Clinical, Neuroanatomical, and Neuropsychological Outcomes in Children with Brain Tumors

by

Nicole Law

A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy

Psychology
University of Toronto

Clinical, Neuroanatomical, and Neuropsychological Outcomes in Children with Brain Tumors

Nicole Law

Doctor of Philosophy

Psychology
University of Toronto

2014

Abstract

This thesis utilized diffusion tensor imaging (DTI) and tractography to examine cerebrocerebellar pathway microstructure, as well as medical and demographic data and measures of executive function (EF) to investigate clinical, neurological, and cognitive/behavioral outcomes following treatment for Posterior fossa (PF) tumors. Further, the influence of neurological outcome (i.e. cerebrocerebellar microstructure) on clinical and cognitive/behavioural sequelae was considered. PF tumors account for approximately half of all pediatric central nervous system malignancies and are treated with surgery, radiation, and chemotherapy. With treatment advances, survival rates have improved dramatically though significant late effects (e.g. neurotoxicity and cognitive morbidity) are often observed. Because of tumor location and treatment, damage to the cerebellum and its input/output pathways can occur in patients; this injury may have impact on clinical and cognitive/behavioural outcomes. First, it was found that a higher tumor grade, larger tumor size, and left handedness predicted Cerebellar Mutism Syndrome (CMS), a postoperative disorder present in approximately 25% of children with PF tumors. CMS was also associated with right cerebellar hemispheric white matter damage within the cerebello-thalamo-cerebral pathway – the main cerebellar efferent. Second, using DTI, neuroanatomical identification and segmentation of reciprocal

cerebrocerebellar pathways was completed; children treated for PF tumors showed damage to these pathways compared to healthy children – particularly within posterior segments. Third, impairment in EF domains (i.e. cognitive efficiency, planning, working memory, emotion regulation) was observed in children treated for PF tumors relative to healthy children. Microstructure of the cerebello-thalamo-cerebral pathway mediated the effect of treatment for PF tumors on EF outcome, specifically in working memory. This thesis a) provides a schema for CMS risk in children with PF tumors based on medical and neurobiological features; b) shows that treatment for PF tumors put patients at risk for damage to cerebrocerebellar circuitry and this neurological injury, in turn, is associated with working memory impairment; and c) elucidates the role of cerebrocerebellar pathways in connecting brain regions important for speech-language and working memory functions. These findings provide a framework for how individual variance in outcome in patients may occur and can inform the implementation of preventative/mitigative therapies to remedy the adverse effects of treatment.

Acknowledgments

It always seems impossible until it's done
-Nelson Mandela

I would first and foremost like to thank my supervisor Dr. Donald Mabbott for everything. He has truly supported me through this entire endeavor and for that I am deeply thankful. He has taught me how to be (and what it means to be) a scientist/researcher and a clinician and has challenged me in all aspects to mold me into what I am today. Thank you, Don, for always supporting me and imparting your wisdom – I hope to someday live up to the clinician-scientist that you are. Thank you for always pushing me to become a better writer, surpassing what I expected I could do, and always knowing what I needed to hear whenever times were rough and I needed the motivation to push through.

Many thanks to my thesis committee, Dr. Mary Lou Smith and Dr. Anthony Ruocco – your support and guidance has meant the world to me. I would also like to thank Dr. Mark Greenberg, Dr. Adam Anderson, Dr. Uri Tabori, Dr. Brian Nieman, Dr. Joanne Rovet, and Dr. M. Douglas Ris for their support and advice along the way.

I am forever grateful for the support of the Pediatric Oncology Group of Ontario (POGO), the POGO Research Unit (PRU), and my "POGO family" – without your generosity, kindness, and encouragement this endeavor would not have been possible. Thank you!!!

I am also honoured to have been educated by numerous mentors at the Hospital for Sick Children: Dr. Maureen Dennis, Dr. David Malkin, Dr. Michael Taylor, Dr. Suzanne Laughlin, and Dr. Eric Bouffet.

To my SickKids family – The Mabbott Lab – Dr. Nadia Scantlebury, Iska Moxon-Emre, Dr. Colleen Dockstader, Cynthia de Medeiros, Dr. Lily Riggs, Jovanka Skocic, Dr. Fang Liu, Lexi Decker, Melanie Orfus, Naomi Smith, Conrad Rockel, and Frank Wang (Eigen creator and script-writer extraordinaire). I love you guys! You have seen me through this process and many have been there for me since day one!

To my mom, Gabrielle (my number one cheerleader), and to my family and friends (the dars) – words cannot express how grateful I am to have you all in my life and how much more difficult this process would have been without you and your words of encouragement. To Jeff – what can I say? You have been my number one source of unwavering support (8 years and counting!) and have stood by me on this journey in its entirety – I could not have asked for a better partner in crime.

Do or do not. There is no try.
-Yoda

Table of Contents

List of Tables

List of Figures

Chapter 1
Background and Rationale

1 Background and Rationale

1.1 Introduction

Brain tumors are among the most common types of pediatric cancer and constitute the largest proportion of solid tumors in childhood. Greater than half of all childhood brain tumors arise within the posterior fossa (PF), an area that contains the cerebellum, pons, medulla, and fourth ventricle. With recent treatment advances in surgical intervention techniques, craniospinal radiation therapy (CRT), and chemotherapy (CTX), survival rates have improved dramatically. However, treatment for PF tumors has been associated with neurotoxicity and cognitive morbidity, including neurocognitive and behavioural deficits and academic declines (Mulhern et al., 1998; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004a; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004; Mabbott et al., 2005; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008). Additionally, Cerebellar mutism syndrome (CMS) – a syndrome that presents with speech-language deficits, behavioural disturbances, and personality changes – has been documented as a perioperative complication in up to 25% of children following resection of PF tumors (Robertson et al., 2006). It is unclear why some children present with or develop these deficits while others do not.

Much research has focused on describing the nature and time course of neurocognitive late effects (i.e. symptoms occurring after recovery from early onset disorders of treatment) in survivors of pediatric PF tumors. Less well understood are the neural mechanisms or correlates of such declines – particularly with respect to examining the microstructure of white matter connections and how injury to specific pathways may relate to deficits. Because treatment for PF tumors target the cerebellum and surrounding area (e.g. resection of tumor, whole-brain and PF/tumor bed radiation), damage to this brain region can occur. As a result, cerebellar input and output pathways may be compromised, disrupting communication between the cerebellum and other brain regions such as the frontal cortex. Cerebrocerebellar white matter pathways and their structure in children treated for PF tumors and healthy children were investigated in the current thesis. It has been proposed that many of the neurocognitive late effects observed in PF tumor survivors result from a reduced ability to obtain information from their surroundings and from having slower rate of processing than their healthy peers, suggesting executive function (EF) compromise in this population. Despite this proposal, a systematic investigation of EF has yet to

be completed in child and adolescent survivors of PF tumors. A comprehensive evaluation of EF in survivors of pediatric PF tumors should be based on conceptual models of EF (i.e. those that identify distinct but cooperative EF processes such as inhibition/shifting of attention, working memory, speed of processing, and planning; this thesis considered several of these models to establish the testing battery used in Chapter 4. Moreover, the ability to regulate emotions (a self-awareness/regulation component of EF) following treatment for PF tumors warrants further examination.

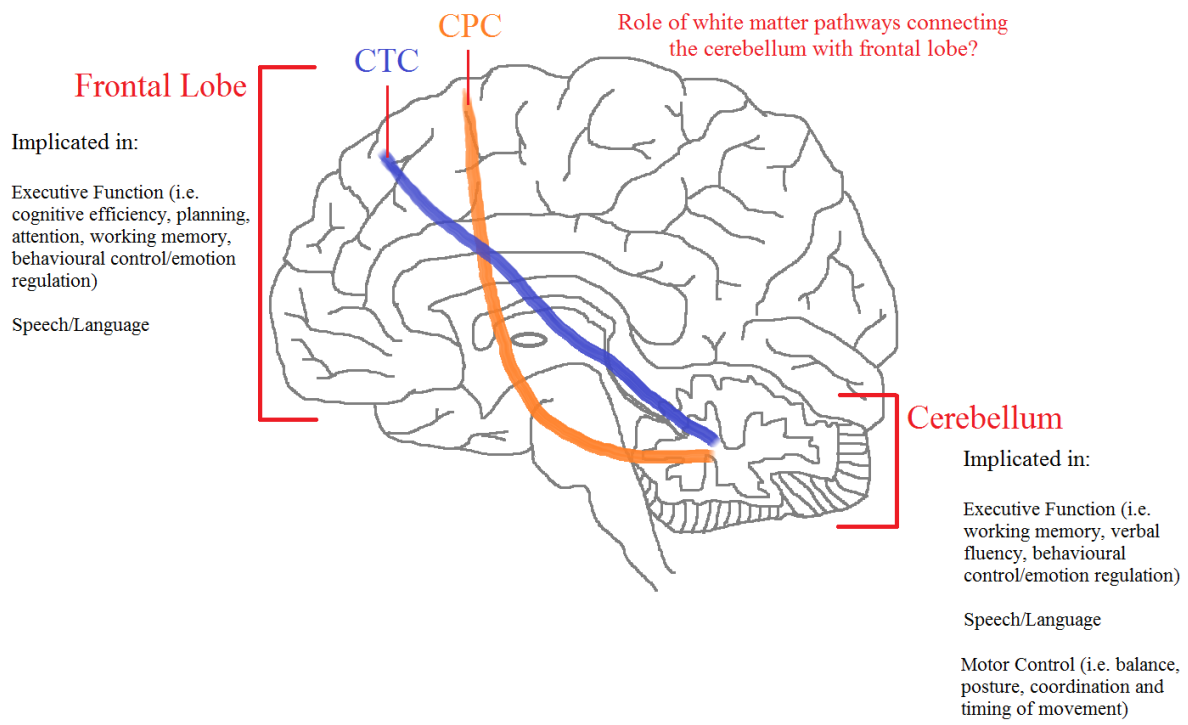
In attempting to eliminate or mitigate the adverse late effects of treatment, it is critical to identify neurological substrates that may predict risk for developing cognitive/behavioural deficits in children with PF tumors. One of the main hypotheses of the current thesis is that cerebrocerebellar connections (and the injury to these connections sustained following PF tumor treatment) play an important role in the many late effects observed in survivors. Specifically, examining the structure of reciprocal cerebrocerebellar pathways may provide a key piece of information for identifying a neurological substrate of specific clinical, cognitive, and behavioural outcomes in pediatric PF tumor survivors. The cerebro-ponto-cerebellar (CPC) pathway is the main input pathway from cortex to cerebellum, while the cerebello-thalamo-cerebral (CTC) pathway is the major outflow pathway from cerebellum to higher cortical areas. These bilateral connections serve as cerebrocerebellar feedforward and feedback mechanisms that are thought to underlie many aspects of cognition, speech-language, and behaviour. Considering the dual insult to the cerebellum via surgical resection of tumor plus the effect of radiation therapy, cerebrocerebellar pathways may be particularly vulnerable to injury. Thus, the microstructure of these pathways may have important implications for clinical, cognitive, and behavioural outcome in children treated for PF tumors.

The current thesis examined three areas of outcome in children treated for PF tumors: clinical (i.e. CMS), neurological/neuroanatomical (i.e. cerebrocerebellar white matter pathways), and cognitive/behavioural (i.e. EF). This thesis integrated clinical measures (i.e. medical and demographic data), neurocognitive and behavioural testing (i.e. objective/standardized and subjective/self-report measures as well as proxy-rated reports), and brain imaging (i.e. diffusion tensor imaging) to address the following questions. First, what are the risk factors for CMS in children treated for PF tumors? Are there clinical or neuroanatomical features that distinguish between patients who present with CMS post-surgically and those who do not? Chapter 2

focuses on these queries. Second, can complete, reciprocal cerebrocerebellar white matter connections be identified in the developing brain using diffusion tensor imaging? Specifically, can we delineate these pathways using diffusion tensor imaging in pediatric PF tumor survivors for which one of the main nodes (i.e. cerebellum) is impacted by the tumor and treatment? Third, what happens to white matter microstructure following treatment for PF tumors? Specifically, are cerebrocerebellar connections vulnerable to treatment effects? Chapter 3 addresses this group of questions. Fourth, what is the fate of EF following treatment for pediatric PF tumors? Which (if any) EF processes are impaired? How is emotion regulation affected? Lastly, is cerebrocerebellar microstructure associated with EF in both healthy children and children treated for PF tumors? The work in Chapter 4 attempts to answer these questions.

Broad questions that this thesis addresses include the following. What is the role of the cerebrocerebellar pathways? Functionally, these white matter circuits serve to connect the cerebellum with the frontal lobe – areas of the brain that are important for many cognitive and behavioural functions – and facilitate cerebellar-cortex communication (Figure 1.1). Thus, are there specific cognitive and behavioural functions that these pathways are implicated in? Examining cerebellar connectivity and the involvement of these circuits in certain tasks or abilities can help elucidate cerebellar function. We can also examine what occurs to the structure of these pathways when they are injured by PF tumors and their treatment. Does injury to these pathways by way of treatment for PF tumors associate with specific clinical, cognitive, or behavioural outcomes? Is EF among the many neurocognitive late effects observed in survivors of childhood PF tumors? If so, are some EFs more affected than others? What is the role of cerebrocerebellar pathways in EF?

Figure 1.1 The cerebellum and frontal lobe: What is the role of white matter pathways connecting these regions?



Both the cerebellum and frontal lobe have been implicated in aspects of executive function, including the control of behaviour and emotion, as well as speech-language. The main efferent connecting the cerebellum with frontal lobe is the cerebello-thalamo-cerebral (CTC) pathway and the main afferent connecting the frontal lobe with cerebellum is the cerebro-ponto-cerebellar (CPC) pathway. One aim of the current thesis was to investigate the role of these white matter pathways in cognitive/behavioural outcomes in the developing healthy and injured brain.

In the current chapter, background information important for addressing the above questions is reviewed including: the cerebellum, cerebellar connections with the frontal lobe, and our understanding of cerebrocerebellar pathway structure and function based on previous literature; DTI and tractography and how these methodologies are used to measure white matter microstructure; PF tumors and their treatment effects (i.e. clinical/medical challenges such as CMS, neurotoxicity, and cognitive morbidity; and the components and neural correlates of EF. At the end of this chapter, an overview of methods and specific study objectives are outlined.

1.2 The Cerebellum

The cerebellum is located within the infratentorial region of the brain and consists of a tightly folded and convoluted layer of cortex with white matter underneath, containing several deep

nuclei. In the medial-lateral direction, the cerebellum is divided into two hemispheres and a midline zone, the cerebellar vermis, and contained within these divisions are ten lobules (lobules I-X). In the anterior-posterior direction, the cerebellum is subdivided into three lobes: the anterior lobe (containing lobules I-V), posterior lobe (containing lobules (VI-IX), and flocculonodular lobe (lobule X).

The role of the cerebellum in the coordination of motor function is well established (Evarts & Thach, 1969). Recent discoveries have also highlighted the role of the cerebellum in modulating cognitive and behavioural function (Akshoomoff & Courchesne, 1992; Leiner, Leiner, & Dow, 1993; Middleton & Strick, 1994; Allen, Buxton, Wong, & Courchesne, 1997; Ramnani et al., 2006; Schmahmann & Caplan, 2006; Timmann & Daum, 2007). In terms of the parcellation of cerebellar structures and their associated functions, the flocculonodular lobe is related to vestibular function, the anterior lobe (particularly lobules IV-V) is considered to be the sensorimotor region of the cerebellum, while the posterior lobe of the cerebellum (specifically, lobules VI, VII – crus I & crus II) is thought to subserve cognition or higher order behaviour (Schmahmann & Caplan, 2006; Stoodley & Schmahmann, 2010). The posterior lobe is thought to perform cognitive and behavioural modulation through reciprocal connections with cerebral association areas – via cerebrocerebellar circuitry (Akshoomoff & Courchesne, 1992; Leiner et al., 1993; Middleton & Strick, 1994; Schmahmann & Pandya, 1995; Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; Schmahmann & Pandya, 1997b; Schmahmann & Caplan, 2006; Timmann & Daum, 2007; Strick, Dum, & Fiez, 2009). Central to this thesis are the reciprocal connections between the posterior lobe of the cerebellum and the frontal cortex.

1.2.1 The Structure of Cerebrocerebellar Connections

The cerebrocerebellar system represents one of the largest white matter pathways in the CNS (Apps & Watson, 2009). The cerebrocerebellar circuit is a closed-loop system comprised of a feedforward (afferent) limb and a feedback (efferent) limb connecting the cerebellum with cerebral cortex. The feedforward loop, the cerebro-ponto-cerebellar (CPC) pathway, connects the frontal cortex with deep cerebellar nuclei via pontine nuclei (Thach, 1972; Brodal, 1978; Thach & Jones, 1979; Asanuma, Thach, & Jones, 1983; Schmahmann, 1996; Brodal & Bjaalie, 1997; Middleton & Strick, 1997; Schmahmann & Pandya, 1997b, 1997a; Middleton & Strick, 2000, 2001). The feedback loop, the cerebello-thalamo-cerebral (CTC) pathway connects deep

cerebellar nuclei (i.e. dentate) with the frontal cortex via thalamic nuclei; this pathway therefore serves to redirect information from the cerebellum back to higher order areas of the cerebral cortex (Thach, 1972; Thach & Jones, 1979; Asanuma et al., 1983; Schmahmann, 1996; Middleton & Strick, 1997; Schmahmann & Pandya, 1997b; Middleton & Strick, 2000, 2001).

Evidence of the basis and structure of these pathways is derived primarily from non-human primate studies; cerebrocerebellar connections have been described post-mortem and in-vivo using virus tracers to label synaptically linked neurons (Middleton & Strick, 1994, 2001; Kelly & Strick, 2003). As the main cerebellar afferent pathway, CPC fibres arise from nerve cells in the frontal cortex (e.g. precentral cortex/premotor cortex and dorsal areas of the prefrontal cortex), and descend through the posterior limb of the internal capsule, terminating on the pontine nuclei (Schmahmann, 1996; Schmahmann & Pandya, 1997b; Bähr, Frotscher, & Duus, 2005). Fibres then decussate within the pons and enter the contralateral cerebellar hemisphere via the middle cerebellar peduncle (Schmahmann, 1996; Schmahmann & Pandya, 1997b; Bähr et al., 2005). Thus, this feedforward portion of the cerebrocerebellar pathway is synaptically interrupted in the pontine nuclei (Brodal & Bjaalie, 1997), forming two segments: cerebro-ponto and ponto-cerebellar pathways. The CTC pathway, the primary cerebellar efferent circuit, originates in deep cerebellar nuclei and projects to the contralateral red nucleus (Schmahmann, 1996; Schmahmann & Pandya, 1997b; Bähr et al., 2005). This pathway then commences from the red nucleus and into synaptic relay nuclei in the thalamus; these fibres then ascend to terminate within frontal cortex (Schmahmann, 1996; Schmahmann & Pandya, 1997b; Bähr et al., 2005). The CTC pathway therefore can be parsed into three component pathways: cerebello-rubro, rubro-thalamo, and thalamo-cerebral.

Functional imaging in adult human populations has provided evidence of these pathways (Kim, Ugurbil, & Strick, 1994; Allen et al., 1997; Middleton & Strick, 1997, 2000; Salmi et al., 2010). Furthermore, cerebellar projections to prefrontal and posterior parietal cortices have been described in a small sample of adult humans using diffusion tensor imaging (DTI) tractography (Jissendi, Baudry, & Baleriaux, 2008). Solitary (e.g. non-reciprocal) connections from cerebellum to frontal cortex have also been outlined in a small sample of adult humans using fMRI/DTI (Salmi et al., 2010), and in children using DTI (Law et al., 2011). DTI has also been used to define prefrontal connections to the cerebral peduncles (Ramnani et al., 2006), and cortico-pontine fibres (Habas & Cabanis, 2007a), both studies producing portions of the CPC

pathway. Similarly a portion of the CTC pathway, projections from the cerebral cortex to red nucleus, has been delineated in adult humans using DTI (Habas & Cabanis, 2006, 2007b). DTI as a brain imaging methodology will be discussed in detail in section 1.2. Chapter 2 focuses on defining the main cerebrocerebellar output pathway – the CTC pathway – using DTI in children treated for PF tumors using the methodology outlined in Law et al. (2011).

However, the main limitations of the above body of literature include a) a lack of utilizing anatomically-defined, known points of synapse within each circuit to aid in defining the pathways, and b) the absence of defining complete, continuous, and reciprocal cerebrocerebellar pathways; we rectified these points in Chapter 3. Further, Chapter 3 investigated the microstructure of reciprocal cerebrocerebellar pathways in the healthy and injured developing brain.

1.2.2 The Function of Cerebrocerebellar Connections: Facilitating Communication between the Cerebellum and Frontal Lobe

Cerebrocerebellar circuits consist of pathways of myelinated axons connecting the cerebellum with frontal lobe. The function of these pathways is to conduct action potentials from one assembly of neurons to another, facilitating the transfer of information between the cerebellum and frontal lobe. To understand what role cerebrocerebellar pathways play in certain functions, we must look to the brain regions that comprise the main nodes of this circuit – the cerebellum and frontal lobe – and what functions they underlie. The cerebellum and frontal lobe are involved in numerous functions including executive control, modulation of behaviour/emotion, and speech-language; as part of a distributed neural system involving reciprocal connectivity between the cerebellum and frontal lobe, cerebrocerebellar circuits are postulated to play a role in the modulation of such functions.

Specifically, cerebrocerebellar pathways have been implicated in motor control (e.g. learning, timing, and calibration of movement) (Glickstein, 1992; Stein & Glickstein, 1992; Glickstein, 1993; Brodal & Bjaalie, 1997; Schmahmann, Ko, & MacMore, 2004), as well as aspects of cognition and behaviour (Akshoomoff & Courchesne, 1992; Ivry & Baldo, 1992; Leiner et al., 1993; Kim et al., 1994; Middleton & Strick, 1994; Fiez et al., 1996; Schmahmann, 1996; Allen et al., 1997; Desmond et al., 1997; Desmond, Gabrieli, & Glover, 1998; Chen & Desmond, 2005; Schmahmann & Caplan, 2006; Timmann & Daum, 2007; Law et al., 2011). The bulk of the

literature on cerebrocerebellar connections and cognition/behaviour describes their involvement in speech-language and some aspects of EF. Specifically, affect regulation or pseudobulbar affect may be associated with damage to regions along the cerebrocerebellar pathways due to the close proximity of this circuit to the corticobulbar tract (a pathway which includes the brainstem, medulla, pons, and frontal lobe) (Kaufman, 2007). Cerebrocerebellar circuitry has also been implicated in verbal working and short-term memory (Kim et al., 1994; Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005; Ravizza et al., 2006; Strick et al., 2009). Pertinent to this thesis is previous literature on cerebrocerebellar associations with EF (e.g. relevant to Chapter 4), and speech-language production/processing (e.g. relevant to Chapter 2 discussing CMS risk), which will be focused on in this section. Previous research regarding the neural correlates of CMS will be discussed further in section 1.5.1 and the neural correlates of EF will be discussed in section 1.5.3.1.1.

First, the cerebellum and frontal lobe are thought to contribute to cognitive control (i.e. EF); studies have shown activation of the cerebellum and prefrontal cortex during the acquisition and retrieval of first-order rules (Balsters & Ramnani, 2008, 2011), and when solving complex pegboard puzzles (Kim et al., 1994). Further, lesions to the cerebellum (Kirschen et al., 2008) or disruption in cerebellar functioning (Desmond, Chen, & Shieh, 2005) produce deficits in verbal working memory. Working memory has consistently been associated with both the activation and structure of regions comprising cerebrocerebellar circuitry. Specifically, several studies have found that the cerebellum interacts with frontal cortex to support working memory function by way of the CTC pathway (Chen & Desmond, 2005; Salmi et al., 2010; Law et al., 2011). A CTC connection between cerebellar and prefrontal areas activated during a nonverbal auditory working memory task has been documented using DTI tractography (Salmi et al., 2010). Law et al. (2011) found damage to the microstructure of the CTC pathway – specifically within cerebellar white matter regions of the pathway – in patients treated for PF tumors compared to healthy children and that working memory deficits found in patients were correlated with measures of pathway damage.

Several studies have shown that the cerebellum is activated during tasks involving complex cognitive paradigms of language/verbal working memory (Desmond et al., 1997; Chen & Desmond, 2005; Kirschen et al., 2005; Hayter, Langdon, & Ramnani, 2007). There is recent DTI evidence that compromise of white matter regions within the CTC pathway, specifically within

the superior cerebellar peduncle, is linked to CMS – a syndrome that affects speech-language processing and production (Morris et al., 2009). Similar to CMS, Cerebellar Cognitive Affective Syndrome (CCAS) is often observed in patients subsequent to cerebellar tumor resection, cerebellar degeneration, and cerebellar hypoplasia (Schmahmann & Caplan, 2006). This latter syndrome presents with behavioural disturbances and personality changes as well as impairment in EF (i.e. planning, set-shifting, abstract reasoning, verbal fluency, working memory), and linguistic and visuo-spatial processing (Pollak, Klein, Rabey, & Schiffer, 1996; Schmahmann & Sherman, 1998; Levisohn, Cronin-Golomb, & Schmahmann, 2000; Schmahmann, 2004; Schmahmann & Caplan, 2006).

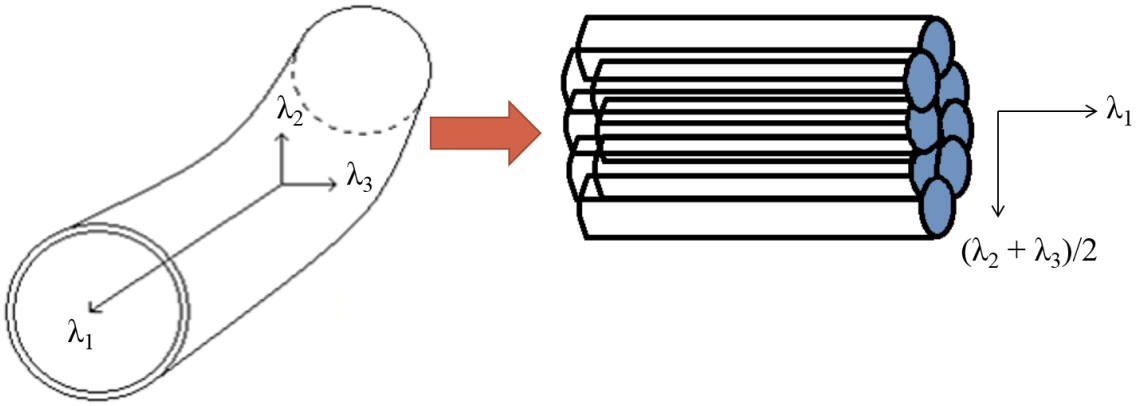
It is evident that the cerebellum and frontal lobe are important for EF (including working memory and behaviour/emotion control) and speech-language production and processing. However, it may be the facilitation of communication between the cerebellum and frontal lobe via cerebrocerebellar pathways that is also important for efficient functioning in these areas.

1.3 Diffusion Tensor Imaging (DTI)

DTI is a type of non-invasive magnetic resonance imaging (MRI) for which the microstructural organization of tissue (i.e. white matter) can be characterized in vivo. DTI allows for the visualization of different aspects of tissue microstructure based on water molecule displacement and directionality (Basser, 1995). DTI yields voxel-wise maps of several measures including diffusivity of water movement, tissue anisotropy, and fibre directionality. These maps are based on three separate diffusivities or directions called eigenvalues, λ_1, λ_2, λ_3 (Figure 1.2), calculated by matrix diagonalization (Basser, 1995; Song et al., 2002). The eigenvalues can be combined to provide summary measures (quantitative DTI indices) of fractional anisotropy (FA) and mean diffusivity (MD), as well as axial and radial diffusivity (AD and RD, respectively). FA reflects the principal diffusion direction within each voxel. Values of FA lie between 0 and 1; values closer to 1 signify high anisotropy (i.e. in white matter, water molecules diffuse more freely along the dominant fibre direction than any other direction). FA can be used to infer white matter microstructure (i.e. myelin structure), as white matter tissue acts as a barrier to free water molecule movement. MD represents the magnitude of water diffusion, or the average diffusion freedom that water molecules have within each voxel, measured in mm^2/s (Basser, 1995). MD is thought to give insight into both axon and myelin structure (Song et al., 2002). The first

eigenvalue (λ_1) is a measure of axial diffusivity, reflecting diffusion parallel to the axonal fibres (Basser, 1995), and is measured in mm^2/s (Figure 1.2). The second and third eigenvalues (λ_2 and λ_3) represent diffusion perpendicular to axonal fibres (Basser, 1995). Radial diffusivity, also measured in mm^2/s, is an overall measure of this perpendicular diffusion and is calculated by taking the average of λ_2 and λ_3 (Basser, 1995) (Figure 1.2). Measures of axial and radial diffusivity are thought to reflect axon and myelin structure, respectively (Song et al., 2002).

Figure 1.2 Visualization of the eigenvectors/directionalities obtained in diffusion tensor imaging.

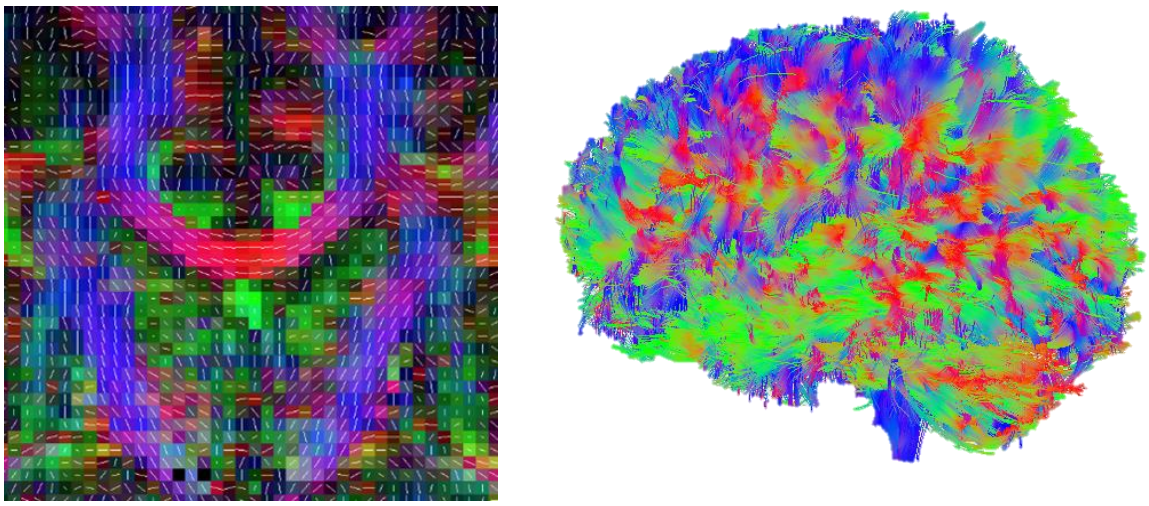


This leftmost portion of this diagram shows the eigenvectors or directionalities of water movement within (or along) a single axon, where λ_1 represents the principal diffusion direction and λ_2 and λ_3 represent perpendicular diffusion. The rightmost portion of the diagram depicts a bundle of axons for which λ_1 again represents the principal direction of water diffusion – axial diffusivity – within and along myelinated axons. The equation used to calculate radial diffusivity, diffusion perpendicular to axons, is also provided.

In DTI tractography, voxel-wise maps of fibre orientation can be used to reconstruct continuous trajectories throughout white matter – producing white matter tracts/pathways (Figure 1.3). Tractography defines white matter pathways based on user-specified regions of interest (ROIs) including a specific start point (i.e. seed point) and areas of relay or endpoints (i.e. way points). Once a tract or pathway is defined using tractography, mean DTI indices can be calculated for the entire pathway (or regions or segments of the pathway). It is pertinent to note that the current thesis used probabilistic tractography, a method that assumes a distribution of orientations (i.e. multiple directions) at each voxel to obtain a connectivity index along a tract or pathway that reflects fibre organization and is sensitive to pathological abnormalities (Ciccarelli et al., 2006). Thus this methodology takes into account, where there are multiple orientations within a voxel,

the probability of each voxel's connection with adjacent voxels in the entire image. This method is in contrast with deterministic or streamlined tractography (not utilized for the present thesis), for which a single orientation at each voxel is assumed.

Figure 1.3 Diffusion tensor imaging tractography: Using directionalities to map white matter pathways.



The leftmost diagram depicts an FA map with directionality vectors (i.e. white lines) (generated with FMRIB Software Library). Red represents fibres running medial-lateral; blue represents pathways running superior-inferior, and green represents fibres running anterior-posterior. The diagram on the right is an example of whole-brain white matter pathways (i.e. no ROIs used) created using directionality information (generated with MedINRIA).

As mentioned above, FA, MD, AD, and RD can in turn be used to infer the microstructural organization of white matter and identify whether injury to white matter regions or pathways (e.g. demyelination, axonal damage) is evident (Song et al., 2002; Mori & Zhang, 2006; Jones & Leemans, 2011). Lower measures of FA and higher measures of MD, AD, and RD are thought to reflect axonal degeneration and compromised myelin sheath structure (Beaulieu, 2002; Song et al., 2002).

Because DTI and tractography can be used to detect even subtle changes or differences in white matter microstructure within white matter regions and pathways, this methodology was used in the current thesis. Chapter 2 of this thesis shows the use of DTI and probabilistic tractography to delineate and examine white matter pathways connecting the cerebellum with frontal lobes via the thalamus (i.e. CTC pathways). The resultant pathways were regionally divided to examine

localized damage to the pathway in children treated for PF tumors with CMS and without CMS. Within Chapter 3 of this thesis, DTI and probabilistic tractography were used to define continuous, reciprocal cerebrocerebellar pathways in children treated for medulloblastoma (MB) and healthy children and segment these pathways into their anatomically-relevant component parts. Chapter 4 uses the same methodology as Chapter 3, though whole-pathway (rather than segmented) cerebrocerebellar white matter microstructure was examined in children treated for MB and healthy children. The following section (1.4) describes PF tumors, the treatment protocol involved, and the adverse neurobiological, neurocognitive, and behavioural effects of treatment in detail and explains why the current thesis is focused on this particular population.

1.4 Types of Posterior Fossa Tumors, their Pathologies, and Treatment Protocols

Brain tumors are the leading cause of death and disability from childhood disease in developed countries (Bleyer, 1999); their incidence accounts for 3.9 to 4.03 cases per 100,000 in the United States and Canada alone (Miltenburg, Louw, & Sutherland, 1996). With advances in medical treatment in the last 20 years, survival rates have improved dramatically; five-year survival rates are approaching 80% (David et al., 1997; Dhall, 2009). Approximately half of all brain tumors in childhood are located within the posterior fossa (PF), an area that contains the cerebellum, pons, medulla, and fourth ventricle (Kline & Sevier, 2003). Tumors arising within the PF can block the flow of cerebrospinal fluid (CSF) and cause increased pressure on the brain and spinal cord, producing hydrocephalus (Kline & Sevier, 2003). As such, PF tumors are initially surgically resected and, dependent on tumor type, given adjuvant craniospinal radiation therapy (CRT) and chemotherapy (CTX) (Bleyer, 1999). Among the most frequent PF tumor diagnoses are MB and low grade gliomas/astrocytoma) (Yachnis, 1997).

MB is a malignant tumor that arises from primitive neuroectodermal tissue and accounts for 30% of all pediatric brain tumors and up to 55% of all PF tumors (Schott, Naidich, & Gan, 1983). As MB is radiosensitive in nature, the standard of treatment includes postoperative CRT with a boost to the PF, followed by 12 months of CTX (Packer, 1999; Mueller & Chang, 2009). This population is of prime focus in the present study and comprises most of our patient sample in Chapter 2, and the entire patient sample in Chapters 3 and 4.

Low-grade gliomas/astrocytoma account for 20% to 25% of all pediatric PF tumors (Schott et al., 1983). While glioma arises from glial cells, particular glial cells called astrocytes give rise to astrocytoma (Yachnis, 1997). The first line of treatment for children with low-grade glioma is surgery; gross total or near gross total tumor resection is the aim (Mueller & Chang, 2009). In general, patients presenting low-grade glioma who undergo complete resection of the tumor do not receive adjuvant therapy (e.g. CRT or CTX), unless there is presence of disease recurrence or progression (Mueller & Chang, 2009). Additional PF tumor types include other low grade gliomas (e.g. ganglioglioma), germ cell tumors (e.g. pure germinoma), ependymoma, and choroid plexus papilloma; these PF tumor pathologies were included in our patient sample in Chapter 2 in addition to MB and low-grade gliomas/astrocytoma.

Though current treatment protocols are often successful and survival is achieved, the adverse effects of treatment are widely documented. The tumor, its location, and resection can produce local (direct) effects and can impact both neurological and functional outcome. Namely, motor, cognitive, and behavioural difficulties may arise from the primary impact of the tumor and surgical resection as most PF tumors are located in the cerebellar hemispheres or the fourth ventricle, requiring access through the vermis (McLaughlin, Fisher, Sutton, & Storm, 2012). Other treatment modalities, such as CRT and CTX are considered to have systemic/diffuse effects. For example, CRT can have adverse late effects on many bodily structures, including endocrine, skeletal, and central nervous systems (Goldwein et al., 1996). Late effects are for the most part irreversible and thus the most destructive and can include sensory and motor deficits (Wong & Van der Kogel, 2004) as well as morbidity in cognitive and behavioural domains. The following section (1.5) discusses the impact of treatment for PF tumors on clinical and neurocognitive/behavioural outcomes.

1.5 Outcome Following Treatment for Posterior Fossa Tumors

1.5.1 Cerebellar Mutism Syndrome (CMS)

CMS is an important medical challenge in the management of pediatric PF tumors and presents in a subset of patients typically 1-2 days post resection. CMS has been found to occur in up to 25% children treated for MB (Robertson et al., 2006). CMS can present as a constellation of symptoms including, but not limited to, complete or partial disruption in speech output, speech-language/linguistic difficulties (e.g. dysarthria), ataxia, and hypotonia, as well as other

neurological and neurocognitive impairments. In some cases, deviations from premorbid behaviour and personality can occur and include irritability, inattention, blunting of affect, disinhibited or inappropriate behaviour, and emotional lability (Schmahmann & Sherman, 1998; Wells, Walsh, Khademian, Keating, & Packer, 2008). These symptoms may result from poor cognitive and behavioural modulation or an inability to regulate and self-monitor (Levisohn et al., 2000; Robertson et al., 2006).

Although some aspects of CMS (e.g. initial mutism/linguistic deficits and behavioural disturbances) are transient, recent studies have documented persistent speech-language, neurological, and cognitive impairments (Levisohn et al., 2000; Siffert et al., 2000; Steinbok, Cochrane, Perrin, & Price, 2003; Huber, Bradley, Spiegler, & Dennis, 2006; Robertson et al., 2006) and poor long term outcomes in these areas (Wells et al., 2008). Namely, full recovery of speech-language abilities is uncommon in patients (Siffert et al., 2000; Steinbok et al., 2003; Huber et al., 2006; Robertson et al., 2006). The most common residual impairments 1 year following CMS diagnosis were speech-language dysfunction, ataxia, and global cognitive deficits (Robertson et al., 2006). Because the symptoms of CMS are not present preoperatively and manifest only after surgery, CMS cannot be accounted for by the presence of the tumor itself. Attempts have been made to a) determine the clinical variables that may increase CMS risk, and b) elucidate the mechanism of injury or neuroanatomical substrate that may explain why some patients present with CMS while others do not.

Multiple clinical factors have been associated with a heightened risk of presenting with CMS post-surgically. Though there is no relation between CMS and age at diagnosis or gender (Grill et al., 2004; Robertson et al., 2006; Turgut, 2008), tumor type and location seem to have bearing on whether a patient presents with CMS or not. Specifically, a higher grade tumor (e.g. MB) and midline tumor location (e.g. vermis) are associated with increased CMS risk (Van Calenbergh, Van de Laar, Plets, Goffin, & Casaer, 1995; Grill et al., 2004; Wells et al., 2008). Larger tumor size has been implicated as a risk factor for CMS in some studies (Catsman-Berrevoets et al., 1999; Gelabert-Gonzalez & Fernandez-Villa, 2001) but not others (Robertson et al., 2006; Wells et al., 2010).

Relative to the clinical and medical research regarding the predictors of CMS, there is a dearth of literature describing the neural correlates of CMS. Thus far, CMS has been associated with

increased brainstem involvement by the tumor and tumor infiltration of normal tissue (Robertson et al., 2006). The absence of CMS has been documented following resection of cerebellar hemispheric tumors not requiring access through the vermis, while resection of vermal/midline tumors is associated with CMS risk (Grill et al., 2004). However, vermal damage does not necessarily result in CMS; damage to surrounding brain structures can also produce CMS. Injury to the dentate nuclei (deep cerebellar nuclei located within each cerebellar hemisphere, thought to be responsible for the planning, initiation, and control of voluntary movements) has been shown in patients with CMS (Ozgur, Berberian, Aryan, Meltzer, & Levy, 2006). Further, bilateral edema within the cerebellar peduncles following surgery has been implicated in CMS (Pollack, Polinko, Albright, Towbin, & Fitz, 1995). The dentate nuclei are the largest single structure linking the cerebellum with the rest of the brain (Sultan, Hamodeh, & Baizer, 2010). The cerebellar peduncles connect the cerebellum with the brainstem and are important components of cerebellar afferent and efferent pathways. Thus, dentate nuclei or cerebellar peduncle compromise may contribute to the disruption of communication between the cerebellum and cortex – resulting in CMS.

Indeed, studies have implicated structures contained within afferent and efferent pathways between cerebellar nuclei (e.g. dentate) and cortex (e.g. frontal, premotor, supplementary motor) in CMS (Pollack et al., 1995; Koh, Turkel, & Baram, 1997; Ozgur et al., 2006). A diaschisis model of pathophysiological injury has been proposed as the mechanism of postsurgical CMS (Meyer, Obara, & Muramatsu, 1993; Germano et al., 1998; Sagiuchi et al., 2001; Marien, Engelborghs, Michiels, & De Deyn, 2003; Miller et al., 2010). Diaschisis is a loss of function of one brain region that is connected with and distal to another brain region that has sustained insult (Meyer et al., 1993). This model is supported by evidence of bilateral surgical damage (indicated by hypoperfusion) to proximal efferent cerebellar pathways (e.g. cerebellar peduncles), in patients with CMS relative to patients without CMS (Miller et al., 2010). Further, multiple white matter anomalies were found in patients with CMS versus patients without CMS across the brain, including areas connecting the cerebellum with cortex (Morris et al., 2009). Based on a diaschisis model, CMS may be the result of disruption of multiple regions along cerebellocerebral pathways.

To date, no study has explicitly examined cerebrocerebellar connections and their involvement in CMS. Further, a comprehensive model of CMS risk integrating clinical, medical, and

neuroanatomical features has yet to be investigated. Chapter 2 focuses on these areas and the rationale for this study will be discussed further in section 1.6.

1.5.2 Neurological Outcome: Effect of Treatment for Posterior Fossa Tumors on White Matter

Treatment for PF tumors has been associated with significant neurotoxicity (Schultheiss, Kun, Ang, & Stephens, 1995; Goldwein et al., 1996). Neurotoxicity can arise as a direct effect of the tumor or as a result of surgical intervention, CRT, or CTX (Van Calenbergh et al., 1995; Steinlin et al., 2003; Aarsen, Van Dongen, Paquier, Van Mourik, & Catsman-Berrevoets, 2004), with higher doses and larger treatment volumes predicting increased morbidity (Mulhern et al., 1998; Grill et al., 1999; Ris et al., 2001).

Neuroimaging studies examining the effects of CRT on brain tissue provide a grim picture of widespread CNS radiation injury. Changes in brain tissue following radiation treatment include glial atrophy, demyelination, white-matter specific necrosis, and declines in normal appearing white matter volume (Schultheiss et al., 1995; Edwards-Brown & Jakacki, 1999; Reddick et al., 2000; Mulhern et al., 2001; Khong et al., 2003; Wong & Van der Kogel, 2004; Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006a; Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006b). For example, volume loss has been documented within the corpus callosum (Palmer et al., 2002) and hippocampus (Nagel et al., 2004) in patients treated with CRT. Further, white matter damage has been documented using DTI within multiple brain regions in children treated for MB compared to healthy children including the corpus callosum (Mabbott et al., 2006b), internal capsule (Mabbott et al., 2006b), pons (Khong et al., 2003), medulla (Khong et al., 2003), cerebellum (Khong et al., 2003; Law et al., 2011), and parietal lobe (Khong et al., 2003) and frontal lobe (Mabbott et al., 2006b) white matter.

