohort (Magee et al. 2011). In order to ensure that the association between magnesium sulfate and CBH was not dependent on concomitant maternal preeclampsia or antenatal steroid administration, we confirmed that the association held in newborns without preeclampsia and in those who received

antenatal steroids. Meta-analyses of randomized controlled trials have shown that antenatal magnesium sulfate reduces the frequency of CP in children born preterm (Crowther et al. 2017). The findings of our study and those of Gano et al. suggest that the neuroprotective effects of magnesium sulfate in preterm newborns may be mediated, at least in part, via reduced CBH. In 2016, only two-thirds of Canadian preterm newborns born at <29 weeks received it (Garfinkle et al. 2019). Our findings should encourage more widespread implementation of this intervention in women at risk of preterm delivery.

4.2 Strengths and limitations

Our study has several distinct strengths that allowed us to more effectively examine the association between CBH and neurodevelopment. First, CBH was precisely quantified and localised. In quantifying the CBH, we also developed a more clinically applicable measure in CBH extent. Previous studies have only qualitatively described CBH size (e.g., punctate vs. limited vs. massive) and location (Boswinkel et al. 2019; Senden et al. 2018). Second, in contrast to most previous studies, we primarily analyzed preterm, rather than TEA MRIs (Senden et al. 2018; Steggerda et al. 2013; Boswinkel et al. 2019; Vesoulis et al. 2019). We showed that CBH volume and extent at TEA were not associated with childhood outcomes, likely due to the involution of CBH over time. Third, we included a broad spectrum of preschool-age outcomes, which better represent long-term outcomes but have not been frequently examined in reference to CBH (Roberts et al. 2010; Villamor-Martinez et al. 2019; Hortensius et al. 2018). In particular, the MABC-2 at 4 years has been shown to be predictive of motor functioning in middle childhood (Griffiths et al. 2017). Fourth, WMI volume, which is a key contributor to neurodevelopment in preterm newborns, was systematically accounted for (Guo et al. 2017). By comparing the neurodevelopmental influence of CBH to that of WMI, we were able to qualify the clinical importance of CBH size. Fifth, we took a conservative approach in our analysis by setting a ceiling to CBH volume so as not to skew the results.

Our study also has limitations. First, the small number of newborns with CBH and small volume of many of the CBH limited the statistical power of our analyses when accounting for multiple comparisons. Yet, the proportion of preterm children impacted by CBH and the size of the lesions in this cohort are consistent with those reported in other smaller cohorts examining this lesion. In our VLSM, we used a criterion of z-score ≥2.00 to report voxels as predictive of

outcome due to the relatively small number of voxels with CBH. Since the VLSM for MABC-2 and Beery VMI-6 did not survive the more stringent permutation thresholding, they should be validated in independent samples. Second, the absence of susceptibility weighted imaging in our cohort could have led to an underestimation of CBH. However, in our validation cohort with SWI imaging, there were no neonates in whom CBH was missed on T1 and T2 weighted imaging and subsequently detected on SWI. In addition, SWI would not be an ideal sequence to measure CBH as it overestimates hemorrhage volume due to blooming (Sun et al. 2018). In confirming the association between magnesium sulfate and reduced CBH in the subset of preterm neonates born without preceding preeclampsia, we attempted to mitigate any confounding by indication. The localisation of CBH was descriptive and we could not delineate the cerebellar lobules or deep nuclei due to resolution-limitations and lack of grey-white contrast. Our findings, however, reflect clinically accessible imaging resolution (Hernandez-Castillo, Limperopoulos, and Diedrichsen 2019). Future work on the neonatal brain can seek to replicate the more detailed cerebellar segmentation that is available in the adult cerebellum (Park et al. 2014). We also recognize that factors other than those included in our models contribute in important ways to preschool neurodevelopment. Our objective, however, was to specifically assess the association between CBH and neurodevelopment. Finally, our outcomes were restricted to global outcome measures at preschool age and our analyses included multiple comparisons. As such, our findings merit replication in older participants at which time even more comprehensive neurodevelopmental outcomes can be reliably assessed.

