White Matter Microstructure and Emotional Functioning in Children Treated for Posterior Fossa Tumours

by

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

Children treated for brain tumours that arise in the posterior fossa (PF) experience lifelong cognitive and emotional difficulties, and exhibit white matter (WM) damage. This thesis combined diffusion tensor imaging (DTI), eye-tracking and standardized measures of cognitive and emotional functioning in children treated for PF tumours and typically developing children, to: 1) characterize outcomes related to decreases in treatment intensity, 2) objectively evaluate emotional functioning, and 3) examine the associations between WM microstructure and emotional functioning. It was found that treatment with the lowest intensity craniospinal irradiation protocol spared WM in the temporal lobe of children treated for malignant PF tumours. In addition, patients treated on lower intensity protocols had largely preserved cognitive, social and affective functioning. However, novel eye-tracking tasks designed to evaluate emotional functioning uncovered some remaining deficits; children treated for PF tumours had difficulty recognizing facial emotions despite attending to the faces, and difficulty regulating their initial attention away from emotional faces. Notably, this eye-tracking measure of emotion regulation was associated with emotional control in daily life. The current work also revealed that relations between WM microstructure and emotional functioning can diverge in the injured and uninjured brain; WM predicted facial emotion recognition in typically developing
children only, whereas WM was associated with emotion regulation in patients only. In a field dominated by findings that characterize negative sequelae, this work highlights the possibility of favourable outcomes for PF tumour patients who are eligible for treatment with lower intensity protocols. Despite these positive outcomes, subtle emotional functioning deficits not captured by standardized questionnaires persist. To better understand how emotional processes are altered in children treated for PF tumours, novel objective measures are required. This thesis detailed one such behavioural marker to evaluate emotion regulation, using eye-tracking technology, and characterized an oculomotor response that may warrant interventional follow-up.
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Chapter 1

Background and Rationale
1 Background and Rationale

1.1 Introduction

Children who develop a brain tumour in the posterior fossa (PF) are typically treated with surgery and they may also receive chemotherapy, with or without radiation. Although craniospinal irradiation (CSI) if often necessary to achieve a cure, this treatment contributes to white matter (WM) damage (Liu et al., 2015; Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006; Nagesh et al., 2008; Reddick et al., 2005). It is well documented that WM damage is associated with cognitive dysfunction in children treated for PF tumours (Law et al., 2011; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Rueckriegel, Bruhn, Thomale, & Hernaiz Driever, 2015) but its effect on emotional functioning has not been considered.

Although, there is evidence that children treated for brain tumours experience social and emotional dysfunction, such as anxiety and depression (Beebe et al., 2005; Bonner et al., 2008; Brinkman et al., 2012; Moitra & Armstrong, 2013; Schultz et al., 2007; Zeltzer et al., 2009). It is possible that brain tumour survivors experience emotional dysfunction in part due to the stress of dealing with a complex medical disorder, but there may be fundamental biological factors that contribute. Critical developmental processes in the brain are actively underway during childhood, and exposure to a series of traumatic insults (i.e., the tumour and its subsequent treatment) may alter neurobiology in a manner that interferes with typical emotional maturation.

Novel intervention programs have been created to help mitigate cognitive decline and promote recovery in brain tumour survivors (reviewed in Krull, Hardy, Kahalley, Schuitema, & Kesler, 2018), yet the development of similar programs focused on preserving and promoting successful emotional functioning have received little attention. Before such interventions can be designed, it is critical to rigorously characterize emotional functioning in children treated for PF tumours.

The overall goal of this thesis was to evaluate how emotional functioning is affected in children treated for PF tumours, and to determine if damage to WM microstructure can help explain their emotional outcomes. To quantify WM microstructure, diffusion tensor imaging (DTI) was used. To characterize fundamental components of emotional functioning that develop throughout childhood, namely, facial emotion recognition and emotion regulation, standardized measures of emotional functioning were combined with behavioural tasks while eye movements were recorded. To monitor eye-movements, eye-tracking technology was utilized for the first time in
children treated for PF tumours due to its ability to objectively capture novel and complementary information about the behavioural processes related to an emotional outcome that cannot be gleaned by standardized outcome measures alone.

This thesis combined DTI, eye-tracking and standardized measures of emotional and cognitive functioning to address the following questions: (1) what is the effect of treatment with different clinically relevant CSI protocols on WM microstructure in children treated for PF tumours? (Chapter 2); (2) how is facial emotion recognition affected in children treated for PF tumours, and does damage to WM pathways implicated in facial emotion recognition explain their functioning? (Chapter 3); and (3) can emotion regulation be evaluated objectively using eye-tracking in children treated for PF tumours, and is there an association between WM microstructure and the eye-tracking measure of emotion regulation developed in this thesis (Chapter 4). The present chapter contains a review of the literature relevant for addressing these questions, and will conclude with an outline of the three studies that were conducted to answer them.

1.1.1 Posterior fossa (PF) tumours, their treatment and medical complications

Central nervous system (CNS) tumours are the leading cause of death and disability from childhood disease in developed countries. An estimated 200 new paediatric brain tumour diagnoses are made in Canada each year (Ellison, De, Mery, Grundy, & Canadian Cancer Society's Steering Committee for Canadian Cancer, 2009). Over half the diagnosed brain tumours are located in the PF, a brain region that contains the cerebellum and brainstem (Kline & Sevier, 2003). The most common tumours that arise in the PF include medulloblastoma, ependymomas and gliomas (Poretti, Meoded, & Huisman, 2012). Nearly all children diagnosed with a PF tumour will undergo surgery in an attempt to achieve a gross total resection of the mass (Mueller & Chang, 2009). Whether a patient then receives adjuvant chemotherapy and radiation depends on the tumour type, and the age at diagnosis. Children younger than 3 years of age are typically spared radiation therapy (Mueller & Chang, 2009).

Medulloblastomas are the most common malignant brain tumours in childhood and their treatment includes CSI with a boost to the tumour site, and chemotherapy (Mueller & Chang, 2009). Not all children with medulloblastoma are treated with the same radiation intensity; rather, treatment intensity is determined by risk status. Average-risk patients have no neuraxis
dissemination and/or no minimal residual tumour following surgery, whereas high-risk patients do (Merchant et al., 2008). As a result, average-risk patients are treated with reduced dose CSI (i.e. 2,340 cGy to the neuraxis) and high-risk patients receive standard dose CSI (i.e. 3,600 cGy) (Pollack, 2011). Traditionally, CSI was followed by a boost to the entire PF, but the past two decades have seen the development of conformal techniques that limit radiation delivery to the tumour bed (TB) (Wolden et al., 2003). However, the boost volume a patient receives is ultimately determined by where they are treated; it depends on the planning capability and quality assurance available at that specific centre (Parkes et al., 2015). Patients with medulloblastoma comprise the largest sample in this thesis; all patients in Chapter 2 (n = 34), and approximately half the patients in Chapters 3 and 4 (n = 17; the same sample was used in both), were treated for medulloblastoma.

Ependymomas are another brain tumour type that are routinely treated with radiation following surgical resection. In contrast with medulloblastoma however, patients treated for ependymoma are often controlled with focal radiation delivered to the tumour site, and chemotherapy is only used in patients with residual or recurrent disease (Mueller & Chang, 2009). Only 5 patients in this thesis were treated for ependymoma.

Low-grade gliomas encompass several subgroups of tumours, including pilocytic astrocytoma that most commonly arises in the PF (Mueller & Chang, 2009). Patients with pilocytic astrocytoma often have excellent prognosis following a gross total resection of their tumour, and adjuvant therapy is often not required (Pollack, 2011). Given that pilocytic astrocytoma arises in the cerebellum, and that patients are typically treated without radiation, they serve as an ideal comparison group to help tease apart the effects of radiation from the effects of the tumour and its surgical excision. Approximately half the patients in Chapters 3 and 4 (n =13) were treated for pilocytic astrocytoma, and they comprise the bulk of patients treated for PF tumours without radiation in this thesis.

Although medulloblastoma, pilocytic astrocytoma and ependymoma are the three most commonly encountered PF tumours in childhood, there are other less common tumours that occasional affect the PF in children (Dunham, 2015); one such tumour is a cribriform neuroepithelial tumour (CRINET), which has favourable prognosis and is often treated without radiation as a result. One patient in our sample had a CRINET.
Patients with PF tumours often present to the hospital with complications that arise due to the location of their tumour, and they most commonly experience postsurgical complications as a result of its removal. Given that complications typically do not differ according to the PF tumour type, they will be introduced generally in the following paragraph.

Patients with PF tumours often develop hydrocephalus; the tumour can compress or displace the fourth ventricle, blocking the flow of cerebral spinal fluid (CSF) and increasing the intracranial pressure as a result (Massimino et al., 2016). During or prior to surgical resection of the PF tumour, interventions to treat hydrocephalus, including the insertion of an extraventricular drain, a ventriculoperitoneal shunt, or a third ventriculostomy, may be performed (Massimino et al., 2016; Muzumdar & Ventureyra, 2010). Patients that continue to experience hydrocephalus following the surgical resection may require multiple additional interventions to successfully divert CSF. Complications that arise following surgical resection of the PF tumour vary in both type and intensity, and typically include: cranial nerve dysfunctions, motor deficits, infection, and cerebellar mutism (Muzumdar & Ventureyra, 2010). Cerebellar mutism is characterized by a variety of symptoms including the transient disruption of speech, language difficulties and dysarthria (Robertson et al., 2006; Van Calenbergh, Van de Laar, Plets, Goffin, & Casaer, 1995).

1.1.2 Cognitive and affective outcomes in patients treated for PF tumours

Although necessary to achieve a cure, the combination of therapies detailed in the previous section contribute to long-term physical, endocrine and neuropsychological impairments in survivors (Mueller & Chang, 2009). Treatment with CSI has been associated with declines in numerous neuropsychological domains including intellectual functioning, visual-perceptual ability, memory, learning, processing speed, attention and executive functioning (Jain, Krull, Brouwers, Chintagumpala, & Woo, 2008; Kieffer-Renaux et al., 2000; Mabbott et al., 2006; Mabbott et al., 2008; Mabbott et al., 2005; Mulhern & Butler, 2004; Mulhern et al., 1998; Palmer, Reddick, & Gajjar, 2007; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004). In addition, CSI boost volume also contributes to intellectual outcome; patients with PF tumours treated with large boost volumes to the entire PF, regardless of the CSI dose they received, were found to have lower intellectual outcomes than patients treated with lower CSI doses and focal boost volumes restricted to the tumour bed (Moxon-Emre et al., 2014).
In addition to treatment-associated factors, the development of hydrocephalus and mutism are associated with a greater risk for poor cognitive outcomes (Hardy, Bonner, Willard, Watral, & Gururangan, 2008; Mabbott et al., 2008; Moxon-Emre et al., 2014). A younger age at diagnosis is also associated with worse cognitive outcomes (Mulhern et al., 2001; Palmer, 2008); it has been proposed that the tumour itself, the treatment required to obtain a cure, and the complications that ensue, have profound effects on a less developed brain by virtue of negatively influencing the processes that contribute to skill acquisition.

Compared to the wealth of studies that have thoroughly documented cognitive function in brain tumour survivors, less attention has been devoted to evaluating patients’ affective outcomes. Regardless, there is mounting evidence that children treated for brain tumours experience emotional dysfunction. A study that evaluated emotional outcomes in children treated for PF tumours demonstrated that although few patients treated for PF tumours had clinically elevated social problems and withdrawn/depressed behaviour scores, the proportion of survivors with clinically elevated scores exceeded population norms (Brinkman et al., 2012). The authors also highlighted that female patients, and patients treated with higher radiation intensity protocols, were at greatest risk for depression (Brinkman et al., 2012). A study that reviewed the literature pertaining to long-term psychiatric outcomes in paediatric PF tumour survivors found that incidences of anxiety, depression and behavioural problems were higher than in the general population, and cited both surgery and CSI as associated risk factors (Shah et al., 2015). Patients treated for PF tumours without radiation have also been shown to experience social problems and more internalizing symptoms (Beebe et al., 2005).

A review that examined the literature on quality of life (QOL) and mental health following treatment for any type of brain tumour in childhood revealed that infratentorial tumours and radiation therapy were risk factors for poor QOL in survivors (Bell, Ownsworth, Lloyd, Sheeran, & Chambers, 2018). Notably, PF tumours are located infratentorially. Moreover, in a study of adolescent survivors of childhood cancer more broadly, patients with brain tumours were found to have higher anxiety, depression and antisocial behaviours compared to their siblings (Schultz et al., 2007). Similarly, a recent systematic review that evaluated mental health of childhood and young adult cancer survivors found that brain tumours and treatment with CSI were specific risk factors for mental health problems, including anxiety and depression (Friend, Feltbower, Hughes, Dye, & Glaser, 2018). The growing body of literature on affective outcomes in children
with cancer consistently demonstrates that patients treated for brain tumours, including those that arise in the PF, are at risk for affective problems.

In addition to affective symptomology, brain tumour survivors appear to have difficulty with fundamental forms of emotional functioning, such as emotion recognition (Bonner et al., 2008) and emotion regulation (Armstrong et al., 2009; Hopyan, Laughlin, & Dennis, 2010; Law et al., 2017). It is possible that difficulties with either of these fundamental components of emotional functioning may contribute to the development of affective disorders in children treated for PF tumours; as such, facial emotion recognition and emotion regulation warrant specific attention, and are the main focus of the emotional functioning section below (section 1.3).

1.2 White matter (WM)

Developmental macrostructural changes occur in the brain throughout childhood and adolescence, and these include decreases in grey matter (GM) volume that is accompanied by WM volume increases (Giedd et al., 2015; Lebel & Beaulieu, 2011; Mills et al., 2016). WM changes throughout development as a result of myelination, a process that includes thickening of the myelin sheath, and axonal growth (Paus, 2010).

Diffusion magnetic resonance imaging dMRI is a neuroimaging technique that has revolutionized the way WM can be investigated in living human brain; it has increased our understanding of how WM develops by providing quantifiable parameters related to tissue microstructure (Tournier, Mori, & Leemans, 2011). Typical quantification of dMRI data uses a DTI (Tamnes, Roalf, Goddings, & Lebel, 2018); this analytic approach to evaluating WM microstructure will be detailed in the following section.

1.2.1 Quantifying WM microstructure: diffusion tensor imaging (DTI)

DTI is a neuroimaging technique that evaluates the restriction of randomly moving water molecules to assess WM structure in vivo. Specifically, it is an imaging technique based on a mathematical model that characterizes diffusion in all directions, which is calculated by collecting data using 6 or more non-collinear diffusion gradient directions (Basser, 1995). DTI generates quantifiable indices based on the displacement and directionality of water and its properties are thought to reflect WM microstructural organization. Using DTI, voxel-wise maps of several measures can be used to evaluate measures of tissue anisotropy, and fibre
directionality. These maps are based on diffusivities or directions, referred to as eigenvalues $\lambda_1$, $\lambda_2$, $\lambda_3$, that are calculated by matrix diagonalization (Pierpaoli & Basser, 1996).

Measures of fractional anisotropy (FA), mean, axial and radial diffusivities (MD/AD/RD) are derived from the DTI eigenvalues (Jones & Leemans, 2011). FA reflects the direction of principal diffusion within each voxel, and yields a value between 0 and 1; values closer to 1 indicate highly directional diffusion (i.e., high anisotropy), as water molecules will diffuse in a restricted manner along the dominant fibre direction, whereas values closer to 0 indicate unrestricted diffusion (i.e., low anisotropy) because water molecules are unrestricted by fibres. Given that WM acts as a barrier to water molecule movement, it is though that FA reflects WM microstructure. MD represents the mean diffusion freedom of water molecules within each voxel, measured in mm$^2$/s, and represents the magnitude of water diffusion (Basser, 1995). AD, also referred to a parallel or longitudinal, reflects diffusivity along the longest axis of the ellipsoid ($\lambda_1$), also measured in mm$^2$/s (Basser, 1995). RD, also referred to as perpendicular or transverse, represents the average of diffusivity values along $\lambda_2$ and $\lambda_3$, the two minor axes of the ellipsoid (Basser, 1995). Lower FA and higher MD/AD/RD are thought to signify compromised myelin sheath structure and axonal degeneration (Song et al., 2002). For instance, animal models have demonstrated that RD is altered by demyelination and remyelination, whereas AD is altered by axonal injury but remains unaltered by myelin changes (Song et al., 2003; Song et al., 2002; Song et al., 2005). Thus, as WM becomes disorganized, diffusion perpendicular to the fibre increases and the resulting FA value decreases (Pierpaoli & Basser, 1996).

Three approaches to evaluate WM were utilized in the current thesis. These include: 1) Tract Based Spatial Statistics (TBSS) (Smith et al., 2006), an unbiased voxelwise approach that evaluates WM microstructure throughout the WM core of the brain, 2) regional analyses, to acquire information about WM microstructure within each lobe of the cerebral cortex (as defined in Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009), and 3) tract based analyses (Ciccarelli et al., 2006) to investigate microstructure of specific WM tracts of interest. Voxelwise analyses were utilized most throughout this thesis; this approach was applied in Chapters 2, 3 and 4. The regional analysis approach was used in Chapter 2 only, and tract based analyses were conducted in Chapter 3 only. Multiple methods to evaluate WM were used in Chapters 2 and 3, as multiple techniques together have the capacity to provide complementary information regarding WM
microstructure. Only one method was used in Chapter 4, as there was no *a priori* hypothesis, and an unbiased voxelwise approach was taken as a result.

Although DTI was used in the current thesis to obtain information about WM microstructure, it is important to recognize that diffusivity can be influenced by a variety of brain micro- and macro-structure, including cell density, axon diameter, myelin content, myelin permeability and water content (Beaulieu, 2002). It has been emphasized that while diffusion parameters are sensitive to such changes, they are not specific to any of them; rather, diffusion imaging only truly measures one thing: the dephasing of spins of protons, when a spatially-varying magnetic field has been applied (Jones, Knosche, & Turner, 2013). Thus, while DTI provides useful information about WM microstructure, in particular as it relates to differences between populations that may result from damage to WM, it is important to keep in mind the true nature of what is being measured, and to resist the temptations to overgeneralize and to limit unsubstantiated claims as a result. With that in mind, the following section will detail what has been reported in the literature regarding the effect of PF tumour treatment on WM microstructure.

### 1.2.2 The effect of treatment for PF tumours on WM

It has been documented that radiation damages WM in children treated for PF tumours (Mabbott et al., 2006; Nagesh et al., 2008; Reddick et al., 2005). For instance, Reddick and colleagues (2005) demonstrated that children with PF tumours who were treated at a younger age, or that required a ventricular shunt, had less developed normal appearing WM. Shortly thereafter, Mabbott and colleagues (2006) used a regional analysis approach to demonstrate that compared to healthy controls, FA was lower in children treated for PF tumours in multiple regions throughout the cerebral hemispheres. Furthermore, a study that imaged patients with PF tumours before and after their treatment, demonstrated that FA within the genu and splenium of the corpus callosum decreased following radiation (Nagesh et al., 2008).

During CSI, the entire brain is exposed to radiation; brain regions that harbour stem and progenitor cells, such as the dentate gyri of the hippocampi are known to be particularly sensitive to radiation effects (Blomstrand et al., 2012). Other brain regions that may be vulnerable include those with protracted developmental trajectories, such as the prefrontal cortex, where WM myelination continues into the third decade of life (Teffer & Semendeferi, 2012; Ullen, 2009).
As detailed in section 1.1.1, the CSI dose delivered is typically determined by risk status, and the boost volume is determined by the protocol being used at that institution. It is reasonable to expect that patients treated with lower intensity protocols would experience less WM damage; it has been shown that treatment with lower doses of CSI is associated with less global WM damage (Khong et al., 2003; Mabbott et al., 2006; Reddick et al., 2000). Although the literature has largely focused on damage to WM in children who received radiation during their PF tumour treatment, there is some evidence that children with PF tumours treated without radiation also experience WM damage (Liu et al., 2015; Partanen et al., 2018; Rueckriegel et al., 2010).

To date, a wealth of studies have demonstrated that WM damage in children treated for PF tumours is associated with poor neurocognitive function, including deficits in processing speed, memory and IQ, regardless of how they were treated (reviewed in Marusak et al., 2018).

1.2.3 Remaining questions

With the CSI dose and boost combinations currently used in clinical practice to treat children with medulloblastoma, there is only one combination that considerably limits radiation exposure to the brain: reduced-dose CSI with a TB boost. Although it is known that treatment with CSI contributes to WM damage, the impact of treatment with different intensity protocols is not yet understood, and DTI has not yet been used to investigate this; in particular, regional differences in the vulnerability and/or resilience of WM have yet to be characterized.

Understanding the implications of treatment with different CSI dose and boost volumes on WM microstructure has immediate clinical relevance; institutions throughout the world currently differ in the volume of the boost they deliver, according to their planning capabilities (Parkes et al., 2015). If there is evidence of spared WM in children treated with lower intensity radiation protocols, then institutions that are still using higher intensity protocols may consider adjusting their protocols accordingly. Chapter 2 will address this issue directly.

Furthermore, given the comparative scarcity of studies that have evaluated WM damage in children treated without radiation, Chapters 3 and 4 include a sample of these children; their WM microstructure will be evaluated, and compared to children treated with radiation, and to typically developing children.
As detailed in sections 1.1.2 & 1.2.2, children treated for PF tumours experience cognitive dysfunction, and it is well documented that WM damage is a contributing factor. It is also possible that WM damage contributes to the affective disturbances detailed in section 1.1.2. The sections that follow will provide information pertaining to assessing emotional functioning in children treated for PF tumours; a critical first step towards evaluating if WM damage is involved in their reported emotional dysfunction.

### 1.3 Emotional functioning

Emotional functioning is a broad term that can be used to encompass a number of aspects related to emotional health. The social-emotional processing model proposed by Ochsner (2008) details a set of processes that encode emotionally relevant information, contextualize their meaning and guide responses. Ochsner (2008) suggested that emotion recognition and emotion regulation are two of several non-distinct skill sets that are necessary for successful social affective processing. For this reason, combined with those that follow, the current thesis will focus on facial emotion recognition and emotion regulation. First, both these aspects of emotional functioning undergo development throughout childhood and adolescence (De Sonneville et al., 2002; Kolb, Wilson, & Taylor, 1992; Lawrence, Campbell, & Skuse, 2015; Zeman, Cassano, Perry-Parrish, & Stegall, 2006), a time period that coincides with the diagnosis and treatment for PF tumours. Second, both these aspects of emotional functioning have been associated with brain structure and function (reviewed in Phillips & Swartz, 2014; reviewed in Wang, Metoki, Alm, & Olson, 2018), and children treated for PF tumours sustain trauma to the brain. And lastly, deficits with either aspect of emotional functioning in childhood have been associated with psychopathology (reviewed in Collin, Bindra, Raju, Gillberg, & Minnis, 2013; and Sheppes & Gross, 2011). Thus, evaluating facial emotion recognition and emotion regulation may provide unique insights into the development of emotional dysfunction in children treated for PF tumours, in a manner that cannot be gleaned by self- or proxy-reports of affective functioning.

Adult survivors of childhood brain tumours are at a greater risk of psychiatric disorders than the normal population (Shah et al., 2015); detecting and understanding the aspects of emotional functioning that are disrupted in childhood survivors of brain tumours may help reveal why this is the case, and hopefully provide clues on where interventions could be beneficial.
1.3.1 Facial emotion recognition and social functioning

The basic ability to discriminate among emotions is thought to precede the capacity to understand emotions (Camras & Shuster, 2013); emotion recognition can therefore be considered one of the earliest and most fundamental components of emotional functioning. The successful identification of facial emotions improves with age; however, there is some discrepancy regarding the developmental trajectory of facial emotion recognition. Some studies have found that children as young as 4 years are able to label basic emotions (sad, anger, happy, fear and disgust) with almost 100% accuracy (Herba, Landau, Russell, Ecker, & Phillips, 2006), while others have suggested there is little improvement in recognition accuracy after 7 years (De Sonneville et al., 2002). Another study demonstrated that facial emotion recognition accuracy improves between 6 and 8 years, and then plateaus until about 13 years, after which there is a second improvement at age 14 where performance reaches adult levels (Kolb et al., 1992). A recent study that utilized a large sample size (478 children) and wide age range (6-16) found that accuracy for recognizing happiness, surprise, fear and disgust increased with age, whereas little change in accuracy was observed for sadness and anger (Lawrence et al., 2015). It is certainly possible that results were influenced by differences among studies, including: the sample size and age range of children tested, the quality and intensity of the facial emotions used, the age of the actors displaying facial emotions, length of time the faces were shown, and whether IQ was included as a covariate. Regardless, although the exact timing of facial emotion recognition improvement differs in these studies, collectively they indicate that a trajectory of improvement exists throughout development.