White matter is composed of glial cells that provide structural and physiological support within the central nervous system and form myelin to insulate axons (Kolb & Whishaw, 1990). This tissue is essential for cognitive efficiency as it propagates the transmission of electrical signals along axons (Kolb & Whishaw, 1990). Thus, damage to these cells in the developing brain can be particularly devastating when considering functional and neurocognitive outcomes. Though beyond the scope of the current thesis, the mechanism(s) of radiation-induced CNS injury in the developing brain involve the inhibition of gliogenesis and neurogenesis, as well as disruption of

the blood-brain barrier (Wong & Van der Kogel, 2004; Nieder, Andratschke, & Astner, 2007). Cell death and subsequent secondary injury may lead to cell loss, tissue damage, and ultimately white matter deficit (Wong & Van der Kogel, 2004; Nieder et al., 2007).

Though the above volumetric and DTI-based measures tell us about regional tissue properties, they do not inform us about white matter connectivity and structure of pathways in the brain that connect distant regions. To the author's knowledge, the work in this thesis is the first to examine specific, anatomically-based white matter pathways in children treated for PF tumors using DTI and compare their microstructure with that of healthy age-matched peers (Chapters 2-4).

1.5.3 Neuropsychological Outcome: Effect of Treatment for Posterior Fossa Tumors on Cognition and Behaviour

The adverse neurocognitive effects of treatment for pediatric PF tumors are well known. Resection of the PF tumor itself can result in long-term deficits in speech-language, EF, visual-spatial ability, adaptive function, and behavioural regulation (Levisohn et al., 2000; Riva & Giorgi, 2000a; Aarsen et al., 2004; Beebe et al., 2005; Huber et al., 2006). The majority of children treated with CRT have problems maintaining their premorbid levels of intellectual development and academic achievement (Mulhern et al., 2004a). Deficits in intelligence (IQ), attention, processing speed, academic ability, and social skills are often apparent following treatment (Mulhern et al., 1998; Ris et al., 2001; Mabbott et al., 2005; Mabbott et al., 2008). Furthermore, in 94% of children treated with CRT, declines of two to four IQ points per year have been documented (Spiegler et al., 2004); these declines attenuate 5-10 years post-treatment and have been found to stabilize 20-30 years after diagnosis (Briere, Scott, McNall-Knapp, & Adams, 2008; Edelstein et al., 2011). Given the steady declines in IQ up to 5 years post-diagnosis, it is logical that, in the years following treatment for PF tumors, patients are at risk for neurocognitive deficits that may impact academic performance, employment opportunities, and overall quality of life (Mulhern et al., 1998; Ris et al., 2001).

It has been suggested that neurocognitive declines, particularly in patients treated with CRT, reflect a reduced ability to obtain novel information from their surroundings and result from acquiring knowledge at a significantly slower rate than healthy peers (Palmer et al., 2001). Many components of EF are required to facilitate the attainment of new knowledge, learn from environmental cues, process information quickly and efficiently, and self-monitor. Thus, it is

possible that multiple EFs are impaired in children with MB and that this impairment contributes to overall neurocognitive and behavioural deficits often observed following treatment.

To the author's knowledge, no explicit, broad-spectrum analysis of EF has been completed in children treated for MB; specifically one based on conceptual models of EF. Further, examining emotion regulation, a self-awareness/regulation component of EF, has been largely neglected in this population. One aim of this thesis was to complete such an analysis of EF in survivors of pediatric PF tumors.

1.5.3.1 Executive Function (EF)

EF is an umbrella term describing a set of complex cognitive abilities necessary to achieve a goal; it is essentially the conscious control over what we say and do. EFs play an important role in a child's ability to acquire novel information, maintain this information, and make use of the information in an efficient and effective manner. EFs also guide goal-directed, purposeful behaviour required to reach a specific, intended outcome. EF encompasses a broad range of processes including action initiation, mental flexibility, organizing/sequencing, cognitive fluency, switching between task sets, inhibition of an inappropriate response or behaviour, planning, strategy development, maintaining attentional set/persistence, working memory, and regulation (e.g. behavioural/emotional) (see Banich, 2004; Jurado & Rosselli, 2007 for review). Many definitions of EF exist and both the components and nomenclature of its subprocesses vary. There is disagreement over whether EF is a unitary construct versus non-unitary concept. That is, is EF a solitary construct with multiple interrelated subprocesses or does it represent a constellation of independent processes?

Luria (1966) proposed a four factor model of EF, based on the observation of impaired self-regulation following frontal lobe injury. The major components were described as anticipation (setting goals or series of goals to complete an endeavor, understanding possible outcomes), planning (organization), execution (ability to maintain set and to be flexible), and self-monitoring (identification of errors, emotional and behavioural control). Two additional theories of EF – models proposed by Stuss and Benson (1986) and Lezak (1995) – are congruent with Luria's (1966) paradigm, but use different naming conventions to describe EF components. Lezak (1995) proposed a four component model of EF, including volition (self-monitoring), planning, purposive action (similar to anticipation), and effective performance (comparable to

execution). Stuss and Benson (1986) described five components of EF: initiation (akin to anticipation), planning, sequencing, organization, and regulation. Organization and regulation are similar to Luria's (1966) execution construct.

Recent studies have employed component or factor analyses to meaningfully group aspects of EF from multiple measures. In healthy populations, a number of studies have grouped EFs into several unitary processes such as switching/flexibility/shifting (e.g. alternating between task demands or cognitive sets) (Miyake et al., 2000), updating/monitoring (e.g. working memory and attentional control; obtaining and maintaining information in the mind to be used toward achieving a goal) (Miyake et al., 2000; Hedden & Yoon, 2006), and inhibition (actively supressing a prepotent response to respond in a relatively novel way) (Miyake et al., 2000; Hedden & Yoon, 2006). A more fine-grained classification of latent EFs in healthy children and adolescents include attentional control (Anderson, 2001; Anderson, 2002), working memory (Diamond, Kirkham, & Amso, 2002; Zelazo & Mueller, 2002; Davidson, Amso, Anderson, & Diamond, 2006; Garon, Bryson, & Smith, 2008), inhibitory control (Diamond et al., 2002; Zelazo & Mueller, 2002; Davidson et al., 2006; Garon et al., 2008), planning/goal setting (Levin et al., 1991; Welsh, Pennington, & Groissier, 1991; Kelly, 2000; Anderson, 2002), problem solving (Garcia-Barrera, Karr, & Kamphaus, 2013), set-shifting/cognitive flexibility (Anderson, 2001; Anderson, 2002; Diamond et al., 2002; Zelazo & Mueller, 2002; Davidson et al., 2006; Garon et al., 2008), fluency (both verbal and design) (Levin et al., 1991; Welsh et al., 1991; Fisk & Sharp, 2004), information processing (Anderson, 2002), and in adults, regulation/self-awareness (including behaviour/emotion regulation) (Stuss & Benson, 1986; Mateer, 1999; Sohlberg & Mateer, 2001).

Several studies have identified deficits in childhood brain tumor survivors for discrete EF-related processes such as attention (Dennis, Hetherington, & Spiegler, 1998; Reeves et al., 2006), processing speed (Waber et al., 2006; Mabbott et al., 2008), organizational skills (Armstrong et al., 2009), and working memory (Dennis et al., 1992; Dennis et al., 1998; Kirschen et al., 2008; Law et al., 2011; Conklin et al., 2012). To our knowledge, only two studies have explicitly examined emotion regulation in survivors of pediatric brain tumors and have found inefficiencies in this domain based on proxy-rated questionnaires (Armstrong et al., 2009) and identifying the tone of music conveying emotion based on the Stroop task (Hopyan, Laughlin, & Dennis, 2010).

At present, it remains unclear which EFs are most sensitive to the treatment effects for MB. The focus of Chapter 4 is describing EF in children treated for MB and healthy children and investigating the role of cerebrocerebellar connections in EF in this population.

1.5.3.1.1 Cerebrocerebellar Contributions to EF

The role of prefrontal areas in executive processing is clearly established (Collette et al., 2005). Many theories of EF have resulted due to observations of individuals sustaining frontal lobe damage – causing EFs to be considered as largely frontal lobe-dependent processes. In general, prefrontal areas such as Brodmann area 9, 46, and 10 as well as the anterior cingulate gyrus are thought to be involved in general executive processes, as these areas are systemically activated by a broad range of executive tasks (Collette & Van der Linden, 2002). Other frontal areas (i.e. BA 6, 8, 44, 45, 47) and parietal regions (i.e. BA 7, 40) are also activated during tasks of EF (Collette et al., 2005). With regard to specific (i.e. "discrete") EFs, the following section summarizes the involvement of the frontal lobe in each process.

Verbal and design fluency, inhibition/shifting, planning, organization, problem solving, and abstract thinking are all EFs that have been associated with DLPFC function (Grafman & Litvan, 1999; Duke & Kaszniak, 2000; Stuss et al., 2000; Malloy & Richardson, 2001). Further, increased activation in the DLPFC, along with the ventromedial and orbitofrontal cortices, has been observed during performance on the Wisconsin Card Sorting Task (WCST), which is thought to reflect set shifting/cognitive flexibility, and problem solving (Grafman & Litvan, 1999; Stuss et al., 2000). Response inhibition has also been linked with activation of the middle/inferior frontal gyri (bilaterally) and the left superior frontal gyrus (Rodrigo et al., 2014). Verbal fluency is sensitive to frontal lobe lesions (left or right hemispheric), both diffuse and focal, though patients with left frontal lesions perform significantly worse than any other frontal lesion group (Stuss et al., 1998; Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001). Many neuroimaging studies have found that working memory (verbal and spatial) is mediated by several specific frontal cortical regions, depending on the type of information to be maintained (McCarthy et al., 1996; Courtney, Petit, Haxby, & Ungerleider, 1998a; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998b; Smith & Jonides, 1999; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000; Curtis & D'Esposito, 2003). Specifically, during verbal working memory tasks, the prefrontal cortex shows bilateral activation (Smith & Jonides, 1999; Prabhakaran et al.,

2000). Furthermore the middle frontal gyrus in the right hemisphere is preferentially activated during spatial working memory tasks while the middle frontal gyrus is bilaterally activated during non-spatial working memory tasks (McCarthy et al., 1996; Prabhakaran et al., 2000). Lesions of the dorsolateral prefrontal cortex (DLPFC), especially those located within and surrounding the principal sulcus (Brodmann area 46) impair working memory performance (Goldman & Rosvold, 1970; Bauer & Fuster, 1976; Funahashi, Bruce, & Goldman-Rakic, 1993; Curtis & D'Esposito, 2003).

The cerebellum has recently been implicated in a range of EFs, though working memory and information processing are the most commonly associated functions (Schmahmann & Caplan, 2006; Bellebaum & Daum, 2007). Cerebellar activations have been observed while performing EF and attention-based tasks (Desmond et al., 1997; Schlosser et al., 1998). For example, activation of bilateral ventral portions of the cerebellar dentate nuclei were found during a variety of tasks involving short-term working memory (Kim et al., 1994). Additionally, an increase in blood flow to the cerebellum was observed during verbal working memory tasks (Fiez et al., 1996). Further, selective deficits in tasks of verbal working memory were found in adult patients with isolated cerebellar lesions or resections compared with healthy adults, leading to a proposal that the cerebellum may contribute to verbal working memory during initial phonological encoding (Ravizza et al., 2006).

Additionally, damage to the cerebellum has been associated with response inhibition and monitoring of performance, leading to the hypothesis that the cerebellum aids in regulating the executive control of voluntary actions (Brunamonti et al., 2014). Both set shifting/cognitive flexibility and problem solving has also been associated with cerebellar hemispheric damage (Karatekin, Lazareff, & Asarnow, 2000). Similarly, more lateral hemispheric regions of the cerebellum are hypothesized to be involved in the modulation of thought and planning and organization (Schmahmann, 1991). Further, dysfunction in the modulation of emotions (i.e. affect regulation) and social behaviours has been linked with damage to the cerebellar vermis (Schmahmann, 1991).

From this work it is evident that the cerebellum and frontal lobes – two of the main nodes comprising cerebrocerebellar circuitry – are implicated in a range of EF. A review of this literature (Royall et al., 2002) emphasized the need to examine neural connections between the

frontal lobes, basal ganglia, and thalamus and their involvement in performance on tasks of EF. Indeed, neural circuits (e.g. subcortical connections) involving the frontal lobes, striatum, and thalamus have been considered important for EF (Miller & Cohen, 2001; Lewis, Dove, Robbins, Barker, & Owen, 2004; Kassubek, Juengling, Ecker, & Landwehrmeyer, 2005; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006).

Based on the main nodes comprising its connections, cerebrocerebellar circuitry may play a key role in EF-related processes. It may be that cerebellar input and output pathways are involved in facilitating the communication between brain regions underlying one or more EFs (e.g. working memory, cognitive control and modulation, behavioural/emotion regulation).

1.5.4 Relating Brain Structure and Function

Neuroimaging measures of white matter tissue damage are robust predictors of adverse cognitive function following CRT (Palmer et al., 2002; Reddick et al., 2003; Mulhern et al., 2004b; Reddick et al., 2005; Khong et al., 2006; Mabbott et al., 2006a; Mabbott et al., 2006b; Law et al., 2011). For example, decreased white matter volume, particularly in frontal and prefrontal regions, predicts poor attention following CRT, which in turn has been related to adverse intellectual outcome (Reddick et al., 2003; Mulhern et al., 2004b). CRT has also been found to result in decreased hippocampal volume and deficits in declarative memory (Nagel et al., 2004). Indeed, reduced hippocampal volume and damage to the uncinate fasciculus were associated with poorer memory outcomes in survivors of PF tumors (Riggs et al., 2014). Using DTI, Mabbott et al. (2006b) found a significant correlation between DTI measures FA and MD and IQ outcome in children treated for MB. Specifically, damage to corpus callosum, internal capsule, and frontal white matter (signified by lower FA and higher MD) in patients relative to controls was associated with adverse intellectual outcome in survivors. Damage to the cerebellar white matter within cerebellar output pathways (e.g. CTC pathway) was associated with poorer performance on working memory tasks in children treated for PF tumors (Law et al., 2011).

The work presented in Chapter 4 compares DTI measures of cerebrocerebellar white matter microstructure and EF to determine if injury to these pathways via treatment for PF tumors has an impact on EF outcome.

1.6 Thesis Objectives

The purpose of this thesis was to investigate the clinical, neurological, and cognitive/behavioral outcomes following treatment for pediatric PF tumors. Further, the influence of neurological outcome (i.e. neuroanatomical measures of white matter microstructure) on clinical and cognitive/behavioural sequelae was considered. First, clinical and demographic variables and cerebellar output pathway-based white matter microstructure were investigated as predictors of CMS. Second, neuroanatomical identification and parcellation of reciprocal cerebrocerebellar pathways – white matter pathways serving as input and output relays between cerebellum and frontal cortex – was undertaken using DTI. This procedure was done to investigate the impact of treatment for pediatric MB on neurological outcome (providing information about neurological vulnerability following treatment for brain tumors). Third, EF was investigated in both healthy children and children treated for MB. Lastly, reciprocal cerebrocerebellar pathway white matter microstructure was associated with measures of EF, including emotion regulation in children treated for MB. The following sections provide a brief outline of the different chapters contained within this thesis and the main questions that each chapter sought to address.

1.6.1 Thesis Overview

1.6.1.1 Chapter 2

A definitive schema for CMS risk in children with PF tumors based on medical and neurological features has yet to be elucidated. For this study, medical and demographic data were obtained in a sample of children treated for PF tumors who presented with CMS following resection and those who did not. Additionally, DTI measures of white matter microstructure were collected for each participant to investigate cerebellar output pathways – connections that have previously been implicated in CMS. The following questions were addressed: (1) are there certain clinical and demographic features that put patients at a higher risk for CMS; (2) is the cerebello-thalamo-cerebral pathway implicated in the presentation of CMS; and (3) can we determine a schema of CMS risk incorporating medical, demographic, and neurological variables?

1.6.1.2 Chapter 3

To date, our knowledge of the structural and functional connectivity of cerebrocerebellar circuits has come from animal models and several adult human studies, but the structure of reciprocal

cerebrocerebellar pathways has not yet been shown in its entirety in humans. Additionally, the localized microstructure of these continuous pathways still requires investigation. Further, it is unclear what can occur to the microstructure of these pathways when the developing brain is injured and if age has an impact on these connections. In Chapter 3, we used MB as a brain injury model due to the known impact of tumor and treatment on the cerebellum. DTI was obtained for children treated for MB and healthy age-matched children to address the following questions: (1) can we define reciprocal cerebrocerebellar pathways in the healthy developing brain using DTI; (2) can we obtain reciprocal cerebrocerebellar pathways in children treated for MB using DTI; (3) are there differences in the microstructure of these pathways (and their segmentations) between healthy children and children treated for MB; (4) what is the impact of age on reciprocal cerebrocerebellar pathways; and (5) are there any regional (e.g. segment) differences in the microstructure of reciprocal cerebrocerebellar pathways across both group and age?

In addition to the above hypotheses, this thesis sought to identify a standardized, reliable method of producing reciprocal cerebrocerebellar pathways in the human developing brain using DTI and synaptically-based, anatomically-defined regions of interest.

1.6.1.3 Chapter 4

Impairment in neurocognitive and behavioural domains following treatment for pediatric MB is well documented. Problems in EF have been suggested in children treated for MB; however, no in-depth investigation of EF has been completed in this population. Further, the role of cerebrocerebellar pathways in EF has yet to be determined, particularly in the injured developing brain. In Chapter 4, we conducted a comprehensive evaluation of EF using a broad range of measures reflective of its many components, including emotion regulation, in children treated for MB and healthy children. We subsequently used a data-reduction analysis to reduce the measures into component parts, producing meaningful factors to determine group differences in EF. Further, DTI was obtained for all participants and reciprocal cerebrocerebellar pathways were defined following the methodology described in Chapter 3. We investigated the involvement of cerebrocerebellar circuitry in EF because these connections are structurally damaged in MB (Chapter 3) and brain areas comprising these circuits have been implicated in EF in both healthy and clinical populations. The following questions were addressed: (1) which (if any) components

of EF are impaired in children treated for MB versus healthy children; (2) are there group differences in the microstructure of complete, continuous (e.g. un-segmented) reciprocal cerebrocerebellar pathways; (3) does cerebrocerebellar microstructure contribute to EF outcomes – specifically, in a path analysis model, is cerebrocerebellar microstructure a mediating factor between treatment for MB and EF outcome?

A corollary hypothesis in this study was that CTC pathway microstructure would be a more robust predictor of EF performance, relative to CPC pathway microstructure. This prediction was also expected to be reflected in our path analysis models (i.e. CTC microstructure as a mediating variable between treatment for MB and EF outcome).

1.6.1.4 Chapter 5

The last chapter of this thesis summarizes the findings from Chapters 2-4 as a whole, discusses the results in the context of previous literature, and provides a description of the challenges in this work and suggestions for future opportunities.

Chapter 2
Clinical and Neuroanatomical Predictors of Cerebellar Mutism Syndrome

Law, N., Greenberg, M., Bouffet, E., Taylor, M. D., Laughlin, S., Strother, D., Fryer, C., McConnell, D., Hukin, J., Kaise, C., Wang, F., & Mabbott, D. J. (2012). Clinical and neuroanatomical predictors of cerebellar mutism syndrome. *Neuro-Oncology*, *14*(10), 1294-1303. doi:10.1093/neuonc/nos160

2 Clinical and Neuroanatomical Predictors of Cerebellar Mutism Syndrome

2.1 Abstract

Cerebellar Mutism Syndrome (CMS) is an important medical challenge in the management of pediatric posterior fossa brain tumors as it occurs in a subset of children following tumor resection. A definitive clinical profile and neuroanatomical substrate associated with CMS remains unclear. We investigated the relationship between presurgical and clinical variables and the incidence of CMS, along with diffusion tensor imaging to characterize the microstructure of cerebello-thalamo-cerebral white matter pathways. Seventeen children with posterior fossa tumors and CMS, 34 children with posterior fossa tumors without CMS, and 28 healthy children were enrolled in this study. Bilateral cerebello-thalamo-cerebral pathways were delineated and segmented into anatomical regions. Mean microstructural measures for each region were compared among children with CMS, children without CMS, and healthy children. Left-handedness, medulloblastoma histology, and larger tumor size distinguished between patients with CMS and patients without CMS (ps<.04). Right cerebellar white matter within the cerebello-thalamo-cerebral pathway was compromised in children with CMS relative to children without CMS and healthy children (ps<.02). We provide a potential schema for CMS risk in children treated for posterior fossa tumors. Left-handed children treated for medulloblastoma may be the most at risk for CMS and unilateral, localized damage within the cerebello-thalamo-cerebral pathway at the level of the right cerebellum is implicated in the presentation of CMS. This disruption in communication between the right cerebellum and left frontal cortex may contribute to speech-language problems observed in children with CMS. Our findings may be relevant for surgical planning and speech-language therapy to mitigate symptoms of CMS.

2.2 Introduction

Cerebellar Mutism Syndrome (CMS) or Posterior Fossa Syndrome (PFS) occurs in up to 25% of children following resection of pediatric posterior fossa (PF) tumors (Van Calenbergh et al., 1995; Pollack, 1997; Robertson et al., 2006). CMS typically manifests 1-2 days postoperatively (Robertson et al., 2006) and is characterized by diminished speech output, dysarthria, and

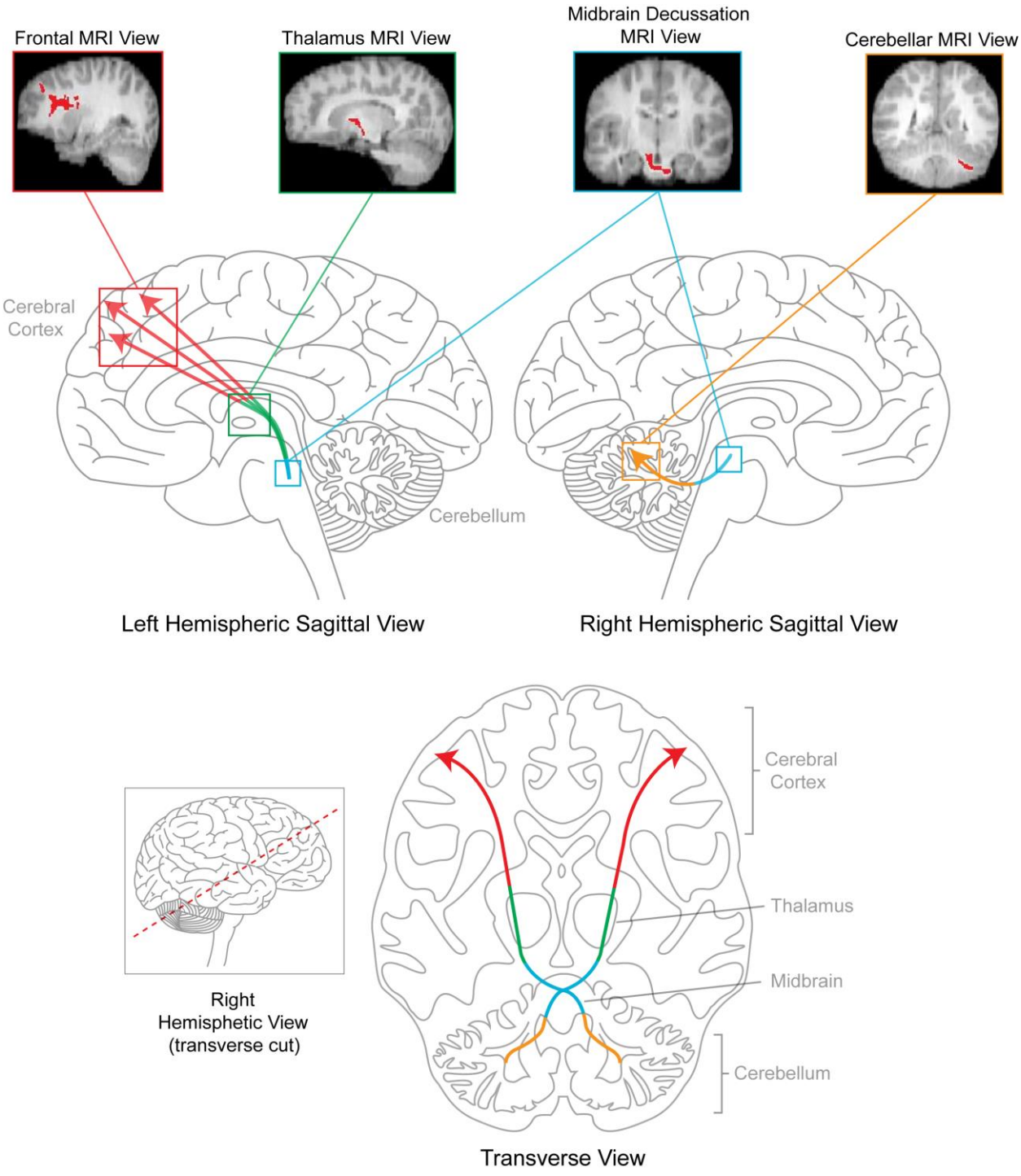
linguistic difficulties (Van Calenbergh et al., 1995; Vandeinse & Hornyak, 1997; Riva & Giorgi, 2000a). Patients may also present with dysphagia, hypotonia, ataxia, emotional lability, and personality/behavioral changes (Catsman-Berrevoets & Aarsen, 2010). Children with CMS can have persistent, long-term neurological, speech-language, and cognitive impairment (Levisohn et al., 2000; Siffert et al., 2000; Steinbok et al., 2003; Robertson et al., 2006). Attempts to discern anatomical and clinical correlates of CMS have been made with variable results. As CMS is a significant neurological complication following resection of pediatric PF tumors, understanding the relations between these risk factors and neuroanatomical insult is crucial. To date, no comprehensive model integrating clinical and neuroanatomical predictors has been developed. Such a model is essential for accurately predicting those patients who may present with CMS and subsequently take steps to mitigate the adverse effects of this syndrome. To develop our model, we examined clinical factors that may predict CMS, defined the primary white matter pathway from the cerebellum that has been previously implicated in CMS, and modeled the relations between these factors. CMS is a disorder of speech and language, which are dependent on hemispheric dominance. Thus, we also included pre-morbid handedness in our model to capture the influence of pre-surgical hemispheric organization on vulnerability to CMS.

First, there are numerous clinical factors that may contribute to CMS (see Wells et al., 2008 for a detailed summary). Previous studies have found no relation between CMS and age at diagnosis or gender (Grill et al., 2004; Robertson et al., 2006; Turgut, 2008). Tumor type and location have been identified as risk factors, with higher rates of CMS found in medulloblastoma relative to other tumor types (Wells et al., 2008), particularly when the tumor is situated in the vermis (Van Calenbergh et al., 1995). Mixed results regarding the effect of tumor size identify this variable as a risk factor in some studies (Catsman-Berrevoets et al., 1999; Gelabert-Gonzalez & Fernandez-Villa, 2001) and inconsequential in predicting CMS in others (Robertson et al., 2006; Wells et al., 2010). Because no well-defined clinical schema of CMS risk exists, our first goal was to investigate and produce a model of pre-surgical and clinical predictors of CMS.

Second, attempts have been made to elucidate the mechanism of injury or neuroanatomical substrate that may explain why some patients present with CMS while others do not. An understanding of such a substrate is only now being uncovered. Increased brainstem involvement by the tumor and tumor infiltration of normal tissue has been associated with CMS (Robertson et

al., 2006). Further, bilateral edema within the cerebellar peduncles following surgery has been implicated in CMS (Pollack et al., 1995). The cerebellar peduncles connect the cerebellum with brainstem and are important components of cerebellar afferent/efferent pathways. Cerebellar peduncle compromise may contribute to the interruption in communication between the cerebellum and cortex – resulting in CMS. For example, bilateral hypoperfusion within proximal efferent cerebellar pathways (e.g. cerebellar peduncles and frontal cortex) was observed in patients with CMS relative to patients without CMS (Miller et al., 2010). Such findings are consistent with a diaschisis model of pathophysiological insult where injury in one brain region results in a loss of function in a distal brain region that is connected to the primary region of injury (Meyer et al., 1993; Germano et al., 1998; Sagiuchi et al., 2001; Marien et al., 2003; Miller et al., 2010). Indeed, using a voxel-wise approach, Morris and colleagues (Morris et al., 2009) found multiple white matter anomalies in patients with CMS versus patients without CMS across the brain, including areas connecting the cerebellum with cortex. They did not, however, delineate and examine the microstructure of the specific structural connections between the cerebellum and cortex via cerebellar peduncles. To define these connections and quantify their structural organization, we used diffusion tensor imaging (DTI) and probabilistic tractography. Our second goal was to determine whether CMS is related to structural damage within the cerebello-thalamo-cerebral (CTC) pathway using DTI methodologies (see Figure 2.1).

Figure 2.1 A schematic of the CTC pathway.



This bilateral CTC pathway originates in deep cerebellar nuclei, ascending through superior cerebellar peduncles, decussating in the rostral midbrain, and routing through ventrolateral thalamic nuclei into frontal cortex. The red, green, blue, and yellow colour portions of the pathway represent the four segmentations we applied to examine regional pathway microstructure (see Figure 2.3).

The CTC pathway is the primary efferent bilateral pathway connecting the cerebellum with cortex (Leiner et al., 1993; Schmahmann, 1996; Schmahmann & Pandya, 1997b; Middleton & Strick, 2001; Morris et al., 2009; Salmi et al., 2010; Law et al., 2011). CTC pathways have been structurally documented using DTI tractography in healthy adults (Salmi et al., 2010) and children (Law et al., 2011), as well as children with PF tumors (Law et al., 2011). Given that this pathway is a major cerebellar output circuit and has been shown to sustain damage following resection of PF tumors (Law et al., 2011) – such damage may contribute to the symptoms of CMS (Schmahmann & Sherman, 1998; Levisohn et al., 2000; Riva & Giorgi, 2000a; Ozgur et al., 2006; Robertson et al., 2006; Wells et al., 2008; Morris et al., 2009). We hypothesized that patients with CMS would show greater structural compromise within the CTC pathway – particularly in the pons and cerebellar regions – than patients without CMS or healthy controls (Pollack et al., 1995; Robertson et al., 2006; Miller et al., 2010).

To develop our comprehensive model, we examined the relations between multiple pre-surgical and clinical variables as well as DTI measures of microstructure of the CTC pathway in children with PF tumors. Comparisons were made between patients with CMS and those without CMS. Comparisons were also made with healthy control children for our DTI measures.

2.3 Materials and Methods

2.3.1 Participants

Seventeen children with PF tumors who presented with CMS following treatment, 34 children treated for PF tumors without CMS, and 28 healthy control children participated in this study. All patients were seen at the Hospital for Sick Children (SickKids), British Columbia Children's Hospital (BCCH), or Alberta Children's Hospital (ACH). Patients were excluded from the study if they had tumors outside the PF (i.e. supratentorial), were treated for recurrent disease, had diffuse brainstem glioma, were receiving palliative care, or had a premorbid history of neurological or learning disabilities. Healthy controls were recruited through advertisement in newspapers and within the hospitals, through families (i.e. siblings), and through friends and family of the investigators; children with any previous neurological or clinical disorders, history of prior acquired brain injury, developmental delay, or learning disability were not included. The protocol for this study was approved by the Research Ethics Boards of each participating site. All

participants provided written informed consent/assent and parental consent was obtained where applicable. Patients were diagnosed with CMS if two criteria were met: a) if patients had undergone resection for PF tumor, and b) if, following the resection (typically 1-3 days post-surgery), patients presented with markedly reduced speech output or no speech output upon clinical examination. Pre-surgical handedness was assessed upon diagnosis at neuropsychological evaluation. Tumor, treatment, and demographic variables were compared between the appropriate groups (see Table 2.1 for means and standard deviations). There were no differences between all groups for sex [$\chi^2(2) = 2.104$, $p = .349$] or age at time of DTI scan [$F(2,76) = .185$, $p = .832$]. There were no age differences between children with CMS and children without CMS for handedness [$F(1,41) = .131$, $p = .719$], sex [$\chi^2(1) = 1.94$, $p = .164$], or tumor type [$F(2,41) = 1.712$, $p = .193$].

Table 2.1 Demographic and medical information.

	CMS n = 17	No CMS n = 34	Controls n = 28
Sex (% males)	41.18	61.76	50.0
Age at testing (years)			
Mean (SD)	11.27 (3.31)	11.23 (3.79)	10.76 (2.79)
Range	7.17 – 17.08	5.33 – 17.33	5.75 – 17.17
Handedness			
Right	11 (64.7%)	33 (97.1%)	25 (89.3%)
Left	6 (35.3%)	1 (2.9%)	3 (10.7%)
Age at diagnosis (years)			
Mean (SD)	7.50 (1.91)	7.98 (3.58)	N/A
Range	4.89 – 12.75	1.40 – 15.66	N/A
Time since diagnosis (years)			
Mean (SD)	3.54 (2.62)	3.25 (3.01)	N/A
Range	0.09 – 7.58	0.00 – 11.42	N/A
Tumor Size (mm^2)[1]			
Mean (SD)	2264 (722)	1653 (924)	N/A
Range	1224 - 3750	28 – 3300	
Tumor Location within PF			
Midline	14 (82.35%)	30 (88.24%)	N/A
Left Hemispheric	0	3 (8.82%)	N/A

[1] Tumor size was calculated by multiplying the two largest measurements of the tumor from an anatomical MRI scan. Measurements are in mm^2. Tumor size dimensions were not available for 9 patients.

Right Hemispheric	3 (17.65%)	1 (2.94%)	N/A
Surgical outcome/extent of resection (%)			
Greater than 95% of the tumor resected	58.82	67.65	N/A
Between 50% and 95% of the tumor resected	23.53	17.65	N/A
Biopsy	17.65	14.70	N/A
Diagnosis			
Low Grade Glioma/Astrocytoma	2 (11.77%)	13 (38.24%)	N/A
Ependymoma	0	6 (17.64%)	N/A
Medulloblastoma	14 (82.35%)	13 (38.24%)	N/A
Germinoma	0	1 (2.94%)	N/A
Choroid Plexus Papilloma	0	1 (2.94%)	N/A
Ganglioglioma	1 (5.88%)	0	N/A
Radiation Field and Dose (cGy)[2]			
Craniospinal Radiation + PF Boost	n = 14	n = 12	N/A
Mean (SD) Head/Spine	2700 (590.70)	2715 (571.58)	N/A
Mean (SD) PF Boost	3099 (675)	2925 (1041)	N/A
Focal PF Radiation	n = 0	n = 7	N/A
Mean (SD) PF/Tumor	N/A	5433 (376)	N/A
Chemotherapy[3]			
Yes	14 (82.35%)	17 (50.00%)	N/A
No	3 (17.65%)	17 (50.00%)	N/A

2.3.2 MR Imaging and Postprocessing

The details of our protocol have been described previously (Law et al., 2011) and are summarized here. MRI measurements were performed at SickKids using a GE LX 1.5T MRI scanner with 8 channel head coil and at the BCCH and ACH using a Siemens 1.5T MRI scanner with 12 channel head coil. The scanning protocol included a 3D-T1 FSPGR gradient echo, inversion recovery-prepared sequence (IR time = 400ms; TE/TR = 4.2/10.056ms; 116-124 contiguous axial slices; NEX = 1; 256 x 192 matrix, interpolated to 256 x 256; FOV = 24 x 24cm; rbw = 162.734kHz; slice thickness = 1.5mm) and a diffusion-weighted sequence (single shot spin echo DTI sequence with EPI readout: 25-31 directions; b = 1000s/mm2; TE/TR =

[2] Note that the remainder of patients in each group were treated with surgery only and were not treated with radiation.
[3] Agents included Carboplatin, Cisplatin, Cyclophosphamide, Lomustine (CCNU), and Vincristine.

85.5/15000ms; 45-50 contiguous axial slices; NEX = 1; 128 x 128 matrix, interpolated to 256 x 256; FOV = 24 x 24cm; rbw = 1953.12kHz; slice thickness = 3mm). Since MRI scanning parameters were different between the three hospitals (verified by differing signal-to-noise ratios), site of MRI scan was included as a covariate in all analyses of imaging data (see Law et al., 2011).

DTI generates quantitative indices that reflect white matter microstructure based on properties of water diffusion (Basser, 1995). These indices include fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). Lower measures of FA and higher measures of MD, AD, and RD are thought to reflect axonal degeneration and compromise to the myelin sheath (Beaulieu, 2002; Song et al., 2002). DTI post processing, seed/waypoint placement and probabilistic tractography were conducted using the FMRIB Software Library (Smith et al., 2004; Woolrich et al., 2009). MRI data were corrected for inhomogeneity and eddy current and DTI indices maps were computed. The probability of connection between all voxels within each image was calculated and served as a basis for fibre tracking analyses (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). Standardized seed and waypoint masks were registered onto each individual's image with no diffusion weighting. Frontal white matter (e.g. medial prefrontal cortex, inferior prefrontal gyrus, superior and middle frontal gyri) was used as the seed point and the thalamus and cerebellar white matter were each used as waypoints for tractography to delineate the CTC pathway bilaterally. Frontal white matter was defined on the surface of the 3D T1 image and then registered into zero-diffusion weighted space and extended 2mm into adjacent white matter. The thalamus was defined on the zero-diffusion weighted image as was hemispheric cerebellar white matter (using the cerebellar peduncles as the superior boundary and the pons as the inferior boundary). Tracts were thresholded and edited to eliminate erroneous streamlines. The resultant CTC pathways were parcellated into regions based on an anatomical template (Kabani, Sled, & Chertkow, 2002; Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009; Law et al., 2011) to examine regional microstructure. Anatomical regions produced from this segmentation included bilateral frontal hemispheric white matter, internal capsule/thalamus, midbrain/pons, and cerebellar hemispheric white matter. Means and standard deviations for all DTI indices (FA, MD, AD, and RD) were calculated for each anatomical region.

2.3.3 Statistics

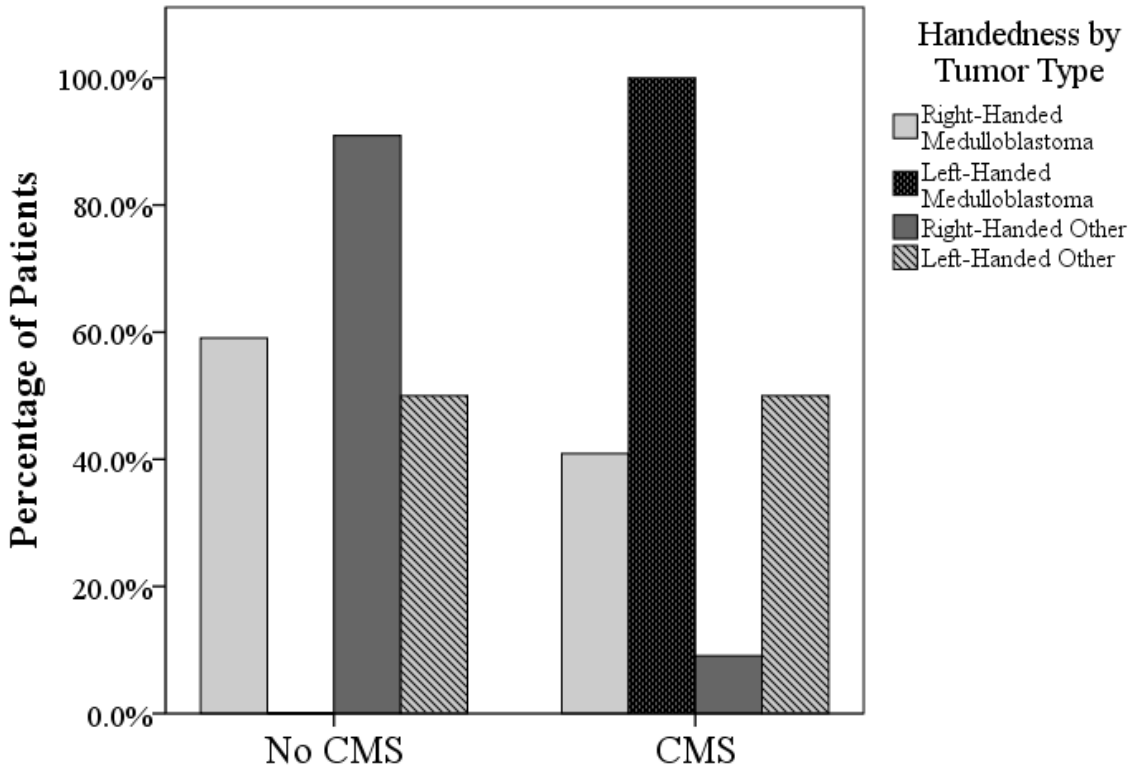
First, pre-surgical and clinical variables were examined between patients with and without CMS using univariate analyses of variance and chi-square tests. Second, a model predicting CMS from those variables found to be statistically significant from the above analyses was tested using logistic regression analyses. Third, we used Multivariate Analysis of Variance (MANOVA), which served to control for multiple comparisons and collinearity in the DTI data, to determine differences between patients with CMS, patients without CMS, and healthy controls for CTC pathway microstructure. Specifically, DTI indices of each anatomical region of the pathway were compared. As part of these omnibus analyses, planned tests of simple effects were used. This was done to examine the a priori hypothesis that patients with CMS show damage to white matter within the CTC pathway relative to patients without CMS and healthy controls. Lastly, a model predicting CTC pathway microstructure from pre-surgical and clinical variables was investigated using linear regression.

2.4 Results

2.4.1 Clinical Predictors of Cerebellar Mutism Syndrome

Children with CMS had larger tumor size [$F(1,40) = 4.676$, $p = .037$] compared to children without CMS and a greater proportion of children with CMS were diagnosed with medulloblastoma [$\chi^2(1) = 8.854$, $p = .003$] (see Table 2.1). Further, a greater proportion of children with CMS were left-handed (35%) compared to those without CMS (3%) [$\chi^2(1) = 10.018$, $p = .004$]. Considering the known base rates for handedness – approximately 10% of the general population is left-handed (Hardyck & Petrinovich, 1977) – a disproportionate number of left-handed children presented with CMS (85%) versus right-handed children (25%). In fact, in our sample, all left-handed patients with medulloblastoma presented with CMS (Figure 2.2).

Figure 2.2 Presurgical and clinical predictors of CMS.



The distribution of handedness and tumor pathology across patients with CMS and without CMS. Bars reflect within-group percentages. In terms of tumor pathology, "Other" signifies any other tumor type in our sample excluding medulloblastoma (e.g., astrocytoma and ependymoma).

Age at diagnosis [$F(1,49) = .266$, $p = .608$], extent of tumor resection [$\chi^2(1) = .399$, $p = .819$], and tumor location [$\chi^2(1) = 4.496$, $p = .106$] did not differ between children with CMS versus children without CMS (see Table 2.1). Although the majority of patients with CMS and without CMS had midline tumors (e.g. vermis, 4th ventricle), 75% of those who had right cerebellar hemispheric tumors presented with CMS. Of the patients with left cerebellar hemispheric tumors, none presented with CMS.

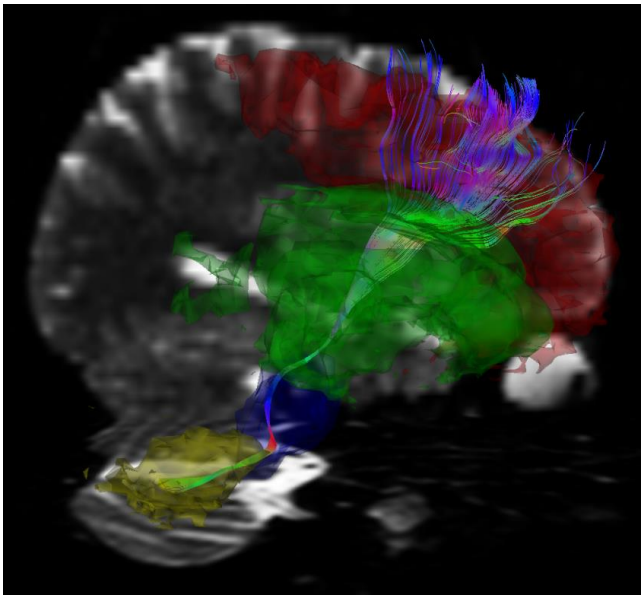
We entered the three predictor variables above – handedness, tumor size, and tumor pathology – into a logistic regression model to determine the greatest predictor(s) of CMS. The omnibus model was significant ($p = .006$) and extracted only handedness as the strongest predictor of CMS ($\beta = -2.71$, $p = .02$). Considering that right-handedness is most prevalent in the general population, we then examined predictors of CMS in only the right-handed patients. No variables

were extracted from this model but tumor pathology and tumor size both approached significance ($p = .067$ and $p = .089$, respectively).