5. Conclusions and future directions

5.1 Conclusions

In conclusion, CBH is associated with preterm brain health in a dose-dependent and topographic-specific manner. Probabilistic CBH and lesion-symptom maps illustrated that CBH typically occur in the inferior aspects of the posterior lobes, and that deeper cerebellar voxels with hemorrhage carried higher odds of motor, visuomotor and behavioural dysfunction than more superficial ones. The identification and quantification of CBH, *even when punctate*, may allow opportunity to improve motor and visuomotor outcomes by providing targeted early intervention.

5.2 Future directions

Further research can investigate the functional pathways between the cerebellum and supratentorial brain structures that mediate the effect of CBH on neurodevelopment in preterm neonates. In addition, future work can seek to understand why preterm CBH does not predict cognition and seek to establish the long-term effects of CBH on later childhood neurodevelopment.

5.2.1 Effect of CBH on cerebellar functional pathways

Although we showed that CBH predicts motor, visuomotor, and behavioural outcomes, our results only allow us to speculate as to the mechanism via which CBH might impact later neurodevelopment. Decades of investigation around preterm WMI has shown that the long-term neurodevelopmental consequences of preterm brain injury are mediated not only by acute destructive insults but also by disruptive effects on subsequent brain maturation in regions adjacent to and remote from the original injury (Back and Miller 2014). Several authors, including Volpe, 2009 and Wang et al, 2014, have proposed the term ‘developmental diaschisis’, as originally used by von Monakow in 1969, to explain that damage in one area can result in damage to remote but connected areas in the context of CBH (Volpe 2009; Wang, Kloth, and Badura 2014; von Monakow 1969). Diaschisis is a neurologic term indicating an important inhibition in activity at a site that is distant from a site of injury but is anatomically linked with it through white matter tracts (Wang, Kloth, and Badura 2014). As such, future work should

explore the impact of CBH on the cerebello-thalamo-cortical pathway and the structures along the pathway.

As previously discussed, the cerebellar hemispheres mediate their interactions with the contralateral cerebral cortex via the cerebello-thalamo-cortical pathway. The cerebellar hemispheres emit output solely through the deep nuclei, and in particular the dentate nucleus for output to the thalamus (D'Angelo 2018). The dentate nucleus efferent projections pass through the ventrolateral thalamic nuclei via the superior cerebellar peduncle (SCP), before being transmitted to the cerebral cortex. Investigation of each of these anatomic structures can yield valuable information on the association between CBH on later brain development.

The SCP consists mainly of efferent fibers including the cerebello-thalamo-cortical tract that runs from a cerebellar hemisphere to the contralateral thalamus, and the cerebello-rubral tract that runs from a cerebellar hemisphere to the contralateral red nucleus. Palesi et al. applied advanced diffusion imaging methods to reconstruct in adults the pathway connecting the cerebellar cortex to the contralateral cerebral cortex, passing through the SCP. Quantitative evaluation of tract projections passing via the SCP showed that the tracts connecting the cerebellar hemispheres to the contralateral associative cerebral cortex (prefrontal, parietal, temporal, and limbic cortices) comprised about 80% of the SCP (Palesi et al. 2015).

Several studies have reported on the development of the SCP in the developing fetus and preterm newborn. Pieterman et al. characterized the cerebello-thalamo-cortical white matter tracts in preterm newborns using high angular resolution diffusion imaging and connections between cerebellum and contralateral cerebral hemisphere were identified as early as 29 weeks (Pieterman et al. 2017). Fractional anisotropy of the SCP increased with postmenstrual age. In a study of children born preterm imaged at 7 years of age, Shany et al. found that fractional anisotropy of the SCP was associated with higher full-scale IQ and that its mean diffusivity was associated with lower MABC-2 motor scores (Shany et al. 2017). They did not find an association between neonatal CBH and later maturation of the SCP, but only eight newborns in their cohort had CBH. Future work can seek to examine the impact of CBH on development of the contralateral SCP. Surprisingly, in a study of adults with focal cerebellar injury, Olivito et al. reported *bilateral* diffusivity differences in the SCP in comparison to controls (Olivito et al. 2017). More specifically, cerebellar injury was associated with increased radial diffusivity and

without significant changes in axial diffusivity, indicating bilateral myelin damage with relative axonal sparing.