The ability to recognize facial emotions is thought to be required for effective participation in one’s social environment (Morris, Weickert, & Loughland, 2009). It has been suggested that better emotion recognition in childhood is associated with greater social competence (Izard et al., 2011). It is well documented that facial emotion recognition deficits are a shared feature of various neurodevelopmental, psychiatric, and acquired brain disorders; children with bipolar affective disorder (McClure et al., 2005; Wegbreit et al., 2015), anxiety (Simonian, Beidel, Turner, Berkes, & Long, 2001; Waters, Neumann, Henry, Craske, & Ornitz, 2008), ADHD (Da Fonseca, Seguier, Santos, Poinso, & Deruelle, 2009), autism (Eussen et al., 2015; Evers, Steyaert, Noens, & Wagemans, 2015; Taylor, Maybery, Grayndler, & Whitehouse, 2015), epilepsy (Edwards, Stewart, Palermo, & Lah, 2017), traumatic brain injury (Mancuso et al.,
2015), and brain tumours (Bonner et al., 2008) all experience some degree of facial emotion recognition deficits. It has been suggested that facial emotion recognition deficits perpetuate the challenges with social relationships that individuals with many of these disorders experience (Collin et al., 2013).

1.3.2 Facial emotion recognition and social functioning in children treated for PF tumours

To date, there are no studies that have evaluated facial emotion recognition abilities exclusively in children treated for PF tumours. There are however, two studies that evaluated facial emotion recognition in children treated for brain tumours more broadly (Bonner et al., 2008; Willard, Hardy, & Bonner, 2009), and one study that evaluated emotion recognition, using music, in children with PF tumours (Hopyan et al., 2010).

In one study that evaluated facial emotion recognition in patients treated for brain tumours, the authors found that compared to children with juvenile rheumatoid arthritis (JRA), children treated for brain tumours made significantly more errors when judging the emotion of adult faces (Bonner et al., 2008). The authors also demonstrated that treatment history and diagnosis age affected performance when judging the emotion of child faces (Bonner et al., 2008). In the other study that evaluated facial emotion recognition, the authors demonstrate that females treated with CSI had more difficulty recognizing low-intensity facial expressions compared to females who did not receive CSI (Willard et al., 2009). The study that evaluated non-facial emotion recognition in children treated for PF tumours found that the ability to recognize happy and sad emotions in music was preserved overall, but that patients with medulloblastoma had difficulty identifying sad emotions (Hopyan et al., 2010).

Children treated for PF tumours also experience social problems. A study that evaluated social functioning, from both parent and teacher reports, documented an increase in social problems over time for childhood PF tumour survivors treated with CSI (Mabbott et al., 2005). Moreover, in children treated for low-grade astrocytoma, where less than 10% of patients were treated with radiation, patients with infratentorial tumours had more social concerns than patients with supratentorial tumours (Aarsen et al., 2006).
It is also well documented that children treated for brain tumours more broadly experience social problems. In the same study that evaluated facial emotion recognition in children treated for brain tumours, the authors demonstrated that patients had impaired social functioning compared to their illness control group (JRA), and that worse social functioning was associated with more facial emotion recognition errors (Bonner et al., 2008). A handful of studies have reviewed the literature on social outcomes in children treated for brain tumours; one study found consistent evidence for social adjustment deficits, regardless of the data gathering technique, the informant type, or the study design (Schulte & Barrera, 2010), and another indicated that brain tumour survivors appear to be at risk for social functioning deficits (Fuemmeler, Elkin, & Mullins, 2002).

1.3.3 WM microstructure and facial emotion recognition

A collection of neuroimaging studies in adults have provided evidence that specific WM pathways are critical for successful facial emotion recognition; these have included studies in patients with brain lesions (Crespi et al., 2014; Philippi, Mehta, Grabowski, Adolphs, & Rudrauf, 2009), traumatic brain injury (Genova et al., 2015), and healthy adults (Coad et al., 2017; Unger, Alm, Collins, O'Leary, & Olson, 2016). The WM tracts implicated in facial emotion recognition include the inferior frontal occipital fasciculus (IFOF), the inferior longitudinal fasciculus (ILF) and the uncinate fasiculus (UF).

The IFOF and ILF have been implicated frequently in face perception; they are both though to connect the occipital regions to other face perception network nodes, including the inferior frontal gyri (IFG) and fusiform gyri respectively (Wang et al., 2018). The IFOF is a long-range WM tract connects the occipital lobe to the infero-lateral and dorso-lateral frontal cortex, via the posterior temporal cortex; it originates in the ventral occipital cortex, runs medially in the temporal lobe and inferiorly in the frontal lobe (Catani, Howard, Pajevic, & Jones, 2002). The ILF is a WM tract that connects the occipital lobe to the temporal lobe; the fibres originate from the extrastriate cortex and terminate in both the lateral and medial temporal cortices, in the region of the amygdalae (Catani, Jones, Donato, & Ffytche, 2003).

Using a combination of ROI based and voxelwise analyses, the following studies in adults with brain pathology have implicated the IFOF and ILF in facial emotion recognition abilities. WM microstructure of the right IFOF and ILF were found to be associated with facial emotion
recognition in patients with amyotrophic lateral sclerosis (ALS); accuracy was positively correlated with FA in both tracts (Crespi et al., 2014). Another study that evaluated patients with brain damage found that damage to the right IFOF and ILF predicted facial emotion recognition deficits (Philippi et al., 2009). In patients with traumatic brain injury (TBI), microstructure of the IFOF and ILF were found to be associated with facial emotion recognition abilities (Genova et al., 2015). Although none of these studies were conducted in children, there is evidence of a relationship between the microstructural development of the right ILF and the age-related increase in the volume of the right fusiform, suggesting that development of the right ILF may be associated with the face perception network (Scherf, Thomas, Doyle, & Behrmann, 2014). WM microstructure of the IFOF and ILF have also been associated with facial emotion recognition performance in healthy adults; FA in the bilateral IFOF and AD in the right ILF were negatively correlated with facial emotion recognition (Unger et al., 2016). Although an association was found, it is noteworthy that higher FA was associated with worse performance in this study.

The UF is a WM tract that connects the anterior temporal lobes to the orbitofrontal cortices; the fibres originate in the temporal pole and amygdala, then make a U-turn to enter the extreme capsule, where they run inferior to the IFOF, and terminate in the lateral orbitofrontal cortex and frontal pole (Catani, Dell'acqua, & Thiebaut de Schotten, 2013). Discrepant results have been reported in studies that evaluated the relations between the UF and facial emotion recognition; one study in healthy adults found that microstructure along the right UF was correlated with increased facial emotion recognition abilities in healthy adults (Coad et al., 2017), whereas another study found no such relation (Unger et al., 2016).

Analogous neuroimaging studies investigating the association between IFOF, ILF and/or UF microstructure and facial emotion recognition capabilities have yet to be conducted in developing populations. There are however, a handful of studies that have associated these three pathways with social cognition, most commonly evaluated using theory of mind (ToM) tasks, in typically developing children. For instance, more organized microstructure of the UF (Anderson, Rice, Chrabaszcz, & Redcay, 2015) and of the right IFOF (Wiesmann, Schreiber, Singer, Steinbeis, & Friederici, 2017) were related to better performance on ToM tasks.

Given that the ILF, IFOF and UF have been implicated in facial emotion recognition, and that these associations have not yet been evaluated in developing populations, it will be a substantive
The focus of Chapter 3; the associations between these WM tracts and facial emotion recognition in children treated for PF tumours, and typically developing children, will be evaluated.

1.3.4 Emotion regulation

Research on emotion regulation has increased substantially over the past few decades; since the 1990s there has been an exponential increase in the number of publications that focus on “emotion regulation” (Gross, 2013), and it has become an active topic of investigation in most of the major areas within psychology (Gross, 2015). Despite this increased interest, many different terms are used to refer to emotion regulation processes, and there is no single accepted definition. However, several descriptions have aligned that provide a comprehensive understanding to what emotion regulation refers. According to Gross and colleagues (2011), emotion regulation requires the presence of a goal to either up- or down-regulate the magnitude or duration of an emotional response. Similarly, Thompson (1994) has described emotion regulation as the intrinsic and extrinsic processes that are involved in monitoring, evaluating and modifying emotional reactions, particularly with respect to their intensity and temporal features, in order to accomplish one’s goals. Together, both these definitions touch on aspects of emotion regulation that will be examined in the current thesis. That is, they focus on: a goal, the modification of an emotional response, and that there is a temporal component to this process.

Based on the definitions provided above, it may seem that emotion regulation is exclusively a deliberate process. It has been proposed however, that emotion regulation can be automatic or deliberate, and that both types exist on opposite ends of a continuum (Mauss, Bunge, & Gross, 2007). Automatic emotion regulation refers to the alteration of any aspect of one’s emotions, without attending to the process of regulating one’s emotions, and without deliberate control (Mauss et al., 2007). The conceptual framework for automatic emotion regulation was built upon the automatic goal-pursuit literature, which posits that goal-pursuit can occur and shape behaviour without conscious awareness (Bargh & Gollwitzer, 1994).

A dual-process model has been proposed to integrate both automatic and deliberate forms of emotion regulation (Gyurak, Gross, & Etkin, 2011). According to this dual-process framework, automatic emotion regulation is implicit, meaning the process is evoked by the stimulus, and it can happen without insight or awareness (Gyurak et al., 2011). In contrast, deliberate emotion regulation is explicit, such that the process requires conscious effort in addition to some insight.
and awareness (Gyurak et al., 2011). Implicit emotion regulation tasks have commonly taken the form of emotional versions of the Stroop paradigm (Stroop, 1935). In an example of such a task: participants are shown an emotional face with an emotional word written over it, and participants are asked to indicate the emotion of the face with a button press (Egner, Etkin, Gale, & Hirsch, 2008). Congruent (i.e., no-conflict) trials are associated with faster response times than incongruent (i.e., conflict) trials (Gyurak et al., 2011).

The dual-process framework of emotion regulation has some parallels with the biased competition theory of attention, which posits that bottom-up processing guides our initial attention, and that top-down control is derived from the specific task demands (Desimone & Duncan, 1995; Miller & Cohen, 2001). Specifically, the automatic emotion regulation component, where sensory encoding of emotionally arousing stimuli occurs automatically, is akin to bottom-up stimulus-driven attentional processing. Similarly, the general cognitive control processes required to regulate an emotional response can be likened to top-down attentional control processes.

Interestingly, affect-biased attention has been proposed as a critical aspect of emotion regulation (Todd, Cunningham, Anderson, & Thompson, 2012; Wadlinger & Isaacowitz, 2011). It has been argued that the predisposition to attend to emotionally salient stimuli is an important part of the emotion regulation process that influences subsequent processing (Todd et al., 2012; Wadlinger & Isaacowitz, 2011); the authors propound that the way one’s attention is biased, say, towards attending to happy faces rather than angry faces, can alter how an emotional experience unfolds, which in this case could result in experiencing less feelings of negative affect during a stressful situation than it would if attention were biased to negative expressions (Todd et al., 2012). Moreover, it has also been suggested that regulating attention is a relevant component of the emotion regulation process, and that attentional regulation can be trained through practice (Wadlinger & Isaacowitz, 2011).

The present thesis will consider both the automatic and deliberate components of emotion regulation, and will consider each from an attentional standpoint, using eye-tracking technology (detailed in section 1.4.1 below). More traditional accounts of emotion regulation strategies, such as cognitive reappraisal and expressive suppression (Gross, 2002), are beyond the scope of this thesis and will not be discussed.
1.3.5 Emotion regulation in children treated for PF tumours

Only a handful of studies have evaluated emotion regulation in PF tumour survivors; in these studies, survivors appear to differ from their typically developing peers. One study documented that children treated for PF tumours had impaired cognitive control of emotions, as evaluated on an emotional tones version of the Stroop task (Hopyan et al., 2010). Specifically, participants were asked to attend to the emotion in the music, and to ignore the emotion conveyed by the lyric; patients with PF tumours, whether they were treated with radiation or not, were less accurate than healthy controls on the incongruent trials (Hopyan et al., 2010). More recently, a study that evaluated emotion regulation as a component of executive function reported that children treated for medulloblastoma made less use of adaptive cognitive emotion regulation strategies than typically developing children (Law et al., 2017). Their measures of adaptive cognitive emotion regulation were obtained from the Cognitive Emotion Regulation Questionnaire, a self-report questionnaire that measures cognitive emotion regulation strategies that can be used following a negative life event (Garnefski, Kraaij, & Spinhoven, 2001).

Studies that have evaluated patients treated for brain tumours more broadly also indicate that survivors have difficulty with emotion regulation. One study found that compared to their siblings, children treated for brain tumours with high doses of CSI exhibited more emotion regulation problems on parent-report questionnaires (Armstrong et al., 2009). A more recent study demonstrated that poor parent-reported emotional control was a strong risk factor for poor self-reported social competence in brain tumours survivors (Barrera et al., 2017).

Although there is a paucity of studies that have directly evaluated emotion regulation in PF tumours patients, there is evidence of a syndrome, termed the Cerebellar Cognitive Affective Syndrome (CCAS) characterized by deficits in executive function, visual-spatial ability, linguistic processing and affective dysregulation, following cerebellar lesions in children and adults (reviewed in Schmahmann, 2019). The affective component has been grouped into several domains, including: attentional control, emotional control, autism spectrum disorders, psychosis spectrum disorders and social skill set (Schmahmann, Weilburg, & Sherman, 2007). In one study that evaluated CCAS in children, 35% of patients treated for PF tumours without radiation had persistent postoperative impaired affect regulation, as documented by a clinician and verified by parents, and extensive damage to the vermis was associated with this dysregulation (Levisohn,
In another study, 79% of patients treated for PF tumours located medially or in the vermis, without radiation, showed evidence of behavioural disturbances such as flattened affect, disinhibited or clingy behaviour and verbal hyper-spontaneity (Aarsen, Van Dongen, Paquier, Van Mourik, & Catsman-Berrevoets, 2004). Many of the studies that evaluate CCAS in children consist of case-reports on small sample sizes, and affective regulation is often reported by clinicians or parents without the use of standardized measures; as such, it is a challenge to compare between studies and to discern how these disturbances relate to emotion regulation in children with PF tumours. Nonetheless, given that affective dysregulation has been documented in children treated for PF tumours, and that emotional control is one of its constituents, it is clearly important to evaluate emotion regulation directly in this patient population.

1.3.6 WM microstructure and emotion regulation

Emotion regulation is thought to rely on circuitry involving the amygdalae and prefrontal cortical (PFC) regions (Phillips & Swartz, 2014); evidence from studies conducted in adults and youths suggest that emotion regulation is subserved by a medial system that includes the orbitofrontal and anterior cingulate cortex, mediodorsal PFC, and hippocampi, whereas voluntary emotion regulation is subserved by a lateral system that includes the dorsolateral prefrontal cortex and ventrolateral PFC (Phillips & Swartz, 2014). It is well documented that the brain regions involved in emotion regulation continue to develop into adulthood (Paus, Keshavan, & Giedd, 2008). In particular, grey matter volume and cortical thickness of the PFC decrease throughout adolescence (Gogtay et al., 2004; Shaw et al., 2008). It has been suggested that this grey matter decline may actually reflect an imaging artefact due to the increase in myelination of intra-cortical axons (Paus et al., 2008).

As the structural connectivity between brain regions involved in emotion regulation develops, greater top-down control can be exerted (Gee et al., 2013). It is thought that improved connectivity is achieved through the WM volume and density increases that occur throughout adolescent development (Giedd et al., 1999; Ostby et al., 2009). Despite this assumption, there are no studies in children that have directly evaluated the relations between emotion regulation and WM. However, a handful of studies have used functional MRI (fMRI) to evaluate the neural bases of emotion regulation throughout development. In one study, an emotional go/no-go task
using emotional and neutral faces was used; children and adolescents had longer reaction times than adults when responding to the fearful go trials, which was accompanied by greater amygdala reactivity in adolescents (Hare et al., 2008). In another similar go/no-go task using emotional and neutral faces, PFC recruitment was positively correlated with accuracy, and adolescents had greater ventral striatum activity compared to children and adults (Somerville, Hare, & Casey, 2011). Together, these studies suggest that when asked to regulate behaviour, adolescents may be driven less by their PFC, and more by their subcortical structures (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015); it is certainly possible that less mature WM, and consequently lower connectivity, is responsible for this phenomenon. A sole study that evaluated age-related changes in the structure and function of PFC-amygdala circuitry was conducted in children and adolescents; greater WM connectivity was found to underlie the enhanced communication between these two brain regions (Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014). Specifically, increased FA in the UF was associated with reduced amygdala activation to emotional faces, as evaluated with fMRI, in children and adolescents (Swartz et al., 2014).

Several WM tracts have been implicated in emotion regulation by virtue of structural differences that have been detected in paediatric affective and psychiatric disorders that are characterized by emotional dysregulation, including borderline personality disorder and conduct disorder (Johnston et al., 2017; New et al., 2013; Sarkar et al., 2013). However, owing to the dearth of information regarding specific WM tracts and emotion regulation as it is conceptualized in the current thesis (that is, as an eye-movement based behavioural measure) an unbiased voxelwise approach was taken to evaluate the relations between WM and emotion regulation.

1.3.7 Remaining questions

Although children treated for brain tumours have a documented facial emotion recognition deficit (Bonner et al., 2008; Willard et al., 2009), it is unclear why this is the case. Attention to the visual stimuli during the task is a critical aspect to consider. If children have difficulty maintaining visual attention to the faces, it could explain why they are having difficulty identifying the emotion. If children attend to the faces yet still have difficulty identifying the emotions, it would suggest that processes other than attention (e.g., neurobiological or cognitive dysfunction) might underlie their deficits. Given that several WM pathways have been
implicated in successful facial emotion recognition in adults (as detailed in section 1.3.3), and that children treated for PF tumours have documented WM damage (as detailed in section 1.2.2), it is certainly possible that WM pathology underlies their facial emotion recognition deficit. Both these novel questions will be addressed directly in Chapter 3.

With the exception of the study by Hopyan and colleagues (2010) standardized questionnaires have been used to evaluate emotion regulation in children treated for PF tumours. Questionnaires provide valuable information about an outcome, but cannot speak to a process in real time. It is important to consider that emotional responses unfold along a time continuum, and capturing the temporal nature could provide novel insights into their deficits. Moreover, questionnaires either require self-insight, or they are proxy reports, and neither is truly objective as a result. Broad behavioural constructs from self or parent-report questionnaires lack the specificity to inform the development of targeted interventions to improve functioning in survivors.

It has been suggested that future research should utilize multi-method and multi-informant approaches to assess functioning in children treated for brain tumours (Brinkman et al., 2012). A study that reviewed the behavioural, emotional and social outcomes in children treated for brain tumours highlighted that evidence for emotional problems is mixed (Fuemmeler et al., 2002); the authors suggest that a more complete assessment of the children’s emotional functioning is required, including assessments of more subtle problems that cannot be gleaned by standardized measures designed to assess psychopathology (Perrin, Stein, & Drotar, 1991), and that the development of new instruments may be required to do so. Chapter 4 will address these issues directly by using a novel eye-tracking approach to objectively evaluate emotion regulation; the sections that follow detail why eye-movement monitoring is an ideal approach to achieve this.

1.4 Eye-movement monitoring

The human visual system features a high-resolution fovea, and a lower resolution periphery (Henderson, Williams, Castelhano, & Falk, 2003). As a result of this organization, detailed visual information is perceived primarily by fixating on regions of interest; multiple times every second, a viewer will select, via a saccadic movement, a region in the environment for perceptual and cognitive processing (Henderson & Hollingworth, 1998). It is thought that both stimulus-bound characteristics, such as colour and movement, as well as internal cognitive processes, such as memory, goals and knowledge, determine how the world is viewed (Hannula et al., 2010).
Eye-movement monitoring, commonly conducted using eye-tracking technology, is a non-invasive procedure that measures and records eye-movements. Although this methodology has not been used in the brain tumour population before, it has been successfully used in other paediatric populations (reviewed in Karatekin, 2007). Arguably, one of the most powerful aspects of eye-tracking methodology, especially when working with cognitively impaired children, is that it overcomes the need for self-insight; eye-tracking does not rely on verbal communication.

Eye-tracking delivers rich information that facilitates the rigorous characterization of attention to visual stimuli; specifically, the orientation and maintenance of attention can be differentiated and quantified with exceptional sensitivity. For instance, it can provide information about what stimulus was attended to, how quickly attention was directed to any stimulus, how long the attention was maintained, either on a fixation basis, or over a specific time period or trial. Eye-tracking is a tool that has the capability to address the questions detailed in the previous section, and that can facilitate the study of emotional functioning as a result. Namely, it can help characterize the visual attention component of facial emotion recognition that is addressed in Chapter 3. It is also ideally suited to provide information about an emotional process in real time, and in an objective manner, which is the focus of Chapter 4. The sections that follow outline how these questions will be answered.

### 1.4.1 Eye-tracking: a technique to probe emotional functioning

Attention to emotional stimuli was historically evaluated using behavioural tasks such as the dot-probe paradigm, where reaction-time to a dot following the presentation of a neutral or emotional face provided an indirect measure of attention (van Rooijen, Ploeger, & Kret, 2017). However, because such reaction-time based approaches are unable to disentangle the processes related to attentional orientation from engagement, eye-tracking studies have been steadily increasing (Armstrong & Olatunji, 2012). Eye-movements are ideally suited to evaluate the attentional system in real time, as they are a direct behavioural manifestation of attentional allocation.

Using eye-tracking, stimuli that capture attention initially (attentional orienting) can be distinguished from stimuli that maintain attention over time (attentional engagement), and the ability to voluntarily regulate these attentional processes can be investigated directly. There is evidence that emotionally arousing stimuli lead to faster orienting and/or enhanced maintenance
of attention. Several studies have demonstrated that when emotional and neutral stimuli are presented simultaneously, participants are more likely to orient their attention towards the emotional stimuli (reviewed in Carretie, 2014). In one study, where emotional stimuli were found to capture attention, the authors demonstrated that participants continued to make their first fixation on the emotional face over the neutral face, regardless of where they were instructed to direct their initial gaze (Nummenmaa, Hyona, & Calvo, 2006). These studies suggest that attentional orienting is automatic, and raise the possibility that overriding (or regulating) this response may be a challenge.

Chapter 3 capitalizes on the ability to detect viewing location using eye-tracking, to quantify attention to the photographs being judged during the facial emotion recognition task. In Chapter 4, a novel eye-tracking task is developed to evaluate emotion regulation. Information about initial eye-movements to each face can be quantified and correlated with standardized psychological and structural brain data. Namely, the objective eye-tracking measure of emotion regulation can be related to a standardized measure of emotional control in daily life, to evaluate if the eye-tracking task is indeed capturing a construct related to emotional control. Developing an objective measure of emotional functioning could have direct clinical utility. As detailed in the previous section, the medical community who care for children treated for PF tumours have indicated that novel ways to evaluate emotional functioning are lacking and should be developed; the current thesis, and Chapter 4 in particular, represents an attempt to achieve this.

1.5 Thesis objectives

The overall goal of this thesis was to evaluate if, and how, emotional functioning is affected by damage to WM. To achieve this, it was essential to begin by clarifying the effect of treatment with radiation on WM microstructure in children treated for PF tumours. Next, novel eye-tracking tasks were developed and combined with standardized measures of emotional functioning, and the relations between emotional functioning and WM microstructure was evaluated. The main hypothesis was that radiation-induced damage to WM would negatively influence emotional functioning in children treated for PF tumours. The section that follows provides an outline of the studies contained within this thesis, and details the questions addressed in each.
1.5.1 Thesis overview

This thesis combined DTI, eye-tracking and standardized measures of emotional and cognitive functioning to evaluate if emotional functioning is affected by damage to WM microstructure in children treated for PF tumours. Three separate studies were conducted to achieve this.

The first study (Chapter 2) characterized the effect of different clinically relevant radiation intensity protocols on WM microstructure in children treated for medulloblastoma. As brain tumour therapy moves increasingly towards risk-adapted therapy, the trade-off between the intensity of treatment and its long-term effects must be rigorously characterized. It is known that CSI damages WM in children treated for medulloblastoma; this study provides the first multi-approach, dual-cohort imaging analysis of the relations between radiation and WM. In one cohort, the trade-off between treatment with clinically relevant radiation protocols and WM damage was evaluated. Patients were divided into those treated with higher intensity protocols (i.e., any CSI dose with a boost to the entire PF), and those treated with the least intensive CSI protocol (i.e., reduced dose CSI, with a focal conformal boost to the tumour bed); both a regional analysis and a voxelwise approach were taken to evaluate WM microstructure in each group, and in a cohort of typically developing children. In a separate cohort of children treated for medulloblastoma, the continuous effect of radiation dose on WM was evaluated in a voxelwise manner; radiation dosimetry maps were acquired for a subsample of patients to achieve this. The following questions were addressed in Chapter 2: 1) is there evidence that treatment with the lowest intensity CSI protocol spares WM in children treated for medulloblastoma, and 2) does increasing radiation dose predict WM indices?

The second study (Chapter 3) marks the transition to evaluating emotional functioning in children treated for PF tumours more broadly. At present, it is well documented that children with various neurodevelopmental, psychiatric and acquired brain disorders have difficulty recognizing facial emotions, and that their social relationships may suffer as a result. To mitigate the negative impact of facial emotion recognition deficits, it is important to understand how these deficits arise. There is mounting evidence that implicates specific WM tracts in the ability to successfully recognize facial emotions: the ILF, IFOF and UF. This is the first study to combine DTI, eye-tracking, and cognitive testing, to directly investigate factors that may contribute to facial emotion recognition in children treated with and without radiation for PF tumours, and in
typically developing children. To evaluate attention to the emotional face stimuli, eye-tracking was used, and to evaluate WM, tract based and voxelwise analyses were conducted. The following questions were addressed in Chapter 3: 1) is there evidence of a facial emotion recognition deficit in our sample of children treated for PF tumours, and 2) does damage to WM tracts implicated in facial emotion recognition, namely the ILF, IFOF and UF, explain their deficit?