2.4.2 Neuroanatomical Differences in Cerebellar Mutism Syndrome

Bilateral CTC pathways were delineated in all children (see Figures 2.1 and 2.3). A multivariate group effect was observed for DTI indices of the right cerebellar region of the CTC pathway connecting this area with left frontal cortex ($\Lambda = .763$, $p = .015$). Specific univariate analyses showed significant group differences in MD [$F(2,72) = 6.737$, $p = .002$], AD [$F(2,72) = 4.814$, $p = .011$], and RD [$F(2,72) = 4.012$, $p = .022$] (see Table 3.2 for means and standard deviations). Post-hoc analyses revealed that children with CMS had higher mean MD and AD ($ps < .01$) within the right cerebellar region compared to children without CMS and healthy controls. A significant difference in RD was also evident between children with CMS and healthy controls ($p < .01$); this effect approached significance between children with CMS and those without CMS ($p = .051$).There were no differences between children without CMS and healthy controls for the right cerebellar region. Further, no differences were found between groups for DTI indices of the remaining regions of the CTC pathway connecting the right cerebellum with left frontal cortex. The groups did not differ on the DTI indices within the CTC pathway connecting the left cerebellar hemisphere with the right frontal cortex.

Figure 2.3 A sagittal view of the CTC pathway connecting right cerebellar hemispheric white matter with left frontal cortex via thalamus (in multicolor).



The left frontal anatomical region of the CTC pathway falls within the red segmentation, the internal capsule/thalamus region of the pathway in the green segmentation, the midbrain/pons region of the pathway in the blue segmentation, and the cerebellar hemispheric white matter region of the pathway in the yellow segmentation. Generated with MedINRIA.

Table 2.2 Means and standard deviations of DTI indices.

CTC Pathway Anatomical Region	CMS				No CMS				Controls			
	FA	MD (mm^2/s)	AD (mm^2/s)	RD (mm^2/s)	FA	MD (mm^2/s)	AD (mm^2/s)	RD (mm^2/s)	FA	MD (mm^2/s)	AD (mm^2/s)	RD(mm^2/s)
Left Frontal	449×10^{-3} (81×10^{-3})	768×10^{-6} (37×10^{-6})	1171×10^{-6} (67×10^{-6})	567×10^{-6} (68×10^{-6})	425×10^{-3} (53×10^{-3})	776×10^{-6} (38×10^{-6})	1156×10^{-6} (67×10^{-6})	578×10^{-6} (121×10^{-6})	423×10^{-3} (52×10^{-3})	777×10^{-6} (35×10^{-6})	1154×10^{-6} (78×10^{-6})	588×10^{-6} (44×10^{-6})
Left Thalamus/Internal Capsule	515×10^{-3} (58×10^{-3})	762×10^{-6} (45×10^{-6})	1237×10^{-6} (64×10^{-6})	524×10^{-6} (62×10^{-6})	539×10^{-3} (67×10^{-3})	746×10^{-6} (36×10^{-6})	1251×10^{-6} (106×10^{-6})	488×10^{-6} (120×10^{-6})	509×10^{-3} (38×10^{-3})	751×10^{-6} (31×10^{-6})	1215×10^{-6} (63×10^{-6})	519×10^{-6} (33×10^{-6})
Left Midbrain/Pons	457×10^{-3} (56×10^{-3})	903×10^{-6} (133×10^{-6})	1346×10^{-6} (150×10^{-6})	682×10^{-6} (132×10^{-6})	491×10^{-3} (67×10^{-3})	809×10^{-6} (105×10^{-6})	1264×10^{-6} (169×10^{-6})	571×10^{-6} (142×10^{-6})	474×10^{-3} (26×10^{-3})	846×10^{-6} (131×10^{-6})	1285×10^{-6} (180×10^{-6})	627×10^{-6} (109×10^{-6})
Right Cerebellum	466×10^{-3} (63×10^{-3})	**$\underline{775 \times 10^{-6}}$** ($101 \times 10^{-6}$)	**$\underline{1191 \times 10^{-6}}$** ($135 \times 10^{-6}$)	**567×10^{-6}** (99×10^{-6})	461×10^{-3} (110×10^{-3})	$\underline{712 \times 10^{-6}}$ (56×10^{-6})	$\underline{1119 \times 10^{-6}}$ (89×10^{-6})	500×10^{-6} (128×10^{-6})	485×10^{-3} (55×10^{-3})	**696×10^{-6}** (61×10^{-6})	**1103×10^{-6}** (90×10^{-6})	**492×10^{-6}** (60×10^{-6})

Means and standard deviations (in parentheses) for regional DTI indices of the CTC pathway connecting the right cerebellar hemisphere with the left frontal cortex via the left thalamic nuclei for children with CMS, children without CMS, and healthy control children. Bolded cells indicate a significant mean difference between children with CMS and healthy control children at $p < 0.01$, while underlined numbers in cells indicates a significant mean difference between patients with CMS and patients without CMS at $p < 0.01$.

Our findings above indicate that damage to the CTC pathway connecting the right cerebellum with left frontal cortex may underlie CMS. Based on the neuroanatomical difference we found between patients with CMS and patients without CMS, other predictor variables may have an effect on neuroanatomical structure. Consequently, we examined whether the pre-surgical and clinical predictors we found to be related with CMS were also associated with right cerebellar microstructure within this pathway. Because MD of the right cerebellar region of the CTC pathway produced the strongest effect between patients with CMS and without CMS, tumor size, handedness, and tumor pathology were regressed on right cerebellar MD. This model was significant [$F(1,37) = 12.108$, $p = .001$], and again, only handedness was a significant predictor of right cerebellar white matter microstructure within the CTC pathway ($\beta = .497$, $p = .001$).

2.5 Discussion

This is the first study to include presurgical and clinical variables as well as neuroimaging to determine the risk factors of CMS following treatment for pediatric PF tumors. We observed a number of novel findings. Based on these findings we have identified a neuroanatomical substrate associated with CMS and have laid the foundation for the development of an integrated model predicting those children most at risk for CMS following surgery.

A novel finding was that the majority of left-handed children in our sample presented with CMS following surgery. Further, CMS was observed more frequently in patients with aggressive tumors (medulloblastoma) and patients with larger tumors. This finding is consistent with previous work showing that CMS occurs more often in patients that require a more radical resection of tumors (Van Calenbergh et al., 1995). Notably, all children who were left-handed and treated for medulloblastoma presented with CMS post-surgically. There is a known vulnerability of left-handed children for neurological problems including learning disabilities (Geschwind & Behan, 1982; Lewin, Kohen, & Mathew, 1993), autism (Lewin et al., 1993), and epilepsy (Lewin et al., 1993).

Novel to the literature, we have demonstrated that compromise to the CTC pathway at the level of the cerebellum is implicated in CMS. Importantly, it is the unilateral damage to right cerebellar white matter that distinguished between patients who presented with CMS and those who did not. The specific insult seen within this pathway region is evidence that PF tumor

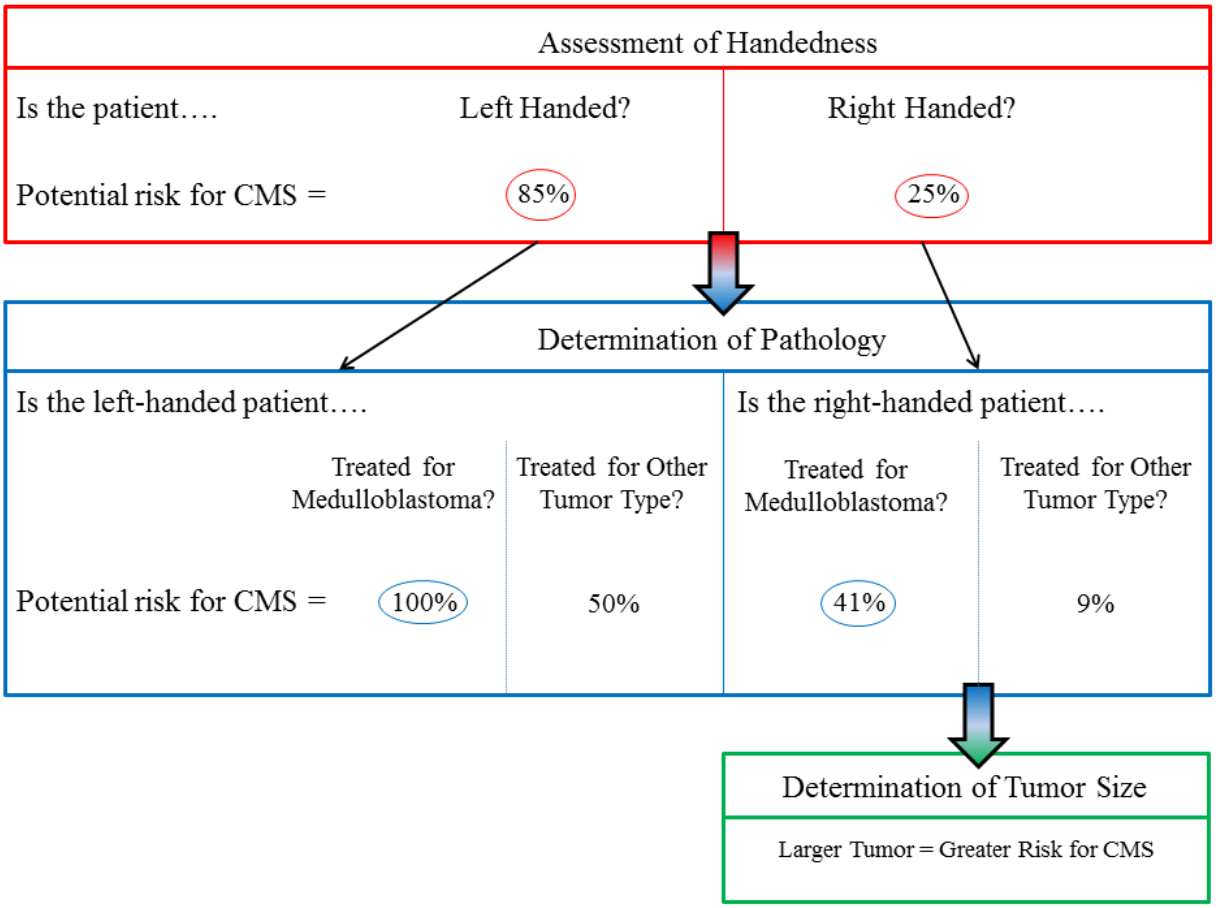
resection may be associated with an interruption of cerebellocerebral communication. This disruption may contribute to the resultant problems in the coordination and processing of speech-language seen in CMS.

Lesions of the cerebellum can produce ataxia and dysarthria – particularly lesions to the right cerebellar hemisphere (Fiez, Petersen, Cheney, & Raichle, 1992) – and functionally, the cerebellum has been implicated in verb generation (Schmahmann, 2004). Deficits in the initiation of language, verbal fluency, and word finding ability have been found in children following PF tumor resection (Levisohn et al., 2000). Interestingly, impairment in verbal intelligence and complex language tasks was observed in children who had undergone resection of cerebellar tumors and subsequently sustained damage to the right cerebellar hemisphere (Riva & Giorgi, 2000a). Lesions of the right cerebellum may deprive left hemispheric cortical language areas of essential modulatory input, resulting in errors in language processing (Fiez et al., 1992). It is known that left frontal regions are important in mediating speech production and expressive language (Broca, 1861; Geschwind, 1971; Mayeux & Kandel, 1991; Knecht et al., 2000a; Knecht et al., 2000b). Hence, we provide evidence that the CTC pathway connecting the right cerebellum with areas of the brain important for speech production and expressive language (left frontal regions) is disrupted in CMS. It may be the axonal degeneration and loss of myelination within the right cerebellar region of the CTC pathway that is associated with CMS. We did not find group differences in any other pathway region. As CMS is typically a post-surgical syndrome, it is logical that we would not initially expect compromise in any other region of the pathway. The deterioration of white matter pathways proximal to the cerebellum may take time to become evident; further damage within the pathway (e.g. in pons and eventually thalamic and frontal cortex) would be expected based on extent of diaschisis (i.e. progression of compromise to areas "downstream" of the initially damaged region at time of resection).

If we can identify patients who have a high risk of presenting with CMS following surgery, clinicians may be able to mitigate its symptoms. CMS may not be due solely to the effects of surgery and pre-surgical variables may play a more prominent role in predicting CMS (Di Rocco et al., 2011). Indeed, our results show that left-handedness predicts both CMS and CTC pathway white matter outcome following treatment for pediatric PF tumors. These parallel findings suggest that left-handed patients are at a greater risk for CMS following surgery as well as being more vulnerable to CTC pathway white matter damage. In right-handed patients it appears that

tumor size, along with pathology may be associated with CMS. In light of our findings, we have proposed a schema for determining level of risk for CMS (Figure 2.4). This model may have implications for the clinical management of PF tumors and in lowering the risk for CMS. If compromise to the right cerebellar hemisphere is probable (e.g. the tumor is within right hemisphere of PF or this hemisphere will sustain damage due to accessing the tumor), steps by surgeons may be warranted to ensure the preservation of healthy tissue within this region. Further, if patients are left-handed and have medulloblastoma, more caution may be warranted for preserving as much right cerebellar hemispheric white matter as possible while still ensuring successful removal of tumor tissue. However, prospective validation of our findings is necessary to confirm that this proposed schema can be applied to the general population of children treated for brain tumors.

Figure 2.4 A potential schema for CMS risk, based on our quantitative and qualitative observations of presurgical and clinical variables.



According to this schema left-handed patients are highly likely to present with CMS (85%); this chance rises to 100% if the left-handed patient is treated for medulloblastoma. Based on our sample, right-handed patients have a 25% chance of presenting with CMS in general; this chance becomes 41% if the right-handed patient is diagnosed with medulloblastoma. Further, larger tumor size is associated with greater risk for CMS in right-handed patients. Tumor size was not found to be a factor for CMS risk in our sample of left-handed patients. Under the determination of pathology section, "Other Tumor Type" includes ependymoma and low grade glioma/astrocytoma, among others.

Our findings also have bearing on the implementation of preventative treatment plans for speech-language deficits following surgical intervention. Administering Bromocriptine (a dopamine agonist) following onset of CMS has shown some promise in mitigating akinetic mutism, (Catsman-Berrevoets, van Dongen, & Zwetsloot, 1992; Caner, Altinors, Benli, Calisaneller, & Albayrak, 1999) and has been shown to produce some (but inconsistent) resolution of cerebellar mutism. However, the mechanism through which these agents act on CMS is unknown and requires further research; knowledge gleaned from our present work is important in examining such mechanisms.

This study encompasses one of the largest samples for which both clinical and imaging data are available in the CMS literature. However, there are some limitations often seen in studies involving clinical samples. Given the low base rate for left handedness in the population and the distribution of tumor pathology in our sample, cell sizes within these particular pre-surgical and clinical variables were relatively small. Further, a family history of sinistrality was not examined for left-handed patients; this demographic information would be important to note in future studies to aid in elucidating whether left-handedness is related to genetic/familial factors or pathological (i.e. due to the neurological illness). Though premorbid handedness was considered to reflect family history in the present study, it may be that the presence of the tumor had an early effect on handedness (i.e. may have facilitated a predisposition for pathological left-handedness). It is important to note that though MB is a fast growing tumor, the median age at time of diagnosis is 7 years (Dhall, 2009), and handedness is relatively well established by age 3 (but degree of lateralization can continue to develop up to 7 years of age) (McManus et al., 1988). Additionally, in order to avoid unnecessary delay in treating critically ill patients, DTI sequences are not typically included in pre-surgical MRI protocols in our institutions. Thus, there was a lack of pre-operative DTI scans to compare CTC pathways pre- and post-treatment (which is the reason we used healthy control children as a comparison). Further, given the delay between surgery and neuroimaging for our study, we cannot distinguish between late DTI changes caused

by functional alterations in CMS versus DTI evidence of surgical injury (which may have caused CMS). It is nevertheless important to understand DTI white matter outcome measures in CMS, whether they are early or late, in our endeavor to predict a neuroanatomical correlate of this syndrome. In future studies it will be important to examine CTC pathway microstructure and the outcome and progression of CMS symptoms. Findings of this nature could also be correlated with changes in CMS symptomology to determine how, for example, mutism or behavioral problems are resolved in the weeks following treatment.

In summary, we have provided a clinical schema based on our quantitative and qualitative observations and have elucidated a neuroanatomical substrate that may contribute to the occurrence of CMS following treatment for PF tumors. We propose that left handedness pre-surgically, larger tumor size, and presence of higher grade tumor, as well as white matter damage within the right cerebellar region of the CTC pathway are associated with CMS. It will be important to prospectively test our model in future clinical samples. Our findings contribute to the growing body of research on the predictors of CMS in pediatric brain tumor patients. This knowledge may be of critical importance to oncological practice for surgical planning and implementation of preventative and/or mitigative measures to reduce speech-language morbidity and other symptoms associated with CMS.

2.6 Acknowledgements

This work was supported by the Pediatric Oncology Group of Ontario Research Unit (PRU), C^{17} Research Network, and the Canadian Cancer Society.

Chapter 3
Visualization and Segmentation of Reciprocal Cerebrocerebellar Pathways in the Healthy and Radiated Brain

Law, N., Greenberg, M., Bouffet, E., Laughlin, S., Taylor, M. D., Malkin, D., Liu, F., Moxon-Emre, I., Scantlebury, N., & Mabbott, D. Visualization and segmentation of reciprocal cerebrocerebellar pathways in the healthy and radiated brain. Under Review, *Human Brain Mapping*.

This Chapter may not exactly replicate the final version submitted to *Human Brain Mapping* (revise and re-submit).

3 Visualization and Segmentation of Reciprocal Cerebrocerebellar Pathways in the Healthy and Radiated Brain

3.1 Abstract

Detailed information regarding the neuroanatomy of reciprocal cerebrocerebellar pathways is based on well-documented animal models. This knowledge has not yet been translated to humans, in that reciprocal cerebrocerebellar pathways have not been shown in their entirety. Little is known about the maturational time course of these pathways or the impact of injury on cerebrocerebellar connections in the developing brain. We investigated the impact of injury and age on cerebrocerebellar pathway microstructure using diffusion tensor imaging (DTI). We used medulloblastoma (MB) as an injury model due to the known impact of tumor and treatment on one of the main nodes of cerebrocerebellar pathways – the cerebellum. Magnetic Resonance Imaging was obtained at the Hospital for Sick Children for 38 healthy children (HC) and 34 children treated for MB. We used DTI and probabilistic tractography to delineate reciprocal cerebrocerebellar pathways and segment the pathways into their component parts: the cerebro-ponto-cerebellar (CPC) pathway into cerebro-ponto and ponto-cerebellar pathways; and the cerebello-thalamo-cerebral (CTC) pathway into cerebello-rubro, rubro-thalamo, and thalamo-cerebral pathways. Means and standard deviations for DTI indices fractional anisotropy (FA) and mean, axial, and radial diffusivity (MD, AD, and RD) were calculated for each segment. Three age groups were considered: childhood (7-11 years), early adolescence (11.01-13.99 years), and late adolescence (14-18 years). We compared pathway DTI measures between HC and MB and across age groups. Children treated for MB showed compromise to cerebrocerebellar pathways compared to controls – particularly within posterior segments of both the CPC and CTC pathways – indicated by lower FA, and higher MD, AD, and RD (ps < .01). Further, differences in pathway microstructure between MB and HC groups were evident in early and late adolescence, but not in childhood (ps < .01). We have outlined, segmented, and examined discrete, reciprocal cerebrocerebellar connections in the developing brain. We found evidence of injury to these pathways in the radiated brain, but this damage was not uniform across the pathways. Posterior segments of the CPC and CTC pathways appeared to be most affected by treatment for MB, though several anterior segments also showed evidence of damage. Group

differences in cerebrocerebellar microstructure were driven by pathway segment (posterior) and age cohort (adolescence), which may reflect the extent of injury the PF sustains following treatment for MB and age cohort differences in radiation treatment protocol. These findings support the late effects literature that white matter injury emerges in the years following treatment for MB.

3.2 Introduction

Our current understanding of the structural and functional connectivity of cerebrocerebellar circuits is based on well-documented animal models and several adult human studies, but the structure of reciprocal cerebrocerebellar pathways has not yet been shown in its entirety in humans. Moreover, a detailed segmentation of these continuous pathways to provide insight into localized microstructure of cerebrocerebellar circuitry has yet to be completed. We established an approach to document these reciprocal connections and their segmentations in the developing human brain and in the injured developing brain. This knowledge is essential to our understanding of both the development of cerebrocerebellar communication and what may occur to these connections when there is a breakdown or disruption to this network. We used medulloblastoma, the most common malignant CNS tumor in childhood, as a brain injury model due to the known impact of tumor and treatment on the cerebellum. We also investigated the impact of age on cerebrocerebellar pathway structure in the healthy and injured developing brain to provide important information regarding the course of cerebrocerebellar communication development and the specificity of white matter damage in a brain injury model. Lastly, pertinent to our brain injury model, medulloblastoma, our findings have the potential to contribute to the understanding of the late effects of treatment for this disease.

The cerebrocerebellar system represents one of the largest white matter pathways in the CNS (Apps & Watson, 2009), comprised of a closed-loop circuit connecting the cerebellum with cerebral cortex. Cerebro-ponto-cerebellar (CPC) connections serve to relay information from the cortex to cerebellum via pontine nuclei; the cerebellum returns these projections to the cerebral cortex by way of thalamic nuclei, via cerebello-thalamo-cerebral (CTC) connections (Thach, 1972; Brodal, 1978; Thach & Jones, 1979; Asanuma et al., 1983; Middleton & Strick, 1997; Schmahmann & Pandya, 1997b, 1997a; Middleton & Strick, 2000, 2001). Thus, CPC and CTC pathways serve as bilateral, reciprocal cerebrocerebellar feedforward and feedback mechanisms.

These connections are thought to underlie not only motor control and timing of movement (Glickstein, 1992; Stein & Glickstein, 1992; Glickstein, 1993; Brodal & Bjaalie, 1997), but many aspects of cognition and behaviour (Ivry & Baldo, 1992; Kim et al., 1994; Fiez et al., 1996; Allen et al., 1997; Desmond et al., 1998; Schmahmann, 2004; Chen & Desmond, 2005; Law et al., 2011).

Evidence for the basis and structure of these pathways is derived primarily from non-human primate studies; cerebrocerebellar connections have been described post-mortem and in-vivo using virus tracers to label synaptically linked neurons (Middleton & Strick, 1994, 2001; Kelly & Strick, 2003). As the main cerebellar afferent pathway, CPC fibres arise from nerve cells in the frontal cortex and descend through the posterior limb of the internal capsule, terminating on the pontine nuclei (Schmahmann, 1996; Bähr et al., 2005). Fibres then decussate within the pons and enter the contralateral cerebellar hemisphere via the middle cerebellar peduncle (Schmahmann, 1996; Bähr et al., 2005). This feedforward portion of the cerebrocerebellar pathway is synaptically interrupted in the pontine nuclei (Brodal & Bjaalie, 1997), hence forming cerebro-ponto and ponto-cerebellar pathways. The CTC pathway is one of the main cerebellar efferent circuits, originating in deep cerebellar nuclei and projecting to the contralateral red nucleus (Schmahmann, 1996; Bähr et al., 2005). From the red nucleus, this pathway continues until it reaches synaptic relay nuclei in the thalamus; these fibres then ascend to terminate within the frontal cortex (Schmahmann, 1996; Bähr et al., 2005). Thus, the CTC pathway can be parsed into component pathways: cerebello-rubro, rubro-thalamo, and thalamo-cerebral.

Functional imaging in adult human populations has shown evidence of these pathways (Kim et al., 1994; Middleton & Strick, 1997, 2000; Dum & Strick, 2003; Allen et al., 2005). Furthermore, solitary (e.g. non-reciprocal) connections from cerebellum to cortex have been outlined using diffusion tensor imaging (DTI). These include cerebellar projections to frontal cortex (Salmi et al., 2010), and to prefrontal and posterior parietal cortices (Jissendi et al., 2008) in small samples of adult humans, and the connection between cerebellum and dorsolateral prefrontal cortex in children (Law et al., 2011; Law et al., 2012). DTI has also been used to define segments of pathways that constitute reciprocal cerebrocerebellar connections in adult humans: prefrontal connections to the cerebral peduncles (Ramnani et al., 2006) and cortico-pontine fibres (Habas & Cabanis, 2007a), comprising portions of the CPC pathway; and projections from the cerebral cortex to red nucleus, representing a portion of the CTC pathway

(Habas & Cabanis, 2006, 2007b). Though detailed information regarding reciprocal cerebrocerebellar pathways is based on well-documented animal models, this knowledge has not yet been translated to humans, in that reciprocal cerebrocerebellar pathways have not been shown in their entirety.

We used DTI and probabilistic tractography to define continuous, reciprocal cerebrocerebellar pathways in the developing human brain. Tractography defines white matter pathways based on regions of interest (ROIs) including a specific start point (i.e. seed point) and areas of relay or endpoints (i.e. way points). The main limitation of the above body of literature is a lack of utilizing anatomically-defined, known points of synapse within the pathways as ROIs to serve as seed and waypoints to define full, continuous, and reciprocal cerebrocerebellar pathways. In the current study, our intent was to rectify this problem by clearly delineating these pathways using DTI tractography combined with anatomically relevant seed and waypoints, based on known animal models of cerebrocerebellar connectivity. Further, we sought to segment these pathways based on synaptically-defined points along the circuits to produce discrete pathways: using cerebro-ponto and ponto-cerebellar segmentations for the CPC pathway, and cerebello-rubro, rubro-thalamo, and thalamo-cerebral segmentations for the CTC pathway. This segmentation is necessary to examine and compare localized regions of the pathway in injury and health, to determine differences in white matter development within each segment, and to identify areas of the pathway most affected by injury.

Once pathways were defined, we then examined their microstructure using DTI. DTI is an ideal technology to employ for these purposes because it generates indices that reflect white matter microstructure based on water molecule displacement and directionality (Basser, 1995). DTI indices include eigenvalues, λ_1, λ_2, λ_3; these eigenvalues are combined to provide summary measures of fractional anisotropy (FA) and mean diffusivity (MD), as well as axial and radial diffusivity (AD and RD, respectively). This data can in turn be used to infer the microstructural organisation of white matter and to identify whether injury to white matter regions or pathways (e.g. demyelination, axonal damage) is evident (Song et al., 2002; Mori & Zhang, 2006; Jones & Leemans, 2011). Lower measures of FA and higher measures of MD, AD, and RD are thought to reflect axonal degeneration and damage to the myelin sheath (Beaulieu, 2002; Song et al., 2002).

Maturation of white matter regions and pathways is an important factor in development throughout childhood and adolescence (Barnea-Goraly et al., 2005). In the healthy developing brain, age-related changes in both cerebral and cerebellar white matter have been documented. FA increases and MD decreases from birth to 11 years of age (Schneider, Il'yasov, Hennig, & Martin, 2004) and continues into adolescence and young adulthood (Qiu, Li, Liu, Xie, & Wang, 2010). However, little is known about the connections between the cerebellum and cortex in the developing brain and how age may impact them. Moreover, it has yet to be determined what happens to these cerebrocerebellar pathways when the developing brain is injured. Hence, we investigated cerebrocerebellar pathway microstructure and the impact of age on these pathways in the healthy developing brain and in a brain injury model: medulloblastoma (MB), the most common malignant pediatric brain tumor arising in the posterior fossa (PF). MB is typically treated with a combination of surgery, craniospinal radiation therapy (CRT), and chemotherapy (CTX) and significant neurotoxicity has been documented in this population post-treatment (Mulhern et al., 2001; Khong et al., 2003; Reddick et al., 2005; Mabbott et al., 2006b; Law et al., 2011; Law et al., 2012). Children treated for MB provide an ideal brain injury model to investigate cerebrocerebellar connections for several reasons. First, children treated for MB may show significant compromise to these connections because one of the main nodes in the pathway is impacted due to mass effect of tumor and both whole-brain and targeted PF/tumor bed CRT. Additionally, the structural organization of these pathways may have important implications for cognitive and behavioural outcome in children following treatment for MB. It is well documented that late effects following treatment for MB include multiple neurocognitive and psychosocial problems, though many of these are attributed to diffuse white matter damage following whole-brain CRT (Mulhern et al., 2001; Reddick et al., 2003; Mabbott et al., 2006a; Mabbott et al., 2006b; Law et al., 2011). Examining cerebrocerebellar connections and their localized segments will provide insight into the regions along these circuits that sustain the most damage from treatment for MB and at what age we may see white matter damage emerge in this population.

We predicted that we would successfully obtain and segment cerebrocerebellar connections into their distinct and reciprocal feedforward and feedback loops in all participants. We also predicted that DTI indices reflective of white matter injury (e.g. lower FA and higher MD, AD, and RD) would be evident in children treated for MB relative to healthy children, particularly for more

posteriorly located pathway segments (i.e. within the PF, such as cerebello-rubro, ponto-cerebellar), as these regions are likely to sustain significant injury due to tumor and treatment effects. Additionally, age may have an effect on pathway structure and contribute to group differences, and will inform us of the developmental bias of certain regions of cerebrocerebellar pathways relative to others. An interaction of group, age, and pathway segment, if found, would indicate that there is an impact of treatment for MB on distinct regions of the cerebrocerebellar pathways relative to others at certain stages of development.

3.3 Methods

3.3.1 Participants

The current sample included 34 children treated for MB treated with surgery, CRT, and CTX, and 38 healthy control children (HC) without any previous neurological or clinical disorders, history of prior acquired brain injury, developmental delay, or learning disability (see table 3.1). Patients were excluded from the study if they had tumors outside the PF (i.e. supratentorial), were treated for recurrent disease, had diffuse brainstem glioma, were receiving palliative care, or had a premorbid history of neurological or learning disabilities. Patients were recruited from the brain tumor program and through oncology and psychology clinics at the Hospital for Sick Children (SickKids) as well as via information letters mailed out to families (following a database review of children treated for MB at SickKids). HC were recruited through advertisement in newspapers and within the hospital, through families (i.e. siblings), and through friends and family of the investigators. All participants were seen at SickKids and the protocol for this study was approved by the Research Ethics Board.

All participants provided written informed consent or assent and parental consent was obtained where applicable. Demographic variables were compared between HC and MB groups (Table 3.1). There were no differences between the groups for sex [$\chi^2_{(1)} = .076$, $p = .782$], age at time of MRI scan [$F(1,70) = .001$, $p = .976$], type of MRI (1.5T versus 3T, see below) [$\chi^2_{(1)} = 2.006$, $p = .157$], and handedness [$\chi^2_{(1)} = .713$, $p = .398$]. Mean full-scale intelligence (FSIQ) [$F(1,70) = 53.437$, $p < .001$], measured by the Wechsler Abbreviated Scale of Intelligence (WASI) was significantly higher in the HC group compared to children treated for MB.

To simplify and examine the impact of age on the structure of cerebrocerebellar pathways, we used two tertiles (11 and 14) to split age across groups into thirds, producing three age bands: 7-11 years, 11.01-13.99 years, and 14 years and over (Table 3.1). Because we had no *a priori* assumption of the time course or trajectory of cerebrocerebellar pathway development, this unbiased approach of splitting participants into age groups was chosen. Though, this tertile split of age roughly coincides with major milestones in development: age 7-11 marks a time of middle childhood or pre-adolescence prior to puberty; age 12-14 is early adolescence in which puberty takes place, and ages 15-18 reflect a transition from late adolescence into young adulthood. No differences were found when examining the distribution of participants in both the HC and MB groups for age tertiles [$\chi^2_{(2)} = 1.714$, $p = .424$]. Within the MB group, there were no differences between age tertiles and age at diagnosis [$F(2,31) = 1.589$, $p = .220$]; there was, however, a significant difference for time since diagnosis/treatment to testing between age tertiles [$F(2,31) = 10.169$, $p < .001$] with the 7-11 year group being fewer years out from treatment compared to the 14 years and over group ($p < .001$). Lastly, when comparing radiation dose between age tertiles, there was no significant difference for treatment with standard- versus reduced-dose CRT + PF/tumor bed boost [$\chi^2_{(2)} = 3.730$, $p = .155$]. A recent study has shown that it may be radiation field size, not radiation dose alone, that has implications for late effects following treatment for MB (Moxon-Emre et al., 2014). Between age tertiles, there was a significant difference when considering radiation dose and field together (i.e. reduced CRT + tumor bed boost versus "other", more intensive protocols: reduced CRT + PF boost, standard CRT + tumor bed boost, and standard CRT + PF boost) [$\chi^2_{(2)} = 6.103$, $p = .047$]. A greater proportion of the childhood group received the less intensive reduced CRT + tumor bed boost while a greater proportion of the late adolescence group were treated with the "other" protocols (see Table 3.1).

Table 3.1 Demographic and medical variables for the MB and HC groups.

	MB n = 34	HC n = 38
Sex (Male : Female)	19 : 15	20 : 18
Age at scan (years)		
Mean (SD)	12.74 (3.29)	12.72 (2.95)
Range	8.04 – 18.98	7.02 – 18.87
Age tertiles		
7-11 years (Childhood)	13	10
11.01-13.99 years (Early Adolescence)	9	15
14 years and over (Late Adolescence)	12	13

Handedness[4]		
Right	27 (79.4%)	33(86.8%)
Left	7 (20.6%)	5 (13.2%)
MRI Scan Type		
1.5T	14 (41.2%)	22 (57.9%)
3T	20 (58.8%)	16 (42.1%)
WASI FSIQ		
Mean (SD)	88.90 (15.82)	113.82 (14.02)
Age at diagnosis (years)		
Mean (SD)	7.12 (2.81)	N/A
Range	1.32 – 15.16	N/A
Age tertiles – Mean (SD)		
Childhood	6.77 (2.17)	N/A
Early Adolescence	6.29 (2.09)	N/A
Late Adolescence	8.31 (3.66)	N/A
Time since diagnosis to testing (years)		
Mean (SD)	5.71 (3.80)	N/A
Range	1.10 – 13.64	N/A
Age tertiles – Mean (SD)		
Childhood	3.00 (1.76)	N/A
Early Adolescence	5.43 (2.35)	N/A
Late Adolescence	8.42 (4.25)	N/A
Tumor Size (mm^2)[5]		
Mean (SD)	2019.31 (817.23)	N/A
Range	957 – 3770	
Tumor Location within PF		
Midline	31 (91.2%)	N/A
Left Hemispheric	1 (2.9%)	N/A
Right Hemispheric	2 (5.9%)	N/A
Surgical outcome/extent of resection (%)		
Greater than 95% of the tumor resected	31 (91.2%)	N/A
Between 50% and 95% of the tumor resected	3 (8.8%)	N/A
Hydrocephalus		
No hydrocephalus	7 (20.6%)	N/A
Hydrocephalus not requiring treatment (resolved)	11 (32.3%)	N/A
Hydrocephalus requiring medical intervention or CSF diversion	16 (47.1%)	N/A
EVD and/or shunt		
Yes	18 (52.9%)	N/A
No	16 (47.1%)	N/A
Ventriculostomy		
Yes	5 (14.7%)	N/A
No	29 (85.3%)	N/A
Presence of post-operative/residual complication[6]		
Yes	31	N/A
No	3	N/A

[4] Numbers reflect handedness at time of current assessment (note that for 3 MB, handedness changed post-operatively). Percentages represent within group totals.

[5] Tumor size was calculated by multiplying the two largest measurements of the tumor from an anatomical MRI scan. Measurements are in mm^2. Tumor size dimensions were not available for 6 MB.

[6] Indicates the presence of a single post-operative or residual complication, whether a cerebellar complication (i.e. ataxia, mutism, dysarthria) or other complications (i.e. hydrocephalus, nystagmus, diplopia, hemiparesis, hearing impairment, cranial nerve deficits). Presence of multiple post-operative complications indicates the incidence of 2 or more of the complications listed above.

Presence of multiple post-operative complications		
Yes	21	N/A
No	13	N/A
Radiation Dose (cGy) and Field[7]		
Standard CRT Dose + Tumor Bed Boost[8]	3	N/A
Median Head/Spine Dose (Range)	3600 (3060 – 3600)	N/A
Median Boost Dose (Range)	1980 (1800 – 2340)	N/A
Standard CRT Dose + PF Boost	6	N/A
Median Head/Spine Dose (Range)	3600 (3060 – 3600)	N/A
Median Boost Dose (Range)	1800 (1800 – 1980)	N/A
Reduced CRT Dose + Tumor Bed Boost	16	N/A
Median Head/Spine Dose (Range)	2340 (1980 – 2340)	N/A
Median Boost Dose (Range)	3240 (3060 – 3240)	N/A
Reduced CRT Dose + PF Boost	9	N/A
Median Head/Spine Dose (Range)	2340 (1980 – 2340)	N/A
Median Boost Dose (Range)	3150 (3060 – 3600)	N/A
Radiation Dose and Field by Age Tertile		
Childhood		
Reduced CRT Dose + Tumor Bed Boost	10	N/A
Other	3	N/A
Early Adolescence		
Reduced CRT Dose + Tumor Bed Boost	2	N/A
Other	7	N/A
Late Adolescence		
Reduced CRT Dose + Tumor Bed Boost	4	N/A
Other	8	N/A
Chemotherapy[9]		
Yes	33 (97.1%)	N/A
No	1 (2.9%)	N/A

3.3.2 Neuroimaging Protocol

MRI measurements were performed at SickKids using either a GE LX 1.5T MRI scanner with 8 channel head coil (22 HC and 14 MB) or a Siemens 3T whole-body MRI scanner (Trio Tim syngo MR B17 system) with a 12-channel head coil (16 HC and 20 MB). The GE LX 1.5T MRI protocol included a 3D-T1 FSPGR gradient echo, inversion recovery-prepared sequence (IR time = 400ms, TE/TR = 4.2/10.056ms, 116-124 contiguous axial slices, NEX = 1, 256 x 192 matrix interpolated to 256 x 256, FOV = 240 x 240mm, rbw = 162.734kHz, slice thickness = 1.5mm) and a diffusion-weighted single shot spin echo DTI sequence with EPI readout (25-31

[7] All in the MB group received CRT at time of diagnosis, with the exception of one patient for which CRT was administered years following diagnosis, upon recurrence (age of diagnosis < 2 years, thus CRT was not considered upon initial treatment).
[8] Four radiation dose and field protocol were considered – reduced CRT dose + tumor bed boost versus "other" protocols: reduced CRT dose + PF boost, standard CRT dose + tumor bed boost, and standard CRT dose + PF boost.
[9] Agents included Carboplatin, Cisplatin, Cyclophosphamide, Lomustine (CCNU), and Vincristine.

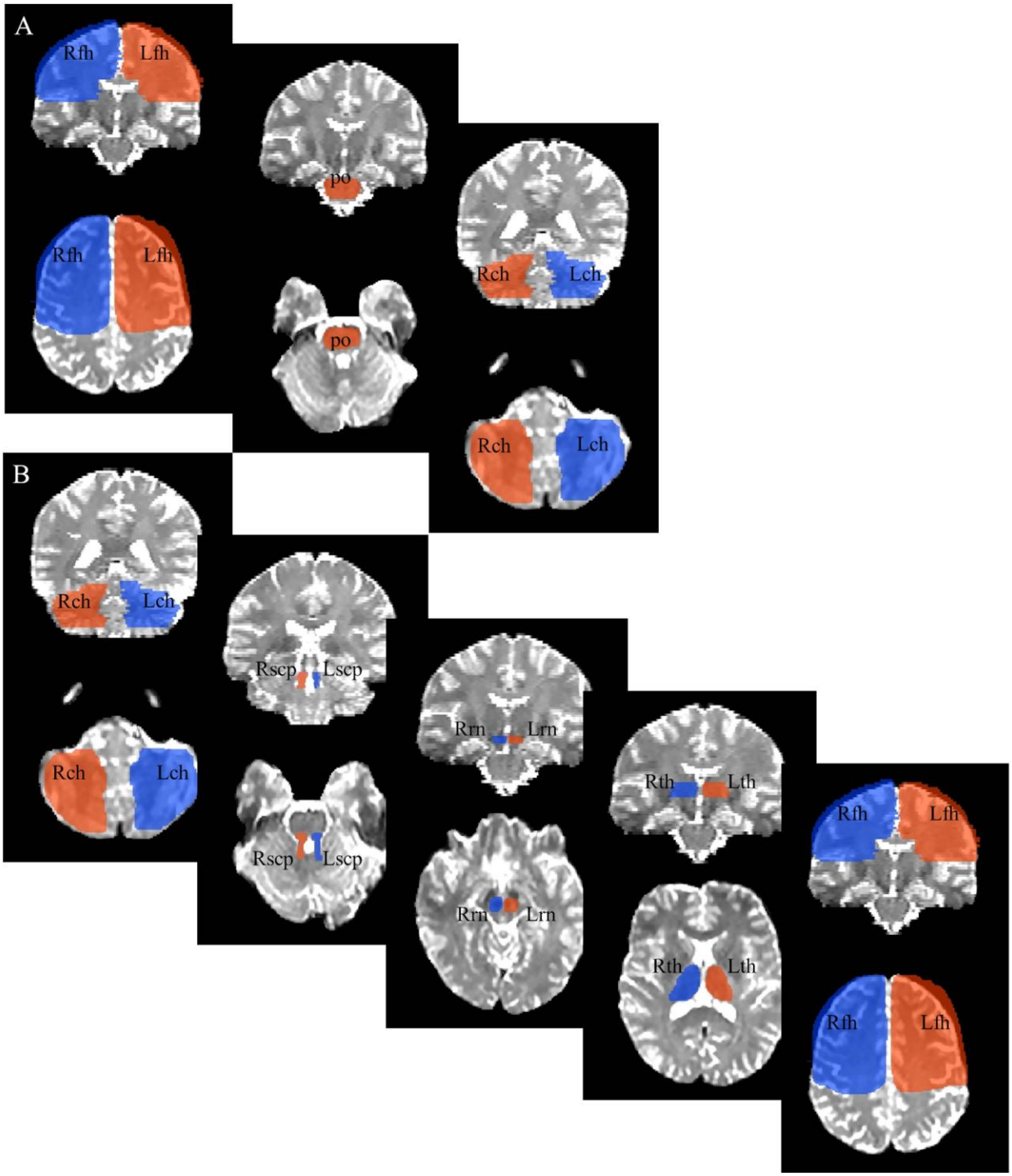
directions, b = 1000s/mm^2, TE/TR = 85.5/15000ms, 45-50 contiguous axial slices, NEX = 1, 128 x 128 matrix interpolated to 256 x 256, FOV = 240 x 240mm, rbw = 1953.12kHz, slice thickness = 3mm). The Siemens 3T MRI protocol utilized a T1 AX 3D MPRAGE Grappa 2 protocol (TE/TR = 3.91/2300ms, 160 contiguous axial slices, flip angle = 9°, 256 x 224 matrix, voxel size = 1mm ISO, FOV = 256 x 224mm) and diffusion-weighted single shot spin echo DTI sequence with EPI readout (30 directions, b = 1000s/mm^2, TE/TR = 90/9000ms, 70 contiguous axial slices, flip angle = 9°, voxel size = 2mm ISO, matrix = 122 x 122 interpolated to 244 x 244, FOV = 244 x 244mm). The images were pre-processed and DTI indices and maps (e.g. eigenvectors, FA, MD, AD, and RD) were calculated using the FMRIB Software Library (FSL) (Behrens et al., 2003a; Behrens et al., 2003b; Smith et al., 2004; Woolrich et al., 2009) to serve as a basis for probabilistic tractography. The 3T MRI was our preference for collecting imaging data for this study due to its higher field strength and thus, higher resolution ability. However, to ensure a greater sample size, it was necessary to use data acquired with the 1.5T MRI. Data was acquired at 1.5T for two reasons. First, due to the presence of external ventricular drains or shunts occasionally required as part of tumor treatment, a proportion of children treated for MB were ineligible to be scanned on the 3T (see Table 3.1); these devices are deemed 3T incompatible as artifact (e.g. susceptibility) is more prevalent at higher field strengths (Olsrud, Latt, Brockstedt, Romner, & Bjorkman-Burtscher, 2005). Second, due to the retrospective nature of this study, MB patients previously seen at 1.5T (when 3T was unavailable) were included in this study. We scanned one individual on both the 1.5T and 3T machines to compare the signal to noise ratios (SNR) for the zero diffusion weighted images (SNR = 28.5 for 1.5T and SNR = 70.7 for 3T). Because of the differing MRI protocol and SNR, we ensured to match HC and MB for scanner type for both the retrospective and newly acquired data. Further, MRI scanner type was included as a covariate in all analyses of imaging data.

