THE IMPACT OF CEREBELLAR MALFORMATIONS ON CEREBRAL DEVELOPMENT AND CHILD FUNCTIONING

by

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There are no seven wonders of the world in the eyes of a child.
There are seven million…
~Walt Streightiff

ABSTRACT

The overall objective of this study was to delineate the impact of cerebellar malformations on cerebral development and child functioning in children aged one to six years.

This study describes a high prevalence of developmental disabilities in children with cerebellar malformations and provides evidence for an important relationship between regional cerebellar volumetric growth and domain specific developmental and functional deficits. Additionally, our data suggests that cerebellar malformations significantly alter region specific cerebral development including, the subgenual white matter, midtemporal white matter, subcortical grey matter and inferior occipital grey matter when compared to healthy age-matched controls. Finally, decreased cerebellar volume significantly predicts total and regional cerebral growth impairments

The results of this study may improve our ability to prognosticate the developmental outcome in young children with cerebellar malformations, and assist in developing targeted early intervention strategies, aimed at minimizing developmental disabilities and optimizing life quality in children with cerebellar malformations.

ABRÉGÉ

L'objectif général de cette étude était de définir l'effet des malformations cérébellaires sur la croissance cérébrale et sur les capacités fonctionnelles des enfants âgés de un à six ans.

Cette étude décrit une forte prévalence de déficits développementaux chez les enfants ayant une malformation cérébellaire et démontre une importante association entre les volumes cérébellaires régionaux et des déficits développementaux et fonctionnels spécifiques. En outre, nos données suggèrent que les malformations cérébellaires affectent significativement le développement de régions cérébrales spécifiques, incluant les régions sous-genual, mi-temporal, et occipitale inférieure lorsque comparées aux témoins jumelés selon l'âge. De plus, une réduction du volume cérébellaire prédit significativement des réductions volumétriques cérébrales tant au niveau global que régional.

Ces résultats peuvent améliorer notre habileté à pronostiquer la trajectoire développementale des jeunes enfants ayant une malformation cérébellaire, et contribuer à développer des stratégies ciblées d'intervention précoce visant à minimiser les limitations fonctionnelles et optimiser la qualité de vie chez les enfants ayant une malformation cérébellaire.

PREFACE

THESIS FORMAT

This is a manuscript-based thesis constructed around three manuscripts. The texts are reproduced exactly as published, or as they will be submitted. The first manuscript is a published comprehensive review of the available literature on the neurodevelopmental outcome of children with cerebellar malformations. The second manuscript answers our first objective and describes the associations between regional cerebellar volumes and functional outcomes in children with cerebellar malformations. The last manuscript, in which our second objective is addressed, compares total and regional cerebral volumes between children with isolated cerebellar malformations and age and gender matched controls.

Manuscript #1 **Neurodevelopmental Outcomes in Children with Cerebellar Malformations: A Systematic Review**

Bolduc, M.-E., & Limperopoulos, C. (2009). Neurodevelopmental Outcomes in Children with Cerebellar Malformations: A Systematic Review. *Developmental Medicine & Child Neurology, 51*(4), 256-267.

Manuscript #2 **Regional cerebellar volumes predict functional outcome in children with cerebellar malformations**

Bolduc, M.-E., du Plessis, A. J., Sullivan, N., Guizard, N., Zhang X., Robertson, R. L., Korner-Bitensy, N., & Limperopoulos, C. *Unpublished manuscript in preparation for submission*

Manuscript #3 **Cerebellar malformations alter regional cerebral development**

Bolduc, M.-E., du Plessis, A. J., Evans, A., N., Guizard, N., Zhang X., Robertson, R. L., Korner-Bitensy, N., & Limperopoulos, C. *Unpublished manuscript in preparation for submission*

CONTRIBUTIONS OF AUTHORS

Marie-Eve Bolduc BSc OT

I, the candidate, am the primary author for all manuscripts included in this thesis. I performed the literature review and selected all standardized outcome measures to be used for this project. I also selected and validated a cerebellar magnetic resonance imaging parcellation scheme to be used in children that was previously developed for use in adult MRI studies. Finally, I completed the image analysis, statistical analyses, data interpretation and discussion.

Adre J du Plessis MD

Dr. du Plessis performed neurological examinations for the children with cerebellar malformations and assisted with the interpretation of results.

Alan Evans PHD

Dr. Evans provided access to the database of MRI scans for healthy controls which were acquired as part as MRI Study of Normal Brain Development funded by the National Institutes of Health.

Nicolas Guizard M.Eng.

Mr. Guizard contributed in the development of computer-based applications in order to perform advanced 3-D MRI parcellation of the cerebellum and the cerebrum.

Nicol Korner-Bitensky PHD

Dr. Korner-Bitensky provided expertise in methodology and data analysis.

Catherine Limperopoulos PHD

Dr. Limperopoulos conducted the *Peabody Developmental Motor Scale*. She also was responsible for overseeing data collection including MRI acquisitions, developmental testing, data entry, and data analysis. Finally, she reviewed all versions of the manuscripts and thesis.

Richard L Robertson MD

Dr. Robertson reviewed all the MRI scans in order to establish the clinical diagnoses of our cohort.

Nancy Sullivan PHD

Dr. Sullivan administered the *Mullen Scales of Early Learning*.

Xun Zhang PHD

Dr. Zhang provided support in statistical analysis.

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Finally, I would like to thank my family for their support, encouragement and understanding throughout the pursuit of this degree. They have been a continuous source of inspiration and motivation. I would like to dedicate this thesis to my husband Ron and our children Liam and Laïka.

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ABBREVIATIONS

MRI	Magnetic resonance imaging
3-D	Three-dimensional
CNS	Central nervous system
DWM	Dandy-Walker malformation
DWV	Dandy-Walker variant
IVH	Inferior vermis hypoplasia
PCH	Pontocerebellar hypoplasia
MCM	Mega cisterna magna
cc	Cubic centimeter

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CHAPTER 1
GENERAL INTRODUCTION

Recent advances in neuroimaging techniques and in particular magnetic resonance imaging (MRI) have greatly enhanced the accuracy with which structural anomalies of the brain are identified. This is particularly true of anomalies in the posterior fossa (Boltshauser, 2004; Sandalcioglu et al., 2006). In fact, cerebellar malformations are now amongst the most commonly diagnosed brain malformations in the fetal and neonatal period. In addition, advances in fetal and neonatal critical care have resulted in higher survival rates and better management of associated complications. However, despite these advances in medical care and neuroimaging, the structural and functional consequences of cerebellar malformations in young children remain poorly defined.

The overall objective of this study was to delineate the impact of cerebellar malformations on cerebral development and child functioning in children aged one to six years. Specifically, we first examined the association between cerebellar volume and developmental and functional outcome in children with cerebellar malformations using advanced three-dimensional (3-D) MRI techniques and standardized developmental outcome measures. We then delineated the impact of cerebellar malformations on cerebral development.

This study provides previously unavailable MRI data for future evaluation and treatment of children with cerebellar malformations and important clinical information regarding the association between structural and functional outcomes. Better definition of the consequences of cerebellar malformations may justify the need for more extensive neurodevelopmental follow-up of this high-risk population, as well as appropriate and careful developmental screening at crucial intervals in the lifespan. Additionally, knowledge of the possible consequences of cerebellar malformations on cerebral development may help us to better understand the extent and nature of developmental and functional limitations in this vulnerable population.

CHAPTER 2
REVIEW OF THE LITERATURE

2.1 The cerebellum: beyond motor function

The role of the cerebellum in motor coordination and execution has been described for over a century (Luciani, 1891). Although cognitive impairments following a lesion to the cerebellum have been reported anecdotally in earlier years, accumulating evidence in primates and humans have only recently suggested an important role for the cerebellum in the development of cognitive, language, and social function (Boltshauser, 2004; Limperopoulos et al., 2007; Limperopoulos et al., 2006; Middleton, & Strick, 2001; Schmahmann, & Pandya, 1997; Steinlin et al., 1999; Tamada et al., 1999). In fact, the cerebellum has been shown to be anatomically organized i) medio-laterally with the lateral hemispheres of the cerebellum believed to be involved in higher cognitive function and motor function, as well as ii) in an anterior-posterior manner with the flocculonodular lobe and anterior cerebellar vermis primarily involved in axial motor control and the fastigial nuclei of the posterior cerebellar lobe and posterior cerebellar vermis involved in the regulation of emotion, social behavior and affect (Desmond et al., 1998; Joyal et al., 2004; Schmahmann, 2004).

The presence of strong anatomical connectivity between regions of the cerebellum and areas of the cerebrum known to be involved in these higher cognitive functions further corroborates this evidence (Habas et al., 2009; Ramnani, & Miall, 2001). The cerebellum's role in motor control has long been demonstrated through the presence of various anatomical pathways connecting the cerebellum to the spinal cord and the cerebral cortex in feedforward and feedback directions (Leiner, & Leiner, 1989). More recently, the use of retrograde transneuronal transport has allowed researchers to demonstrate a strong efferent association between the dentate nucleus and the prefrontal cortex through the thalamus in primates (Middleton, & Strick, 2001). Specifically, the deep nuclei of the cerebellum are connected to the motor, supplementary motor, prefrontal, posterior parietal and superior temporal cortices, in addition to the cingulate and parahippocampal gyri through the thalamus (Schmahmann, & Pandya, 1997). Output connections from the dentate nucleus to the inferior parietal lobule and the dorsolateral prefrontal cortex have also been described (Allen et al., 2005). Thus, this further reinforces the important cerebellar contribution to cognitive, behavioral and affective/emotional functions.

2.2 Normal cerebellar development

Embryologically, the cerebellum has a protracted developmental course, beginning from the first weeks of embryonic development to the second year of postnatal life (Limperopoulos, & du Plessis, 2006; ten Donkelaar, 2009). More specifically, around the 15th gestational day, the central nervous system (CNS) arises from the neural plate, which then thickens around the 17th day of gestation and starts to fold (Barkovich, 2000). Subsequently, this forms the neural tube at about 20 gestational days (Barkovich, 2000). Seven to eight days later, the tube is closed and three vesicles appear at the rostral end of the neural tube creating the prosencephalon, the mesencephalon and the rhombencephalon (Barkovich, 2000), followed by the emergence of the rhombic lips from a bilateral thickening of the alar plate of the rhombencephalon during the fifth week (Barkovich, 2000; Barkovich et al., 1989; Demaerel, 2002). Around the sixth gestational week, the cerebellum starts developing from the rhombic lip (Demaerel, 2002). The formation of the vermis is completed at 16-18 weeks (Barkovich, 2000; Demaerel, 2002; Limperopoulos, & du Plessis, 2006) followed by the cerebellar hemispheres around 20-22 weeks of gestation (Demaerel, 2002). However, the cerebellar cortex will not reach its final three-layer organization before 12 months post-natally (Barkovich, 2000).

2.3 Cerebellar malformations

A cerebellar malformation is defined as a defect that occurs during embryologic development; however our current understanding of the pathogenesis of these abnormalities remains limited (Patel, & Barkovich, 2002). A number of exogenous and endogenous factors have been proposed in the genesis of cerebellar malformations (ten Donkelaar, 2009). For example, mutations or anomalies of several genes have been linked with cerebellar malformations (Millen, & Gleeson, 2008). Additionally, exposure to drugs or irradiation has also been described as potential risk factors for cerebellar malformations (ten Donkelaar, 2009).

Advances in MRI have resulted in the increased identification of what were once considered rare malformations, such as rhombencephalosynapsis, (Boltshauser, 2004) and of new variations of known cerebellar malformations (Sandalcioglu et al., 2006). Cerebellar malformations comprise a variety of malformations with Dandy-Walker complex being one of the most commonly diagnosed cerebellar malformations. The Dandy-Walker complex is

characterized by different degrees of malformation of the cerebellar vermis (Parisi, & Dobyns, 2003) and includes Dandy-Walker malformation (DWM) and mega cisterna magna, as well as other cerebellar malformations. Dandy-Walker malformation can be described as a cystic dilation of the fourth ventricle combined with various degrees of vermian agenesis, and elevated tentorium (Barkovich, 2005). Mega-cisterna magna is characterized by an enlarged cisterna magna with a normal fourth ventricle and cerebellar vermis (Barkovich, 2005). Dandy-Walker variant (DWV) has also been used to describe a malformation within the Dandy-Walker complex. It was most commonly used to describe a combination of hypoplasia to the cerebellar vermis and a cystic dilation of the fourth ventricle, without enlargement of the posterior fossa (Barkovich, 2005). However, other authors did not include the presence of a cystic dilation of the fourth ventricle as an essential diagnostic criteria (Ecker et al., 2000; Estroff et al., 1992), or use the term DWV interchangeably with inferior vermis hypoplasia (IVH) (described below). Consequently, due to these multiple definitions, it has been strongly recommended that the use of DWV be discarded (Barkovich, 2005). In this thesis, DWV is used as a diagnostic category only when making reference to cases that have previously been described in the context of the existing literature. The term DWV is not used as a diagnostic category for the children accrued as part of this research project. Finally, IVH is characterized by incomplete development of the inferior portion of the vermis (Limperopoulos et al., 2006).

Other less common cerebellar malformations include: rhombencephalosynapsis, molar tooth sign malformations (including Joubert syndrome), cerebellar aplasia, hypoplasia, dysplasia, and cerebellar agenesis. Rhombencephalosynapsis can be described as the fusion of the cerebellar hemispheres and agenesis of the vermis (Barkovich, 2000). The molar tooth sign is characterized by an anomaly of the deep interpeduncular fossa, enlarged superior cerebellar peduncles that are more horizontally oriented, and a hypoplastic cerebellar vermis (Maria et al., 2001). Joubert syndrome is the best known syndrome typified by the molar tooth sign, and is associated with developmental delays, hypotonia, breathing anomalies and abnormal eye movement (Maria et al., 1999). Cerebellar aplasia and hypoplasia are characterized by complete or incomplete failure of development of the cerebellum respectively (ten Donkelaar et al., 2003), while cerebellar dysplasia can be described as an abnormality of the cerebellar cortex or pattern of the folia (Barkovich, 2000). Lastly, cerebellar agenesis is a total or near total absence of the cerebellum (Sans-Fito et al., 2002).

Cerebellar malformations can also be associated with a variety a supratentorial abnormalities, including agenesis of the corpus callosum and cerebral heterotopias (Volpe, 2001) and genetic syndromes such as Trisomy 9, Trisomy 13, Trisomy 18, Wolfe syndrome and Fragile X syndrome (Barkovich, 2000).

2.4 Developmental outcome of children with cerebellar malformations

Introduction

In recent years, the greater availability of MRI has allowed us to detect more subtle cerebellar abnormalities that would have previously remained undiagnosed or misdiagnosed as idiopathic developmental delay (Boltshauser, 2004; Sandalcioglu et al., 2006). Moreover, prior to the availability of MRI, the diagnosis of cerebellar malformations often relied on the presence of hydrocephalus, with an average age of presentation of three months (Kalidasan et al., 1995). Due to the presence of prolonged increased intracranial pressure, secondary insult to the cerebellum and cerebrum often occurred. Additionally, improvements in shunting procedures have resulted in better management of hydrocephalus (Kumar et al., 2001). The implementation of these earlier and improved medical interventions has likely resulted in improved overall outcome for children with cerebellar malformations over the last ten years.

To better define the current impact of cerebellar malformations on child function, we performed a review of the available literature describing the neurodevelopmental outcomes in these children. In the manuscript that follows, available evidence on the neurodevelopmental outcome of the cerebellar malformations is described using traditional diagnostic categories.

NEURODEVELOPMENTAL OUTCOMES IN CHILDREN WITH CEREBELLAR MALFORMATIONS: A SYSTEMATIC REVIEW

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2.4.1 Abstract

Cerebellar malformations are increasingly diagnosed in the fetal period. Consequently, their consideration requires stressful and often critical decisions from both clinicians and families. This has resulted in an emergent need to understand better the impact of these early life lesions on child development. We performed a comprehensive literature search of studies describing neurodevelopmental outcomes of cerebellar malformations between January 1997 and December 2007. Overall, data suggested that children with isolated inferior vermis hypoplasia (IVH) and mega cisterna magna (MCM) have a good developmental outcome, whereas children with molar tooth sign/Joubert syndrome, vermis hypoplasia, pontocerebellar hypoplasia (PCH) Type II, and cerebellar agenesis experience moderate to severe global developmental delays. Reports for Dandy-Walker malformation (DWM) were conflicting; however the presence of a normally lobulated vermis and the absence of associated brain anomalies were associated with a more favourable outcome. Finally, children with isolated cerebellar hypoplasia experienced fewer impairments. Important methodological limitations highlighted include a lack of standardized outcome measure use in 79% of studies and, the predominant use of retrospective study designs (85%) with 40% limited to case reports or case-series. In summary, rigorous outcome studies describing the spectrum of disabilities in survivors are urgently needed to accurately delineate the long-term neurodevelopmental consequences of cerebellar malformations.

2.4.2 Introduction

Recent advances in neonatal intensive care and neuroimaging techniques, in particular magnetic resonance imaging have greatly enhanced our ability to detect structural anomalies of the brain. This is particularly true for anomalies in the posterior fossa[1-2]. The incidence of posterior fossa malformations diagnosed in the newborn period is estimated to be 1 out of every 5000 live births[3]. Fetal posterior fossa malformations on imaging are now amongst the most commonly diagnosed brain malformations in utero, though the actual prevalence is unknown. Advances in our ability to diagnose accurately cerebellar malformations have increased the need for a greater understanding of the impact of these early life lesions on child function. Despite these advances, the long-term neurodevelopmental consequences of cerebellar malformations in children remain poorly defined. However, their consideration requires stressful and often critical decisions from both clinicians and families. This is particularly important in view of the fact that studies are now showing that up to 80% of parents choose to terminate their pregnancy following a prenatal diagnosis of a cerebellar malformation, even in the absence of rigorous outcomes data[4-5].

In recent years, the traditional role of the cerebellum has been repeatedly challenged. The cerebellum, once underestimated as a simple center for motor coordination and execution, is now increasingly recognized as a center for higher cognitive functions as well. There is growing evidence in primate and adult literature to support an important role for the cerebellum in perceptual, linguistic, cognitive and affective functions[1, 6-9]. In fact, Schmahmann and Sherman[10] and Schmahmann[11] have described the cerebellar cognitive affective syndrome in adults with lesions or malformations confined to the cerebellum. These patients were found to have a constellation of symptoms including cognitive, affective and behavioural deficits[12]. It has been hypothesized that the cerebellum acts as a modulator for all the cerebrocerebellar subsystems that control motor, sensory, cognitive, affective and autonomic domains[10]. Moreover, the cerebellum has been associated with deficits in spatial navigation, autism and, mutism and with impaired ability to learn music[13].

Despite this accumulating evidence, it is unclear whether these higher-order cognitive functions have been systematically evaluated in children with cerebellar malformations. Therefore, the objective of this paper was to summarize our current knowledge of the neurodevelopmental outcomes in children with cerebellar malformations. Studies describing

cognitive, language, socialization, behavioural or neuromotor outcomes published over the last decade were systematically reviewed.

2.4.3 Methods

To delineate better the current impact of cerebellar malformations on child development, we performed a systematic review of the literature on neurodevelopmental outcomes in children with cerebellar malformations limited to studies published in the last ten years (January 1997 to December 2007). Our systematic search was performed using PudMed, Medline and CINAHL using the following keywords: cerebellar malformation; cerebellar dysgenesis; posterior fossa malformation; posterior fossa dysgenesis; cerebellar hypoplasia, cerebellar dysplasia, cerebellar agenesis; DWM; Dandy-Walker variant (DWV); Dandy-Walker complex; Dandy-Walker syndrome; vermis hypoplasia; rhombencephalo-synapsis; pontocerebellar atrophy; PCH; Joubert syndrome, molar tooth sign, development, and outcome. English language studies describing neurodevelopmental outcomes in children (0-18y) were retained for this review. The reference list of selected articles was also searched.

2.4.4 Results

The spectrum of dysgenetic abnormalities of the cerebellum is broad, ranging from subtle to very significant malformations. The most commonly described entity of cerebellar malformations is often referred to as the Dandy-Walker complex or continuum, a term used to characterize the different degrees of malformations of the cerebellar vermis and includes DWM, DWV or inferior vermian hypoplasia (IVH) and mega-cisterna magna (MCM) (described below)[14-15]. Other malformations that are summarized in the current review include the molar tooth sign, rhombencephalosynapsis, cerebellar hypoplasia/dysplasia, vermis hypoplasia, PCH and vermis hypoplasia. A total of 46 studies were reviewed based on our search strategy that specifically described neurodevelopmental outcomes in children with cerebellar malformations, and are summarized in Table 1. An overall summary of the prevalence of developmental, cognitive, language, behavioural and motor disabilities, as well as neurological abnormalities over our 10-year review period are provided in Table 2. The frequency of occurrence of central nervous system (CNS) and extra-CNS findings are presented in Table 3.

Dandy-Walker Malformation

The most common and striking of these cerebellar malformations is known as the DWM with an estimated incidence of 1 in 5000 live born infants[16]. Dandy-Walker malformation is characterized by partial or complete agenesis of the cerebellar vermis, cystic dilation of the fourth ventricle and an enlarged posterior fossa combined with a superior displacement of the cerebellar hemisphere[17](Figure 1). However, variations in the definition of DWM were evident over our 10-year review period. For instance, some authors included features such as the presence of hydrocephalus[18-19] or the presence of communication between the posterior fossa cyst and the fourth ventricle as a fundamental criterion for the diagnosis of DWM[20]. Conversely, some studies used the term Dandy-Walker complex, to describe what most define as DWM. As a result, the generalizability of the data is limited and the importance of a universally accepted classification schemes for cerebellar malformation is a priority.

Overall, reports on the outcome of DWM were conflicting. Although one study reported that all children with DWM experienced some degree of cognitive impairment[19], other studies have reported a more favourable outcome[17, 20]. Overall, up to one-third of survivors were reported to be developing normally[4, 21-22]. Specifically, Boddaert et al.[17] compared the IQ of 21 children with DWM with and without normal vermis lobulation and showed that 82% of children in the former group had a normal IQ as opposed to none in the latter. Furthermore, among the subgroup with normal vermis lobulation and abnormal IQ, all children had associated CNS and extra-CNS abnormalities. Similarly, Klein et al.[20] divided 26 children into two groups, one with partial agenesis of the vermis with normal lobulation, and a second with severe vermis malformations. In the former group the majority (90%) had a normal IQ and developmental quotients as opposed to none in the latter group. However, it is important to note that one of the two children with partial agenesis of the vermis who scored in the impaired range had fragile X, and the other severe periventricular leukomalacia resulting from being born preterm. It is also worthy of mention that all children with severe vermis malformations had associated cerebral anomalies, three of which had agenesis of the corpus callosum.

Language and communication abilities in survivors of DWM have not been well described. In fact, language deficits were only described in a single chart review and two case reports[19, 23-24]. Conversely, neurological abnormalities have been reported in up to 50% of

survivors[4, 18, 21-22] and included hypotonia (50%)[21, 23-24], signs of cerebellar dysfunction (not further described; 42%)[18] and hemiparesis (5%)[18].

Associated anomalies in both the CNS and other systems have been reported in up to 86% of children[4]. Specifically, CNS abnormalities have been described in 13 to 67% of cases[17-22], with the most common anomaly being ventriculomegaly, observed in 36% to 67% of children[4, 17, 21-22]. Other common CNS malformations included agenesis of corpus callosum, reported in 5% to 50% of children[5, 18, 21, 23]. Interestingly, agenesis of the corpus callosum was observed in 60 to100% of the children with abnormal vermis lobulation[17, 20]. In studies where comparison of children with isolated DWM and those who had associated CNS anomalies was possible, we found that all children with DWM who were developing normally had no associated CNS malformations[17, 20-21]. Conversely, all but one with developmental delays had associated CNS anomalies or epilepsy [17, 19-21]. However, many studies clustered those with and with concurrent CNS findings, and therefore further analysis was not possible. Extra-CNS anomalies were less common, and were reported in 9% to 44% of children[18, 22] and included structural heart defects, renal, extremity and facial anomalies and single umbilical artery [4, 17-18, 21-24].

Two studies in the literature have collectively described the outcome of children with DWM and DWV without differentiating between the two diagnostic groups. Forazo et al.[5] compared the outcome in 34 children with isolated and non-isolated DWM and DWV diagnosed prenatally. Interestingly, 68% of parents elected to terminate the pregnancy. Among survivors, 40% were developing normally, of which half were diagnosed with associated syndromes[5] including occipital encephalocoele. In a second study[25] all children with atypical development had associated anomalies; however, the presence of CNS anomalies did not predict a poorer outcome. Associated (CNS and non-CNS) anomalies were reported in 83% of cases[25].