In the third and final study (Chapter 4) the investigation into emotional functioning in children treated for PF tumours is continued. It is well documented that achieving a cure in children diagnosed for PF tumours is accompanied by profound social and emotional dysfunction that decreases their quality of life. There are currently no objective behavioural markers to detect emotional dysfunction in this vulnerable population. This study is the first to integrate eye-tracking technology with a novel behavioural paradigm of attention to emotional faces to objectively evaluate emotion regulation, using the same sample of participants as in Chapter 3. As there were no a priori hypotheses regarding the WM tracts involved, or relations between WM and emotion regulation, an unbiased voxelwise approach was taken. Chapter 4 addresses the following questions: 1) can emotion regulation be evaluated objectively using eye-tracking technology in children treated with and without radiation for PF tumours, 2) is this eye-tracking measure of emotion regulation associated with emotional control in daily life, and 3) is there an association between WM microstructure and the eye-tracking measure of emotion regulation?

The final chapter of this thesis (Chapter 5) integrates the findings detailed in Chapters 2-4; the results are discussed within the context of the literature that preceded it, and that laid the foundation for this work. The final chapter also details the challenges that were faced, indicates the limitations of this work, and provides suggestions for future research aimed at ameliorating quality of life in children who have the misfortune of having a PF tumour.
Chapter 2

Vulnerability of White Matter to Insult during Childhood: Evidence from Patients Treated for Medulloblastoma


This Chapter may not exactly replicate the final version published in the *Journal of Neurosurgery: Pediatrics*
2 Vulnerability of White Matter to Insult during Childhood: Evidence from Patients Treated for Medulloblastoma

2.1 Abstract

Object: Craniospinal irradiation damages white matter in children treated for medulloblastoma, but treatment intensity effects are unclear. In a cross-sectional retrospective study, we evaluated the effect of: 1) treatment with the least intensive radiation protocol vs. protocols that deliver more radiation to the brain, and 2) continuous radiation dose, on white matter architecture.

Methods: We used diffusion tensor imaging to assess fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity. First, regional white matter analyses and tract based spatial statistics were conducted in 34 medulloblastoma patients and 38 healthy controls. Patients were stratified according to those treated with: 1) the least intensive radiation protocol: specifically, reduced-dose craniospinal irradiation plus a boost to the tumour bed only (n=17), or 2) any other dose and boost combination that delivers more radiation to the brain: termed the ‘all-other-treatments’ group (n=17), comprised of patients treated with standard-dose craniospinal irradiation plus a posterior fossa boost, standard-dose craniospinal irradiation plus a tumour bed boost, and reduced-dose craniospinal irradiation plus a posterior fossa boost. Second, we conducted voxelwise dose-distribution analyses in a separate cohort of medulloblastoma patients (n=15). Results: The all-other-treatments group, but not the reduced-dose craniospinal irradiation plus tumour bed group, had lower fractional anisotropy and higher radial diffusivity than controls in all brain regions (all $P<0.05$). The reduced-dose craniospinal irradiation plus tumour bed boost group had higher fractional anisotropy ($P=0.05$) and lower radial diffusivity ($P=0.04$) in the temporal region, and higher fractional anisotropy in the frontal region ($P=0.04$) than the all-other-treatments group. Linear mixed-effects modeling revealed that dose and age-at-diagnosis together: a) better predicted fractional anisotropy in the temporal region than models with either alone ($P<0.005$), b) did not better predict fractional anisotropy than dose alone in the occipital region ($P>0.05$). Conclusion: Together, we show that white matter damage has a clear relation with increasing radiation dose, and that treatment with reduced dose craniospinal irradiation plus tumour bed boost appears to preserve white matter in some brain regions.
2.2 Introduction

A critical issue in cancer therapy is characterizing the trade-off between the intensity of treatment and its long-term effects. This understanding is integral to providing care that maximizes cure rates while minimizing negative sequelae. Children with brain tumours are a particularly informative population in which to study this interplay, and they stand to benefit from treatment adjustment. In two medulloblastoma patient cohorts, we evaluated the relations between white matter (WM) architecture and: 1) radiation treatment intensity (i.e. protocols that deliver varying degrees of radiation to the brain), 2) radiation dose-distributions, respectively.

Medulloblastoma is the most common childhood malignant central nervous system (CNS) tumour, accounting for 50% of all posterior fossa (PF) tumours (Pollack, 2011). Current treatment protocols include surgery, craniospinal irradiation (CSI) with a boost to the tumour site, and chemotherapy. Although this therapy combination is life-saving, it contributes to long-term physical, endocrine and neuropsychological impairments in survivors (Mueller & Chang, 2009). CSI treatment for medulloblastoma contributes to WM damage, and dose-dependent volumetric and structural changes have been reported (Khong et al., 2003; Mabbott et al., 2006; Nagesh et al., 2008; Reddick et al., 2000). However, the impact of clinically-relevant CSI dose and boost volume combinations on region-specific WM architecture is unknown. It is also unclear if reduced radiation preserves WM. To bridge these gaps, we used Diffusion Tensor Imaging (DTI) to compare WM architecture as a function of radiation treatment protocol and radiation dose.

Historically, patients with medulloblastoma were stratified into average- or high-risk disease groups (Pollack, 2011). A lack of neuraxis dissemination and/or no minimal residual tumour following surgery characterizes average-risk disease (Merchant et al., 2008). Typically, average- and high-risk patients receive reduced (i.e. 2,340 cGy) and standard (i.e. 3,600 cGy) dose CSI to the neuraxis, respectively (Pollack, 2011). Initially, CSI was followed by a boost to the entire PF, but the past two decades have seen the development of conformal techniques limit radiation delivery to the tumour bed (TB) (Wolden et al., 2003). Event-free survival in children treated with PF vs. TB boosts is uncertain, but is the focus of The Children’s Oncology Group ACNS0331 trial. The PF boost delivers more radiation to structures located outside the targeted area, especially the temporal lobes, than a boost to the TB (Wolden et al., 2003). Thus, with these
CSI doses and boosts, there is only one combination considerably limits radiation exposure to the brain: reduced-dose CSI+TB boost. Although overall WM volume changes have been documented as a function of conventional vs. reduced radiation dose (Reddick et al., 2000), we are the first to use DTI to evaluate the impact of radiation on WM according to treatment protocols that differ in boost volume, and also to consider dose-distributions.

DTI generates quantifiable indices based on the displacement and directionality of water, and its properties are thought to reflect WM organization (Basser, 1995). These indices include fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) (Jones & Leemans, 2011). Lower FA and higher MD/AD/RD are thought to signify compromised myelin sheath integrity and axonal degeneration (Song et al., 2002). For instance, as WM is perturbed, diffusion perpendicular to the fibre increases and the FA value decreases (Pierpaoli & Basser, 1996). Moreover, increasing AD correlates with axonal damage (Song et al., 2005), and increasing RD is a sensitive marker of demyelination (Janve et al., 2013). This level of architectural detail cannot be gleaned from volumetric studies of WM.

Regional differences must be considered in order to appropriately capture the effect of radiation on WM. During CSI, no brain regions are shielded from radiation; however, not all structures are equally susceptible to radiation-induced damage. Brain regions harbouring stem and progenitor cells that continue to undergo neurogenesis are known to be particularly sensitive (Blomstrand et al., 2012). Structures and tracts with long periods of development may also be especially vulnerable to insult during childhood. Whole brain WM volume increases during childhood and adolescence (Lebel & Beaulieu, 2011), and prefrontal cortex myelination continues into the third decade of life (Teffer & Semendeferi, 2012).

To our knowledge, the present study is the first to evaluate the effect of clinically relevant CSI dose and boost volume combinations, and to consider the continuous effect of radiation dose-distribution, on WM architecture using DTI. We expect that treatment with reduced dose CSI+TB boost will be accompanied by less WM damage (Khong et al., 2003; Mabbott et al., 2006; Nagesh et al., 2008; Reddick et al., 2000), and possibly WM sparing.
2.3 Methods

2.3.1 Participants

Thirty-four children treated for medulloblastoma between 1998-2012 at the Hospital for Sick Children (SickKids; Toronto, Canada) and thirty-eight healthy control children participated. We evaluated the impact of treatment intensity protocols in this cohort. In a separate cohort of fifteen patients, we evaluated dose-distribution effects. Demographic variables for these cohorts are summarized in Tables 2.1 and 2.2 respectively. Patients were excluded if they had recurrent disease, premorbid neurological disorders, or were receiving palliative care. Controls were free of neurological or clinical disorders, and had normal MRI scans (confirmed by a neuroradiologist [S.L.]). Patients were informed of this study via mailed letters, or during routine clinic visits when applicable. Controls were either recruited from the community, were siblings of patients, or family members of SickKids staff. This study was approved by our Research Ethics Board (REB# 1000010907). Prior to participation, parents provided written informed consent and children provided assent.

2.3.2 Patient treatment information

2.3.2.1 Radiation therapy

All patients were treated with photon beam CSI, and received either standard (3060-3940 cGy) or reduced (1800-2340 cGy) dose. Due to treatment protocol changes, patients seen before 2006 received a lateral-beam boost to the PF, whereas from 2006 onwards patients routinely received an IMRT boost with a 1-cm margin around the TB (SJMB03 protocol). We leveraged this protocol change and divided patients into those treated with: 1) the least intensive radiation protocol: reduced-dose CSI+TB boost and 2) any other dose and boost combination that delivers more radiation to the brain: ‘all-other-treatments’ (i.e. standard-dose CSI+PF boost, reduced-dose CSI+PF boost, and standard-dose CSI+TB boost). Medical variables are summarized in Table 2.1.

2.3.2.2 Chemotherapy

Patients were treated on a number of different protocols (i.e. SJMB03, POG9631, CCG9961, MOPP and ACNS0331), and received different chemotherapy agents as a result. The number of patients treated on each protocol, and the agents used in each are provided in Tables 2.1 and 2.2.
### Table 2.1 Demographic and medical variables: treatment intensity protocol cohort

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th>Reduced-dose CSI+TB</th>
<th>All-other-treatments</th>
<th>( P^{*} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n=38 )</td>
<td>( n=17 )</td>
<td>( n=17 )</td>
<td></td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>( n )</td>
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<td></td>
</tr>
<tr>
<td><strong>Age-at-Diagnosis (years)</strong></td>
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<td></td>
<td></td>
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<td>5.37 (2.06)</td>
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<td>1.3-9.6</td>
<td></td>
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<td></td>
<td></td>
<td>0.03</td>
</tr>
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<td>Median (SD)</td>
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<td>10.65 (2.62)</td>
<td>14.62 (3.39)</td>
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</tr>
<tr>
<td>Range</td>
<td>6.9-18.6</td>
<td>7.9-16.4</td>
<td>8.2-18.7</td>
<td></td>
</tr>
<tr>
<td><strong>Time-Since-Diagnosis (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (SD)</td>
<td>-</td>
<td>2.17 (1.55)</td>
<td>7.43 (3.12)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>-</td>
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<td>3.0-13.6</td>
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</tr>
<tr>
<td><strong>Craniospinal Irradiation</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Standard + PF boost</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Standard + TB boost</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Reduced + PF boost</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Reduced + TB boost</td>
<td>-</td>
<td>17</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protocol (number of patients treated)</td>
<td>-</td>
<td>SJMB03 (17)</td>
<td>SJMB03 (2) / POG9631 (5) / CCG9961 (7) MOPP (1) / ACNS0331 (1)</td>
<td></td>
</tr>
<tr>
<td><strong>Gross Total Resection</strong></td>
<td>-</td>
<td>17 (100%)</td>
<td>14 (82.4%)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Clinical Risk (Average Risk)</strong></td>
<td>-</td>
<td>17 (100%)</td>
<td>8 (47.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hydrocephalus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence at diagnosis</td>
<td>-</td>
<td>15 (88.2%)</td>
<td>12 (70.6%)</td>
<td>0.20</td>
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<tr>
<td>Hydrocephalus requiring CSF</td>
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<td>8 (47.1%)</td>
<td>0.16</td>
</tr>
<tr>
<td>diversion</td>
<td>-</td>
<td>3 (17.6%)</td>
<td>2 (11.8%)</td>
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<tr>
<td>3rd ventriculostomy</td>
<td>-</td>
<td>7 (41.2%)</td>
<td>4 (23.5%)</td>
<td>0.27</td>
</tr>
<tr>
<td>EVD only</td>
<td>-</td>
<td>3 (17.6%)</td>
<td>4 (23.5%)</td>
<td>0.67</td>
</tr>
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<td>VPS</td>
<td>-</td>
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<td>3 (17.6%)</td>
<td>0.29</td>
</tr>
<tr>
<td>One or more revisions</td>
<td>-</td>
<td>3 (17.6%)</td>
<td>7 (41.2%)</td>
<td>0.13</td>
</tr>
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<td>7 (41.2%)</td>
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<tr>
<td>Motor Deficits</td>
<td>-</td>
<td>14 (82.4%)</td>
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<td>0.67</td>
</tr>
<tr>
<td>Cranial Nerve Deficits</td>
<td>-</td>
<td>4 (23.5%)</td>
<td>3 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>Multiple Post-operative</td>
<td>-</td>
<td>11 (68.8%)</td>
<td>10 (58.8%)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>MRI Scan Type</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>1.5 T</td>
<td>22 (57.9%)</td>
<td>8 (47.1%)</td>
<td>6 (35.3%)</td>
<td></td>
</tr>
<tr>
<td>3.0 T</td>
<td>16 (42.1%)</td>
<td>9 (52.9%)</td>
<td>11 (64.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour Size (mm(^2))</strong></td>
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<td></td>
<td></td>
<td>0.14</td>
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<tr>
<td>Mean (SD)</td>
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<td>2227.4 (894.66)</td>
<td>1753.77 (696.33)</td>
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<tr>
<td>Range</td>
<td>-</td>
<td>1050-3770</td>
<td>957-3000</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; CSI, craniospinal irradiation; EVD, external ventricular drain; PF, posterior fossa; SD, standard deviation; TB, tumour bed; VPS, ventriculoperitoneal shunt.

* \( P^{*} \) values reflect: \( X^2 \) tests for categorical variables, t-tests between patient groups, or one way ANOVAs between the three groups

Percentages reflect within-group totals

\(^{a}\) For the entire patient sample, the median age-at-diagnosis was: 7.09 (2.83), range: 1.32–15.16, whereas the median age at CSI was: 7.20 (2.87), range: 1.99–15.31. The patient diagnosed at 1.3 years received CSI at 2 years. In most instances, the time between diagnosis and CSI was shorter: mean (SD)=0.11 (0.21)
Chemotherapy protocols and their associated agents: SJMB03 (Vincristine, Cisplatin, Cyclophosphamide); POG9631 (Topside, Cisplatin, Cyclophosphamide, Vincristine); CCG9961 (Vincristine, Lomustine/cyclophosphamide, Cisplatin); MOPP (Mechloroethamine, Vincristine, Procarbazine, Prednisone); ACNS0331 (Vincristine, Cisplatin, Lomustine, Cyclophosphamide)

- Mutism: diminished speech output, linguistic difficulties or dysarthria following surgery
- Motor deficits: ataxia, dysmetria or hemiparesis on neurological exams
- Cranial nerve deficits: cranial nerve palsy on neurological exams
- Tumour size was calculated by multiplying the two largest measurements of the tumour from an anatomical MRI scan. Data was unavailable for 6 patients (reduced dose CSI+TB group=2; all-other-treatments group=4)

**Table 2.2 Demographic and medical variables: dose-distribution cohort**

<table>
<thead>
<tr>
<th>Medulloblastoma patients</th>
<th>n=15</th>
</tr>
</thead>
<tbody>
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<td><strong>Male sex</strong></td>
<td>9 (60%)</td>
</tr>
<tr>
<td><strong>Age-at-Diagnosis (years)</strong></td>
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</tr>
<tr>
<td>Median (SD)</td>
<td>7.73 (2.93)</td>
</tr>
<tr>
<td>Range</td>
<td>4.8-15.0</td>
</tr>
<tr>
<td><strong>Age-at-Scan (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Median (SD)</td>
<td>9.9 (2.58)</td>
</tr>
<tr>
<td>Range</td>
<td>6.2-15.4</td>
</tr>
<tr>
<td><strong>Time-Since-Diagnosis (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Median (SD)</td>
<td>1.94 (1.36)</td>
</tr>
<tr>
<td>Range</td>
<td>0.3-5.0</td>
</tr>
<tr>
<td><strong>Craniospinal Irradiation</strong></td>
<td></td>
</tr>
<tr>
<td>Standard + PF boost</td>
<td>1</td>
</tr>
<tr>
<td>Standard + TB boost</td>
<td>2</td>
</tr>
<tr>
<td>Reduced + PF boost</td>
<td>2</td>
</tr>
<tr>
<td>Reduced + TB boost</td>
<td>10</td>
</tr>
<tr>
<td><strong>Chemotherapy a</strong></td>
<td>SJMB03 (12) / POG9631 (1) / CCG9961 (1) / ACNS0331 (1)</td>
</tr>
<tr>
<td><strong>Gross Total Resection</strong></td>
<td>13 (86.7%)</td>
</tr>
<tr>
<td><strong>Clinical Risk (Average Risk)</strong></td>
<td>12 (80%)</td>
</tr>
<tr>
<td><strong>Hydrocephalus</strong></td>
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</tr>
<tr>
<td>Presence at diagnosis</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Hydrocephalus requiring CSF diversion</td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td>3rd ventriculostomy</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>EVD only</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>VPS</td>
<td>0</td>
</tr>
<tr>
<td>One or more revisions</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mutism b</strong></td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td><strong>Motor Deficits c</strong></td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td><strong>Cranial Nerve Deficits d</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Multiple Post-operative Complications</strong></td>
<td>6 (40%)</td>
</tr>
<tr>
<td><strong>MRI Scan Type</strong></td>
<td>1.5 T</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; EVD, external ventricular drain; PF, posterior fossa; SD, standard deviation; TB, tumour bed; VPS, ventriculoperitoneal shunt

- Chemotherapy protocols and their associated agents: SJMB03 (Vincristine, Cisplatin, Cyclophosphamide); POG9631 (Topside, Cisplatin, Cyclophosphamide, Vincristine); CCG9961 (Vincristine, Lomustine/cyclophosphamide, Cisplatin); MOPP (Mechloroethamine, Vincristine, Procarbazine, Prednisone); ACNS0331 (Vincristine, Cisplatin, Lomustine, Cyclophosphamide)
Lomustine/cyclophosphamide, Cisplatin); MOPP (Mechloroethamine, Vincristine, Procarbazine, Prednisone); ACNS0331 (Vincristine, Cisplatin, Lomustine, Cyclophosphamide)

- Mutism: diminished speech output, linguistic difficulties or dysarthria following surgery
- Motor deficits: ataxia, dysmetria or hemiparesis on neurological exams
- Cranial nerve deficits: cranial nerve palsy on neurological exams

During radiation therapy, patients treated on the POG9631 protocol received oral etoposide, patients treated on the CCG9961 protocol received weekly vincristine, and patients treated on the ACNS0331 protocol received weekly vincristine. Patients treated on the SJBM03 an MOPP protocols did not receive concurrent chemotherapy during radiation therapy. All patients received chemotherapy after radiation therapy.

2.3.3 Neuroimaging protocol

Magnetic Resonance Imaging (MRI) was performed at SickKids using either a GE LX 1.5T MRI scanner with an 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 (T1=400ms, TE/TR=4.2/10.056ms, 116-124 contiguous axial slices, flip angle=20°, 256x192 matrix interpolated to 256x256, FOV=240x240mm, slice thickness=1.5mm) and a diffusion-weighted single shot spin echo DTI sequence with EPI readout (25-31 directions, b=1000s/mm², TE/TR=85.5/15000ms, 45-50 contiguous axial slices, flip angle=90°, 128x128 matrix interpolated to 256x256, FOV=240x240mm, slice thickness=3mm). The Siemens 3T MRI protocol utilized a T1 AX 3D MPRAGE Grappa 2 protocol (T1=900ms, TE/TR=3.91/2300ms, 160 contiguous axial slices, flip angle=9°, 256x224 matrix, FOV=256x224mm, voxel size=1mm ISO) and diffusion-weighted single shot spin echo DTI sequence with EPI readout (30 directions, b=1000s/mm², TE/TR=90/9000ms, 70 contiguous axial slices, flip angle=90°, 122x122 matrix interpolated to 244x244, FOV=244x244mm, voxel size=2mm ISO). MRI Images were eddy corrected for current distortions and DTI indices (FA/MD/AD/RD) were calculated using the FMRIB Software Library (FSL) version 4.1.8 (Smith et al., 2004). Patients were scanned at 1.5T or 3T, based on their radiological indication or cohort. Scanning one individual on both the 1.5T and 3T revealed signal to noise ratios (SNR) of 28.5 and 70.7 respectively, for the zero diffusion weighted images. We thus matched the groups for scanner type, and we included MRI scanner type as a covariate in the regional and TBSS analyses of imaging data in order to control for SNR differences across the 1.5T and 3T scanners.
2.3.4 Analytic plan

First, medical and demographic variables were compared between the groups using $\chi^2$ tests, t-tests or one-way ANOVAs as appropriate. $P$ values for all comparisons are provided in Table 2.1. Next, we evaluated the relations between WM and clinically relevant protocols using regional WM and Tract Based Spatial Statistics (TBSS) analyses, controlling for variables that differed between the groups where appropriate. Lastly, we evaluated the relations between FA, dose, age-at-diagnosis, and time-since-diagnosis in a voxelwise manner.

2.3.4.1 Regional analyses

T1-weighted images were segmented into grey matter (GM), WM and cerebrospinal fluid (CSF) using FSL-FMRIB’s Automatic Segmentation Tool [FSL-FAST] (Zhang, Brady, & Smith, 2001). WM segmentations included eight cerebral regions (i.e. bilateral frontal, parietal, temporal and occipital) and four PF regions (i.e. pons, vermis and bilateral cerebellar hemispheres), based on a template modified from Kabani et al. (2002) as defined in Mabbott et al. (2009). Using an affine transformation, this template was applied to produce WM segmentations for all participants, then transformed into DTI space using linear and non-linear transformations (Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998; Woods, Grafton, Watson, Sicotte, & Mazziotta, 1998). Collapsing across hemisphere for frontal, temporal, parietal and occipital regions, and across PF regions, yielded five regions of interest (ROI). Due to individual variations in brain volume, the total number of voxels in each ROI differed across participants.

As DTI indices are non-orthogonal, we conducted a multivariate analysis of variance (MANOVA) comparing FA/MD/AD/RD for each WM ROI between healthy controls and both patient groups. We followed-up with a series of univariate ANOVAs between the patient groups as defined above, and between patients treated with reduced dose only in order to directly compare the TB and PF boosts. Including covariates was deemed an appropriate method to correct for the effect of demographic and treatment variables on our outcome measure because they overlapped in our groups (Li, Kleinman, & Gillman, 2014). All post-hoc pairwise comparisons were Bonferroni-corrected.
2.3.4.2 TBSS analyses

Voxelwise analyses were conducted with TBSS (Smith et al., 2006). All subjects’ FA data were aligned into a common space (MNI152; Montreal Neurological Institute, McGill, Canada) using the nonlinear registration tool FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b). Then, a cross-subject mean FA image was created and used to generate a ‘skeleton’ FA map representing the center common to all tracts, thresholded at FA>0.20. Finally, participant-specific FA maps were aligned with the skeleton, and values along the width of each tract were considered in the cross-subject voxelwise statistics, with clusters defined by $T>3$.

TBSS controls for family-wise errors using a permutation methodology. The null distribution of the cluster-size statistic was built up over 5000 random permutations. Cluster size was thresholded at $P<0.05$, which is fully corrected for multiple comparisons. A mask was made for each significant cluster, and the anatomic extent of each was labeled with reference to the MNI Structural and JHU White-Matter Tractography Atlases (Hua et al., 2008; Mazziotta et al., 2001).

2.3.4.3 Voxelwise dose-distribution analyses

WM was segmented as described in the regional analyses section above. Dose-distribution maps, from treatment planning, were co-registered with patients’ FA images, then aligned into common space. Each voxel thus had a corresponding radiation dose and FA value. Each brain region was exposed to a different radiation dose range, as follows: Frontal: 1871 – 5423 cGy; Temporal: 2013 – 5755 cGy; Parietal: 1863 – 5557 cGy; Occipital: 1912 – 5820 cGy; Posterior Fossa: 2450 – 5987 cGy. There was considerable variation in the number of voxels exposed to the different doses within each region (Figure 2.1). We performed linear mixed-effects analyses to evaluate the relationships between dose, age-at-diagnosis, time-since-diagnosis, and FA in the temporal and occipital regions only (i.e. brain regions containing sufficient voxels exposed to a wide range of radiation doses – see Figure 2.1). Dose, age-at-diagnosis and time-since-diagnosis were entered as fixed effects, and random intercepts were included for participants. We conducted a series of model comparisons and evaluated the added contribution of each significant fixed effect. $P$-values were obtained from the likelihood ratio tests comparing the full model with the effect of interest to a model without it.
Figure 2.1 Histograms depicting the number of voxels exposed to specific radiation doses in each brain region

(A) The temporal and occipital regions contained many voxels that were exposed to different doses of radiation. These brain regions were included in the linear mixed-effects model comparisons designed to evaluate the continuous effect of dose on FA (see Table 2.4). (B) The majority of voxels in the frontal, parietal and posterior fossa regions were exposed to the same dose, and the linearity assumption was violated as a result. These brain regions were not included in the linear mixed-effects model comparisons. Each brain region contained all the voxels from the patients in our sample (n=15; see Table 2.2). For each graph, the upper limit of the Y-axis was set to the total number of voxels included for that brain region.