3.3.3 ROI Placement and Standardization for DTI Tractography

To provide a standardized protocol for ROI placement, all ROIs were drawn on axial sections of the zero diffusion-weighted (B0) images of 10 randomly selected HC. The following ROIs were produced for all 10 individuals using FSL (Behrens et al., 2003a; Behrens et al., 2003b; Smith et al., 2004; Woolrich et al., 2009): left and right frontal hemispheric white matter; left and right thalamus; left and right red nucleus; pons; left and right superior cerebellar peduncles; and left

and right cerebellar hemispheric white matter (See Figure 3.1 for detailed description of ROI placement). The 10 sets of individually-delineated ROIs (11 ROIs per individual) were then combined into a single composite volume using Analyze Software (AnalyzeDirect) and registered to a template brain using Automated Image Registration (AIR) (Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998) software to produce template ROIs. Prior to tractography, the resultant template ROIs were registered onto each participant's B0 image using AIR (Woods et al., 1998). Once ROIs were brought into the native space for each participant, they were visually examined and, if necessary, smaller ROIs (e.g. superior cerebellar peduncle, red nucleus) were manually refined so that they covered only the appropriate region. For an outline of pathways of interest, their segmentations, and ROIs used, see Table 3.2.

Figure 3.1 ROIs used for probabilistic tractography.



Panel A: the ROIs used to delineate the bilateral CPC pathway. Panel B: the ROIs used to delineate the bilateral CTC pathway. Top boxes depict coronal sections and bottom boxes axial sections (in radiological orientation). Because left frontal hemisphere (Lfh) and right frontal hemisphere (Rfh) ROIs included the whole of the frontal lobe, an existing anatomical template protocol (described in Kabani et al., 2002; Mabbott et al., 2009; Law et al., 2011; Law et al., 2012) was employed to delineate these ROIs. Left thalamus (Lth) and right thalamus (Rth) ROIs were delineated using the third ventricle as the medial boundary and genu and posterior limb of the internal capsule

as anterior and lateral boundaries, respectively. At its most ventral and posterior aspect, Lth and Rth ROIs were terminated once the anterior and posterior commissures were no longer visible. The pons (po) ROI was drawn on the first dorsal/anterior slice that it was visible (e.g. trigeminal nerve and fourth ventricle just becoming apparent), using midbrain structures (e.g. cerebral peduncles) as the anterior boundaries, and medial lemniscus as caudal/posterior boundary, and was terminated once the first segment of basilar pons was encountered. The left red nucleus (Lrn) and right red nucleus (Rrn) ROIs were drawn on the first rostral midbrain slice in which it becomes visible, using the cerebral peduncles and substantia nigra as anterior/rostral and posterior/caudal reference points, respectively. The left superior cerebellar peduncle (Lscp) and right superior cerebellar peduncle (Rscp) ROIs were defined on the most dorsal slice in which the structure became present, avoiding the pons rostrally and the fourth ventricle caudally and medially, terminating once middle cerebellar peduncles were evident. Lastly, left cerebellar hemisphere (Lch) and right cerebellar hemisphere (Rch) ROIs included the cerebellar hemispheres, avoiding the vermis and fourth ventricle medially, and concluding once cerebellar white matter was no longer evident. ROIs of the same colour depict those used to define a pathway, with the exception of po, which was used for both the left and right (bilateral) CPC pathways.

Table 3.2 Delineating CPC and CTC pathways. Pathway type, side, and segmentations are detailed, as well as the ROIs used for probabilistic tractography.

Pathway	**CPC**		**CTC**	
Side	Left	Right	Left	Right
ROIs	**Seed point**: Left frontal hemisphere/lobe (Lfh)	**Seed point**: Right frontal hemisphere/lobe (Rfh)	**Seed point**: Left cerebellar hemisphere (Lch)	**Seed point**: Right cerebellar hemisphere (Rch)
	Way points: pons (po), Right cerebellar hemisphere (Rch)	**Way points**: pons (po), Left cerebellar hemisphere (Lch)	**Way points**: Left superior cerebellar peduncle (Lscp), Right red nucleus (Rrn), Right thalamus (Rth), Right frontal hemisphere/lobe (Rfh)	**Way points**: Right superior cerebellar peduncle (Rscp), Left red nucleus (Lrn), Left thalamus (Lth), Left frontal hemisphere/lobe (Lfh)
Segmentations	cerebro-ponto	cerebro-ponto	cerebello-rubro	cerebello-rubro
	ponto-cerebellar	ponto-cerebellar	rubro-thalamo	rubro-thalamo
			thalamo-cerebral	thalamo-cerebral

3.3.4 DTI Probabilistic Tractography and Pathway Segmentation

Probabilistic tractography was used to delineate bilateral CPC and CTC pathways connecting each cerebellar hemisphere with contralateral frontal cortex and to examine the microstructure of

pathways. This process was completed using FSL's Diffusion Toolbox (FDT) (Pollack, 1997; Robertson et al., 2006). To delineate the CPC pathway (Figure. 3.1A), the left (or right) frontal hemisphere was used as a seed point and the pons and right (or left) cerebellar hemisphere were waypoints. To delineate the CTC pathway (Figure 3.1B), the left (or right) cerebellar hemisphere was used as a seed point and the left (or right) superior cerebellar peduncle, right (or left) red nucleus, right (or left) thalamus, and right (or left) frontal hemisphere were waypoints (see Table 3.2). Thresholds of 10% were set for all pathways and, if necessary, pathways were edited to eliminate erroneous streamlines. Following the delineation of each pathway in its entirety, manual segmentation into component pathways was completed to examine discrete, localized microstructure of white matter comprising the pathways. Segmentations were based on known points of synapse within cerebrocerebellar pathways documented in animal models. The bilateral CPC pathway was parsed into two segments: cerebro-ponto and ponto-cerebellar pathways. Cerebro-ponto pathways included the whole of the CPC pathway within the forebrain and concluded once entrance into the pons was attained. Ponto-cerebellar pathways included the remainder of the CPC pathway from pons to contralateral cerebellum. The bilateral CTC was parsed into three segments: cerebello-rubro, rubro-thalamo, and thalamo-cerebral pathways. Cerebello-rubro pathways included the CTC pathway within the cerebellum and ipsilateral superior cerebellar peduncles, and concluded once it reached contralateral red nucleus. Rubro-thalamo pathways began within the red nucleus and terminated at its entrance into the thalamus. Thalamo-cerebral pathways thus comprised the remainder of the CTC pathway from thalamus to frontal cortex. Means and standard deviations for DTI indices FA, MD, AD, and RD were calculated for each segment of each pathway.

3.3.5 Statistics/Analytic Approach

We performed eight repeated-measures ANOVAs (side x segment), running DTI indices separately, with group and age tertiles as between-subject variables. The first four of these models examined FA, MD, AD, and RD of the CPC pathway between group and age using 2 side (left or right) x 2 segment (cerebro-ponto or ponto-cerebellar) repeated measures ANOVAs. The next four models examined FA, MD, AD, and RD of the CTC pathway using 2 side (left or right) x 3 segment (cerebello-rubro, rubro-thalamo or thalamo-cerebral) repeated measures ANOVAs. As part of these analyses, planned tests of simple effects were used to examine the *a*

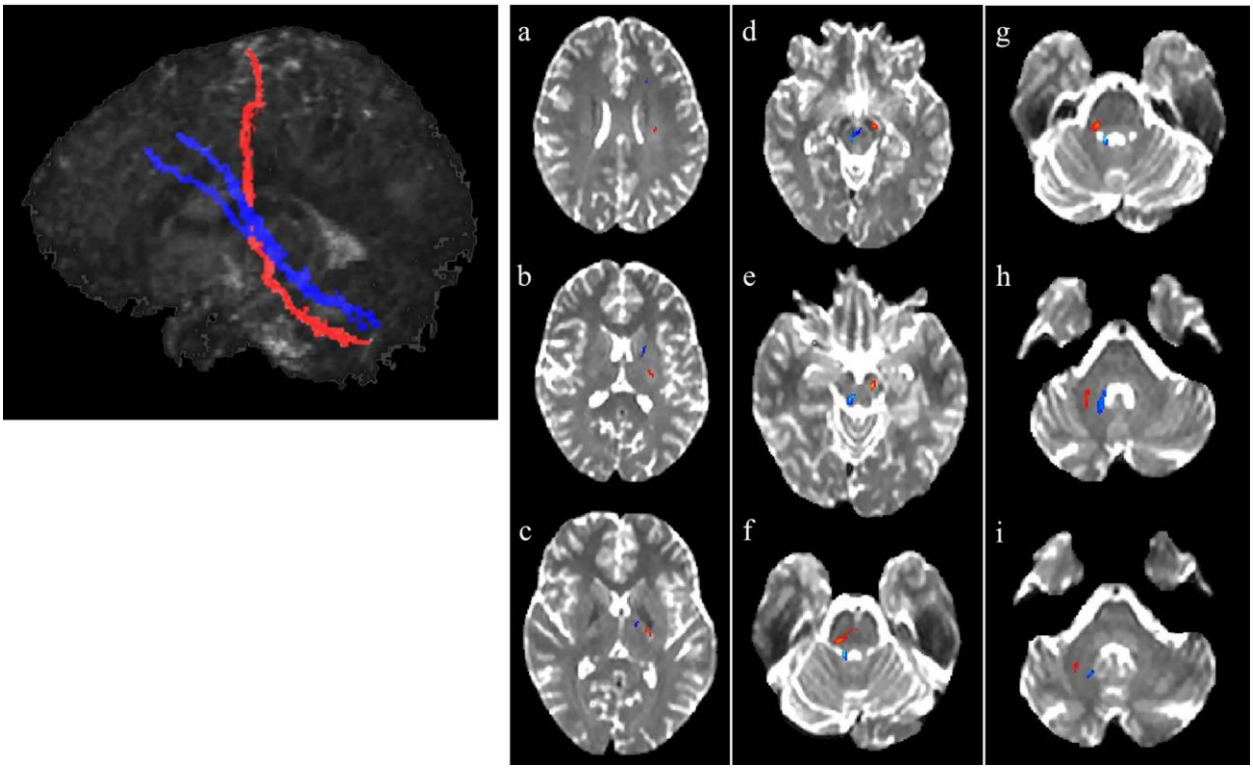
priori hypothesis that MB patients show compromise to white matter microstructure within the CPC and CTC pathways relative to HC. Due to the large number of contrasts, we corrected for multiple comparisons using the Bonferroni correction for all planned tests of simple effects.

3.4 Results

3.4.1 Visualization and Examination of Bilateral Reciprocal Cerebrocerebellar Pathways

CPC and CTC pathways were produced in all participants (Figure 3.2). Regardless of group, pathways were qualitatively similar. Pathway anatomical locations were confirmed by a neuroradiologist (SL). The CPC pathway connected frontal cortex with pontine nuclei via internal capsule and cerebral peduncle; after decussating in the pons, the CPC pathway proceeded into cerebellar hemispheric white matter via middle cerebellar peduncle. The CTC pathway connected cerebellar hemispheric white matter with contralateral red nucleus via superior cerebellar peduncle (decussating in the midbrain); from there, the CTC pathway continued ipsilaterally to thalamic nuclei before proceeding to frontal white matter.

Figure 3.2 CPC and CTC pathways connecting left frontal hemisphere with right cerebellar hemisphere in a healthy brain (radiological orientation).



The leftmost panel depicts the CPC (in orange) and CTC (in blue) pathways in their entirety in sagittal view (for visualization purposes). Panels a-i depict the CPC and CTC pathways from the frontal lobe to the cerebellum in axial sections. Panels a-c: the CPC and CTC pathways within the forebrain. Note the more rostral and anterior position of the CTC relative to the CPC pathway (which is more posterior and dorsal). Panels a-b depict the CPC and CTC pathways as they are situated within the frontal cortex. Panel c shows the CPC and CTC pathways after exiting the cerebral cortex but prior to entering midbrain. The CTC pathway is within the thalamus while the CPC pathway runs through the posterior limb of the internal capsule. Panel d-e: CPC and CTC pathways within the midbrain. Panel d shows the CTC pathway progressing through the red nucleus and beginning its decussation. The CPC pathway runs through the cerebral peduncles. Panel e shows the CPC pathway continuing through the cerebral peduncles and the CTC completing its decussation and progressing toward superior cerebellar peduncles. Panels f-i: CPC and CTC pathways within the hindbrain. Panels f-g show the CPC pathway as it decussates within the pons (f) and proceeds through middle cerebellar peduncles (g) while the CTC pathway progresses through the superior cerebellar peduncles. Panels h-i show the CPC and CTC pathways within cerebellar hemispheric white matter. Note the more medial position of the CTC pathway relative to the lateral location of the CPC pathway. Generated with FMRIB's FSL Suite Software.

3.4.2 Microstructure of Reciprocal Cerebrocerebellar Pathways – Impact of Injury and Age

All main effects and interactions are shown in Table 3.3. We found significant main effects of group for CPC pathway FA ($p = .001$; Figure 3.3a), MD ($p < .001$), and RD ($p < .001$). For CPC FA, there was a main effect of segment ($p = .01$), with higher FA in cerebro-ponto versus ponto-

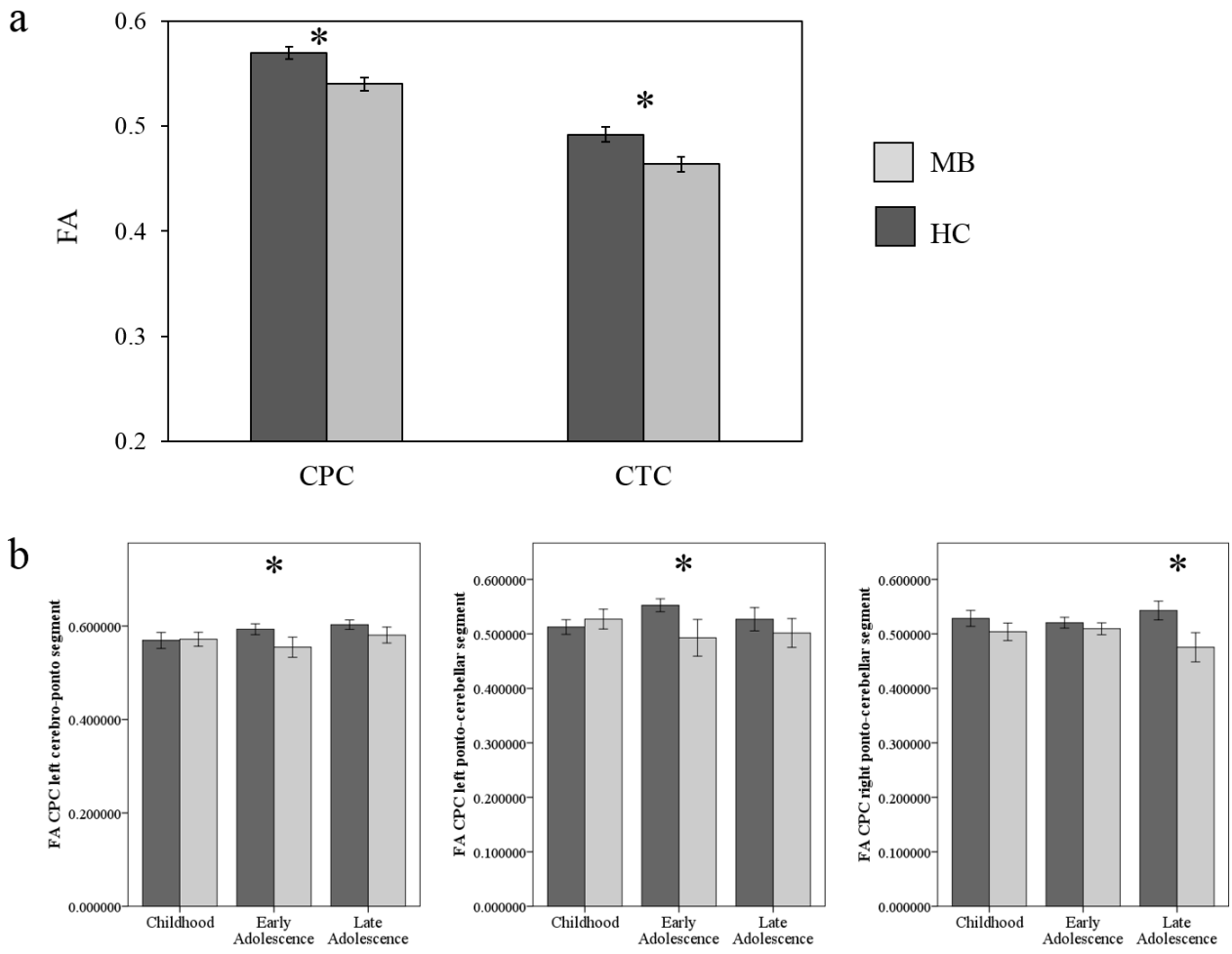
cerebellar pathways. There were group x side interactions for CPC MD and RD; higher measures of both were found for the left CPC pathway for the MB group compared to HC. We also found a significant group x age x side x segment interaction for FA ($p = .04$). Tests of simple effects showed no effect of group in childhood; however, we observed group effects in early adolescence for the left cerebro-ponto ($p = .005$) and left ponto-cerebellar pathways ($p = .008$), as well as in late adolescence for the right ponto-cerebellar segment ($p = .002$) (see Figure 3.3b).

Our analyses also revealed significant main effects of group for CTC pathway FA ($p = .007$; Figure 3.3a), MD ($p < .001$), and AD ($p = .003$). For CTC FA, analyses revealed a significant main effect of side ($p = .02$); the left CTC pathway had lower FA than the right. A significant main effect of segment was evident for CTC FA and AD ($p < .001$, $p = .003$); lower FA and higher MD was found for the cerebello-rubro segment relative to both the thalamo-cerebral segment ($p < .001$), and the rubro-thalamo segment ($p = .001$). We found a group x segment interaction for CTC FA ($p < .05$), MD ($p = .005$), AD ($p = .008$), and RD ($p = .003$); this interaction was driven by group differences in the cerebello-rubro ($p = .003$) and rubro-thalamo ($p = .02$) segments for FA, MD, and RD, and the cerebello-rubro ($p =.001$) and thalamo-cerebral ($p = .007$) segments for AD. Lastly, we found a significant group x age x side interaction for CTC FA ($p = .004$). Again, group effects were not seen in childhood, but were present in both early and late adolescence, for the left CTC pathway ($p = .01$) and the right CTC pathway ($p = .005$), respectively. Thus, for both the CPC and CTC pathways, it appears that group differences in pathway microstructure interact with both age and the side/segment of the pathways.

Table 3.3 Significant main effects and interactions across cerebrocerebellar pathways for the HC and MB groups.

	Pathway							
	CPC				CTC			
Main Effect	FA	MD	AD	RD	FA	MD	AD	RD
Group								
F (p)	11.53 (.001)	12.97 (.001)	-	17.69 (<.001)	7.88 (.007)	17.80 (<.001)	9.83 (.003)	17.73 (<.001)
Side								
F (p)	-	-	-	-	6.142 (.02)	-	-	-
Segment								
F (p)	6.40 (.01)	-	-	-	10.62 (<.001)	-	6.38 (.003)	-
Interactions								
Group x Side								
F (p)	-	6.85 (.01)	-	5.34 (.02)	-	-	-	-
Group x Segment								
F (p)	-	-	-	-	3.19 (<.05)	5.67 (.005)	5.25 (.008)	6.27 (.003)
Group x Age x Side								
F (p)	-	-	-	-	5.97 (.004)	-	-	-
Group x Age x Side x Segment								
F (p)	3.36 (.04)	-	-	-	-	-	-	-

Figure 3.3 Cerebrocerebellar pathway microstructure as a function of group and age tertile.



Panel a depicts the main effect of group for FA of the CPC and CTC pathways (bars represent estimated marginal means; error bars represent the standard error of the mean). HC group = dark grey bars, MB group = light grey bars. Panel b shows FA of the CPC pathway for each group (HC = dark grey bars, MB = light grey bars) across age groups. From left to right: FA of the left cerebro-ponto segment, FA of the left ponto-cerebellar segment, and FA of the right ponto-cerebellar segment. Error bars reflect standard error.

3.5 Discussion

We have detailed and outlined a reliable, standardized approach to obtain and visualize cerebrocerebellar pathways. We have used this methodology to visualize and examine complete, continuous, and reciprocal cerebrocerebellar pathways in the human brain. We examined bilateral reciprocal cerebrocerebellar white matter using DTI, and for the first time in the

developing brain, we have compared the microstructure of these distinct pathways in healthy children and in children who have been treated for MB. Using the above method, we parsed the pathways into anatomically relevant, synaptically defined segments to examine localized microstructure within each bilateral pathway. Our findings revealed that children treated for MB showed damage to select segments of the cerebrocerebellar pathways compared to controls – specifically, within the posterior segments of both CPC and CTC pathways. Further, our study is the first that we are aware of to examine the impact of age on reciprocal cerebrocerebellar pathways. We showed that differences in pathway microstructure between healthy children and those treated for MB were driven by specific areas of the pathway (e.g. posterior segments of the CPC and CTC pathways), and by age cohort (e.g. adolescence).

Our methodology, utilizing previously identified anatomical landmarks of cerebrocerebellar pathways in animal models, enabled us to describe continuous, reciprocal, and bilateral pathways connecting the cerebellum with frontal lobe. CPC pathways connecting frontal white matter with contralateral cerebellar white matter via pontine nuclei and middle cerebellar peduncle were obtained in all participants. CTC pathways were also defined in all participants connecting cerebellar white matter with contralateral frontal white matter via superior cerebellar peduncle, red nucleus, and thalamic nuclei. Connections we have obtained for both pathways replicate previous findings in animal models (Middleton & Strick, 1994, 2001; Kelly & Strick, 2003) and expand on findings describing solitary connections between cerebellum and cortex (Jissendi et al., 2008; Salmi et al., 2010; Law et al., 2011) and portions of cerebrocerebellar connections (Ramnani et al., 2006; Habas & Cabanis, 2007a, 2007b) detailed in adult human models. We also successfully segmented the reciprocal bilateral pathways into anatomically relevant, synaptically defined components to examine localized microstructure in the developing brain.

Though regional white matter damage has been described previously in children treated for MB (Mulhern et al., 1999; Khong et al., 2006; Mabbott et al., 2006b; Qiu, Kwong, Chan, Leung, & Khong, 2007; Law et al., 2011), our study is the first to examine specific, anatomically-based white matter pathways in this population using DTI and compare their microstructure with that of healthy age-matched peers. Considering the dual insult to the cerebellum/PF from resection of tumor and the effect of CRT, cerebrocerebellar pathways may be particularly vulnerable to injury. Our findings revealed a significant group effect of both side and segment of the pathways. Children treated for MB showed the most substantial damage to posterior segments of

both the CPC and CTC pathways compared to controls. This damage was indicated by DTI measures of lower FA and higher MD, and RD within the bilateral ponto-cerebellar segments of the CPC pathway and lower FA and higher MD and AD in bilateral cerebello-rubro and rubro-thalamo segments of the CTC pathway. As the main impact of treatment for MB is within the PF, we predicted that the most damage would be observed in posterior segments of the pathways contained within this "vulnerable" area.

Group differences were also found between MB and HC for anterior segments of the CPC (i.e. left cerebro-ponto) and CTC pathway (i.e. bilateral thalamo-cerebral). These differences may be a result of the direct effect of whole-brain CRT, affecting not only the PF region, but supratentorial regions as well. This result may also reflect the indirect effect of injury occurring to one part of the system (e.g. cerebellum, pontine nuclei) that produces eventual injury or compromise to another, more distant region – a diaschisis effect. The primary mechanism of diaschisis is thought to be functional deafferentiation (Finger, Koehler, & Jagella, 2004). Other potential mechanisms by which injury to the PF via treatment might exert an effect on distal regions of the brain include edema, reduced cerebral blood flow, altered neuronal excitability or neurotransmitter receptor expression, or the release of neurochemical or other factors (Sist, Baskar, & Winship, 2012). Thus, compromise to the entire CPC or CTC circuit (e.g. damage to all segments, as indicated by lower FA and higher MD, AD, and RD) may reflect a combined effect of diffuse CRT and progressive white matter injury to the PF that impacts other distant, but connected areas of the brain. Further, we observed a left-hemispheric bias for damage to the CTC pathway. This pattern of greater left-hemispheric-specific damage may reflect previous developmental findings postulating a right to left hemispheric lateralization gradient of neuronal differentiation and maturation (Kucyi, Moayedi, Weissman-Fogel, Hodaie, & Davis, 2012), findings of higher white matter volume in right versus left frontal lobe (Siffert et al., 2000), and findings of a greater preponderance of cortical grey matter (and thus, less white matter) within left versus right hemispheres (de Lacoste, Horvath, & Woodward, 1991; Filipek, Richelme, Kennedy, & Caviness, 1994; Reiss, Abrams, Singer, Ross, & Denckla, 1996).

Our study is the first that we are aware of to examine the impact of age on reciprocal cerebrocerebellar pathways. While there appeared to be no main effect of age on cerebrocerebellar pathways themselves (at least within the cohort we sampled), there was a significant group x age x side x segment interaction for the CPC pathway and group x age x side

interaction for the CTC pathway. Interpreted in the context of this highest-order interaction, for the CPC pathway we observed group effects in early adolescence for the left cerebro-ponto and left ponto-cerebellar pathways, as well as in late adolescence for the right ponto-cerebellar segment. Group effects were also found for the left and right CTC pathways in both early and late adolescence. No differences were observed between the MB and HC groups for CPC and CTC pathway microstructure in childhood.

There were group differences in radiation dose and field size in our sample and it is likely that we observed age tertile effects on cerebrocerebellar pathway microstructure because of this reason. Thus, rather than age itself impacting group differences in cerebrocerebellar microstructure, CRT protocol cohort effects emerged in the MB group when we split our sample by age tertiles. Recent literature has shown that it is the combination of radiation dose and field size that contributes to outcome in MB (Moxon-Emre et al., 2014). We found a significant difference between age tertiles when considering radiation protocols; the childhood group had a larger proportion of individuals treated with lower dose, less invasive radiation protocol (i.e. reduced CRT dose + tumor bed boost). Other, more intensive radiation protocols (i.e. reduced CRT dose + PF boost, standard CRT dose + tumor bed boost, and standard CRT dose + PF boost) were apparent in a greater proportion of patients in the adolescent groups.

Additionally, participants treated for MB in the early and late adolescence groups were further out from treatment than those in the childhood group. Because our childhood group was fewer years out from treatment compared to our adolescent groups, the late effects of treatment on white matter were not yet evident. It is possible that the further out from treatment, the more opportunity for developmental injury to manifest itself. A delay of emergence of white matter injury would justify why we observed damage to prominent cerebellar input and output pathways in our sample of adolescents following treatment for MB in childhood and not in childhood itself (e.g. fewer years out from treatment). Indeed, late effects emerge and continue to develop years after treatment for MB and greater time since diagnosis has been shown to predict functional and neurocognitive declines (Dennis, Spiegler, Hetherington, & Greenberg, 1996; Spiegler et al., 2004; Mabbott et al., 2005; Briere et al., 2008). Future investigations using longitudinal models of cerebrocerebellar development is necessary to confirm our findings.

Lastly, it is possible that we did not see group differences in pathway microstructure in childhood simply because brain areas that constitute cerebrocerebellar white matter are not yet fully developed. Throughout childhood, adolescence, and into young adulthood, age-related increases in FA and decreases in MD are consistently documented (Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Morriss, Zimmerman, Bilaniuk, Hunter, & Haselgrove, 1999; Mukherjee et al., 2001; Schmithorst, Wilke, Dardzinski, & Holland, 2002; Schneider et al., 2004; Barnea-Goraly et al., 2005; Zhang et al., 2005; Ashtari et al., 2007; Qiu, Tan, Zhou, & Khong, 2008). Voxel-wise analyses reveal increased FA and decreased MD, AD, and RD from late childhood to young adulthood, within the cerebellum and temporal, frontal, and parietal white matter (Qiu et al., 2008). Major white matter pathways show a similar pattern with respect to DTI indices; connections within the frontal and temporal lobes tend to mature more slowly in relation to other pathways (Schneiderman et al., 2007; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Tamnes et al., 2010). It is possible that the rate of development of these pathways are comparatively slow (e.g. do not fully develop until late adolescence), and thus group differences do not manifest until the pathways are more fully formed.

That we saw greater damage to cerebrocerebellar pathway microstructure in adolescence but not in childhood is somewhat counterintuitive; generally, it is younger age at treatment for MB in which we see the most morbidity/detrimental outcomes. However, there were no differences between the age tertiles and age at diagnosis, meaning all in our sample were treated for MB at the same age. Overall, our childhood cohort received less intensive radiation protocol and were closer to treatment upon assessment for this study (e.g. less time for treatment effects to manifest or produce white matter injury to cerebrocerebellar microstructure), compared to our adolescent cohorts. Thus, it is likely that both of these factors contributed to why we observed age differences for cerebrocerebellar pathway microstructure.

Though we found novel evidence of the impact of CRT (i.e. CRT protocol cohort effects, made apparent by an age tertile split) on cerebrocerebellar microstructure, several limitations must be considered. Due to the nature of DTI, this imaging method does not provide sufficient resolution to determine precise thalamic nuclei or cerebellar nuclei – therefore we were able to note only the relative positions of the reciprocal pathways and could not comment on precise thalamic or cerebellar nuclei. Further, utilizing imaging data with "mixed" field strengths may be of concern, though it has been documented that the inclusion of 1.5T in studies utilizing 3T data does not

necessarily reduce the validity of group analyses (Han & Talavage, 2011). As radiation dose and field size may influence neurocognitive outcome in MB, it is pertinent to examine whether these parameters have an impact on cerebrocerebellar circuitry development. There were differences between the age tertiles for radiation dose and field (i.e. a larger proportion of patients in the childhood group were treated with reduced CRT + tumor bed boost versus "other" protocols). However, in the current study, our cell sizes were too small to consider the effect of both age tertile and CRT dose and field (i.e. tumor bed versus PF) on CTC and CPC pathway microstructure. Further, though we used several established animal models as reference for our delineation of cerebrocerebellar pathways (i.e. seed and waypoints), caution should be taken when directly translating neuroanatomical animal models to that of humans. Indeed, there may be phenotypic differences in neuroanatomy (i.e. structural and connectivity differences) across species, however using murine, rodent, or primate models of cerebrocerebellar circuitry provides us with a basis to begin our structural delineation of these pathways in humans. Lastly, though we took care in recruiting representative HC participants and predominantly aimed to recruit healthy siblings of patients, we acknowledge that our HC sample had, on average, higher IQ measures than that of the normative mean (and thus, may not be fully representative of the average typically developing child). One reason this anomaly may have occurred was because several of our HC participants were children of our colleagues at SickKids (i.e. children whose parents are physicians or scientists with a greater number of years spent in the education system, which could have an impact on the child's global intellectual function). In future, it is necessary to match patients and controls on important demographic/SES variables, so as to minimize the influence of these variables on any neuroanatomical differences between groups.

We have delineated and segmented, for the first time in the developing brain, discrete and complete reciprocal cerebrocerebellar connections using DTI. Our findings provide a glimpse of what may occur structurally to the pediatric brain following resection of a PF tumor as well as the combined effect of whole-brain radiation plus boost dose to the PF/tumor bed and CTX. Our findings support the notion that CRT (particularly, whole-brain CRT and PF/Tumor Bed boost) has an effect on the PF beyond the initial insult of the tumor/resection, as well as supratentorial brain regions. DTI measures reflective of white matter injury were evident in children treated for MB versus controls, within many segments of the bilateral CPC and CTC pathways. Interestingly, not all white matter is damaged following CRT. Greater compromise was found for

posterior segments of CPC and CTC pathways in patients compared to controls, and age differences in CRT protocol in our patient group contributed to these differences. Group effects were evident in early and late adolescence, but not in childhood, possibly reflecting the timing and impact of treatment for brain tumors on white matter. Using our methodology to define reciprocal cerebrocerebellar pathways, future studies can begin to examine the relations between the microstructure of such connections and cognitive and behavioural outcome in survivors of childhood brain tumors. Additionally, further research can expand upon our model by elucidating the effects of treatment cohort (CRT dose and field) on cerebrocerebellar structure and function. Discovering a specific location of white matter loss or damage in MB may be of great importance for predicting the potential impact on mental processes and late effects following treatment. Given that CPC and CTC connections exist as the major cerebellar information input, output and modulation pathways and that both the cerebellum and frontal lobe are involved in mediating language, behavioural regulation, executive function, and working memory, damage to these feedforward and feedback mechanisms may produce widespread deficits.

3.6 Acknowledgements and Funding

We thank all of the participants and their families that took part in this research at the Hospital for Sick Children. This work was supported by the Pediatric Oncology Group of Ontario Research Unit, Genome Canada, Canadian Cancer Society, and the C^{17} Children's Cancer & Blood Disorders Research Grant.

Chapter 4
Executive Function in Pediatric Medulloblastoma: The Role of Cerebrocerebellar Connections

Law, N., Smith, M. L., Greenberg, M., Bouffet, E., Taylor, M. D., Laughlin, S., Malkin, D., Liu, F., Moxon-Emre, I., Scantlebury, N., & Mabbott, D. Submitted to *Neuropsychologia*.

4 Executive Function in Pediatric Medulloblastoma: The Role of Cerebrocerebellar Connections

4.1 Abstract

It is well documented that cognitive and behavioural declines are often observed following treatment for pediatric medulloblastoma (MB). Executive functions (EFs) are involved in the attainment, maintenance, and integration of information; these functions may play a key role in the cognitive and behavioural outcome in this population. At present, it remains unclear which EFs are most sensitive to the treatment effects for MB. We completed a comprehensive evaluation of multiple measures of EF in children treated for MB and age-matched healthy control (HC) children. We subsequently distilled these measures into components to determine which EFs are most impaired in MB. We then compared the microstructure of cerebrocerebellar circuitry – cerebro-ponto-cerebellar (CPC) and cerebello-thalamo-cerebral (CTC) pathways – between children treated for MB and HC; this information was used to predict EF outcome following treatment for MB. Twenty-four children treated for MB and twenty HC children participated in this study. All participants were seen for neurocognitive testing and MRI, including diffusion tensor imaging (DTI). The Delis-Kaplan Executive Function System, the Working Memory Test Battery for Children, and the Cognitive Emotion Regulation Questionnaire were administered to obtain a broad spectrum of EF, including emotion regulation. We used a Principal Components Analysis (PCA) to identify and describe the latent component structure of our EF measures. The resultant components of EF were then compared between the MB and HC groups using MANOVA. DTI measures of reciprocal cerebrocerebellar connections identified previously (Law et al., under review) were compared between the MB and HC groups to determine differences in pathway microstructure. Multiple regression analyses were used to predict the effect of treatment for MB and the mediating impact of cerebrocerebellar pathway microstructure on EF outcome. PCA revealed six components (C1-C6) of EF extracted from our model: C1 reflected a cognitive efficiency construct; C2 reflected a planning/problem solving component; C3 reflected a positive cognitive emotion regulation factor; C4 reflected a working memory construct; C5 reflected a negative cognitive emotion regulation dimension; and C6 reflected a mixed cognitive emotion regulation component. Multivariate analyses revealed group differences across four of the six EF components; for C1, C2, C3, and C4 the MB group had

scores significantly below that of the HC group, reflecting poorer performance on tasks of EF and less use of positive cognitive strategies for emotion regulation. We found that the microstructure of bilateral CPC and CTC pathways was compromised in the MB group relative to the HC group. Additionally, group and white matter microstructure of the CTC pathway connecting the left cerebellar hemisphere and the right frontal lobe were both associated with performance on C4. Considering the mediating effect of injury to the left CTC pathway, treatment for MB predicted poorer scores on EF tasks of working memory. Our results reveal that EF is affected in children with MB relative to age-matched peers including cognitive efficiency, planning/problem solving, and working memory. Interestingly, we found that children treated for MB also differed from HC in terms of cognitive emotion regulation, a regulation/self-awareness component of EF. We also found that cerebrocerebellar circuitry has a mediating impact on EF outcome following treatment for MB and thus plays a role in one component of EF – working memory.

4.2 Introduction

Impairment in neurocognitive and behavioural domains following treatment for pediatric medulloblastoma (MB) is well documented. Previous studies have described primarily global intellectual measures of outcome following treatment for MB. It is important to identify core areas of neurocognitive impairment using broad, yet comprehensive and specific measures in this population in order to provide both predictive models of neurocognitive decline in MB and targeted cognitive interventions. Though impairment in Executive Function (EF) in survivors has been suggested, an explicit and systematic examination of EF in children treated for MB has yet to be completed. EFs are core cognitive processes important to daily functioning and impairment in EF may lead to widespread deficits in other neurocognitive domains. At present, it remains unclear which components of EF, including emotion regulation, are most sensitive to the treatment effects of MB. Further, a potential neural basis for EF deficits in pediatric MB is unknown. We completed a comprehensive evaluation of EF in children treated for MB and age-matched healthy control (HC) children, using multiple measures of EF. We investigated the role of cerebrocerebellar circuitry in EF, as these connections are structurally damaged in MB and brain areas comprising these circuits have been implicated in EF in both healthy and clinical populations.

MB is a high grade tumor that arises in the posterior fossa (PF), accounting for 30% of all pediatric brain tumors and approximately half of all PF tumors (Schott et al., 1983). As MB is radiosensitive in nature, craniospinal radiation (CRT) is the most common adjuvant therapy following resection (Mueller & Chang, 2009). Chemotherapy (CTX) is typically administered during and after CRT (Bleyer, 1999). Though long-term survival is often achieved, late effects (i.e. symptoms occurring after recovery from early onset disorders of treatment) are evident in children with MB post-treatment, including significant neurotoxicity and cognitive and behavioural deficits (Schultheiss et al., 1995; Goldwein et al., 1996; Mulhern et al., 1999; Mulhern et al., 2001; Khong et al., 2003; Reddick et al., 2003; Mulhern et al., 2004a; Mabbott et al., 2005; Reddick et al., 2005; Mabbott et al., 2006a; Mabbott et al., 2006b; Qiu et al., 2007; Mabbott et al., 2008; Law et al., 2011; Law et al., 2012).

It has been suggested that neurocognitive and behavioural declines, particularly in patients treated with CRT, reflect a reduced ability to obtain novel information from their surroundings and result from acquiring knowledge at a significantly slower rate than healthy peers (Palmer et al., 2001). Many EF components are required to facilitate the attainment of new knowledge, learn from environmental cues, self-monitor, and efficiently process new information. Thus, it is possible that multiple EFs are impaired in MB and that this impairment contributes to overall neurocognitive and behavioural deficits often observed following treatment for MB.

EFs play an important role in a child's ability to acquire novel information, maintain this information, and make use of the information in an efficient and effective manner. EFs also guide goal-directed, purposeful behaviour required to reach a specific, intended outcome. EF encompasses such a broad range of processes (see Banich, 2004; Jurado & Rosselli, 2007 for review) that there is debate over their nomenclature and classification, as well as which functions are part of one overarching process versus independent, separable cognitive processes (Miyake et al., 2000; Hull, Martin, Beier, Lane, & Hamilton, 2008). Thus, meaningfully grouping EF from multiple measures using component or factor analyses has been of recent interest. In healthy populations, a number of studies have grouped EFs into several unitary processes to provide conceptual models of EF: switching/flexibility/shifting (e.g. alternating between task demands or cognitive sets) (Miyake et al., 2000), updating/monitoring (e.g. working memory and attentional control; obtaining and maintaining information in the mind to be used toward achieving a goal) (Miyake et al., 2000; Hedden & Yoon, 2006), and inhibition (actively supressing a prepotent

response to respond in a relatively novel way) (Miyake et al., 2000; Hedden & Yoon, 2006). A more fine-grained classification of latent EFs in healthy children and adolescents include attentional control (Anderson, 2001; Anderson, 2002), working memory (Diamond et al., 2002; Zelazo & Mueller, 2002; Davidson et al., 2006; Garon et al., 2008), inhibitory control (Diamond et al., 2002; Zelazo & Mueller, 2002; Davidson et al., 2006; Garon et al., 2008), planning/goal setting (Levin et al., 1991; Welsh et al., 1991; Kelly, 2000; Anderson, 2002), problem solving (Garcia-Barrera et al., 2013), set-shifting/cognitive flexibility (Anderson, 2001; Anderson, 2002; Diamond et al., 2002; Zelazo & Mueller, 2002; Davidson et al., 2006; Garon et al., 2008), fluency (both verbal and design) (Levin et al., 1991; Welsh et al., 1991; Fisk & Sharp, 2004), information processing (Anderson, 2002), and, in adults, regulation/self-awareness (including behaviour/emotion regulation) (Stuss & Benson, 1986; Mateer, 1999; Sohlberg & Mateer, 2001). Studies using clinical populations (e.g. patients with prefrontal cortex lesions, attention deficit hyperactive disorder, or schizophrenia) have elucidated a similar pattern of latent EFs as in healthy populations (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Stuss, Binns, Murphy, & Alexander, 2002; Chan, Chen, Cheung, Chen, & Cheung, 2006).

Problems in EF have been suggested in children treated for MB; however, no in-depth investigation of EF has been completed in this population based on conceptual models of EF. Several studies have begun to identify distinct neurocognitive impairments in childhood brain tumor survivors focusing on discrete EF-related processes such as attention/inhibition/shifting (Dennis et al., 1998; Reeves et al., 2006; Vaquero, Gomez, Quintero, Gonzalez-Rosa, & Marquez, 2008), processing speed (Waber et al., 2006; Mabbott et al., 2008), organizational skills (Armstrong et al., 2009), and working memory (Dennis et al., 1992; Dennis et al., 1998; Kirschen et al., 2008; Vaquero et al., 2008; Law et al., 2011; Conklin et al., 2012). In both the acute and chronic stages of treatment for PF tumors, behavioural and affective problems can occur in patients, including personality changes, blunting of affect, emotional lability, impulsivity, and inability to regulate emotion (Levisohn et al., 2000; Riva & Giorgi, 2000a; Steinlin et al., 2003; Aarsen et al., 2004; Richter et al., 2005). In some survivors of pediatric PF tumors, these problems have been found to persist into adulthood (Steinlin et al., 2003), which can in turn impact psychosocial functioning and overall quality of life. To our knowledge, only two studies have explicitly examined emotion regulation in survivors of pediatric brain tumors. Based on parent-rated questionnaires, problems in emotion regulation were found in a greater

proportion of survivors of childhood brain tumors compared to their healthy siblings (Armstrong et al., 2009). Children treated for cerebellar tumors (including MB) were found to have a relatively preserved ability for emotion identification (measured by their ability to identify happy or sad music) but impaired cognitive control of emotions (identifying the tone of music based on the Stroop task) (Hopyan et al., 2010).

Our approach for the current study was to use a comprehensive array of EF measures and subsequently reduce these measures into meaningful, latent components of EF using Principal Components Analysis (PCA). Specifically, we chose a set of measures designed to assess multiple aspects of EF based on the most commonly identified latent EFs outlined in previous conceptual models, ensuring each were appropriate for use in clinical populations. We used subtests of the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) to assess multiple EFs including fluency, processing speed, inhibition, switching, planning, and problem solving. We also used subtests of the Working Memory Test Battery for Children (WMTB-C) (Pickering & Gathercole, 2001) to measure working memory and attentional control abilities. To measure the emotion regulation aspect of EF – the evaluation of which has been largely neglected in children treated for MB – we used the Cognitive Emotion Regulation Questionnaire (CERQ) (Garnefski, Kraaij, & Spinhoven, 2001). The CERQ is a self-rated questionnaire that assesses the use of both positive and negative cognitive emotion regulation strategies in everyday life. Lastly, we attempted to elucidate the role of cerebrocerebellar connections in EF in pediatric MB, a clinical population that has been shown to have both white matter vulnerability (i.e. neurotoxicity due to treatment effects) and deficits in EF-related processes.