The SCP synapses in the red nucleus and the ventrolateral nuclei of the thalamus, which then projects to the cortex. As such, examination of thalamus may also offer insight into how CBH mediates its effects on neurodevelopment. Once regarded as a simple passive relay of information to the cerebral cortex, the thalamus is now viewed as a key neural processor and integrator for the activities of the forebrain (Sherman 2016). The thalamus receives cerebellar inputs and plays a critical role in transferring and transforming cerebellar output to the cortex in order to optimize or correct its processing (Habas, Manto, and Cabaraux 2019). Two main parts can be distinguished in the thalamus: the dorsal and ventral regions. Cerebellar efferents traveling in the SCP terminate in the ventral nuclei of the thalamus (Bernard et al. 2014). In preterm newborns, thalamic volumetric growth has been shown to correlate with primary visual cortical activation, suggesting that there is developmental synergy between thalamic morphologic development and the emergence of thalamocortical connections in the third trimester (Ceschin et al. 2015). In addition, very preterm children manifest delayed thalamic growth during early childhood and this delayed development contributes to reduced motor and cognitive function at 7 years (Loh et al. 2019). Future work should establish the impact of CBH on downstream ventrolateral thalamic morphologic development.

Finally, CBH may mediate its effect on neurodevelopment via the cerebral cortex. As previously discussed, resting state fMRI studies of adults and neonates have demonstrated functional connectivity between the cerebellar hemispheres and different regions of the cortex (Herzmann et al. 2019; Buckner et al. 2011). As such, it would be of interest to investigate the remote cortical impairments secondary to CBH. In adult patients with cerebellar injury, using voxel-based morphometry, Clausi et al. showed diminished cortical grey matter volume in the left frontal, parietal, and temporal lobes after right cerebellar injury (Clausi et al. 2009).

Previously, large CBH in the preterm newborn has been associated with impaired growth of the uninjured contralateral cerebral hemisphere, with impairment evident at TEA (Limperopoulos, Soul, et al. 2005). Unilateral CBH resulted in decreased contralateral cerebral white and grey matter volume, whereas bilateral CBH was associated with bilateral reductions in cerebral brain volumes. In order to study the regional specificity of the remote trophic effects of CBH, the same authors parcellated each cerebral hemisphere into 8 regions on

MRIs performed around 3 years of age (Limperopoulos et al. 2010). In the newborns with unilateral CBH, cortical grey matter volumes were significantly smaller in the contralateral dorsolateral frontal, premotor, and supplementary motor cortices. On the contrary, after bilateral CBH, there was no significant difference between the ipsilateral and contralateral cortical volumes in any of the regions. The cortical regions most affected by contralateral CBH are areas known to have significant functional connectivity with the cerebellum, supporting the notion that regional cerebral developmental attenuation is due to interruption of cerebello-thalamo-cortical tracts. In order to examine the relationship between regional reductions of cerebral volumetric growth and later development, the children were brought back for neurodevelopmental testing at 8 years (Limperopoulos et al. 2014). The authors found associations between early signs of autism and dorsolateral prefrontal cortical volume; gross motor scores and sensorimotor cortical volume; and cognitive and expressive language scores and premotor volume. In establishing these relationships, they linked regional secondary impairment of remote cerebral cortical growth and neurodevelopmental disabilities in survivors of CBH.