2.4 Results

2.4.1 Participant and treatment information

Age-at-scan differed between the three groups (P=0.03), and age-at-diagnosis and time-since-diagnosis differed between the patient groups (all P<0.005). Given that DTI indices change with age (Yoshida, Oishi, Faria, & Mori, 2013), and that age-at-diagnosis and time-since-diagnosis may contribute to poor outcome in patients (Pollack, 2011) we controlled for these variables in subsequent analyses where appropriate. Because we deliberately stratified patients according to treatment protocol, the patient groups differed in clinical risk, craniospinal irradiation and chemotherapy (all P<0.001). These variables were not controlled for in subsequent analyses.
2.4.2 Regional analyses

*WM of patients treated with higher-intensity radiation protocols differs from healthy controls in all brain regions:* Significant multivariate main effects were found for DTI indices in all brain regions (all $F(8,130)>2.19$, all $P<0.03$), and were qualified by significant univariate effects and pairwise comparisons. The all-other-treatments group had lower FA and higher RD relative to controls in all brain regions (all $P<0.05$; Figure 2.2A), and higher MD in temporal, occipital and PF regions (all $P<0.05$). The reduced-dose CSI+TB boost group had higher FA relative to the all-other-treatments group, in temporal, parietal, occipital and PF regions (all $P<0.005$), lower RD in temporal and occipital regions (all $P<0.005$; Figure 2.2A), and lower MD in the temporal region ($P<0.001$). Notably, FA did not differ between controls and patients in the reduced-dose CSI+TB boost group in any brain region (all $P>0.05$). RD and MD were higher in the reduced-dose CSI+TB boost group than in controls in the PF only (all $P<0.05$; Figure 2.2A). No group differences in AD emerged. MRI scanner type and age-at-scan were included as covariates in these analyses.

*WM differs between patient groups:* We limited our analyses to FA/RD as these indices showed the most robust differences in analyses including controls. Relative to patients in the all-other-treatments group, patients treated with reduced-dose CSI+TB boost had higher FA ($F=4.2$, $P=0.05$) and lower RD ($F=4.68$, $P=0.04$) in the temporal region, and higher FA in the frontal region ($F=4.78$, $P=0.04$; Figure 2.2B). Comparing patients treated with reduced-dose revealed that receiving a TB vs. a PF boost was associated with higher FA in the occipital region ($F=4.42$, $P=0.05$) and lower RD in the frontal ($F=5.07$, $P=0.04$), temporal ($F=5.22$, $P=0.03$) and occipital ($F=10.24$, $P=0.005$) regions (Figure 2.2C). MRI scanner type, age-at-scan, age-at-diagnosis and time-since-diagnosis, were included as covariates in these analyses.
Figure 2.2 Reduced-dose CSI+TB boost treatment is less damaging to WM than higher-intensity protocols

Means and standard errors of FA and RD for the five brain regions examined (collapsed across hemisphere) (A) in healthy controls, patients treated with reduced-dose CSI+TB boost and patients treated with all-other-treatments, controlling for scanner and age-at-scan. * P<0.05; ** P<0.01; *** P<0.001. Not shown: Mean and standard errors of MD in: 1) all-other-treatments vs. healthy controls in the temporal region: 0.000847(0.0000094) vs. 0.000799(0.0000061), P<0.001; occipital region: 0.000789(0.0000094) vs. 0.00076(0.0000061), P=0.04; PF region: 0.000816(0.000014) vs. 0.000747(0.0000093), P<0.001. 2) patients treated with reduced-dose CSI+TB vs. all-other-treatments in the temporal region: 0.00079(0.0000093) vs. 0.000847(0.0000094), P<0.001. 3) patients treated with reduced-dose CSI+TB vs. healthy controls in the PF region: 0.000791(0.000014) vs. 0.000747(0.0000093), P=0.03.

Means and standard errors of FA and RD for the five brain regions examined (collapsed across hemisphere), (B) in patients treated with reduced-dose CSI+TB boost and all-other-treatments, controlling for scanner, age-at-scan, and two additional covariates that were not applicable to healthy controls: age-at-diagnosis and time-since-diagnosis, and (C) in patients treated with reduced-dose CSI+TB boost and reduced dose CSI+PF boost, controlling for scanner, age-at-scan, age-at-diagnosis and time-since-diagnosis. * P<0.05; ** P<0.01; *** P<0.001

2.4.3 TBSS

Treatment with reduced-dose CSI+TB boost spares WM: FA and RD differed between patients and controls in many WM tracts throughout the brain (all \( F > 9 \); all \( P < 0.001 \)). Post-hoc pairwise comparisons revealed many voxels where, compared to controls, the all-other-treatments group had lower FA and higher RD (all \( T > 2.05 \); all \( P < 0.001 \); Figure 2.3A, Table 2.3), and where
patients treated with reduced-dose CSI+TB boost had lower FA and higher RD (all \( T > 1.9 \), all \( P < 0.01 \); Figure 2.3B, Table 2.3). Patients in the reduced-dose CSI+TB boost group had many voxels with higher FA and lower RD than patients in the all-other-treatments group (all \( T > 1.84 \), \( P < 0.01 \); Figure 2.3C, Table 2.3), but none where the reverse was true. This last comparison did not remain significant when age-at-diagnosis and time-since-diagnosis were included as covariates. For visualization purposes, TBSS maps were overlaid on representative dose-distributions; highlighting that differences between patient groups were largely confined to brain regions exposed to the maximum dose (i.e. \( \sim 5500 \) cGy) following a PF boost. Identical brain regions were exposed to less radiation (i.e. \( \sim 3200 \) cGy) following a TB boost (Figure 2.4).

**Figure 2.3 Treatment with less radiation spares WM in the temporal region**

Difference in FA between medulloblastoma treatment groups and healthy control children. Clusters of voxels with significantly reduced FA (\( P < 0.05 \)) in (A) patients treated with all-other-treatments compared to controls, (B) patients treated with reduced-dose CSI+TB boost compared to controls, and (C) patients treated with all-other-treatments compared to patients treated with reduced-dose CSI+TB boost. Clusters are displayed in red, and superimposed on FMRIB FA template. Images are in radiological convention. Numbers represent Montreal Neurological Institute (MNI) Z-coordinates. White arrows indicate areas where patients treated with all-other-treatments differ from controls, but where patients treated with reduced-dose CSI+TB boost do not. Note that there
are greater differences between controls and patients in the all-other-treatments group, than between controls and patients treated with reduced-dose CSI+TB boost, particularly in the temporal lobes. Only FA is shown, but similar patterns of differences were observed with RD. Cluster details are provided in Table 2.3.

**Table 2.3 FA and RD TBSS analysis: clusters that differ between groups**

<table>
<thead>
<tr>
<th>FA</th>
<th>Contrast</th>
<th>Cluster (number of voxels)</th>
<th>Cluster Family-Wise Error Corrected P</th>
<th>Brain regions a encompassed</th>
<th>WM structures b encompassed</th>
<th>Mean T value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-other-treatments &lt; Healthy controls</td>
<td>93202</td>
<td>&lt;0.001</td>
<td>Cerebellum, parietal lobe, temporal lobe, occipital lobe, frontal lobe, thalamus, putamen, caudate and insula</td>
<td>Forceps minor, IFOF, SLF, ATR, ILF, forceps major, CST, SLF (temporal part), UF, cingulum (cingulate gyrus + hippocampus)</td>
<td>2.24</td>
</tr>
<tr>
<td></td>
<td>Reduced + TB boost &lt; Healthy controls</td>
<td>29860</td>
<td>&lt;0.001</td>
<td>Parietal lobe, frontal lobe, occipital lobe, temporal lobe, insula, caudate</td>
<td>Forceps minor, SLF, forceps major, SLF (temporal part), CST, IFOF, ILF, ATR, cingulum (hippocampus), UF</td>
<td>1.93</td>
</tr>
<tr>
<td></td>
<td>All-other-treatments &lt; Reduced + TB boost</td>
<td>12994</td>
<td>0.003</td>
<td>Cerebellum, thalamus, temporal lobe, frontal lobe, putamen, caudate, insula, parietal lobe, occipital lobe</td>
<td>ATR, IFOF, CST, ILF, UF, SLF, SLF (temporal part), forceps minor, cingulum (hippocampus), right cingulum (cingulate gyrus)</td>
<td>2.17</td>
</tr>
<tr>
<td></td>
<td>Reduced + TB boost &gt; Healthy controls</td>
<td>17769</td>
<td>0.005</td>
<td>Temporal lobe, occipital lobe, parietal lobe, cerebellum, putamen, frontal lobe, thalamus, caudate, insula</td>
<td>IFOF, right ILF, forceps minor, CST, ATR, forceps major, SLF, SLF (temporal part), cingulum (cingulate gyrus + hippocampus), UF</td>
<td>1.85</td>
</tr>
<tr>
<td></td>
<td>All-other-treatments &gt; Reduced + TB boost</td>
<td>11193</td>
<td>0.006</td>
<td>Temporal lobe, occipital lobe, parietal lobe, putamen, thalamus, frontal lobe, insula, caudate</td>
<td>ILF, IFOF, ATR, SLF (temporal part), forceps major, left CST, left UF, left cingulum (cingulate gyrus + hippocampus), forceps minor</td>
<td>1.99</td>
</tr>
<tr>
<td>RD</td>
<td>All-other-treatments &gt; Healthy controls</td>
<td>80716</td>
<td>&lt;0.001</td>
<td>Cerebellum, parietal lobe, temporal lobe, thalamus, frontal lobe, occipital lobe, putamen, caudate, insula</td>
<td>Forceps minor, SLF, IFOF, ATL, ILF, forceps major, SLF (temporal part), CST, UF, cingulum (cingulate gyrus + hippocampus)</td>
<td>2.06</td>
</tr>
<tr>
<td></td>
<td>Reduced + TB boost &gt; Healthy controls</td>
<td>17163</td>
<td>0.002</td>
<td>Parietal lobe, frontal lobe, temporal lobe, occipital lobe, insula, caudate</td>
<td>SLF, forceps minor, SLF (temporal part), CST, forceps major, cingulum (cingulate gyrus and hippocampus), ILF, IFOF, ATR, UF</td>
<td>2.09</td>
</tr>
<tr>
<td></td>
<td>All-other-treatments &gt; Reduced + TB boost</td>
<td>2280</td>
<td>0.005</td>
<td>Thalamus, caudate, parietal lobe, temporal lobe</td>
<td>ATR, right CST, right cingulum (cingulate gyrus + hippocampus), forceps minor, right SLF, right IFOF</td>
<td>3.22</td>
</tr>
</tbody>
</table>

Abbreviations: ATR, anterior thalamic radiation; CST, corticospinal tract; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; RD, radial diffusivity; SLF, superior longitudinal fasciculus; TB, tumour bed; TBSS, tract based spatial statistics; UF, uncinate fasciculus

a Brain regions: defined by the MNI structural atlas
WM structures: defined by the JHU White-Matter Tractography Atlas. Unless otherwise specified, structures listed refer to bilateral counterparts. All structures are listed in order from greatest to least probability of being a member of the labelled regions within the respective atlas. Significant clusters containing <100 voxels were excluded.

**Figure 2.4** WM appears spared in brain regions exposed to less radiation following a TB boost

Note that the clusters (displayed in yellow) depicted in (A) and (B) are identical. This figure demonstrates that a lower dose/smaller field of radiation is delivered to the brain following a TB boost (B) compared to a PF boost (A). Radiosurgery dosages indicate a gradient of radiation doses ranging from 2300 (blue) to 5500 (pink) cGy. Clusters indicate where RD is decreased ($P<0.05$) in patients treated with reduced-dose CSI+TB boost versus the all-other-treatments group. Clusters are superimposed on radiation dose-distributions (shown in blue, purple and pink). Images are in radiological convention. Numbers represent Montreal Neurological Institute (MNI) X, Y & Z-coordinates for sagittal, coronal, and axial planes respectively. Dose distributions, as determined during treatment planning, were first co-registered with the patient’s FA image, then aligned into a common space. For visualization purposes, two dose-distributions, each from a single patient treated with reduced-dose CSI are shown. Boxed areas are magnified and placed side-by-side in order to emphasize the relation between voxels that differed between patient groups, and the corresponding doses administered to those exact brain regions. The clusters of difference in RD between the two patient groups correspond to areas where the dose delivered is ~3200 cGy (purple areas) in the reduced-dose CSI+TB boost group, and ~5500 cGy (pink areas) in patients treated with a larger boost volume. WM may be relatively “spared” in the group treated with reduced dose CSI+TB boost. Only RD is shown, but similar patterns of difference were observed with FA. Cluster details are provided in Table 2.3.
2.4.4 Voxelwise dose-distribution analyses

Across voxels in temporal and occipital regions, decreasing dose and increasing age-at-diagnosis was associated with increasing FA (all $T>2.47$, all $P<0.05$; Table 2.4). In the temporal region, a model including age-at-diagnosis and dose together was a better predictor of FA than models with either alone (all $P<0.005$). In the occipital region, a model including age-at-diagnosis and dose together was a better predictor of FA than age-at-diagnosis alone (all $P<0.001$), but not a better predictor than dose alone (all $P>0.05$; Table 2.4). Time-since-diagnosis never predicted FA.

Table 2.4 Predicting FA with linear mixed-effects models

<table>
<thead>
<tr>
<th>Region</th>
<th>Fixed effect included in model</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>t-value</th>
<th>$P^a$</th>
<th>$P^b$: added benefit of a model that includes both Dose and Age-at-diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal</td>
<td>Dose</td>
<td>-0.000016</td>
<td>0.000004</td>
<td>-44.20</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Age-at-diagnosis</td>
<td>0.008</td>
<td>0.002</td>
<td>4.37</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Occipital</td>
<td>Dose</td>
<td>-0.00002</td>
<td>0.000006</td>
<td>-40.94</td>
<td>&lt;0.001</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Age-at-diagnosis</td>
<td>0.007</td>
<td>0.003</td>
<td>2.47</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

A series of linear mixed-effects models and model comparisons were conducted to evaluate the continuous effects of dose and age-at-diagnosis, on FA. $^a$P-values correspond to the significance of the model with either fixed effect alone. $^b$P-values were obtained from the likelihood ratio test of the model that included both fixed effects against models that included either fixed effect alone.

2.5 Discussion

As new stratification and dose de-escalation strategies are considered in the treatment of medulloblastoma, it is important to understand the implications of reducing treatment. We evaluated the relation between radiation exposure and WM architecture by evaluating: 1) DTI indices between healthy controls and a cohort of patients treated with different clinically relevant protocols, and 2) voxelwise dose-distribution effects in temporal and occipital regions, in a separate patient cohort. We observed that: (i) treatment with reduced-dose CSI+TB boost may spare WM; (ii) decreasing radiation dose predicts WM sparing.

Regional WM analyses revealed that reduced-dose CSI+TB treatment was associated with higher FA and lower RD in the temporal region, and higher FA in the frontal region, even when controlling for variables that differed between the patient groups. Specifically, we controlled for
time-since-diagnosis and age-at-diagnosis, as these variables have the capacity to influence outcome (Pollack, 2011). As expected, reduced-dose CSI+TB boost treatment appears less damaging to WM than treatment with protocols that deliver more radiation to the brain. Notably, FA and RD may not have differed in the PF between patients treated with reduced dose and PF vs. TB boosts, as trauma associated with surgical excision and radiation delivery is maximal in this region for both groups.

TBSS revealed that patients treated with reduced-dose CSI+TB boost differed less from controls than the all-other-treatments group. There were also many voxels where the reduced-dose CSI+TB boost group did not differ from controls. Because this patient group was treated homogeneously, we can infer that treatment with reduced-dose CSI+TB boost has the capacity to spare WM in some structures; particularly the temporal lobes, internal capsule, and splenium of the corpus callosum. TBSS also revealed many voxels where patient groups differed in FA and RD. However, the potential contributions of age-at-diagnosis and time-since diagnosis could not be ruled out in this analysis.

To more directly consider the impact of dose, age-at-diagnosis and time-since diagnosis, we conducted voxelwise dose-distribution analyses in a separate cohort of patients. These data provide evidence that decreasing dose and increasing age are associated with WM sparing.

Unlike volumetric WM analyses, DTI can be used to evaluate the architecture of neuronal tissue and its pathological changes. FA and RD are thought to reflect overall WM, and myelin architecture, respectively (Song et al., 2002; Song et al., 2005). Myelin synthesis is actively occurring during childhood (Spreen, Risser, & Edgell, 1995), and radiation disrupts oligodendrocyte mitosis (Sheline, Wara, & Smith, 1980). Because RD is thought to correspond to demyelination (Klawiter et al., 2011; Song et al., 2005), it is logical that RD differed according to treatment intensity protocols. In contrast, AD did not differ between the patient groups and controls. This may suggest that axons are less susceptible than myelin to treatment with radiation. Moreover, our TBSS results are consistent with studies that found frontal WM to be especially vulnerable following whole brain CSI (Qiu, Kwong, Chan, Leung, & Khong, 2007; Qiu, Leung, Kwong, Chan, & Khong, 2006).

The WM sparing we observed is exciting as it may help explain the preserved intellectual function in patients treated with reduced-dose CSI+TB boost (Moxon-Emre et al., 2014).
Temporal WM may be critical to performing cognitive tasks. Indeed, a recent study found an association between radiation dose to the hippocampus and temporal lobes in paediatric patients, and a decline in their neurocognitive skills (Redmond, Mahone, & Horska, 2013).

The present study should be considered in light of some limitations. First, patients treated with reduced-dose CSI+TB boost had the shortest follow-up time from treatment. The degree to which WM sparing remains over time is unknown; it is possible that WM indices change slowly over time, and that this apparent WM sparing would gradually diminish. However, we note that time-since-diagnosis did not predict FA in our voxelwise dose-distribution analyses. Second, although our sample size was large, it became smaller when stratified by treatment protocol. Third, our sample included participants with various treatment histories. For instance, chemotherapy protocols have changed over the time period captured, and this may be an unavoidable confounding factor. Patients in the reduced-dose CSI+TB group received vincristine, cisplatin and cyclophosphamide. Patients in the all-other-treatments group were treated on several different protocols and received differing combinations of vincristine, cisplatin and cyclophosphamide, lomustine, topside, mechloroethamine, procarbazine and prednisone. Although chemotherapy has been associated with reduced WM volume (Edelmann et al., 2014), WM pathology has not consistently been reported (Genschaft et al., 2013). Lastly, the different image processing protocols may explain some of the apparent inconsistencies between the regional and TBSS analyses; regional analyses are based on DTI indices calculated from each participant’s anatomical WM segmentations, whereas TBSS is performed in reference to the WM skeleton common to all participants.

Future directions include: (i) understanding how structural changes predict neurocognitive function, (ii) clarifying the unique effects of radiation by evaluating children treated with chemotherapy only (e.g. ALL patients), and (iii) assessing the implications of medical complications such as mutism and hydrocephalus.

2.5.1 Conclusion

We have demonstrated that radiation, whether evaluated according to treatment intensity protocols or dose-distribution maps, compromises white matter. We also show, not surprisingly, that a younger age-at-diagnosis is an important factor. We found that reduced dose CSI+TB boost appears to preserve WM in some brain regions. The PF boost delivers more radiation to the
temporal lobes, than a boost to the TB (Wolden et al., 2003); our regional and TBSS analyses suggest WM damage accompanies this increased exposure. In the context of excellent survival with the TB boost (Moxon-Emre et al., 2014), our findings suggest the PF boost be reconsidered. Our study is the first to characterize the regional effects of treatment intensity protocols on WM, and to evaluate voxelwise dose-effects in parallel. Our findings provide a better understanding of radiation-induced WM vulnerability, and suggest there may be a threshold beyond which toxicity increases substantially. Importantly, our findings offer the possibility of superior outcomes for patients eligible for treatment with reduced-dose CSI+TB boost.

2.6 Acknowledgements and funding

We thank Ruth A. Weiss (MRT MR, R., CAMRT, CMRTO, SMRT; Hospital for Sick Children, MRI technologist) and Tammy Rayner (MRT, MR, R; Hospital for Sick Children, MRI technologist) for assistance with MRI data collection.

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Chapter 3

Facial Emotion Recognition in Children Treated for Posterior Fossa Tumours and Typically Developing Children: a Divergence of Predictors


This chapter may not exactly replicate the final version submitted to NeuroImage: Clinical (revise and resubmit)
3 Facial Emotion Recognition in Children Treated for Posterior Fossa Tumours and Typically Developing Children: a Divergence of Predictors

3.1 Abstract
Facial emotion recognition (FER) deficits are evident and pervasive across neurodevelopmental, psychiatric, and acquired brain disorders in children, including children treated for brain tumours. Such deficits are thought to perpetuate challenges with social relationships and decrease quality of life. The present study combined eye-tracking, neuroimaging and cognitive assessments to evaluate if visual attention, brain structure, and general cognitive function contribute to FER in children treated for posterior fossa (PF) tumours (patients: n=36) and typically developing children (controls: n=18). To assess FER, all participants completed the Diagnostic Analysis of Nonverbal Accuracy (DANVA-2), a computerized task that measures facial emotion recognition using photographs while their eye-movements were recorded. We confirm that patients made more FER errors than controls (p=0.02). Although we detected subtle deficits in visual attention and general cognitive function in patients, we found no associations with FER. Compared to controls, patients had lower FA and higher RD in multiple regions throughout the brain (all p<0.05), but not in specific WM tracts associated with FER. Despite the distributed WM differences between groups, WM predicted FER in controls only. In patients, factors associated with their disease and treatment consistently predicted FER. Our study provides insight into predictors of FER that may be unique to children treated for PF tumours, and highlights a divergence in associations between brain structure and behavioural outcomes in typically developing and clinical populations; a concept that may be broadly applicable to other neurodevelopmental and clinical populations that experience FER deficits.

3.2 Introduction
Facial emotions provide rich non-verbal information in real-time, and their correct interpretation is critical to participation in one’s social environment (Collin et al., 2013). Facial emotion recognition (FER) deficits are evident and pervasive across various neurodevelopmental, psychiatric, and acquired brain disorders in children; namely, schizophrenia/psychosis, mood disorders, anxiety, ADHD, conduct disorder (reviewed in Collin et al., 2013), autism (Eussen et al., 2015; Evers et al., 2015; Taylor et al., 2015), epilepsy (Edwards et al., 2017), traumatic brain
injury (Mancuso et al., 2015), and brain tumours (Bonner et al., 2008). FER deficits have been proposed to perpetuate the challenges with social relationships that individuals with many of these disorders experience (Collin et al., 2013). Factors that contribute to FER remain poorly understood in children, yet their identification is necessary in the effort to mitigate the deleterious effects of FER deficits.

Here, we consider three factors that may contribute to FER: visual attention, brain structure and general cognitive function. Children treated for tumours that arise in the posterior fossa (PF) of the brain have the potential to provide insight on how FER is disrupted; this clinical population has a documented FER deficit (Bonner et al., 2008) and they experience 1) attention problems, 2) altered brain structure (i.e., white matter (WM) and cerebellar damage), and 3) cognitive deficits (reviewed in Padovani, Andre, Constine, & Muracciole, 2012).

Children treated for brain tumours may experience FER deficits for a number of reasons. First, they may not effectively attend to the visual stimuli. To evaluate visual attention, we recorded participant’s eye-movements while they performed a FER task. Second, alterations to their brain structure may contribute to FER deficits. Studies in adults with brain lesions, traumatic brain injury (reviewed in Wang et al., 2018) and healthy adults (Coad et al., 2017) suggest the following WM tracts are associated with FER: the inferior-frontal occipital fasciculus (IFOF) and the inferior-longitudinal fasciculus (ILF), tracts that connect the occipital cortex to the orbitofrontal cortex and anterior temporal lobe respectively, and the uncinate fasciculus (UF), tracts that connect the anterior temporal lobe to the orbitofrontal cortex (Catani & Thiebaut de Schotten, 2012). Analogous studies are lacking in children. To evaluate WM, we used diffusion tensor imaging (DTI), a technique that generates quantifiable indices based on the directionality and displacement of water that are thought to reflect WM organization (Basser, 1995; Jones & Leemans, 2011). The cerebellum has also been implicated in emotion recognition (reviewed in Clausi et al., 2017), and is important for oculomotor control (Beh, Frohman, & Frohman, 2017), thus we evaluated grey and white matter volumes in the cerebellum. Lastly, their general cognitive problems may be a contributing factor. General cognitive ability correlates positively with FER in typically developing children (Lawrence et al., 2015) as does theory of mind (ToM); the ability to perspective-take and infer mental states and behaviours of others (Cotter et al., 2018; Lee et al., 2014). To evaluate general cognitive function, we administered an abbreviated intelligence test (Wechsler, 2011) and two ToM measures (Dennis et al., 2013; Hutchins,
Given that FER deficits can contribute to social problems, we also evaluated parent-reported social functioning in our sample.