In summary, available evidence on the outcome of DWM suggests that a more favourable neurodevelopmental outcome in children with no supratentorial findings and in those with a normally lobulated vermis.

Dandy-Walker Variant

Dandy-Walker variant has been used to describe a combination of cystic dilation of the fourth ventricle and hypoplastic cerebellar vermis in the absence of an enlargement of the posterior fossa[14]. However, in recent years, it has been strongly advocated that the term DWV be abandoned altogether, given its multiple and variable definitions[14]. To date, these inconsistencies have prevented the meaningful comparison of diagnosis and outcome among published series, thereby compromising accurate prognostication. As such, it is now recommended that the term DWV be abandoned altogether. However, for the purpose of this review, we have summarized the literature that has described the outcome of DWV to date.

Some reports indicate that over half of children with DWV were developing normally[4]. On the other hand, in a study by Has et al.[22], all children with DWV experienced neurological sequelae including microcephaly in 21%.

Associated anomalies (CNS and non-CNS) have been described in up to 71% of children with DWV, with the most common being ventriculomegaly (27-71%)[4, 22] and agenesis of corpus callosum (14%)[4, 22]. Extra-CNS anomalies have also been reported in up to 65%[4, 22], with cardiac, renal, extremity and facial anomalies occurring most frequently[4, 22].

Inferior Vermis Hypoplasia

Inferior vermis hypoplasia is characterized by partial absence of the inferior portion of the cerebellar vermis with normal- or near normal–shaped cerebellar hemispheres, a normal-sized posterior fossa without obvious cystic lesions, and normal supratentorial structures[26] (Figure 2). Inferior vermis hypoplasia represents an arrested incomplete downward growth of the vermis, leaving an enlarged midline cerebrospinal-fluid space, which may be mistaken for a cystic lesion. It is important to note that the diagnostic entity of IVH continues to be inconsistently used. For example, some investigators consider this anomaly a normal variant, while others have used the term DWV interchangeably, even in the absence of a cystic fourth ventricle and with a normal-sized posterior fossa.

Normal development was reported in 77% of children with isolated IVH[26]. In the subgroup of children (23%) with isolated IVH who had delayed development, gross and fine motor disabilities, as well as social and communication deficits were reported. Furthermore, 15% of these children were found to have behavioural problems, particularly symptoms of

disruptive behavior[26]. Moreover 23% of the children with IVH were found to be hypotonic on neurological examination.

Mega Cisterna Magna

Mega cistern magna is characterized by an enlarged cisterna magna with a normal fourth ventricle and cerebellar hemispheres and vermis[14] (Figure 3). The developmental outcome of children with MCM was generally described as favourable, with the majority of children (92-100%) with isolated MCM developing normally[5, 25, 27]. In fact, based on medical record reviews only one patient was presenting with delayed motor development[5, 25]. However, available data in adults with MCM[28] suggests that higher cognitive functions and language abilities, such as verbal memory and fluency, executive functions and semantic fluency, may be impaired in this population. It is possible that more subtle deficits may be undiagnosed due to the lack of in-depth neuropsychological testing performed in the pediatric studies that were reviewed, or that some of these higher cognitive deficits present in later life.

More than two-thirds of children with MCM and associated CNS (e.g. ventriculomegaly) and non-CNS anomalies (e.g. orthopaedic malformations)[5] were reported to be developing normally[5, 25] on the basis of medical chart reviews. In the remaining one-third, the spectrum of disability included cognitive and language delay as well as delayed motor development and neurological abnormalities (e.g., cerebellar ataxia)[25]. Only one patient had severe cognitive impairment; however, this patient was also diagnosed with cytomegalovirus infection and therefore deficits cannot be directly linked to the cerebellar malformation. Ventriculomegaly was the most common CNS finding associated with MCM reported in 46% to 66% of children[5, 25], whereas a renal defect was the most frequent non-CNS anomaly described in approximately one-third[5, 25]. Agenesis of the corpus callosum, cardiac and liver anomalies were also reported however they were less frequent (4%)[25].

In summary, the presence of concomitant CNS anomalies in children with MCM was associated with a poorer prognosis albeit most children were developing normally and impairments were found to be mild in severity.

Molar tooth sign / Joubert syndrome

The molar tooth sign is characterized by an abnormally deep interpeduncular fossa, enlarged superior cerebellar peduncles that are more horizontally oriented and a hypoplastic cerebellar vermis[29] (Figure 4). Joubert syndrome is the most known syndrome typified and is associated with developmental delays, hypotonia, breathing anomalies, abnormal eye movement and facial dysmorphia[30]. More than eight different types of Joubert syndrome-related disorders have been identified and were found to have various genotypes and phenotypes[31]. Although the different types of Joubert syndrome related disorders may have diverse outcomes, it was not possible in the context of the literature reviewed to identify the specific impact of each type of Joubert syndrome on neurodevelopmental outcome.

Nevertheless, available evidence suggests that impaired cognitive function or developmental delay was present in all children, with the majority experiencing severe disability[30, 32-39]. Moreover, in addition to delayed developmental milestones and impaired developmental quotients, immediate and delayed memory, conceptual development, perceptual discrimination and daily living skills were reported to be impaired[32-33, 38, 40]. Language abilities were also affected in all children with molar tooth sign or Joubert syndrome[32, 34, 37-38, 40-41]. In particular, deficits in expressive language[38], verbal fluency[33] and vocabulary were noted[32, 34]. Furthermore, approximately half of children with Joubert syndrome were found to have impaired concept development, as evaluated by the Bracken Basic Concept Scale[32]. Behavioural and social problems were also found to be prevalent in two study[32, 38]. In fact, 100% of parents reported their children as being demanding or strong willed, the children were also described as hyperactive (50%) or aggressive (25%). Additionally, in a case report a child was reported to be have significant social deficits[38] and two other children had behavioural difficulties (tendency to aggression)[40]. Moreover significant motor delays were frequently reported[30, 32, 34, 37-38, 40-41].

Neurological impairments were present in all cases[30, 32, 34, 40], and were characterized by ataxia (100%)[30, 32], hypotonia, (97-100%)[30, 33-34, 36-40] and oculomotor disturbances (42-77%)[30, 33-34, 36, 38, 40]. In addition, visuomotor deficits were also found to be prevalent[32]. Associated CNS anomalies were less prevalent, with the most common CNS abnormality being dysgenesis of the corpus callosum in 5 to 29% of children[30, 33, 37]. Atrophy of the cerebrum[33], anomalies of the mesencephalon[30] and of the pontomesencephalic junction[33], brainstem hypoplasia[37], dilation of the ventricular system[37], as well as delayed myelination[33] and white

matter lesions[37] were also reported. The most common extra-CNS anomalies included breathing abnormalities (38- 86%)[30, 33-34, 37], facial dysmorphism (71%)[30, 38] and extremity malformations (8-43%)[30, 33-34, 37].

Rhombencephalosynapsis

Rhombencephalosynapsis is considered a rare cerebellar malformation that includes agenesis of the cerebellar vermis and fusion of the cerebellar hemispheres[14] (Figure 5). Data describing cognitive development in this population has been conflicting, some have reported normal cognitive abilities[42-43] whereas others have reported severe learning disability* and developmental delay[44-47]. Neuromotor impairments were reported in all case reports of rhombencephalosynapsis[42-48] including delayed motor development[44, 48], hypotonia[44, 48], cerebral palsy[43], decreased balance[46] and oculomotor disturbances[44, 46]. Language deficits were reported in a single case report[44]. Irritability was reported in on child[45].

Importantly, CNS abnormalities have also been reported in the majority of cases with rhombencephalosynapsis[42-44, 46-47], including agenesis or thinning of the corpus callosum, hypdrocephalus and ventriculomegaly. Non-CNS malformations included facial dysmorphism[42, 45] as well as extremity[45] anomalies. Interestingly, the presence of CNS or extra CNS malformations was not found to be predictive of a poorer outcome in this population. However, it is important to note that the majority of studies did not use standardized outcome measures.

* North American usage: mental retardation

Cerebellar Hypoplasia and Dysplasia

Cerebellar hypoplasia is characterized by incomplete or underdevelopment of the cerebellum[49] whereas cerebellar dysplasia is characterized by an abnormality in maturation of tissue cells[50]. The studies presented herein described the outcome of children with focal cerebellar hemispheric hypoplasia and global cerebellar hypoplasia. Children with vermis hypoplasia were also included if the study design did not allow for separate analysis. It is important to note that the clustering of children with various types of hypoplasia is a recurrent limitation in the available literature. Consequently, this affects our ability to characterize reliably the outcome of the different types of hypoplasias or dysplasias. For

example, unilateral hypoplasias are thought to be the result of a prenatal lesion rather than being true malformations[1]. However, whenever possible, we presented a summary of the outcome in children with unilateral and bilateral hypoplasia separately.

Available evidence showed that well over half of children (53-87%)[51-54] were found to have developmental delay or cognitive impairments, among whom over one-third (38%) had severe deficits[54]. Although one case report described a child with "normal neural development" at 6 month follow-up, no information was provided[55]. Overall, language deficits were found to be prevalent in the majority of studies, but were reported as infrequent by others (6% to 95%)[51-54, 56] and the levels of disability ranged from mild impairment (76%) to severe impairment or total absence of language development (19%)[54]. Furthermore, 5 to 20% were reported to present with autistic features[52, 54], 81% were found to have an impaired affect[55] and 71% social or behavioural difficulties. Delayed motor development was variable, observed in 18 to 90% of children[51-54, 56].

Neurological abnormalities were described in up to 100%[53]. They included increased tone (58%)[52], ataxia and/or decreased coordination (12-49%)[51-52, 54], hypotonia (49-93%)[51-52, 54, 56], oculomotor disturbances (35-57%)[51-52, 56] and abnormal movements such as tremor, dysdiaochokinesis or head titubation (9-100%)[52, 54]. It is noteworthy that all reported cases had associated cerebral anomalies in one of the larger study[52]: 22% suffered from cerebral atrophy or periventricular leukomalacia, 20% were microcephalic, 16% had neuronal migrational defects and 11% had anomalies of corpus callosum. Moreover, 20% of cases had associated syndromes or disorders[52]. Associated non-CNS anomalies included facial dysmorphism[51, 56], skeletal[52] and kidney malformations[51].

In two chart reviews of children with isolated cerebellar dysgeneses[56-57], 40 to 71% were described to have normal cognitive development, 40% showed mild impairment and 20% moderate impairment[57]. Moreover, language skills were affected in all children, with 80% being mildly impaired and 20% moderately impaired[57]. Affect was reported to be normal in 60%, whereas 20% had a mild impairment and 20% a moderate impairment[57]. In addition, 14 to 80% of the children were reported to have emotional, social or behavioural difficulties[56-57]. Finally, 71-100% had motor impairments as well[56-57].

In the subset of articles in which we were able to distinguish between unilateral and bilateral hypoplasia/dysplasia, bilateral cerebellar lesions were found to be associated with a poorer outcome. Specifically, children with bilateral cerebellar hypoplasia presented a high

prevalence of cognitive/developmental delay (60%-100%), compared with those children with unilateral lesions (17%-50%)[51, 54, 56-57]. Similarly, language impairment was reported in 44% to 89% in the former group and 17% to 100% in the latter [51, 54, 56-57]. Behavioural difficulties, neurological deficits, and associated CNS anomalies were also reported more frequently in children with bilateral cerebellar hypoplasia and dysplasia[51, 54-57].

In summary, outcome data on children with hypoplasia and dysplasia of the cerebellum are inconsistent. The presence of a large and variable spectrum of disability among survivors described in the present studies could be explained by the important differences in the topography and severity of the lesions. However children with isolated hypoplasia of the cerebellar hemispheres appear to have a more favourable prognosis[57].

Vermis Hypoplasia

Vermis hypoplasia is characterized by incomplete or underdevelopment of the cerebellar vermis. A subgroup of five children with partial or complete hypoplasia of the cerebellar vermis was reported by Tavano et al.[54]. All children presented with developmental delays: 80% with severe delay and 20% with moderate deficits. Moreover, language skills were affected in all children, with 80% presenting severe deficits and 20% with complete absence of language skills. In addition, all children showed impairment in behaviour modulation. Motor development was found to be delayed in all children but to a lesser degree, with 80% displaying a moderate deficit and 20% a severe deficit. Neurological abnormalities included hypotonia (100%), ataxia (80%) and intention tremor (20%).

Additionally, Bruck et al.[58] reported a case of two siblings with vermis hypoplasia, one of which was described as having normal cognitive skills. However, language and motor skills were impaired in both children and both presented with hypotonia. Furthermore, severe cognitive and language impairments as well as motor disabilities were described in a case report of a 15 year old male with cerebellar vermis hypoplasia[59] Neurological findings included hypotonia, occulomotor dysfunction and ataxia. The presence of CNS (megalocephaly) and extra-CNS (e.g. micrognathy and syndactyly) were also reported.

Finally, three patients with vermis hypoplasia were described by Ventura et al.[56], of which two were found to have impaired cognition, and one was reported to show motor delay and anxiety.

In summary, available data suggest that the majority of children with partial or near-complete hypoplasia of the vermis present with global developmental delay, as well as language, motor and neurological disabilities.

Pontocerebellar hypoplasia

Pontocerebellar hypoplasia is a heterogeneous group of conditions characterized by hypoplasia of the cerebellum and the ventral pons[60]. It can be divided in type I and type II[62]. Type I is characterized by spinal anterior horn involvement and death in infancy, and consequently will not be addressed in this review[61]. Type II pontocerebellar atrophy is characterized by progressive microcephaly, severe cognitive and motor delays, in addition to dyskinesia and dystonia[61]. It is noteworthy that some authors classify PCH as a degenerative disorder rather than a true malformation[62].

In a chart review of 24 children with PCH type II, significant developmental and language delays were reported in all children[60]. A series of case reports have also been published[63-65] in which all four children presented with developmental delay and two were reported to have language deficits[63]. Neurological findings included microcephaly in all children[60, 63-65], seizures (25%)[60], respiratory abnormalities (46%)[60], hypotonia (16%)[60, 65], hypertonia (13%)[60, 63-64], oculomotor anomalies[63], ataxia (8%)[60], dyskenetic and choreic movements (58%)[60, 64-65].

Associated CNS malformations included ventriculomegaly and reduced white mater were present in about half of the children described from chart review[60], ventricular and sulci widening and myelination delay in two children in a case report[64], and thinning of the corpus callosum in one[64]. Facial dysmorphism and orthopaedic anomalies were described in one child[63].

Overall, pontocerebellar hypoplasia type II is associated with significant global developmental delays and neurological deficits.

Cerebellar agenesis

Cerebellar agenesis is characterized by a complete or near complete absence of the cerebellum[66] (Figure 6). Very few studies have described the outcome of children with cerebellar agenesis. Titomanlio[67] presented a case of a 17-year-old male with isolated cerebellar agenesis. Mild cognitive impairment, ataxia and dysmetria were documented.

However, no standardized outcome measures were used. On the other hand, near-total absence of the cerebellum was reported in five children[68]. All children had developmental delay, including one with severe developmental delay. Moreover, 100% of children had delayed language development. Only one case was reported to have associated cerebral malformations; however they were not further described[68].

2.4.5 Discussion

Cerebellar malformations are now diagnosed with increasing frequency in the fetal and neonatal period[69-70]. As such, the importance of accurate prognostic information to guide parental decision-making has become essential. However, despite recent advances in neuroimaging and the growing interest in the role of the cerebellum in higher-order cognitive functions, our review of the literature suggests that the neurodevelopmental and functional outcome of children with cerebellar malformations remains poorly defined. Important inconsistencies in the outcomes reported are frequent and the spectrum of disability is often broad, ranging from normal or near-normal to profound disability, for a given malformation. Furthermore, the results of this comprehensive review show that clear diagnostic criteria for the different types of cerebellar malformations are lacking, resulting in the description of heterogeneous study populations, with results that are not easily generalizable.

However, certain global trends in the neurodevelopmental outcome in survivors of cerebellar malformations were evident. Overall, children with MCM and isolated IVH show good developmental progress, whereas children with molar tooth sign/Joubert syndrome, vermis hypoplasia, PCH type II and cerebellar agenesis are likely to experience moderate to severe global developmental delay. Outcome data remain conflicting in children with DWM; however the presence of a normally lobulated vermis and the absence of associated CNS anomalies appear to be associated with a better neurodevelopmental outcome. Finally, cases with isolated cerebellar hypoplasia (not including the vermis) appear to have a more favourable prognosis.

Our review over the 10-year period highlighted wide-ranging outcomes in children with cerebellar malformations. These inconsistencies can be partly explained by the lack of a widely accepted classification scheme for cerebellar malformations. For example, several studies collapsed different diagnostic groups and described the developmental outcome of survivors collectively. Consequently, children with different types of cerebellar

malformations were often clustered together, which further impeded our understanding of the relative contribution of individual cerebellar diagnostic groups on subsequent neurodevelopmental disabilities. Furthermore, the reported wide-ranging outcomes identified underscored in the current review may also be attributed to the overall lack of rigorous study designs and standardized outcome measures, where a prominent 83% of the reviewed studies were conducted retrospectively. Consequently, children with normal development or mild impairments may be underrepresented. Moreover, just under half (39%) of the reviewed studies were case reports or case series. The complete absence of any longitudinal data over this 10-year review period is quite striking. Longitudinal studies are essential, particularly in assessing and monitoring children's progress during important developmental transitions through the lifespan. Furthermore, the wide age at testing introduces of lot of noise in the studies, and consequently, the appreciation of specific outcome information at key intervals in child development was limited.

It is noteworthy that the lack of standardized assessment tools in 74% of the studies reviewed was also an important limitation of the current literature. Furthermore, studies primarily focused on mortality and morbidities such as IQ, neurological impairments and other biomedical markers. Cognitive, language, social and behavioural disabilities were seldom investigated. Given the growing evidence supporting an important role of the cerebellum in cognitive function, including language, perception, and social skills, outcome measures used to date prove to be largely insufficient in this population[10]. Additionally, measures of quality of life and parental burden were completely absent in our 10-year review. These are essential in capturing the added impact of these malformations in the child and their family.

2.4.6 Limitations

Several limitations of our study should be highlighted. First, it was limited to English-language literature, and therefore studies published in other languages were not included. Second, given that there is no universally accepted classification scheme for posterior fossa malformations, the diagnostic categories proposed by the different studies in this review often varied from one study to another. Moreover, cerebellar diagnostic groups were at times collapsed by some authors because of small sample size. Consequently, it is likely that certain aspects of the outcome data described in this review may not reflect accurately the

developmental outcome of survivors of cerebellar malformations. Finally, given that our review extended on a 10-year period, recent advances in genetics and neuroimaging that have permitted more accurate identification of cerebellar malformations and their associated chromosomal anomalies were not necessarily reflected in the current paper.

2.4.7 Conclusion

Rigorous longitudinal outcome studies that incorporate advanced neuroimaging techniques and genetic testing are urgently needed to delineate better the long-term functional significance of cerebellar malformations. Furthermore, more holistic measures that assess a larger number of functional domains are required in order to capture the entire spectrum of disability in children with cerebellar malformations that extends far beyond the motor and cognitive domains. These measures must not be limited to evaluating impairments but also their functional impact on daily activities, school performance and societal roles.

Collectively, such studies will assist in the development of a rational and clinically useful classification and ultimately improve our understanding of the functional consequences of cerebellar malformations at key intervals during lifespan.

Finally, a better understanding of the developmental and functional consequences of cerebellar malformations on the developing child will allow earlier and possibly more effective therapeutic interventions, since cerebellar development is not fully completed before the end of the first postnatal years[49]. Additionally, given the greater plasticity of the younger brain coupled with the highly plastic properties of the cerebellum[71], early-targeted intervention could potentially translate into reorganization of the cerebellar circuitry and result in improved outcome.

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Table 1. Summary of manuscripts describing neurodevelopmental outcomes of children with cerebellar malformations over the 10-year review period

Author	Year	Diagnosis	Study design	N	Age range (mean/median)	Standardized outcome measures
Dandy-Walker complex (DWC)						
Forzano et al.	2007	DWC, MCM	Chart review	56	2 days-5 months (1 month)	No
Poot et al.	2007	DWM	Case report	1	10 years (n/a)	No
Limperopoulos et al.	2006	IVH	Cross-sectional	19	Range not specified (19.2 months)	Yes
Abdel-Salam et al.	2006	DWM	Case report	2	6 - 8 years (7 years)	No
Long et al.	2006	DWM, DWV, MCM	Chart review	86	Range not specified (96 months)	No
Has et al.	2004	DWM, DWV	Chart review	78	3 months-5.5 years (n/a)	No
Boddaert et al.	2003	DWM	Chart review	21	9 months-34 years	Yes*
Klein et al.	2003	DWM	Chart review	26	Not specified (10.5 years)	Yes*
Kumar et al.	2001	DWS	Chart review	42	9 months-12 years (3.8 years)	No
Ecker et al.	2000	DWC, DWV	Chart review	99	6 weeks (n/a)	No
Kölble et al.	2000	DWM	Chart review	10	4 weeks-21 months (n/a)	No
Aletebi et al.	1999	DWM,	Chart	15	23-50 months	Yes*

		MCM	review		(n/a)	
Haimovici et al	1997	MCM	Chart review	15	Days-69 months (n/a)	No
Molar-tooth sign/Joubert syndrome						
Kumar et al.	2007	Joubert	Case report	1	1 year	No
Ray et al.	2007	Joubert	Case report	1	7 months	No
Braddock et al.	2006	Joubert	Cross-sectional	21	32 months-19 years (10.4 years)	Yes
Romano et al.	2006	Molar tooth	Chart review	13	2 to 16 years (n/a)	No
Hodgkins et al.	2004	Joubert	Chart review	18	3 months-21 years (10.9 years)	Yes*
Kumandas et al.	2004	Joubert	Cross-sectional	7	4 days-8 years (n/a)	No
Torres et al.	2001	Joubert	Case report	1	40 months	Yes*
Fennell et al.	1999	Joubert	Cross-sectional	51	11 months-17 years (n/a)	Yes
Maria et al.	1999	Joubert	Cross-sectional	61	1.3-17 years (7.5 years)	No
Gitten et al.	1998	Joubert	Cross-sectional	32	14-204 months (68.7 months)	Yes
Steinlin et al.	1997	Joubert	Chart review	19	1.5-37 years (n/a)	No
Rhombencephalosynapsis (RCS)						
Chemli et al.	2007	RCS	Case report	1	3.5 years	No
Odemis et al.	2003	RCS	Case report	1	8 months	No

Jellinger et al.	2002	RCS	Case report	1	7 years	No
Toelle et al.	2002	RCS	Cross-sectional	9	1.5-6years (n/a)	No
Danon et al.	2000	RCS	Case report	1	5 years	No
Utsunomiya et al.	1998	RCS	Case report	2	Infancy-4 years	No
Aydingoz et al.	1997	RCS	Case report	1	17 months	No
Cerebellar hypoplasia/Dysplasia						
Tavano et al.	2007	Hypoplasia Dysplasia	Cross-sectional	27	3-34 years (11.1 years)	Yes
Tavano et al.	2007	Dysgenesis	Chart review	5	2-11years (n/a)	Yes*
Ventura et al.	2006	Hypoplasia	Chart review	14	4-20 years (n/a)	Yes*
Yapici et al.	2005	Hypoplasia	Chart review	2	5-12 years	No
McCollom et al.	2003	Hypoplasia	Case report	1	6 months	No
Wassmer et al.	2003	Hypoplasia	Chart review	45	Not specified (children)	No
Soto-Ares et al.	2000	Dysplasia	Chart review	46	10 days to 14 years (n/a)	No
Vermis hypoplasia						
Bruck et al.	2000	Hypoplasia	Case report	2	2 and 9 years	No
Koutsouraki et al.	2007	Hypoplasia	Case report	1	15 years	No

Pontocerebellar hypoplasia type II (PCH)						
Steinlin et al.	2007	PCH	Chart review	21	4 months-11.2 years (49 months)	No
Dilber et al.	2002	PCH	Case report	2	30 months and 17 years	No
Sans-Fito et al.	2001	PCH	Case report	1	3 years	No
Coppola et al.	2000	PCH	Case report	2	18 months and 5 years	No
Cerebellar Agenesis						
Titomanlio et al.	2007	Agenesis	Case report	1	17 years	No
Gardner et al	2001	Agenesis	Chart review	5	2-17 years (n/a)	No

n/a : not available

* Standardized outcome measures extracted from chart review

DWC: Dandy-Walker complex, DWM: Dandy-Walker malformation, DWS: Dandy-Walker syndrome, DWV: Dandy-Walker variant, IVH: inferior vermian hypoplasia, MCM: Mega cisterna magna, PCH: Pontocerebellar hypoplasia, RCS: Rhombencephalosynapsis