Recently, a retrospective case series study examined cortical development at TEA in five neonates with isolated unilateral CBH (Dijkshoorn et al. 2020). This study focused on two distinct aspects of cortical development: cortical surface area and cortical thickness. Each of these measures of cortical development are thought to be driven by discrete genetic mechanisms and could be differentially affected by neonatal morbidity (Winkler et al. 2018). The authors hypothesized that unilateral CBH in very preterm infants would be associated with reduced contralateral cortical thickness and cortical surface area at TEA. In the five neonates with large unilateral CBH, there were no lateralization effects in that the contralateral cortex was not thinner and did not have a reduced surface area relative to the ipsilateral cortex. In addition, the cortices of the neonates with CBH were not thinner and did not have reduced surface area relative to matched controls. There are several possible explanations for the lack of association between CBH and contralateral cortical maldevelopment, which was first reported in the Limperopoulos studies (Limperopoulos et al. 2010; Limperopoulos, Soul, et al. 2005). First, like our cohort, the cohort of Dijkshoorn et al. was contemporary in that the CBH were smaller than those reported by Limperopoulos, whose cohort was born in 1998-2005. In addition, MRIs in the Dijkshoorn et al. study were performed at TEA whereas those in the Limperopopos et al. cohorts

were performed in early childhood. It is possible that the developmental diaschisis effects are only evident on MRI later in childhood rather than at TEA.

As a next step, we will aim to examine the role of remote thalamic and cortical maldevelopment in the context of CBH. Our aims will be to (1) examine the association between neonatal CBH size and location and childhood thalamic and cortical regional development and (2) examine the association between remote regional thalamic and cortical maldevelopment and the specific neurodevelopmental domains associated with CBH. We hypothesize that (1) the laterality of CBH would be associated with a difference between left and right regional thalamic and cortical volumes and that (2) reductions in thalamic and cortical volumes at 8 years would be associated with childhood neurodevelopmental function. Many of the participants in the cohort analyzed herein are currently undergoing brain MRI at 8 years of age as part of a separate research study. To extract thalamic volumes, we will apply MAGeT Brain (Pipitone et al. 2014) and to extract triangulated cortical surface at 8 years, we will apply CIVET, which is a well-established imaging pipeline (Kim et al. 2005).

5.2.2 Evaluation of cerebellar reserve

Cerebellar reserve refers to the capacity of the cerebellum to compensate for tissue damage or loss of function (Mitoma et al. 2020). The concept was first described in humans in patients with gunshot wounds by Gordon Holmes in 1917 (Holmes 1917). Holmes described the recovery process of motor incoordination in two patients with isolated gunshot wounds to the cerebellum. Despite significant damage, both patients walked months later. As such, cerebellar reserve can result in clinical tolerance to pathology or resilience to impairment and can be defined as a moderator between pathology and outcome.

In a consensus paper describing cerebellar reserve, Mitoma et al. proposed that following an acute cerebellar lesion, impaired cerebellar function may be compensated for by other cerebellar or extracerebellar areas not directly affected by the lesion (Mitoma et al. 2020). Experimental studies, performed mainly in rodents, have demonstrated that following cerebellar injury a substantial recovery ensues (Petrosini, Molinari, and Gremoli 1990). The developmental timing of the induced cerebellar lesion in animals is a key factor: lesions occurring early in cerebellar development stage have less immediate and less predictable consequences than those that occur in adulthood (Gramsbergen 2001). In addition, early in development, there is a lack of

correlation between the severity of deficits and the size of the lesion such that a large cerebellar lesion may induce only subtle deficits. Neurobiologically, in hemicerebellectomy in rats, cerebellar compensation comprises a non-random remodeling of both cerebellar networks and cerebello-thalamo-cortical pathways (Hillman and Chen 1985). When in addition to the hemicerebellectomy the contralateral cortex is also ablated, the rat is unable to relearn the motor task, demonstrating the importance of cerebello-cortical pathways in functional recovery (Ben Taib et al. 2005).

In human adults, recovery from stroke or cerebellar trauma indicates the existence of self-recovery capacity within the cerebellum (Stoodley et al. 2016; Kelly et al. 2001). Our findings suggest that cognition, in contrast to motor, visuomotor, and behavioural function, was not associated with CBH size and location. Cerebellar cognitive reserve may underly the lack of association between CBH and cognitive outcome in preterm neonates. The original description of the CCAS noted improvements in verbal and visual memory and problem solving over the months following the cerebellar insult (Schmahmann and Sherman 1998). The exact mechanisms that favor cognitive resilience in preterm neonates with CBH are not established. However, exploring the cerebello-cerebral connections may allow for a better understanding of this cognitive reserve.