In this study, we evaluated if visual attention, brain structure and general cognitive function contribute to FER in typically developing children and children treated for PF tumours. We began by evaluating how these factors differ in our typically developing and clinical sample. Next, we tested variations of a model to evaluate the relations between these factors, and to examine if they predicted FER. Our main hypothesis was that damage to the ILF, IFOF and UF in our clinical sample will negatively influence FER abilities directly, and that disrupted visual attention and general cognitive processing may also contribute. If certain factors predict FER deficits in our clinical sample, we may acquire unique insights into the pathology associated with FER deficits experienced by children with various developmental and clinical disorders alike.

3.3 Materials and methods

3.3.1 Participants

Fifty-four youth between the ages of 8 and 17 completed this study; 36 children treated for PF tumours (17 patients treated with surgery with or without chemotherapy, and 19 patients treated with surgery, chemotherapy and radiation) at the Hospital for Sick Children (SickKids; Toronto, Canada) and 18 healthy control children. 6 participants did not undergo MRI, but completed all other components. Participant demographic and medical variables are summarized in Table 3.1. Five controls were siblings of PF tumour patients who completed the present study, and another five controls were siblings of brain tumour patients who participated in other studies at the hospital (i.e., non-PF tumour patients). Thus, 10/18 (56%) of our control sample was related to brain tumour patients. All patients were > 1 year post diagnosis and had completed all therapy. Patients were excluded from participation if they had premorbid neurological disorders, or if they were receiving palliative care. Healthy controls were (self-described as) free of all neurological or clinical disorders. Patients were informed of this study via mailed letters, and/or were approached during their routine clinic visits when applicable. Healthy controls were either recruited from the community, were siblings of patients, or family members of SickKids staff. This study was approved by the hospital’s Research Ethics Board. Prior to participation, parents provided written informed consent and children provided assent. When deemed capable to do so, participants (typically adolescents) provided their own written consent.
Table 3.1 Participant characteristics and patient treatment information

<table>
<thead>
<tr>
<th></th>
<th>Healthy control</th>
<th>Surgery</th>
<th>Radiation</th>
<th><em>P</em> value</th>
</tr>
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<tbody>
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<td><strong>n</strong></td>
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<td>17</td>
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<tr>
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<td>11</td>
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<tr>
<td><strong>Average Parental Education (years)</strong></td>
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<td>---------------------------------------------------------------</td>
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<td>14</td>
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<tr>
<td>2</td>
<td></td>
<td>1</td>
<td>4</td>
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<td>Focal (5400-5940 cGy)</td>
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<td>Reduced dose cranial-Spinal (2340 cGy) + TB Boost (3240 cGy)</td>
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<td>Chemotherapy</td>
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<td>5</td>
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<td>COG99703 (thiotepa, carboplatin)</td>
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<td></td>
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<tr>
<td>POG9631 (etoposide, cisplatin, cyclophosphamide, vincristine)</td>
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<td></td>
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<tr>
<td>SJMB96 &amp; SJMB03 (vincristine, cisplatin, cyclophosphamide)</td>
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<td>9</td>
<td></td>
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<tr>
<td>Vinblastine monotherapy</td>
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</tbody>
</table>

$^a$ Tumour size was unavailable for 6 patients (3 surgery, 3 radiation)

$^b$ Patients were classified as having mutism if they had diminished speech output, linguistic difficulties or dysarthria following surgery. Mutism is a transient dysfunction and had resolved in all participants by the time of baseline assessment.
3.3.2 Patient treatment information

All patients had surgical intervention for their PF tumours, and a subset of patients received chemotherapy with or without radiation. We divided our patient sample into two groups - patients who received radiation and patients who did not (herein referred to as radiation and surgery groups, respectively). In the radiation group, patients treated with photon beam CSI received either standard (3060-3940 centigray (cGy)) or reduced (1800-2340 cGy) dose, and a boost to the tumour bed, whereas patients treated with focal radiation received 5400-5940 cGy to their tumour site. Medical variables for these two treatment groups are summarized in Table 3.1. The patient groups did not differ on most medical variables, except that the radiation group had fewer patients without hydrocephalus (p = 0.03, Fisher's exact test), and more patients with motor deficits (p = 0.02, Fisher's exact test). The only other differences between the groups arose from factors that determined their groupings; namely, patients in the radiation group were diagnosed with metastatic PF tumours (either medulloblastoma or ependymoma), whereas patients in the surgery group were primarily diagnosed with benign PF tumours (most commonly pilocytic astrocytoma), or patients were younger than 3 years at diagnosis and consequently did not receive radiation (p < 0.0001, Fisher's exact test). Moreover, the chemotherapy protocols (p = 0.01, Fisher's exact test) and the radiation type differed between groups (p < 0.0001, Fisher's exact test).

3.3.3 FER: diagnostic analysis of nonverbal accuracy (DANVA2) task

To assess FER, all participants completed the DANVA2, a computerized task using 48 photographs of males and females (24 children and 24 adults) (Baum & Nowicki, 1998). Participants were asked to look at each photograph and to decide if the individual felt happy, sad, angry, or fearful (scared). Each photograph was displayed on the screen, along with four response boxes indicating the emotions to choose from. The photograph remained on the screen for 2000 ms, whereas the response boxes remained on the screen until a decision about the emotion was made. In order for eye-movements to be recorded during this task (to assess visual attention), an eye-tracking version of the DANVA2 task was created, using the raw images from the original computer program (Baum & Nowicki, 1998).
3.3.4 Assessing visual attention

3.3.4.1 Eye-tracking apparatus and setup for DANVA2 task

Eye movements were recorded throughout the entire DANVA2 task using a SR Research Ltd. Eyelink 1000 plus (Mississauga, Canada) eye-tracking desktop monocular system. A sampling rate of 500 Hz and a spatial resolution of 0.01° was used. A 9-point calibration was performed prior to the experiment. Images were displayed on a 14.5 x 12.5 inch LCD monitor with a 1280 x 1024 pixel resolution. Photographs displaying facial emotions were 1425 x 810 pixels in size, and response boxes listing the emotions were 173 x 53 pixels in size. Participants were seated 26 inches from the monitor and a chin rest was used to limit head movements. The experiment was built using the Experiment Builder software provided with the SR Research Ltd eye-tracker. Measures of visual attention included: the number of fixations, and total time spent looking at the photograph (i.e., total dwell time) during the FER task.

3.3.5 Evaluating brain structure

3.3.5.1 Neuroimaging protocol

Magnetic Resonance Imaging (MRI) was performed at SickKids using a Siemens 3T whole-body MRI scanner (Prisma fit) with a 20-channel head and neck coil. Imaging included a T1 AX 3D MPRAGE Grappa 2 protocol (T1=900ms, TE/TR=3.83/2300ms, 160 contiguous axial slices, flip angle=9°, 256x224 matrix, FOV=256x224mm, voxel size=1mm ISO) and diffusion-weighted single shot spin echo DTI sequence with EPI readout (30 directions, b=1000s/mm², TE/TR=90/9000ms, 70 contiguous axial slices, flip angle=90°, 122x122 matrix interpolated to 244x244, FOV=244x244mm, voxel size=2mm ISO, interpolated to 1x1x2mm).

3.3.5.2 MRI pre-processing

Cortical reconstruction and volumetric segmentation of the anatomical T1 images was performed with the FreeSurfer image analysis suite, as documented online (http://surfer.nmr.mgh.harvard.edu/), and we parcellated the cortex into 164 brain regions using a well-validated cortical atlas (Destrieux, Fischl, Dale, & Halgren, 2010; Fischl et al., 2004). Although the utility of this parcellation was primarily for the additional processing steps detailed below, cerebellar grey and WM volumes from this parcellation were included in our analysis. Diffusion weighted images (DWI) were denoised, eddy current corrected for current distortions,
motion corrected and bias corrected to correct B1 field inhomogeneities, with the MRTRix3 package (www.mrtrix.org) that utilizes FSL’s eddy tool. All DWI images were non-linearly registered to T1 (Talairach) space, using ANTs (Avants et al., 2011). The automated cortical reconstruction and volumetric segmentation steps were not successful in 3 patients, likely as a result of their atypical anatomy (enlarged ventricles and lack of an intact cerebellum); they were not included in the probabilistic tractography analyses as a result.

### 3.3.5.3 Probabilistic Tractography

Fibre orientation distributions (FOD) were estimated using a constrained spherical deconvolution (CSD) model (Tournier, Calamante, & Connelly, 2013), DTI index maps (FA and RD) were created, and whole-brain probabilistic tractography was performed between all 164 cortical regions detailed above, using the MRTRix3 package (www.mrtrix.org). Initially, 100 million streamlines were generated; these were filtered to 20 million streamlines using the spherical-deconvolution informed filtering of tractograms (SIFT) algorithm (Smith, Tournier, Calamante, & Connelly, 2013) to improve the fit between the FOD and number of streamlines in every voxel.

To reconstruct the IFOF, ILF, UF and CST from the whole brain probabilistic tractography, we identified anterior and posterior cortical termination points for each tract based on previously published reports (Hau et al., 2016; Latini et al., 2017; Pannek, Chalk, Finnigan, & Rose, 2009; Seo & Jang, 2013; Wakana et al., 2007). Cortical regions from the atlas that corresponded to termination points for each tract were combined to create anterior and posterior ROIs (Table 3.2). For each tract in each hemisphere, a waypoint of identical size was placed in the same location on each participant’s FA image (Table 3.2 & Figure 3.1). To confirm that tracts were reconstructed appropriately, they were qualitatively compared to tracts published in an atlas (Catani & Thiebaut de Schotten, 2012). The total number of streamlines contributing to each reconstructed tract, as provided by MRTRix3, were recorded.

To obtain mean FA and RD along the reconstructed tracts, each tract was made into a mask that was then binarized (thresholded at 0.01), and multiplied by the individual’s FA and RD images. We limited our analyses to FA and RD, as these indices differed most robustly between patients and healthy controls in our previous study (Moxon-Emre et al., 2016). Examples of the reconstructed tracts, from a single healthy control participant, are shown in Figure 3.1.
### Table 3.2 Regions of interest (ROIs) used to reconstruct WM tracts

<table>
<thead>
<tr>
<th>Tract</th>
<th>Anterior ROI</th>
<th>Posterior ROI</th>
<th>Waypoints/exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFOF</td>
<td>- Inferior frontal gyrus (pars opercularis, pars triangularis and pars orbitalis)</td>
<td>- Inferior occipital gyrus and sulcus - Middle occipital gyrus - Lingual gyrus - Superior parietal lobule - Anterior transverse temporal gyrus - Temporal plane of the superior temporal gyrus - Occipital pole - Cuneus - Lateral occipito-temporal gyrus (fusiform gyrus) - Angular gyrus</td>
<td>A rectangular ROI was placed over the most ventral portion of the external capsule (spanning 5 axial, 10 coronal, and 10 sagittal slices; volume = 500 mm$^3$)</td>
</tr>
<tr>
<td>ILF</td>
<td>- Anterior transverse temporal gyrus - Superior temporal gyrus (lateral aspect, planum polare and temporal plane) - Middle temporal gyrus - Inferior temporal gyrus - Parahippocampal gyrus - Temporal pole</td>
<td>- Superior occipital gyrus - Middle occipital gyrus - Lateral occipito-temporal gyrus (fusiform gyrus) - Cuneus - Lingual gyrus - Occipital pole</td>
<td>The first slice of the rectangular ROI was placed in the most posterior coronal slice where the temporal lobe was not attached to the frontal lobe (spanning 5 coronal, 15 sagittal, and 15 axial slices; volume = 1125 mm$^3$)</td>
</tr>
<tr>
<td>UF</td>
<td>- Inferior frontal gyrus (pars opercularis, pars triangularis and pars orbitalis) - Orbital gyri and sulci - Straight gyrus - Suborbital sulcus - Fronto-marginal gyrus - Transverse frontopolar gyri and sulci</td>
<td>- Temporal pole - Superior temporal gyrus (lateral aspect, planum polare) - Inferior temporal gyrus - Middle temporal gyrus - Parahippocampal gyrus - Lateral occipito-temporal gyrus (fusiform gyrus) - Amygdala</td>
<td>A rectangular ROI was placed where the ‘elbow’ of the UF is located (spanning 5 coronal, 10 axial and 10 sagittal slices; volume = 500 mm$^3$). An exclusion mask ROI that covered the entire cerebral hemisphere was placed on the first coronal slice posterior to the amygdala</td>
</tr>
<tr>
<td>CST (control tract)</td>
<td></td>
<td>- Precentral gyrus</td>
<td>A rectangular ROI was placed over the cerebral peduncle (spanning 5 coronal, 15 axial and 15 sagittal slices; volume = 1125 mm$^3$). Two exclusion masks were created: 1) A single ROI that covered the entire cerebral hemisphere was placed in the midline, in the sagittal place 2) A single ROI that covered the entire brainstem was placed in the axial view</td>
</tr>
</tbody>
</table>

Regions of interest (ROIs) from the automated cortical and subcortical parcellation that were combined to create custom anterior, posterior, and waypoint ROIs to reconstruct the ILF, IFOF, UF and CST from the whole-brain probabilistic tractography. Abbreviations: IFOF = inferior frontal occipital fasciculus; ILF = inferior longitudinal fasciculus; UF = uncinate fasciculus; CST = corticospinal tract; ROI = region of interest
Figure 3.1 Reconstructed WM tracts

Examples of the reconstructed WM tracts from a single healthy control participant. Streamlines are overlaid on the FA map and shown in axial, coronal and sagittal planes for: all WM tracts shown together, the inferior frontal occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF), and corticospinal tract (CST). Colours of the streamlines represent the fibre orientations: red = medial-lateral; green = anterior-posterior; blue = dorsal-ventral. Right panel: the anterior, posterior and waypoint regions of interest (ROIs) used to reconstruct these tracts from the whole-brain probabilistic tractography. White lines indicate exclusion mask placement. For the IFOF, ILF, and UF: green = right anterior ROI; yellow = left anterior ROI; red = right posterior ROI; blue = left posterior ROI. For the CST: blue = right ROI; purple = left ROI. For all tracts: purple = right waypoint; orange = left waypoint. L = left; R = right; A = anterior; P = posterior.
3.3.5.4 Tract based spatial statistics (TBSS)

Voxelwise analyses were conducted with TBSS (Smith et al., 2006). All participants’ FA data were aligned into a common space (MNI152; Montreal Neurological Institute, McGill, Canada) using the nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b). Then, a cross-subject mean FA image was created and used to generate a ‘skeleton’ FA map representing the center common to all tracts, thresholded at FA>0.20. Finally, participant-specific FA and RD maps were aligned with the skeleton, and values along the width of each tract were considered in the cross-subject voxelwise statistics.

3.3.6 General cognitive function

3.3.6.1 Theory of mind (ToM)

Two measures were used to assess ToM. (i) The ability to perspective-take in emotional contexts was measured with a shortened (10-question) version of the 25-question Emotional and Emotive Faces task (EEFT) (Dennis et al., 2013; Dennis, Barnes, Wilkinson, & Humphreys, 1998). In this task, participants were read short narratives about a child, and were then asked to indicate how the child actually feels (emotion identification), and what facial expression the child would show in that situation given what it is expected the observer will think and feel (emotive communication). Participants selected the emotion from a board containing 11 drawings of 6 emotions (happy, sad, angry, scared, yucky and neutral), of varying intensity (i.e., very happy, a little bit happy), and this yielded a Feel Inside score (how well they identified the real emotion), Look on Face (how well they identified the concealed emotion) and Concealment (for correctly identifying the reason for concealing the emotion). This task evaluates a child’s understanding of, and ability to distinguish between, real emotions, and emotions that are expressed for social purposes. (ii) A parent questionnaire designed to examine a child’s ToM capabilities by proxy, the ToM Inventory (ToMI) (Hutchins et al., 2012), was also used. This measure yields three subscales: early, basic and advanced ToM. These subscales capture a child’s ability to read affect and share attention (early), make use of mental representations and acknowledge them as such (basic), and use complex recursion and to understand that the mind is an active interpreter (advanced) (Hutchins et al., 2012).
3.3.6.2 Intelligence

The vocabulary and matrix reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI-II) (Wechsler, 2011) were used to obtain an estimate of intellectual functioning (IQ).

3.3.7 Social functioning

The Child Behaviour Checklist (CBCL) (Achenbach, 1991), a parent-report measure designed to evaluate a child’s social, academic, behavioural and emotional functioning, was used. The social problems subscale from the CBCL was utilized to capture social functioning in the current study. The parent version of the Conners-3 (Conners, 2008) to assess ADHD symptoms; it’s peer relations subscale was used to capture an additional aspect of social functioning.

3.3.8 Analytic plan

First, we examined how our measures of visual attention, brain structure and general cognitive function differed between our typically developing and clinical samples. We then tested a model to evaluate the relations among these measures, and examined if they predicted FER. Our primary analyses were conducted to test the hypothesis that treatment for PF tumours would be associated with damage to the ILF, IFOF and UF, and that this would negatively influence FER abilities. In this model we also evaluated if disrupted visual attention and general cognitive function negatively influenced FER abilities. Our secondary analyses were exploratory; we tested variations on the same model to evaluate if WM damage more broadly (i.e., on a voxelwise basis), or damage to the cerebellum (i.e., cerebellar grey and WM volumes), instead of the abovementioned WM tracts, or contribute to patients’ FER deficit.

3.3.8.1 FER

Number of errors on the DANVA2 task were compared between healthy control, surgery and radiation groups using an analysis of variance (ANOVA). Performance on the DANVA2 task is herein referred to as FER. The following are factors that may contribute to FER:

3.3.8.2 Visual attention

We compared the number of fixations, and total time spent looking at the photograph (i.e., total dwell time) during the FER task, between healthy control, surgery and radiation groups using a
multivariate ANOVA (MANOVA), as these eye-tracking metrics are non-orthogonal. The number of fixations and dwell time on trials judged correctly vs. incorrectly, within and between groups, were evaluated with repeated measures ANOVAs. Age was included as a covariate in all analyses.

3.3.8.3 Brain structure

3.3.8.3.1 Planned analysis

**Probabilistic Tractography:** For each reconstructed WM tract (ILF, IFOF, UF and CST), two MANOVAs were conducted to compare: i) FA and RD in each hemisphere, and ii) streamline counts in each hemisphere, between healthy control, surgery and radiation groups, controlling for age. In each group, a series of partial correlations were conducted between FA/RD and FER, for each WM tract in each hemisphere, controlling for age. Given that 16 separate correlations were conducted, results were false discovery rate (FDR) corrected at q = 0.1.

3.3.8.3.2 Exploratory analyses

**Voxelwise analyses:** TBSS controls for family-wise errors using a permutation methodology. The null distribution of the cluster-size statistic was built up over 5000 random permutations. Cluster size was thresholded at p < 0.05, which is fully corrected for multiple comparisons. First, we evaluated voxels that differed between healthy controls and all patients considered together, as well as between the healthy control, surgery and radiation groups considered separately. Next, we assessed if any voxels throughout the brain correlated with FER, in healthy control and all patients considered together, and between healthy control and patient groups considered separately. Age at testing was included as a covariate in all analyses. A mask was made for each significant cluster of > 100 voxels, and the anatomic extent of each was labeled with reference to the JHU White-Matter Tractography Atlases (Hua et al., 2008).

**Cerebellar volume:** grey and WM cerebellar volumes in each hemisphere, normalized to intracranial volume (ICV) (i.e., divided by the total ICV and multiplied by 100), were compared between healthy control, surgery and radiation groups using a MANOVA.
3.3.8.4 General cognitive function

**Theory of Mind:** Performance on the ToM task (EEFT and ToMI) measures were compared between the healthy control, surgery and radiation groups using two MANOVAs, controlling for age.

**Intelligence:** Age-standardized scores from the WASI-II (2-subtest IQ) were compared between the healthy control, surgery and radiation groups using an ANOVA.

3.3.8.5 Social functioning

Age-standardized scores from the CBCL (the social problems subscale) and Conners-3 (peer relations subscale) were compared between the healthy control, surgery and radiation groups, using two separate ANOVAs.

In order to extend our analyses from descriptive to that of causality, we conducted PLS path modeling, as follows:

3.3.8.6 Model testing – PLS path modeling

PLS Path Modeling was performed in R (version 3.3.2), using PLSpm, with 200 bootstraps (Sanchez, 2013). In all models, we began by testing the accuracy of the model as follows: 1) we examined the relationship between the latent constructs and their associated measures (i.e., loading). 2) We assessed how well each measure corresponded to their latent constructs using Dillon–Goldstein’s rho. 3) We evaluated the discriminant validity of the model by confirming that cross-loadings for each measure were larger for measures contained in its own latent construct than for cross-loadings with measures belonging to other latent constructs. To assess the quality of the structural model, we evaluated: 1) the significance of the regression paths (t-test), 2) $R^2$ coefficients of the endogenous variables, with values < 0.2 considered low, and values between 0.2 and 0.5 considered moderate, 3) the average variance extracted (AVE) and 4) goodness-of-fit (GoF), the geometric mean of the average communality and average $R^2$. GoF values > 0.36 were considered a good fit (Tenenhaus M., Vinzi V. E., Chatelin Y. M., & Lauro C, 2005), and bootstrap confidence intervals for path weights and $R^2$ did not contain zero. PLS path modeling cannot accommodate missing data; thus, participants without MRI data, and/or with missing parent-questionnaire data, were excluded from path analyses (final n = 42).
In light of our smaller sample size for the PLS analysis, and the heterogeneity of treatment within our surgery and radiation groups, we elected to characterize our participants along a continuum of treatment type, intensity, complications and time (herein referred to as “medical variables”). We used information from 3 of the 4 domains from the Neurological Predictor Scale (NPS) (Micklewright, King, Morris, & Krawiecki, 2008); for each participant, scores on the surgery, chemotherapy and radiation domains were calculated and summed (NPS score range = 0-7). We created a composite score to capture post-surgical details by attributing each of the following a value of 1: presence of hydrocephalus requiring CSF diversion, cerebellar mutism, and any post-surgical complication (i.e., experiencing any one, or any combination of the following, would yield a score of 1: motor deficits, cranial nerve deficit, visual impairment and hearing impairment) (post-surgical details score range = 0-3). Thus, healthy control participants always scored 0, whereas a patient with a score of 10 on the combined NPS and post-surgical detail score would have received maximal therapy, and experienced considerable post-surgical complications; namely, they would have undergone multiple surgeries, received chemotherapy, craniospinal radiation, developed hydrocephalus that required CSF diversion, cerebellar mutism, and had at least one other post-surgical complication. As it is well documented that some deficits experienced by PF tumour patients, such as cognitive problems, become more apparent over time, time since diagnosis was also included as a medical variable (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004).

**Model testing, primary analyses:** we hypothesized that the medical variables associated with treatment for PF tumours, would have direct and indirect effects on FER via WM tracts known to be involved in FER (IFOF, ILF, UF – *model 1*; Figure 3.2B), but not our control tract (CST - *model 2*; Figure 3.2C), and potentially also through its effects on visual attention (i.e., eye-movements), and general cognitive function (i.e., ToM and IQ). The full model structure, and all paths tested, are provided in Figure 3.2A (top panel).

**Model testing, secondary analyses:** The PLS path models were unchanged from the primary analyses except that the WM tracts were replaced with: FA/RD from voxels that differed significantly between patients and healthy controls in the 2-group TBSS analysis (*model 3*; Figure 3.2D), and cerebellar grey and WM volumes (*model 4*; Figure 3.2E). The full model structure, and all paths tested, are provided in Figure 3.2A (top panel).
Figure 3.2 PLS path models

A. Full model structure – all paths tested

Latent construct indicators:
A = Age at testing
B = NPS score
C = Complications score
D = Time since diagnosis
E = Number of fixations
F = Total dwell time
G = Advanced ToM
H = EEFT total score
I = IQ
J = Incorrect responses (DANVA2)
1-20: MRI metrics used. Differs in each model. Refer to legend.

B - E. Model results – significant paths only

B. Model 1
C. Model 2

D. Model 3
E. Model 4

Our PLS path models designed to test if visual attention, brain structure and general cognitive function contribute to FER. A. The full model structure, showing all paths tested. We predicted that age and medical variables will have direct and indirect effects on the number of FER errors, through visual attention (i.e., eye-tracking), brain structure (differs according to model tested) and general cognitive function (i.e., theory of mind and/or IQ) processes. B-E, four PLS path models tested with only the significant paths shown. Indicators that contribute to the latent constructs remain unchanged in all models, except for those that contribute to the brain structure latent construct, as follows: B, model 1: 1-4 = FA and RD of the left and right IFOF; 5-8 = FA and RD of the left and right ILF; 9-10 = RD of the left and right UF. C, model 2: 11-14: FA and RD of the left and right CST. D, model 2: 15-16: FA ad RD from voxels that differed significantly between patients and healthy controls in the 2-group TBSS analysis. E, model 4: 17-20: cerebellar grey and WM volume in left and right hemisphere. NPS = neurological predictor scale; ToM = theory of mind; EEFT = emotional and emotive faces task; IQ = intelligence quotient.