Table 2. Summary of developmental/cognitive delays, language, behavioral deficits and neurological abnormalities in children with cerebellar malformations

Diagnostic Group	**Developmental/ Cognitive delay (%)**	**Language deficits (%)**	**Social/ Behavioral deficits (%)**	**Neurological abnormalities (%)**
Molar tooth Sign/ Joubert Syndrome	100%	100%	100%	100%
Vermis hypoplasia	100%	100%	100%	20-100%
Pontocerebellar hypoplasia type II	100%	n/a	n/a	100%
Cerebellar agenesis	100%	100%	n/a	80%
Dandy-Walker malformation	67-100%	50%	n/a	50%-100%
Cerebellar hypoplasia/ Dysplasia	53-87%	6-100%	14-71%	67-100%
Rhombencephalosynapsis	56%	25%	61%	94%
Dandy-Walker variant	46%	n/a	n/a	100%
Isolated inferior vermis hypoplasia	23%	23%	23%	23%
Mega cisterna magna	0-8%	n/a	n/a	0%

n/a : not available

Table 3. Summary of CNS and non-CNS anomalies in children with cerebellar malformations

Diagnostic Group	**Associated CNS anomalies (%)**	**Associated non-CNS anomalies (%)**
Cerebellar hypoplasia/ Dysplasia	20-88%	29-47%
Rhombencephalosynapsis	56%	25%
Dandy-Walker malformation	43-67%	9-75%
Dandy-Walker variant	35-71%	64-65%
Pontocerebellar hypoplasia type II	55%	n/a
Mega cisterna magna	36-66%	18-62%
Molar tooth sign/ Joubert syndrome	0-38%	2-71%
Cerebellar agenesis	20%	n/a
Vermis hypoplasia	n/a	n/a

n/a : not available

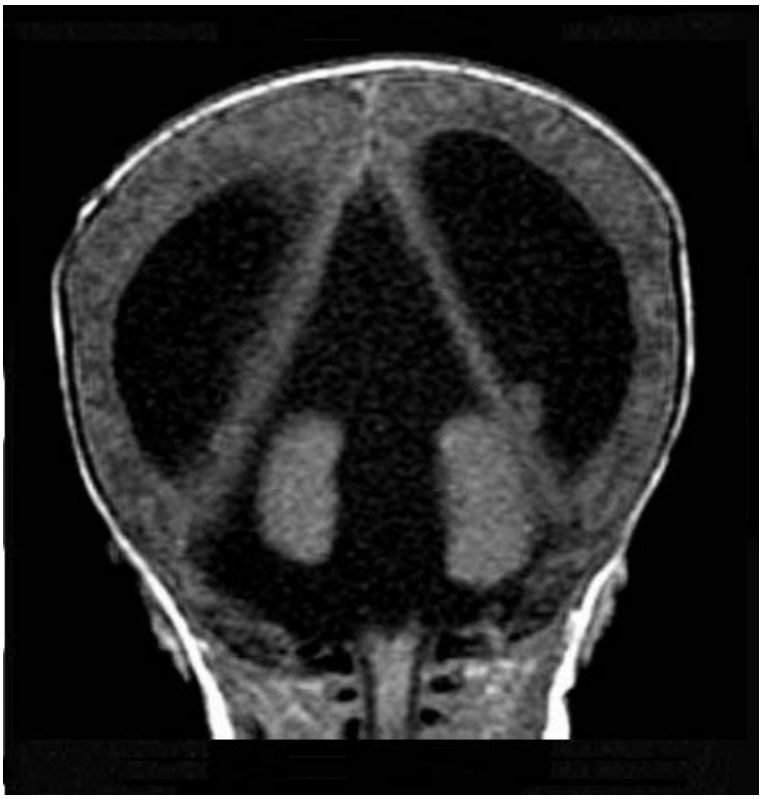

Figure 1. T1-weigthed coronal magnetic resonance image of a term infant with Dandy-Walker malformation, characterized by hypoplasia of the cerebellar vermis, massive cystic dilation of the fourth ventricle and elevated tentorium.

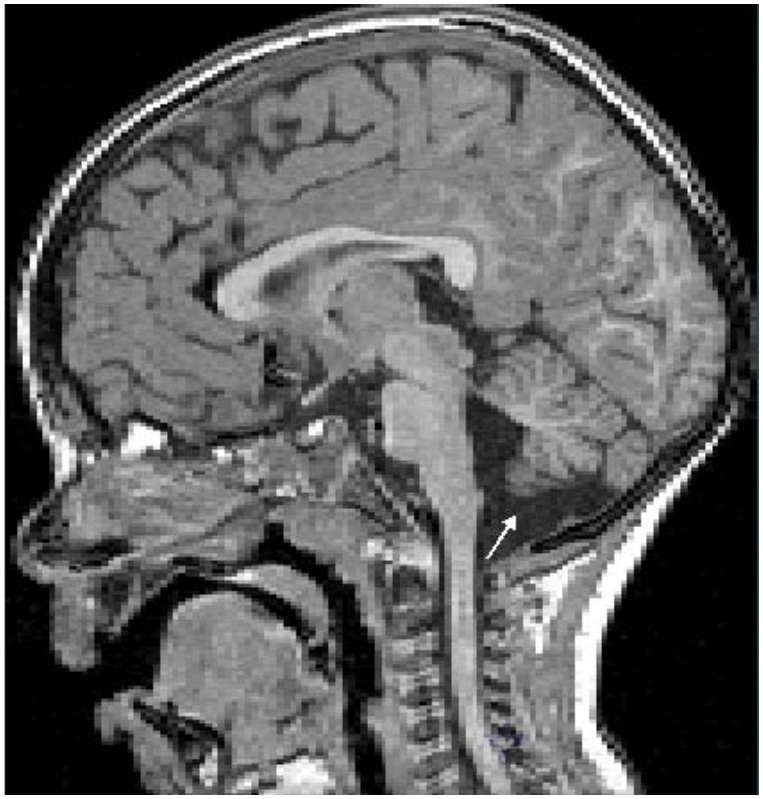

Figure 2. T1-weighted magnetic resonance image of the midline sagittal view illustrating incomplete downgrowth of the vermis (arrow) in an 18-month-old child with inferior vermian hypoplasia.

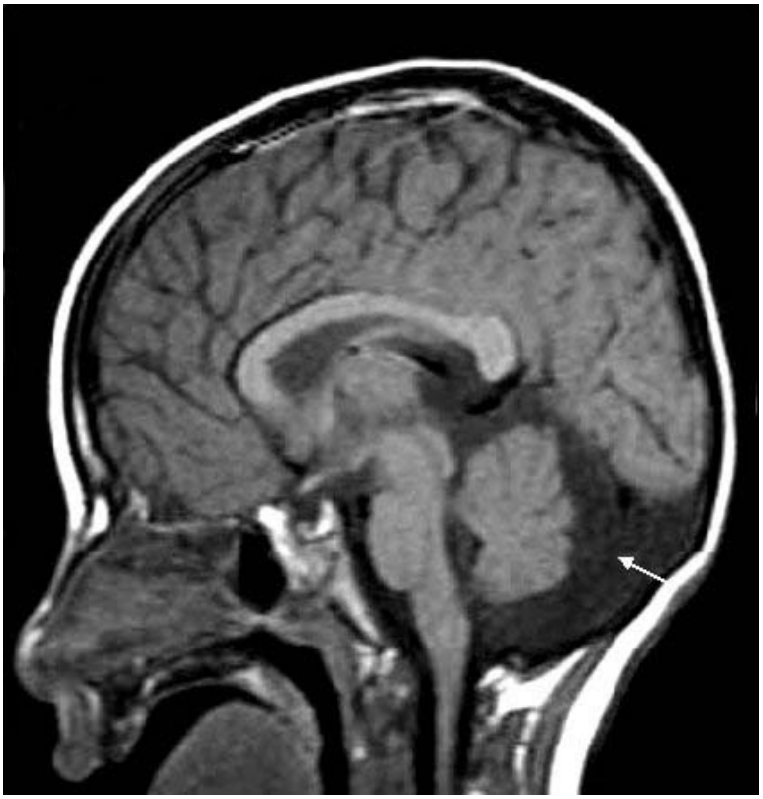

Figure 3. T1-weighted sagittal magnetic resonance image showing an enlarged cistern magna (arrow) and normal fourth ventricle and cerebellar hemispheres and vermis in a 2-year-old child with mega cistern magna.

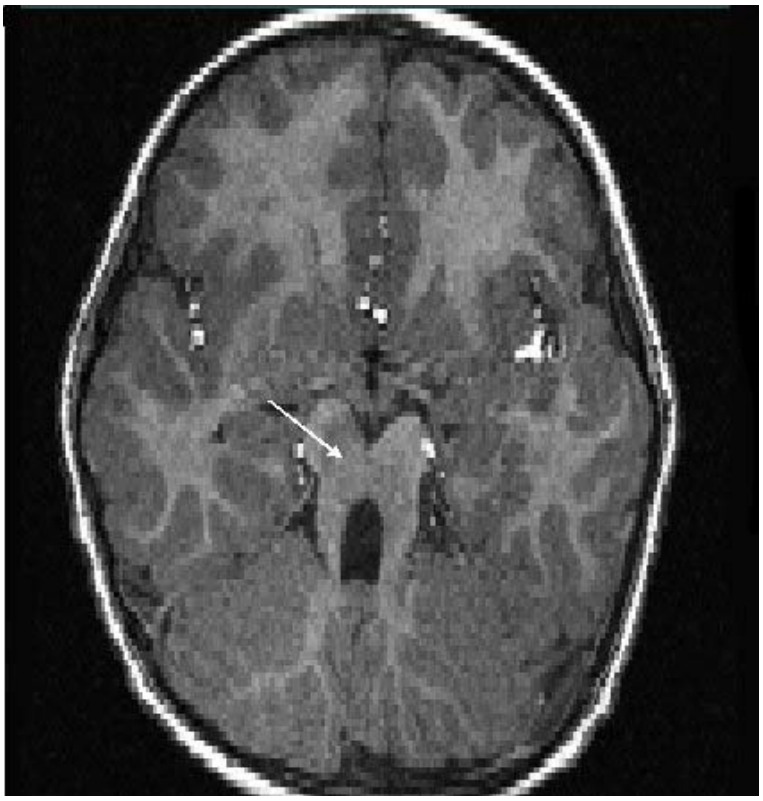

Figure 4. T1-weighted axial magnetic resonance image at the level of the brainstem showing deep interpeduncular cistern (as a result of reduced pyramidal decussation (arrow)), thick superior cerebellar peduncles, and enlarged fourth ventricle representing the molar tooth sign in a 3-year-old with Joubert syndrome.

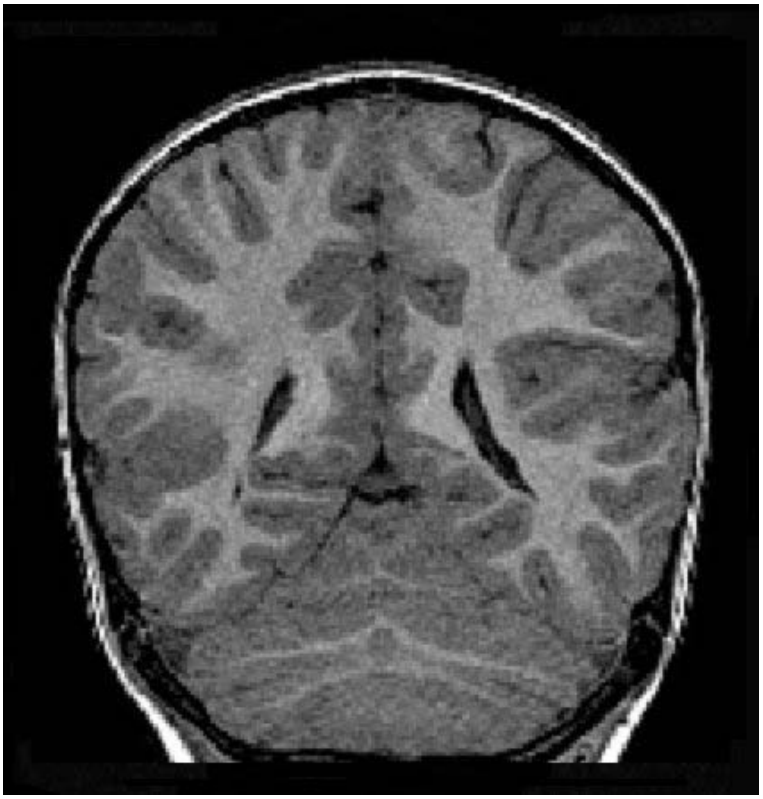

Figure 5. T1-weigthed coronal magnetic resonance image of a 3-year-old child with rhombencephalosynapsis, demonstrating a complete absence of the vermis and fusion of the cerebellar hemispheres.

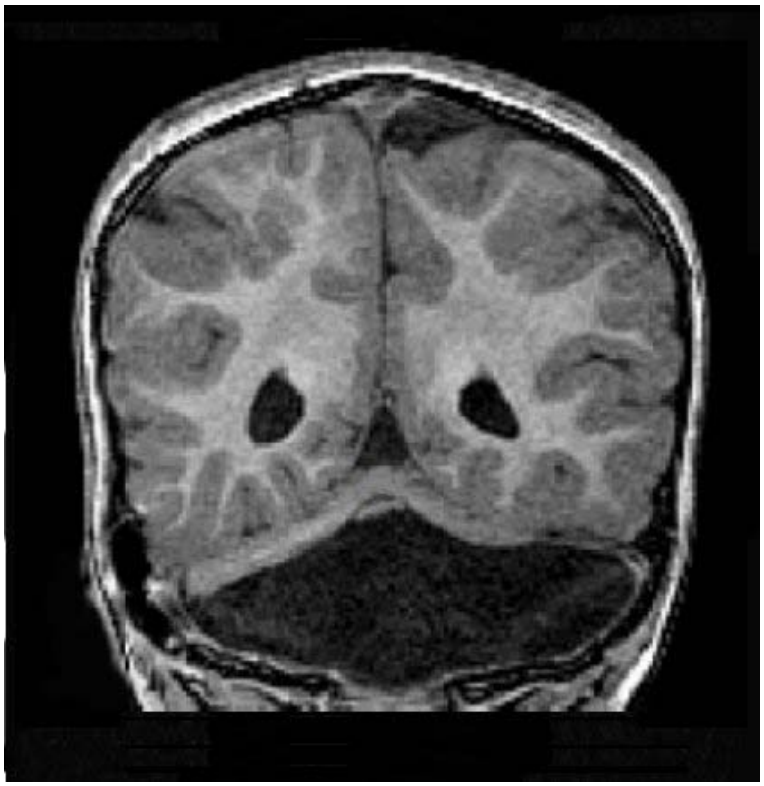

Figure 6. T1-weigthed coronal magnetic resonance image representing near-complete absence of the cerebellum in an 18-month-old child.

2.5 Classification of cerebellar malformations

The lack of a widely accepted classification system has been a major obstacle to better defining the outcome of children with cerebellar malformations (Patel, & Barkovich, 2002). Accurate classification of malformations is essential to obtain information on prognosis and to help better define therapy needs (Barkovich, 2000). Various classification schemes have been described since the 1980s. The use of traditional diagnostic categories, as described previously, has been commonly used in the past decades. More recent classification systems can be divided in two broad categories: the ones based on embryologic development and the others relying on anatomic structures.

Classification schemes based on embryology rely on our current understanding of the pathogenesis and cerebellar embryology, which is rather limited (Patel, & Barkovich, 2002). For example, Parisi and Dobyns (2003), presented a classification based on embryologic development. More specifically, the malformations were grouped based on the midbrain and/or hindbrain structures that are predominantly affected. Additionally, Niesen (2002) has proposed a scheme for the classification of posterior fossa malformations based on embryologic development using four main categories: cranial vault abnormalities; paleocerebellar dysgenesis; neocerebellar dysgenesis and pontine dysgenesis.

Recently, Patel and Barkovich (2002), proposed a new anatomy-based classification developed from the review of 70 patients with cerebellar malformations, in which malformations are divided into two large categories: cerebellar hypoplasia and cerebellar dysplasia and, subsequently grouped into smaller categories. While cerebellar anatomy is far better understood than cerebellar embryology and the pathogenesis of cerebellar malformations, the choice of imaging technique has led to variations in structural details identified and has caused changes in the definitions of the malformations (Klein et al., 2003). For example, Klein et al. (2003) reported that, in a 1984 publication, classification of cerebellar malformations based on images obtained by computed tomography led to an erroneous diagnosis in one-third of their patients. The diagnoses were revised when MRI images were obtained.

Despite the various contemporary frameworks for the classification of cerebellar malformations that have been proposed, to date there is still no universally accepted classification scheme for these malformations. Consequently, children with different malformations and a wide spectrum of disability are clustered together, which further limits

our current knowledge of the neurodevelopmental disabilities associated with cerebellar anomalies. The development of a universally accepted classification method that would allow us to better study the consequences of each type of cerebellar malformation on developmental and functional skills is of the utmost importance. Alternatively, in the absence of a widely accepted classification scheme, the potential application of advanced 3-D MRI techniques to further our understanding of the clinical-neuroimaging correlates of cerebellar malformations offers an exciting, currently underexplored area of research (described later in section 3.4.7).

2.6 Predictors of functional disabilities

To date, the primary determinants of outcome for children with cerebellar malformation are the presence of CNS and extra-CNS anomalies, and the severity of the malformations (Volpe, 2001). Moreover, greater functional impairment has been associated with an earlier diagnosis, which presumably is reflective of the severity of the malformation. Specifically, for children with DWM who are diagnosed in utero or in the neonatal period, mortality rates are as high as 40% and cognitive impairments are present in 75 % of the children (Volpe, 2001). Our review of the literature, presented in section 2.4, also suggests that the absence of CNS anomalies and the presence of a normally lobulated vermis is associated with a favorable outcome (Bolduc, & Limperopoulos, 2009).

2.7 Impact of a cerebellar malformation on cerebral development

Another important factor that should be carefully examined, in order to better understand the spectrum of functional disabilities observed in children with cerebellar malformations, is the possible impact of cerebellar malformation on cerebral development. The presence of cerebello-cerebral diaschisis, which can be described as impaired function in the cerebrum subsequent to a cerebellar lesion has been reported in several studies, mainly in adult populations with acquired lesions to the cerebellum (Attig et al., 1991; Baillieux et al., 2009; Boni et al., 1992; Broich et al., 1987; De Smet et al., 2009; Deguchi et al., 1994; Komaba et al., 2000; Miller et al., 2009). Hallmark features of cerebello-cerebral diaschisis include hypoperfusion, reduced metabolism and decreased oxygen consumption (Miller et al., 2009). The mechanisms for this can be explained by the presence of important cerebello-cerebral anatomical pathways, namely the cerebello-basal ganglia-cortical pathway and

cerebello-thalamo-cerebral pathway (Broich et al., 1987; Deguchi et al., 1994). Hypoperfusion has been reported in several studies in the premotor, prefrontal, and frontal cortices, the basal ganglia, the thalamus and striatum, as well as the parietal, temporal and occipital lobes in children and adults with acquired lesions to the cerebellum, using single photon emission computed tomography and dynamic susceptibility contrast MRI (Attig et al., 1991; Baillieux et al., 2009; Boni et al., 1992; Broich et al., 1987; De Smet et al., 2009; Komaba et al., 2000; Miller et al., 2009; Sagiuchi et al., 2001). Only one study has examined cerebello-cerebral diaschisis in an adult with cerebellar malformations, using single photon emission computed tomography. Normal perfusion was described in the frontal region of this adult patient with cerebellar. Interestingly the remaining four patients in that same study, all had acquired lesions to the cerebellum and did show decreased perfusion in that same cerebral region (Boni et al., 1992). Accordingly, it has been hypothesized that because of neural remodeling in patients with cerebellar malformations, cerebral development could be affected in a different way than in patients with cerebellar lesions that occurred later in life (Boni et al., 1992).

Available evidence suggests that diaschisis can also be associated with long-lasting structural changes in the brain (Chakravarty, 2002). Taking this knowledge into consideration, two studies by our group have examined the impact of acquired cerebellar injury in children who were born prematurely, using advanced 3-D volumetric MRI measurements. In the first study, significantly smaller volumes in the contralateral cerebral hemisphere were found in ex-preterm infants with unilateral cerebellar injury as early as term equivalent (Limperopoulos et al., 2005). In the second study, regional cerebral volumes and tissue types were calculated in ex-preterm children with unilateral cerebellar injury. Significantly smaller volumes in the contralateral cerebral grey and white matter, as well as subcortical grey matter were described. Furthermore, lesser regional volumes in the contralateral dorsolateral prefrontal, prefrontal, premotor, sensorimotor and midtemporal region were also reported suggesting interruption of cerebellar projection pathways (Limperopoulos et al., 2010).

The presence of decreased cerebral perfusion as a result of cerebellar lesions or malformations raises the important question of whether the developmental and functional limitations that are observed in children with cerebellar malformations are exclusively associated with the primarily cerebellar malformation, or whether secondary impairment of

cerebral growth can also play a role in the prevalence of these developmental disabilities. Indeed, we hypothesized that cerebral growth impairment is present in children with cerebellar malformations as a result of trophic withdrawal caused by deactivation of the cerebello-cerebral circuitry.

2.8 The contribution of advanced MRI techniques

The application of new and improved imaging techniques has shown great potential to expand our understanding of brain development and structure-function correlations. Magnetic resonance imaging is the method of choice for studying the developing brain because this technique provides increased tissue resolution allowing for greater differentiation of tissue classes (such as cortical grey matter, subcortical grey matter and white matter) (Huppi, & Inder, 2001). Consequently, the extent and the location of the anomalies can be more accurately described and quantified. Moreover, MRI relies on the magnetic properties of the hydrogen nuclei (mainly from water) that is produced when it spins on its axes to acquire images, rather than utilizing ionizing radiation used for computed tomography (Huppi, & Inder, 2001). Thus, MRI is a safer imaging technique than computed tomography (Huppi, & Inder, 2001).

While conventional MRI, which provides a macroscopic qualitative evaluation of the brain anatomical structures, can be useful in detecting anomalies or injuries, the development of more advanced MRI techniques allows for a more objective and reproducible evaluation of cerebral structures and their physiology (Counsell, & Boardman, 2005; Huppi, & Inder, 2001). Advanced MRI techniques also facilitate the detection of more subtle anomalies or impairment in brain growth that may not be evident using conventional MRI studies (Neil, & Inder, 2004).

Specifically, three-dimensional quantitative MRI is a powerful technique that enables us to reconstruct the brain in all planes and to quantify brain growth by measuring total brain volume and its tissue classes based on their anatomical location and signal intensity (Huppi, 2002; Huppi, & Inder, 2001). Partition of the various regions of interest can be obtained from their contours and volumes can be computed (Huppi, & Inder, 2001). Subsequently, the rich data generated from computing the partitioned volumes offer a unique opportunity to relate regional brain structure and function, therefore contributing to a better understanding of the causes and consequences of a disability. Recent clinical-neuroimaging

studies have provided compelling evidence to support strong correlations between 3-D volumetric brain growth and function in high-risk pediatric populations including prematurity (Mewes et al., 2006; Shah et al., 2006; Woodward et al., 2005), autism (McAlonan et al., 2005; Palmen et al., 2005; Rojas et al., 2006) and attention deficit hyperactivity disorder (Evans, & Brain Development Cooperative Group, 2006).

In addition to 3-D volumetric and brain tissue classification methods, surfaced-based cerebral parcellation techniques have also been used to measure the impact of localized brain injury on regional cerebral volume in children (Limperopoulos et al., 2010; Peterson et al., 2003; Thompson et al., 2007). Similarly, surface-based cerebellar parcellation techniques have also been developed based on known cerebellar anatomical landmarks and functional organization to study the effect of regional cerebellar volumes on neurological and cognitive outcomes (Makris et al., 2003). These powerful MRI techniques can be used to examine the structure-function correlates in young children with cerebellar malformations, and the impact of these malformations on cerebral development (volume), thus contributing to a better understanding the wide-range consequences of cerebellar malformations and providing more adequate prognostic information that will allow earlier and more specific multidisciplinary interventions.

In summary, recent advances in fetal and neonatal brain MRI techniques have permitted better visualization and evaluation of cerebellar anatomy. As a result, the accuracy with which structural anomalies are being diagnosed has been markedly improved (Boltshauser, 2004). Given the complex topographical organization of the cerebellum, these advanced MRI techniques allow for quantitative evaluation of specific regions of interest in order to delineate the extent to which malformations to these regions may affect various domains of child functioning. Furthermore, application of these novel imaging techniques and post-imaging analyses permits more accurate identification of the cerebral tissues and regions whose development is at risk of being impacted by cerebellar malformations.