5.2.3 Impact of CBH on the childhood outcomes

Later childhood and adolescent outcomes following preterm CBH should be explored since they may better reflect actual function, and in particular cognitive, social, and behavioural function (Kilbride et al. 2017). Indeed, predicting the patterns and severity of adult outcomes improves over time as abilities mature (Synnes and Hicks 2018).

Mental health is also important to assess later in childhood. At the clinical level, a meta-analysis of five studies reported a prevalence ranging from 21-28% for psychiatric disorders in preterm children and adolescents and an OR of 3.66 (95% CI, 2.57-5.21) compared to full-term controls (Burnett et al. 2011). As previously discussed, the disorders observed in preterm children and adolescents include attention-deficit/hyperactivity disorder, depressive and anxiety disorders, and autism spectrum disorder (Johnson and Marlow 2011). In very preterm adults, an individual participant data meta-analysis of six preterm cohort studies found higher scores for internalizing problems but lower scores for externalizing problems compared with controls

(Pyhälä et al. 2017). In a longitudinal study of very preterm children, Allin et al. linked cerebellar hemispheric volume at 14-15 years with reduced executive, visuo-spatial and language function (Allin et al. 2005). Furthermore, when reimaged in early adulthood, the same group reported a reduction in cerebellar volume between adolescence and young adulthood in very preterm individuals but not term-born controls. The reduction in cerebellar volume was associated with reduced self-reported wellbeing (Parker et al. 2008).

The impact of CBH on later childhood emotional and mental health has not been explored. Cerebellar contributions to autism spectrum disorder, personality disorders, and posttraumatic stress disorder reveal alterations in cerebello-cerebral circuits (Lupo et al. 2018; Schmahmann et al. 2019). Cerebellar structure and function differences are among the most frequent neuroanatomical findings in autism spectrum disorder (D'Mello and Stoodley 2015). In addition, rodent models have revealed that disruption to the cerebellar circuitry is sufficient to produce restricted and repetitive behaviours and impairments in social behaviours (Stoodley et al. 2017).

The findings in our study represent pre-school outcomes but it remains to be determined if the association between CBH size and topography and neurodevelopment persists into later childhood, adolescence, and adulthood and whether CBH is associated with neuropsychiatric presentations. Studies examining the association between CBH and later childhood or adolescent outcomes have not yet been performed. Many of children enrolled in the cohort we described have been enrolled in another study in which participants undergo neurodevelopmental testing at 8 years of age. Subjects undergo motor testing with the MABC-2, visuomotor testing with the Beery-VMI-6, and cognitive testing with the WISC-V, and complete the CBCL to assess behaviour. We aim to verify whether the dose- and location-dependent associations between CBH and neurodevelopment hold true at 8 years of age.

5.2.4 Future directions – summary

We demonstrated that CBH occurred in a particular spatial distribution affecting the inferior posterior lobe and that the localization and quantification of CBH were important and independent determinants of later motor, visuomotor, and behavioural outcomes but not cognitive outcome. Our findings suggest that there is a dose- and location-dependent relationship between CBH and specific outcomes and provide some clarity on the relationship between

preterm CBH and outcome. In addition, our findings reinforce the importance of administering antenatal magnesium sulfate to woman at risk for very preterm delivery.

Going forward, it will be important to establish the circuitry through which CBH mediates its effects on childhood neurodevelopment, explore cognitive cerebellar reserve, and verify the impact of CBH on later childhood outcomes. We aim to realize these objectives by examining structures along the cerebello-thalamo-cortical pathway and investigating outcomes at 8 years of age. A better understanding of the long-term implications and mechanisms of CBH-mediated neurodevelopmental challenges could ultimately pave the way for targeted therapeutics, even including non-invasive cerebellar stimulation (Miterko et al. 2019). The overarching goal of further examination of preterm CBH is to better understand its consequences in order to optimize neurodevelopment and neurodevelopmental interventions.

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