3.4 Results

3.4.1 FER

Patients make more errors than healthy controls. The groups differed in FER errors on the DANVA2 task (F(2,50) = 4.03, p = 0.024). Both the radiation and surgery groups made more errors than the healthy control group; the radiation group differed significantly (p = 0.039; Figure 3.3A), whereas the surgery group approached significance (p = 0.075; Figure 3.3A).
Figure 3.3 Behavioural and eye-tracking results from the DANVA2

Boxplots showing all data points with the median (black line) in healthy control, surgery and radiation groups for:

A. The total number of FER errors. B. The total number of fixations made on the photograph. C. The total time spent looking at the photographs (i.e., total dwell time). * p < 0.05.
3.4.2 Visual attention

The radiation group processes the photographs less extensively, but all groups appear to be attending to the photographs. The groups differed in visual attention (number of fixations and total dwell time) \( F(2,50) = 7.18, p = 0.002 \). The radiation group made fewer fixations on the photographs than the healthy control group \( p = 0.028 \); Figure 3.3B) and surgery group \( p = 0.024 \); Figure 3.3B). The radiation group also had a lower total dwell time on the photographs than the healthy control group \( p = 0.02 \); Figure 3.3C), but not the surgery group \( p = 0.41 \); Figure 3.3C). The number of fixations and total dwell time did not differ when viewing photographs that were judged incorrectly vs. correctly, in any group \( F(2,50) > 0.39, \) all \( p < 0.05 \); Figure 3.4A-B). Overall, all participants made more fixations on trials that were judged incorrectly vs. correctly \( p = 0.048 \), even though the total dwell time did not differ \( p = 0.13 \). Heat maps provide a summary of the fixations made across participants in each group, for each trial; visual inspection of these heat maps revealed that participants in all groups spent most of their time attending to the face when judging the emotion depicted in the photograph (one trial is shown in Figure 3.4C).

Figure 3.4 Eye-tracking results from the DANVA2
A-B. Boxplots showing all data points with the median (black line) in healthy control, surgery and radiation groups for: A, The total number of fixations made on the photograph on correct and incorrect trials. B, The total time spent looking at the photographs (i.e., total dwell time) on correct and incorrect trials. C. Heat maps summarizing the fixations made across all individuals in each group, on a single DANVA2 trial. Warmer colours reflect longer fixations made at that location. The upper limit of the heat map legend reflects the longest fixation made, and this was unique to each group. Visual inspection reveals that individuals in all three groups spent most of their time attending to the face when judging the emotion depicted in the photograph.

3.4.3 Brain structure

3.4.3.1 Planned analyses

Probabilistic Tractography

The IFOF, ILF, UF and CST do not differ between healthy control and patient groups. FA and RD did not differ between healthy control and patients groups, in either hemisphere, in any WM tract evaluated (all F(4,39) < 2.6, all p > 0.05; Table 3.3), and neither did streamline count (all F(2,41) < 3.2, all p > 0.05; Table 3.3).

Table 3.3 FA, RD and streamline count of the ILF, IFOF, UF, CST, in addition to grey and WM volumes of the cerebellum

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Surgery</th>
<th>Radiation</th>
<th>F value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFOF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.474 (0.019)</td>
<td>0.469 (0.021)</td>
<td>0.474 (0.020)</td>
<td>0.34</td>
<td>0.71</td>
</tr>
<tr>
<td>Right</td>
<td>0.477 (0.020)</td>
<td>0.475 (0.021)</td>
<td>0.477 (0.025)</td>
<td>0.09</td>
<td>0.91</td>
</tr>
<tr>
<td>RD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.00058 (0.00002)</td>
<td>0.00060 (0.00004)</td>
<td>0.00059 (0.00004)</td>
<td>1.56</td>
<td>0.22</td>
</tr>
<tr>
<td>Right</td>
<td>0.00058 (0.00003)</td>
<td>0.00060 (0.00003)</td>
<td>0.00058 (0.00005)</td>
<td>1.32</td>
<td>0.28</td>
</tr>
<tr>
<td>Streamline count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>22.12 (15.374)</td>
<td>21.46 (16.071)</td>
<td>21.93 (18.258)</td>
<td>0.02</td>
<td>0.98</td>
</tr>
<tr>
<td>Right</td>
<td>26.71 (24.443)</td>
<td>27.62 (14.327)</td>
<td>32.20 (21.492)</td>
<td>0.09</td>
<td>0.92</td>
</tr>
<tr>
<td>ILF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.427 (0.027)</td>
<td>0.424 (0.021)</td>
<td>0.430 (0.029)</td>
<td>0.19</td>
<td>0.83</td>
</tr>
</tbody>
</table>
Matching letters in different rows indicate a significant difference (p < 0.05) between groups as follows. Mean: a, p < 0.0001 between healthy control and surgery groups; b, p = 0.02 between surgery and radiation groups; c, p < 0.0001 between healthy control and surgery groups; d, p = 0.001, between healthy control and radiation groups; e, p = 0.02, between healthy control and radiation groups; f, p < 0.0001 between healthy control and surgery groups; g, p = 0.006 between healthy control and radiation groups.

Abbreviations: IFOF = inferior frontal occipital fasciculus; ILF = inferior longitudinal fasciculus; UF = uncinate fasciculus; CST = corticospinal tract; FA = fractional anisotropy; RD = radial diffusivity

The left UF correlates with FER in healthy controls only. After FDR correction, FA and RD in the left UF remained significantly correlated with FER in healthy controls only (all r(13) > 0.63, all p < 0.05, all q < 0.1; Figure 3.5), indicating that higher FA/lower RD is associated with fewer FER errors. Notably, FER was not correlated with FA or RD of the CST. Regardless of whether patients were considered as a single group, or separated by their treatment, there were no significant correlations between FA or RD of any tract and FER, before or after FDR correction (all r(25) < 0.3, all p > 0.05, Figure 3.5; all patients are considered together).
Figure 3.5 Correlations between FER and DTI indices from the IFOF, ILF, UF and CST
Partial correlations between FER errors from the DANVA2 task, and FA/RD of the left and right IFOF, ILF, UF and CST, after controlling for age. Partial correlations for healthy controls (black) and patients (red) were conducted separately, but are plotted together to facilitate visual comparison. *Significant correlations (p < 0.05); however, only those indicated with (FDR) survived correction for multiple comparisons (q < 0.1).
3.4.3.2 Exploratory analyses

**Voxelwise analyses**

Both patient groups differ from healthy controls, whereas the patient groups do not differ from each other. Despite not differing in the tracts examined, FA and RD differed between healthy control and patient groups (both when considered together, and separated by their treatment), in many clusters of voxels throughout the entire brain (all F > 8; all p < 0.05). Post-hoc pairwise comparisons revealed many voxels where, compared to the healthy control group, the surgery group had lower FA and higher RD (all T > 1.85; all p < 0.05; Figure 3.6A&C, Table 3.4), and where the radiation group had lower FA and higher RD (all T > 1.74; all p < 0.05; Figure 3.6B&D, Table 3.4). There were no voxels in either patient group where FA was higher, and RD was lower, than healthy controls. Furthermore, FA and RD did not differ in any voxels between the surgery and radiation groups (all p > 0.05; Figure 3.6E, Table 3.4).

**Figure 3.6 Differences in FA and RD between healthy control and patient groups**
A-B. Clusters of voxels with significantly reduced FA (red; \( p < 0.05 \)) in the radiation (A) and surgery (B) groups, compared to healthy controls. C-D, Clusters of voxels with significantly higher RD (blue; \( p < 0.05 \)) in the radiation (C) and surgery (D) groups, compared to healthy controls. E, Comparisons where FA and RD did not differ between groups. Clusters of significant voxels are superimposed on the FMRIB FA template. Images are shown in radiological convention. Numbers represent MNI z-coordinates. Cluster details are provided in Table 3.4 L = left; R = right.

Table 3.4 Clusters of voxels that differ between healthy control, surgery and radiation groups

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Cluster (number of voxels)</th>
<th>Cluster Family-Wise Error Corrected p</th>
<th>WM structures * encompassed</th>
<th>Mean T value</th>
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<tr>
<td>FA</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Radiation &lt; Control</td>
<td>11270</td>
<td>0.009</td>
<td>Forceps minor, CST, forceps major, SLF, cingulum (cingulate gyrus), IFOF, ATR, ILF, UF (L), SLF (temporal part), cingulum (hippocampus)</td>
<td>2.02</td>
</tr>
<tr>
<td>Radiation &lt; Surgery</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>---------------------</td>
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<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Surgery &lt; Control</td>
<td>12722</td>
<td>0.011</td>
<td>IFOF, ILF, SLF, forceps major and minor, CST, SLF (temporal part), cingulum (cingulate gyrus), ATR, cingulum (hippocampus), UF</td>
<td>1.9</td>
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<tr>
<td></td>
<td>5197</td>
<td>0.021</td>
<td>ATR, CST, IFOF, ILF, UF (L), SLF, SLF (temporal part), forceps minor, cingulum (hippocampus) (L), cingulum (cingulate gyrus) (R)</td>
<td>2.0</td>
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<tr>
<td></td>
<td>2425</td>
<td>0.033</td>
<td>ATR, CST</td>
<td>2.15</td>
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<td>1575</td>
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<tr>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Surgery &lt; Radiation</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Control &lt; Surgery</td>
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**RD**

<table>
<thead>
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<th>-</th>
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<th>-</th>
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<td>-</td>
<td>-</td>
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<td>CST, forceps major, IFOF, cingulum (cingulate gyrus), SLF, forceps minor, ATR, ILF, cingulum (hippocampus), SLF (temporal part)</td>
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<tr>
<td></td>
<td>1229</td>
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<td>ATR</td>
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</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Control &lt; Surgery</td>
<td>19209</td>
<td>0.008</td>
<td>Forceps minor, SLF, forceps major, IFOF, ILF, CST, SLF (temporal part), cingulum (cingulate gyrus), ATR, UF, cingulum (hippocampus)</td>
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<tr>
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<td>1.9</td>
</tr>
<tr>
<td></td>
<td>3500</td>
<td>0.026</td>
<td>CST (R), ATR (R), IFOF (R)</td>
<td>2.27</td>
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</tbody>
</table>

*WM structures: defined by the JHU White-Matter Tractography Atlas. Unless otherwise specified, structures listed refer to bilateral counterparts
All structures are listed in order from greatest to least probability of being a member of the labelled regions within the atlas

Abbreviations: ATR=anterior thalamic radiation; CST=corticospinal tract; IFOF=inferior fronto-occipital fasciculus; ILF=inferior longitudinal fasciculus; SLF=superior longitudinal fasciculus; UF=uncinate fasciculus
Significant clusters (\(P < 0.05\)) containing <100 voxels were excluded.
**RD in many voxels correlates with FER in healthy controls only.** RD, but not FA, was significantly correlated with FER in many voxels throughout the brain, in healthy controls only (all $T > 1.72$; all $p < 0.05$; Figure 3.7, Table 3.5). Notably, voxels located along the ILF, IFOF and UF (i.e., tracts that we hypothesized would be involved in FER) correlated with performance; however, voxels in many other regions throughout the brain also correlated with performance, the CST (i.e., our control tract) included.

**Figure 3.7 Correlations between FA/RD and the number of FER errors on the DANVA2**

**A.** Voxels where RD was positively correlated with the number of incorrect responses on the DANVA2 in healthy controls (pink; $p < 0.05$). **B.** Correlations in healthy control and patient groups where FA and RD were not correlated with the number of errors on the DANVA2. Clusters of significant voxels are superimposed on the FMRIB FA template. Images are shown in radiological convention. Numbers represent MNI z-coordinates. Cluster details are provided in Table 3.5. L = left; R = right.
### Table 3.5 Clusters of voxels that correlate with the number of FER errors on the DANVA2

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Cluster (number of voxels)</th>
<th>Cluster Family-Wise Error Corrected p</th>
<th>WM structures a encompassed</th>
<th>Mean T value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive correlation</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Negative correlation</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>RD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive correlation</td>
<td>5016</td>
<td>0.028</td>
<td>CST, SLF (R), IFOF (R), SLF (temporal part) (R), forceps minor, ILF (R), cingulum (cingulate gyrus) (R), forceps major, ATR, UF (R), cingulum (hippocampus) (R)</td>
<td>1.72</td>
</tr>
<tr>
<td></td>
<td>4315</td>
<td>0.031</td>
<td>Forceps minor, ATR, IFOF (L), CST (L), UF (L), SLF (L), ILF (L), SLF (temporal part), cingulum (cingulate gyrus)</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>692</td>
<td>0.04</td>
<td>Forceps major, IFOF (R), ILF (R), SLF (R), cingulum (hippocampus), ATR (R), cingulum (cingulate gyrus) (R)</td>
<td>1.91</td>
</tr>
<tr>
<td></td>
<td>331</td>
<td>0.038</td>
<td>IFOF (L), ILF (L), SLF (temporal part) (L), SLF (L), UF (L), ATR (L), forceps minor, cingulum (hippocampus) (L)</td>
<td>2.07</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td>0.042</td>
<td>CST (L), SLF, ATR, cingulum (cingulate gyrus) (L), SLF (temporal part) (R)</td>
<td>2.77</td>
</tr>
<tr>
<td></td>
<td>162</td>
<td>0.035</td>
<td>SLF (L), SLF (temporal part) (L)</td>
<td>3.14</td>
</tr>
<tr>
<td>Negative correlation</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive correlation</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Negative correlation</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>RD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive correlation</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Negative correlation</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a WM structures: defined by the JHU White-Matter Tractography Atlas. Unless otherwise specified, structures listed refer to bilateral counterparts. All structures are listed in order from greatest to least probability of being a member of the labelled regions within the atlas.

Abbreviations: ATR=anterior thalamic radiation; CST=corticospinal tract; IFOF=inferior fronto-occipital fasciculus; ILF=inferior longitudinal fasciculus; SLF=superior longitudinal fasciculus; UF=uncinate fasciculus.

Significant clusters (p < 0.05) containing <100 voxels were excluded.

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### Cerebellar volume

Given that patients had their PF tumours surgically removed, patients have smaller cerebellar grey and WM volumes than healthy controls. The groups differed in cerebellar grey and WM volumes (F(4,40) = 7.57, p = 0.0001; Table 3.3). In the right hemisphere, the...
radiation and surgery groups had smaller grey and WM volumes than the healthy control group (all \( p < 0.05 \); Table 3.3). In the left hemisphere, the radiation group had smaller WM volumes than both the surgery and healthy control groups (all \( p < 0.05 \); Table 3.3), and smaller grey matter volume than healthy controls only (all \( p < 0.05 \); Table 3.3).

3.4.4 General cognitive function

The radiation group has more difficulty with perspective taking in emotional contexts than healthy controls. The effect of group was significant (\( F(4,48) = 3.63; p = 0.01 \)); the healthy control and patient groups differed in the Feel Inside, Concealment and Total Scores on the EEFT (all \( F(2,50) > 5.14 p < 0.01 \); Table 3.6). Post-hoc analyses revealed group differences between the radiation group and healthy control group, whereas the surgery group did not differ significantly from the other groups; namely, relative to the healthy control group, the radiation group performed more poorly in the Concealment and Total Score (all \( p < 0.05 \)), and their Feel Inside score was marginally lower (\( p = 0.056 \)). Thus, the radiation group appeared to have difficulty with this task overall, and in particular with identifying the reason an emoter may want to conceal an emotion from an observer (i.e., Concealment score). They may also have had difficulty selecting which emotion an emoter will express given a particular emotional scenario (i.e., Feel Inside score).

Table 3.6 Scores on measures used to evaluate general cognitive function, and social functioning

<table>
<thead>
<tr>
<th>Measure</th>
<th>Healthy control</th>
<th>Surgery</th>
<th>Radiation</th>
<th>F value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEFT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel Inside</td>
<td>8.17 (1.47)</td>
<td>7.41 (1.62)</td>
<td>7.58 (1.22)</td>
<td>3.38</td>
<td>0.04</td>
</tr>
<tr>
<td>Look on Face</td>
<td>13.17 (3.82)</td>
<td>14.29 (3.98)</td>
<td>12.37 (3.00)</td>
<td>1.25</td>
<td>0.30</td>
</tr>
<tr>
<td>Concealment</td>
<td>8.00 (2.03)a</td>
<td>7.29 (2.62)</td>
<td>5.63 (2.93)a</td>
<td>5.15</td>
<td>0.009</td>
</tr>
<tr>
<td>Total Score</td>
<td>30.22 (5.34)b</td>
<td>29.00 (6.22)</td>
<td>25.58 (4.56)b</td>
<td>5.54</td>
<td>0.007</td>
</tr>
<tr>
<td>ToMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>135.31 (4.39)</td>
<td>134.61 (8.53)</td>
<td>134.29 (7.14)</td>
<td>0.21</td>
<td>0.81</td>
</tr>
<tr>
<td>Basic</td>
<td>361.69 (27.61)</td>
<td>361.69 (19.49)</td>
<td>371.63 (8.99)</td>
<td>0.66</td>
<td>0.52</td>
</tr>
<tr>
<td>Advanced</td>
<td>291.98 (32.11)</td>
<td>290.52 (24.28)</td>
<td>293.09 (23.64)</td>
<td>0.53</td>
<td>0.60</td>
</tr>
<tr>
<td>WASI-II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-subtest IQ</td>
<td>115.72 (10.55)a</td>
<td>103.35 (17.44)c</td>
<td>97.83 (15.46)d</td>
<td>6.97</td>
<td>0.002</td>
</tr>
<tr>
<td>CBCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Problems</td>
<td>54.17 (4.77)</td>
<td>55.47 (6.09)</td>
<td>58.33 (10.47)</td>
<td>1.36</td>
<td>0.27</td>
</tr>
<tr>
<td>Conners-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peer Relations</td>
<td>52.11 (7.68)</td>
<td>58.88 (15.82)</td>
<td>61.27 (17.60)</td>
<td>1.92</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Matching letters in different rows indicate a significant difference (\( p < 0.05 \)) between groups as follows. Mean: a, \( p = 0.009 \) between healthy control and radiation groups; b, \( p = 0.007 \) between healthy control and radiation groups; c, \( p = 0.049 \) between healthy control and surgery groups; d, \( p = 0.002 \), between healthy control and radiation groups.
Although there was a main effect of group for Feel Inside, the pairwise comparison between the healthy control and radiation groups was not significant (p = 0.056).

Abbreviations: EEFT = Emotional and Emotive Faces task; ToMI = Theory of Mind Inventory; WASI-II = Weschler Abbreviated Scale of Intelligence; CBCL = Child Behaviour Checklist

**Parent-reported ToM does not highlight any group differences.** The effect of group on the ToMI was not significant (F(3,45) = 1.23; p = 0.31). Healthy control and patient groups did not differ in their early, basic or advanced ToM scores (all F(2,46) < 0.67, all p > 0.05; Table 3.6).

**Both patient groups have lower IQ than healthy controls.** The effect of group on IQ was significant (F(2,50) = 6.97, p = 0.002; Table 3.6); post-hoc analyses revealed that the healthy control group had higher full scale IQ than both patient groups (all p < 0.05; Table 3.6). It is notable, however, that both patient groups performed very close to the normative mean of 100 (SD = 15). Given that 56% of our controls were siblings of brain tumour patients, this may reflect a true difference in functioning, rather than one driven by the inclusion of controls that do not necessarily represent the general (i.e., children of clinicians and hospital research staff).

3.4.5 Social functioning

**Our healthy control and patient groups do not differ in their parent reported social functioning.** The groups did not differ in their parent-reported social problems (F(2,47) = 1.36, p = 0.27; Table 3.6) or peer relations scores (F(2,47) = 1.92, p = 0.16; Table 3.6).

For the ToMI, CBCL and Conners-3, data was missing for 5 patients; the parent-questionnaires were not returned.

3.4.6 Model testing – PLS path modeling

3.4.6.1 Primary analyses

In our primary model, we tested the accuracy of a measurement model with the following latent constructs (indicators that were included initially are listed in parentheses): participant (age at testing, parental education, sex), medical variables (NPS score, complications score, time since diagnosis), MRI (FA and RD of the IFOF, ILF, UF in each hemisphere; RD values were multiplied by -1 to prevent negative loadings), IQ (WASI-II score), ToM (early, basic and advanced scores from ToMI; feel inside, concealment and total scores on the EEFT), eye-
tracking (fixation count and total dwell time), facial emotion errors (number of incorrect responses on the DANVA2) (Figure 3.2A). In our control model, all latent constructs remained unchanged, except that we replaced the MRI indicators with FA and RD of the CST (i.e., our control tract) in each hemisphere. All indicators for both models loaded at > 0.7 on their latent constructs, except for parental education, sex, early ToMI score, basic ToMI score, the EEFT concealment score, and FA of the UF in both hemispheres. These indicators were removed from the model as a result. Thus, the participant latent construct reflects age at testing only, and is herein referred to as age. With all remaining indicators, the latent constructs were all homogenous and unidimensional; Dillon-Goldstein’s rho for all latent constructs were > 0.78. In addition, each indicator had a higher cross-loading with the construct it was intended to measure, than with the other latent constructs.

**Model 1** (Figure 3.2B): medical variables predicted facial emotion errors \[\beta = 0.47 \ (CI_{95}: 0.08, 0.91), t = 2.4, p = 0.02\] and IQ \[\beta = -0.46 \ (CI_{95}: -0.69, -0.19), t = -3.49, p = 0.001\]. We also observed that age predicted WM of the ILF, IFOF and UF \[\beta = 0.40 \ (CI_{95}: 0.17, 0.67), t = 2.54, p = 0.02\] and ToM \[\beta = 0.54 \ (CI_{95}: 0.24, 0.81), t = 4.08, p = 0.0002\], WM of the ILF, IFOF and UF predicted IQ \[\beta = 0.29 \ (CI_{95}: 0.09, 0.52), t = 2.2, p = 0.03\], and IQ predicted ToM \[\beta = 0.29 \ (CI_{95}: 0.01, 0.55), t = 2.07, p = 0.045\]. No other paths reached statistical significance. The coefficients of determination \((R^2)\) for each latent construct were: WM of the ILF, IFOF and UF = 0.15 \((CI_{95}: 0.05, 0.42)\), IQ = 0.33 \((CI_{95}: 0.14, 0.57)\), eye-tracking = 0.19 \((CI_{95}: 0.09, 0.53)\), ToM = 0.56 \((CI_{95}: 0.38, 0.79)\) and facial emotion errors = 0.33 \((CI_{95}: 0.20, 0.64)\). Model 1 had a GoF of 0.47.

**Model 2** (Figure 3.2C): medical variables predicted facial emotion errors \[\beta = 0.53 \ (CI_{95}: 0.16, 0.84), t = 2.85, p = 0.007\], IQ \[\beta = -0.48 \ (CI_{95}: -0.67, -0.26), t = -3.58, p = 0.0009\], and eye-tracking \[\beta = -0.40 \ (CI_{95}: -0.65, -0.01), t = -2.61, p = 0.01\]. We also observed that age predicted ToM \[\beta = 0.60 \ (CI_{95}: 0.26, 0.83), t = 4.67, p = 0.00004\], and that WM of the CST predicted facial emotion errors \[\beta = -0.35 \ (CI_{95}: -0.61, -0.07), t = -2.51, p = 0.02\]. No other paths reached statistical significance. The coefficients of determination \((R^2)\) for each latent construct were: WM of the CST = 0.05 \((CI_{95}: 0.01, 0.26)\), IQ = 0.31 \((CI_{95}: 0.13, 0.55)\), eye-tracking = 0.22 \((CI_{95}: 0.10, 0.47)\), ToM = 0.55 \((CI_{95}: 0.37, 0.77)\) and facial emotion errors = 0.42 \((CI_{95}: 0.26, 0.66)\). Model 2 had a GoF of 0.48.
3.4.6.2 Secondary analyses

In our secondary models, all latent constructs remained unchanged from the original PLS model detailed above, except for the MRI indicators, as follows: model 3 = FA and RD from voxels that differed significantly between the healthy control and patient groups in the TBSS analysis; model 4 = cerebellar grey and WM volumes in each hemisphere.

**Model 3** (Figure 3.2D): medical variables predicted facial emotion errors [$\beta = 0.44$ (CI$_{95}$: 0.03, 0.82), $t = 2.25$, $p = 0.03$)], and FA/RD from voxels that differed between patients and healthy controls [$\beta = -0.53$ (CI$_{95}$: -0.78, -0.28), $t = -3.75$, $p = 0.0006$)]. We also observed that age predicted ToM [$\beta = 0.52$ (CI$_{95}$: 0.30, 0.74), $t = 4.29$, $p = 0.0001$]), and FA/RD from voxels that differed between patients and healthy controls [$\beta = 0.27$ (CI$_{95}$: 0.13, 0.44), $t = 1.95$, $p = 0.06$], became significant after bootstrapping], and that IQ predicted ToM [$\beta = 0.30$ (CI$_{95}$: 0.07, 0.55), $t = 2.32$, $p = 0.03$]). No other paths reached statistical significance. The coefficients of determination ($R^2$) for each latent construct were: FA/RD from TBSS = 0.28 (CI$_{95}$: 0.09, 0.60), IQ = 0.25 (CI$_{95}$: 0.07, 0.51), eye-tracking = 0.20 (CI$_{95}$: 0.08, 0.51), ToM = 0.58 (CI$_{95}$: 0.44, 0.80) and facial emotion errors = 0.30 (CI$_{95}$: 0.22, 0.59). Model 4 had a GoF of 0.50.