It is well known that EFs are predominantly frontally-mediated (Goldman-Rakic, 1995, 1996; Koechlin, Corrado, Pietrini, & Grafman, 2000; Stuss & Alexander, 2000; Stuss & Levine, 2002; Collette et al., 2005). However, the cerebellum has recently been implicated in aspects of EF (Schmahmann & Caplan, 2006; Bellebaum & Daum, 2007); cerebellar activation has been documented during performance of executive function and attention-based tasks (Desmond et al., 1997; Schlosser et al., 1998). Further, neural circuits (e.g. subcortical connections) involving the frontal lobes, striatum, and thalamus have also been considered important for EF (Miller & Cohen, 2001; Lewis et al., 2004; Kassubek et al., 2005; Monchi et al., 2006). In a review, Royall et al. (2002) emphasized the need to examine neural connections between the frontal lobes, basal

ganglia, and thalamus and their involvement in performance on tasks of EF. Based on the main nodes comprising its connections, cerebrocerebellar circuitry may play a key role in EF-related processes. It may be that cerebellar input and output pathways are important in the transfer of information between two regions that underlie one or more EFs – the cerebellum and frontal lobe.

We examined the cerebrocerebellar system in children treated for MB and healthy children, and its involvement in EF. The cerebrocerebellar system is comprised of a bilateral closed-loop circuit connecting the cerebellum with contralateral cerebral cortex (Law et al., under review; Thach, 1972; Brodal, 1978; Thach & Jones, 1979; Asanuma et al., 1983; Kim et al., 1994; Middleton & Strick, 1994, 1997; Schmahmann & Pandya, 1997b; Middleton & Strick, 2000, 2001; Dum & Strick, 2003; Kelly & Strick, 2003; Allen et al., 2005; Ramnani et al., 2006; Habas & Cabanis, 2007b; Jissendi et al., 2008; Morris et al., 2009; Salmi et al., 2010). Cerebro-ponto-cerebellar (CPC) connections serve to relay information from the cortex to cerebellum via pontine nuclei and constitute the cerebrocerebellar feedforward loop. The cerebellum returns these projections to the cerebral cortex by way of thalamic nuclei, via cerebello-thalamo-cerebral (CTC) connections; the feedback portion of the circuit.

The precise locations of discrete reciprocal cerebrocerebellar pathways have recently been mapped and their microstructure examined in healthy children and children treated for MB using diffusion tensor imaging (DTI) and tractography (Law et al., under review). Tractography generates structural maps of white matter connections based on regions of interest (ROIs) that serve to specify a start point (i.e. seed) and one or more throughput/endpoints (i.e. way points) of the pathway. Once tractography is completed, DTI allows us to infer the microstructural organization of white matter regions or pathways and to identify whether injury (e.g. demyelination, axonal damage) is evident (Song et al., 2002; Mori & Zhang, 2006; Jones & Leemans, 2011). DTI indices include measures of fractional anisotropy (FA) and mean diffusivity (MD), as well as axial and radial diffusivity (AD and RD, respectively). Lower measures of FA and higher measures of MD, AD, and RD are thought to reflect axonal degeneration and compromised myelin sheath (Beaulieu, 2002; Song et al., 2002).

It is well documented that multiple neurocognitive and psychosocial problems in survivors of pediatric MB are attributed to diffuse white matter damage following CRT (Mulhern et al., 2001;

Reddick et al., 2003; Mabbott et al., 2006a; Mabbott et al., 2006b; Law et al., 2011). Indeed, white matter damage has been documented following treatment for MB in many regions of the brain including the frontal lobe (Mabbott et al., 2006b), cerebellum (Law et al., 2011), and within white matter pathways connecting these areas (Law et al., under review; Law et al., 2011). It is possible that damage to these connections contribute to EF impairment in MB (Schatz, Kramer, Ablin, & Matthay, 2000), by interrupting communication between the cerebellum and frontal lobe. To our knowledge, only one study has examined the involvement of cerebrocerebellar pathways in EF, specifically in working memory performance. We documented impaired performance on the Working Memory Index of the Wechsler Intelligence Scale for Children in children treated for PF tumors; impairment was associated with damage to cerebellar white matter within cerebellar-frontal connections (Law et al., 2011).

We hypothesized that multiple components of EF would be disrupted in children treated for MB compared to healthy children, and that damage to cerebrocerebellar connections would be observed in MB compared to their healthy peers, adding to previous findings (Law et al., under review; Law et al., 2011; Law et al., 2012). Because circuits involving the frontal lobe and thalamus are postulated to be of specific importance during tasks of EF (Miller & Cohen, 2001; Royall et al., 2002; Lewis et al., 2004; Kassubek et al., 2005; Monchi et al., 2006), we expected that CTC pathway microstructure would be a more robust predictor EF performance, relative to CPC pathway microstructure. Lastly, we hypothesized that, in a path analysis model, the microstructure of cerebrocerebellar connections (i.e. CTC) would be a potential mediating factor between treatment for MB and EF outcome. If it is shown that damage to white matter pathways connecting the cerebellum with frontal lobe predicts poor EF outcome following treatment for MB, our findings will lend evidence to the importance of cerebrocerebellar pathways in EF and a white matter injury model of EF impairment.

4.3 Methods

4.3.1 Participants

Twenty-five children treated for MB with surgery, CRT, and CTX and 20 healthy control (HC) children participated in this study (see Table 4.1). Patients were excluded from the study if they had tumors outside the PF (i.e. supratentorial), were treated for recurrent disease, had diffuse brainstem glioma, were receiving palliative care, or had a premorbid history of neurological or

learning disabilities. Children free of any previous neurological or clinical disorders and with no history of prior acquired brain injury, developmental delay, or learning disability were eligible to participate in the HC group. Patients were recruited from the brain tumor program and through oncology and psychology clinics at the Hospital for Sick Children (SickKids) as well as via information letters mailed out to families (following a database review of children treated for MB at SickKids). HC were recruited through advertisement in newspapers and within the hospital, through families (i.e. siblings), and through friends and family of the investigators. All participants were seen for neuropsychological testing and magnetic resonance imaging (MRI) and DTI at SickKids and the protocol for this study was approved by the Research Ethics Board.

All participants provided written informed consent or assent and parental consent was obtained where applicable. Demographic variables were compared between groups (Table 4.1). There were no differences between the groups for sex [$\chi^2_{(1)} = .073$, $p = .787$], age at time of testing/MRI [$F(1,43) = .024$, $p = .879$], type of MRI (1.5T versus 3T, see below) [$\chi^2_{(1)} = .155$, $p = .734$], and handedness [$\chi^2_{(1)} = .190$, $p = .663$]. The average number of years of parental education was higher for the HC group relative to the MB group [$F(1,39) = 4.887$, $p = .033$], as was mean full-scale intelligence (FSIQ) [$F(1,43) = 26.775$, $p < .001$], verbal IQ (VIQ) [$F(1,43) = 31.174$, $p < .001$], and performance IQ (PIQ) [$F(1,43) = 14.176$, $p = .001$], measured by the Wechsler Abbreviated Scale of Intelligence (WASI) (Table 4.1). Given these differences, FSIQ was used as a covariate in subsequent analyses of EF between groups.

Table 4.1 Demographic and medical information for the HC and MB groups.

	MB n = 25	HC n = 20
Sex (Male : Female)	14 : 11	12 : 8
Age at scan/testing (years)		
Mean (SD)	13.30 (3.47)	13.15 (2.99)
Range	8.04 – 18.98	7.84 – 18.87
Handedness[10]		
Right	20 (80%)	17 (85%)
Left	5 (20%)	3 (15%)
Average parental education (years)[11]		
Mean (SD)	15.45 (2.10)	17.03 (2.45)

[10] Numbers reflect handedness at time of current assessment (note that for 3 MB, handedness changed post-operatively: 2 changed from left to right handedness, 1 changed from right to left handedness). Percentages represent within group totals.
[11] Parental education information was not available or for 4 cases (4 MB).

Range	10.5 – 20.0	12.5 – 22.5
WASI FSIQ Mean (SD)	91.88 (15.30)	113.80 (12.48)
WASI VIQ Mean (SD)	94.52 (12.26)	113.40 (9.89)
WASI PIQ Mean (SD)	91.12 (19.00)	111.20 (16.10)
MRI Scan Type[12]		
1.5T	6 (25%)	4 (20%)
3T	18 (75%)	16 (80%)
Age at diagnosis (years)		
Mean (SD)	7.02 (2.66)	N/A
Range	3.00 – 15.16	N/A
Time since diagnosis (years)		
Mean (SD)	6.28 (4.09)	N/A
Range	1.16 – 13.64	N/A
Tumor Size (mm^2)[13]		
Mean (SD)	1913.6 (815.95)	N/A
Range	957 – 3723	
Tumor Location within PF		
Midline	24 (96%)	N/A
Left Hemispheric	0 (0%)	N/A
Right Hemispheric	1 (4%)	N/A
Surgical outcome/extent of resection (%)		
Greater than 95% of the tumor resected	22 (88.0%)	N/A
Between 50% and 95% of the tumor resected	3 (12.0%)	N/A
Hydrocephalus		
No hydrocephalus	7 (28%)	N/A
Hydrocephalus not requiring treatment (resolved)	9 (36%)	N/A
Hydrocephalus requiring medical intervention or CSF diversion	9 (36%)	N/A
EVD and/or shunt		
Yes	10 (40%)	N/A
No	15 (60%)	N/A
Ventriculostomy		
Yes	5 (20%)	N/A
No	20 (80%)	N/A
Presence of post-operative/residual complication[14]		
Yes	23 (92%)	N/A
No	2 (8%)	N/A
Presence of multiple post-operative complications		
Yes	15 (60%)	N/A
No	10 (40%)	N/A
Radiation Dose (cGy)		
Craniospinal radiation + PF/TB boost		
Mean (SD) head/spine	2722 (577)	N/A
Range	2340 – 3600	
Mean (SD) PF/TB boost	2783 (623)	N/A
Range	1800 – 3240	
Mean (SD) PF/TB (+boost) total dose	5520 (87)	N/A

[12] One participant (MB) was ineligible to participate in an MRI due to braces (metal artefact).
[13] Tumor size was calculated by multiplying the two largest measurements of the tumor from an anatomical MRI scan. Measurements are in mm^2. Tumor size dimensions were not available for 6 MB.
[14] Indicates the presence of a single post-operative or residual complication, whether a cerebellar complication (i.e. ataxia, mutism, dysarthria) or other complications (i.e. hydrocephalus, nystagmus, diplopia, hemiparesis, hearing impairment, cranial nerve deficits). Presence of multiple post-operative complications indicates the incidence of 2 or more of the complications listed above.

Range	5400 – 5580	
Radiation Dose and Field		
Reduced TB	13 (52%)	N/A
Other	12 (48%)	N/A
Chemotherapy[15]		
Yes	24 (96%)	N/A
No	1 (4%)	N/A

4.3.2 Measures of Executive Function

4.3.2.1 The Delis-Kaplan Executive Function System (D-KEFS)

We used the Verbal Fluency, Colour-Word Interference, Twenty Questions, and Tower subtests of the D-KEFS (Delis et al., 2001) (Table 4.2). The Verbal Fluency subtest had three conditions, letter fluency, category fluency, and category switching; each participant was required to verbally generate words based on cues or a set of rules within the time frame of one minute. Performing sufficiently on these tasks required intact verbal fluency along with the ability to spontaneously and efficiently employ a strategy and generate ideas. Scores were based on the total number of words produced by the participant across the three conditions. The Colour-Word Interference subtest had four conditions – colour naming, word reading, inhibition (Stroop task), and inhibition/switching (modified Stroop task). These tasks required the participant to visually attend to an array of colour patches or words on a page and name/read the items on the stimulus page as quickly as possible. The abilities necessary to complete these tasks successfully include inhibition (e.g. the ability to stop a prepotent, learned response in order to respond in a novel way) and switching (e.g. maintenance of cognitive sets and ability to shift back and forth between these sets), as well as speed of processing. The completion times (in seconds) for each condition were summed to produce an overall score for each child. The Twenty Questions subtest included four conditions that required the child to attend to an arrangement of objects on a page and ask the examiner yes/no questions in order to deduce the correct response (each condition had a different correct object), using the examiners feedback to formulate subsequent questions. Scores for this task were based on the summed number of questions asked (i.e. total questions; a lower score equates to a more successful deduction of the correct object), the strategy or problem solving skills employed to eliminate the greatest number of objects with the

[15] Agents included Carboplatin, Cisplatin, Cyclophosphamide, Lomustine (CCNU), and Vincristine.

first question asked (i.e. initial abstraction score), and a total weighted achievement score. The Tower subtest involved the reconstruction of visually-presented towers on pegs using rings of different sizes, while following a set of rules. Spatial planning, rule learning, and problem solving were among the skills needed to successfully complete this subtest. The time (in seconds) and the number of moves taken to arrive at the correct solution were recorded to calculate a total achievement score for each participant.

Table 4.2 Summary, description, and scoring criteria of the EF measures.

Test	Subtest/Concept	Description	Scoring	EF Measures
D-KEFS	**Verbal Fluency**	Consisted of three conditions: **Letter Fluency**, **Category Fluency**, and **Category Switching**. The participant was required to produce verbal responses in accordance with set rules (e.g. words beginning with a specific letter or belonging to a certain category) within a one-minute time period.	All Conditions yielded one score which corresponded to the number of correct responses, with the exception of Category Switching, which had an additional Accuracy Score (e.g. correct switches); all were converted to individual scaled scores.	Cognitive efficiency (initiation, verbal fluency)
	Colour-Word	Four Conditions: **Colour Naming** (naming patches of colour on a page), **Word Reading** (reading colour names on a page), **Inhibition** (inhibiting a prepotent response - saying the ink colour of the word rather than reading the word, e.g. Stroop task), **Inhibition/Switching** (e.g. Stroop task with an additional rule).	All Conditions yielded timed scores (in seconds); these were converted to individual scaled scores.	Cognitive efficiency (initiation, inhibition, flexibility, and processing speed
	Twenty Questions	Participants were required to identify the target stimulus from a visual array of objects by asking the examiner yes/no questions, coming to the solution using the fewest number of questions as possible.	Trial scores were summed to produce three separate measures: initial abstraction score, total questions asked, and total weighted achievement score.	Planning (e.g. problem solving, goal setting, organization, and generative thinking)
	Tower Test	Participants were required to construct towers with a set of coloured rings and pegs based on a visual representation. This task increased in complexity with each trial, with set rules and time restrictions.	One score reflecting total weighted achievement was calculated and converted into a scaled score.	Planning, goal setting, and inhibition

WMTB-C	**Digit Recall**	Participants listened to a list of numbers and were required to immediately recall the numbers as presented; increased in difficulty as the trials progressed.	All subtests were administered in blocks of six trials with the series/sequence of numbers, words, or blocks increasing in length by one for each block. If the participant scored four correct trials in any block, the next block was administered. Each task was concluded once any three trials within a block were scored as incorrect.	Working memory (audio-verbal and visuo-spatial) and attentional control
	Word List Recall	Participants listened to a list of words and were required to immediately recall the words as presented; increased in difficulty as the trials progressed.		
	Block Recall	Participants watched a series of blocks being tapped and were required to immediately touch the blocks in the same sequence as presented; increased in difficulty as the trials progressed.		
	Backward Digit Recall	Participants listened to a list of numbers and were required to immediately recall the numbers in backward order as presented; increased in difficulty as the trials progressed.		
CERQ (-k)	**Acceptance**	A rating of having thoughts of acceptance and resignation in regard to a negative life experience (e.g. "I think I have to accept that this has happened, there is nothing I can do about it after the fact").	All questions were rated by participants using a five-point Likert scale (1 = almost never, 5 = almost always). Four of thirty-six of the questions in the CERQ (-k) pertain to each of the nine concepts; scores on these four questions were summed and averaged to produce a final raw score.	Emotion regulation, including positive and negative cognitive emotion regulation strategies
	Positive Refocusing	A rating of having positive, happy, and pleasant thoughts instead of thinking about the negative life experience (e.g. "I think of something nice instead of what has happened").		
	Refocus on Planning	A rating of having thoughts about how to handle the negative life experience (e.g. "I think about a plan of what I can do best, I think about how I can change this situation").		
	Positive Reappraisal	A rating of having thoughts of giving a positive meaning to the negative life experience in contribution to personal growth (e.g. "I think I can learn something from the situation, I think I can become a stronger person as a result").		
	Putting into Perspective	A rating of having thoughts of comparing the negative life experience to other experiences (e.g. "I think that it all could have been much worse").		

	Self Blame	A rating of having thoughts that blame oneself for the negative life experience (e.g. "I feel that I am the one who is responsible for what has happened").		
	Rumination	A rating of having perseverative thoughts about the feelings and beliefs associated with the negative life experience (e.g. "I often think about how I feel about what happened").		
	Catastrophizing	A rating of having thoughts that accentuate the negativity of the experience (e.g. "I often think about how horrible the situation was").		
	Blaming Others	A rating of having thoughts that blame others or point to others as the source of the negative experience (e.g. I feel that others are to blame for it, I think that it's the fault of others").		

4.3.2.2 The Working Memory Test Battery for Children (WMTB-C)

We used the Digit Recall, Word List Recall, Block Span, and Backward Digit Recall subtests of the WMTB-C (Pickering & Gathercole, 2001) to measure working memory ability (Table 4.2). For the Digit Recall and Word List Recall tasks, participants were orally given a series of numbers or words and asked to immediately repeat the series back to the examiner. Backward Digit Recall was similar to Digit Recall, though participants had to repeat each series of digits in backward order than what was orally presented to them. For Block Recall, participants were required to tap a series of blocks in the same order as presented to them by the examiner. For all subtests each series increased in length (i.e. one digit, word, or block added to the series upon completion of each trial) as the test progressed. Separate scores were obtained for each subtest based on the number of correct trials achieved.

4.3.2.3 The Cognitive Emotion Regulation Questionnaire (CERQ)

We used the CERQ or the Cognitive Emotion Regulation Questionnaire for Children (CERQ-k; for children under 12 years of age, containing the same questions as the CERQ but phrased more simply) to measure emotion regulation (Garnefski et al., 2001) (Table 4.2). The CERQ (-k) is a self-reported questionnaire that contains 36 items measuring cognitive emotion regulation strategies that a participant might use following the experience of a negative or unpleasant life

event (Garnefski et al., 2001). Prior to completing the CERQ, participants were given the following instructions: “Sometimes nice things happen in your life and sometimes unpleasant things might happen. When something unpleasant happens, you can think about it for a long time. When something unpleasant happens to you, what do you usually think?” (Garnefski et al., 2001). The CERQ (-k) is based on nine conceptually separate cognitive emotion regulation strategies (e.g. cognitive coping). These cognitive emotion regulation strategies can be adaptive (i.e. Acceptance, Positive Refocusing, Refocus on Planning, Positive Reappraisal, and Putting into Perspective) or maladaptive (i.e. Self Blame, Rumination, Catastrophizing, and Blaming Others). Higher scores are indicative of a greater likelihood of a participant to use that particular cognitive emotion regulation strategy following an unpleasant life experience.

4.3.3 Neuroimaging Protocol

The neuroimaging protocol used in the current study has been described previously (Law et al., under review) and is summarized here. MRI measurements were performed at SickKids using either a GE LX 1.5T MRI scanner with 8 channel head coil or a Siemens 3T whole-body MRI scanner (Trio Tim syngo MR B17 system) with a 12-channel head coil. The GE LX 1.5T MRI protocol included a 3D-T1 FSPGR gradient echo, inversion recovery-prepared sequence (IR time = 400ms, TE/TR = 4.2/10.056ms, 116-124 contiguous axial slices, NEX = 1, 256 x 192 matrix interpolated to 256 x 256, FOV = 240 x 240mm, rbw = 162.734kHz, slice thickness = 1.5mm) and a diffusion-weighted single shot spin echo DTI sequence with EPI readout (25-31 directions, b = 1000s/mm^2, TE/TR = 85.5/15000ms, 45-50 contiguous axial slices, NEX = 1, 128 x 128 matrix interpolated to 256 x 256, FOV = 240 x 240mm, rbw = 1953.12kHz, slice thickness = 3mm). The Siemens 3T MRI protocol utilized a T1 AX 3D MPRAGE Grappa 2 protocol (TE/TR = 3.91/2300ms, 160 contiguous axial slices, flip angle = 9°, 256 x 224 matrix, voxel size = 1mm ISO, FOV = 256 x 224mm) and diffusion-weighted single shot spin echo DTI sequence with EPI readout (30 directions, b = 1000s/mm^2, TE/TR = 90/9000ms, 70 contiguous axial slices, flip angle = 9°, voxel size = 2mm ISO, matrix = 122 x 122 interpolated to 244 x 244, FOV = 244 x 244mm). Images were eddy-corrected and non-brain (e.g. skull) was stripped prior to tractography. The FMRIB Software Library (Behrens et al., 2003a; Behrens et al., 2003b; Smith et al., 2004; Woolrich et al., 2009) was used to calculate DTI maps (e.g. eigenvalues, FA, MD) and indices (e.g. FA, MD, AD, RD). Because of the field strength differences between 1.5T and

3T scanners, MRI scan type was included as a covariate in all analyses of imaging data (see Law et al., under review for a detailed explanation of rationale).

4.3.4 ROI Placement and DTI Probabilistic Tractography

ROI placement protocol and probabilistic tractography methodology have been described previously (refer Chapter 3, Law et al., under review, for detailed description of ROI generation and placement). ROIs included left and right frontal lobe; left and right thalamus; left and right red nucleus; pons; left and right superior cerebellar peduncles; and left and right cerebellar hemisphere. Probabilistic tractography was used to generate the left and right CPC pathways (seed point: left/right frontal lobe; way points: pons and right/left cerebellar hemisphere) and the left and right CTC pathways (seed point: left/right cerebellar hemisphere; way points: left/right superior cerebellar peduncle, right/left red nucleus, right/left thalamus, right/left frontal lobe). Means and standard deviations for DTI indices FA, MD, AD, and RD were calculated for each pathway.

4.3.5 Statistics/Analytic Approach

First, we used PCA to reduce our data into component factors that represented underlying/latent EFs across our entire sample. As part of a data quality examination process we used the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) and Bartlett's Test of Sphericity to determine the suitability of our data to enter into PCA for factor/structure detection. A Varimax (orthogonal) rotation was employed. The factor solution was based on those components with eigenvalues greater than 1.0 and the interpretability of the components (e.g. loadings >.45 and/or the highest loadings on each component). Any components identified from the PCA were considered for subsequent analyses of EF differences between MB and HC groups.

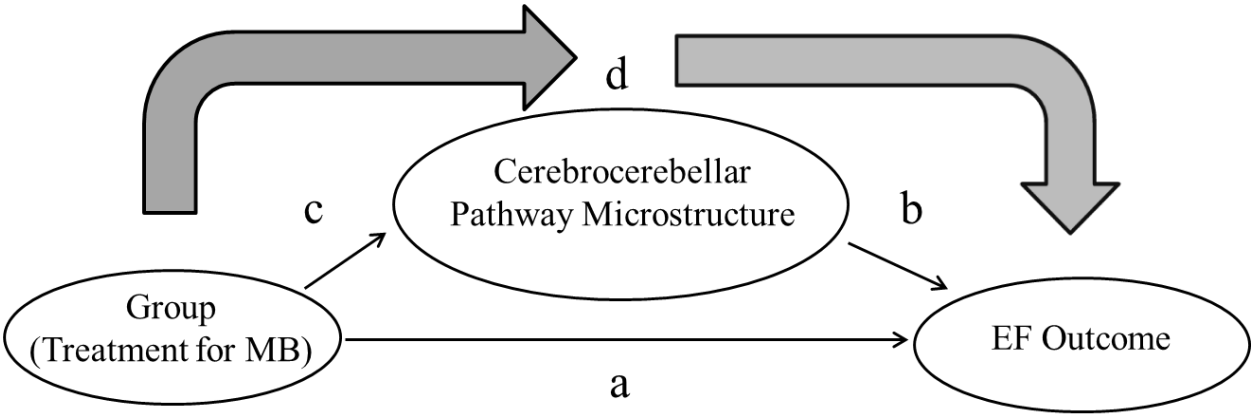
Second, a Multivariate Analysis of Variance (MANOVA) was performed using the EF components extracted from the PCA, with group as a between-subjects variable. We considered the EF components in two different ways. We used mean regression factor scores (residuals extracted for each participant) from the PCA to compare group differences in the EF components. For normalization and graphic visualization purposes, a constant was added to the regression factor scores (to eliminate negative values) and log-transformed prior to MANOVA. We also calculated a mean composite score for each component, based on the average of the

observed scores (e.g. raw or scaled scores, dependent on the measure) of all measures loading onto each component. Mean composite component scores were also used to elucidate group differences in the EF components. Because of their interpretability and clinical relevance in comparison to regression factor scores, mean composite component scores were used for the remainder of the analyses.

Third, we performed four Multivariate Analysis of Variance (MANOVA), considering each pathway separately (e.g. Left CPC, Right CPC, Left CTC, Right CTC), with group as a between-subjects variable.

Finally, we used a modelling approach to determine if white matter differences in cerebrocerebellar pathway microstructure predicted EF outcome among our groups (Figure 4.1). Specifically, multiple regression analyses were conducted to generate a path model of how treatment for MB, cerebrocerebellar microstructure, and EF components may be related to each other, as well as predict EF outcome. The most significant results (e.g. highest partial η^2 and corresponding p values) from both the EF component analysis and the cerebrocerebellar pathway analyses served as a framework for our path modelling analyses. Our path models resulted in a total of 18 comparisons based on the p values of each beta weight obtained. To reduce the potential Type 1 error from multiple comparisons, we employed a standard false discovery rate (FDR) correction using the conventionally accepted false-positive rate of 5% ($q \leq .05$) (Benjamini & Hochberg, 1995; Bennett, Wolford, & Miller, 2009).

Figure 4.1 Framework for the path analysis model.



Our model depicts the direct (small arrows) and indirect (large arrows) effects of group and cerebrocerebellar pathway microstructure on EF outcome. Specifically, we investigated (a) the direct effect of group (treatment for MB) on EF outcome, (b) the direct effect of cerebrocerebellar pathway microstructure on EF outcome, (c) the direct effect of group (treatment for MB) on cerebrocerebellar pathway microstructure, and (d) represented by the large grey arrows, the indirect effect of group (treatment for MB) on EF outcome (b*c). This indirect effect considers the mediating effect of cerebrocerebellar pathway microstructure. We also considered the total effect of group (treatment for MB) on EF outcome (d + a).

4.4 Results

4.4.1 Components of Executive Function

PCA extracted six latent components in our data; these components were independent of each other and reflected independent aspects of EF to be compared between the MB and HC groups. KMO and Bartlett's test validated that structure detection was appropriate for our data (e.g. the set of variables was adequately related for factor analysis) (KMO = .702; χ^2 = 747.1, p <.001). The component loadings for our 25 measures of EF are provided in Table 4.3. Together, these six components accounted for approximately 72% of the variance in the set of original variables. The first component (C1) explained 24.6% of the variance in the data and reflected a cognitive efficiency dimension. Measures that loaded highly on this component included all conditions of the D-KEFS Verbal Fluency and Colour-Word subtests.

Table 4.3 Factor structure and factor loadings (>.45 and/or highest loading) after Varimax Rotation of twenty-five measures of EF in the HC and MB groups (n = 44).

EF Measure	C1	C2	C3	C4	C5	C6
WMTB-C Digit Recall	-	-	-	.787	-	-
WMTB-C Word List Recall	-	-	-	.496	-	-
WMTB-C Block Recall	-	-	-	.472	-	-
WMTB-C Backward Digit Recall	-	-	-	.604	-	-
D-KEFS Verbal Fluency: Letter Fluency	.667	-	-	-	-	-
D-KEFS Verbal Fluency: Category Fluency	.784	-	-	-	-	-
D-KEFS Verbal Fluency: Category Switching	.840	-	-	-	-	-
D-KEFS Verbal Fluency: Category Switching (Switching Accuracy)	.804	-	-	-	-	-
D-KEFS Colour-Word Interference: Colour Naming	.786	-	-	-	-	-

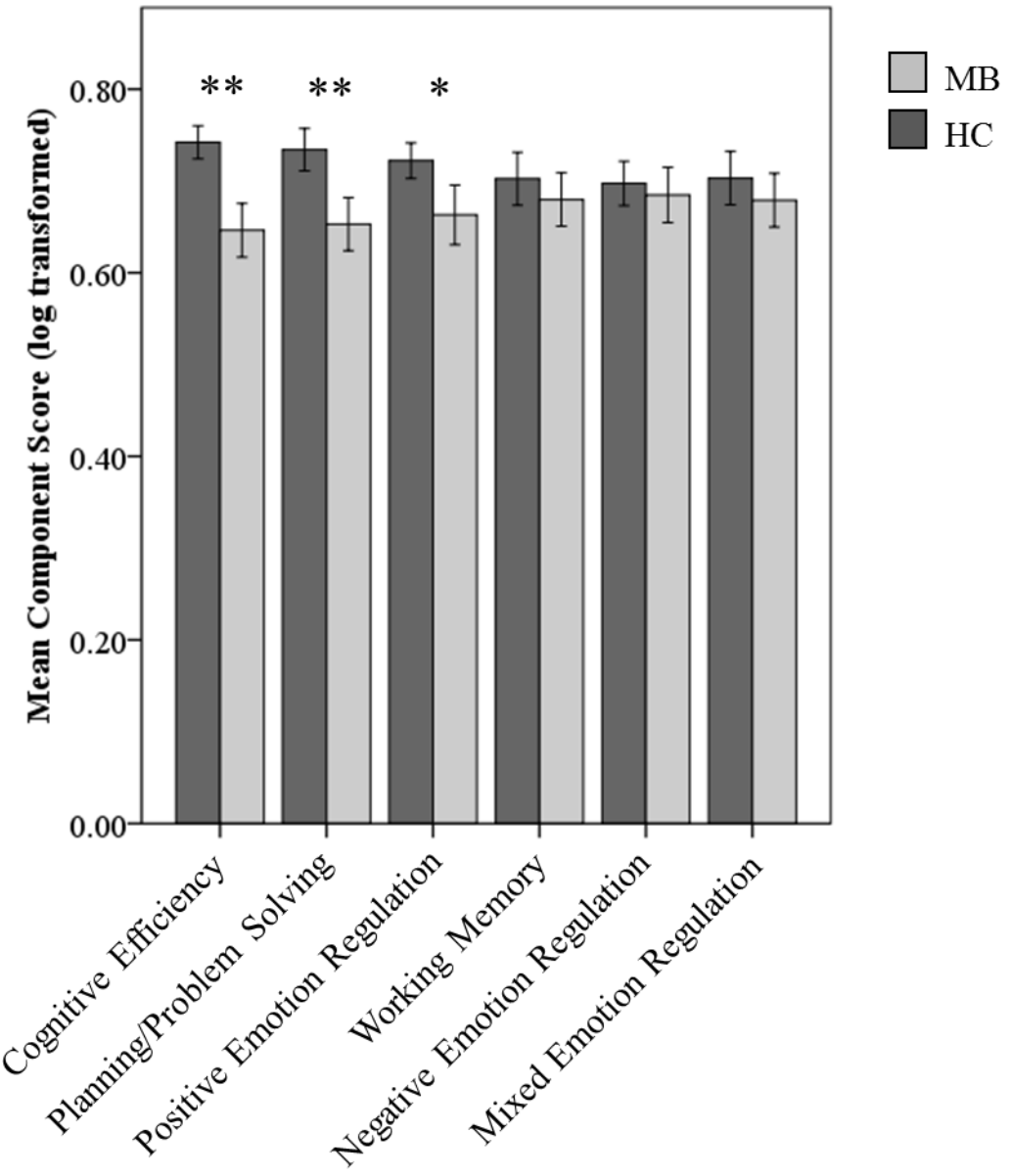
D-KEFS Colour-Word Interference: Word Reading	.784	-	-	-	-	-
D-KEFS Colour-Word Interference: Inhibition	.772	-	-	-	-	-
D-KEFS Colour-Word Interference: Inhibition/Switching	.768	-	-	-	-	-
D-KEFS Twenty Questions: Initial Abstraction	-	.459	-	-	-	-
D-KEFS Twenty Questions: Total Questions	-	.663	-	-	-	-
D-KEFS Twenty Questions: Total Weighted Achievement	-	.776	-	-	-	-
D-KEFS Tower Test: Total Achievement	-	.654	-	-	-	-
CERQ Self Blame	-	-	-	-	-	.578
CERQ Acceptance	-	-	-	-	-	.813
CERQ Rumination	-	-	-	-	.781	-
CERQ Positive Refocusing	-	-	.842	-	-	-
CERQ Refocus on Planning	-	-	.835	-	-	-
CERQ Positive Reappraisal	-	-	.735	-	-	-
CERQ Putting into Perspective	-	-	.497	-	-	-
CERQ Catastrophizing	-	-	-	-	.813	-
CERQ Other Blame	-	-	-	-	.624	-

The highest loadings on the second component (C2), explaining 10.5% of the variance, reflected a planning/problem solving component of EF. Specifically, measures of EF gleaned from the D-KEFS Twenty Questions and Tower Test subtests were included in this dimension. Explaining 10.2% of the variance, the third component (C3) reflected a behaviour regulation component of EF – specifically, positive cognitive emotion regulation. The fourth component (C4) reflected a working memory dimension of EF and accounted for 10% of the variance. Loadings on C4 included all subtests of the WMTB-C (e.g. Digit Recall, Word List Recall, Block Recall, and Backward Digit Recall). The fifth component (C5) explained 8.7% of the variance and signified another behaviour regulation component of EF; negative cognitive emotion regulation. The loadings for the sixth component (C6) explained 8% of the variance and reflected a final behavioural regulation component of EF, a mixed (e.g. positive and negative aspects) strategy of cognitive emotion regulation.

4.4.2 Group Differences in Executive Function

First, we found group differences across three of the six EF components when regression factor scores from the PCA were used ($\lambda = .394$, $F = 9.478$, $p < .001$) (see Figure 4.2). The MB group had scores significantly below that of the HC group for C1 [$F(1,42) = 15.95$, $p < .001$], C2 [$F(1,42) = 10.26$, $p = .003$], and C3[$F(1,42) = 4.98$, $p = .031$]. Scores for C4, C5, and C6 did not significantly differ between the groups.

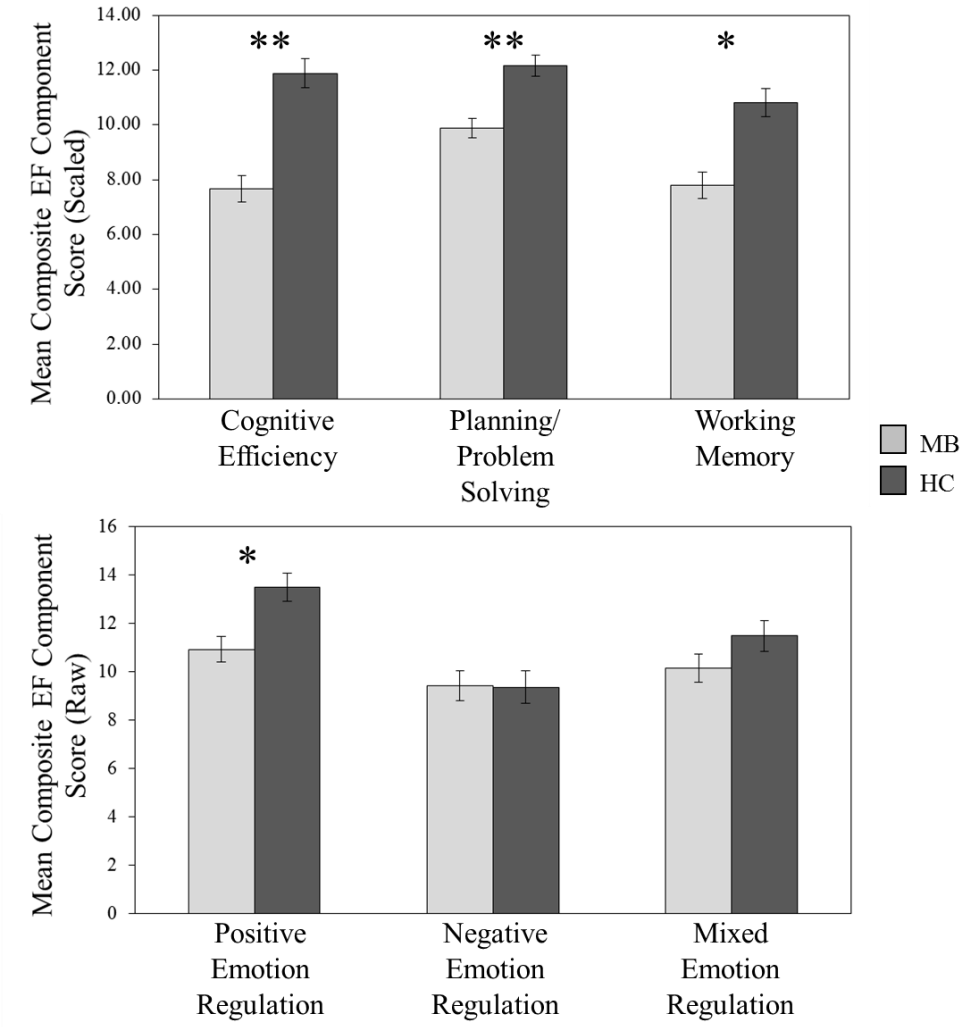
Figure 4.2 Mean EF component scores across the HC and MB groups (based on regression factor scores).



Bars represent mean regression factor scores extracted from the PCA for each group (log transformed data). A double asterisk indicates significant group differences at $p < .01$ and a single asterisk indicates significant group differences at $p < .04$. Dark grey bars represent the HC group while light grey bars reflect the MB group. Error bars represent standard error.

Second, we found group differences in four of the six EF components when we analysed mean composite component scores: C1, C2, C3, and C4 ($\lambda = .419$, $F = 8.542$, $p < .001$) (Figure 4.3). Similarly, the MB group had scores significantly below that of the HC group for C1 [$F(1,42) = 41.34$, $p < .001$], C2 [$F(1,42) = 19.97$, $p < .001$], and C3[$F(1,42) = 10.42$, $p = .002$]. Additionally, the MB group had lower scores for C4 [$F(1,42) = 9.15$, $p = .004$] compared to the HC group. Group mean scaled (and raw) scores and standard deviations of each EF measure are provided in Table 4.4, broken down by EF component.

Figure 4.3 Mean EF composite component scores across the HC and MB groups.



Bars represent mean scaled (C1 – Cognitive Efficiency, C2 – Planning/Problem Solving, C4 – Working Memory) and mean raw (C3 – Positive Emotion Regulation, C5 – Negative Emotion Regulation, C6 – Mixed Emotion Regulation) composite component scores. A double asterisk indicates significant group differences at $p < .001$ and a single asterisk indicates significant group differences at $p < .04$. Dark grey bars represent the HC group while light grey bars reflect the MB group. Error bars represent standard error.

Table 4.4 Group means and standard deviations for each measure of EF as a function of EF component.

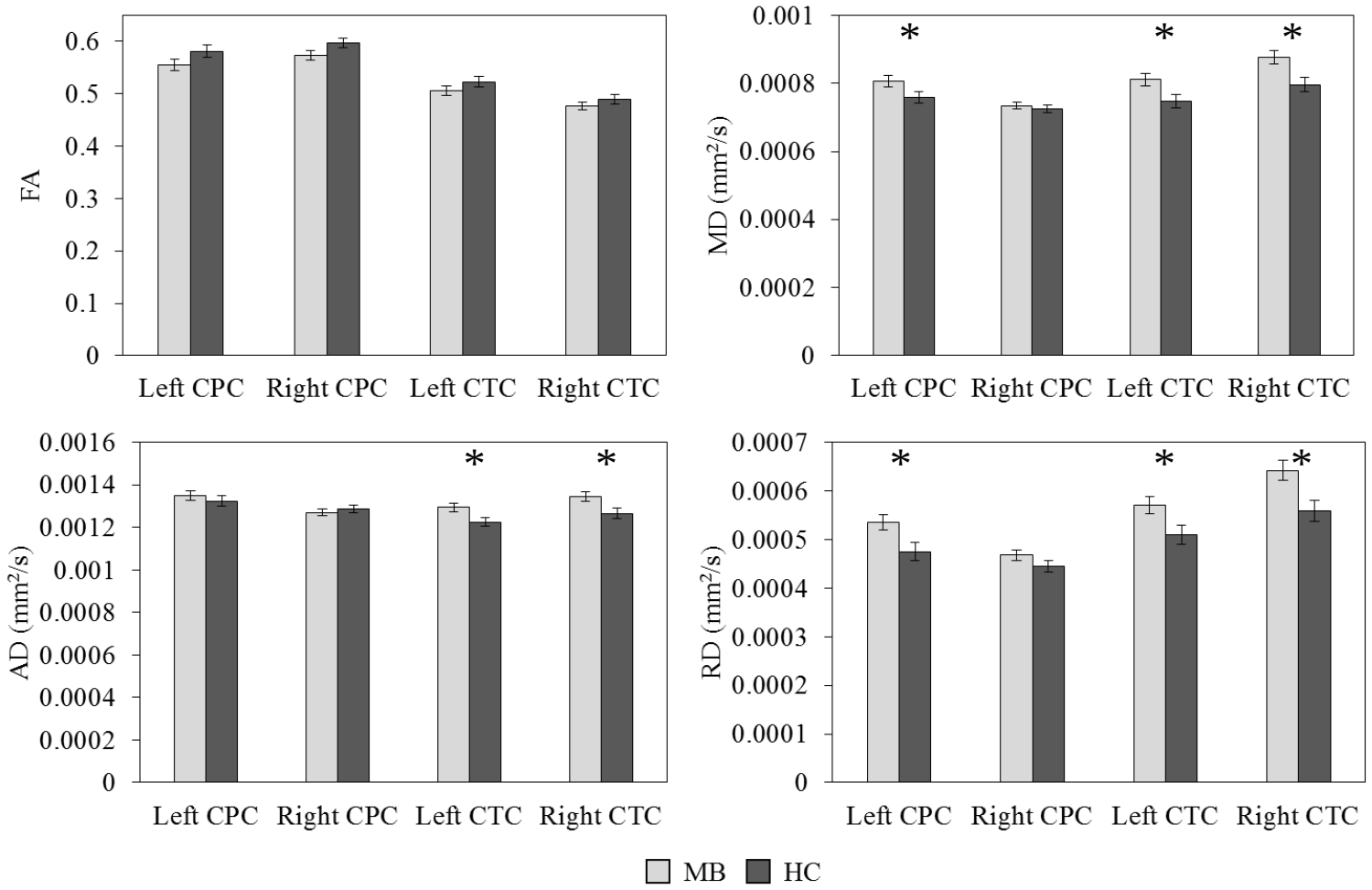
	MB n = 25	HC n = 20
C1 – Cognitive Efficiency		
D-KEFS Letter Fluency (scaled)		
Mean (SD)	9.08 (3.23)	12.05 (3.35)
D-KEFS Category Fluency (scaled)		
Mean (SD)	8.96 (3.12)	13.65 (3.38)
D-KEFS Category Switching (scaled)		
Mean (SD)	7.48 (3.28)	11.70 (3.06)
D-KEFS Category Switching Accuracy (scaled)		
Mean (SD)	7.68 (3.07)	11.65 (2.91)
D-KEFS Colour Naming (scaled)		
Mean (SD)	6.84 (3.64)	11.55 (1.88)
D-KEFS Word Reading (scaled)		
Mean (SD)	6.68 (3.67)	11.95 (1.36)
D-KEFS Inhibition (scaled)		
Mean (SD)	6.92 (3.44)	10.95 (2.80)
D-KEFS Inhibition/Switching (scaled)		
Mean (SD)	7.00 (3.83)	11.45 (2.40)
C2 – Planning/Problem Solving		
D-KEFS Twenty Questions Initial Abstraction (scaled)		
Mean (SD)	10.40 (2.99)	12.20 (3.22)
D-KEFS Twenty Questions Total Questions (scaled)		
Mean (SD)	10.20 (2.43)	12.30 (1.22)
D-KEFS Twenty Questions Total Weighted Achievement (scaled)		
Mean (SD)	10.12 (2.39)	12.70 (1.90)
D-KEFS Tower Test Total Achievement (scaled)		
Mean (SD)	8.92 (3.20)	11.45 (2.01)
C3 – Positive Cognitive Emotion Regulation		
CERQ Positive Refocusing (raw)		
Mean (SD)	10.20 (4.13)	11.50 (4.07)
CERQ Positive Refocusing (raw)		
Mean (SD)	10.42 (3.49)	13.90 (2.38)
CERQ Positive Refocusing (raw)		
Mean (SD)	11.63 (3.40)	14.20 (3.12)
CERQ Positive Refocusing (raw)		
Mean (SD)	11.38 (4.27)	14.25 (2.57)
C4 – Working Memory		
WMTB-C Digit Recall (scaled)		
Mean (SD)	8.24 (2.99)	10.05 (2.96)
WMTB-C Word Recall (scaled)		
Mean (SD)	9.40 (3.30)	12.95 (2.96)
WMTB-C Block Recall (scaled)		
Mean (SD)	5.48 (3.44)	10.65 (2.87)

WMTB-C Backward Digit Recall (scaled)		
Mean (SD)	8.04 (3.61)	9.60 (2.50)
C5 – Negative Cognitive Emotion Regulation		
CERQ Rumination (raw)		
Mean (SD)	9.42 (3.19)	11.75 (3.86)
CERQ Catastrophizing (raw)		
Mean (SD)	9.54 (4.19)	8.00 (3.08)
CERQ Other Blame (raw)		
Mean (SD)	9.25 (4.88)	8.30 (2.83)
C6 – Mixed Cognitive Emotion Regulation		
CERQ Acceptance (raw)		
Mean (SD)	12.17 (3.41)	12.60 (3.84)
CERQ Self Blame (raw)		
Mean (SD)	8.13 (2.98)	10.35 (2.60)

4.4.3 Group Differences in Cerebrocerebellar Microstructure

Considering each cerebrocerebellar pathway separately, four MANOVAs were completed comparing DTI indices (FA, MD, AD, and RD) between groups. A multivariate effect was observed for the Right CPC ($\lambda = .773$, $F = 2.856$, $p = .036$, $\eta^2 = .227$), Left CTC ($\lambda = .700$, $F = 4.181$, $p = .007$, $\eta^2 = .300$), and Right CTC ($\lambda = .778$, $F = 2.774$, $p = .04$, $\eta^2 = .222$) pathways. No univariate effects were observed for the Right CPC pathway. For the Left CTC pathway, higher MD [$F(1,42) = 5.923$, $p = .019$], AD [$F(1,42) = 5.234$, $p = .027$], and RD [$F(1,42) = 5.230$, $p = .027$] were found for the MB group relative to the HC group (Figure 4.4). For the Right CTC pathway, higher MD [$F(1,42) = 7.800$, $p = .008$], AD [$F(1,42) = 5.735$, $p = .021$], and RD [$F(1,42) = 8.221$, $p = .006$) were again evident for the MB group compared to the HC group (Figure 4.4). Univariate effects for MD [$F(1,42) = 4.431$, $p = .041$] and RD [$F(1,42) = 6.057$, $p = .018$], but no multivariate effect, were apparent for the Left CPC pathway; both measures were higher in the MB group versus the HC group.