2.9 Rationale

Recent advances in the care of high-risk newborns, as well as advances in MRI techniques have facilitated the early and accurate diagnosis of cerebellar malformations. However, there is a glaring lack of comprehensive outcome studies that precisely define the nature and extent of developmental disabilities and activity limitations in children with cerebellar malformations. To date, no study has systematically characterized the outcome of survivors of cerebellar malformations using comprehensive and standardized measures that examine multiple developmental and functional domains. Furthermore, the relationship between structural cerebellar development and functional outcomes has not been examined using advanced MRI techniques. Finally, the impact of a cerebellar malformation on cerebral development has been poorly investigated. Consequently, this study proposes a global approach to delineating the impact of cerebellar malformations on the child's function (Appendix A).

There is accruing evidence, mostly in adult with acquired cerebellar lesions, that the cerebellum acts as an important modulator of multiple functions that far exceed the motor domain. Taking into consideration the topographical organization of the cerebellum and the wide-spectrum of disability associated with cerebellar lesions, advanced 3-D MRI techniques can now be used to improve our comprehension of the impact of cerebellar malformations on functional outcome. This data can provide important, currently unavailable evidence to explain why children with similar malformations experience a wide range of outcomes ranging from normal development to severe disability and consequently improve prognostic information.

In addition, data from adults with stroke suggest that cerebellar insults result in cerebello-cerebral diaschisis. However, the impact of cerebellar malformations on cerebral development has not been investigated. The presence of regional cerebral volumetric impairments in children with cerebellar malformations, even in the absence of obvious supratentorial anomalies, may serve as an important mechanism to explain the severity and extent of the functional disabilities experienced by children with cerebellar malformations.

The brain and particularly the cerebellum are believed to be a highly plastic structure, especially in the first postnatal years (Bonnier, 2008; Swinny et al., 2005). Therefore therapeutic interventions have the potential to improve some of the observed functional impairments. In current clinical practice, most health care professionals design their

treatment plan based on the functional deficits that are observed. However, because most of the non-motor impairments cannot be evaluated until later in the child's life, sometimes as late as the fifth or sixth year, a precious window of treatment may potentially be lost. Early intervention is recommended as an effective way to improve various functional outcomes in children with an established risk of developmental disability (Casto, & Mastropieri, 1986; Majnemer, 1998). In fact, early stimulation programs have been shown to alter brain function and structure (Als et al., 2004). Consequently, if reliable prognostication information is available, multidisciplinary follow-up programs can be developed to target specific skills that are at risk of being impaired even before deficits are formally identified (e.g. language impairments and behavior/socialization problems), thus minimizing disabilities in children with cerebellar malformations.

CHAPTER 3
OBJECTIVES AND METHODOLOGY

3.1 Objectives

The overall objective of this study was to delineate the impact of cerebellar malformations on cerebral development and child functioning in children aged one to six years.

Specific objective 1: To estimate the extent to which total and regional cerebellar volumes are associated with motor function, cognitive function, expressive language, social-behavioral skills and global development in children with cerebellar malformations.

Specific objective 2: To compare total and regional cerebral volumes and their tissue classes (cortical grey matter, white matter and subcortical grey matter) in children with isolated cerebellar malformations and healthy age and gender-matched controls, using 3-D volumetric MRI. Additionally, to examine the extent to which greater cerebellar volume reductions (difference between cases and controls) predict total and regional cerebral volumes in children with cerebellar malformations.

3.2 Statement of hypotheses

Hypothesis specific objective 1: We hypothesized that decreased total cerebellar volume is associated with global developmental delay. We also hypothesized that lateral cerebellar volumes are associated with cognitive, language and motor function. Moreover, we postulated that the cerebellar vermis volume is associated with social-behavioral skills.

Hypothesis specific objective 2: We hypothesized that when compared to age-matched children with normal MRI scans, children with isolated (in the absence of primary cerebral dysgenesis) cerebellar malformations show significantly decreased regional cerebral volume in known projection areas of the cerebellum when compared to healthy controls. In addition, we hypothesized that greater cerebellar volume reductions would be predictive of smaller total and regional volumes in specific regions of the cerebrum in children with cerebellar malformations.

3.3 Research design

Specific to objective 1

In addressing objective 1, a cross-sectional design was used to investigate the association between total cerebellar volume and seven regional cerebellar volumes (right and left lateral hemisphere, right and left midhemisphere, right and left medial hemisphere and vermis) (as defined in section 3.4.8) and seven functional outcomes (global development, gross and fine motor skills, cognition, expressive language, behavior and socialization) (as defined in section 3.4.6) in a cohort of children aged one to six with cerebellar malformations.

Specific to objective 2

In addressing objective 2, a case-control design was used to compare total cerebral volume and tissue classes (i.e. cortical grey matter, white matter, and subcortical grey matter), as well as eight regional cerebral volumes (as defined in section 3.4.8) and their tissue classes in children with isolated cerebellar malformations and children with normal MRI scans. In addition, the association between cerebellar volume reductions (difference between cases and controls) in cases with cerebellar malformations and total and regional cerebral volumes (as described above) was examined. Each case was matched to two controls according to their age and gender.

3.4 Methods and procedures

3.4.1 Definition of the populations

The target population for objective 1 consisted of children one to six years of age who were diagnosed with a cerebellar malformation.

The target population for objective 2 consisted of children one to six years of age with isolated cerebellar malformations (absence of supratentorial or chromosomal anomalies), as well as healthy children with normal MRI scans and scores within normal ranges on the development tests administered as part of the MRI Study of Normal Brain Development (see section 3.4.4).

3.4.2 Inclusion criteria

English speaking full-term children with a cerebellar malformation diagnosed by fetal or neonatal MRI, as per the diagnostic criteria described below, were eligible.

a) DWM: Partial or complete absence of the cerebellar vermis with continuity between the cisterna magna and the fourth ventricle, and enlargement of the posterior fossa with upward displacement of the torcula.
b) IVH: Incomplete caudal growth of the inferior vermis over the fourth ventricle.
c) Vermis hypoplasia: A malformation that affected more than 1/3 or the cerebellar vermis.
d) Rhombencephalosynapsis: Absent vermis and fusion of the cerebellar hemispheres.
e) Joubert syndrome: Presence of a molar tooth sign on axial plane, characterized by deep interpeduncular fossa, enlarged superior cerebellar peduncles that are oriented horizontally and hypoplasia of the cerebellar vermis.
f) Cerebellar hypoplasia: Underdevelopment of one or both cerebellar hemispheres (unilateral or bilateral).

3.4.3 Exclusion criteria

Infants with fetal or neonatal CNS infection, major intracranial birth trauma, inherited metabolic disease, or major pre- or postnatal cerebral ischemia were excluded based on the medical chart review. These conditions were excluded given that they are known to be associated with important neurodevelopmental sequelae (Härtel et al., 2004; Olsson et al., 2008; Scheld et al., 2004; Sreenan et al., 2000) and would be confounding the study of the effect of cerebellar malformations. Children with ventricular peritoneal shunts were excluded if reliable cerebral or cerebellar volumes could not be obtained due to the presence of metal artifact. Finally, children with mega cisterna magna and posterior fossa cysts were not included, because they represent cystic lesions rather than true cerebellar malformations.

3.4.4 Overview of the population of healthy controls

Healthy controls were obtained from a large public database available through the multi-centered MRI Study of Normal Brain Development funded by the National Institutes of Health (Almli et al., 2007; Evans, & Brain Development Cooperative Group, 2006). They were selected based on age and gender to match the children with cerebellar malformations.

Matching criteria are based on evidence showing that cerebral and cerebellar volume vary in relation to age and gender (Chunga et al., 2005; Reiss et al., 1996). Children accrued for the MRI Study of Normal Brain Development were selected by means of a population-based sampling method (Evans, & Brain Development Cooperative Group, 2006). All children had undergone a battery of cognitive, neuropsychological and behavioral assessments. The specific tests and procedures have been previously described (Evans, & Brain Development Cooperative Group, 2006). Medical and neurological history has also been previously reported (Evans, & Brain Development Cooperative Group, 2006). As part of the MRI Study of Normal Brain Development, children were excluded if they demonstrated cognitive, behavioral or neuropsychological problems on the test. Children presenting any factor with an established or potential risk to have a negative effect of normal brain development or children with contraindications for MRI scanning were also excluded (Evans, & Brain Development Cooperative Group, 2006).

3.4.5 Procedures

Children aged one to six years diagnosed with cerebellar malformations pre- or post-natally between 2003 and 2008, were identified through a systematic electronic search of the radiology MRI database of the Children's Hospital Boston. A pediatric neuroradiologist (R.R), who was blind to the clinical diagnosis and other neurological findings, then reviewed all MRI images to confirm the diagnosis (diagnostic criteria are described in section 3.4.2). Once a child was confirmed as having a cerebellar malformation and met the inclusion criteria (see sections 3.4.2 and 3.4.3), the pediatrician of record was contacted to verify that the child was still alive. If the child was alive, a letter (which included a self-addressed response card) was sent to the family describing the study and asking if they could be contacted by telephone to discuss the study. If no response was received within three weeks, the address was verified with the pediatrician and the mailing was repeated. When a telephone contact was made with the parents or tutor, the study coordinator discussed the study and answered all questions. Parent(s)/caregiver were then asked if they would agree to participate in the study. For the parent(s)/caregiver who agreed to participate, arrangements, at a convenient time for the child and family member, were made for scheduling two evaluation sessions at the hospital; a first session to perform standardized functional assessments and a second for MRI scanning. Subsequently, a package containing the Child

Behavior Checklist (Achenbach, & Rescorla, 2000) and the Modified Checklist for autism in Toddlers (Robins et al., 1999) was mailed. These standardized questionnaires were to be completed at home by the primary caregiver, prior to the assessment day.

On the day of the first appointment, the complete protocol was reviewed and free and informed written consent was obtained. All functional outcome measures were performed on the same day. However the order of administration was randomized to eliminate bias due to fatigue. The Mullen Scales of Early Learning were administered by a licensed child psychologist (N.S) who was trained to administer this specific outcome measure. Likewise, an experienced pediatric occupational therapist (C.L) administered the Peabody Developmental Motor Scales. Administration times for the Mullen Scales of Early Learning and Peabody Developmental Motor Scales are between 15 and 60 minutes (with older children undergoing longer assessments) and between 45 to 60 minutes respectively. The psychologist and the occupational therapist were blinded to the clinical diagnosis, neonatal complications, neurological and MRI findings, and each other's clinical findings. During the second visit a 45-minute MRI imaging protocol was completed. The imaging protocol is detailed in section 3.4.7.

The Committee on Clinical Investigation at Children's Hospital Boston provided scientific and ethics approval for this study, and written free and informed consent was obtained from the parents or caregivers for all children with cerebellar malformations.

3.4.6 Standardized outcome measures

First, to characterize our sample, we abstracted information from the medical records on pertinent demographic and clinical information (e.g., gender, gestational age, chromosome anomalies). We documented the results of routine karyotype analyses performed on the newborn infant or during amniocentesis.

Clinical measurement of gross and fine motor skills, cognitive function, language, global development, behavior and socialization were selected on the basis of their evaluative and discriminative ability in identifying developmental delays in young children across different developmental domains. In order to obtain the most valid data, assessment tools that could be used across all study ages were chosen. The following outcome measures were performed on the children.

a. Cognitive function, language and global development

Cognition refers to the ability to process, store, retrieve and manipulate information (Trombly, 1995). In children one to six years of age, cognition encompasses constructs such as perception, memory, language, and problem solving. Cognition, language skills and global development were assessed using the *Mullen Scales of Early Learning* (Mullen, 1995). The Mullen Scales of Early Learning is a standardized, norm-referenced developmental evaluation that assesses early development in children aged 0 to 68 months. It is divided into five subscales including receptive language, expressive language, visual reception skills and gross and fine motor skills. Together these subtests yield an early learning composite quotient, which reflects global development. In this thesis, for more precision, the term 'cognition' is used to describe visual reception.

Each subtest of The Mullen Scales of Early Learning has been separately tested for validity and reliability. They have all been shown to have excellent inter-rater (ranges from 0.91 to 0.99) and good construct validity (Mullen, 1995). The latter is supported by the increase in scores across ages. It is commonly used in children with various diagnostic, including Trisomy and autism (Akshoomoff, 2006; Fidler et al., 2006). The Mullen Scales of Early Learning demonstrated strong concurrent validity with other well-known developmental tests of motor, language, and cognitive development including the Bayley Scales of Infant Development, the Preschool Language Assessment, and the Peabody Fine Motor Scale (Mullen, 1995). Internal consistency of the five subdomains ranges from 0.75 to 0.83, evidence that the subscales measure distinct abilities.

The scores obtained on the various items were added up to obtain a raw score for each subscale, and a total score (early learning composite quotient). These were then converted in standard scores using normative data. These continuous scores have a mean of 50 and a standard deviation of 10 (Mullen, 1995). Higher scores indicate better functional outcome.

b. Motor Function

Motor function relates to the ability to control movements and can be divided into gross and fine motor skills. Gross motor skills involve larger muscles, such as in the arms and legs and fine motor skills involve the small muscles, such as in the hands. The *Peabody Developmental Motor Scales* (Folio, & Fewell, 1983) was used to assess motor function. The Peabody Developmental Motor Scales is a standardized test that objectively measures gross

and fine motor function in children from birth through 83 months of age. The Peabody Developmental Motor Scales is a discriminative and evaluative measure used to identify children with delayed motor development and to assess motor development over time.

The Peabody Developmental Motor Scales is widely used due to its strong psychometric properties. Inter-rater reliability for children with developmental delay was found to be 0.97 (Stokes et al., 1990). Good content and concurrent validity has also been demonstrated (Wiart, & Darrah, 2001).

The raw scores for the subtests are converted into standard scores using normative values (mean=100, SD =15), in which a higher score is indicative of better functional outcome (Folio, & Fewell, 1983).

c. Social-Behavioral Skills

The *Child Behavior Checklist* (Achenbach, & Rescorla, 2000) is a caregiver report that assesses behavioral and emotional difficulties in children aged 1.5 to 5 years. It can be self-administered or can be completed by means of an interview. It includes 99 items rated on a three-point scale. The scores are then categorized as, anxious/depressed, emotionally reactive, withdrawn, sleep problems, somatic complaints, aggressive behavior and attention problems and a total problem score is obtained. The scores are expressed as T-scores, a score ≥64 was defined as abnormal, a score between 60 and 63 as borderline and a score < 60 as normal (Achenbach, & Rescorla, 2000). The Child Behavior Checklist has shown very good test-retest reliability (mean 0.84) and inter-rater reliability (means of 0.61 to 0.65). The scores have also been found to reflect clinical data (Achenbach, & Ruffle, 2000).

The *Modified Checklist for Autism in Toddlers* (Robins et al., 1999) is a screening test used to assess the risk of autism spectrum disorders in children aged 16 to 30 months. It is a parent-report checklist that includes 23 yes/no items, including 6 critical items that are particularly important in determining function. Internal reliability was described as good (0.85) and its sensitivity was established at 0.97 for the 23 items and 0.95 for the best 6 items (Robins et al., 2001). Specificity is 0.99 for the 23 items and 0.98 for the best 6 items. Finally, positive predictive power is 0.68 and 0.79 and negative predictive power is 0.99 and 0.99, for the 23 items and for the 6 critical items respectively. Higher scores are indicative of the presence of more autistic features.

3.4.7 MRI acquisition

MRI scanning was selected as a preferred imaging technique because it has been proven to be safer (no radiation involved) than computed tomography and offers superior tissue contrast and resolution (Huppi, & Inder, 2001). All MRI scans were performed using a 1.5 Tesla General Electric System (GE-Medical Systems, Milwaukee, WI). First, through the use of an automated shimming procedure, a sagittal localizer image is acquired. Then, two different imaging modes were applied: a 3-D Fourier-transform spoiled gradient recalled sequence (1.5-mm coronal slices; flip angle: 45°; repetition time: 35 milliseconds; echo time: 5 milliseconds; field of view: 18 cm; matrix: 256 x 256; 124 slices) and a double-echo (proton density and T2-weighted) spin-echo sequence (3-mm axial slices; repetition time: 3000 milliseconds; echo times: 36 and 162 milliseconds; field of view: 18 cm; matrix: 256 x 256, interleaved acquisition; 68 slices). This allowed 3-D reconstruction of the brain. MRI scans for healthy controls were also acquired using a 1.5 Tesla field strength on General Electric or Siemens Medical Systems (Almli et al., 2007; Evans, & Brain Development Cooperative Group, 2006). Similar to our imaging protocol, the MRI Study of Normal Brain Development used spoiled gradient recalled and dual echo sequences. The complete imaging protocol has been previously described (Almli et al., 2007; Evans, & Brain Development Cooperative Group, 2006).

3.4.8 Image analysis

Three-dimensional volumetric MRI measurements were made using advanced post acquisition techniques to obtain quantitative measures of specific brain regions. Linear registration of the T1 images into an age matched normal infant Talairach-like space template was first completed (Collins et al., 1994; Fonov et al., 2009). Then, total brain volume (including the cerebellum) was automatically generated for each subject using the Brain Extraction Tool (Smith, 2002). In addition, cerebral and cerebellar tissue classification was performed using INSECT (Intensity-Normalized Stereotaxic Environment for Classification of Tissues) (Zijdenbos et al., 1998), in order to obtain volumes of white matter and cortical grey matter. INSECT is an automatic algorithm used for tissue classification, in which, based on the MRI signal properties, each voxel is labelled as belonging to one of the two tissue classes. Subcortical grey matter (basal ganglia and thalamus) was identified by non-linearly warping of an age specific template into each MRI scan (Collins, & Evans, 1997). The

cerebellum was then extracted by manual voxel labeling using the Display visualization tool. The Display tool is an in-house visualization software developed at the McConnell Brain Imaging Centre of the Montreal Neurological Institute (MacDonald, 2003). The outlines obtained for the total cerebral volume and cerebral tissue classes were manually corrected using the Display tool (Appendix B). Volumes were computed for the cerebellum, total cerebrum, and for each tissue class.

Subsequently, I, the candidate parcellated the cerebellum mediolaterally into seven zones (right and left lateral hemispheric, right and left midhemispheric and, right and left medial hemispheric), as well as vermis, as suggested by Makris et al. (2003). The cerebellum was divided using three curves, of which two were located in each hemisphere and one on the margin of the vermis. Three tag points were manually positioned to create each curve. The medial boundary was positioned by placing a first point at the junction of the intraculminate fissure and the cerebellar border, a second point at the intersection the secondary fissure and the cerebellar margin and a control point on the horizontal fissure at the medial one-third distance between the center of the cerebellum and the hemispheric edge. The lateral boundary was defined by positioning one point at the intersection of the superior posterior fissure and the cerebellar border, a second point at the junction of the ansoparamedian fissure and the cerebellar margin and a third point on the horizontal fissure at the lateral one-third distance between the hemispheric border and the center of the cerebellum. Finally, three points were positioned on the exterior margins on each side of the vermis. By means of a cubic function, the points were joined by a curve (Appendix C). This parcellation scheme was previously developed and validated based on cerebellar anatomical landmarks and on available evidence of cerebellar histology and connectivity, in addition to the cerebellar functional and behavioral associations (Makris et al., 2003; Makris et al., 2005). The intra-rater reliability for this parcellation method was established using inter-class coefficients which averaged 0.950 (range: 0.824-0.995) and inter-rater reliability which averaged 0.950 (range: 0.840-0.998) for all regions (Makris et al., 2005). In order to maximize reliability of our volume measures, I, the candidate, was rigorously trained to identify the appropriate anatomical landmarks. Moreover, each scan was reviewed by an experienced researcher in pediatric advanced MRI research studies (C.L) to verify the placement of the reference points. Finally, five scans were selected across ages which were parcellated a second time by the same investigator (M.B) to estimate the intra-rater reliability of our

parcellation. Volumes for total cerebellar volume were all within 2.75 cubic centimetres (cc) with an average difference of 0.79 cc. Moreover, 85% of volumes for all parcellated regions were within 5.47 cc and averaged 2.55 cc.

The cerebrum was then partitioned by a single evaluator (M.B.) into eight different regions using a previously validated parcellation scheme (Kennedy et al., 1998; Peterson et al., 2003). The first step consisted of dividing the cerebrum into right and left hemispheres. Next, each hemisphere was segmented into eight regions using three reference points manually located on the anterior commissure, posterior commissure and genu of the corpus callosum. Three coronal planes and one axial plane passing through the anterior and posterior commissures were then positioned. As a result, the cerebrum was divided into dorsolateral prefrontal, orbitofrontal, premotor, subgenual, sensorimotor, midtemporal, parieto-occipital and inferior occipital regions. Finally, volumes were calculated in centimeter cube for all eight regions of the cerebrum. This parcellation scheme is based on the anatomical landmarks of the brain. Inter-rater reliability was described as percentage in common voxel assignment to a defined cerebral region (Caviness et al., 1996). The average voxel assignment agreement was 80.2% and ranged from 62% to 99%. To ensure consistency in our volume measurements the same operator performed all parcellations and was trained to identify the correct anatomical landmarks. The same parcellation method was completed a second time on five different scans selected across ages, of which 85% regions parcellated twice were within 10.43 cc, and the volume difference averaged 5.29 cc.

3.4.9 Data Analysis

As previously suggested (Johnson, & Marlow, 2006), a cut-off score less than two standard deviations below the normative mean was used to define a score in the impaired range when describing the results of the Mullen Scales of Early Learning and Peabody Developmental Motor Scales. Scores were also dichotomized for descriptive purposed on the Child Behavior Checklist: a score equal to or$\geq$ 60 was considered as impaired (Achenbach, & Rescorla, 2000). On the Modified Checklist for Autism in Toddlers failing three items or two critical items was used as a cut-off (Robins et al., 1999).

Our primary outcomes for specific objective 1 are cognition (visual reception skills), language (expressive), global development (The Mullen Scales of Early Learning), fine and gross motor skills (Peabody Developmental Motor Scales), behavior (Child Behavior

Checklist) and socialization (Modified Checklist for Autism in Toddlers). Our exposure was total and regional cerebellar volumes: right and left lateral hemisphere, right and left midhemisphere, right and left medial hemisphere and vermis.

For specific objective 2, MRI measures of cerebellar volume, as well as total and regional cerebral volume and their tissue classes (total cerebral volume, white matter, cortical grey matter, subcortical grey matter, dorsolateral prefrontal white and grey matter, orbitofrontal white and grey matter, premotor white and grey matter, subgenual white and grey matter, sensorimotor white and grey matter, midtemporal white and grey matter, parieto-occipital white and grey matter and inferior occipital white and grey matter) were used to compare cerebral volumes in children with cerebellar malformations and to normal age and gender matched controls.

The effect of socio-economic status as a potential confounding variable was examined using The *modified Hollingshead Scale for Socioeconomic Status* (Hollingshead, 1957). The Hollingshead Two Factor Index of Social Status provides information on parental highest level of education and type of occupation. However, socio-economic status was not used as a confounder in our analyses because it was not significantly correlated with outcome.

Detailed statistical analyses for each specific objective are described in chapters 4 and 5.

3.4.10 Sample Size

Sample size calculations were carried out for specific objective 1 and 2.

For specific aim 1, sample size calculations for our regression models were based on pilot data, using a statistical power of 0.8, an alpha of 0.5. The minimum sample size required for specific aim 1 was 33. Pilot data was collected as part of a larger study examining the impact of both acquired and developmental cerebellar injuries.

For specific aim 2, the expected difference between our two groups was hypothesized based on pilot data. Given a statistical power of 0.8 and an alpha of 0.5, the minimum sample size required was 25.

3.5 Results

3.5.1 Description of population of children with cerebellar malformation

A total of 63 children were identified through the systematic electronic search of the radiology MRI database of the Children's Hospital Boston, of which five were not eligible (two for prematurity, three were not English speaking), four had died in early infancy and three were lost to follow-up. The remaining children were approached for consent. Of the remaining 51 families, 48 consented to enrollment in the study, although one consented for developmental testing only. Seven children could not complete the MRI scanning (one died before the MRI study had been scheduled, and six could not successfully complete the MRI study as they woke up during the MRI scanning procedure and could not go back to sleep) and eight children with ventricular peritoneal shunts were excluded because their cerebellar anatomy was obscured to some extent by metal artifacts. The remaining 32 children composed our sample for objective 1. Twelve of these children had associated supratentorial or chromosome anomalies and, consequently, were excluded for objective 2. MRI scanning was scheduled within nine months of functional testing in 85% of the children (mean= 5.25 months). Detailed descriptions of study samples and results for objective 1 and 2 are reported in chapters 4 and 5.