**Model 4** (Figure 3.2E): medical variables predicted facial emotion errors [$\beta = 0.57$ (CI$_{95}$: 0.07, 1.09), $t = 2.18$, $p = 0.04$)], IQ [$\beta = -0.49$ (CI$_{95}$: -0.84, -0.15), $t = -2.68$, $p = 0.01$]), and cerebellar volume [$\beta = -0.73$ (CI$_{95}$: -0.87, -0.57), $t = -5.86$, $p < 0.0001$]). We also observed that age predicted ToM [$\beta = 0.53$ (CI$_{95}$: 0.26, 0.81), $t = 3.91$, $p = 0.0004$]), and that IQ predicted ToM [$\beta = 0.36$ (CI$_{95}$: 0.01, 0.57), $t = 2.50$, $p = 0.02$]). No other paths reached statistical significance. The coefficients of determination ($R^2$) for each latent construct were: cerebellar volume = 0.47 (CI$_{95}$: 0.32, 0.69), IQ = 0.25 (CI$_{95}$: 0.12, 0.48), eye-tracking = 0.22 (CI$_{95}$: 0.09, 0.54), ToM = 0.54 (CI$_{95}$: 0.39, 0.76) and facial emotion errors = 0.30 (CI$_{95}$: 0.22, 0.64) Model 3 had a GoF of 0.49.

In all abovementioned PLS models, the average variance extracted (AVE), a measure of the variance that is captured by the latent construct in relation to the variance that results from measurement error, was above the recommended cut-off of 0.5 (Sanchez, 2013). Across all four models tested, medical variables associated with treatment for PF tumours predicted worse FER, and an older age at testing predicted better ToM capabilities. In three models, medical variables predicted lower IQ, and a lower IQ predicted poorer ToM capabilities. Medical variables
predicted lower FA/higher RD values in voxels that differed between patient and healthy control groups, and smaller cerebellar volumes, but neither of these structural metrics predicted FER.

3.4.6.2.1 Additional within-group models

In light of the correlations we observed between multiple WM measures and FER errors in healthy controls only, we tested a series of PLS path models in both healthy controls and patients to evaluate if increasing age predicts better FER abilities through the ILF/IFOF/UF, and not the CST, in healthy controls only.

We tested the following two models in healthy controls (n = 16) and patients (n = 26) separately. **In our first model,** we tested the accuracy of a measurement model with the following latent constructs (indicators listed in parentheses): age at testing, MRI (FA and RD of the IFOF, ILF, UF in each hemisphere), facial emotion errors (number of incorrect responses on the DANVA2). In our **second model,** the MRI indicators were changed to FA and RD of the CST in each hemisphere. Indicators for all models loaded at > 0.7 on their latent constructs, except for FA of the UF in both hemispheres, and these were removed from the model as a result. With all remaining indicators, the latent constructs were homogenous and unidimensional (Dillon-Goldstein’s rho for all latent constructs were > 0.9), and each indicator had a higher cross-loading with the construct it was intended to measure, than with the other latent constructs.

**Healthy controls - Model 1:** age predicted facial emotion errors [$\beta = -0.40$ (CI$_{95\%}$: -0.75, -0.04), t = -1.88, p = 0.08 – became significant after bootstrapping]), and WM of the ILF, IFOF and UF also predicted facial emotion errors [$\beta = -0.45$ (CI$_{95\%}$: -0.85, -0.15), t = -2.37, p = 0.03)]. No other paths reached statistical significance. The coefficients of determination ($R^2$) for each latent construct were: WM of the ILF, IFOF and UF = 0.20 (CI$_{95\%}$: 0.03, 0.60), FER = 0.57 (CI$_{95\%}$: 0.36, 0.85). Model 1 GoF was 0.536.

**Healthy controls - Model 2:** age predicted facial emotion errors [$\beta = -0.54$ (CI$_{95\%}$: -0.83, -0.22), t = -2.64, p = 0.02)]. No other paths reached statistical significance. The coefficients of determination ($R^2$) for each latent construct were: WM of the CST = 0.06 (CI$_{95\%}$: 0.004, 0.50), FER = 0.48 (CI$_{95\%}$: 0.12, 0.83). Model 2 GoF was 0.501.

**Patients – Models 1 & 2:** No paths reached statistical significance, and the GoF’s were 0.217 and 0.191 respectively, suggesting the data did not fit either model.
Together these models demonstrate that increasing age and higher FA/lower RD of the ILF, IFOF and UF, predict better FER in healthy controls only.

3.5 Discussion

Our study is the first to combine eye-tracking, neuroimaging and cognitive testing in typically developing children and in children treated for PF tumours, to directly investigate three factors that may contribute to FER: visual attention, brain structure and general cognitive function. We demonstrate that WM, and potentially the ILF, IFOF and UF, are associated with FER in typically developing children only. This association was not present in children treated for PF tumours; it may either be altered, or overshadowed by factors associated with their medical condition and treatment. We also demonstrate that although subtle differences in visual attention and general cognitive functioning emerged, these factors were not associated with FER. In light of these findings, we focus our discussion primarily on the relations between WM and FER, and how it manifests differently in patients treated for PF tumours and typically developing children.

Three lines of evidence in our study converged on the finding that WM is associated with FER in typically developing but not children in treated for PF tumours. Although the associations between WM pathways and FER have been investigated in adults (reviewed in Wang et al., 2018), analogous studies are lacking in children. First, we observed that FER correlated with higher FA and lower RD along the left UF, in typically developing children only. Similarly, in typically developing children only, RD in thousands of voxels throughout the brain, anatomically located within but not limited to the ILF, IFOF, UF, and the CST (our control tract), correlated with FER. Lower RD in these voxels predicted fewer errors. Lastly, our PLS path models designed to test the associations between age and FER directly, as well as through their effect on WM (our latent construct measuring FA and RD along the ILF and IFOF bilaterally, and of RD along the UF bilaterally), conducted in typically developing children and children treated for PF tumours separately, revealed that WM predicted FER in typically developing children only. Interestingly, RD, a measure thought to reflect myelin architecture (Song et al., 2002; Song et al., 2005) correlated with FER more consistently than FA. Myelin synthesis is actively occurring during childhood (Dean et al., 2015; Deoni, Dean, O'Muircheartaigh, Dirks, & Jerskey, 2012; Lebel & Beaulieu, 2011); a developmental process that may contribute to the increasing speed
and accuracy with which typically developing children recognize emotions as they age (De Sonneville et al., 2002; Kolb et al., 1992).

We confirm that children treated for PF tumours in our sample have difficulty recognizing facial emotions (Bonner et al., 2008) despite attending to the photographs; however, WM indices of the ILF, IFOF and UF did not predict FER despite being structurally intact. Our main hypothesis was therefore not supported. That no structural damage was detected, yet the relationship differed from that of typically developing children, suggests structural preservation of these tracts is not sufficient to support their successful FER. It also suggests there is something unique about the patient brain that is preventing an observable relationship with FER. It is possible that factors related to their medical condition and treatment overshadowed the association between WM and FER. Indeed, medical variables (capturing treatment type and intensity, post-surgical complications, and time since diagnosis) consistently and directly predicted FER difficulties, independent of the measures used to assess visual attention, brain structure, and general cognitive function. It appears that aspects of their medical experience, not disentangled in the present study, are contributing more strongly to their FER deficit than WM. This divergence of FER predictors highlights the variable associations between brain structure and behavioural outcomes, and cautions against assuming that normal appearing brain structure will play the same functional role in typically developing and clinical populations.

Knowledge that the same brain structure can have different functions has been highlighted as a fundamental problem about making reverse inferences from functional neuroimaging data in cognitive neuroscience (Poldrack, 2012). A recent study conducted in children with autism demonstrated that networks underlying intelligence differ from typically developing children (Pua, Malpas, Bowden, & Seal, 2018). Another study, conducted in children born very preterm, identified an absence of an association between DTI metrics and neurodevelopmental outcome that was present in term born children, but found their WM to be less connected (Young et al., 2018). It is possible that FER relies more heavily on brain networks rather than individual tracts, and that network analyses may have been more sensitive to brain differences that are driving our clinical sample’s FER deficit.

Across all participants, we found that age predicted ToM directly. Our primary PLS path model also suggests that the age-dependent improvement of ToM may be partially related to maturation
of the ILF, IFOF and UF, through their effect on IQ. Meaning, WM structure (i.e., a higher FA/lower RD) increases with age, which is associated with a higher IQ, and a higher IQ predicts better ToM performance. Fittingly, a recent study documented that WM maturation in early childhood is associated with ToM development (Wiesmann et al., 2017). Given that children treated for PF tumours did not differ from typically developing children in ToM, that their IQ was within normal limits, and that they attended to the photographs, it is not surprising that our measures of general cognitive function and visual attention were not associated with their FER abilities. However, our study highlights that some of the deficits currently experienced by children treated for PF tumours are subtle (i.e., impairments in FER, despite general cognitive function within normal limits), and that they could be overlooked if not assessed directly.

It is well documented that children treated for brain tumours, in particular those who received more intensive treatment, experience social difficulties (Bonner et al., 2008; Brinkman et al., 2012; Schultz et al., 2007). Our groups did not differ on parent-reported measures of social functioning; this either suggests the FER deficits experienced by patients are not currently causing social problems in our sample, or the proxy measures we used to assess social functioning lacked the sensitivity to detect their problems. If patients are indeed not currently experiencing social problems, their FER deficit could still have negative implications in the future, in particular as patients enter adulthood, when social dynamics and expectations evolve from that of childhood.

Some limitations to the current study should be noted, and some future directions proposed. First, only a subset of our sample was included in the PLS-path modeling as this technique requires complete data for all included measures. Thus, patients who did not undergo MRI, and patients who did not return questionnaires, were excluded. Second, the abbreviated version of the Wechsler intelligence scale may lack the sensitivity to capture the full range of deficits experienced by patients. For instance, processing speed, a domain particularly affected by treatment with radiation (Mabbott et al., 2008; Scantlebury et al., 2016), is not evaluated as a part of the WASI-II. Thus, the IQ scores for patients in our radiation group in particular, may represent overestimates. Third, the parent-reported measures of social functioning used in the present study may have lacked the sensitivity to capture the full range of social problems experienced by patients. Notably, the CBCL was designed for use in typically developing children, and its use in chronically ill populations has been criticized (Perrin et al., 1991). And
lastly, although the present study investigated factors we expected to contribute to FER, it is likely that we did not capture all the relevant factors. Future studies may consider examining WM pathways thought to be involved in emotional and/or visual processing, such as WM pathways that connect the cerebellum to the limbic system (Blatt, Oblak, & Schmahmann, 2013) and the optic radiations, respectively. It may also be worthwhile to evaluate differences in the speed of neural processing between typically developing children and children treated for a PF tumour during task performance, as children treated with radiation have been shown to exhibit delayed visual latencies in a visual-motor reaction time task (Dockstader et al., 2013). Additionally, larger sample sizes and more homogenous treatment groups will likely be required to disentangle how medical variables are contributing to their emotion recognition deficit.

3.5.1 Conclusion

In the present study, we found a divergence of FER predictors, with WM predicting FER in typically developing children, and medical variables predicting the deficit experienced by children treated for PF tumours. We found no associations between visual attention, or general cognitive function, and FER. To mitigate the negative impact of FER deficits in children and adolescents, it is important to understand which factors contribute to their deficit, and how; it is clear that further studies are required to disentangle the role of factors we evaluated, and to examine if factors not captured in the present study also contribute. Importantly, our study provides some insight into predictors that may be specific to children treated for PF tumours, and captured a divergence of associations between typically developing and clinical populations; a concept that may be broadly applicable to other neurodevelopmental and clinical populations that experience FER deficits.

3.6 Acknowledgments and funding

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Chapter 4

Eye-movements and White Matter are Associated with Emotional Control in Children Treated for Brain Tumours

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4 Eye-movements and White Matter are Associated with Emotional Control in Children Treated for Brain Tumours

4.1 Abstract

Paediatric brain tumour survivors often suffer from lifelong emotional disabilities that impair their daily functioning, and decrease their quality of life. There are no behavioural markers to objectively detect and quantify this impairment, and the neuroanatomic basis is unknown.

We monitored eye-movements during the control of attention to emotional faces to measure emotion regulation (n=36 brain tumour survivors [patients] / n=18 controls; 8-17 years). Relative to controls, patients had difficulty inhibiting attentional capture by emotional faces, and performance correlated with a parent-reported measure of emotional control in daily life. In patients, white matter of the splenium was associated with our emotion regulation measure.

Our novel behavioural marker is associated with daily function, suggesting an early oculomotor measure of attention can inform complex human behaviour. Although longitudinal research is needed, our findings may help identify children at risk for poor post-treatment outcomes, and suggest a candidate neuroanatomic substrate of emotion regulation.

4.2 Introduction

The ability to effectively regulate emotions is critical to successful functioning in daily life; it allows individuals to modify how they experience and express emotions over time. Children with acquired brain injury often have difficulty regulating their emotions, but there are currently limited means to objectively evaluate their emotional processing in real-time. Such information is critical to improve the quality of life for children at risk for emotional dysfunction.

Children treated for brain tumours, including those that arise in the posterior fossa (PF), often experience social and emotional dysfunction, in turn decreasing their quality of life. It is well documented that children treated with radiation for brain tumours are at risk for developing anxiety and depression (Schultz et al., 2007; Zeltzer et al., 2009), and that children treated without radiation also exhibit emotional functioning difficulties (Beebe et al., 2005); however, there are no behavioural markers to objectively evaluate emotional functioning in these vulnerable children. Emotional dysfunction, such as anxiety and depression, are characterized in
part by poor regulation of emotional responses (Joormann & Quinn, 2014) and ineffective modulation of attention to emotional stimuli (MacNamara & Proudfit, 2014). Here we asked whether emotional control in daily life, and the regulation of attention to emotional stimuli, are disturbed in a population of children with an acquired brain injury due to their brain tumour and associated life-saving treatment. Further, we evaluated a novel eye-tracking measure of emotion regulation in these children; a critical step towards identifying children at greatest risk for poor outcomes and for developing targeted interventions to improve emotional functioning in daily life.

Emotional functioning in children treated for brain tumours is typically evaluated using standardized parent-report or self-report questionnaires (Beebe et al., 2005; Schultz et al., 2007; Zeltzer et al., 2009). These clinical tools are not designed to capture subclinical, but potentially still functionally important levels of emotional dysfunction. Furthermore, subjective measures are not designed to investigate the underlying behavioural processes that may contribute to an emotional outcome. All emotional experiences unfold along a time continuum; the way an emotion is initially experienced or regulated is not necessarily how it will continue to be experienced or regulated over time. Parent-report questionnaires of a child’s past behaviour are not capable of capturing this temporal complexity. To investigate emotional functioning as a process, it should be assessed in real-time; evaluating attention and the control of attention to emotional stimuli can help achieve this. Eye-movements are ideally suited to evaluate the attentional system in real-time, as they are a direct manifestation of attentional allocation, and emotional stimuli are known to enhance attention (Dolan, 2002; Nummenmaa et al., 2006). Thus, we monitored eye-movements using eye-tracking technology to understand real-time emotional functioning in children treated for brain tumours.

Eye-tracking is an inexpensive, non-invasive technique that has been effectively used to examine visual processing in normative and atypical development (Constantino et al., 2017; Dalton et al., 2005; Karatekin, 2007). Emotion regulation is thought to involve implicit and explicit processes (Phillips, Ladouceur, & Drevets, 2008), and eye-movements are ideally suited for detecting components of this involuntary and voluntary processing; exogenous saccades that are automatic and based on stimuli without instructions (bottom-up) reflect implicit processes, whereas endogenous saccades that are voluntary following instructions (top-down) reflect explicit processes (Mulckhuyse, 2018). Using eye-tracking, stimuli that initially capture attention
(attentional orienting) can be distinguished from stimuli that maintain attention over time (attentional engagement), and the ability to voluntarily regulate these attentional processes can be investigated directly. Real-time evaluation of attention during an emotional response may help reveal if specific attentional components (e.g., immediate vs. prolonged) are associated with poor outcome. Identifying temporal components of attention is critical for optimizing attention-training interventions designed to improve emotion regulation. Furthermore, characterizing a non-invasive and objective behavioural marker of emotional dysfunction that does not rely on verbal communication has great potential for identifying clinically relevant emotional outcomes in daily life in children treated for brain tumours, and potentially children with acquired brain injury more broadly.

All children treated for PF tumours, irrespective of treatment modality, experience white matter (WM) compromise (Liu et al., 2015; Mabbott et al., 2006; Moxon-Emre et al., 2016). Although it is known that brain structure is associated with cognitive outcomes in children treated for brain tumours (Mabbott et al., 2006; Rueckriegel et al., 2015), little attention has been devoted to evaluating the neuroanatomical substrates of emotional dysfunction. To appropriately identify candidate neuroanatomical substrates of emotion regulation, it is critical to relate brain structure to measures of emotion regulation that are directly controlled by brain function. Attention and visual processing, components central to eye-movements, fulfill this requirement, whereas parent-report measures do not. As such, an objective eye-tracking measure of emotion regulation is better suited to interrogate brain-behaviour relations than standardized measures of emotional outcomes.

We developed an eye-tracking task to evaluate the control of attention to emotional faces and compared performance between 3 groups: children treated (i) with and (ii) without radiation for PF tumours and (iii) age-matched typically developing children (herein referred to as surgery, radiation and control groups respectively). To evaluate if eye-movements related to emotion regulation is associated with broad emotional behaviour in daily life, we correlated performance on the eye-tracking emotion regulation task, with a parent-report measure of their child’s emotional control. Lastly, we evaluated the associations between emotion regulation and WM organization using Diffusion Tensor Imaging (DTI). The experimental procedure is detailed in Figure 4.1.
Figure 4.1 Experimental procedure

(a) Eye-tracking paradigm designed to evaluate emotion regulation, (b) MRI to evaluate white matter (WM) microstructure, (c) Parental Behaviour Rating Inventory of Executive Function (BRIEF) questionnaire; the emotional control scale was used to evaluate their child’s ability to modulate emotional responses in daily life.

The present study tested four hypotheses, and had one exploratory aim. Hypothesis: (1) emotional faces will capture attention: children in all groups will exhibit an orienting preference to the emotional face; (2) children treated for brain tumours will have difficulty regulating this attentional capture, and will continue to attend to the emotional face despite being instructed not to; (3) children treated for brain tumours will have worse emotional control, and will experience more symptoms of anxiety and depression than typically developing children; (4) our eye-tracking measure of emotion regulation will relate to emotional control in daily life. In our
exploratory aim, we took an unbiased voxelwise approach to evaluate the association between WM and our eye-tracking measure of emotion regulation.

4.3 Results

4.3.1 Emotional faces capture attention

We tested participants on two conditions of an eye-tracking task. First, we verified that emotional faces captured attention in a baseline condition of the eye-tracking task. In this condition we used a well-established paradigm of attentional control where pairs of faces are presented - one displaying a neutral expression and the other displaying an emotional expression (Figure 4.2a) (Hu et al., 2017; Nummenmaa et al., 2006). Children viewed the faces freely; we recorded the amount of time taken to maintain visual gaze, or fixate, on one of the target faces (i.e., time to first fixation, or fixation latency). By evaluating viewing patterns in this manner we obtained a measure of attentional orienting.

*Attentional orienting:* we found that emotional faces captured attention in all groups; there was a main effect of emotion for the time to first fixation, with the first fixation being made earlier to the emotional face ($F_{(1,51)} = 32.18$, $p < 0.0001$; Figure 4.3a). In each group, children were faster to make their first fixation on the emotional face compared to the neutral face (all $p < 0.05$). However, children in the radiation group were slower to make their first fixations, to either face; a main effect of group ($F_{(2,51)} = 4.0$, $p = 0.02$) indicated that patients treated with radiation had longer first fixation latencies compared to controls ($t = 2.82$, $p = 0.02$). Overall, all children were also more likely to make their first fixation on the emotional face; there was a main effect of emotion for the probability of first fixation ($F_{(1,51)} = 13.34$, $p = 0.0006$). However, because post-hoc pairwise comparisons revealed that patients in the surgery group did not exhibit this effect, the more consistent fixation latency, rather than fixation probability score, was used as our baseline measure of attentional orienting for cross-task comparisons and correlations. Viewing patterns for specific emotions that together constituted the emotional/neutral condition (i.e., happy/neutral, angry/neutral and sad/neutral) generally followed this overall pattern of emotion-related capture, as detailed in Supplementary Figures 4.1 & 4.2.

Findings from our baseline condition indicate that emotional faces captured attention in all groups.
Figure 4.2 Eye-tracking paradigm to quantify emotional attentional capture

**a**

General Instructions

“Look at the center of the dot whenever it appears”

**b**

Free viewing condition

“Look at the faces freely”

Directed viewing condition

“Follow the instructions on the screen”

**i.** Original images

**ii.** Edited images

---

**a-b.** Two versions of an eye-tracking task were designed to evaluate: (a) attention to emotional vs. neutral faces (baseline condition - free-viewing), and the ability to regulate attention to the emotional faces (regulate condition – directed viewing). Examples of viewing patterns to the faces are shown. Blue circles = fixations, yellow lines = saccades. (b) i. Examples of original images from three different emotional face databases used in the paradigm (left image = NIMH-chEF database; middle image = Radboud faces database; right image = NimStim database). ii. The same images, edited for the paradigm. To maximize attention to the faces: all bright coloured clothing was changed to black and facial features were aligned (black dotted lines). Only fixations made to the faces (i.e., inside the blue circles) were included in the analyses.
4.3.2 Children treated for brain tumours have difficulty regulating the attentional capture of emotional faces

After establishing that emotional faces capture attention in all groups, we next asked participants to regulate this tendency in the second phase of the eye-tracking task by attending to the neutral rather than emotional face stimuli. The regulate condition was identical to the baseline condition, except this time we instructed children to “look at the face that is NOT emotional” (Figure 4.2a). We evaluated viewing patterns and recorded the number of fixations and dwell time for each face over the entire trial - reflecting attentional engagement, and the time to first fixation – reflecting attentional orienting.
**Attentional engagement:** viewing patterns throughout the entire trial duration (5 seconds) of the regulate condition revealed that children in all groups were capable of successfully completing the emotion regulation task; across all groups, children made more fixations, and had longer dwell times, on the neutral face compared to the emotional face (all $p < 0.05$; Supplementary Figure 4.2).

**Attentional orienting:** we found that only typically developing children were able to override the attentional capture of emotional faces when instructed to; a significant emotion by group interaction ($F_{(2,51)} = 5.58, p = 0.007$; Figure 4.3b) revealed that only the healthy control group had a shorter fixation latency to the neutral face than to the emotional face ($F_{(1,51)} = 13.04, p = 0.0007$). Fixation latencies between the emotional and neutral faces in the surgery and radiation groups did not differ (all $p > 0.05$), indicating that patients were unable to override the attentional capture of emotional faces and orient more quickly to the neutral face.

Viewing patterns during each emotional face trial type (i.e., happy/neutral, angry/neutral and sad/neutral), that together constituted the emotional/neutral condition, are provided in Supplementary Figures 4.1 & 4.2.

Findings from our regulate condition indicated a divergence in emotion regulation capabilities during the earliest components of the visual response; typically developing children were able to override the attentional capture of emotional faces, whereas children treated for a brain tumour were not.

4.3.3 Daily emotional control is mildly impaired in paediatric brain tumour patients

We evaluated if patients and healthy controls differed in emotional control scores from a widely used parent-report measure from the Behaviour Rating Inventory of Executive Function (BRIEF); all patients exhibited worse emotional control than healthy controls ($F_{(1,47)} = 4.63, p = 0.04$). When evaluating differences in emotional control between the three groups (surgery, radiation and healthy control) no differences emerged ($F_{(2,46)} = 2.27, p = 0.11$; Figure 4.4a). Although patients differed from the control group the mean scores for all three groups were within the normal range indicating that overall, patients in our sample are not experiencing clinically significant emotional control difficulties. However, patients displayed more variability
in their scores, and the proportion of children with mildly to clinically elevated scores differed between the groups ($\chi^2 (1, \text{N}=49) = 3.97, p = 0.046$): the percentage of patients with mildly to clinically elevated scores was 19.36% in the patient group, compared to 0% in the healthy control group.

As problems with emotion regulation may contribute to the development of affective disorders we also evaluated anxiety and depression using self-report questionnaires from the Screen for Child Anxiety-Related Emotional Disorders (SCARED), and the Children’s Depression Inventory 2 (CDI-2), respectively. We found that the surgery and radiation groups did not experience heightened levels of anxiety or depression compared to the healthy control group (all $p > 0.05$; Table 4.1). Unlike the emotional control scores from the BRIEF, patients do not display more variability in their SCARED and CDI-2 scores; the proportion of children with mildly to clinically elevated scores did not differ between patient and control groups on the SCARED ($\chi^2 (1, \text{N}=54) = 0.04, p = 0.84$) or CDI-2 ($\chi^2 (1, \text{N}=54) = 1.53, p = 0.22$).

Findings from our standardized questionnaires indicate that patients treated for brain tumours have mild impairments in emotional control, yet they display no evidence of heightened anxiety or depression.