Figure 4.4 Cerebrocerebellar pathway microstructure for the MB and HC groups.



Left and right CPC and CTC whole-pathway DTI measures (FA, MD, AD, and RD) are depicted. An asterisk indicates a significant group difference at $p < .04$. Dark grey bars represent the HC group while light grey bars reflect the MB group. Error bars represent standard error.

4.4.4 Association of Cerebrocerebellar Microstructure and Executive Function in Medulloblastoma

Path analysis models were tested to determine the mediating influence of cerebrocerebellar microstructure on EF outcome following treatment for MB (Figure 4.1). The exogenous variable in these analyses was group (MB versus HC), while the endogenous variables were CPC and CTC pathway DTI measures and EF components. To build our path analysis models, we considered the four EF components that significantly differed between the groups (i.e. C1-C4). We also considered only those cerebrocerebellar pathways for which there was a significant multivariate group effect, qualified by significant univariate effect(s), and those with the highest η^2 values. Based on these criteria, we considered both the left CTC and right CTC pathways in our path modelling, but neither of the CPC pathways. For the left CTC and right CTC pathways, MD, AD, and RD significantly differed between the MB and HC groups. However, RD for each of the pathways had the comparatively highest η^2 value (Left CTC: $\eta^2 = .164$; Right CTC: $\eta^2 = .111$), so RD was the only pathway DTI measure considered in our analyses.

Eight separate regression models were completed. For the first four models, group and left CTC pathway RD were regressed on C1, C2, C3, and C4 separately to obtain the direct effect of treatment and the direct effect of pathway microstructure on each component of EF (eight comparisons). For the other four models, group and right CTC pathway RD were regressed on C1, C2, C3, and C4 separately to obtain the direct effect of treatment and the direct effect of pathway microstructure on each component of EF (eight comparisons). Subsequently, group was regressed on RD for the right or left CTC pathway to obtain the direct effect treatment for MB on cerebrocerebellar pathway microstructure (two comparisons). We controlled for multiple comparisons with a FDR correction across all 18 comparisons. Upon completion of the eight regression models, only those for which all three direct effects were significant were reported, producing our final path model. That is, if both a) an EF component was predicted by both group and cerebrocerebellar pathway microstructure, and b) cerebrocerebellar pathway microstructure was predicted by group, were found.

Group significantly predicted the EF component ($q < .02$) in all models; this was expected based on our findings of group differences across C1-C4. Group also significantly predicted right CTC pathway RD ($q = .01$), replicating our findings of group differences in right CTC pathway

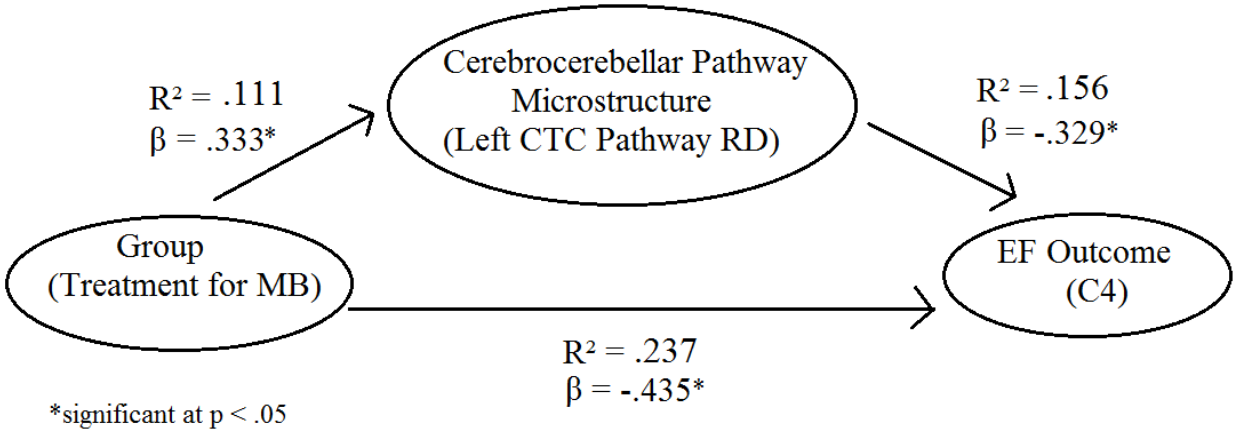
microstructure. However, there was only one model in which all direct effects were significant at $p < .05$ (Table 4.4, Figure 4.5). First, both group and left CTC pathway RD were found to significantly predict C4 and accounted for 39.2% of its variance. To obtain the amount of individual variance that each of these variables contribute to C4, we partitioned their combined R^2 value using the product measure method (Pratt, 1987). From this method, the direct effect of group (-.435) accounted for 23.7% of the variance in C4 and the direct effect of left CTC pathway RD (-.329) accounted for 15.6% of the variance in C4. Second, the direct effect of group (.333) accounted for 11.1% of the variance in left CTC pathway RD. The indirect effect that considers how treatment for MB impinges on cerebrocerebellar pathway microstructure to influence EF outcome was manually calculated from the direct effects (Figure 4.5). From this calculation, the indirect effect (-.110) of treatment for MB and the mediating effect of left CTC pathway RD accounted for 1.7% of the variance in C4. Finally, the total effect (-.545) of treatment for MB, considering mediating effect of left CTC pathway microstructure, explained approximately 3% of the variance in C4.

Table 4.5 Multiple regression model (with FDR correction) for the direct effect of both group (MB versus HC) and left CTC pathway RD on C4.

	Regression Coefficients					FDR	
Regression Model	R	R^2	F	β	p	Critical p	FDR q
Group and left CTC pathway RD regressed on C4	0.626	0.392	13.23**				
1. Group				-0.435	0.002	0.0167	0.005
2. Left CTC RD				-0.329	0.015	0.0278	0.026
Group regressed on left CTC RD	0.333	0.111	5.23*				
1. Group				0.333	0.027	0.0306	0.045

* significant at $p < 0.03$
** significant at $p < 0.001$

Figure 4.5 Path analysis model depicting the relations between group (treatment for MB versus no treatment, HC), cerebrocerebellar pathway microstructure (left CTC pathway RD), and EF outcome (C4: working memory).



Indirect β = (.333)(-.329)
= -.110

Total effect = (-.110) + (-.435)
= -.545

Direct effects are depicted adjacent to arrows. The indirect effect of group on EF outcome considering the mediating effect of cerebrocerebellar pathway microstructure was manually calculated as a product of the direct effects. The total effect of group on EF outcome considering the mediating effect of cerebrocerebellar pathway microstructure was manually calculated as a sum of the indirect and direct effect of group on EF outcome.

Group and left CTC pathway RD together did not significantly predict any other EF component. Further, when group and right CTC pathway RD were used in the multiple regression analyses, the resultant models did not significantly predict any EF component.

4.5 Discussion

EF has been suggested as a domain at risk for decline following treatment for MB and may have impact on global intellectual and academic deficits in survivors. To our knowledge, no explicit, broad-spectrum analysis of EF has been completed in children treated for MB based on conceptual models of EF. Further, examining emotion regulation as an EF has been largely neglected in this population. We used a population-specific, data-driven analysis of EF to determine which aspects of EF were most affected following treatment for pediatric MB. Our findings substantiate the notion that EF deficits are present in children treated for MB relative to

age-matched peers; in our sample we found deficits in cognitive efficiency, planning/problem solving, and working memory in patients relative to controls. Additionally, we found that children treated for MB differed from their healthy peers in how they regulate emotions. We examined cerebrocerebellar circuitry as a potential neural substrate of EF, as these connections have been shown to be structurally damaged in MB and brain areas comprising these circuits have been implicated in one aspect of EF – working memory. We have provided novel evidence that cerebrocerebellar circuitry has a mediating impact on EF outcome, specifically working memory function, following treatment for MB.

Our data-reduction analysis allowed us to reduce our EF measures into components, producing six distinct, meaningful factors to compare between our patient and control groups. Our first component, C1, reflected a cognitive efficiency construct of EF. Loadings on this component included measures of verbal fluency, inhibition, switching/shifting/flexibility, and speed of processing. Several studies consider the components of shifting/flexibility/inhibition (Miyake et al., 2000; Hedden & Yoon, 2006) and verbal fluency (Levin et al., 1991; Welsh et al., 1991; Fisk & Sharp, 2004) as separate EFs. That we did not find these functions to load on separate components may mean that cognitive efficiency is an overarching aspect of EF that encompasses both cognitive flexibility and fluency.

C2 reflected a planning/problem solving component of EF. Loadings on C2 included tasks involving abstract thinking, spatial planning, deductive reasoning, rule-learning to plan and achieve a goal, and incorporating feedback to revise and refine the plans made to reach a goal. Our finding that planning/problem solving (C2) represented its own component of EF is consistent with several previous studies (Levin et al., 1991; Welsh et al., 1991; Kelly, 2000; Anderson, 2002), but incongruent with others (Borkowski & Burke, 1996; Garcia-Barrera et al., 2013). C3 reflected the first of our regulation components – a positive cognitive emotion regulation aspect of EF. Loadings on this factor were adaptive cognitive emotion regulation strategies: Positive Refocusing, Refocus on Planning, Positive Reappraisal, and Putting into Perspective. All of these are positive cognitive coping strategies that aid in rationalizing a negative or stressful event and reassigning it into a more benign, meaningful event that can be learned from. C4 comprised a working memory component of EF. Measures that loaded onto this factor involved both verbal and non-verbal (spatial) working memory and memory span abilities. That we found a working memory dimension of EF is congruent with previous work (Miyake et

al., 2000). C5 and C6 constituted two additional regulation components of EF: a negative cognitive emotion regulation aspect, and a mixed (i.e. positive and negative) cognitive emotion regulation aspect, respectively. Loadings on C5 were comprised of maladaptive cognitive emotion regulation strategies (i.e. Rumination, Blaming Others, and Catastrophizing), all involving negative, perseverative ways of coping with stress. Finally, C6 included a combination of positive and negative emotion regulation strategies (i.e. Acceptance and Self Blame). This component appeared to involve mixed, internalizing coping strategies in which the person looks towards the self in order to deal with stressful events.

Overall, our EF components were congruent with that of conceptual models describing multiple latent factors of EF (Stuss & Benson, 1986; Levin et al., 1991; Welsh et al., 1991; Mateer, 1999; Miyake et al., 2000; Sohlberg & Mateer, 2001; Anderson, 2002; Fisk & Sharp, 2004; Hedden & Yoon, 2006). However, we believe that our loadings on each component parsed aspects of EF in a novel way due to the broad range of measures used in our study and the fact that we elucidated our components from an extensive array of EF measures using a data reduction analysis, also expanding on previous models by including measures of emotion regulation. Our measures of cognitive emotion regulation loaded onto three components of EF; this finding was not expected. However, it is logical that they loaded this way because of the distinct categories of positive and negative coping strategies in the CERQ.

We determined that there were differences in four of our six EF components between children treated for MB and healthy children when composite EF component scores were considered. First, we found that children treated for MB had significantly lower scores on tasks of cognitive efficiency (C1), planning/problem solving (C2), and working memory (C4) compared to our HC sample. However, it is noted that though our MB sample had scores below that of our HC group for our planning/problem solving component, mean group performance on this component of EF was still considered to fall within the average range compared to normative data. Our findings contribute to that of previous studies, confirming impairments in aspects of cognitive efficiency (i.e. speed of processing, inhibition/switching) (Waber et al., 2006; Mabbott et al., 2008; Vaquero et al., 2008; Palmer et al., 2013) and working memory (Dennis et al., 1992; Dennis et al., 1998; Davidson et al., 2006; Kirschen et al., 2008; Vaquero et al., 2008; Law et al., 2011; Conklin et al., 2012; Palmer et al., 2013; Knight et al., 2014) in MB. To our knowledge, our

study is the first to describe select deficits of EF in other domains of cognitive efficiency and suggest a potential deficit in planning/problem solving in survivors of MB, based on our sample.

Both speed of processing and working memory are associated with performance on tasks of fluid intelligence (Kail & Salthouse, 1994). Working memory performance has been found to correlate with overall intellectual functioning in survivors of pediatric MB (Conklin et al., 2012). Further, planning and problem solving skills are a necessary part of daily life and are used in many academic domains, including mathematics. It may be that working memory, cognitive efficiency, and planning/problem solving abilities are particularly vulnerable to the effects of treatment for MB (Schatz et al., 2000). Thus, impairment in these EF domains put children treated for MB at risk for declines in IQ, academic skills, and overall quality of life in the years following treatment, putting them at a significant disadvantage compared to age-matched peers.

Second, we provide novel evidence that survivors of pediatric MB regulate their emotions differently than their healthy peers – specifically, in what cognitive coping strategies they employ in their daily life. We found that children treated for MB made less use of positive, adaptive cognitive emotion regulation strategies (C3) compared to their healthy peers. Failing to use adaptive mechanisms of emotion regulation when experiencing negative, stressful events can have implications on the coping strategies used during times of emotional stress (Garnefski et al., 2001), and can in turn, have an impact on mental health. The use of positive cognitive emotion regulation strategies (i.e. Positive Reappraisal) is associated with declines in perceived stress and improved mental health outcomes (Helgeson, Reynolds, & Tomich, 2006), as well as the reduction of the physiological impact of stress (Cruess et al., 2000; McGregor et al., 2004; Tugade & Fredrickson, 2004; Carrico et al., 2006; Bower, Low, Moscowitz, Sepah, & Epel, 2008).

We did not find differences between the groups for negative cognitive emotion regulation (C5) and mixed cognitive emotion regulation (C6) components. These findings are encouraging, in that in children who have been treated for cancer (a decidedly negative life event) do not seem to resort to negative coping strategies (e.g. ruminating on the negative event, catastrophizing the situation, blaming others), in the face of environmental stressors.

Third, evidence of cerebrocerebellar circuitry compromise has been shown in MB (Law et al., under review; Law et al., 2011; Law et al., 2012); our findings contribute to this growing body of

literature. Our study is novel in that we compared whole-pathway bilateral reciprocal cerebrocerebellar microstructure between MB and HC, and found that these continuous pathways were damaged in children treated for MB compared to HC. These findings compliment previous literature documenting damage to singular regions of cerebrocerebellar output pathways (i.e. injury to cerebellar white matter within the CTC pathway; Law et al., 2011), as well as neuroanatomically-defined segments of cerebrocerebellar input and output pathways (Law et al., under review). Our findings lend further evidence to the notion of diffuse white matter damage within cerebrocerebellar circuitry following treatment for MB.

Lastly, we provide novel evidence that cerebrocerebellar connections are involved in EF, specifically in working memory ability. In our path analysis model, group (treatment for MB) was the most significant direct contributor while left CTC pathway RD was the second most important direct contributor to predicting variance in working memory (C4) outcome. Not only did we find a direct impact of treatment for pediatric MB on working memory, but we also found this effect to be mediated by cerebrocerebellar pathway microstructure, an indirect effect. Though the variance in C4 accounted for by our indirect and total effects of treatment for MB via the mediating influence of cerebrocerebellar pathway microstructure was small, our model was still significant. Our findings verify the vulnerability of neural networks involving the cerebellum, thalamus, and frontal lobe in MB and that these circuits are implicated in working memory. Further, we provide evidence that working memory is not an exclusively frontally-mediated EF.

Previous studies in healthy adults have found that the cerebellum interacts with frontal cortex to support working memory function by way of the CTC pathway (Chen & Desmond, 2005; Salmi et al., 2010). Similarly, a connection between cerebellar and prefrontal areas activated during a nonverbal auditory working memory task has been documented using fMRI and DTI tractography (Salmi et al., 2010). Selective deficits in tasks of verbal working memory were found in adult patients with isolated cerebellar lesions compared with healthy adults, leading to a proposal that the cerebellum may contribute to verbal working memory during initial phonological encoding (Ravizza et al., 2006). Thus, it may be that the left CTC pathway plays an important role in specific working memory and memory span aspects of EF (e.g. subvocal rehearsal mechanisms and timing/modulation of verbal response). Based on our findings, this pathway does not appear to be implicated in other aspects of EF (i.e. cognitive efficiency,

planning/problem solving, or emotion regulation). Additionally, we did not find CPC or CTC pathway involvement in any of our remaining EF components. This evidence substantiates the importance of the CTC pathway for connecting brain regions that underlie working memory function – the cerebellum and frontal lobe. Our findings also show that injury to the CTC pathway interrupts communication between the cerebellum and frontal lobe (impacting the feedback loop), and in turn, is associated with poorer working memory performance. Future research could examine the involvement of white matter pathways involving the cerebellar vermis, which has been implicated in emotion/affect regulation. Because we examined cognitive emotion regulation, we studied pathways involving the posterior lobe of the cerebellum – the region that is thought to be involved in the cognitive control of emotions. The role of the CPC and CTC pathways (or lack thereof) in emotion regulation requires further investigation.

Our findings should be interpreted in light of several limitations. We do not presume that EFs are controlled by a single brain region or are regulated by one specific network, but are represented by the interactions of multiple cortical/subcortical neural systems (Gazzaniga, Ivry, & Mangun, 2002). Thus, by no means is cerebrocerebellar circuitry solely or even primarily responsible for all EF, but we find it to play a role in one domain of EF. Future research is necessary to examine the interplay between cerebrocerebellar circuitry and other diverse neural networks and the combined impact of these systems on EF. Additionally, the assessment of cognitive emotion regulation in our sample consisted of self-reported measures and thus may involve some level of bias. Specifically, participants may have under- or over-estimated the extent to which they apply certain cognitive emotion regulation strategies in the real world. Though the CERQ (-k) was designed to probe cognitive emotion regulation in children and adolescents and though all aspects of the questionnaire (i.e. purpose, each question, and rating scale) were explained to participants, the meaning and intent of certain questions may have been lost when interpreted by the child or adolescent. Further, we were unable to determine premorbid measures of IQ or EF in children with MB due to the urgency with which they must undergo surgery and begin their treatment protocol. Moreover, though our recruitment approach enabled us to obtain HC participants who came from similar backgrounds as our MB group, as well as represent a broad range of races, ethnicities, and socioeconomic (SES) backgrounds, our HC sample may not have been adequately representative of the general “healthy” population. Though we took care in recruiting representative HC participants and predominantly aimed to recruit healthy siblings of

patients, we acknowledge that our HC sample had higher IQ measures than that of the normative mean and higher average years of parental education. This anomaly may have been a result of several HC participants being children of our colleagues at SickKids (i.e. whose parents are physicians or scientists with a greater number of years spent in the education system). In future, it is necessary to match patients and controls on important demographic/SES variables, so as to minimize the influence of these variables on any neuropsychological differences between groups. Lastly, caution should be paid when interpreting our findings from the PCA; we acknowledge that our relatively low sample size (i.e. < 100) and low participants to variables ratio (ours is approximately 2:1) limits the reliability and validity of our PCA (Comrey & Lee, 1992; Osborne & Costello, 2004). However, determining an "adequate sample size" for PCA is difficult and "strong data" can also be interpreted as uniformly high communalities (i.e. > 0.8) without cross loadings, in addition to several variables loading strongly (i.e. > 0.7) on each factor (Costello & Osborne, 2005). When our data were examined, relatively high communalities (> 0.7) were found for approximately 80% of our items and many of our variables loaded strongly (i.e. > 0.7) and cleanly (i.e. no cross loadings; cutoff was loadings > 0.45) onto each factor (see Table 4.3). In light of these findings, we are confident (albeit cautious) that our PCA findings can be considered as valid.

Pediatric cancer research is becoming increasingly focused on the development of targeted and individualized medical therapies for children with brain tumors; so too is it important to focus on developing targeted cognitive and behavioural interventions for survivors. The vast majority of pediatric cancer literature has focused on global measures of neurocognitive function, which does not provide information specific enough to begin to develop targeted cognitive/behavioural interventions. We provide evidence of deficits in core EFs in children treated for MB including cognitive efficiency, planning/problem solving, working memory, and cognitive emotion regulation. Our findings have implications for the clinical management of children with brain tumors, in that we have shown explicit, core EF impairments in this population; specific and targeted rehabilitation programs/therapies should focus on these areas. For example, we have shown that survivors of pediatric MB make less use of positive coping strategies; this may have an impact on mental health outcomes and future emotion regulation in response to stressful events. Mindfulness-based stress and pain management courses (i.e. meditation-centred interventions) involve refocusing and reappraising a stressful event as a positive one by revoking

the initial, negative appraisal and attenuating any adverse stigma associated with the event (Garland, Gaylord, & Park, 2009). Employing mindfulness practice has been shown to promote the use of an adaptive emotion regulation strategy – positive reappraisal – which in turn, may substantially reduce stress (Garland, Gaylord, & Fredrickson, 2011). Providing this therapy to survivors of pediatric MB could serve to modify cognitive emotion regulation, particularly, increasing the use of positive reappraisal coping. We have also shown that cerebellar output pathway microstructure mediates the treatment effects of MB on EF. Identifying vulnerable neural systems following treatment for pediatric brain tumors and the relation of these systems and neurocognitive outcome will play a role in the modification of existing treatment protocols and how we view/measure functional and cognitive/behavioural outcome in pediatric cancer survivors. Specifically, if the CTC pathway is particularly susceptible to the treatment effects of MB, and we provide evidence that this pathway is implicated in working memory outcome, working memory interventions can be employed as either pre-emptive or mitigative strategies to preserve as much of this EF as is possible.

4.6 Acknowledgements and Funding

This work was supported by the Pediatric Oncology Group of Ontario Research Unit, Genome Canada, Canadian Cancer Society, and the C17 Children's Cancer & Blood Disorders Research Grant.

Chapter 5
Clinical, Theoretical, and Methodological Contributions and Concluding Remarks

5 Clinical, Theoretical, and Methodological Contributions and Concluding Remarks

This thesis described, in detail, reciprocal cerebrocerebellar pathway microstructure in the healthy and injured pediatric brain using DTI (Chapter 3; Law et al., under review). This work also utilized information about neurological vulnerability to the adverse effects of treatment for pediatric PF tumors to predict patients most at risk for presenting with CMS (Chapter 2) and those susceptible to developing problems in EF (Chapter 4). Specifically, this thesis elucidated the role of cerebrocerebellar pathways in facilitating the communication and information transfer between the cerebellum and frontal lobes to underlie working memory (Chapter 4) and the speech-language symptoms of CMS (Chapter 2). This thesis also investigated potential clinical and medical variables implicated in CMS following treatment for PF tumors to produce a schema of CMS risk (Chapter 2; Law et al., 2011). Finally, this thesis examined EF as a late effect of treatment for PF tumors, obtaining a profile of core EF deficits in survivors. Findings from this work have bearing on a) our understanding of the structure and function of white matter pathways connecting the cerebellum with frontal lobe, b) risk stratification for CMS, c) EF as a late effect of treatment in pediatric PF tumor populations, d) conceptual models of EF and our understanding of EF in the developing brain, and e) the application of DTI and tractography to define and examine white matter pathways in the developing brain.

This thesis integrates information and methodologies from several different disciplines. Work from this thesis has the potential to contribute to the field of neurooncology in that findings will contribute to the growing body of research on the perioperative and late effects of pediatric brain tumors. Further, the current findings may inform clinicians of several risk factors for CMS, and aid in the clinical management of this syndrome in future patient populations. This thesis also identified core EF impairments in survivors of PF tumors. These findings may have implications for the modulation of treatment protocol (e.g. surgery) and implementation of preemptive or mitigative intervention therapies (e.g. speech-language, and cognition/EF) for patients with PF tumors as well as those with cerebellar lesions/abnormalities. Lastly, this thesis identified the vulnerability of white matter circuits connecting the cerebellum with frontal lobe in children treated for brain tumors and their importance in speech-language and working memory outcomes in survivors.

Work from this thesis also contributes to the field of neuroanatomy by identifying parts of the brain vulnerable to a specific type of brain injury, providing information about the structure and function of cerebrocerebellar pathways in the developing brain using DTI, and describing how these connections are affected by injury. Moreover, findings from this thesis contribute to the field of neuropsychology by broadening our knowledge of EF in the healthy and injured developing brain and by contributing to conceptual models of EF. Specifically this thesis elucidated six distinct, but interrelated components of EF in healthy children and children treated for MB using a comprehensive array of measures of EF including emotion regulation. Finally, work from this thesis contributes to the field of neuroscience (e.g. brain structure-function relations) in that it elucidated the structure of cerebrocerebellar connections in the developing brain, how they are affected by injury, and their role in speech-language/CMS and EF.

The final chapter of this thesis provides a summary of its clinical, theoretical and methodological contributions as well as the challenges and opportunities arising from this work.

5.1 Cerebrocerebellar Connections

Knowledge of the structure of cerebrocerebellar connections contributes to our understanding of the cerebellum, how the cerebellum communicates with the frontal cortex, the functions these reciprocal circuits are implicated in, and lastly, what occurs when these circuits are damaged. The current work elucidated the structure of reciprocal cerebrocerebellar pathways in their entirety using DTI in healthy children and in a brain injury model – children treated for PF tumors (Chapter 3; Law et al., under review). This work described a detailed segmentation of these continuous pathways, providing insight into the localized microstructure of cerebrocerebellar circuitry (Chapter 3; Law et al., under review). Lastly, the role of reciprocal cerebrocerebellar microstructure in EF and CMS was examined (Chapter 4 and Chapter 2; Law et al., 2012, respectively).

All pathways obtained in patients and controls were consistent with previous neuroanatomical animal models that have detailed both the CPC and CTC pathways (Middleton & Strick, 1994, 2001; Kelly & Strick, 2003). Bilateral CPC pathways connected each frontal hemisphere with the contralateral cerebellar hemisphere via pontine nuclei (decussation point) and middle cerebellar peduncle. Bilateral CTC pathways connected each cerebellar hemisphere with the contralateral frontal hemisphere by way of the ipsilateral superior cerebellar peduncle, contralateral red

nucleus (decussating prior to this point, within the midbrain), and thalamus. Verifying these pathways in humans based on well-described animal models allowed this work to be confirmatory rather than exploratory – lending greater evidence to the organization of these pathways. Further, it was important to characterize cerebrocerebellar pathways in the human brain using a structural rather than functional investigation to provide insight into how the cerebellum and frontal lobe are connected. Functional studies provide insight into arrays of neurons firing together (e.g. correlated functional signals) and can be used to infer connectivity, while the product of DTI tractography is structural connectivity maps. Moreover, by comprehensively mapping these connections between the cerebellum and frontal cortex using DTI, this work was able to quantitatively examine the differences in the microstructure of these pathways in the healthy and injured developing brain. Defining these pathways also enabled this work to explore the relation between cerebrocerebellar microstructure and speech-language and EF (i.e. whether there was an association between pathway damage and poorer speech-language and EF outcomes).

The findings from Chapters 2, 3, and 4 of this thesis demonstrated the vulnerability of cerebrocerebellar connections to the treatment effects of PF tumors. Though cerebrocerebellar connections were relatively qualitatively similar in patients and controls, there were significant microstructural differences in the pathways between groups. First, damage to whole-pathway bilateral reciprocal cerebrocerebellar pathways were evident in children treated for MB compared to controls (Chapter 4). This damage was indicated by higher MD, AD, and RD for the right CPC and right and left CTC pathways in patients relative to controls. Second, children treated for MB showed the most substantial damage to posterior segments of the CPC and CTC pathways compared to controls (i.e. lower FA and higher MD and RD for bilateral ponto-cerebellar segments and lower FA and higher MD and AD in bilateral cerebello-rubro, and rubro-thalamo segments) (Chapter 3). However, compromise to anterior segments of the CPC (i.e. left cerebro-ponto) and CTC (i.e. bilateral thalamo-cerebral) pathways were also found in patients relative to controls, though these were less robust (e.g. only one significant DTI measure) (Chapter 3). Third, damage to the cerebellar region of the right CTC pathway was evident in patients treated for PF tumors (who presented with CMS) compared to controls (Chapter 2).

This work contributes to the growing body of literature reporting neurotoxicity as a late effect in children treated for PF tumors and provides evidence for the particular vulnerability of cerebrocerebellar pathways in this population. Overall, this thesis demonstrated that cerebrocerebellar pathways sustain the greatest compromise to their posterior portions in children treated for PF tumors. Particularly, it is the damage to posterior segments of the cerebellar output (CTC) pathways that is the most robust finding in the current thesis. However, more anterior segments of the CTC pathway and multiple segments of the CPC pathways were also affected. This injury may reflect a diaschisis effect (which is typically thought to be transient, but may be permanent - see Smith, 1984 for a review of the diaschisis effect following brain injury) or result from the combined consequences of diffuse CRT and progressive white matter injury to the PF region. Thus, injury at one site (i.e. the initial damage to the cerebellum or within PF via treatment, reflected in damaged cerebello-rubro segments) results in subsequent injury to another, more distant site (i.e. damage to rubro-thalamo and thalamo-cerebral segments). Additionally, CTC pathways may sustain the most damage because they include throughputs such as the superior cerebellar peduncle; this region is relatively small in addition to residing medially in the brain, compared to the middle cerebellar peduncle (a larger relay within the CPC pathway that sits more laterally, further away from midline/4th ventricle).

The function of cerebrocerebellar pathways is to facilitate the transfer of electrical signals between the cerebellum and frontal lobe – brain regions that underlie aspects of EF and speech-language. Thus the pathways play an important role in the communication/information transfer between these two regions. In the current thesis, damage to the CTC pathway was associated with deficits in working memory and CMS. Specifically, the microstructure of the left CTC pathway had a mediating impact on working memory outcome in children treated for MB (e.g. greater damage predicted poorer outcome). Additionally, damage to the microstructure of the right CTC pathway (within the cerebellar region) predicted CMS in children treated for PF tumors. Both of these post-treatment effects/complications may be a result of disrupted communication between the cerebellum and frontal lobe, interfering with the efficient transfer of information.

It is known that the cerebellum is involved in the motoric aspects of speech (e.g. control of vocal tract muscles) and cerebellar damage or abnormality is associated with ataxia and dysarthria (Fiez et al., 1992). Further, the cerebellum is implicated in higher-order aspects of speech

production and perception (i.e. putting together proper sentences and generating fluent speech, planning of articulatory movement patterns, identification of distinct speech sound categories) (Ackermann, Mathiak, & Riecker, 2007). Consequently, damage to the right cerebellar hemisphere (in particular) is associated with agrammatism (Ackermann et al., 2007) and impaired performance on verbal intelligence and complex language tasks (Riva & Giorgi, 2000a). Patients with lesions of the left ventral prefrontal cortex and those with lesions to the cerebellum show poor articulatory control over their utterances (Ravizza et al., 2006). It is well known that left frontal regions are important in mediating speech production and expressive language (Broca, 1861; Geschwind, 1971; Mayeux & Kandel, 1991; Knecht et al., 2000a; Knecht et al., 2000b). Injury to the right cerebellar hemisphere may deprive left hemispheric cortical language areas of modulatory input, resulting in language processing errors (Fiez et al., 1992). It is logical that this thesis would find speech-language deficits in children treated for PF tumors and that CMS was related to CTC pathway damage at the level of the right cerebellum. It may be that right cerebellar hemisphere damage disrupts the modulatory input the cerebellum has to the frontal cortex; the planning of articulatory movement and identification of speech sounds begins within the right cerebellum and this information has to make its way to the left frontal lobe (e.g. areas responsible for turning the speech planning into grammatical verbal output).

The cerebellum has also been implicated in verbal EF (e.g. verbal fluency, working memory) and memory tasks (Ackermann et al., 2007). Indeed, isolated lesions within either cerebellar hemisphere have been related to memory deficits (de Ribaupierre, Ryser, Villemure, & Clarke, 2008) and impairment in verbal working memory (Ravizza et al., 2006). Right frontal cortex activation has been associated with both verbal and spatial working memory while left frontal cortex activation is apparent only in non-spatial working memory (Fiez et al., 1996; Courtney et al., 1998b; Prabhakaran et al., 2000). The cerebellum and frontal lobe consistently show increased activation during tasks of working memory; these regions have been postulated as essential for the rehearsal of items that are being actively remembered (Paulesu, Frith, & Frackowiak, 1993). Indeed, involved in "subvocal" articulatory rehearsal are the right cerebellar hemisphere, left inferior frontal gyrus, supplementary motor area, and insula (Paulesu et al., 1993). Previous findings demonstrate the involvement of both the cerebellum and frontal lobe in verbal/language production/processing and verbal working memory. It may be that the cerebellum underlies subvocal rehearsal mechanisms important for verbal working memory and

the timing/modulation of verbal responses (Ravizza et al., 2006). These findings support the notion that an interruption in cerebrocerebellar communication (i.e. feedback loop) impairs verbal processing/production and subvocal articulatory rehearsal mechanisms used during verbal working memory tasks.

Accordingly, the CTC pathway may house both an initiation/timing mechanism and a subvocal articulatory rehearsal mechanism that precede the output of speech; it is possible that this mechanism is localized to the cerebellar hemispheres, but the frontal lobe is also implicated. Damage to this pathway (e.g. via treatment for PF tumors) disrupts these mechanisms, impacting cerebellar feedback on frontal areas responsible for speech production and other aspects of verbal/spatial working memory – manifesting as both working memory deficits and symptoms of CMS in survivors. Work from this thesis provides evidence that brain function may not solely be based on one or multiple brain regions that underlie a specific common function – the connections that facilitate the communication between these distinct neural assemblies are also important.

These findings imply a close relationship between speech-language and working memory processes. Why do we see both speech-language and working memory deficits when the CTC pathway is damaged? This link between impairment in speech-language and working memory may be that compromised articulatory planning and rehearsal processes (thought to be housed within the cerebellum) impact the production and perception of verbal responses (residing within left frontal hemisphere). Developmental deficits in language skills have been linked to impairment in working memory, and is thought to be due to the inability to briefly store and process information (Montgomery, 2000; Archibald & Gathercole, 2006; Montgomery, Magimairaj, & Finney, 2010). The cerebellum has been postulated to represent an “inter-area functional coordinator” (Ackermann et al., 2007), underlying the timing and sequential organization of verbal utterances (Molinari, Leggio, & Silveri, 1997). It has also been postulated that speech-language difficulties (e.g. reduced verbal fluency) might reflect a disruption in temporal synchrony between the application of linguistic rules (e.g. syntax structure) and the retrieval of words (e.g. the availability of grammatical morphemes) temporarily stored in working memory (Ackermann et al., 2007). Conversely, subvocal articulatory rehearsal aspects of working memory may rely on speech-language areas (e.g. engaging a prearticulatory verbal

code and aiding in the recruitment of internal speech) (Ackermann et al., 2007; Ackermann, 2013).

It is important to note that both post-treatment outcomes were related to damage to the cerebellar output pathway, though each implicated a different cerebellar-cerebral laterality. Lesions of the right cerebellar hemisphere have been associated with verbal deficits while left cerebellar hemisphere lesions are associated with non-verbal deficits (Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004). Thus, it may be that the right CTC pathway has a greater involvement in the timing and modulation of verbal output while the left CTC pathway is more important in non-verbal aspects of speech-language (which could include subvocal articulatory rehearsal or verbal processing) that facilitate working memory. The working memory measures used in the current work were predominantly verbal tasks but one non-verbal task was also included. However, the current work did find associations between the microstructure of the right CTC pathway and working memory outcome in children treated for PF tumors (though when put into the final model, they were not as robust as those of the left CTC pathway in mediating the effect of treatment on working memory outcome). More data are needed to elucidate whether there is indeed a laterality effect with respect to working memory function or if bilateral CTC pathways are equally involved in working memory; it would also be interesting to see if handedness is associated with verbal working memory. Further, it would be pertinent to investigate whether the same neural components underlie performance on verbal and spatial working memory tasks (or if this is lateralized as well). These findings would have implications for a number of clinical populations; for example, patients with lesions to any portion of the CTC pathway may be most at risk for these deficits, and impairment may depend on locale and laterality of damage.

Obtaining information about the vulnerability of white matter circuits helps us to better understand the functioning of the main nodes such pathways serve to connect. Because the cerebellum and frontal lobe are both involved in speech-language and working memory, it is logical that the connection between these regions is also important for such functions. The CTC pathway is comprised of multiple nodes; it can be inferred that brain regions like the red nucleus and thalamus (within CTC connections) are similarly important in facilitating communication between the cerebellum and frontal lobe and are also implicated in speech-language and working memory function. It would be interesting to try to dissociate whether lesions along CTC circuits produce similar deficits seen in the current study in children with PF tumors. For example, future

research could investigate whether frontal, red nucleus, or thalamic lesions produce similar deficits (though these lesions would have to localize to very specific regions in order to perturb the CTC pathway). For example, though the role of the red nucleus is unclear, one of its functions is to receive inputs from the cerebellum and project to ventrolateral thalamic nuclei (which, in turn project to cortex) – all which make up the CTC pathway. However, the red nucleus is assumed to be involved in speech-language because it has been implicated in certain disorders affecting the articulation of structures important for producing speech (e.g. palatopharyngolaryngeal myoclonus) (Duffy, 2013). These principles can also be applied to the understanding the structure and function of other connections like the corpus callosum and uncinate fasciculus and what may occur when these circuits are damaged.

The majority of patients in the current work had midline PF tumors, thus structures closer to midline were assumed to be the most affected by treatment. Future studies could be conducted to determine the relation between tumor/lesion location and cerebrocerebellar pathway microstructure in survivors. For example, it would be interesting to determine if patients with midline tumors/lesions (e.g. the bulk of the tissue damage being within midline PF) show more or less damage to CPC and CTC pathways than those with left or right cerebellar hemispheric tumors. If they showed less damage it would mean that white matter within cerebellar portion of CTC pathway was spared and the microstructure should be similar to that of controls. However, midline PF tumors could result in greater compromise to superior cerebellar peduncles and CTC pathways would show greater damage. Tumor size and locale are also hypothesized to have an impact on the function of these pathways and should be investigated in future studies. Further, for patients with lateralized damage, it would be interesting to examine if a greater proportion of those with right cerebellar involvement had speech-language deficits versus those with left cerebellar involvement. These findings would contribute to the CMS risk schema that was proposed in the current work.

Lastly, this work could be applied to populations with deficits in both language and working memory. These deficits often co-occur in children with specific learning disabilities and ADHD (Archibald & Gathercole, 2006). For example, children with working memory impairments were found to have language/communication deficits even when they did not meet the criteria for a specific language impairment (Archibald & Gathercole, 2006). Language tasks, when they are relatively complex, place high demands on working memory (Baddeley, 2003). A working

memory deficit alone can impede academic performance. However, working memory impairment may also have bearing on meeting the language demands present in the classroom (Archibald & Gathercole, 2006). Thus, it is feasible that if a language task arises at school that exceeds their working memory capacity, children with working memory impairment are at risk for failure (Archibald & Gathercole, 2006). Future work could examine whether CTC pathways are impacted in these populations and whether damage to CTC microstructure plays a role in the severity of language and working memory impairments.

5.2 Executive Function

To provide a comprehensive understanding of EF in both healthy and clinical populations, recent studies have begun to utilize PCA or factor analyses to group a broad range of EF measures into meaningful component functions; the current work used this approach in both healthy children and children treated for PF tumors. Analyses from the current work yielded a congruent set of EF components with conceptual models of EF present in the literature; the factor loadings reflected distinct cognitive efficiency, planning/problem solving, working memory, and emotion regulation components. However, Chapter 4 of the current thesis is the first study to incorporate traditional measures of EF based on conceptual models (i.e. working memory, cognitive fluency, inhibition/switching, planning) with self-report measures of emotion regulation within one omnibus model, and to do so in children treated for MB. This thesis also investigated the role of reciprocal cerebrocerebellar connections in EF. Based on a path analysis model, CTC pathway microstructure was found to mediate the effects of treatment for MB on working memory outcome. This work supports previous evidence that EFs are not exclusively frontally-mediated functions (Kim et al., 1994; Fiez et al., 1996; Desmond et al., 1997; Schlosser et al., 1998; Ravizza et al., 2006; Schmahmann & Caplan, 2006; Bellebaum & Daum, 2007), and that cerebellar output pathways play an important role in working memory.

Debated in the literature is whether EF should be conceptualized as a unitary construct (i.e. one overarching function) versus a non-unitary construct (i.e. several diverse functions) (see Stuss & Alexander, 2000 for a review of EF as a unitary versus non-unitary process). For example, some view EFs as sharing a common executive attention component (i.e. unitary view) (see Shallice & Burgess, 1993 for review), while others maintain that EFs are best conceptualized as distinct, yet loosely related processes (i.e. non-unitary) (see Blair, Zelazo, & Greenberg, 2005 for review).

This work supports a non-unitary view of EF in that our EF components represented a collection of dissociable, relatively independent processes (supported by the PCA component loadings). However, recent findings have settled on characterizing EF as both a unitary and non-unitary concept (i.e. consisting of both unity and diversity of function) (Banich, 2004; Banich, 2009). The current findings also lend support to this contemporary view of EF as both a unitary and non-unitary concept; though measures of EF used in the current study were dissociable (i.e. loaded relatively cleanly onto separate components in PCA), several of the component structure coefficients from the PCA were correlated with each other (i.e. not completely independent). This component collinearity may have been due to the finding that some of the neurocognitive measures loading onto the cognitive efficiency and working memory components were correlated.

The current work observed select deficits in cognitive efficiency, planning/problem solving, working memory, and emotion regulation in children treated for MB compared to controls. These findings support previous work showing that this population is vulnerable to impairments in aspects of cognitive efficiency (i.e. processing speed and inhibition/switching) (Waber et al., 2006; Mabbott et al., 2008; Vaquero et al., 2008; Palmer et al., 2013) and working memory (Dennis et al., 1992; Dennis et al., 1998; Davidson et al., 2006; Kirschen et al., 2008; Vaquero et al., 2008; Law et al., 2011; Conklin et al., 2012; Palmer et al., 2013; Knight et al., 2014). This thesis also described deficits in other domains of cognitive efficiency (i.e. verbal fluency) and planning/problem solving. The finding of deficits in an EF component that includes verbal fluency in children treated for MB complements previous findings of impairment in verbal intellectual ability, word finding and verb generation, and complex language tasks in survivors of PF tumors and patients with cerebellar lesions (Levisohn et al., 2000; Riva & Giorgi, 2000b, 2000a; Schmahmann, 2004). Evidence of inhibition/switching problems in the current sample mirrors previous findings of impairment in task switching (Berger et al., 2005) and poor planning abilities (Grafman et al., 1992) following cerebellar damage, and deficits in set-shifting/flexibility in survivors of PF tumors (Vaquero et al., 2008).