CHAPTER 4
INTRODUCTION

The literature review that we performed clearly underscored the lack of rigorous study designs and an urgent need for standardized outcome measures to be incorporated in studies describing the outcome of children with cerebellar malformations. Additionally, the use of traditional cerebellar diagnostic categories for prognostication appears to be inadequate as children with cerebellar malformations of varying severity and topography are often grouped together within the same diagnostic category. Accordingly, these heterogeneous diagnostic groups often encompass a wide spectrum of disability sometimes ranging from normal to severe impairments. As a result, the functional outcome of children with cerebellar malformations remained poorly defined and our understanding of how structure and function correlate in this population was limited. In order to better counsel families and establish more effective follow-up and early intervention programs, the functional consequences of cerebellar malformations needed better definition. Hence, the overall objective of this study was to delineate the impact of cerebellar malformations on cerebral development and child functioning in children aged one to six years.

The manuscript that follows addresses our first specific objective. In order to delineate the impact of cerebellar malformations on child development, we first describe the developmental outcome of children with cerebellar malformations using standardized outcome assessments for global development, cognitive, language skills, motor function, as well as social-behavior problems. We then examine the relationship between total and regional cerebellar volumes and specific developmental and functional domains. The presence of associated CNS or non-CNS malformations is also documented to control for its possible effect on cerebellar volume and child function. A greater understanding of the relationship between cerebellar anatomy and child function will allow for more targeted early intervention programs.

REGIONAL CEREBELLAR VOLUMES PREDICT FUNCTIONAL OUTCOME IN CHILDREN WITH CEREBELLAR MALFORMATIONS

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4.1 Abstract

The cerebellum is increasingly recognized for its role in high-order functions, including cognition, language, and behavior. Recent studies have also begun to describe a functional topography of the mature cerebellum that includes organization on a mediolateral axis. However, no study to date has examined the relationship between regional cerebellar volume and developmental disabilities in children with cerebellar malformations.

Objective: The objective of this study was to estimate the extent to which total and regional cerebellar volumes are associated with developmental disabilities in a cohort of children with cerebellar malformations.

Methods: Potential candidates for this study were identified through a systematic electronic search of the MRI database at Children's Hospital Boston. We selected all English-speaking full-term children born between 2003 and 2008 with the prenatal or postnatal diagnosis of cerebellar malformation. Standardized outcome measures and quantitative MRI scanning were performed on all children. The cerebellum was parcellated into seven mediolateral zones (three for each hemisphere plus the vermis) for regional volume analysis.

Results: In our cohort of 32 children with cerebellar malformations, total cerebellar volume was associated with gross motor function ($p=0.02$) and the right lateral hemispheric zone with expressive language ($p=0.01$) and gross motor skills ($p=0.03$). Additionally, lower vermis volumes were associated with global development delays ($p=0.001$), and impairments in cognition ($p<0.001$), language ($p=0.002$) and motor function ($p<0.001$). The vermis was also associated with behavior problems ($p<0.001$) and higher rate of positive autism spectrum disorder screening ($p=0.03$). In children with isolated cerebellar malformations, decreased total cerebellar volume was associated with delays in global development ($p=0.002$), expressive language ($p=0.01$), cognition ($p=0.01$), as well as gross and fine motor function ($p=0.03$ for both). Decreased volume in the right lateral cerebellar hemisphere were related to impaired cognition ($p=0.04$), expressive language ($p=0.01$), and gross motor function ($p=0.03$). Lesser vermis volume was associated with impaired global development ($p=0.004$), cognition ($p<0.001$), expressive language ($p=0.01$) and, gross and fine motor skills ($p=0.001$ and $p=0.01$ respectively), as well as behavior problems ($p=0.008$) and a higher rate of positive on the autism spectrum screening test ($p=0.04$).

Conclusion: These results begin to define the structural topography of functional outcome in children with cerebellar malformations and should lead to greater accuracy of prognostication as well as timely early developmental interventions.

4.2 Introduction

It is increasingly accepted that the cerebellum plays a role that far exceeds motor control and coordination (Schmahmann, 2004, Schmahmann and Sherman, 1998). Over a decade ago, Schmahmann and Sherman (Schmahmann, 2004, Schmahmann, & Sherman, 1998) described the cerebellar cognitive affective syndrome in adults with cerebellar disorders, characterized by impairment in executive functions, visuo-spatial skills, language, and affect. Stimulated by these insights, subsequent studies in humans and primates have begun to define a topographic map of the different cerebellar functions (Desmond et al., 1998, Konczak, & Timman, 2007, Schmahmann, 1998b, Schmahmann, 2004). The proposed functional divisions run along both medio-lateral and anterior-posterior axes. Specifically, the lateral hemispheres of the cerebellum appear to be involved in higher cognitive function. Conversely, the flocculonodular lobe and anterior vermis are primarily involved in axial motor control and the fastigial nuclei of the posterior cerebellar lobe and posterior vermis regulate emotion, social behavior, and affect (Desmond et al., 1998, Joyal et al., 2004, Middleton, & Strick, 2001, Schmahmann, 2004). Currently there appears to be little or no overlap of function over the topographic organization of the mature cerebellum.

In spite of accumulating evidence of a cerebellar topographic organization, it remains unclear whether and, if so, to what extent developmental anomalies of the cerebellum affect functional abilities in young children with cerebellar malformations. In previous work, we have demonstrated that the developmental outcome of cerebellar malformations in children is variable, ranging from normal or near normal development to severe developmental disabilities (Bolduc, & Limperopoulos, 2009). However, no study to date has examined the relationship between regional cerebellar volumes and specific developmental disabilities in children with cerebellar malformations. Because the cerebellum continues to develop over the early years of life (Barkovich, 2005, Limperopoulos, & du Plessis, 2006), greater understanding of the potential functional deficits associated with the type and severity of the malformation could help to guide early intervention strategies thereby minimizing developmental disabilities and optimizing functional outcomes. The objective of this study was to estimate the extent to which total and regional cerebellar volumes are associated with global development, as well as motor, cognitive, language (expressive), and social-behavioral skills in a cohort of children with cerebellar malformations. We hypothesized that decreased total cerebellar volume is associated with global developmental delay. We also predicted that

lateral cerebellar volumes are associated with cognitive, language and motor function. Moreover, we postulated that the cerebellar vermis volume is associated with social-behavioral skills.

4.3 Patients and Methods

Potential candidates for this study were identified through a systematic electronic search of the MRI database at Children's Hospital Boston. We selected all English-speaking full-term children (gestational age >37 weeks) born between 2003 and 2008 with the prenatal or postnatal diagnosis of cerebellar malformation including: Dandy-Walker malformation, inferior vermis hypoplasia, cerebellar and/or vermis hypoplasia, rhombencephalosynapsis, and Joubert syndrome. Our exclusion criteria included fetal or neonatal central nervous system infection, major intracranial birth trauma, inherited metabolic disease, or major pre- or postnatal cerebral ischemic injury.

To characterize our sample, we obtained pertinent clinical information through a systematic medical record review of all subjects (e.g., gender, gestational age, chromosome anomalies). Scientific and ethics approval was obtained from the Committee on Clinical Investigation at Children's Hospital Boston, and written informed consent was obtained in all cases.

4.3.1 MRI acquisition

A uniform protocol for all MR scans was used and all sequences were acquired at Children's Hospital Boston. Imaging was performed with a 1.5 Tesla General Electric System (GE-Medical Systems, Milwaukee, WI) using a quadrature or 8-channel phased array head coil. First, through the use of an automated shimming procedure, a sagittal localizer image was acquired. Two different imaging modes were applied: a 3-dimensional Fourier-transform spoiled gradient recalled sequence (coronal acquisition; slice thickness: 1.5mm; in-plane resolution: 0.78125mm x 0.78125mm; flip angle: 45°; repetition time: 35 milliseconds; echo time: 5 milliseconds; field of view: 18 cm; matrix: 256 x 256; 124 slices) and a double-echo (proton density and T2-weighted) spin-echo sequence (3-mm axial slices; repetition time: 3000 milliseconds; echo times: 36 and 162 milliseconds; field of view: 18 cm; matrix: 256 x 256, interleaved acquisition; 68 slices).

4.3.2 Cerebellar diagnostic groups

The MRI diagnosis of cerebellar malformation and its categorization were confirmed by an experienced pediatric neuroradiologist (R.R.) blinded to past medical history and developmental outcome.

4.3.3 Image analysis

Manual voxel labeling using Display, an in-house visualization tool developed at the McConell Brain Imaging Centre of the Montreal Neurological Institute (MacDonald, 2003), was used to outline the cerebellum. Subsequently, the cerebellum was parcellated in seven regions. Each cerebellar hemisphere was parcellated into three zones, i.e., medial hemispheric, midhemispheric (lateral hemispheric zone 1 by Makris et al. (2003)), lateral hemispheric (lateral hemispheric zone 2 by Makris et al. (2003)), and vermis was outlined, using a previously validated technique described by Makris and colleagues (Makris et al., 2003, Makris et al., 2005). The first line was drawn by joining one point created by the intersection of the intraculminate fissure and the cerebellar margin and another point at the meeting point of the secondary fissure and the cerebellar margin. A control point was placed on the horizontal fissure at the medial one-third distance between the center of the cerebellum and the hemispheric margin. The second line was drawn using the intersection of the superior posterior fissure and the cerebellar margin and a second point located at the junction of the ansoparamedian fissure and the cerebellar margin. A second control point was placed on the horizontal fissure at the lateral one-third distance between the hemispheric margin and the center of the cerebellum. Three points were also positioned on each side of the vermis. The curves joining the three points were drawn using a cubic function (Figure 1). Anatomical landmarks were identified by the same investigator (M.B) and their position was verified by a senior investigator (C.L.). Each parcellated cerebellum was then reviewed, and manual corrections were made when necessary. Volumes in cubic centimeters were calculated for the total cerebellum and each of the seven outlined regions. This parcellation method was validated on the basis of anatomical landmarks, cerebellar histology and connectivity (Makris et al., 2003). Functional and behavioral associations have also been taken into consideration in its development. Inter-class coefficients were used to evaluate intra-rater and inter-rater reliability, which averaged 0.95 for both measures (Makris, et al., 2005). In addition, consistency in our volume measurements were examined by selecting five

MRI scans to be parcellated a second time using the same parcellation method, by the same investigator (M.B.). Total cerebellar volume differences averaged 0.79 cc and volume differences in all parcellated cerebellar regions averaged 2.5 cc.

4.3.4 Standardized outcome measures

Standardized assessments were used to evaluate developmental and functional skills in all children with cerebellar malformations. These included the *Mullen Scales of Early Learning (*Mullen, 1995) administered by a licensed child psychologist (N.S.), the *Peabody Developmental Motor Scales* (Folio, & Fewell, 1983) administered by a pediatric occupational therapist (C.L.), and the *Child Behavior Checklist* and *Modified Checklist for Autism in Toddlers* (caregiver reports). All evaluators were blind to MRI findings, perinatal and neonatal complications, neurological findings, and each other's clinical findings.

The Mullen Scales of Early Learning (Mullen, 1995) was used to evaluate each child's development. It is divided into five subscales including receptive language, expressive language, visual reception skills (visual memory and discrimination), and gross and fine motor skills, in addition to the early learning composite quotient. In this study, we refer to visual reception skills as cognitive skills. The gross motor scores of the Mullen Scales of Early Learning are not applicable to children over 33 months. The Peabody Developmental Motor Scales (Folio, & Fewell, 1983) is a standardized test for assessing gross and fine motor function in children from birth through 83 months of age. Continuous scores were used for analyzing the association between total and regional cerebellar volumes and functional outcomes. For all the above described assessment tools, a score below two standard deviations of the normative mean was defined as being indicative of an impairment when describing the developmental outcome of children with cerebellar malformations.

In addition, the Child Behavior Checklist (Achenbach, & Rescorla, 2000) is a care-giver report that was used to assess maladaptive behaviors. The total problem scale score is expressed as a T-score and was used as a continuous score in analyzing the association between cerebellar volume and behavioral outcomes; however, a score equal or above 60 was defined as being in the impaired range of functioning. The Modified Checklist for Autism in Toddlers (Robins et al., 1999) is a parental report used as a screening test for early detection of autistic behaviors. Failing of 3 items total or 2 critical items is used as a cut-off.

4.3.5 Statistical analysis

Descriptive statistics were used to characterize our sample. Developmental, MRI, and clinical characteristics of the patients were summarized using means for continuous data and proportions for categorical data. Based on a-priori hypotheses the following were selected as developmental and functional outcomes: cognitive skills (i.e. visual reception), expressive language, and early learning composite quotient of the Mullen Scales of Early Learning, gross and fine motor scores of Peabody Developmental Motor Scales, the total problem score on the Child Behavior Checklist and total score on the Modified Checklist for Autism in Toddlers. Linear regression analyses were then used to examine the relationship between total and regional cerebellar volumes and continuous developmental and functional outcome measures (Mullen Scales of Early Learning, Peabody Developmental Motor Scales and, Child Behavior Checklist) and logistic regression analyses were used for the dichotomous outcome (Modified Checklist for Autism in Toddlers), in the overall cohort (n=32) and in a subgroup of children with isolated cerebellar malformations (n=20). Because of our sample size, each regional cerebellar volume was examined using a separate linear regression. Raw p-values are presented and associations that remain significant after Bonferroni adjustments for multiple comparisons are described because of the controversy around this correction method (Perneger, 1998). All assumptions for linear regressions were met. Correlations were examined to identify the presence of potential confounding variables. Known confounders were entered in the all models including age, presence of associated CNS malformations, chromosome anomalies and total cerebellar volume. Differences in regional volumes and outcome between children with isolated cerebellar malformations and those with cerebellar malformations and associated supratentorial/chromosome anomalies were analyzed using independent-samples t-test for continuous data and Pearson's chi-square for dichotomous outcome. Statistical analyses were performed using SPSS Statistics version 17.0 (IBM Company, Chicago, Illinois, USA).

4.4 Results

4.4.1 Characteristics of the cohort

Fifty-eight children with cerebellar malformations met our inclusion criteria. Of these, four died in infancy and three were lost to follow-up. Of the remaining 51 families, 48 (94%) consented to enrollment in the study, although one consented for developmental

testing only. Seven children could not complete the MRI scanning and eight children with ventricular peritoneal shunts were excluded because their cerebellar anatomy was obscured to some extent by metal artifacts. The remaining 32 children composed the core of our study sample. However, in two subjects with severe cerebellar malformations the anatomical landmarks for cerebellar hemispheres parcellation could not be clearly identified, therefore in these children we obtained only volumes for total cerebellum and vermis. The study population is presented in Figure 2.

The clinical radiological diagnoses of our sample are summarized in Table 1. The mean (SD) gestational age was 39.2 (2.2) weeks and the mean birth weight was 3426.6 (674.8) grams. Children underwent developmental testing at a mean age of 28.8 (14.8) months (range 12 to 73 months) and MRI scans at a mean of 28.0 (16.7) months (range 10 to 72 months). Our sample was composed of 19 males (59%) and 13 females (41%). Twenty children (63%) had isolated cerebellar malformations and 12 children (37%) had associated supratentorial abnormalities and/or chromosomal findings (24%) including agenesis/hypoplasia of the corpus callosum (7), abnormal gyral pattern (3), nodular heterotopias (2), decreased white matter (1), absence of septum pellucidum (1), periventricular white matter abnormalities (1) and ventriculomegaly (1). Chromosomal abnormalities included Joubert syndrome (1), CHARGE association (2) and chromosome 10 anomalies (1).

4.4.2 Developmental outcomes of the cohort

Two-thirds (68%) of children with cerebellar malformations experienced important gross motor disabilities, and 50% experienced delayed global development and cognitive impairments. Additionally, almost half the cohort (47%) demonstrated delays in expressive language skills and 41% in receptive language skills. Fine motor function was impaired in 38% of children and behavioral problems (Child Behavior Checklist) were present in just under half (47%) of the children. Finally, 59% of the cohort had a positive screening for early signs of autism features (Modified Checklist for Autism in Toddlers). Given the proportion of children with associated supratentorial anomalies and chromosomal abnormalities in our cohort (n=12), we also compared the developmental outcomes of those with isolated cerebellar malformations (n=20) and those with combined supratentorial/chromosomal abnormalities. Overall, children with cerebellar malformations and associated supratentorial anomalies and chromosomal abnormalities presented

significantly more severe developmental and functional impairments when compared to those with isolated cerebellar malformations on all outcome measures except on the total problem scale of the Child Behavior Checklist (Table 2).

4.4.3 Association between total and regional cerebellar volumes and outcome in the overall cohort

We first examined the relationship between total and regional cerebellar volumes and developmental outcomes in our entire cohort, controlling for the presence of supratentorial and/or chromosomal anomalies and age at testing for all analyses. We also controlled for total cerebellar volume when analyzing the effect of regional cerebellar volumes on developmental outcomes. The total and regional cerebellar volume measures of our sample are presented in Table 3. Decreased total cerebellar volume was associated with deficits in gross motor function ($p=0.02$). Volumetric loss in the right lateral hemispheric zone was associated with expressive language ($p=0.01$), and gross motor deficits ($p=0.03$). Additionally, reduced vermis volume was associated with global developmental delays ($p=0.001$), as well as deficits in cognition ($p<0.001$), language ($p=0.002$), gross motor skills ($p<0.001$), and behavioral problems ($p<0.001$). Finally, lower vermis volumes were associated with a higher rate of autistic features ($p=0.03$). There were no statistically significant associations between medial hemispheric and midhemispheric zones and functional outcome. After correcting for multiple analyses using the Bonferroni method (Bland, & Altman, 1995), smaller vermis volume remained predictive of global developmental delays, as well as cognition, language, gross motor, and behavioral problems. The relationship between total and regional cerebellar volumes and developmental outcomes is detailed in Table 4.

4.4.4 Association between total and regional cerebellar volumes and outcome in children with isolated cerebellar malformations

(i) Total cerebellar volume and outcome

We then examined the relationship between total and regional cerebellar volume and global development and functional skills, controlling for age, in children with isolated cerebellar malformation (i.e., no associated supratentorial or chromosomal abnormalities). Total and regional volumes of children with isolated cerebellar malformations were

compared to those of children with associated supratentorial/chromosome anomalies. The results are presented in Table 5. On bivariate analyses, lesser total cerebellar volumes were associated with global developmental delay (p=0.002) and cognitive delays (p=0.01) and with deficits in gross and fine motor skills (p=0.03 for both), as well as with expressive language skills (p=0.01). The association between total cerebellar volume and global development remained significant when adjusting for multiple comparisons.

(ii) Lateral hemispheric volume and outcome

When examining laterality (left versus right lateral hemispheric volume), decreased volume in the right lateral hemisphere was associated with deficits in cognition (p=0.04), expressive language (p=0.01), and gross motor skills (p=0.03). Conversely, there was no association between reduced cerebellar volume in the left lateral hemisphere and specific functional skills in children with isolated cerebellar malformations. These associations did not remain significant following Bonferroni correction. The results are described in Table 6.

(iii) Midhemispheric volume and outcome

There were no significant associations between midhemispheric volumes and developmental and functional scores in children with isolated cerebellar malformations.

(iv) Medial hemispheric volume and outcome

There were no significant associations between medial hemispheric volumes and developmental and functional outcome in our cohort of children with isolated cerebellar malformations.

(iv) Vermis volume and outcome

There was a highly significant relationship between decreased vermis volume and global developmental delay (p=0.004), cognition (p<0.001), expressive language (p=0.01) gross motor (p=0.001), fine motor (p=0.01). Moreover, smaller vermis volumes were associated with behavioral problems (p=0.008) and a higher prevalence of a screening test (p=0.04). The associations between vermis volume and global development, cognition, expressive language and, gross and fine motor skills remain significant after Bonferroni

corrections. The relationship between vermis volume and the outcome measures are summarized in Table 7.

4.5 Discussion

Currently used diagnostic categories for cerebellar malformations are often associated with a wide range of neurodevelopmental outcomes, which frequently limit reliable prognostication (Bolduc, & Limperopoulos, 2009; Tavano et al., 2007). To our knowledge, this is the first report in which advanced quantitative cerebellar MRI volumetric and parcellation techniques have been used to examine the relationship between regional cerebellar volumes and developmental and functional outcomes. Our study provides new insights into the functional topography of disturbed cerebellar growth in the developing child. Specifically, decreased total cerebellar volume was associated with global developmental delay, cognitive and language impairments, motor deficits, and functional disabilities in children with isolated cerebellar malformations. Our data also demonstrate important relationships between regional cerebellar volumes and domain-specific developmental and functional skills. The most striking finding is the apparent pervasive functional impact of disturbed cerebellar vermis growth at this young age. The wide-ranging impact of decreased vermis volume in both motor and non-motor functions, including deficits in global development, cognition, expressive language, and behavioral skills is remarkable. Additionally, decreased vermis volume was associated with a higher prevalence of positive the autism spectrum disorder screening. We also showed that the lateral zones of the cerebellum, specifically the right lateral hemisphere, are associated with specific and lateralized dysfunction. Expressive language, cognition, and gross motor function were significantly affected by reduced volume of the lateral-most region of the right but not left cerebellar hemisphere. Conversely, there was no significant association between cerebellar volumes in the medial hemispheric and midhemispheric regions and specific functional skills.

Recent evidence from primates, adult, and older children links the vermis to motor, cognitive and behavioral functions. Two previous studies have reported a significant association between severe malformations of the cerebellar vermis and intelligence quotient (Boddaert et al., 2003 ; Klein et al., 2003); however, these studies used a qualitative description of the vermian malformation. Moreover, tumor resection in the region of the cerebellar vermis have resulted in significant difficulties in behavior and attention (Levisohn

et al., 2000; Riva, & Giorgi, 2000; Schmahmann, 2004) as well as mutism and dysarthria (Riva, & Giorgi, 2000; Schmahmann, 2004). There is also evidence that the midline structures are involved in gait and posture (Konczak, & Timman, 2007). A recent study of intrinsic connectivity networks also demonstrated that the vermis was extensively connected to a various cortical regions that are involved in cognition, language and emotions (Habas et al., 2009). Finally, there also is a growing body of data demonstrating a link between the vermis and autism spectrum disorders (Courchesne et al., 1994; Courchesne et al., 1988; Filipek, 1995; Piven et al., 1997; Webb et al., 2009). In a previous study, our group demonstrated an association between cerebellar vermis injury and positive autism screen in survivors of extreme preterm birth (Limperopoulos et al., 2007). This current study also found a statistically significant relationship between the vermis and positive screening for early signs of autistic features in children with cerebellar malformations. The results of our current study also support the important association between the cerebellar vermis region and global development, cognitive, language, and motor function, as well as behavior outcomes. Striking in our study was the strong association between reduced vermis volume and a broad spectrum of cognitive, behavioral, language, and motor dysfunction. This compelling finding suggests that during early development structural elements in the midline cerebellum play an important role in the subsequent development of a broad spectrum of neurologic functions. In the mature brain these functions have a more distributed topography, with less concentration in the midline region of the cerebellum.

In contrast to our current findings, children in our earlier studies with isolated inferior vermis hypoplasia had a largely favorable outcome (Limperopoulos et al., 2006). The reason for these differences are unclear but could potentially be related to the quantitative versus qualitative methodological differences between the studies, or more fundamental differences (e.g., isolated hypoplasia versus dysgenesis) between lesions in these studies. This is an important question in need of more detailed study.

In previous literature the fastigial nuclei (anatomically located within the medial hemispheric zone) have been implicated in the regulation of emotions, affect, and behavior in adults (Hu et al., 2008; Schmahmann, 2004; Schutter, & van Honk, 2005). Additionally, the medial zones have been shown to be associated with maintenance of balance, sensorimotor function, cognition and eye movement (Makris et al., 2003, Schmahmann, 1998a, Schmahmann et al., 2000). In our cohort, we did not find a significant relationship

between the medial hemispheric zone and our developmental outcomes. One potential explanation for this may be the young age at which our children were tested (mean age 29 months), at a time when domain specific development and skill differentiation is still actively underway. Long-term follow-up of our cohort will assist in elucidated the role of the medial cerebellum in child development.

Available evidence from adults and older children suggests that the lateral hemispheres are associated with cognitive tasks, language, and motor control of the upper limbs (Dum et al., 2002; Konczak, & Timman, 2007; Leiner et al., 1989; Leiner et al., 1991; Makris et al., 2003; Marien et al., 2001). Two previous studies in older children with tumor resection of the lateral cerebellar hemisphere(s) have reported that the right hemisphere is involved in auditory sequential memory and language, whereas the left hemisphere is linked to visual and spatial sequential memory (Levisohn et al., 2000; Riva, & Giorgi, 2000). However, it is important to note that these studies did not measure regional cerebellar volumes. Moreover, the midhemispheric has not been studied independently from the lateral hemispheric zone in children or adults with cerebellar lesions or malformations. Our findings support the role of the lateral hemisphere in cognitive skills and language and also corroborate the stronger association between language skills and the right cerebellar hemisphere (Levisohn et al., 2000; Riva, & Giorgi, 2000). In our study, the absence of cognitive impairment associated with decreased volume in the midhemispheric zone could be explained by the young age of the children, in whom several cognitive skills are still emerging.