This thesis also provides novel evidence that survivors of MB regulate their emotions differently than their healthy peers. It was found that children treated for MB made less use of positive cognitive emotion regulation strategies than healthy children. However, no differences were found between patients and controls for other emotion regulation components – the use of

negative cognitive emotion regulation strategies and mixed (a combination of positive and negative) cognitive emotion regulation strategies. These findings have implications for how children treated for MB rationalize or cope with negative, stressful events compared to their healthy peers. The use of positive cognitive emotion regulation strategies, such as reappraising a negative/stressful situation in a more positive way, is associated with lower levels of perceived stress and more favourable mental health outcomes (Helgeson et al., 2006). High rates of depression, anxiety, and adjustment disorders have recently been reported in a sample of survivors of pediatric MB (Campen, Ashby, Fisher, & Monje, 2012). Impaired cognitive emotion regulation in survivors of PF tumors may contribute to these mental health problems (or vice versa). Further investigation into the relation between emotion regulation and mental health outcome in children treated for PF tumors is required; findings can have implications on preventative therapy in this domain.

Findings from Chapter 4 of this thesis also have implications for the theory that as long as EFs are intact, even a person who has sustained substantial cognitive deficit can remain a productive and independent individual (Lezak, Howieson, & Loring, 2004). If this tenet is assumed, children treated for PF tumors with a range of core EF deficits will have problems in other functional and cognitive domains. In contrast, research in this domain in children treated for PF tumors (who may sustain diffuse white matter damage due to treatment effects) could be contrasted with that of patients with frontal lesions. For example, patients who sustain injury to the frontal lobe and have EF deficits may not show impairment in all cognitive domains (see Stuss & Benson, 1986; Stuss & Alexander, 2000 for review). Conversely, if we rehabilitate one or a number of EFs, would we see changes in overall cognitive functioning in survivors? EFs are essential for success in school, the workplace, and daily life. The ability to shift our mind set quickly and inhibit inappropriate behaviour allows us to adapt to the changing environment (Jurado & Rosselli, 2007). Planning and problem solving are also crucial skills that contribute to our ability to adapt to many situations; these abilities also enable us to create a plan, initiate its execution, and persevere until the task is completed (Jurado & Rosselli, 2007). Thus, deficits in multiple components of EF can have a substantial effect on other cognitive and behavioural functions, and impact performance in academic and occupational domains. Further research must be completed to elucidate the role of discrete EFs in overall cognitive outcome in survivors; findings could be applied to rehabilitation/intervention in select areas of EF. It is possible that one (or more) EFs

are crucial for certain cognitive processes (and thus, deficits in one will produce deficits in the other), while other EFs have no effect on the same processes (and even if they are affected, cognitive processes will not be). For example, in healthy adults, working memory/updating (as a latent variable of EF) has been found to predict IQ, while inhibition/shifting does not (Friedman et al., 2006).

Chapter 4 described novel findings of EF deficits of cognitive efficiency in children treated for PF tumors relative to healthy controls. It is unknown whether these findings represent slower speed of processing in patients, which is a frequently documented late effect in survivors of PF tumors (Mabbott et al., 2008; Palmer et al., 2013). One limitation of some the measures used to examine the EF cognitive efficiency construct is that they included a time factor (e.g. time taken to complete the task or a requirement to respond within a predetermined amount of time factored into the score assigned to each participant). Future studies should attempt to tease apart a "true" cognitive efficiency construct from a processing speed construct. It is possible that processing speed is a subcomponent of cognitive efficiency, though this should be explicitly investigated in future studies. Further, future studies should longitudinally examine EF in survivors of PF tumors to determine when these deficits emerge and whether recovery of these functions can occur.

The above issue prompts the discussion of the potential problems in measuring EFs. Limitations of measuring EF in both a healthy and clinical population include the issue of low construct validity or task impurity (i.e. EF tasks mapping onto multiple cognitive processes) and task dependency (i.e. there are no universally agreed-upon task or set of tasks to measure specific EFs) (Brocki & Bohlin, 2004). In attempt to counter these issues we used a comprehensive array of measures of EF, including multiple tasks within each EF domain. Additionally, in Chapter 4, a PCA was used to elucidate latent EF variables in a "mixed" population (i.e. both clinical and healthy populations were considered in the same model); however, this method has been used in previous studies (e.g. Caprihan, Pearlson, & Calhoun, 2008). In the current work, the goal of the PCA was not to discriminate between the groups – MANOVA was applied subsequent to PCA to determine group differences in components; PCA was used to reduce the data dimensionality without removing the essential features of the dataset.

5.3 Clinical Risk Stratification, Treatment Modification, and Intervention

Findings from this thesis are relevant for changing practice in children with brain tumors. Specifically, work from Chapter 2 may have implications for the overall medical management of PF tumors as well as the risk/benefit communication of therapy to patients and families. If it is known that CMS risk is higher in individuals with greater right cerebellar hemisphere injury, left-handedness, and higher tumor grade, and an incoming patient has these risk factors, this information can be given to the patients and their families to prepare them for this medical complication in the event it may occur. Additionally, this CMS risk schema is important information for the clinical care team to consider prior to treatment. If a patient presents with these risks, preemptive speech-language therapy can be commenced either prior to or within days following resection. This preemptive or anticipatory speech-language therapy is an alternative to a more mitigative therapy approach (e.g. waiting until the patient presents with CMS, then implementing speech-language therapy). Though this preemptive therapy may not preclude mutism itself, it may aid in lessening longer-term speech-language complications. Further, work from Chapter 2 may have bearing on best practices for providing clinical care to children treated for PF tumors. In determining CMS risk, this thesis found that damage to the CTC pathway at the level of the right cerebellar hemisphere distinguished between patients who presented with CMS and those who did not. Thus, these findings may have bearing on how children with PF tumors are treated surgically. Specifically, when surgical planning is taking place, explicit attention can be paid to the right cerebellar hemisphere (e.g. degree of tumor invasion within this area, amount of tissue damage in this area that can be predicted) in attempt to spare as much of this tissue as is possible, while still achieving maximal tumor resection. Though a minimal damage approach is assumed in current surgical practice, it is still important to be aware of the potential risk of right cerebellar damage and its impact on future speech-language outcome in patients.

Insight into the neurological basis of EF deficits (Chapter 4) can also have bearing on how we treat children with PF tumors. This thesis demonstrated that the CTC pathway is involved in working memory function. Particularly, it is the microstructure of the CTC pathway connecting the left cerebellar hemisphere with right frontal lobe that is implicated in working memory. Thus, if a child presents with a PF tumor located within the left cerebellar hemisphere, they may be at greater risk for working memory deficits due to the prospective damage to this region of the

cerebellum via resection of tumor. In cases for which there is left cerebellar involvement and surgical sparing of tissue is unavoidable, it may be pertinent to implement working memory training (i.e. Cogmed, see below) prophylactically.

Work from Chapter 4 has bearing on the late effects literature and has implications for improving long-term cognitive and behavioural outcomes in survivors. This thesis utilized specific tasks/measures of EF (relative to more global measures of cognitive function) to better inform us of the difficulties that may emerge in this domain following treatment for PF tumors. This work found that core EF deficits were present in survivors of PF tumors including cognitive efficiency (i.e. verbal fluency, inhibition/switching), planning/problem solving, working memory, and emotion regulation; these EFs should be what we look to when we develop targeted interventions for this population.

Preventing or mitigating EF impairment in children with PF tumors should be of prime focus, especially given the relation between EF and IQ (Friedman et al., 2006; Conklin et al., 2012) and the prevalence of global intellectual declines in survivors. For example, because the current work found working memory deficits in this population, working memory training can be implemented even prior to the problems emerging. For example, Cogmed Working Memory Training is an evidence-based computerized program that helps children and adolescents improve their ability to concentrate and increase their working memory capacity (http://www.cogmed.com). This program has shown some evidence of improving working memory in children with attention-deficit/hyperactivity disorder (ADHD) (Klingberg et al., 2005). Working memory training using Cogmed in survivors of childhood brain tumors is currently underway (http://www.cogmed.com/). Similar preventative/mitigative strategies can be applied for problems in planning/problem solving. For example, implementing planners, calendars, log sheets, step-by-step checklists would enable the child/adolescent to have a record of what is required of them to achieve a goal, promoting more efficient planning skills.

Further, the current work described problems in emotion regulation in children treated for PF tumors relative to healthy children; the use of positive, more adaptive cognitive emotion regulation strategies in the face of negative/stressful events was significantly lower in patients compared to controls. Failing to use adaptive mechanisms of emotion regulation can have implications on the coping strategies that are applied during times of stress and can in turn

impact mental health outcomes (Garnefski et al., 2001). Using less adaptive coping mechanisms may play a role in the elevated levels of depression and anxiety observed in survivors of MB (Campen et al., 2012). Thus, implementing interventions that teach patients positive emotion regulation strategies (i.e. refocusing and reappraising a stressful event in a more positive light) can promote the use of adaptive coping strategies. For example, the use of mindfulness-based stress and pain management courses focus on this type of therapy and have been shown not only to eliminate defective coping strategies but to substantially reduce stress (Garland et al., 2011).

The work in Chapter 2 did not explicitly consider the degree or duration of speech-language outcomes (i.e. degree of impairment and details of speech-language complications). Further, though the current thesis examined emotion regulation and CMS in survivors of PF tumors separately (i.e. Chapter 2 and Chapter 4), it is pertinent to investigate if deficits in emotion regulation are more prevalent in those who presented with CMS following treatment. It may be that children presenting with CMS are at a higher risk for persistent emotional/behavioural deficits and could be related to similar neural mechanisms being damaged. Future work should investigate whether more severe speech-language outcomes in CMS are related to a greater extent of damage (e.g. greater white matter volume loss, lower FA, and higher MD, AD, and RD) within the CTC pathway, or if there is a threshold for which pathway damage contributes to speech-language deficits. Additionally, subsequent research could determine the role (if any) of the CTC (or CPC) pathway in the behaviour/emotion/personality changes in children treated for PF tumors that present with CMS.

5.4 Methodological Contributions

One challenge of using DTI and tractography is validating the pathways that are obtained – this thesis benefitted from using animal models to guide tractography, one of the first studies to do so in children treated for PF tumors. This work produced a standardized template for obtaining and examining reciprocal cerebrocerebellar pathways in the developing brain (i.e. children and adolescents ages 7-18); future studies will be able to use this methodology (i.e. template ROIs) to replicate these pathways in other clinical populations. This work also outlined a reliable method of obtaining reciprocal cerebrocerebellar pathways using DTI based on 11 anatomically defined ROIs (established using synaptically relevant nodes from animal models). Unique ROI-based templates were also created from this work to segment cerebrocerebellar pathways into their

component parts. The methodology used in the current work also has broader applications in that it can be used to identify white matter pathways not yet found in humans.

The methodology for obtaining the pathways improved between Chapter 2 (CTC pathway only) and Chapters 3 and 4 (both the CPC and CTC pathways were obtained). Parsing reciprocal cerebrocerebellar pathways (e.g. disentangling tracts that run through pontine nuclei versus those that course though thalamic nuclei and fibres running through the superior cerebellar peduncle versus the middle cerebellar peduncle) was a difficult process. Cerebrocerebellar pathways are comprised of several different tracts/fibre bundles (i.e. thalamo-cortical, rubro-thalamo), which may be shared with other circuits/pathways. It was discovered that employing multiple ROIs (again, based on anatomical landmarks of the pathways described in animal models) solved this problem. Thus, five ROI templates were created to sufficiently and consistently obtain the CPC pathway (i.e. right and left cerebellar hemisphere, pons, and right and left frontal lobe), while ten ROI templates were used for the CTC pathway (i.e. right and left cerebellar hemisphere, right and left superior cerebellar peduncle, right and left red nucleus, right and left thalamus, and right and left frontal lobe). This tractography approach used in this work ensured the consideration of only those fibres connecting all ROIs inputted (i.e. for the CTC pathway, only fibres that ran though cerebellum, superior cerebellar peduncle, red nucleus, thalamus, and frontal lobe were considered to produce the pathways). This methodology also ensured minimal identification of erroneous fibres (i.e. those not constituting the CPC or CTC pathways). These findings have bearing on the identification of other white matter pathways that involve multiple nodes and are comprised of different tracts (i.e. long range pathways like the fronto-occipital fasciculus) in the human brain.

5.5 Challenges and Opportunities

The challenges in this overall program of research were recruiting a sufficient number of clinical participants as well as finding appropriate control samples. For example, some patient populations were difficult to recruit (i.e. children treated for astrocytoma), and thus were not included in Chapters 3 and 4. This population is ideal as a patient control group (i.e. “surgical control”) to tease apart the effect of surgery alone versus surgery plus CRT and CTX in children treated for PF tumors on neurological and cognitive/behavioural outcome. As children with astrocytoma are typically treated with surgery only, they do not require adjuvant therapy and the

resultant number hospital and clinic visits are less than that of a child treated for MB, making it more difficult to contact this particular group. Measures could be taken in the future to reach out to this patient population at time of initial treatment and inform them of opportunities to participate in research studies; the clinical team and researchers would have to work together in this regard (e.g. making the recruitment of participants for research part of the intake process for new patients). This thesis was also unable to parse the effects of CRT versus CTX on neurological outcome in survivors of PF tumors. Currently there are no treatment protocols for PF tumors that provide CTX as the only therapy; studies are thus focusing on comparing pediatric brain tumor populations who have received reduced doses CRT versus standard CRT. Future research is necessary to attempt to tease apart the neurotoxic effects of CRT and CTX. For example, pediatric cancer populations that are treated solely with CTX, such as children with acute lymphoblastic leukemia, could serve as a "CTX control" for their counterparts treated with CRT and CTX and this could help inform what impact CTX has on white matter for other pediatric cancer populations.

In Chapters 2, 3, and 4, DTI was used to examine the microstructure of cerebrocerebellar pathways in children treated for PF tumors and healthy controls. To ensure large sample sizes, it was necessary to use imaging data acquired from two different MRI scanners – at 1.5T and 3T. Though there have been some concerns of using imaging data with "mixed" field strengths, it has been concluded that using 1.5T and 3T data together does not necessarily reduce the validity of group analyses (Han & Talavage, 2011), especially when data from a scanner-matched control group are obtained.

Though DTI and tractography are useful for examining the microstructure of white matter pathways in vivo and using this information to compare microstructural between the healthy and injured brain, there are several limitations of this methodology. Like many imaging techniques, DTI suffers from image distortions like susceptibility artifacts, eddy current artifacts, and signal intensity loss (Lascola, 2005). These issues were remedied in the current study by using image correction tools: motion and eddy current corrections, and non-linear transformations and registrations during the pre-processing of images phase. The partial volume effect (PVE; when a voxel contains more than one kind of tissue type, blurring the intensity distinction between tissue classes at the border of the two tissues) is a particular problem for tractography, especially when 1.5T or a lower SNR is used (Vos, Jones, Viergever, & Leemans, 2011). Partial volume effects

may influence local diffusivity results, especially in small white matter tracts, and in turn, could skew DTI measures; the findings of this thesis should be considered in light of these limitations. However, all of the images in the current sample were susceptible to these effects; images from both control and patient groups had an equal chance of being effected by PVE. Further, both the CPC and CTC are relatively large, long-range pathways that do not run near the ventricles (i.e. cerebrospinal fluid), which slightly minimizes their susceptibility to PVE (Cao, Gold, & Zhang, 2008). Additionally, there are currently no reference norms for white matter microstructure in vivo, for white matter regions or pathways in the developing (or adult) brain. To rectify this problem, age-matched healthy control populations were included as references for "normal" white matter pathway microstructure to compare with our patient samples. Likewise, in attempting to tease apart the effect of injury on cerebrocerebellar pathways, it may be useful for subsequent research to obtain imaging data for other clinical populations (i.e. to act as "clinical control" groups). For example, examining cerebrocerebellar microstructure in patients with localized thalamic lesions or frontal lesions (who have not undergone treatment with radiation) may show a different pattern of white matter injury to these pathways. This analysis would be interesting in that both the frontal lobe and thalamus has been implicated in EF; injury to the frontal lobe is typically associated with disturbances in EF (Stuss & Benson, 1986; Stuss & Alexander, 2000), while damage to the thalamus is associated with dysexecutive or "prefrontal" symptoms (which may occur alone or in conjunction with memory problems) (Daum & Ackermann, 1994; Van der Werf, Witter, Uylings, & Jolles, 2000). Thus, examining both cerebrocerebellar microstructure and EF in these populations will provide insight into the potential regional specificity of these pathways and their role in EF (i.e. is it injury to the posterior portions of these pathways only that is associated with specific EF deficits, or is focal injury to thalamic or frontal nuclei strictly within these pathways sufficient to produce EF deficits?).

The current work presents several areas for future research. First, future work in this area should focus on neuroimaging techniques that provide functional connectivity measures and a temporal component (e.g. fMRI, EEG) in children treated for PF tumors or in patients with CTC pathway lesions. These techniques could reveal what regions of the brain are becoming active or "online" (and how close in time they are doing so) during speech-language and working memory tasks – especially those that call upon subvocal articulatory rehearsal. It would be interesting to not only

show cerebellar and frontal lobe involvement in such tasks, but the lateralization of activation and the timing of each region's contribution to the task at hand. Doing so would help elucidate whether both main nodes within the CTC circuit are activating in children treated for PF tumors (or patients with specific CTC pathway lesions), and whether this feedback pathway is inactive (supporting that the connections are truly damaged) or just slow in its synchrony (supporting that myelin, but not necessarily axon structure is damaged).

Second, research examining structure-function relations suggest that neuroanatomical regions of the cerebellum are involved in different processes; the vermis governs emotional-affective processing, the anterior lobe is implicated in motor control, and the posterior cerebellum is thought to mediate complex cognitive processing (Schmahmann & Sherman, 1998; Levisohn et al., 2000; Schmahmann, 2004; Schmahmann, Weilburg, & Sherman, 2007; Tavano et al., 2007; Stoodley & Schmahmann, 2009, 2010). White matter pathways connecting the anterior cerebellum or the vermis with other brain regions were not investigated in the current thesis; future work should consider the structure of such pathways (e.g. using DTI to examine their microstructure) as well as the functions they may subserve. For example, pathways involving the vermis may be implicated in emotion/affect control – examining the impact of treatment for PF tumors on vermal pathways could provide insight into the neural basis of behavioural problems observed in survivors. Further, other brain regions and pathways are likely to be involved in complex EF processes and speech-language and should be investigated, particularly in children treated for PF tumors. For instance, fronto-parietal networks have been implicated in working memory (Barbey et al., 2012); damage to this pathway could also contribute to EF deficits in survivors.

Further, to fully elucidate the role of the cerebrocerebellar pathways in specific cognitive/behavioural functions, we would have to investigate a range of neurocognitive domains to determine those functions that are not associated with cerebrocerebellar microstructure. Additionally, pathways other than those investigated in the present work should be delineated using DTI and associated with EF or CMS outcome in survivors. Future work could delineate, for example, cortico-spinal pathways in survivors of PF tumors. The cortico-spinal tract originates in upper motor neurons within the cerebral cortex and terminates in the spinal cord. This pathway is involved in the movement of muscles in the body and damage to its structure is associated with motor signs and symptoms (Eisen & Shaw, 2007). This thesis determined an

association between the microstructure of cerebellar input and output pathways to the frontal lobe in working memory and the involvement of a cerebellar output pathway in CMS. Using this information, we would first try to establish an association between poorer performance on hand motor tasks (e.g. grooved pegboard test) and cortico-spinal pathway microstructure in MB and HC. Then, if we could subsequently determine that there was no association between cortico-spinal pathway microstructure and working memory performance, and likewise, no association between cerebrocerebellar pathway microstructure and hand motor task performance, we would have evidence for a double dissociation.

Third, applying DTI principles described in the present study for obtaining other (e.g. supratentorial) white matter pathways that may be implicated in impaired function in brain tumor survivors is a direction for future research. For example, children treated for MB show long-term impairments in declarative memory – decreased hippocampal volume and uncinate fasciculus damage have been identified as potential neural correlates (Riggs et al., 2014). The uncinate fasciculus connects the limbic system (i.e. hippocampus and amygdala) with frontal cortical areas. Besides being implicated in mental illness, this pathway has been found to play a role in memory, language, and social emotional processing (see Von Der Heide, Skipper, Klobusicky, & Olson, 2013 for a review). It might be interesting to delineate and examine such pathways and how they relate to memory, EF, CMS, and emotional/behavioural outcome in children treated for brain tumors. Because this pathway is outside of the PF, damage to its structure could be the result of CRT alone in survivors of PF tumors. It would also be interesting to examine if there were differences in uncinate fasciculus structure between patients treated with reduced versus standard CRT. Knowledge of white matter pathways and their role in specific functions, as well as principles of how to define and examine the pathways in the human brain, could be transferred to other populations with white matter disorders (e.g. multiple sclerosis, progressive multifocal leukoencephalopathy, post-infectious encephalitis) or traumatic brain injury.

References

Aarsen, F. K., Van Dongen, H. R., Paquier, P. F., Van Mourik, M., & Catsman-Berrevoets, C. E. (2004). Long-term sequelae in children after cerebellar astrocytoma surgery. *Neurology, 62*(8), 1311-1316.

Ackermann, H. (2013). The contribution of the cerebellum to speech and language. *Brain Lang, 127*(3), 315-316. doi: 10.1016/j.bandl.2013.10.006

Ackermann, H., Mathiak, K., & Riecker, A. (2007). The contribution of the cerebellum to speech production and speech perception: clinical and functional imaging data. *Cerebellum, 6*(3), 202-213. doi: 10.1080/14734220701266742

Akshoomoff, N. A., & Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. *Behav Neurosci, 106*(5), 731-738.

Allen, G., Buxton, R. B., Wong, E. C., & Courchesne, E. (1997). Attentional activation of the cerebellum independent of motor involvement. *Science, 275*(5308), 1940-1943.

Allen, G., McColl, R., Barnard, H., Ringe, W. K., Fleckenstein, J., & Cullum, C. M. (2005). Magnetic resonance imaging of cerebellar-prefrontal and cerebellar-parietal functional connectivity. *Neuroimage, 28*(1), 39-48. doi: 10.1016/j.neuroimage.2005.06.013

AnalyzeDirect. Analyze 11.0: Mayo Clinic.

Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychol, 8*(2), 71-82. doi: 10.1076/chin.8.2.71.8724

Anderson, V. (2001). Assessing executive functions in children: biological, psychological, and developmental considerationst. *Pediatr Rehabil, 4*(3), 119-136.

Apps, R., & Watson, T. C. (2009). The Cerebellum and its Connections. In Snell, R. S. (Ed.), *Clinical Neuroanatomy* (7 ed.): Lippincott, Williams & Wilkins.

Archibald, L. M., & Gathercole, S. E. (2006). Short-term and working memory in specific language impairment. *Int J Lang Commun Disord, 41*(6), 675-693. doi: 10.1080/13682820500442602

Armstrong, G. T., Liu, Q., Yasui, Y., Huang, S., Ness, K. K., Leisenring, W., Hudson, M. M., Donaldson, S. S., King, A. A., Stovall, M., Krull, K. R., Robison, L. L., & Packer, R. J. (2009). Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst, 101*(13), 946-958. doi: 10.1093/jnci/djp148

Asanuma, C., Thach, W. T., & Jones, E. G. (1983). Distribution of cerebellar terminations and their relation to other afferent terminations in the ventral lateral thalamic region of the monkey. *Brain Res, 286*(3), 237-265.

Ashtari, M., Cervellione, K. L., Hasan, K. M., Wu, J., McIlree, C., Kester, H., Ardekani, B. A., Roofeh, D., Szeszko, P. R., & Kumra, S. (2007). White matter development during late adolescence in healthy males: a cross-sectional diffusion tensor imaging study. *Neuroimage, 35*(2), 501-510. doi: 10.1016/j.neuroimage.2006.10.047

Baddeley, A. (2003). Working memory and language: an overview. *J Commun Disord, 36*(3), 189-208.

Bähr, M., Frotscher, M., & Duus, P. (2005). *Duus' topical diagnosis in neurology : anatomy, physiology, signs, symptoms* (4th, completely rev. ed.). Stuttgart ; New York: Thieme.

Baldo, J. V., Shimamura, A. P., Delis, D. C., Kramer, J., & Kaplan, E. (2001). Verbal and design fluency in patients with frontal lobe lesions. *J Int Neuropsychol Soc, 7*(5), 586-596.

Balsters, J. H., & Ramnani, N. (2008). Symbolic representations of action in the human cerebellum. *Neuroimage, 43*(2), 388-398. doi: 10.1016/j.neuroimage.2008.07.010

Balsters, J. H., & Ramnani, N. (2011). Cerebellar plasticity and the automation of first-order rules. *J Neurosci, 31*(6), 2305-2312. doi: 10.1523/JNEUROSCI.4358-10.2011

Banich, M. T. (2004). *Cognitive neuroscience and neuropsychology* (2nd ed.). Boston: Houghton Mifflin Co.

Banich, M. T. (2009). Executive function: The search for an integrated account. *Current Directions in Psychological Science, 18*, 89-94.

Barbey, A. K., Colom, R., Solomon, J., Krueger, F., Forbes, C., & Grafman, J. (2012). An integrative architecture for general intelligence and executive function revealed by lesion mapping. *Brain, 135*(Pt 4), 1154-1164. doi: 10.1093/brain/aws021

Barkley, R. A., Edwards, G., Laneri, M., Fletcher, K., & Metevia, L. (2001). Executive functioning, temporal discounting, and sense of time in adolescents with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). *J Abnorm Child Psychol, 29*(6), 541-556.

Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., Dant, C. C., & Reiss, A. L. (2005). White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cereb Cortex, 15*(12), 1848-1854. doi: 10.1093/cercor/bhi062

Basser, P. J. (1995). Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR Biomed, 8*(7-8), 333-344.

Bauer, R. H., & Fuster, J. M. (1976). Delayed-matching and delayed-response deficit from cooling dorsolateral prefrontal cortex in monkeys. *J Comp Physiol Psychol, 90*(3), 293-302.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed, 15*(7-8), 435-455. doi: 10.1002/nbm.782

Beebe, D. W., Ris, M. D., Armstrong, F. D., Fontanesi, J., Mulhern, R., Holmes, E., & Wisoff, J. H. (2005). Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: evidence of diminished cognitive and adaptive functioning in National Collaborative Research Studies (CCG 9891/POG 9130). *J Clin Oncol, 23*(22), 5198-5204. doi: 10.1200/JCO.2005.06.117

Behrens, T. E., Berg, H. J., Jbabdi, S., Rushworth, M. F., & Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *Neuroimage, 34*(1), 144-155. doi: 10.1016/j.neuroimage.2006.09.018

Behrens, T. E., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A., Boulby, P. A., Barker, G. J., Sillery, E. L., Sheehan, K., Ciccarelli, O., Thompson, A. J., Brady, J. M., & Matthews, P. M. (2003a). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci, 6*(7), 750-757. doi: 10.1038/nn1075

Behrens, T. E., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., Matthews, P. M., Brady, J. M., & Smith, S. M. (2003b). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med, 50*(5), 1077-1088. doi: 10.1002/mrm.10609

Bellebaum, C., & Daum, I. (2007). Cerebellar involvement in executive control. *Cerebellum, 6*(3), 184-192. doi: 10.1080/14734220601169707

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, 57*(1), 289-300.

Bennett, C. M., Wolford, G. L., & Miller, M. B. (2009). The principled control of false positives in neuroimaging. *Soc Cogn Affect Neurosci, 4*(4), 417-422. doi: 10.1093/scan/nsp053

Berger, A., Sadeh, M., Tzur, G., Shuper, A., Kornreich, L., Inbar, D., Cohen, I. J., Michowiz, S., Yaniv, I., Constantini, S., Kessler, Y., & Meiran, N. (2005). Task switching after cerebellar damage. *Neuropsychology, 19*(3), 362-370. doi: 10.1037/0894-4105.19.3.362

Blair, C., Zelazo, P. D., & Greenberg, M. T. (2005). The measurement of executive function in early childhood. *Dev Neuropsychol, 28*(2), 561-571. doi: 10.1207/s15326942dn2802_1

Bleyer, W. A. (1999). Epidemiologic impact of children with brain tumors. *Childs Nerv Syst, 15*(11-12), 758-763.

Borkowski, J. G., & Burke, J. E. (1996). Attention, memory, and executive function. In Lyon, G. R. & Krasnegor, N. A. (Eds.), *Theories, models, and measurements of executive functioning: An information processing perspective.* (pp. 235-261). Baltimore, MD: Paul Brookes.

Bower, J., Low, C., Moscowitz, J., Sepah, S., & Epel, E. (2008). Benefit finding and physical health: Positive psychological changes and enhanced allostasis. *Social and Personality Psychology Compass, 2*(1), 223-244.

Briere, M. E., Scott, J. G., McNall-Knapp, R. Y., & Adams, R. L. (2008). Cognitive outcome in pediatric brain tumor survivors: delayed attention deficit at long-term follow-up. *Pediatr Blood Cancer, 50*(2), 337-340. doi: 10.1002/pbc.21223

Broca, P. (1861). Remarks on the seat of the faculty of articulated language, following an observation of aphemia (loss of speech). *Bulletin de la Societe Anatomique, 6*, 330-357.

Brocki, K. C., & Bohlin, G. (2004). Executive functions in children aged 6 to 13: a dimensional and developmental study. *Dev Neuropsychol, 26*(2), 571-593. doi: 10.1207/s15326942dn2602_3

Brodal, P. (1978). Principles of organization of the monkey corticopontine projection. *Brain Res, 148*(1), 214-218.

Brodal, P., & Bjaalie, J. G. (1997). Salient anatomic features of the cortico-ponto-cerebellar pathway. *Prog Brain Res, 114*, 227-249.

Brunamonti, E., Chiricozzi, F. R., Clausi, S., Olivito, G., Giusti, M. A., Molinari, M., Ferraina, S., & Leggio, M. (2014). Cerebellar damage impairs executive control and monitoring of movement generation. *PLoS One, 9*(1), e85997. doi: 10.1371/journal.pone.0085997

Campen, C. J., Ashby, D., Fisher, P. G., & Monje, M. (2012). Psychiatric symptoms in children with medulloblastoma. *Neuro Oncol, 14*, i125-i139. doi: 10.1093/neuonc/nos106

Caner, H., Altinors, N., Benli, S., Calisaneller, T., & Albayrak, A. (1999). Akinetic mutism after fourth ventricle choroid plexus papilloma: treatment with a dopamine agonist. *Surg Neurol, 51*(2), 181-184.

Cao, N., Gold, B. T., & Zhang, J. (2008). Partial volume effect of cingulum tract in diffusion-tensor MRI. *Physiology, Function, and Structure from Medical Images.* Retrieved March 12, 2008

Caprihan, A., Pearlson, G. D., & Calhoun, V. D. (2008). Application of principal component analysis to distinguish patients with schizophrenia from healthy controls based on fractional anisotropy measurements. *Neuroimage, 42*(2), 675-682. doi: 10.1016/j.neuroimage.2008.04.255

Carrico, A. W., Ironson, G., Antoni, M. H., Lechner, S. C., Duran, R. E., Kumar, M., & Schneiderman, N. (2006). A path model of the effects of spirituality on depressive symptoms and 24-h urinary-free cortisol in HIV-positive persons. *J Psychosom Res, 61*(1), 51-58. doi: 10.1016/j.jpsychores.2006.04.005

Catsman-Berrevoets, C. E., & Aarsen, F. K. (2010). The spectrum of neurobehavioural deficits in the Posterior Fossa Syndrome in children after cerebellar tumour surgery. *Cortex, 46*(7), 933-946. doi: 10.1016/j.cortex.2009.10.007

Catsman-Berrevoets, C. E., Van Dongen, H. R., Mulder, P. G., Paz y Geuze, D., Paquier, P. F., & Lequin, M. H. (1999). Tumour type and size are high risk factors for the syndrome of "cerebellar" mutism and subsequent dysarthria. *J Neurol Neurosurg Psychiatry, 67*(6), 755-757.

Catsman-Berrevoets, C. E., van Dongen, H. R., & Zwetsloot, C. P. (1992). Transient loss of speech followed by dysarthria after removal of posterior fossa tumour. *Dev Med Child Neurol, 34*(12), 1102-1109.

Chan, R. C., Chen, E. Y., Cheung, E. F., Chen, R. Y., & Cheung, H. K. (2006). The components of executive functioning in a cohort of patients with chronic schizophrenia: a multiple single-case study design. *Schizophr Res, 81*(2-3), 173-189. doi: 10.1016/j.schres.2005.08.011

Chen, S. H., & Desmond, J. E. (2005). Cerebrocerebellar networks during articulatory rehearsal and verbal working memory tasks. *Neuroimage, 24*(2), 332-338. doi: 10.1016/j.neuroimage.2004.08.032

Ciccarelli, O., Behrens, T. E., Altmann, D. R., Orrell, R. W., Howard, R. S., Johansen-Berg, H., Miller, D. H., Matthews, P. M., & Thompson, A. J. (2006). Probabilistic diffusion tractography: a potential tool to assess the rate of disease progression in amyotrophic lateral sclerosis. *Brain, 129*(Pt 7), 1859-1871. doi: 10.1093/brain/awl100

Collette, F., & Van der Linden, M. (2002). Brain imaging of the central executive component of working memory. *Neurosci Biobehav Rev, 26*(2), 105-125.

Collette, F., Van der Linden, M., Laureys, S., Delfiore, G., Degueldre, C., Luxen, A., & Salmon, E. (2005). Exploring the unity and diversity of the neural substrates of executive functioning. *Hum Brain Mapp, 25*(4), 409-423. doi: 10.1002/hbm.20118

Comrey, A. L., & Lee, H. B. (1992). *A first course in factor analysis* (2nd ed.). Hillsdale, N.J.: L. Erlbaum Associates.

Conklin, H. M., Ashford, J. M., Howarth, R. A., Merchant, T. E., Ogg, R. J., Santana, V. M., Reddick, W. E., Wu, S., & Xiong, X. (2012). Working memory performance among childhood brain tumor survivors. *J Int Neuropsychol Soc, 18*(6), 996-1005. doi: 10.1017/S1355617712000793

Costello, A. B., & Osborne, J. W. (2005). Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. *Practical Assessment, Research, & Evaluation, 10*(7).

Courtney, S. M., Petit, L., Haxby, J. V., & Ungerleider, L. G. (1998a). The role of prefrontal cortex in working memory: examining the contents of consciousness. *Philos Trans R Soc Lond B Biol Sci, 353*(1377), 1819-1828. doi: 10.1098/rstb.1998.0334

Courtney, S. M., Petit, L., Maisog, J. M., Ungerleider, L. G., & Haxby, J. V. (1998b). An area specialized for spatial working memory in human frontal cortex. *Science, 279*(5355), 1347-1351.

Cruess, D. G., Antoni, M. H., Schneiderman, N., Ironson, G., McCabe, P., Fernandez, J. B., Cruess, S. E., Klimas, N., & Kumar, M. (2000). Cognitive-behavioral stress management

increases free testosterone and decreases psychological distress in HIV-seropositive men. *Health Psychol, 19*(1), 12-20.

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends Cogn Sci, 7*(9), 415-423.

Daum, I., & Ackermann, H. (1994). Frontal-type memory impairment associated with thalamic damage. *Int J Neurosci, 77*(3-4), 187-198.

David, K. M., Casey, A. T., Hayward, R. D., Harkness, W. F., Phipps, K., & Wade, A. M. (1997). Medulloblastoma: is the 5-year survival rate improving? A review of 80 cases from a single institution. *J Neurosurg, 86*(1), 13-21. doi: 10.3171/jns.1997.86.1.0013

Davidson, M. C., Amso, D., Anderson, L. C., & Diamond, A. (2006). Development of cognitive control and executive functions from 4 to 13 years: evidence from manipulations of memory, inhibition, and task switching. *Neuropsychologia, 44*(11), 2037-2078. doi: 10.1016/j.neuropsychologia.2006.02.006

de Lacoste, M. C., Horvath, D. S., & Woodward, D. J. (1991). Possible sex differences in the developing human fetal brain. *J Clin Exp Neuropsychol, 13*(6), 831-846. doi: 10.1080/01688639108405101

de Ribaupierre, S., Ryser, C., Villemure, J. G., & Clarke, S. (2008). Cerebellar lesions: is there a lateralisation effect on memory deficits? *Acta Neurochir (Wien), 150*(6), 545-550; discussion 550. doi: 10.1007/s00701-008-1562-5

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan Executive Function System (D-KEFS).* San Antonio, TX: The Psychological Corporation.

Dennis, M., Hetherington, C. R., & Spiegler, B. J. (1998). Memory and attention after childhood brain tumors. *Med Pediatr Oncol, Suppl 1*, 25-33.

Dennis, M., Spiegler, B. J., Hetherington, C. R., & Greenberg, M. L. (1996). Neuropsychological sequelae of the treatment of children with medulloblastoma. *J Neurooncol, 29*(1), 91-101.

Dennis, M., Spiegler, B. J., Obonsawin, M. C., Maria, B. L., Cowell, C., Hoffman, H. J., Hendrick, E. B., Humphreys, R. P., Bailey, J. D., & Ehrlich, R. M. (1992). Brain tumors in children and adolescents--III. Effects of radiation and hormone status on intelligence and on working, associative and serial-order memory. *Neuropsychologia, 30*(3), 257-275.

Desmond, J. E., Chen, S. H., & Shieh, P. B. (2005). Cerebellar transcranial magnetic stimulation impairs verbal working memory. *Ann Neurol, 58*(4), 553-560. doi: 10.1002/ana.20604

Desmond, J. E., Gabrieli, J. D., & Glover, G. H. (1998). Dissociation of frontal and cerebellar activity in a cognitive task: evidence for a distinction between selection and search. *Neuroimage, 7*(4 Pt 1), 368-376. doi: 10.1006/nimg.1998.0340

Desmond, J. E., Gabrieli, J. D., Wagner, A. D., Ginier, B. L., & Glover, G. H. (1997). Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functional MRI. *J Neurosci, 17*(24), 9675-9685.

Dhall, G. (2009). Medulloblastoma. *J Child Neurol, 24*(11), 1418-1430. doi: 10.1177/0883073809341668

Di Rocco, C., Chieffo, D., Frassanito, P., Caldarelli, M., Massimi, L., & Tamburrini, G. (2011). Heralding cerebellar mutism: evidence for pre-surgical language impairment as primary risk factor in posterior fossa surgery. *Cerebellum, 10*(3), 551-562. doi: 10.1007/s12311-011-0273-2

Diamond, A., Kirkham, N., & Amso, D. (2002). Conditions under which young children can hold two rules in mind and inhibit a prepotent response. *Dev Psychol, 38*(3), 352-362.

Duffy, J. R. (2013). *Motor speech disorders : substrates, differential diagnosis, and management* (Third edition. ed.). St. Louis, Missouri: Elsevier.

Duke, L. M., & Kaszniak, A. W. (2000). Executive control functions in degenerative dementias: a comparative review. *Neuropsychol Rev, 10*(2), 75-99.

Dum, R. P., & Strick, P. L. (2003). An unfolded map of the cerebellar dentate nucleus and its projections to the cerebral cortex. *J Neurophysiol, 89*(1), 634-639. doi: 10.1152/jn.00626.2002

Edelstein, K., Spiegler, B. J., Fung, S., Panzarella, T., Mabbott, D. J., Jewitt, N., D'Agostino, N. M., Mason, W. P., Bouffet, E., Tabori, U., Laperriere, N., & Hodgson, D. C. (2011). Early aging in adult survivors of childhood medulloblastoma: long-term neurocognitive, functional, and physical outcomes. *Neuro Oncol, 13*(5), 536-545. doi: 10.1093/neuonc/nor015

Edwards-Brown, M. K., & Jakacki, R. I. (1999). Imaging the central nervous system effects of radiation and chemotherapy of pediatric tumors. *Neuroimaging Clin N Am, 9*(1), 177-193.

Eisen, A., & Shaw, P. J. (2007). *Motor neuron disorders and related diseases*. Edinburgh ; New York: Elsevier.

Evarts, E. V., & Thach, W. T. (1969). Motor mechanisms of the CNS: cerebrocerebellar interrelations. *Annu Rev Physiol, 31*, 451-498. doi: 10.1146/annurev.ph.31.030169.002315

Fiez, J. A., Petersen, S. E., Cheney, M. K., & Raichle, M. E. (1992). Impaired non-motor learning and error detection associated with cerebellar damage. A single case study. *Brain, 115 Pt 1*, 155-178.

Fiez, J. A., Raife, E. A., Balota, D. A., Schwarz, J. P., Raichle, M. E., & Petersen, S. E. (1996). A positron emission tomography study of the short-term maintenance of verbal information. *J Neurosci, 16*(2), 808-822.

Filipek, P. A., Richelme, C., Kennedy, D. N., & Caviness, V. S., Jr. (1994). The young adult human brain: an MRI-based morphometric analysis. *Cereb Cortex, 4*(4), 344-360.

Finger, S., Koehler, P. J., & Jagella, C. (2004). The Monakow concept of diaschisis: origins and perspectives. *Arch Neurol, 61*(2), 283-288. doi: 10.1001/archneur.61.2.283

Fisk, J. E., & Sharp, C. A. (2004). Age-related impairment in executive functioning: updating, inhibition, shifting, and access. *J Clin Exp Neuropsychol, 26*(7), 874-890. doi: 10.1080/13803390490510680

Friedman, N. P., Miyake, A., Corley, R. P., Young, S. E., Defries, J. C., & Hewitt, J. K. (2006). Not all executive functions are related to intelligence. *Psychol Sci, 17*(2), 172-179. doi: 10.1111/j.1467-9280.2006.01681.x

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic "scotomas". *J Neurosci, 13*(4), 1479-1497.

Garcia-Barrera, M. A., Karr, J. E., & Kamphaus, R. W. (2013). Longitudinal applications of a behavioral screener of executive functioning: assessing factorial invariance and exploring latent growth. *Psychol Assess, 25*(4), 1300-1313. doi: 10.1037/a0034046

Garland, E. L., Gaylord, S. A., & Fredrickson, B. L. (2011). Positive reappraisal mediates the stress-reductive effects of mindfulness: An upward spiral process. *Mindfulness, 2*(1), 59-67.

Garland, E. L., Gaylord, S. A., & Park, J. (2009). The role of mindfulness in positive reappraisal. *Explore (NY), 5*(1), 37-44.

Garnefski, N., Kraaij, V., & Spinhoven, P. (2001). Negative life events, cognitive emotion regulation, and emotional problems. *Personality and Individual Differences, 30*, 1311-1327.

Garon, N., Bryson, S. E., & Smith, I. M. (2008). Executive function in preschoolers: a review using an integrative framework. *Psychol Bull, 134*(1), 31-60. doi: 10.1037/0033-2909.134.1.31

Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (2002). *Cognitive neuroscience : the biology of the mind* (2nd ed.). New York: Norton.

Gelabert-Gonzalez, M., & Fernandez-Villa, J. (2001). Mutism after posterior fossa surgery. Review of the literature. *Clin Neurol Neurosurg, 103*(2), 111-114.

Germano, A., Baldari, S., Caruso, G., Caffo, M., Montemagno, G., Cardia, E., & Tomasello, F. (1998). Reversible cerebral perfusion alterations in children with transient mutism after posterior fossa surgery. *Childs Nerv Syst, 14*(3), 114-119.

Geschwind, N. (1971). Current concepts: aphasia. *N Engl J Med, 284*(12), 654-656. doi: 10.1056/NEJM197103252841206

Geschwind, N., & Behan, P. (1982). Left-handedness: association with immune disease, migraine, and developmental learning disorder. *Proc Natl Acad Sci U S A, 79*(16), 5097-5100.

Glickstein, M. (1992). The cerebellum and motor learning. *Curr Opin Neurobiol, 2*(6), 802-806.

Glickstein, M. (1993). Motor skills but not cognitive tasks. *Trends Neurosci, 16*(11), 450-451; discussion 453-454.

Goldman-Rakic, P. S. (1995). Architecture of the prefrontal cortex and the central executive. *Ann N Y Acad Sci, 769*, 71-83.

Goldman-Rakic, P. S. (1996). The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Philos Trans R Soc Lond B Biol Sci, 351*(1346), 1445-1453. doi: 10.1098/rstb.1996.0129

Goldman, P. S., & Rosvold, H. E. (1970). Localization of function within the dorsolateral prefrontal cortex of the rhesus monkey. *Exp Neurol, 27*(2), 291-304.

Goldwein, J. W., Radcliffe, J., Johnson, J., Moshang, T., Packer, R. J., Sutton, L. N., Rorke, L. B., & D'Angio, G. J. (1996). Updated results of a pilot study of low dose craniospinal irradiation plus chemotherapy for children under five with cerebellar primitive neuroectodermal tumors (medulloblastoma). *Int J Radiat Oncol Biol Phys, 34*(4), 899-904.

Gottwald, B., Wilde, B., Mihajlovic, Z., & Mehdorn, H. M. (2004). Evidence for distinct cognitive deficits after focal cerebellar lesions. *J Neurol Neurosurg Psychiatry, 75*(11), 1524-1531. doi: 10.1136/jnnp.2003.018093

Grafman, J., & Litvan, I. (1999). Importance of deficits in executive functions. *Lancet, 354*(9194), 1921-1923. doi: 10.1016/S0140-6736(99)90438-5

Grafman, J., Litvan, I., Massaquoi, S., Stewart, M., Sirigu, A., & Hallett, M. (1992). Cognitive planning deficit in patients with cerebellar atrophy. *Neurology, 42*(8), 1493-1496.

Grill, J., Renaux, V. K., Bulteau, C., Viguier, D., Levy-Piebois, C., Sainte-Rose, C., Dellatolas, G., Raquin, M. A., Jambaque, I., & Kalifa, C. (1999). Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes. *Int J Radiat Oncol Biol Phys, 45*(1), 137-145.

Grill, J., Viguier, D., Kieffer, V., Bulteau, C., Sainte-Rose, C., Hartmann, O., Kalifa, C., & Dellatolas, G. (2004). Critical risk factors for intellectual impairment in children with posterior fossa tumors: the role of cerebellar damage. *J Neurosurg, 101*(2 Suppl), 152-158. doi: 10.3171/ped.2004.101.2.0152

Habas, C., & Cabanis, E. A. (2006). Cortical projections to the human red nucleus: a diffusion tensor tractography study with a 1.5-T MRI machine. *Neuroradiology, 48*(10), 755-762. doi: 10.1007/s00234-006-0117-9

Habas, C., & Cabanis, E. A. (2007a). Anatomical parcellation of the brainstem and cerebellar white matter: a preliminary probabilistic tractography study at 3 T. *Neuroradiology, 49*(10), 849-863. doi: 10.1007/s00234-007-0267-4

Habas, C., & Cabanis, E. A. (2007b). Cortical projection to the human red nucleus: complementary results with probabilistic tractography at 3 T. *Neuroradiology, 49*(9), 777-784. doi: 10.1007/s00234-007-0260-y

Han, K., & Talavage, T. M. (2011). Effects of combining field strengths on auditory functional MRI group analysis: 1.5T and 3T. *J Magn Reson Imaging, 34*(6), 1480-1488. doi: 10.1002/jmri.22823

Hardyck, C., & Petrinovich, L. F. (1977). Left-handedness. *Psychol Bull, 84*(3), 385-404.

Hayter, A. L., Langdon, D. W., & Ramnani, N. (2007). Cerebellar contributions to working memory. *Neuroimage, 36*(3), 943-954. doi: 10.1016/j.neuroimage.2007.03.011

Hedden, T., & Yoon, C. (2006). Individual differences in executive processing predict susceptibility to interference in verbal working memory. *Neuropsychology, 20*(5), 511-528. doi: 10.1037/0894-4105.20.5.511

Helgeson, V. S., Reynolds, K. A., & Tomich, P. L. (2006). A meta-analytic review of benefit finding and growth. *J Consult Clin Psychol, 74*(5), 797-816. doi: 10.1037/0022-006X.74.5.797

Hopyan, T., Laughlin, S., & Dennis, M. (2010). Emotions and their cognitive control in children with cerebellar tumors. *J Int Neuropsychol Soc, 16*(6), 1027-1038. doi: 10.1017/S1355617710000974

Huber, J. F., Bradley, K., Spiegler, B. J., & Dennis, M. (2006). Long-term effects of transient cerebellar mutism after cerebellar astrocytoma or medulloblastoma tumor resection in childhood. *Childs Nerv Syst, 22*(2), 132-138. doi: 10.1007/s00381-005-1223-4

Hull, R., Martin, R. C., Beier, M. E., Lane, D., & Hamilton, A. C. (2008). Executive function in older adults: a structural equation modeling approach. *Neuropsychology, 22*(4), 508-522. doi: 10.1037/0894-4105.22.4.508

Ivry, R. B., & Baldo, J. V. (1992). Is the cerebellum involved in learning and cognition? *Curr Opin Neurobiol, 2*(2), 212-216.

Jissendi, P., Baudry, S., & Baleriaux, D. (2008). Diffusion tensor imaging (DTI) and tractography of the cerebellar projections to prefrontal and posterior parietal cortices: a study at 3T. *J Neuroradiol, 35*(1), 42-50. doi: 10.1016/j.neurad.2007.11.001

Jones, D. K., & Leemans, A. (2011). Diffusion tensor imaging. *Methods Mol Biol, 711,* 127-144. doi: 10.1007/978-1-61737-992-5_6

Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: a review of our current understanding. *Neuropsychol Rev, 17*(3), 213-233. doi: 10.1007/s11065-007-9040-z

Kabani, N. J., Sled, J. G., & Chertkow, H. (2002). Magnetization transfer ratio in mild cognitive impairment and dementia of Alzheimer's type. *Neuroimage, 15*(3), 604-610. doi: 10.1006/nimg.2001.0992

Kail, R., & Salthouse, T. A. (1994). Processing speed as a mental capacity. *Acta Psychol (Amst), 86*(2-3), 199-225.

Karatekin, C., Lazareff, J. A., & Asarnow, R. F. (2000). Relevance of the cerebellar hemispheres for executive functions. *Pediatr Neurol, 22*(2), 106-112.

Kassubek, J., Juengling, F. D., Ecker, D., & Landwehrmeyer, G. B. (2005). Thalamic atrophy in Huntington's disease co-varies with cognitive performance: a morphometric MRI analysis. *Cereb Cortex, 15*(6), 846-853. doi: 10.1093/cercor/bhh185

Kaufman, D. M. (2007). *Clinical neurology for psychiatrists* (6th ed.). Philadelphia,: Saunders/Elsevier.

Kelly, R. M., & Strick, P. L. (2003). Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *J Neurosci, 23*(23), 8432-8444.

Kelly, T. (2000). The development of executive function in school-aged children. *Clinical Neuropsychological Assessment, 1*, 38-55.

Khong, P. L., Kwong, D. L., Chan, G. C., Sham, J. S., Chan, F. L., & Ooi, G. C. (2003). Diffusion-tensor imaging for the detection and quantification of treatment-induced white matter injury in children with medulloblastoma: a pilot study. *AJNR Am J Neuroradiol, 24*(4), 734-740.

Khong, P. L., Leung, L. H., Fung, A. S., Fong, D. Y., Qiu, D., Kwong, D. L., Ooi, G. C., McAlonan, G., Cao, G., & Chan, G. C. (2006). White matter anisotropy in post-treatment childhood cancer survivors: preliminary evidence of association with neurocognitive function. *J Clin Oncol, 24*(6), 884-890. doi: 10.1200/JCO.2005.02.4505

Kim, S. G., Ugurbil, K., & Strick, P. L. (1994). Activation of a cerebellar output nucleus during cognitive processing. *Science, 265*(5174), 949-951.

Kirschen, M. P., Chen, S. H., Schraedley-Desmond, P., & Desmond, J. E. (2005). Load- and practice-dependent increases in cerebro-cerebellar activation in verbal working memory: an fMRI study. *Neuroimage, 24*(2), 462-472. doi: 10.1016/j.neuroimage.2004.08.036

Kirschen, M. P., Davis-Ratner, M. S., Milner, M. W., Chen, S. H., Schraedley-Desmond, P., Fisher, P. G., & Desmond, J. E. (2008). Verbal memory impairments in children after cerebellar tumor resection. *Behav Neurol, 20*(1-2), 39-53. doi: 10.3233/BEN-2008-0216

Kline, N. E., & Sevier, N. (2003). Solid tumors in children. *J Pediatr Nurs, 18*(2), 96-102. doi: 10.1053/jpdn.2003.12

Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlstrom, K., Gillberg, C. G., Forssberg, H., & Westerberg, H. (2005). Computerized training of working memory in children with ADHD--a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry, 44*(2), 177-186. doi: 10.1097/00004583-200502000-00010

Klingberg, T., Vaidya, C. J., Gabrieli, J. D., Moseley, M. E., & Hedehus, M. (1999). Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. *Neuroreport, 10*(13), 2817-2821.

Knecht, S., Deppe, M., Drager, B., Bobe, L., Lohmann, H., Ringelstein, E., & Henningsen, H. (2000a). Language lateralization in healthy right-handers. *Brain, 123 (Pt 1)*, 74-81.

Knecht, S., Drager, B., Deppe, M., Bobe, L., Lohmann, H., Floel, A., Ringelstein, E. B., & Henningsen, H. (2000b). Handedness and hemispheric language dominance in healthy humans. *Brain, 123 Pt 12*, 2512-2518.

Knight, S. J., Conklin, H. M., Palmer, S. L., Schreiber, J. E., Armstrong, C. L., Wallace, D., Bonner, M., Swain, M. A., Evankovich, K. D., Mabbott, D. J., Boyle, R., Huang, Q., Zhang, H., Anderson, V. A., & Gajjar, A. (2014). Working Memory Abilities Among Children Treated for Medulloblastoma: Parent Report and Child Performance. *J Pediatr Psychol*. doi: 10.1093/jpepsy/jsu009

Koechlin, E., Corrado, G., Pietrini, P., & Grafman, J. (2000). Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. *Proc Natl Acad Sci U S A, 97*(13), 7651-7656. doi: 10.1073/pnas.130177397

Koh, S., Turkel, S. B., & Baram, T. Z. (1997). Cerebellar mutism in children: report of six cases and potential mechanisms. *Pediatr Neurol, 16*(3), 218-219.

Kolb, B., & Whishaw, I. Q. (1990). *Fundamentals of human neuropsychology* (3rd ed.). New York: Freeman.

Kucyi, A., Moayedi, M., Weissman-Fogel, I., Hodaie, M., & Davis, K. D. (2012). Hemispheric asymmetry in white matter connectivity of the temporoparietal junction with the insula and prefrontal cortex. *PLoS One, 7*(4), e35589. doi: 10.1371/journal.pone.0035589

Lascola, C. D. (2005). Diffusion tensor tractography: exploring the cost-benefit ratio of incorporating CSF suppression into fiber tracing algorithms. *AJNR Am J Neuroradiol, 26*(4), 693-694.

Law, N., Bouffet, E., Laughlin, S., Laperriere, N., Briere, M. E., Strother, D., McConnell, D., Hukin, J., Fryer, C., Rockel, C., Dickson, J., & Mabbott, D. (2011). Cerebello-thalamo-cerebral connections in pediatric brain tumor patients: impact on working memory. *Neuroimage, 56*(4), 2238-2248. doi: 10.1016/j.neuroimage.2011.03.065

Law, N., Greenberg, M., Bouffet, E., Laughlin, S., Taylor, M. D., Malkin, D., Liu, F., Moxon-Emre, I., Scantlebury, N., & Mabbott, D. Visualization and segmentation of reciprocal cerebrocerebellar pathways in the healthy and radiated brain. *Under review, Human Brain Mapping*.

Law, N., Greenberg, M., Bouffet, E., Taylor, M. D., Laughlin, S., Strother, D., Fryer, C., McConnell, D., Hukin, J., Kaise, C., Wang, F., & Mabbott, D. J. (2012). Clinical and neuroanatomical predictors of cerebellar mutism syndrome. *Neuro Oncol, 14*(10), 1294-1303. doi: 10.1093/neuonc/nos160

Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage, 40*(3), 1044-1055. doi: 10.1016/j.neuroimage.2007.12.053

Leiner, H. C., Leiner, A. L., & Dow, R. S. (1993). Cognitive and language functions of the human cerebellum. *Trends Neurosci, 16*(11), 444-447.

Levin, H., Culhane, K., Hartmann, J., Evankovich, K., Mattson, A., & Harwood, H. (1991). Developmental changes in performance on tests of purported frontal lobe functions. *Dev Neuropsychol, 7*, 377-396.

Levisohn, L., Cronin-Golomb, A., & Schmahmann, J. D. (2000). Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain, 123 (Pt 5)*, 1041-1050.

Lewin, J., Kohen, D., & Mathew, G. (1993). Handedness in mental handicap: investigation into populations of Down's syndrome, epilepsy and autism. *Br J Psychiatry, 163*, 674-676.

Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2004). Striatal contributions to working memory: a functional magnetic resonance imaging study in humans. *Eur J Neurosci, 19*(3), 755-760.

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). New York: Oxford University Press.

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological assessment.* (4th ed.). New York: Oxford University Press.

Luria, A. R. (1966). *Human brain and psychological processes.* New York: Harper and Row.

Mabbott, D. J., Noseworthy, M., Bouffet, E., Laughlin, S., & Rockel, C. (2006a). White matter growth as a mechanism of cognitive development in children. *Neuroimage, 33*(3), 936-946. doi: 10.1016/j.neuroimage.2006.07.024

Mabbott, D. J., Noseworthy, M. D., Bouffet, E., Rockel, C., & Laughlin, S. (2006b). Diffusion tensor imaging of white matter after cranial radiation in children for medulloblastoma: correlation with IQ. *Neuro Oncol, 8*(3), 244-252. doi: 10.1215/15228517-2006-002

Mabbott, D. J., Penkman, L., Witol, A., Strother, D., & Bouffet, E. (2008). Core neurocognitive functions in children treated for posterior fossa tumors. *Neuropsychology, 22*(2), 159-168. doi: 10.1037/0894-4105.22.2.159

Mabbott, D. J., Rovet, J., Noseworthy, M. D., Smith, M. L., & Rockel, C. (2009). The relations between white matter and declarative memory in older children and adolescents. *Brain Res, 1294*, 80-90. doi: 10.1016/j.brainres.2009.07.046

Mabbott, D. J., Spiegler, B. J., Greenberg, M. L., Rutka, J. T., Hyder, D. J., & Bouffet, E. (2005). Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. *J Clin Oncol, 23*(10), 2256-2263. doi: 10.1200/JCO.2005.01.158

Malloy, P. F., & Richardson, E. D. (2001). Assessment of frontal lobe functions. In Salloway, S. P., Malloy, P. F. & Duffy, J. D. (Eds.), *The frontal lobes and neuropsychiatric illness* (pp. 125-137). Washington, DC: American Psychiatric Publishing, Inc.

Marien, P., Engelborghs, S., Michiels, E., & De Deyn, P. P. (2003). Cognitive and linguistic disturbances in the posterior fossa syndrome in children: a diaschisis phenomenon? *Brain Lang, 87*(1), 162-162.

Mateer, C. A. (1999). Executive function disorders: rehabilitation challenges and strategies. *Semin Clin Neuropsychiatry, 4*(1), 50-59. doi: 10.1053/SCNP00400050

Mayeux, R., & Kandel, E. R. (1991). Disorders of language: the aphasias. In Kandel, E. R., H., S. J. & Jessell, T. M. (Eds.), *Principle of Neural Science* (3rd ed., pp. 839-851). London: Prentice Hall.

McCarthy, G., Puce, A., Constable, R. T., Krystal, J. H., Gore, J. C., & Goldman-Rakic, P. (1996). Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. *Cereb Cortex, 6*(4), 600-611.

McGregor, B. A., Antoni, M. H., Boyers, A., Alferi, S. M., Blomberg, B. B., & Carver, C. S. (2004). Cognitive-behavioral stress management increases benefit finding and immune function among women with early-stage breast cancer. *J Psychosom Res, 56*(1), 1-8. doi: 10.1016/S0022-3999(03)00036-9

McLaughlin, E. J., Fisher, M. J., Sutton, L. N., & Storm, P. B. (2012). Brain Tumors. In Coran, A. G., Caldamone, A., Adzick, N. S., Krummel, T. M., Laberge, J.-M. & Shamberger, R. (Eds.), *Pediatric Surgery: Expert Consult* (7th ed., pp. p. 594). Philadelphia, PA: Elsevier Health Sciences.

McManus, I. C., Sik, G., Cole, D. R., Mellon, A. F., Wong, J., & Kloss, J. (1988). The development of handedness in children. *British Journal of Developmental Psychology*, *6*(3), 257-273.

Meyer, J. S., Obara, K., & Muramatsu, K. (1993). Diaschisis. *Neurol Res, 15*(6), 362-366.

Middleton, F. A., & Strick, P. L. (1994). Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science, 266*(5184), 458-461.

Middleton, F. A., & Strick, P. L. (1997). Cerebellar output channels. *Int Rev Neurobiol, 41*, 61-82.

Middleton, F. A., & Strick, P. L. (2000). Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Brain Res Rev, 31*(2-3), 236-250.

Middleton, F. A., & Strick, P. L. (2001). Cerebellar projections to the prefrontal cortex of the primate. *J Neurosci, 21*(2), 700-712.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu Rev Neurosci, 24*, 167-202. doi: 10.1146/annurev.neuro.24.1.167

Miller, N. G., Reddick, W. E., Kocak, M., Glass, J. O., Lobel, U., Morris, B., Gajjar, A., & Patay, Z. (2010). Cerebellocerebral diaschisis is the likely mechanism of postsurgical posterior fossa syndrome in pediatric patients with midline cerebellar tumors. *AJNR Am J Neuroradiol, 31*(2), 288-294. doi: 10.3174/ajnr.A1821

Miltenburg, D., Louw, D. F., & Sutherland, G. R. (1996). Epidemiology of childhood brain tumors. *Can J Neurol Sci, 23*(2), 118-122.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol, 41*(1), 49-100. doi: 10.1006/cogp.1999.0734

Molinari, M., Leggio, M. G., & Silveri, M. C. (1997). Verbal fluency and agrammatism. *Int Rev Neurobiol, 41*, 325-339.

Monchi, O., Petrides, M., Strafella, A. P., Worsley, K. J., & Doyon, J. (2006). Functional role of the basal ganglia in the planning and execution of actions. *Ann Neurol, 59*(2), 257-264. doi: 10.1002/ana.20742

Montgomery, J. (2000). Understanding the language difficulties of children with specific language impairment: Does verbal working memory matter? *American Journal of Speech-Language Pathology, 11*, 77-91.

Montgomery, J. W., Magimairaj, B. M., & Finney, M. C. (2010). Working memory and specific language impairment: an update on the relation and perspectives on assessment and treatment. *Am J Speech Lang Pathol, 19*(1), 78-94. doi: 10.1044/1058-0360(2009/09-0028)

Mori, S., & Zhang, J. (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron, 51*(5), 527-539. doi: 10.1016/j.neuron.2006.08.012

Morris, E. B., Phillips, N. S., Laningham, F. H., Patay, Z., Gajjar, A., Wallace, D., Boop, F., Sanford, R., Ness, K. K., & Ogg, R. J. (2009). Proximal dentatothalamocortical tract involvement in posterior fossa syndrome. *Brain, 132*(Pt 11), 3087-3095. doi: 10.1093/brain/awp241

Morriss, M. C., Zimmerman, R. A., Bilaniuk, L. T., Hunter, J. V., & Haselgrove, J. C. (1999). Changes in brain water diffusion during childhood. *Neuroradiology, 41*(12), 929-934.

Moxon-Emre, I., Bouffet, E., Taylor, M. D., Laperriere, N., Scantlebury, N., Law, N., Spiegler, B. J., Malkin, D., Janzen, L., & Mabbott, D. (2014). Impact of Craniospinal Dose, Boost Volume, and Neurologic Complications on Intellectual Outcome in Patients With Medulloblastoma. *J Clin Oncol*. doi: 10.1200/JCO.2013.52.3290

Mueller, S., & Chang, S. (2009). Pediatric brain tumors: current treatment strategies and future therapeutic approaches. *Neurotherapeutics, 6*(3), 570-586. doi: 10.1016/j.nurt.2009.04.006

Mukherjee, P., Miller, J. H., Shimony, J. S., Conturo, T. E., Lee, B. C., Almli, C. R., & McKinstry, R. C. (2001). Normal brain maturation during childhood: developmental trends characterized with diffusion-tensor MR imaging. *Radiology, 221*(2), 349-358. doi: 10.1148/radiol.2212001702

Mulhern, R. K., Kepner, J. L., Thomas, P. R., Armstrong, F. D., Friedman, H. S., & Kun, L. E. (1998). Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. *J Clin Oncol, 16*(5), 1723-1728.

Mulhern, R. K., Merchant, T. E., Gajjar, A., Reddick, W. E., & Kun, L. E. (2004a). Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncol, 5*(7), 399-408. doi: 10.1016/S1470-2045(04)01507-4

Mulhern, R. K., Palmer, S. L., Reddick, W. E., Glass, J. O., Kun, L. E., Taylor, J., Langston, J., & Gajjar, A. (2001). Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. *J Clin Oncol, 19*(2), 472-479.

Mulhern, R. K., Reddick, W. E., Palmer, S. L., Glass, J. O., Elkin, T. D., Kun, L. E., Taylor, J., Langston, J., & Gajjar, A. (1999). Neurocognitive deficits in medulloblastoma survivors and white matter loss. *Ann Neurol, 46*(6), 834-841.

Mulhern, R. K., White, H. A., Glass, J. O., Kun, L. E., Leigh, L., Thompson, S. J., & Reddick, W. E. (2004b). Attentional functioning and white matter integrity among survivors of malignant brain tumors of childhood. *J Int Neuropsychol Soc, 10*(2), 180-189. doi: 10.1017/S135561770410204X

Nagel, B. J., Palmer, S. L., Reddick, W. E., Glass, J. O., Helton, K. J., Wu, S., Xiong, X., Kun, L. E., Gajjar, A., & Mulhern, R. K. (2004). Abnormal hippocampal development in children with medulloblastoma treated with risk-adapted irradiation. *AJNR Am J Neuroradiol, 25*(9), 1575-1582.

Nieder, C., Andratschke, N., & Astner, S. T. (2007). Experimental concepts for toxicity prevention and tissue restoration after central nervous system irradiation. *Radiat Oncol, 2*, 23. doi: 10.1186/1748-717X-2-23

Olsrud, J., Latt, J., Brockstedt, S., Romner, B., & Bjorkman-Burtscher, I. M. (2005). Magnetic resonance imaging artifacts caused by aneurysm clips and shunt valves: dependence on field strength (1.5 and 3 T) and imaging parameters. *J Magn Reson Imaging, 22*(3), 433-437. doi: 10.1002/jmri.20391

Osborne, J. W., & Costello, A. B. (2004). Sample size and subject to item ratio in principal components analysis. *Practical Assessment, Research, & Evaluation, 9*(11).

Ozgur, B. M., Berberian, J., Aryan, H. E., Meltzer, H. S., & Levy, M. L. (2006). The pathophysiologic mechanism of cerebellar mutism. *Surg Neurol, 66*(1), 18-25. doi: 10.1016/j.surneu.2005.12.003

Packer, R. J. (1999). Brain tumors in children. *Arch Neurol, 56*(4), 421-425.

Palmer, S. L., Armstrong, C., Onar-Thomas, A., Wu, S., Wallace, D., Bonner, M. J., Schreiber, J., Swain, M., Chapieski, L., Mabbott, D., Knight, S., Boyle, R., & Gajjar, A. (2013). Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. *J Clin Oncol, 31*(28), 3494-3500. doi: 10.1200/JCO.2012.47.4775

Palmer, S. L., Goloubeva, O., Reddick, W. E., Glass, J. O., Gajjar, A., Kun, L., Merchant, T. E., & Mulhern, R. K. (2001). Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. *J Clin Oncol, 19*(8), 2302-2308.

Palmer, S. L., Reddick, W. E., Glass, J. O., Gajjar, A., Goloubeva, O., & Mulhern, R. K. (2002). Decline in corpus callosum volume among pediatric patients with medulloblastoma: longitudinal MR imaging study. *AJNR Am J Neuroradiol, 23*(7), 1088-1094.

Paulesu, E., Frith, C. D., & Frackowiak, R. S. (1993). The neural correlates of the verbal component of working memory. *Nature, 362*(6418), 342-345. doi: 10.1038/362342a0

Pickering, S. J., & Gathercole, S. (2001). *Working Memory Test Battery for Children (WMTB-C) Manual.* London: Psychological Corporation Ltd.

Pollack, I. F. (1997). Posterior fossa syndrome. *Int Rev Neurobiol, 41*, 411-432.

Pollack, I. F., Polinko, P., Albright, A. L., Towbin, R., & Fitz, C. (1995). Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. *Neurosurgery, 37*(5), 885-893.

Pollak, L., Klein, C., Rabey, J. M., & Schiffer, J. (1996). Posterior fossa lesions associated with neuropsychiatric symptomatology. *Int J Neurosci, 87*(3-4), 119-126.

Prabhakaran, V., Narayanan, K., Zhao, Z., & Gabrieli, J. D. (2000). Integration of diverse information in working memory within the frontal lobe. *Nat Neurosci, 3*(1), 85-90. doi: 10.1038/71156

Pratt, J. W. (1987). Dividing the indivisible: Using simple symmetry to partition variance explained. In Pukilla, T. & Duntaneu, S. (Eds.), *Proceedings of Second Tampere Conference in Statistics* (pp. 245-260). Finland: University of Tampere.

Qiu, D., Kwong, D. L., Chan, G. C., Leung, L. H., & Khong, P. L. (2007). Diffusion tensor magnetic resonance imaging finding of discrepant fractional anisotropy between the frontal and parietal lobes after whole-brain irradiation in childhood medulloblastoma survivors: reflection of regional white matter radiosensitivity? *Int J Radiat Oncol Biol Phys, 69*(3), 846-851. doi: 10.1016/j.ijrobp.2007.04.041

Qiu, D., Tan, L. H., Zhou, K., & Khong, P. L. (2008). Diffusion tensor imaging of normal white matter maturation from late childhood to young adulthood: voxel-wise evaluation of mean diffusivity, fractional anisotropy, radial and axial diffusivities, and correlation with

reading development. *Neuroimage, 41*(2), 223-232. doi: 10.1016/j.neuroimage.2008.02.023

Qiu, M., Li, Q., Liu, G., Xie, B., & Wang, J. (2010). Voxel-based analysis of white matter during adolescence and young adulthood. *Brain Dev, 32*(7), 531-537. doi: 10.1016/j.braindev.2009.08.006

Ramnani, N., Behrens, T. E., Johansen-Berg, H., Richter, M. C., Pinsk, M. A., Andersson, J. L., Rudebeck, P., Ciccarelli, O., Richter, W., Thompson, A. J., Gross, C. G., Robson, M. D., Kastner, S., & Matthews, P. M. (2006). The evolution of prefrontal inputs to the cortico-pontine system: diffusion imaging evidence from Macaque monkeys and humans. *Cereb Cortex, 16*(6), 811-818. doi: 10.1093/cercor/bhj024

Ravizza, S. M., McCormick, C. A., Schlerf, J. E., Justus, T., Ivry, R. B., & Fiez, J. A. (2006). Cerebellar damage produces selective deficits in verbal working memory. *Brain, 129*(Pt 2), 306-320. doi: 10.1093/brain/awh685

Reddick, W. E., Glass, J. O., Palmer, S. L., Wu, S., Gajjar, A., Langston, J. W., Kun, L. E., Xiong, X., & Mulhern, R. K. (2005). Atypical white matter volume development in children following craniospinal irradiation. *Neuro Oncol, 7*(1), 12-19. doi: 10.1215/S1152851704000079

Reddick, W. E., Russell, J. M., Glass, J. O., Xiong, X., Mulhern, R. K., Langston, J. W., Merchant, T. E., Kun, L. E., & Gajjar, A. (2000). Subtle white matter volume differences in children treated for medulloblastoma with conventional or reduced dose craniospinal irradiation. *Magn Reson Imaging, 18*(7), 787-793.

Reddick, W. E., White, H. A., Glass, J. O., Wheeler, G. C., Thompson, S. J., Gajjar, A., Leigh, L., & Mulhern, R. K. (2003). Developmental model relating white matter volume to neurocognitive deficits in pediatric brain tumor survivors. *Cancer, 97*(10), 2512-2519. doi: 10.1002/cncr.11355

Reeves, C. B., Palmer, S. L., Reddick, W. E., Merchant, T. E., Buchanan, G. M., Gajjar, A., & Mulhern, R. K. (2006). Attention and memory functioning among pediatric patients with medulloblastoma. *J Pediatr Psychol, 31*(3), 272-280. doi: 10.1093/jpepsy/jsj019

Reiss, A. L., Abrams, M. T., Singer, H. S., Ross, J. L., & Denckla, M. B. (1996). Brain development, gender and IQ in children. A volumetric imaging study. *Brain, 119 (Pt 5)*, 1763-1774.

Richter, S., Schoch, B., Kaiser, O., Groetschel, H., Dimitrova, A., Hein-Kropp, C., Maschke, M., Gizewski, E. R., & Timmann, D. (2005). Behavioral and affective changes in children and adolescents with chronic cerebellar lesions. *Neurosci Lett, 381*(1-2), 102-107. doi: 10.1016/j.neulet.2005.02.011

Riggs, L., Bouffet, E., Laughlin, S., Laperriere, N., Liu, F., Skocic, J., Scantlebury, N., Wang, F., Schoenhoff, N. J., Strother, D., Hukin, J., Fryer, C., McConnell, D., & Mabbott, D. J. (2014). Changes to memory structures in children treated for posterior fossa tumors. *J Int Neuropsychol Soc, 20*(2), 168-180. doi: 10.1017/S135561771300129X

Ris, M. D., Packer, R., Goldwein, J., Jones-Wallace, D., & Boyett, J. M. (2001). Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. *J Clin Oncol, 19*(15), 3470-3476.

Riva, D., & Giorgi, C. (2000a). The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain, 123 (Pt 5)*, 1051-1061.

Riva, D., & Giorgi, C. (2000b). The contribution of the cerebellum to mental and social functions in developmental age. *Fiziol Cheloveka, 26*(1), 27-31.

Robertson, P. L., Muraszko, K. M., Holmes, E. J., Sposto, R., Packer, R. J., Gajjar, A., Dias, M. S., & Allen, J. C. (2006). Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. *J Neurosurg, 105*(6 Suppl), 444-451. doi: 10.3171/ped.2006.105.6.444

Rodrigo, A. H., Di Domenico, S. L., Ayaz, H., Gulrajani, S. G., Lam, J., & Ruocco, A. C. (2014). Differentiating functions of the lateral and medial prefrontal cortex in motor response inhibition. *Neuroimage, 85*, 423-431. doi: 10.1016/j.neuroimage.2013.01.059

Royall, D. R., Lauterbach, E. C., Cummings, J. L., Reeve, A., Rummans, T. A., Kaufer, D. I., LaFrance, W. C., Jr., & Coffey, C. E. (2002). Executive control function: a review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. *J Neuropsychiatry Clin Neurosci, 14*(4), 377-405.

Sagiuchi, T., Ishii, K., Aoki, Y., Kan, S., Utsuki, S., Tanaka, R., Fujii, K., & Hayakawa, K. (2001). Bilateral crossed cerebello-cerebral diaschisis and mutism after surgery for cerebellar medulloblastoma. *Ann Nucl Med, 15*(2), 157-160.

Salmi, J., Pallesen, K. J., Neuvonen, T., Brattico, E., Korvenoja, A., Salonen, O., & Carlson, S. (2010). Cognitive and motor loops of the human cerebro-cerebellar system. *J Cogn Neurosci, 22*(11), 2663-2676. doi: 10.1162/jocn.2009.21382

Schatz, J., Kramer, J. H., Ablin, A., & Matthay, K. K. (2000). Processing speed, working memory, and IQ: a developmental model of cognitive deficits following cranial radiation therapy. *Neuropsychology, 14*(2), 189-200.

Schlosser, R., Hutchinson, M., Joseffer, S., Rusinek, H., Saarimaki, A., Stevenson, J., Dewey, S. L., & Brodie, J. D. (1998). Functional magnetic resonance imaging of human brain activity in a verbal fluency task. *J Neurol Neurosurg Psychiatry, 64*(4), 492-498.

Schmahmann, J. D. (1991). An emerging concept. The cerebellar contribution to higher function. *Arch Neurol, 48*(11), 1178-1187.

Schmahmann, J. D. (1996). From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. *Hum Brain Mapp, 4*(3), 174-198. doi: 10.1002/(SICI)1097-0193(1996)4:3<174::AID-HBM3>3.0.CO;2-0

Schmahmann, J. D. (2004). Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci, 16*(3), 367-378. doi: 10.1176/appi.neuropsych.16.3.367

Schmahmann, J. D., & Caplan, D. (2006). Cognition, emotion and the cerebellum. *Brain, 129*(Pt 2), 290-292. doi: 10.1093/brain/awh729

Schmahmann, J. D., Ko, R., & MacMore, J. (2004). The human basis pontis: motor syndromes and topographic organization. *Brain, 127*(Pt 6), 1269-1291. doi: 10.1093/brain/awh138

Schmahmann, J. D., & Pandya, D. N. (1995). Prefrontal cortex projections to the basilar pons in rhesus monkey: implications for the cerebellar contribution to higher function. *Neurosci Lett, 199*(3), 175-178.

Schmahmann, J. D., & Pandya, D. N. (1997a). Anatomic organization of the basilar pontine projections from prefrontal cortices in rhesus monkey. *J Neurosci, 17*(1), 438-458.

Schmahmann, J. D., & Pandya, D. N. (1997b). The cerebrocerebellar system. *Int Rev Neurobiol, 41*, 31-60.

Schmahmann, J. D., & Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain, 121 (Pt 4)*, 561-579.

Schmahmann, J. D., Weilburg, J. B., & Sherman, J. C. (2007). The neuropsychiatry of the cerebellum - insights from the clinic. *Cerebellum, 6*(3), 254-267. doi: 10.1080/14734220701490995

Schmithorst, V. J., Wilke, M., Dardzinski, B. J., & Holland, S. K. (2002). Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. *Radiology, 222*(1), 212-218. doi: 10.1148/radiol.2221010626

Schneider, J. F., Il'yasov, K. A., Hennig, J., & Martin, E. (2004). Fast quantitative diffusion-tensor imaging of cerebral white matter from the neonatal period to adolescence. *Neuroradiology, 46*(4), 258-266. doi: 10.1007/s00234-003-1154-2

Schneiderman, J. S., Buchsbaum, M. S., Haznedar, M. M., Hazlett, E. A., Brickman, A. M., Shihabuddin, L., Brand, J. G., Torosjan, Y., Newmark, R. E., Tang, C., Aronowitz, J., Paul-Odouard, R., Byne, W., & Hof, P. R. (2007). Diffusion tensor anisotropy in adolescents and adults. *Neuropsychobiology, 55*(2), 96-111. doi: 10.1159/000104277

Schott, L. H., Naidich, T. P., & Gan, J. (1983). Common pediatric brain tumors. Typical computed tomographic appearances. *J Comput Tomogr, 7*(1), 3-15.

Schultheiss, T. E., Kun, L. E., Ang, K. K., & Stephens, L. C. (1995). Radiation response of the central nervous system. *Int J Radiat Oncol Biol Phys, 31*(5), 1093-1112.

Shallice, T., & Burgess, P. (1993). Supervisory control of action and thought selection. In Baddeley, A. & Weiskrantz, L. (Eds.), *Attention, awareness, and control* (pp. 171-187). Oxford: Oxford University Press.

Siffert, J., Poussaint, T. Y., Goumnerova, L. C., Scott, R. M., LaValley, B., Tarbell, N. J., & Pomeroy, S. L. (2000). Neurological dysfunction associated with postoperative cerebellar mutism. *J Neurooncol, 48*(1), 75-81.

Sist, B., Baskar, S. J., & Winship, I. R. (2012). *Diaschisis, degeneration, and adaptive plasticity after focal ischemic stroke.*: InTech.

Smith, A. (1984). Early and long-term recovery from brain damage in children and adults: Evolution of concepts of localization, plasticity, and recovery. In Almli, C. R. & Finger, S. (Eds.), *Early brain damage VI: Research Orientations and Clinical Observations* (pp. 299-306). Orlando: Academic Press.

Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283*(5408), 1657-1661.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23 Suppl 1,* S208-219. doi: 10.1016/j.neuroimage.2004.07.051

Sohlberg, M. M., & Mateer, C. A. (2001). Improving attention and managing attentional problems. Adapting rehabilitation techniques to adults with ADD. *Ann N Y Acad Sci, 931*, 359-375.

Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage, 17*(3), 1429-1436.

Spiegler, B. J., Bouffet, E., Greenberg, M. L., Rutka, J. T., & Mabbott, D. J. (2004). Change in neurocognitive functioning after treatment with cranial radiation in childhood. *J Clin Oncol, 22*(4), 706-713. doi: 10.1200/JCO.2004.05.186

Stein, J. F., & Glickstein, M. (1992). Role of the cerebellum in visual guidance of movement. *Physiol Rev, 72*(4), 967-1017.

Steinbok, P., Cochrane, D. D., Perrin, R., & Price, A. (2003). Mutism after posterior fossa tumour resection in children: incomplete recovery on long-term follow-up. *Pediatr Neurosurg, 39*(4), 179-183. doi: 72468

Steinlin, M., Imfeld, S., Zulauf, P., Boltshauser, E., Lovblad, K. O., Ridolfi Luthy, A., Perrig, W., & Kaufmann, F. (2003). Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. *Brain, 126*(Pt 9), 1998-2008. doi: 10.1093/brain/awg195

Stoodley, C. J., & Schmahmann, J. D. (2009). Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. *Neuroimage, 44*(2), 489-501. doi: 10.1016/j.neuroimage.2008.08.039

Stoodley, C. J., & Schmahmann, J. D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex, 46*(7), 831-844. doi: 10.1016/j.cortex.2009.11.008

Strick, P. L., Dum, R. P., & Fiez, J. A. (2009). Cerebellum and nonmotor function. *Annu Rev Neurosci, 32*, 413-434. doi: 10.1146/annurev.neuro.31.060407.125606

Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobes: a conceptual view. *Psychol Res, 63*(3-4), 289-298.

Stuss, D. T., Alexander, M. P., Hamer, L., Palumbo, C., Dempster, R., Binns, M., Levine, B., & Izukawa, D. (1998). The effects of focal anterior and posterior brain lesions on verbal fluency. *J Int Neuropsychol Soc, 4*(3), 265-278.

Stuss, D. T., & Benson, D. F. (1986). *The frontal lobes*. New York: Raven Press.

Stuss, D. T., Binns, M. A., Murphy, K. J., & Alexander, M. P. (2002). Dissociations within the anterior attentional system: effects of task complexity and irrelevant information on reaction time speed and accuracy. *Neuropsychology, 16*(4), 500-513.

Stuss, D. T., & Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annu Rev Psychol, 53*, 401-433. doi: 10.1146/annurev.psych.53.100901.135220

Stuss, D. T., Levine, B., Alexander, M. P., Hong, J., Palumbo, C., Hamer, L., Murphy, K. J., & Izukawa, D. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia, 38*(4), 388-402.

Sultan, F., Hamodeh, S., & Baizer, J. S. (2010). The human dentate nucleus: a complex shape untangled. *Neuroscience, 167*(4), 965-968. doi: 10.1016/j.neuroscience.2010.03.007

Tamnes, C. K., Ostby, Y., Fjell, A. M., Westlye, L. T., Due-Tonnessen, P., & Walhovd, K. B. (2010). Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. *Cereb Cortex, 20*(3), 534-548. doi: 10.1093/cercor/bhp118

Tavano, A., Grasso, R., Gagliardi, C., Triulzi, F., Bresolin, N., Fabbro, F., & Borgatti, R. (2007). Disorders of cognitive and affective development in cerebellar malformations. *Brain, 130*(Pt 10), 2646-2660. doi: 10.1093/brain/awm201

Thach, W. T. (1972). Cerebellar output: properties, synthesis and uses. *Brain Res, 40*(1), 89-102.

Thach, W. T., & Jones, E. G. (1979). The cerebellar dentatothalamic connection: terminal field, lamellae, rods and somatotopy. *Brain Res, 169*(1), 168-172.

Timmann, D., & Daum, I. (2007). Cerebellar contributions to cognitive functions: a progress report after two decades of research. *Cerebellum, 6*(3), 159-162. doi: 10.1080/14734220701496448

Tugade, M. M., & Fredrickson, B. L. (2004). Resilient individuals use positive emotions to bounce back from negative emotional experiences. *J Pers Soc Psychol, 86*(2), 320-333. doi: 10.1037/0022-3514.86.2.320

Turgut, M. (2008). Cerebellar mutism. *J Neurosurg Pediatr, 1*(3), 262. doi: 10.3171/PED/2008/1/3/262

Van Calenbergh, F., Van de Laar, A., Plets, C., Goffin, J., & Casaer, P. (1995). Transient cerebellar mutism after posterior fossa surgery in children. *Neurosurgery, 37*(5), 894-898.

Van der Werf, Y. D., Witter, M. P., Uylings, H. B., & Jolles, J. (2000). Neuropsychology of infarctions in the thalamus: a review. *Neuropsychologia, 38*(5), 613-627.

Vandeinse, D., & Hornyak, J. E. (1997). Linguistic and cognitive deficits associated with cerebellar mutism. *Pediatr Rehabil, 1*(1), 41-44.

Vaquero, E., Gomez, C. M., Quintero, E. A., Gonzalez-Rosa, J. J., & Marquez, J. (2008). Differential prefrontal-like deficit in children after cerebellar astrocytoma and medulloblastoma tumor. *Behav Brain Funct, 4*, 18. doi: 10.1186/1744-9081-4-18

Von Der Heide, R. J., Skipper, L. M., Klobusicky, E., & Olson, I. R. (2013). Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. *Brain, 136*(Pt 6), 1692-1707. doi: 10.1093/brain/awt094

Vos, S. B., Jones, D. K., Viergever, M. A., & Leemans, A. (2011). Partial volume effect as a hidden covariate in DTI analyses. *Neuroimage, 55*(4), 1566-1576. doi: 10.1016/j.neuroimage.2011.01.048

Waber, D. P., Pomeroy, S. L., Chiverton, A. M., Kieran, M. W., Scott, R. M., Goumnerova, L. C., & Rivkin, M. J. (2006). Everyday cognitive function after craniopharyngioma in childhood. *Pediatr Neurol, 34*(1), 13-19. doi: 10.1016/j.pediatrneurol.2005.06.002

Wells, E. M., Khademian, Z. P., Walsh, K. S., Vezina, G., Sposto, R., Keating, R. F., & Packer, R. J. (2010). Postoperative cerebellar mutism syndrome following treatment of medulloblastoma: neuroradiographic features and origin. *J Neurosurg Pediatr, 5*(4), 329-334. doi: 10.3171/2009.11.PEDS09131

Wells, E. M., Walsh, K. S., Khademian, Z. P., Keating, R. F., & Packer, R. J. (2008). The cerebellar mutism syndrome and its relation to cerebellar cognitive function and the cerebellar cognitive affective disorder. *Dev Disabil Res Rev, 14*(3), 221-228. doi: 10.1002/ddrr.25

Welsh, M. C., Pennington, B. F., & Groissier, D. B. (1991). A normative developmental study of executive functions: A window on prefrontal function in children. *Dev Neuropsychol, 7*, 131-149.

Wong, C. S., & Van der Kogel, A. J. (2004). Mechanisms of radiation injury to the central nervous system: implications for neuroprotection. *Mol Interv, 4*(5), 273-284. doi: 10.1124/mi.4.5.7

Woods, R. P., Grafton, S. T., Holmes, C. J., Cherry, S. R., & Mazziotta, J. C. (1998). Automated image registration: I. General methods and intrasubject, intramodality validation. *J Comput Assist Tomogr, 22*(1), 139-152.

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., & Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *Neuroimage, 45*(1 Suppl), S173-186. doi: 10.1016/j.neuroimage.2008.10.055

Yachnis, A. T. (1997). Neuropathology of pediatric brain tumors. *Semin Pediatr Neurol, 4*(4), 282-291.

Zelazo, P. D., & Mueller, U. (2002). Executive function in typical and atypical development. In Goswami, U. (Ed.), *Handbook of childhood cognitive development.* (pp. 445-469). Oxford: Blackwell.

Zhang, L., Thomas, K. M., Davidson, M. C., Casey, B. J., Heier, L. A., & Ulug, A. M. (2005). MR quantitation of volume and diffusion changes in the developing brain. *AJNR Am J Neuroradiol, 26*(1), 45-49.