This is the first study to show an association between volumetric loss, measured by advanced 3-dimensional quantitative MRI in the cerebellum, and specific functional deficits using standardized outcome measures. However, our study also has several important potential limitations. First, although this study represents one the largest samples of children with cerebellar malformations, it may have lacked the statistical power to detect more specific regional volume-function relationships. Second, given the young age of our cohort, many critical language and cognitive functions are not completely developed or may not be differentiated at the current developmental level, thus precluding more detailed structure-function analyses. Given the cross-sectional nature of the study design, long-term follow-up of these children will be necessary in order to address this important question.

4.6 Conclusion

In summary, this study demonstrates that the medio-lateral topographical organization of the cerebellum, previously described in adults has important similarities in young children with cerebellar malformations. Specifically we show a significant relationship between regional volumetric growth and global and domain specific developmental and functional deficits in young children with cerebellar malformations. Most remarkable is the broad functional spectrum of functional deficits, including modulation of both motor and non-motor functions, seen in children with reduced vermian volume. The results of this study may increase the prognostic accuracy in infant with cerebellar malformations, based on the location and extent of regional cerebellar volumetric loss. Furthermore, our results may also help to direct targeted early intervention strategies, prior to the completion of cerebellar development, aimed at minimizing developmental disabilities and optimizing life quality in young children with cerebellar malformations.

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TABLE 1. Cerebellar malformation diagnostic groups

Diagnostic group	**Frequency (%)** **N=32**
Cerebellar hypoplasia	11 (34%)
Inferior vermis hypoplasia	11 (34%)
Vermis hypoplasia	5 (16%)
Rhombencephalosynapsis	3 (9%)
Dandy-Walker malformation	1 (3%)
Joubert syndrome	1 (3%)

TABLE 2. Comparison of outcome in children with isolated cerebellar malformation versus those with CNS or chromosomal anomalies

	Isolated cerebellar malformation Mean (SD) N=20	**Cerebellar malformation associated with CNS or chromosome anomaly Mean (SD) N=12**	**Mean difference between the two groups**	**p-value**
Peabody Developmental Motor Scales				
Gross motor	76.00 (9.87)	65.33 (1.16)	10.67	<0.001
Fine motor	78.95 (7.78)	68.33 (4.98)	10.62	<0.001
Mullen Scales of Early Learning				
Cognitive skills	41.70 (5.18)	24.08 (7.87)	17.62	0.001
Expressive language	36.80 (12.15)	26.17 (10.30)	10.63	0.02
Early learning composite	83.00 (20.43)	59.17 (15.87)	23.83	0.002
Child Behavior Checklist				
Total problem scale	49.50 (11.77)	57.67 (10.89)	8.17	0.06
Modified Checklist for Autism in Toddlers				
Total score	3.95 (4.71)	9.08 (5.27)	5.13	0.004

TABLE 3. Total and regional cerebellar volumetric measurements of our cohort (N=32)

Total and regional cerebellar volumes (cc)	**Mean (SD) (cc)**	**Range (cc)**
Total Cerebellar volume	83.88 (42.63)	3.22-166.67
Right lateral hemispheric	5.92 (3.19)	0.42-12.35
Left lateral hemispheric	6.40 (3.06)	0.60-13.76
Right midhemispheric	21.87 (10.15)	2.61-44.70
Left midhemispheric	23.44 (10.10)	2.46-49.65
Right medial hemispheric	14.19 (7.44)	1.09-26.45
Left medial hemispheric	15.00 (7.08)	1.87-30.72
Vermis	3.20 (2.36)	0.00-9.15

SD: standard deviation

TABLE 4. Association between total and regional cerebellar volumes and developmental outcomes in children with cerebellar malformations (N=32)

Regional cerebellar volumes (cc)	Developmental disabilities	Estimate of effect[+]	95% Confidence Interval	p-value
Total cerebellum	**Peabody Developmental Motor Scales**			
	Gross motor function	0.087	0.013-0.161	0.02
Right lateral hemispheric zone	**Mullen Scales of Early Learning**			
	Expressive language	3.181	0.868-5.495	0.01
	Peabody Developmental Motor Scales			
	Gross motor function	1.922	0.236-3.608	0.03
Vermis	**Mullen Scales of Early Learning**			
	Early learning composite	5.057	2.143-7.972	0.001
	Cognitive skills	4.168	2.378-5.956	<0.001
	Expressive language	3.112	1.253-4.972	0.002
	Peabody Developmental Motor Scales			
	Gross motor function	2.770	1.637-3.902	<0.001
	Child Behavior Checklist			
	Total problem scale	-3.550	(5.254)-(1.847)	<0.001
	Modified Checklist for Autism in Toddlers			
	Total score	0.528*	0.301-0.928	0.03

[+] Estimate of effect**:** Relationship between total and regional cerebellar volumes and functional outcome

[*] Odds ratio and confidence interval for the odds ration from logistic regression

TABLE 5. Comparison of cerebral volumes in children with isolated cerebellar malformation versus those with CNS or chromosomal anomalies

Total and regional cerebellar volumes (cc)	**Isolated cerebellar malformation Mean (SD) N=20**	**Cerebellar malformation associated with CNS or chromosome anomaly Mean (SD) N=12**	**Mean difference between the two groups**	**p-value**
Total cerebellar volume	96.66 (38.92)	62.58 (41.39)	34.08	0.03
Right lateral hemispheric	6.57 (3.40)	4.64 (2.37)	1.93	0.12
Left lateral hemispheric	6.86 (3.14)	5.38 (2.75)	1.48	0.23
Right midhemispheric	23.09 (1.03)	19.41 (9.88)	3.68	0.36
Left midhemispheric	24.42 (9.58)	21.26 (11.44)	3.16	0.48
Right medial hemispheric	15.36 (7.93)	11.86 (6.04)	3.50	0.23
Left medial hemispheric	16.44 (7.24)	11.80 (5.87)	4.64	0.10
Vermis	4.09 (2.33)	1.70 (1.55)	2.39	0.004

TABLE 6. Association between right lateral volume and developmental outcomes in children with isolated cerebellar malformations (N=20).

Outcome Measures	**Estimate of effect**[+]	**95% Confidence Interval**	**p-value**
Mullen Scales of Early Learning			
Cognitive skills	2.959	0.137-5.781	0.04
Expressive language	2.998	0.772-5.223	0.01
Peabody Developmental Motor Scales			
Gross motor	2.345	0.253-4.437	0.03

[+] Estimate of effect**:** Relationship between vermis volume and functional outcome

TABLE 7. Association between cerebellar vermis volume and developmental outcome in children with isolated cerebellar malformations (N=20).

Outcome Measures	**Estimate of effect**[+]	**95% Confidence Interval**	**P-value**
Mullen Scales of Early Learning			
Early learning composite	4.995	1.854-8.136	0.004
Cognitive skills	4.784	2.810-6.757	<0.001
Expressive language	3.028	0.0811-5.246	0.01
Peabody Developmental Motor Scales			
Gross motor	3.397	1.710-5.025	0.001
Fine motor	2.013	0.486-3.541	0.01
Child Behavior Checklist			
Total problem scale	(3.047)	(5.199-0.896)	0.008
M-CHAT			
Total score	0.446*	0.205-0.970	0.04

[+] Estimate of effect**:** Relationship between vermis volume and functional outcome

*Odds ratio and confidence interval for the odds ration from logistic regression

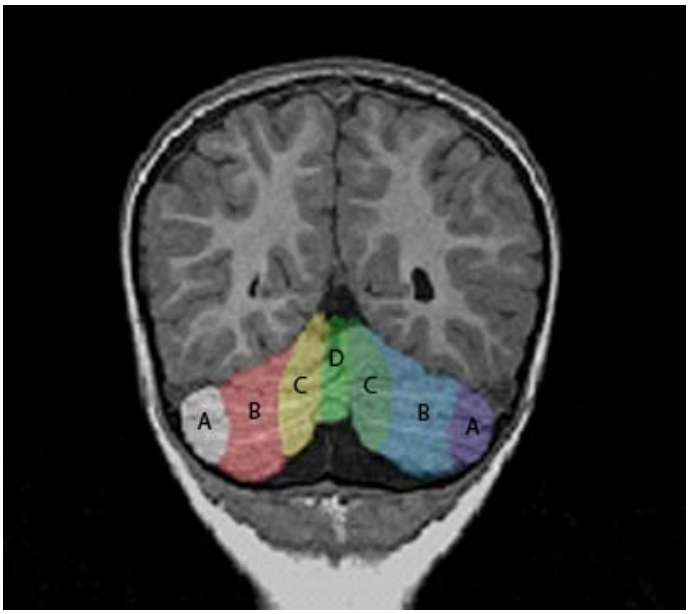

Figure 1. An example of the parcellation scheme used to divide the cerebellum into seven regions, A represents the right and left lateral hemispheric zones; B represents the right and left midhemispheric zones; C the right and left medial hemispheric zones; and D the vermis.

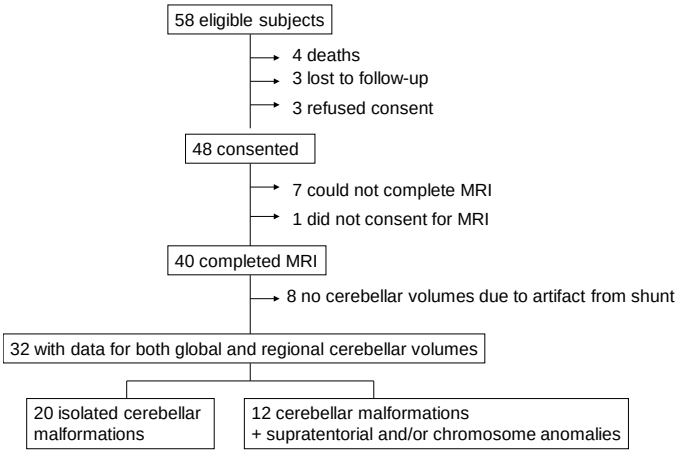

Figure 2. Flow-chart detailing the study population.

CHAPTER 5
INTRODUCTION

In the previous chapter, we demonstrated that children with cerebellar malformations experience a high prevalence of developmental and functional disabilities that extend far beyond the motor domain to include, cognitive, language, and social-behavioral problems. Additionally, our data showed that smaller volumes in specific cerebellar regions volumetric are associated with domain defined developmental and functional disabilities. These important insights into the topographical organization of the cerebellum in children with cerebellar malformations provide new insights in understanding of the wide spectrum of disability experienced by children with cerebellar malformations.

However, given the intricate pathways that connect the cerebellum to the cerebrum, another important consideration in the genesis of development disabilities in children with cerebellar malformations is the potential role for disturbed cerebral growth and development, even in the absence of obvious primary supratentorial lesions. Available evidence from adult and pediatric populations with acquired injury to the cerebellum suggest that cerebellar injury leads to impaired perfusion and trophic deactivation in remote cerebral regions, which are known projection areas of the cerebellum. However, very little is known about the impact of cerebellar malformations on the developing cerebrum during a critical period of accelerated development in utero and throughout the first years of life postnatally.

The following manuscript addresses our second objective for which we examined the impact of cerebellar malformations on cerebral development. Specifically, using advanced 3-D quantitative MRI, we compared total and regional cerebral volume in children with isolated cerebellar malformations and healthy age and gender matched controls. We also examined the impact of cerebellar volume reduction on total and regional cerebral growth (volume). These results will contribute to a better understanding of the impact of cerebellar malformations on subsequent cerebral growth and development in this high-risk population.

CEREBELLAR MALFORMATIONS ALTER REGIONAL CEREBRAL DEVELOPMENT

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5.1 Abstract

Cerebellar malformations are associated with global and pervasive developmental and functional deficits. However, the mechanisms underlying the nature and extent of these developmental deficits remain poorly understood. The presence of strong efferent connections between the cerebellum and the cerebrum raises the question whether trophic deactivation of the cerebello-cerebral pathways caused by impaired cerebellar growth could lead to impaired cerebral growth in young children with cerebellar malformations.

Objective: The objective of this study was to compare total and regional cerebral volumes and their tissue classes (cortical grey matter, white matter, and subcortical grey matter) in children with isolated cerebellar malformations and healthy age and gender-matched controls, using advanced three-dimensional (3-D) volumetric magnetic resonance imaging (MRI) and parcellation techniques, as well as to examine the extent to which cerebellar volumetric reductions predict total and regional cerebral volumes in children with cerebellar malformations.

Methods: Children born between 2003 and 2008 with the prenatal or postnatal diagnosis of isolated cerebellar malformations were identified though a systematic electronic search of the MRI database at Children's Hospital Boston. Each case was matched to two controls according to their age and gender. Healthy controls were selected from the database of the MRI Study of Normal Brain Development funded by the National Institutes of Health. Using advanced 3-D MRI volumetric and parcellation techniques, the cerebrum was segmented into three tissue classes (cortical grey matter, white matter, and subcortical grey matter) and then partitioned into eight regions using a previously validated parcellation scheme.

Results: Magnetic resonance imaging scanning was performed at a mean age of 27.1 (16.1) months for the 20 children with cerebellar malformations and at 27.0 (17.1) months for the 40 healthy controls. Children with cerebellar malformations showed significantly smaller regional volumes in the subcortical grey matter (basal ganglia and thalamus) ($p<0.001$), subgenual white matter ($p=0.03$), midtemporal white matter ($p=0.02$), and inferior occipital grey matter ($p=0.03$) when compared to healthy age and gender matched controls. Additionally, greater cerebellar volumetric reduction in children with cerebellar malformations was predictive of decreased total cerebral volume ($p=0.02$), cortical grey matter ($p=0.01$), subcortical grey matter (0.02) and regional volume in the subgenual white

(p=0.001) and grey matter (p=0.001), midtemporal white (p=0.02) and grey matter (p=0.01) and, parieto-occipital grey matter (p=0.004).

Conclusion: We show for the first time that cerebellar malformations are associated with impaired regional cerebral volumetric growth, suggesting deactivation of principal cerebello-cerebral pathways, during critical phases of cerebral development.

5.2 Introduction

The contribution of the cerebellum beyond motor function, such as cognition, affect and behavior, has long been overlooked. Converging evidence from clinical and neuroimaging studies in adults with cerebellar lesions increasingly supports the involvement of the cerebellum in high-order cognitive skills, behavior and affect (Habas, et al., 2009; Schmahmann, 2004; Schmahmann, & Sherman, 1998). These new insights into the expanded functional role of the cerebellum have paved the way to a more comprehensive understanding of the impact of cerebellar malformations on subsequent cerebral development.

Normal brain development is dependent on appropriate neuronal activation through developing neural circuits. The cerebro-cerebellar circuitry is composed of both feedforward and feedback connections. The cerebellar output projects from the deep cerebellar nuclei through the red nucleus to the thalamus, and from there to the motor cortex and the supplementary motor area, the posterior and inferior parietal cortex, the superior temporal cortex, the prefrontal cortex as well as the cingulate gyrus and the parahippocampal gyrus (Allen, et al., 2005; Middleton, & Strick, 2001; Schmahmann, & Pandya, 1997). The presence of these strong efferent connections between the cerebellum and the cerebrum raises the important question of whether trophic deactivation of the cerebello-cerebral pathways caused by impaired cerebellar development could result secondarily in altered cerebral development.

Cerebello-cerebral diaschisis, defined as a loss of function in the cerebral cortex following a cerebellar lesion, has been previously reported in the adult population and in older children following cerebellar tumor resection (Attig, et al., 1991; Baillieux, et al., 2009; Boni, et al., 1992; Broich, et al., 1987; De Smet, et al., 2009; Deguchi, et al., 1994; Komaba, et al., 2000; Miller, et al., 2009). Decreased perfusion, metabolism and oxygen consumption are characteristics of this phenomenon that is presumed to be present in up to 77% of patients following posterior fossa injury (Attig, et al., 1991; Baillieux, et al., 2009; Boni, et al., 1992; De Smet, et al., 2009; Deguchi, et al., 1994; Komaba, et al., 2000; Miller, et al., 2009). Using single photon emission computed tomography and dynamic susceptibility contrast magnetic resonance imaging (MRI), cerebello-cerebral diaschisis has been reported in the basal ganglia, thalamus, striatum, prefrontal, frontal, parietal and temporal regions and has been attributed to changes in the cerebello-cortical pathways (Attig, et al., 1991; Baillieux, et al., 2009; Boni,

et al., 1992; Broich, et al., 1987; De Smet, et al., 2009; Komaba, et al., 2000; Miller, et al., 2009; Sagiuchi, et al., 2001). However, these studies examined the effects of acquired injury in adults or older children following tumor resection. Consequently, very little is known about the impact of congenital cerebellar anomalies on early cerebral development.

It is increasingly appreciated that cerebellar malformations are associated with global and pervasive developmental and functional deficits (Bolduc, & Limperopoulos, 2009; Schmahmann, 1997). In previous work we have shown that, up to 50% of children with cerebellar malformations experienced global developmental delay, motor and cognitive (i.e. visual reception) and language deficits, maladaptive behaviors and a high prevalence of a positive screening for autism spectrum disorder (Bolduc et al. 2010). The potential contribution of secondary cerebral growth impairment in the high prevalence of neurodevelopmental impairment in children with cerebellar malformations remains unclear.

The objective of this study was to compare total and regional cerebral volumes and their tissue classes (cortical grey matter, white matter, and subcortical grey matter) in children with cerebellar malformations and healthy age and gender-matched controls, using advanced three-dimensional (3-D) volumetric MRI and parcellation techniques. We also examined the extent to which cerebellar volumetric reductions predict total and regional cerebral volumes in children with cerebellar malformations. We hypothesized that children with isolated cerebellar malformations would show decreased regional cerebral volume in known projection areas of the cerebellum when compared to healthy age-matched controls. We also postulated that greater reductions in cerebellar volumes would be associated with volumetric reductions in specific regions of the cerebrum.

5.3 Patients and methods

5.3.1 Procedures

Children born between 2003 and 2008 with the prenatal or postnatal diagnosis of isolated (i.e. absence of supratentorial lesions, as well as the absence of chromosomal abnormalities and syndromic diagnoses) cerebellar malformations were identified though a systematic electronic search of the MRI database at Children's Hospital Boston for this case-control study. Each case was matched to two healthy controls according to their age and gender for MRI comparisons. The controls were selected on the basis of their age and gender from the database of the MRI Study of Normal Brain Development funded by the

National Institutes of Health (Almli, et al., 2007; Evans, & Brain Development Cooperative Group, 2006). Full-term infants (≥ 37 gestational weeks) who were diagnosed with a Dandy-Walker malformation, an inferior vermis hypoplasia, a cerebellar and/or vermis hypoplasia or a rhombencephalosynapsis were accrued for this study. Children with fetal or neonatal central nervous system infection, major intracranial birth trauma, an inherited metabolic disease, or a major pre- or postnatal cerebral ischemia were excluded. Patients with ventricular peritoneal were also excluded because reliable cerebral volumes could not be obtained, due to the presence of metal artifacts on the MRI scans. The study was approved by The Children's Hospital Boston's Committee on Clinical Investigation.

5.3.2 MRI acquisition

MRI scans for children with cerebellar malformations were acquired at Children's Hospital Boston using a standardized protocol. A 1.5 Tesla General Electric System (GE-Medical Systems, Milwaukee, WI) was used to image all children using a quadrature or 8-channel phased array head coil. First, a sagittal localizer image was acquired by means of an automated shimming procedure. Then, two imaging modes were applied: a three-dimensional Fourier-transform spoiled gradient recalled sequence (coronal acquisition slice thickness: 1.5-mm; in-plane resolution: 0.78125mm x 0.78125mm flip angle: 45°; repetition time: 35 milliseconds; echo time: 5 milliseconds; field of view: 18 cm; matrix: 256 x 256; 124 slices) and a double-echo (proton density and T2-weighted) spin-echo sequence (3-mm axial slices; repetition time: 3000 milliseconds; echo times: 36 and 162 milliseconds; field of view: 18 cm; matrix: 256 x 256, interleaved acquisition; 68 slices). Normative MRI data in the multi-center NBD study funded by the NIH were also acquired with a 1.5 Tesla system at all sites (Almli, et al., 2007) using a similar acquisition protocol that was previously described (Almli, et al., 2007; Evans, & Brain Development Cooperative Group, 2006).

5.3.3 MRI analysis

Conventional MRI analysis: An experienced pediatric neuroradiologist (R.R.) blinded to medical history and developmental outcome of the child, reviewed the conventional T_1 and T_2 images to categorize the cerebellar malformations.

Quantitative MRI analysis: Linux Workstations were used for quantitative post-image processing. First, the T1 images were linearly registered (Collins, et al., 1994) to an age-

matched normal infant Talairach space template (Fonov, et al., 2009). The brain was then automatically extracted for each subject using the Brain Extraction Tool (Smith, 2002). Subsequently, cerebral and cerebellar tissue classification was performed using INSECT (Intensity-Normalized Stereotaxic Environment for Classification of Tissues), in order to obtain volumes of the cortical grey matter and white matter (Zijdenbos, et al., 1998). This automatic algorithm used for tissue classification labels each voxel as belonging to one of the two tissue classes based on its MRI signal. Manual outlining of the subcortical grey matter (basal ganglia and thalamus) of the age specific template were non-linearly warped into the subject space to delineate these structures on each subject's MRI (Collins, & Evans, 1997). Finally, the cerebellum was manually outlined and extracted using the Display software, an in-house visualization tool (MacDonald, 2003). Manual corrections were made when necessary using the Display software for each step of image processing. Volumetric measurements in cubic centimeters (cc) were obtained for cerebellar volume, total cerebral volume, cerebral white matter and cortical grey matter and subcortical grey matter (Figure 1).

The cerebrum was then partitioned into eight regions using the parcellation scheme previously described and validated by Peterson et al. (Peterson, et al., 2003) and our group (Limperopoulos, et al. 2010). The cerebellum was extracted from the brain before parcellating the cerebrum, in order to specifically compare regional cerebral volume in cases and controls. The first step consisted in dividing the cerebrum into right and left hemispheres. Subsequently, three reference points were manually positioned on the i) anterior-commissure, ii) posterior commissure and iii) genu of the corpus callosum. Four planes were then traced: first an axial plane through the anterior commissure and posterior commissure line and then three coronal planes. Discrete volumetric measures for eight anatomical regions in each hemisphere were then obtained: dorsolateral prefrontal, orbitofrontal, premotor, subgenual, sensorimotor, midtemporal, parieto-occipital and inferior occipital (Figure 2). Finally, volumetric data (cc) were computed for all eight regions of the cerebrum and their tissue types. Inter-rater reliability for this cerebral parcellation scheme was previously described using voxel assignment agreement, which was averaged to 80.2% (Caviness et al., 1996). In the current study, the same operator (M.B) performed all parcellations and was rigorously trained to identify the correct anatomical landmarks, in order to ensure consistency in our volume measurements. Parcellation was performed a second time on five different scans, 85% regions parcellated twice were $\pm$10.43 cc, and the

volume difference for all regions averaged 5.29 cc. Volumes for total cerebellar volume were all ± 2.75 cc with an average difference of 0.79 cc.

Because the majority of children in our cohort with cerebellar malformations affected both hemispheres or were midline anomalies involving the vermis (85%) we did not analyze the right and left cerebral hemispheres separately.

5.3.4 Statistical analysis

Each case was matched to two healthy controls according to their age and gender for the analyses. Clinical characteristics of the cases and controls were summarized by means and standard deviations for continuous data and by proportions for categorical data. Analysis of variance was performed using a mixed effect (both fixed and random effects) model in order to compare total cerebral volume, total white matter, total cortical grey matter, subcortical grey matter and 16 regional cerebral volumes between children with cerebellar malformations and healthy age and gender matched controls. In addition, linear regressions were used to examine if cerebellar volume reduction (determined by subtracting the total cerebellar volume of each case to the average total cerebellar volume of the two age and gender matched cases), were associated with total cerebral volume, total white matter, total cortical grey matter, subcortical grey matter and the 16 regional cerebral volumes in children with cerebellar malformations. Estimates of effect and confidence intervals are reported. All assumptions were verified for ANOVA and linear regression models. Statistical analyses were performed using SPSS Statistics version 17.0 (IBM Company, Chicago, Illinois, USA) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

5.4 Results

5.4.1 Characteristics of the cohort

Thirty-eight children with isolated cerebellar malformations met our inclusion criteria. Amongst these children, four died in infancy and three were lost to follow-up. Twenty-seven (87%) of the 31 families consented for the MRI scans; however imaging could not be completed in seven children. The remaining 20 children that composed the sample of cases in this study were then matched to 40 healthy age and gender-matched controls.

The clinical diagnoses of the children with cerebellar malformations are described in Table 1. MRI scans were performed at a mean age of 27.1 ±16.1 months for the children

with cerebellar malformations and at a mean age of 27.0 ± 17.1 months for the healthy controls (p=0.99), of which 85% of children were matched +/- 6 months. Our sample was composed of 10 males (50%) and 10 females (50%) with cerebellar malformations who were matched to 20 healthy males (50%) and 20 healthy females (50%).

5.4.2 Comparison of cerebellar, total cerebral, and tissue classes volumes in children with cerebellar malformations and healthy controls

Children with cerebellar malformations showed a statistically significantly decrease in total cerebellar volume (p=0.002) and in the subcortical grey matter (basal ganglia and thalamus) (p<0.001) compared to controls. Total cerebral volume and total cortical grey and white matter volumes, although smaller in the cases, were not significantly different between the two groups. The results are presented in Table 2.

5.4.3 Comparison of regional cerebral volumes in children with cerebellar malformations and healthy controls

The ANOVA models demonstrated statistically significant reductions in regional cerebral volumes between children with cerebellar malformations and age and gender matched controls in the cortical grey matter of the inferior occipital region (p=0.03). Significant decreases in white matter volume were evident in the subgenual (p=0.03) and midtemporal regions (p=0.02). In addition, grey matter volumes were smaller in the subgenual and the sensorimotor regions, although the differences were not statistically significant. In children with cerebellar malformations white matter volumes were also smaller in the dorsolateral prefrontal, orbitofrontal, parieto-occipital and inferior occipital regions but the differences were not statistically significant. The results are presented in Table 3.

5.4.4 Association between cerebellar volume and cerebral development

Linear regression analyses showed that cerebellar volume reductions in children with cerebellar malformations were significantly associated with smaller total cerebral volume by 1.28 (p=0.02), total grey matter by 0.82 (p=0.01) and subcortical grey volumes by 0.04 (p=0.02). In addition, cerebellar volume reduction was predictive of lower volumes of subgenual white and grey matter by 0.06 (p=0.001) and 0.07 (p=0.001) respectively, midtemporal white by 0.20 (p=0.02) and grey matter by 0.08 (p=0.01), as well as parieto-

occipital grey matter by 0.34 (p=0.004). Results are presented in Table 4. Finally, there was a borderline association between the cerebellar volume reduction and the dorsolateral prefrontal grey matter by 0.10 (p=0.06), premotor grey matter by 0.09 (p=0.07) and parieto-occipital white matter by 0.17 (p=0.06).

5.5 Discussion

In the present study we used quantitative MRI techniques to demonstrate that children with congenital cerebellar malformations have significantly reduced volumes in specific regions of the cerebral hemispheres when compared to healthy age and gender matched controls at long-term follow-up. These regions include the subcortical (basal ganglia and thalamus) and inferior occipital grey matter, and the subgenual and midtemporal white matter. We also show that greater volumetric reduction of a malformed cerebellum was predictive of decreased total cerebral volume, cerebral grey matter and subcortical grey matter volumes, as well as regional volume reductions in the subgenual white and grey matter, midtemporal white and grey matter and parieto-occipital grey matter. A borderline association between cerebellar volume reduction and the dorsolateral prefrontal, premotor grey matter and parieto-occipital regions white matter was also present. To our knowledge, this is the first 3-D volumetric MRI study to demonstrate total and regional growth impairment of the cerebral hemispheres in children with cerebellar malformations.

Crossed cerebello-cerebral diaschisis is described as a decrease in neuronal activation and blood flow in uninjured regions of the cerebrum remote from but neurally connected to an area of acute cerebellar injury (Miller, et al., 2009). In some descriptions this regional decrease in cerebral blood flow is followed by cerebral structural changes in the same area over time (Chakravarty, 2002; Tien, & Ashdown, 1992). Evidence of the presence of crossed cerebello-cerebral diaschisis in adult stroke patients and in children following tumor ressection is accruing (Attig, et al., 1991; Boni, et al., 1992; Broich, et al., 1987; De Smet, et al., 2009; Komaba, et al., 2000; Miller, et al., 2009; Sagiuchi, et al., 2001). Several scintigraphic single photon emission computed tomograhic studies and one dynamic susceptibility contrast MRI report have described hypoperfusion in specific cerebral regions (predominantly in the contralateral cerebral hemisphere) including: the prefrontal cortex, the basal ganglia, the thalamus, the striatum, as well as the frontal, parietal and temporal lobes (Attig, et al., 1991; Boni, et al., 1992; Broich, et al., 1987; De Smet, et al., 2009; Komaba, et

al., 2000; Miller, et al., 2009; Sagiuchi, et al., 2001). The presence of decreased blood flow in these regions has been attributed to a deactivation of the cerebello-ponto-thalamo-cerebral pathways (Attig, et al., 1991; Broich, et al., 1987). Finally, there has been a report of decreased blood flow in the occipital lobe in two children following posterior fossa tumor resection (De Smet, et al., 2009).

Two studies by our group have described volumetric loss in the cerebrum following early life cerebellar hemorrhagic injury in survivors of preterm birth (Limperopoulos, et al., 2010; Limperopoulos, et al., 2005). In these studies we reported decreased total contralateral cerebral growth in preterm infants with unilateral cerebellar hemorrhagic injury as early as term equivalent (Limperopoulos, et al., 2005). Our group also recently described regional reductions in grey and white matter volumes in the contralateral dorsolateral prefrontal, premotor, sensorimotor, midtemporal and subcortical grey matter in children with unilateral cerebellar injury (Limperopoulos, et al., 2010).

Noteworthy is that fact that very few studies have examined the impact of cerebellar malformations on cerebral development. One study reported normal perfusion in the frontal region in an adult patient with cerebellar hypoplasia (Boni, et al., 1992). Interestingly, all four subjects with acquired cerebellar damage showed decreased frontal lobe neuronal activity in the same study (Boni, et al., 1992). The authors speculate that developmental remodeling could be the basis of this disparity.

Our results are in agreement with previous studies suggesting that lesions to the cerebellum result in decreased neuronal activity in the subcortical grey matter (basal ganglia/thalamus) and the temporal lobe (Attig, et al., 1991; De Smet, et al., 2009; Deguchi, et al., 1994; Komaba, et al., 2000; Limperopoulos, et al., 2010; Miller, et al., 2009), which are known projection areas for efferent cerebellar pathways. We also show that the extent of a cerebellar malformation predicts greater volumetric loss in these regions. Moreover, greater cerebellar volume loss was also predictive of smaller volumes in the parieto-occipital grey matter. Interestingly, the parietal lobe is also a projection area for the cerebellar efferent connections (Schmahmann, & Pandya, 1997). Although no study to date has described an association between cerebellar malformations and volumetric reductions in the subgenual white and grey matter regions of the cerebrum, hypoperfusion has been described in frontal and temporal regions in a number of studies (Attig, et al., 1991; Baillieux, et al., 2009; Boni, et al., 1992; Broich, et al., 1987; De Smet, et al., 2009; Deguchi, et al., 1994; Komaba, et al.,

2000; Miller, et al., 2009). From a functional perspective, the subgenual region is known to be involved in emotion modulation, language function, and behavior (Kandel, et al., 2000), which are functional domains that are commonly affected in children with cerebellar malformations (Bolduc, et al., 2010).

Finally, our data show that children with cerebellar malformations have volumetric reductions in the inferior occipital grey matter when compared to healthy controls. These data are in line with a previous study by De Smet and colleagues (De Smet, et al., 2009) that described changes in perfusion of the occipital lobe in patients with cerebellar injury (De Smet, et al., 2009). Although there are no known anatomical efferent pathways that connect the cerebellum to the occipital regions, recent functional imaging studies support the presence of connections between the cerebellum and the occipital lobe through the red nucleus (Allen, et al., 2005; Nioche, et al., 2009). Given the numerous regions that connect the cerebellum and cerebrum, 'global' cerebral disruption has been postulated following an insult to the cerebellar-cerebral circuitry (Miller, et al., 2009). Nevertheless, the exact mechanisms underlying regional reductions in occipital volume remain unclear.

Unlike our previous study in ex-premature infants with cerebellar injury (Limperopoulos, et al., 2010), the current results do not show a significant volumetric difference in prefrontal and frontal regions in children with cerebellar malformations when compared to healthy controls. However, our data revealed a borderline significant association between cerebellar volumetric differences in cases and controls in the dorsolateral prefrontal and premotor grey matter regions. The presence of key output connections from the cerebellum to these regions has been previously demonstrated and the effect of acquired cerebellar injury on the prefrontal and frontal regions have been reported (Limperopoulos, et al., 2010). We hypothesize that the lack of significant relationship in these regions can be partly explained by our small sample size combined and high variability in regional cerebral volumes in our cohort. Conversely, the possibility that cerebellar malformations impact cerebral development in a different manner than acquired cerebellar injury also needs to be considered and warrants further study.

Children with cerebellar malformations experience a wide spectrum of developmental and functional disabilities that affect global development, cognition, language, motor skills and behavior (Bolduc, & Limperopoulos, 2009). Although the functional impact of these regional volumetric reductions in the cerebrum is presently unknown our data

suggest that the extent of cerebellar volumetric impairments predicts altered growth in specific regions of the cerebrum, which could, in turn, contribute to the presence of functional disabilities.

Several potential limitations of this study are worthy of note. Due to the size of our sample and the amount of variability in the volume of the different regions of the cerebrum, it is likely that our study was underpowered to detect all statistically significant region-specific volumetric differences in the cerebrum in children with cerebellar malformations. Moreover, a substantial proportion of children in our study had isolated inferior vermis hypoplasia, a less severe form of cerebellar dysgenesis, which has been shown to be associated with a favorable outcome (Bolduc, & Limperopoulos, 2009; Ecker, et al., 2000; Limperopoulos, et al., 2006). Therefore, cerebral development may not be significantly altered in this subgroup of children. Moreover, because of the heterogeneity of our sample, specific regional volumetric impairments may have been difficult to detect. Finally, the causal relationship between cerebellar malformations and impaired cerebellar growth cannot be formally established due to the nature of our study design and the developmental nature of the cerebellar malformations; however the sample of children was carefully selected to exclude the presence of associated supratentorial or chromosome anomalies.

In summary, this is the first study to show that cerebellar malformations are associated with impaired regional cerebral growth. We speculate that these findings originate from disturbed development of the major cerebello-cerebral pathways decreasing the normal trophic activation of these projection areas during critical phases of cerebral development. Longitudinal structure-function studies are needed to better delineate the impact of cerebellar malformations on cerebral development and child function. Future voxel-based morphometry studies may help to better elucidate local differences in cerebral development in children with cerebellar malformations compared to their healthy aged-peers

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Table 1. Clinical diagnoses of the cohort

	Frequency (%) **N=20**
Inferior vermis hypoplasia	9 (45%)
Cerebellar hypoplasia	4 (20%)
Unilateral cerebellar hypoplasia	3 (15%)
Vermis hypoplasia	2 (10%)
Rhombencephalosynapsis	1 (5%)
Dandy-Walker malformation	1 (5%)

Table 2. Cerebellar volume, total cerebral volume, and tissue classes in children with cerebellar malformations compared to healthy controls

Regional cerebellar and cerebral volumes (cc)	Cases Mean ± SD (cc)	Controls Mean ±SD (cc)	Average difference (cc)	p-value
Total cerebellar volume	93.11±38.77	115.11±13.39	-22.00	0.002*
Total cerebral volume	899.21±146.88	922.24±126.43	-23.66	0.522
Total cerebral grey matter volume	601.39±85.41	609.32±71.19	-7.93	0.707
Total cerebral white matter volume	269.94±66.10	280.31±72.17	-10.38	0.593
Subcortical grey matter	27.88±4.53	33.23±4.78	-5.36	<0.001*

*Indicates a significant volumetric difference between cases and controls

SD-standard deviation

Table 3. Regional cerebral volumes in children with cerebellar malformations compared to healthy controls

Regional cerebral volumes (cc)	Cases Mean ± SD (n=20)	Controls Mean ± SD (n=40)	Average difference (cc)	p-value
Dorsolateral prefrontal white matter	25.20±9.38	27.23±8.40	-2.03	0.402
Dorsolateral prefrontal grey matter	64.67±13.69	64.31±11.08	0.36	0.913
Orbitofrontal white matter	6.47±3.87	6.99±5.27	-0.52	0.697
Orbitofrontal grey matter	25.20±7.33	25.20±7.81	0.00	1.00
Premotor white matter	38.77±10.83	37.80±12.04	0.97	0.763
Premotor grey matter	69.59±12.60	67.56±13.05	2.03	0.569
Subgenual white matter	18.93±4.90	22.50±6.00	-3.57	0.026*
Subgenual grey matter	45.19±5.56	45.84±6.00	-0.66	0.685
Sensorimotor white matter	48.94±12.60	48.13±12.65	0.81	0.817
Sensorimotor grey matter	73.25±12.11	75.81±8.82	-2.57	0.357
Midtemporal white matter	6.87±218	9.06±3.70	-2.43	0.018*
Midtemporal grey matter	40.35±7.80	40.33±8.68	0.01	0.995
Parieto-occipital white matter	94.69±23.74	96.30±24.64	-1.61	0.811
Parieto-occipital grey matter	202.36±30.78	198.89±29.98	3.47	0.678
Inferior occipital white matter	30.07±9.75	32.30±9.59	-2.23	0.403
Inferior occipital grey matter	80.78±19.87	91.36±16.07	-10.58	0.031*

*Indicates a significant volumetric difference between cases and controls

Table 4. Estimates of the effect of cerebellar volumetric reductions on total and regional cerebral volume

Regional Cerebral Volumes (cc)	**Estimate of effect**[+]	**95% Confidence interval**	**p-value**
Total cerebral	1.281	0.181-2.381	0.024*
Total cerebral white matter	0.419	(0.092)-0.931	0.105
Total cerebral grey matter	0.821	0.192-1.450	0.012*
Subcortical grey matter	0.041	0.007-0.074	0.020*
Dorsolateral prefrontal white matter	0.056	(0.017)-0.129	0.131
Dorsolateral prefrontal grey Matter	0.102	(0.002)-0.206	0.055
Orbitofrontal white matter	-0.006	(0.037)-0.025	0.696
Orbitofrontal grey matter	0.008	(0.051)-0.066	0.794
Premotor white matter	0.054	(0.031)-0.139	0.210
Premotor grey matter	0.089	(0.008)-0.186	0.070
Subgenual white matter	0.059	0.025-0.093	0.001*
Subgenual grey matter	0.071	0.033-0.109	0.001*
Sensorimotor white matter	0.075	(0.023)-0.173	0.129
Sensorimotor grey matter	0.075	(0.018)-0.169	0.112
Midtemporal white matter	0.020	0.003-0.036	0.019*
Midtemporal grey matter	0.081	0.024-0.138	0.006*
Parieto-occipital white matter	0.172	(0010)-0.353	0.064
Parieto-occipital grey matter	0.335	0.114-0.555	0.004*
Inferior occipital white matter	-0.009	(0.087)-0.069	0.816
Inferior occipital grey matter	0.060	(0.098)-0.218	0.444

+ Estimate of effect: Relationship between cerebellar volume reduction (difference between cases and controls) and total and regional cerebral volumes in children with cerebellar malformations

*Indicates a significant volumetric difference between cases and controls

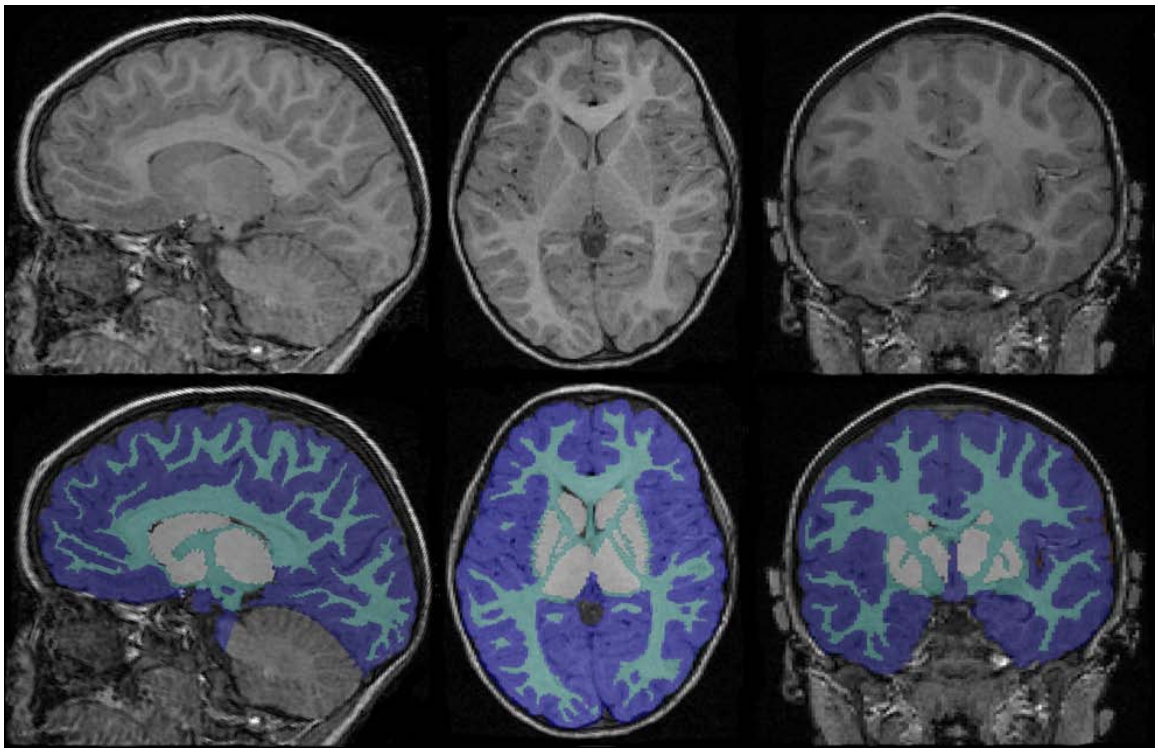

Figure 1. Brain segmentation into tissue classes, where dark blue represents grey matter, light blue white matter and white subcortical grey matter.

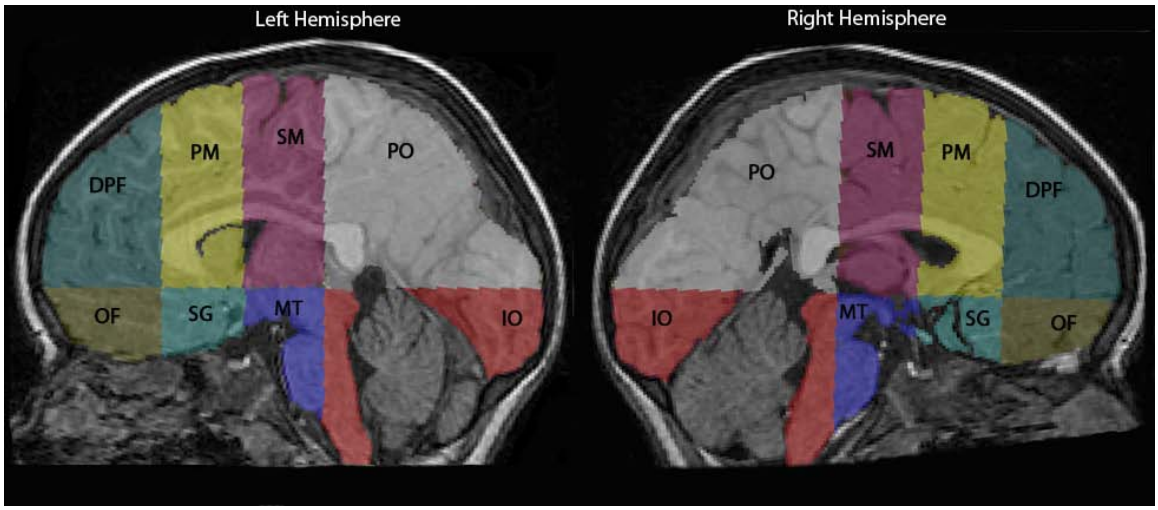

Figure 2. Cerebral parcellation into eight regions: dorsolateral prefrontal (DPF), orbitofrontal (OF), premotor (PM), subgenual (SG), sensorimotor (SM), midtemporal (MT), parieto-occipital (PO) and inferior occipital (IO).

CHAPTER 6
DISCUSSION

A better understanding of the impact of cerebellar malformations on child function and cerebral development was urgently needed. This study offers new insights on the far-reaching structural and functional consequences of cerebellar malformations in young children. In fact, it is the largest study to date to describe the spectrum of developmental disabilities in young children with cerebellar malformations using standardized outcome measures. Furthermore, this is the first study to explore how structure and function correlate. Specifically, using quantitative 3-D volumetric MRI techniques together with standardized outcome measures, we examined the impact of total and regional cerebellar volumes on specific developmental and functional skills in children with cerebellar malformations. This study also sheds new light on the critical impact of cerebellar malformations on subsequent cerebral growth and development. In this final chapter, I will summarize our main results and discuss their clinical relevance. Finally, I will discuss potential limitations of this study and will propose directions for future studies.

6.1 Developmental and functional outcomes in children with cerebellar malformations

Evidence from adult literature describing a fundamental role for the cerebellum in higher cognitive function and social skills is mounting (Boddaert et al., 2003; De Smet et al., 2009; Leiner et al., 1991; Limperopoulos et al., 2007; Schmahmann, 1997; Schmahmann, 1998). Conversely, outcome studies in children with cerebellar malformations have primarily focused on global cognitive functioning (e.g., intelligence quotient), motor and neurological impairments. Moreover, the majority of these studies (74%) did not use standardized outcome measures and most were conducted retrospectively (83%). As a result, the outcome data in children with cerebellar malformations was conflicting (Bolduc, & Limperopoulos, 2009). Collectively, these data underscored a lack of standardized approach to outcome ascertainment and the urgent need for comprehensive assessment tools to delineate the developmental outcome of children with cerebellar malformations. In addition to carefully selecting an outcome measure based on its sound psychometric properties and its ability to best evaluate the selected construct (Majnemer, & Limperopoulos, 2002), it is of utmost

importance not to limit our studies to body structure and body function, but to expend the scope of our examination to include their impact on the child's activities (Majnemer, & Limperopoulos, 2002). Adopting a more holistic approach ensures that we capture the true impact of a condition on the life of the person (Majnemer, & Limperopoulos, 2002). Regrettably, to date, the majority of the outcome studies in this population did not address the multidimensional aspect of functioning and mostly focused on a limited descriptive documentation of impairments in body function and structure only.

In the current study, we proposed a multidimensional approach for evaluating the impact of cerebellar malformations on child function. Specifically, we examined the impact of cerebellar malformations on body structure (cerebral development), body function (motor function, cognition, language and behavior) and activities (socialization). Prior to examining the structure-function relationship, we first characterized the developmental outcome of children with cerebellar malformations, using a battery of standardized outcome measures. The results of our study demonstrated that cerebellar malformations are associated with a high prevalence of developmental and functional disabilities including both motor and non-motor functions. In particular, a large portion of children with cerebellar malformations (39%) demonstrated global developmental delay and cognitive impairments, as well as expressive language deficits. We also reported a high prevalence of gross (52%) and fine (41%) motor disabilities in our cohort. Additionally, our study demonstrated that 47% of children with cerebellar malformations experience behavior problems. Finally, more than half (59%) of the children with cerebellar malformations had a positive screening for early signs of autism. The clinical significance of this initial positive screening score remains to be defined. Our cohort is currently undergoing formal diagnostic testing for autism spectrum disorder.

Taken together, our study underscores that cerebellar malformations are associated with global pervasive developmental disabilities that extend far beyond the motor domain, to include cognition, language, as well as social and behavioral skills. These data highlight the importance for clinicians to implement routine and comprehensive outcome testing in order to best capture the wide-ranging impact of early life brain anomalies on child functioning. This, in turn, will allow health professionals to design rehabilitation programs that best address the therapeutic needs of the child.

6.2 Impact of total and regional cerebellar volumes on functional outcome

The results of our literature review drew attention to the lack of clear diagnostic criteria used for the different types of cerebellar malformations. Regrettably, children with different types and severity of malformations are often clustered together into the same diagnostic categories and as a consequence prognostication of these heterogeneous groups presents a great challenge for clinicians. Fortunately, the recent successful application of advanced neuroimaging techniques and computational analysis in young children can now assist us to better understand the relationship between cerebellar anatomy and developmental outcome (Desmond et al., 1998; Joyal et al., 2004; Schmahmann, 2004).

Neuroimaging data from adult literature suggest that the cerebellum is topographically organized medio-laterally with the lateral hemispheres primarily involved in motor and cognitive function and the vermis in emotions, socialization and affect (Desmond et al., 1998; Joyal et al., 2004; Schmahmann, 2004). Taking this previous knowledge into consideration, and capitalizing on the availability of a previously validated cerebellar scheme that reliably partitions the cerebellum into three hemispheric zones and the vermis, we examined the relationship between total and regional cerebellar volume and domain specific developmental skills.

In our cohort of children with cerebellar malformations, total cerebellar volume was associated with gross motor function, whereas the right lateral hemispheric zone was related to expressive language and gross motor skills. Additionally, a lower vermis volume was associated with global development delays, and impairments in cognition, language and motor function. Vermis volume was also associated with significant behavior problems and higher rates of positive screening for early signs of autistic features. In the subgroup of children with isolated cerebellar malformations, a lower total cerebellar volume was associated with global developmental delay, cognitive and expressive language impairments, and gross and fine motor disabilities. Similarly, a lower cerebellar volume in the right lateral hemispheric region was associated with gross motor, cognitive and expressive language deficits. In addition, there was a significant relationship between volumetric loss in the cerebellar vermis and global development delays, and impaired cognition, expressive language, as well as gross and fine motor. A smaller vermis volume was predictive of significant behavioral problems and a high prevalence of a positive screening for early autism spectrum features in our cohort.

Although no study has previously measured regional cerebellar volume and its relationship to specific developmental disabilities in children, qualitative reports have described an association between the lateral hemispheres and cognition, language and motor skills, mostly in normal adult populations and in adults and children with acquired lesions to the cerebellum. (Dum et al., 2002; Konczak, & Timman, 2007; Leiner, & Leiner, 1989; Leiner et al., 1991; Makris et al., 2003; Marien et al., 2001). Laterality has also been described in children with tumor resection. Specifically, auditory sequential memory and language were associated with the right lateral cerebellar hemisphere. Conversely, a significant association between the left cerebellar hemisphere and visual and spatial sequential memory has been reported (Levisohn et al., 2000; Riva, & Giorgi, 2000). Of note, prior studies did not subdivide the midhemispheric and lateral hemispheric zones as proposed in the current study, using a validated parcellation schemed by Makris et al. (2003). Studies in healthy adults and in adults with acquired lesion to the cerebellum have also reported a relationship between regulation of behavior and affect, as well as balance, sensorimotor function, cognition and eye movement and the medial region of the cerebellum (Makris et al., 2003; Schmahmann, 1998; Schmahmann, 2004; Schmahmann et al., 2000). Lastly, developmental anomaly and acquired injury of the cerebellar vermis have also been associated with global cognitive deficits, gross motor, language, behavior and attention problems, as well as autism (Bauman, & Kemper, 2005; Boddaert et al., 2003; Courchesne et al., 1994; Courchesne et al., 1988; Klein et al., 2003; Konczak, & Timman, 2007; Levisohn et al., 2000; Limperopoulos et al., 2007; Piven et al., 1997; Riva, & Giorgi, 2000; Schmahmann, 2004; Webb et al., 2009).

The findings of the present study support our primary hypotheses and corroborate a fundamental role of the vermis and the lateral hemispheres that was previously reported in older children and adults with acquired lesions to the cerebellum (Boddaert et al., 2003; Klein et al., 2003; Konczak, & Timman, 2007; Levisohn et al., 2000; Limperopoulos et al., 2007; Riva, & Giorgi, 2000; Schmahmann, 2004). The broad spectrum of clinically important deficits in global development, cognition, expressive language, behavior and motor skills, as well as the high rate of positive screening for early autistic features that were significantly associated with volumetric reductions in the cerebellar vermis is striking. These wide-reaching deficits are supported by a recent study demonstrating the presence of important intrinsic connections between the vermis and multiple cerebral regions involved in cognition, language and emotions (Habas et al., 2009). Additionally, Boddaert et al. (2003) and Klein et

al. (2003) have also highlighted the importance of an intact vermian anatomy for normal cognitive development in children with cerebellar malformations. The lack of a significant relationship between the medial hemispheric and midhemispheric regions and developmental outcomes in our cohort, could be explained by the young age of our subjects in whom cognitive, language, behavioral and social skills are still emerging. Alternatively, the topographical organization of the developing cerebellum could differ from the organization of the mature cerebellum.

In summary, our data support a topographical organization of the cerebellum in young children with cerebellar malformations and provide evidence that regional volumetric reductions of the cerebellum are associated with defined developmental and functional deficits. Central to our findings is the critical role of the vermis in the high-prevalence of pervasive developmental disabilities in children with cerebellar malformations. The presence of lateralized functions at such an early age is also quite remarkable, and corroborates previous reports in which language is associated with the right cerebellar hemisphere (Levisohn et al., 2000; Riva, & Giorgi, 2000).

A better understanding of the spectrum of disabilities in children with cerebellar malformations coupled with knowledge of the possible deficits that are associated with volumetric reductions in specific regions of the cerebellum, will allow better counseling of families, and more effective and targeted early intervention programs. Prior knowledge of the topography of the cerebellar lesion, may allow rehabilitation specialists to now target specific developmental skills that are at risk of being impaired. Early intervention strategies have been shown to improve function in populations of children who are at high risk of having functional impairments (Casto, & Mastropieri, 1986).

6.3 Impact of cerebellar malformations on cerebral development

The results that were presented in the previous section demonstrate that children with cerebellar malformations experience important developmental and functional disabilities that affect a multitude of domains. Moreover, we have shown that distinct functional deficits are associated with regional specific volumetric reductions of the cerebellum. While the exact mechanism underlying the broad spectrum of disability in children with cerebellar malformation remains to be defined, it has been hypothesized that impaired cerebello-cerebral circuitry could play an under recognized role in the wide-ranging impact of

cerebellar malformations on child development (Steinlin, 2008). The cerebellum shares extensive afferent and efferent connections with the cerebrum (Leiner, & Leiner, 1989; Ramnani, & Miall, 2001). Therefore, supratentorial neuronal stimulation that results from activation of the cerebello-cerebral pathways is undoubtedly essential for normal brain development. Consequently, the second and final objective of this study compares total and regional cerebral volumes in children with cerebellar malformations and healthy age and gender-matched controls. We also examined the effect of cerebellar volume reduction on total and regional cerebral volumes.

Using advanced 3-D volumetric MRI and parcellation techniques, we demonstrated for the first time that cerebellar malformations are associated with regional supratentorial volume impairment suggesting trophic deactivation of the cerebello-cerebral pathways. Specifically, children with cerebellar malformations showed decreased volume in the subcortical grey matter, subgenual white matter, midtemporal white matter and occipital grey matter when compared to healthy gender and age-matched controls. In addition, we demonstrated that greater cerebellar volume reductions were predictive of smaller total cerebral volume, cortical grey matter, and subcortical grey matter, subgenual white and grey matter, midtemporal white and grey matter and parieto-occipital grey matter volumes. There was also a borderline significant association between cerebellar volume reductions and the dorsolateral prefrontal grey matter, premotor grey matter and parieto-occipital white matter regions.

Although no study to date has previously examined the impact of cerebellar malformations on cerebral volumetric growth in children with cerebellar malformations, several studies, mainly in adult populations, have described hypoperfusion in regions of the brain following acquired cerebellar injury (i.e. a hemorrhagic lesion or tumor resection). These regions of hypoperfusion include: the premotor and prefrontal cortex, the basal ganglia, the thalamus, the striatum, the frontal, parietal and temporal lobes (Attig et al., 1991; Baillieux et al., 2009; Boni et al., 1992; Broich et al., 1987; De Smet et al., 2009; Komaba et al., 2000; Miller et al., 2009; Sagiuchi et al., 2001). Diaschisis has also been associated with subsequent structural changes in the brain (Chakravarty, 2002). A recent study has also reported the presence of impaired white and grey matter development in specific cerebral regions, namely: the contralateral dorsolateral prefrontal, prefrontal, premotor, sensorimotor and midtemporal region, as well as the subcortical grey matter, in ex-premature children who

had suffered early life hemorrhagic (acquired) cerebellar injury (Limperopoulos et al., 2010). Only one single photon emission computed tomography study has described cerebral function in an adult with a cerebellar malformation. This study reported normal perfusion in the frontal lobe of a man with cerebellar hypoplasia (Boni et al., 1992). Interestingly, in this same study, all subjects with acquired cerebellar lesions showed hypoperfusion in the frontal lobe (Boni et al., 1992). The authors speculated that the effect of deactivation of the cerebello-cerebral pathways on subsequent cerebral development may differ in patients with cerebellar malformations compared to those with lesions acquired later in life, because of the developmental nature of the anomaly and possible neural remodeling that takes place in fetal and early life development (Boni et al., 1992).

The results of our study are in accordance with prior reports of hypoperfusion in the subcortical grey matter and the temporal and occipital lobe (Attig et al., 1991; De Smet et al., 2009; Deguchi et al., 1994; Komaba et al., 2000; Miller et al., 2009). However, this is the first study to provide quantitative evidence of volumetric loss in those same regions in children with cerebellar malformations. In fact, cerebellar volumetric reductions predicted smaller volumes in the subcortical grey matter, midtemporal, parieto-occipital and occipital regions. Of interest, subcortical grey matter, temporal and parietal regions are known cerebellar projection areas (Schmahmann, & Pandya, 1997).

We also demonstrated a significant association between developmental anomalies of the cerebellum and impaired cerebral development in the subgenual region. In the parcellation scheme that was used in this study, the subgenual region was part of both the frontal and temporal lobes (Kennedy et al., 1998). Although no study had specifically examined hypoperfusion in this parcellated region, decreased blood flow had been reported in both the frontal and temporal regions in several reports (Attig et al., 1991; Baillieux et al., 2009; Boni et al., 1992; Broich et al., 1987; De Smet et al., 2009; Deguchi et al., 1994; Komaba et al., 2000; Miller et al., 2009).

In a previously described study by Boni et al. (1992), all patients with acquired cerebellar injury demonstrated hypoperfusion in the front lobe. Conversely, the single patient with a cerebellar malformation in the same study did not show this regional frontal hypoperfusion. Similarly, our data did not demonstrate a significant volumetric loss in the sensorimotor, premotor and prefrontal regions. Noteworthy was the presence of a borderline association between volumetric loss in the cerebellum and the dorsolateral prefrontal and

premotor regions. The absence of a significant volumetric difference in these frontal regions could be explained by a lack of statistical power due to the size of our sample. Large variability in cerebral regional volumes the healthy controls may have also contributed to this borderline association. Alternatively, previous reports describing hypoperfusion in the frontal region had primarily described impaired cerebral growth and perfusion in patients with acquired cerebellar lesions, in which the mechanism, and timing of injury is different. Accordingly, potential reorganization of brain circuitry following a developmental anomaly of the cerebellum may result in a different pattern of deactivation and warrants further study. Finally, due to the topographical organization of the cerebellum, the location of the lesion within the cerebellum may also play an important role in delineating regional cerebral predilection. Further studies examining the impact of cerebellar regional volumetric reductions on regional cerebral development may help elucidate this important question.

In summary, while the impact of cerebellar malformations on regional cerebral development still needs better definition it is clear from our data that cerebellar malformations are associated with regional specific supratentorial growth impairments. The potential contribution of this altered regional cerebral development on the extent and nature of developmental and functional impairments experienced in children with cerebellar malformations remains to be defined. Of interest, reductions in regional cerebral volumes have previously been associated with developmental and functional deficits (Baillieux et al., 2009; Nosarti et al., 2008; Peterson et al., 2003). Moreover, available evidence suggests that early intervention programs can positively alter brain structure in populations at high risk of developmental deficits (Als et al., 2004). Therefore, the implementation of early intervention programs may improve microstructrual organization of the brain resulting in better functional recovery. This is an exciting area of research that is urgently needed.

6.4 Significance

Over the past decades, our understanding of the role of the cerebellum, in motor control and coordination has been repeatedly challenged. Its contribution to higher cognitive function, affect and behavior is now increasingly endorsed. Concurrent with these trends, cerebellar malformations have been increasingly and more accurately diagnosed early in life (i.e., in utero) as a result of advanced neuroimaging techniques (Boltshauser, 2004; Kalidasan et al., 1995; Sandalcioglu et al., 2006). Despite these advances, there was a glaring lack of standardized outcome data in survivors of cerebellar malformations, and our knowledge of clinical-neuroimaging correlates was very limited.

Capitalizing on its rigorous methodology and the selection of a battery of well-validated neurodevelopmental outcome tools, this study enriches our understanding of the functional consequences of cerebellar malformations on the developing child. The findings of this study can also be used by health professionals to better counsel families during the early stages when the initial diagnosis is made. The timing of parental counseling is essential given that cerebellar malformation are more frequently diagnosed in utero and studies have shown that up to 80 % of parents choose to terminate their pregnancy following a fetal diagnostic of cerebellar malformation (Ecker et al., 2000; Forzano et al., 2007). Parents can now have access to more accurate information about developmental outcomes in children with cerebellar malformations that can guide their decision making process.

Using the information obtained from this study we can now better inform families regarding the outcome of their child diagnosed with a cerebellar malformation. This information can assist families in having realistic expectations and goals for their child. It has been well-documented that parents need information about their child's condition in order to feel empowered and to promote a collaborative relationship with health care providers (Fisher, 2001). Consequently, we anticipate that the results of this study can assist in establishing the best possible conditions in order to maximize child function by providing accurate information on the possible functional deficits that are associated with cerebellar malformations. Our results can also be used to implement routine developmental screening for early identification of disabilities in this high-risk population, as well as to design individual rehabilitation programs that anticipate and capture the spectrum of developmental disabilities experienced by children with cerebellar malformations, so as to minimize long-term morbidity, optimize function and maximize quality of life. Likewise, improved

knowledge of the needs of children with cerebellar malformations will facilitate proper resource allocation.

Furthermore, our compelling structure-function data provide the first scientific evidence of the topographical organization of the cerebellum in children with cerebellar malformations. These critical, previously unavailable data can be used by rehabilitation professionals to assist in developing specific early intervention therapies based on prior knowledge of the topography of the malformation. Using this information, rehabilitation therapists can now begin to stimulate emerging developmental skills (e.g., motor skills, language development, and social skills) that are at risk of being impaired even before delays are clinically evident. Taking full advantage of the protracted development of the cerebellum and its high plasticity, treatment plans can be implemented earlier and individually tailored to target specific developmental domains in order to maximize function and quality of life for the children with cerebellar malformations (Als et al., 2004; Casto, & Mastropieri, 1986). Even in the presence of long-lasting impairments, our data can help put into place the proper resources and compensatory techniques for these children in order to facilitate integration into their environment and maximize activities, participation and ultimately quality of life. Consequently, the impact of cerebellar malformations on the child and the society may be reduced.

6.5 Limitations

While this study presents novel insights of the impact of cerebellar malformations on cerebellar and cerebral development as well as child function, it has several limitations that require consideration. Due to the nature of the study design, this study did not allow for observation of the changes in developmental skills over time. Ongoing longitudinal studies are needed to examine the structural and functional evolution of children with cerebellar malformations.

Additionally, due to the young age of the children, a number of skills (i.e. language and higher order cognitive skills) were not yet completely differentiated. Consequently, this limited the analysis of more detailed structure-function associations.

Finally, although this project included one of the largest samples of children with cerebellar malformations, we may have been underpowered to detect additional regional specific structure-function relationships. Accordingly, we may have failed to identify regional

cerebral impairments when comparing supratentorial development in children with cerebellar malformations compared to healthy controls. The proportion of children with isolated cerebellar malformations versus those with associated CNS/chromosome anomalies was difficult to estimate a priori. Consequently, there was a the high number of children with CNS/chromosome anomalies in our study which resulted in a smaller number of children with isolated cerebellar malformations available for analyses. A future multi-centre prospective study can address this limitation.

6.6 Future Directions

This study provides new evidence of the functional consequences of cerebellar malformations in young children. Longitudinal studies are now needed in order to determine the evolution of functional impairments and disabilities over time so as to better understand if these deficits are transient or persistent in nature. The children from this cohort are currently undergoing follow-up assessments to investigate their functional progress at school age. Multi-center studies with larger sample sizes using advanced MRI techniques and standardized outcomes measures are needed to confirm the results of this study. Finally, based on our preliminary results, future studies can begin to examine the impact of earlier and more targeted developmental intervention on functional outcomes.

6.7 Summary

To our knowledge, this is the largest study to date that incorporated standardized outcome measures to assess a wide range of functional domains in children. Our data demonstrate that cerebellar malformations result in important and wide-ranging developmental and functional disabilities including gross and fine motor function, cognition, language abilities and social-behavior problems. Additionally, this study provides in vivo evidence of a significant relationship between volumetric reductions in specific regions of the cerebellum and domain specific functional skills. Finally, this is the first study to show that cerebellar malformations are associated with growth impairment in specific cerebral regions that are known projection areas of the cerebellum. Greater appreciation of the prevalence and the type of developmental and functional impairments that are associated with cerebellar malformations, together with improved understanding of how structure and function correlated will allow better counseling of families along with the implementation of earlier and more targeted developmental intervention. This in turn will assist in minimizing developmental disabilities and optimizing life quality in these children, by providing clinicians with important prognostic information so that effective early intervention programs that address the spectrum of disabilities experienced by this high-risk population can be implemented.

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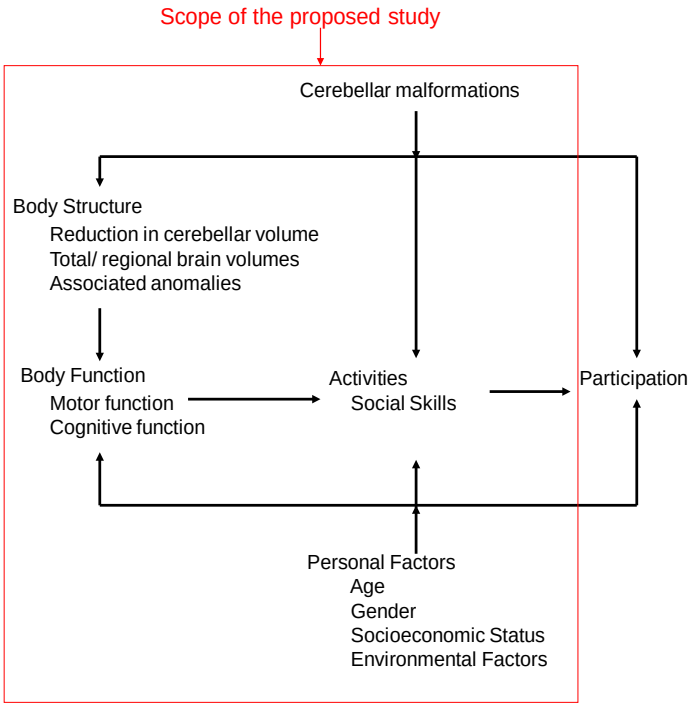
APPENDIX A

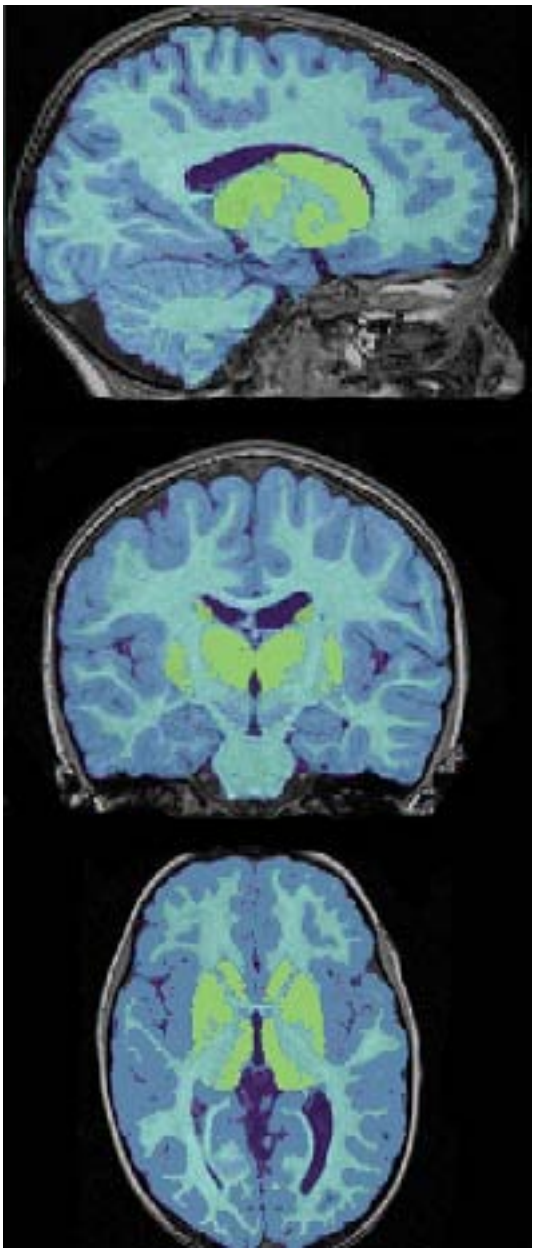
Theoretical framework



Theoretical framework describing how cerebellar malformations can affect cerebral development and child function.

APPENDIX B

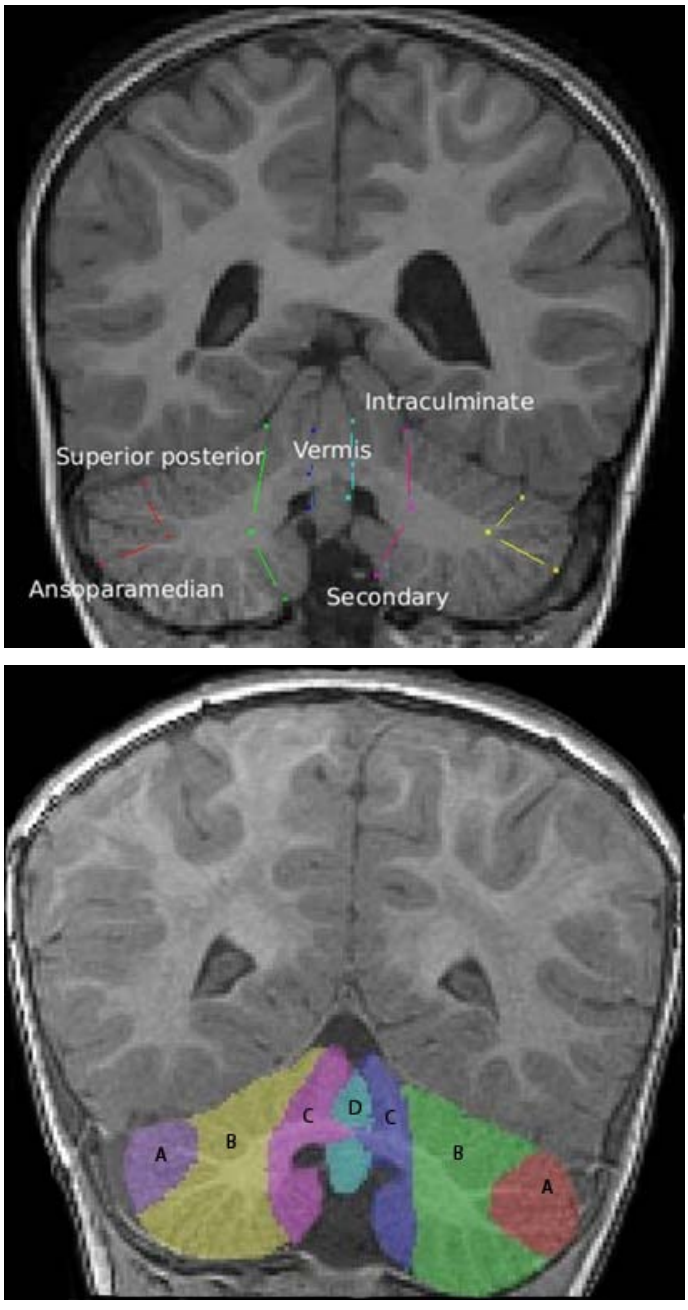
Brain segmentation



Brain segmentation into tissue classes where light blue represents white matter, dark blue cortical grey matter and green subcortical grey matter (basal ganglia and thalamus)

APPENDIX C

Cerebellar parcellation



The cerebellum was parcellated into seven medio-lateral regions using specific anatomical landmarks, as pictured on the top image. On the bottom image, the seven regions are identified; A represents the lateral hemispheric zones, B the midhemispheric zones, C the medial hemispheric zones and D the vermis.