Figure 4.4 Poorer performance on the directed viewing task is correlated with worse emotional control in daily life
Emotional control scores from the Behaviour Rating Inventory of Executive Function (BRIEF) scale. The emotion regulation score (calculated by subtracting the latency of first fixation to the target (i.e., neutral) from the non-target (i.e., emotional) face, during the directed viewing task) correlated with the emotional control scale from the BRIEF. Higher emotion regulation and BRIEF scores both indicate worse functioning in daily life. Thus, children who have difficulty overriding the attentional capture of emotional faces during the earliest components of their visual response displayed poorer emotional control in daily life.

### Table 4.1 Scores on self and parent questionnaires

<table>
<thead>
<tr>
<th>Measure</th>
<th>Healthy Control</th>
<th>Surgery</th>
<th>Radiation</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRIEF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Control</td>
<td>44.56 (2.20)</td>
<td>50.59 (2.27)</td>
<td>50.29 (2.50)</td>
<td>2.27</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>CDI-2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>55.22 (2.12)</td>
<td>51.53 (2.18)</td>
<td>49.05 (2.06)</td>
<td>2.20</td>
<td>0.12</td>
</tr>
<tr>
<td>Emotional Problems</td>
<td>55.50 (1.96)a</td>
<td>51.82 (2.01)</td>
<td>47.79 (1.91)a</td>
<td>3.97</td>
<td>0.02*</td>
</tr>
<tr>
<td>Negative Mood</td>
<td>55.89 (2.74)</td>
<td>50.94 (2.82)</td>
<td>48.63 (2.67)</td>
<td>1.86</td>
<td>0.17</td>
</tr>
<tr>
<td>Negative Self-Esteem</td>
<td>53.83 (1.66)b,c</td>
<td>47.94 (1.70)b</td>
<td>47.21 (1.62)c</td>
<td>4.84</td>
<td>0.01*</td>
</tr>
<tr>
<td>Functional Problems</td>
<td>53.44 (2.19)</td>
<td>50.59 (2.25)</td>
<td>50.63 (2.13)</td>
<td>0.56</td>
<td>0.58</td>
</tr>
<tr>
<td>Ineffectiveness</td>
<td>53.33 (2.01)</td>
<td>50.21 (1.96)</td>
<td>49.12 (2.07)</td>
<td>1.16</td>
<td>0.32</td>
</tr>
<tr>
<td>Interpersonal Problems</td>
<td>50.83 (2.68)</td>
<td>51.47 (2.76)</td>
<td>49.37 (2.61)</td>
<td>0.16</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>SCARED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>20.50 (2.91)</td>
<td>25.00 (3.00)</td>
<td>23.11 (2.83)</td>
<td>0.59</td>
<td>0.56</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>6.11 (1.05)</td>
<td>5.12 (1.08)</td>
<td>4.21 (1.02)</td>
<td>0.47</td>
<td>0.63</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>6.01 (1.04)</td>
<td>5.88 (1.07)</td>
<td>5.79 (1.01)</td>
<td>0.02</td>
<td>0.98</td>
</tr>
<tr>
<td>Separation Anxiety</td>
<td>3.33 (0.84)</td>
<td>5.29 (0.86)</td>
<td>4.2 (0.82)</td>
<td>1.33</td>
<td>0.27</td>
</tr>
<tr>
<td>Social Anxiety</td>
<td>5.11 (0.95)</td>
<td>7.29 (0.95)</td>
<td>7.68 (0.93)</td>
<td>2.14</td>
<td>0.13</td>
</tr>
<tr>
<td>School Avoidance</td>
<td>0.67 (0.39)</td>
<td>1.41 (0.40)</td>
<td>1.68 (0.38)</td>
<td>1.85</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Matching letters in different rows indicate a significant difference (p < 0.05) between groups as follows: a P = 0.02; b P = 0.049; c P = 0.02. Note that higher values for CDI-2 measures indicate more problems.

Abbreviations: BRIEF = Behaviour Rating Inventory of Executive Function; CDI-2 = The Children’s Depression Inventory 2; SCARED = Screen for Child Anxiety-Related Emotional Disorders

### 4.3.4 Early oculomotor response in emotion regulation is associated with behaviour in daily life

We then asked if control of the early fixation latency, a real-time behavioural marker of emotion regulation, in the regulate condition of our eye tracking task, was associated with emotional behaviour in daily life. To do this we correlated our eye-tracking measure of emotion regulation, (calculated by subtracting the time to first fixation on the target face [i.e., the neutral face] from the time to first fixation on the non-target face [i.e., the emotional face]), to the emotional control score from the BRIEF.

This correlation showed that across all children, the eye-tracking emotion regulation score was positively correlated with the emotional control score on the BRIEF (r = 0.29, p = 0.045; Figure
4.4b), indicating that children who had difficulty overriding the attentional capture of emotional faces displayed the worst emotional control in daily life.

Given that our eye-tracking measure of emotion regulation was associated with emotional control in daily life, we have confidence that it is measuring a construct related to emotional regulation, and that it may be useful for identifying children who are at risk for poor emotional outcomes.

4.3.5 Greater microstructural organization of white matter in the splenium is associated with worse emotion regulation in brain tumour patients

Lastly, given that the neuroanatomical basis of emotion regulation capabilities are unknown in children treated for a brain tumour, we took an unbiased approach; namely, we correlated our eye-tracking measure of emotion regulation with WM throughout the brain in patients and healthy controls considered separately. We evaluated fractional anisotropy (FA) and radial diffusivity (RD), indices derived from DTI that provide an indirect measure of WM microstructural organization. All patients were considered together because we recently demonstrated that children treated with radiation and surgery in the current cohort did not differ in WM microstructure (Moxon-Emre et al., Submitted), and also because they did not differ in their performance on the eye-tracking emotion regulation task.

Notably, in children treated for brain tumours, after controlling for age, we identified a cluster of 308 voxels, where RD was negatively correlated with the eye-tracking emotion regulation score (higher score = worse regulation) (p = 0.037; Figure 4.5a), and a cluster of 1585 voxels, where FA was positively correlated with the eye-tracking emotion regulation composite score (p = 0.03; Figure 4.5b), located mostly in the splenium. In healthy controls, there were no voxels where RD or FA correlated with the eye-tracking emotion regulation score (all p > 0.05).

Together, these findings indicate that among children treated for brain tumours, those with more organized WM microstructure in the splenium of the corpus callosum experienced more difficulty overriding the attentional capture of emotional faces.
Figure 4.5 Greater organization of white matter microstructure in the splenium is associated with worse emotion regulation in brain tumour patients

(a-b). Controlling for age, voxels where (a) RD (red-yellow) was negatively correlated, and (b) FA (dark blue-light blue) was positively correlated, with the eye-tracking emotion regulation score (higher scores = worse regulation). In children treated for brain tumours, those who had more organized WM microstructure in the splenium appeared less able to endogenously override the attentional capture of emotional faces. No correlations were observed in healthy controls. Clusters of significant voxels are superimposed on the FMRIB FA template. Images are shown in radiological convention. Numbers represent MNI z-coordinates. A = anterior; L = left; P = posterior; R = right.
4.4 Discussion

There are currently no behavioural markers to objectively evaluate emotional functioning in children treated for brain tumours. The present study addressed this critical gap by describing an eye-tracking measure of emotion regulation that is associated with emotional control in daily life. We began by demonstrating that all children experienced heightened attentional orienting to emotional faces, indicating attentional capture. We then demonstrated that children treated for brain tumours had difficulty regulating this attentional capture. Our findings revealed that the earliest oculomotor measure of emotion regulation, characterized by the latency of the first fixation, was altered in children treated for brain tumours, and is related to emotional behaviour in daily life. Finally, we identified that WM in the splenium of the corpus callosum is a candidate neuroanatomical substrate of our eye-tracking measure of emotion regulation in children treated for brain tumours.

Previous eye-tracking studies have demonstrated that emotional stimuli capture attention more effectively than neutral stimuli (Nummenmaa et al., 2006). In line with this research, our baseline condition revealed that emotional faces capture automatic (i.e., exogenous) attention in typically developing and children treated for brain tumours alike; the first fixation was made more quickly to the emotional face. That children treated for brain tumours also exhibited this automatic response suggests their bottom-up processing of emotional information is preserved. It is notable that although children in all groups experienced attentional capture of the emotional face in the baseline condition, children in the radiation group were slower to make their first fixation to either face. Children treated with radiation for PF tumours experience considerable WM damage (Mabbott et al., 2006; Moxon-Emre et al., 2016); this damage is associated with processing speed deficits (Mabbott et al., 2008; Scantlebury et al., 2016) and may also result in slower eye-movements.

Once we determined that emotional faces captured attention, we were able to assess emotion regulation by evaluating participants’ ability to deliberately (i.e., endogenously) override this attention in a top-down manner. We demonstrated that typically developing children were able to override the attentional capture of emotional faces during the earliest components of the visual response, whereas children treated for brain tumours were not; only healthy controls made their first fixation more quickly to the neutral face. The inability to override the attentional capture of
emotional faces suggests that top-down processing of emotional information may be compromised in children treated for brain tumours.

Previous studies have suggested that healthy children and adults are unable to override attentional capture when instructed (Lagattuta & Kramer, 2017; Nummenmaa et al., 2006); in contrast with these findings, we demonstrated that typically developing children in our sample were capable of doing so. Some notable differences in the design of our study may help explain this discrepancy. In Nummenmaa and colleagues (2006) the stimuli presented were scenes and not faces. Our use of two faces of the same actor side-by-side reduced the potential for differences in the content of the scenes from driving attentional orientation. Although Lagattuta and Kramer (2017) showed pictures of faces, they paired two emotional faces together, whereas we presented an emotional with a neutral face. That typically developing children in our study were able to regulate their initial orienting away from the emotional face suggests our task design was sensitive enough to detect subtle differences in the regulation of attention to emotional stimuli. There is evidence that the ability to override attentional capture differs between individuals, and that it is strongly predicted by working memory capacity (Fukuda & Vogel, 2009). Although not assessed in the present study, children treated for brain tumours are known to experience working memory deficits (Conklin et al., 2012); it is possible that patients have difficulty controlling their orienting attention away from the emotional face in part due to their compromised working memory. However, it is notable that our eye-tracking paradigm contained almost no working memory load, and that patients had no difficulty completing the task.

We also demonstrate that the ability to override the attentional capture of emotional faces was associated with functional outcome in daily life across all children. It is notable that although children in all groups had parent-reported emotional control scores within the normal range, approximately 20 percent of children treated for brain tumours had mildly to clinically elevated scores; our eye-tracking measure of emotion regulation not only detected differences between patients and controls, it also identified those children at greatest risk for emotional dysfunction. Parent-report questionnaires report on observations of past behaviour whereas our objective measure captures an active process in real-time; as a result, our objective eye-tracking measure of emotion regulation may have the sensitivity to detect subtle perturbations in the ability to control emotions that cannot be gleaned by measures designed to capture broad clinical issues.
The ability to detect subtle deficits in emotion regulation could improve the identification of those children who are at risk for poor emotional outcomes but who may not meet the diagnostic criteria on standardized measures. Although children treated for brain tumours in our sample did not report clinically significant affective symptoms such as anxiety and depression, it is possible that these patients experience subtle issues that are not being captured in our questionnaire-based approaches. Moreover, that the earliest component of a visual response was associated with a later behavioural outcome suggests complex behaviour may be guided, at least in part, by involuntary attentional processing. Shimojo and colleagues (2003) also demonstrated that the earliest components of a visual response can be associated with later outcomes. The gaze cascade effect is a proposed concept, based on the role of initial orienting in the preference-decision making process; initial gaze results in increased exposure of that stimulus, which reinforces the initial selection and ultimately influences decision making (Shimojo, Simion, Shimojo, & Scheier, 2003).

Interventions that aim to modify behaviour in children at risk for poor emotional outcomes may need to carefully consider the entire time course of attentional processing in order to determine where an intervention would be most beneficial. It has been proposed that regulating attention is a critical component of the emotion regulation process, and that it can be trained through practice (Wadlinger & Isaacowitz, 2011). Given that attentional processing is controlled by brain function, an understanding of the neuroanatomical substrates related to our eye-tracking emotion regulation measure may also help inform the future development of interventions; it may provide clues regarding strategies that can be used promote the recruitment of networks to achieve more effective attentional control. For instance, evidence suggests there are at least three distinct attentional networks (alerting, orienting and executive), and that different training techniques may be used to modify or recruit these networks in unique ways (Raz & Buhle, 2006).

Children treated for brain tumours experience considerable WM damage (Liu et al., 2015; Mabbott et al., 2006; Moxon-Emre et al., 2016), including to the corpus callosum (Palmer et al., 2012). It is notable that microstructural organization of WM in the splenium of the corpus callosum was associated with emotion regulation in children treated for brain tumours only. The splenium facilitates interhemispheric communication between the visual cortices (Putnam, Steven, Doron, Riggall, & Gazzaniga, 2010), and has been associated with visual processing (Davis & Cabeza, 2015; Schulte, Muller-Oehring, Rohlfing, Pfefferbaum, & Sullivan, 2010).
Moreover, networks of top-down attention control have been shown to modulate activity in the visual cortex (Hopfinger, Buonocore, & Mangun, 2000). Altered WM within the splenium has been identified as a shared feature between children with neurodevelopmental disorders that are characterized in part by attentional challenges: autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) (Ameis et al., 2016). Thus, the splenium of the corpus callosum appears to be an appropriate neuroanatomic substrate for the control of attention in children treated for brain tumours.

Although reduced microstructural organization has typically been associated with functional impairments in children treated for brain tumours (Mabbott et al., 2006; Palmer et al., 2012; Rueckriegel et al., 2015), we demonstrate the opposite: greater microstructural organization of WM of the splenium (i.e., higher FA and lower RD), typically thought of as ‘healthier’, was associated with worse emotion regulation in children treated for brain tumours. Although counter-intuitive, a couple of studies have also reported that higher FA in the corpus callosum is associated with worse performance on cognitive control tasks in children; higher FA in the splenium was associated with worse task-switching ability in adolescents (Seghete, Herting, & Nagel, 2013) and higher FA in the frontal projections of the corpus callosum was associated with worse inhibitory control in children (Treit, Chen, Rasmussen, & Beaulieu, 2014). It is possible that in children treated for brain tumours, within the context of sustained WM damage, more organized WM in the splenium is not functionally advantageous. Although speculative, this greater organization may be associated with more effective sustained attention that comes at a time cost for disengaging attention.

It should be noted that the present study only considered attentional components of emotion regulation. There are other aspects of emotion regulation that evolve over a much longer time course, and that are not captured in the present study. For instance, the ability to use cognitive strategies to regulate an emotional response following mood induction, a common paradigm used in emotion regulation research, was beyond the scope of this study. However, our eye-tracking measure of emotion regulation was able to detect children with elevated emotional control scores; as such, it could directly inform strategies for early identification of children at risk for poor emotional functioning in daily life. Given that the ability to override attentional capture has been related to working memory capacity (Fukuda & Vogel, 2009), future studies should evaluate working memory in children who complete our objective eye-tracking emotion.
regulation task. If working memory indeed predicts poor emotion regulation, training programs that have been shown to improve working memory performance in children treated for brain tumours (Conklin et al., 2017; Conklin et al., 2015) may serve to enhance cognitive capacity in a manner that generalizes to improvements in emotional functioning. In addition, enhancing attentional control, through gaze training for example, could have positive downstream effects on emotion regulation, and warrants future investigation. Thus, our findings both inform early strategies to identify children at risk for emotional dysfunction, and provide the basis for future approaches to intervention.

We are the first to combine an objective eye-tracking measure with a standardized measure of emotional control to characterize the processes that contribute to emotional functioning in children treated for brain tumours. In doing so, we have developed a behavioural marker of emotion regulation that is associated with daily emotional function. We have also highlighted that the splenium of the corpus callosum may represent a neuroanatomical substrate for emotion regulation capabilities in children treated for brain tumours. Our findings may help identify children at risk for negative emotional outcomes, and those who may benefit from novel interventions. By providing a better understanding of the attentional processes that contribute to poor emotional outcomes, we have laid the foundation for future intervention studies that aim to improve functioning in daily life. If such interventions prove successful, the emotional and financial burden of the deficits experienced by children treated for brain tumours could be diminished in the future, and their quality of life could be substantially improved.

4.5 Methods

4.5.1 Participants

Fifty-four children between the ages of 8 and 17 participated in this study; 36 children treated for PF tumours (17 patients treated with surgery with or without chemotherapy, and 19 patients treated with surgery, chemotherapy and radiation) at the Hospital for Sick Children (SickKids; Toronto, Canada) and 18 typically developing (healthy control) children. Demographic variables for these participants are summarized in Table 4.2. Five controls were siblings of PF tumour patients who completed the present study, and another five controls were siblings of brain tumour patients who participated in other studies at the hospital (i.e., non-PF tumour patients). Thus, 10/18 (56%) of our control sample was related to brain tumour patients. All patients were
> 1 year post diagnosis and had completed all therapy. Patients were excluded from participation if they had premorbid neurological disorders or if they were receiving palliative care. Healthy controls were free of all neurological or clinical disorders. Patients were recruited to the study via mailed letters, and/or were approached during their routine clinic visits. Healthy controls were either recruited from the community, were siblings of patients, or family members/friends of SickKids staff. All children were either native English speakers, or had completed at least two years of schooling in English at the time of participation. This study was approved by the SickKids’ Research Ethics Board. Prior to participation, parents provided written informed consent and children provided assent. When deemed capable to do so, participants (typically adolescents) provided their own written consent.

4.5.2 Patient treatment information

All patients had surgical intervention for their PF tumours, and a subset of patients received chemotherapy with or without radiation. We divided our patient sample into two groups - patients who received radiation and patients who did not (referred to as radiation and surgery groups, respectively). In the radiation group, patients treated with photon beam craniospinal irradiation (CSI) received either standard (3060-3940 cGy) or reduced (1800-2340 cGy) dose, and a boost to the tumour bed, whereas patients treated with focal radiation received 5400-5940 cGy to their tumour site. Medical variables for these two treatment groups are summarized in Table 4.2. The patient groups did not differ on most medical variables, except that the radiation group had more patients with hydrocephalus (p = 0.03). The other differences between the groups arise from factors that determined their groupings; namely, patients in the radiation group were diagnosed with metastatic PF tumours (either medulloblastoma or ependymoma), whereas patients in the surgery group were primarily diagnosed with benign PF tumours (most commonly pilocytic astrocytoma), or were diagnosed with medulloblastoma before the age of 3 and consequently did not receive radiation (p < 0.0001). Moreover, the chemotherapy protocols and radiation delivered differed between the groups (all p < 0.01).
<table>
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<td></td>
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<tr>
<td><strong>Treated with Chemotherapy</strong></td>
<td></td>
<td>5</td>
<td>14</td>
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</table>

a Patients were classified as having mutism if they had diminished speech output, linguistic difficulties or dysarthria following surgery. Mutism is a transient dysfunction and had resolved in all participants by the time of assessment.
4.5.3 Emotional face stimuli

Selection process: In order to include images of children and adults of multiple ethnicities, emotional faces from three databases were used. The Radboud faces database contains images of 39 Caucasian adults, 18 Moroccan males, and 10 Caucasian children, most of unknown age (Langner et al., 2010). The NimStim database contains 43 multi-ethnic adults, ranging from 21-30 years (Tottenham et al., 2009) and the NIMH-chEF database contains 59 multi-ethnic children, ranging from 10-17 years (Egger et al., 2011).

Given that brain tumour patients have difficulty identifying facial emotions (Bonner et al., 2008), and that lower intensity expressions are most difficult to interpret, it was important to select images of faces displaying clear emotions. All images displaying angry, sad, happy and neutral faces from each database were screened and those displaying clear expressions were identified for potential inclusion. For each of the 3 face pair categories (angry/neutral, happy/neutral, sad/neutral), actors were paired together; pairs were rated by the study author (IME) from 1-10 on: 1) clarity of emotional expression and 2) image quality. Ratings were added, and sorted from highest to lowest. The highest rated pairs from each actor face pair condition were selected for use in the eye-tracking task. Non-overlapping actor face pairs, containing an equal number of males, females, adults and children, and the same number of faces from each database were selected. This yielded 48 unique face pairs: 8 pairs in each of the 3 mood pair types (angry/neutral, happy/neutral and sad/neutral) for both the baseline and regulate conditions. In each mood pair type, four face pairs were children and four face pairs were adults, two pairs were male and two pairs were female. To validate the rating process, two additional individuals rated expression clarity (a = .72) and image quality (a = .92) for 36 face pairs selected at random.

Image editing: All images from the Radboud and NIMH-chEF databases were cropped just above shoulder level, whereas the NimStim images were not cropped. The background was set to grey for all images; this was done to maximize eye-tracking by limiting pupil constriction that occurs when viewing bright or white stimuli. Coloured clothing worn by children in the NIMH-chEF database was edited to black, to prevent it from attracting attention. Edited images were then subject to face normalization in MATLAB to ensure that the position of the eyes, nose and mouth were in the same physical location in each image. Examples of raw and edited images are provided in Figure 4.2b.
4.5.4 Eye-tracking apparatus

Eye-movements were recorded throughout all tasks using a SR Research Ltd. Eyelink 1000 plus (Mississauga, Canada) eye-tracking desktop monocular system. A sampling rate of 500 Hz and a spatial resolution of 0.01° was used. A 9-point calibration was performed prior to the experiment. Images were displayed on a 14.5 x 12.5 inch LCD monitor with a 1280 x 1024 pixel resolution. Photographs displaying facial emotions were 506 x 650 pixels in size. Participants were seated 26 inches from the monitor and a chin rest was used to limit head movement. The experiment was built using the Experiment Builder software provided with the SR Research Ltd. eye-tracker.

4.5.5 Self and parent questionnaires

4.5.5.1 Emotion regulation

*The Behaviour Rating Inventory of Executive Function (BRIEF)*: a parent-report measure designed to assess everyday executive function (Gioia, Isquith, Retzlaff, & Espy, 2002). To evaluate a child’s ability to appropriately modulate their emotional responses, the ‘emotional control’ scale was used. Data was missing for 5 participants, as parents did not return the BRIEF questionnaire.

4.5.5.2 Depression

*The Children’s Depression Inventory 2 (CDI-2)*: a developmentally appropriate self-report screening tool for depression (Kovacs, 1985, 2011), capable of differentiating depression from anxiety and behavioural disorders (Kovacs, 1985). All scales from the CDI-2 (i.e., total score, emotional problems, negative mood, negative self-esteem, functional problems, ineffectiveness and interpersonal problems) were included.

4.5.5.3 Anxiety

*The Screen for Child Anxiety-Related Emotional Disorders (SCARED)*: a self-report questionnaire designed to evaluate symptoms of anxiety (Birmaher et al., 1999). All scales from the SCARED (i.e., total score, panic disorder, generalized anxiety disorder, separation anxiety, social anxiety, and school avoidance) were included.
4.5.6 Eye-tracking task

An overview of the experimental paradigm is provided in Figure 4.1. Two conditions of an eye-tracking task, detailed in Figure 4.2a, were designed:

1. *Baseline (free-viewing) condition:* Images of angry/neutral, happy/neutral and sad/neutral face pairs were presented side-by-side, and participants were instructed to look at the faces freely.

2. *Regulate (directed-viewing) condition:* A second set of angry/neutral, happy/neutral and sad/neutral face pairs were presented side-by-side, and participants were instructed to look at the non-emotional face only. The instructions, (i.e., “Look at the face that is NOT angry”) were presented on the screen for 3 seconds, and were also stated verbally by the examiner.

To prevent viewing biases, all trials in both conditions included two faces from a single actor displaying different emotions. All face pairs were presented for 5 seconds, after which the participant would fixate on a circle in the middle of the screen. Only when this fixation was made, would the next face pair appear. This was done to ensure the participants had an equal chance of making their first fixation to each image. The positions of the faces in the display were counterbalanced according to emotion, sex and age (i.e., child vs. adult). Each condition included 24 trials: 8 angry/neutral, 8 happy/neutral and 8 sad/neutral.

4.5.7 Neuroimaging protocol

Magnetic resonance imaging (MRI) was performed at SickKids using a Siemens 3T whole-body MRI scanner (Prisma fit) with a 20-channel head and neck coil. Imaging included a T1 AX 3D MPRAGE Grappa 2 protocol (T1=900ms, TE/TR=3.83/2300ms, 160 contiguous axial slices, flip angle=9°, 256x224 matrix, FOV=256x224mm, voxel size=1mm ISO) and diffusion-weighted single shot spin echo DTI sequence with EPI readout (30 directions, b=1000s/mm², TE/TR=90/9000ms, 70 contiguous axial slices, flip angle=90°, 122x122 matrix interpolated to 244x244, FOV=244x244mm, voxel size=2mm ISO, interpolated to 1x1x2mm). Diffusion weighted images (DWI) were denoised, eddy corrected for current distortions, motion corrected and bias corrected to correct B1 field inhomogeneities, with the MRTrix3 package ([www.mrtrix.org](http://www.mrtrix.org)) that utilizes FSL’s eddy tool. DTI index maps (FA and RD) were also created using MRTrix3. Six participants did not undergo MRI, either because they had braces (n=3; 2
patients, 1 control), had MRI-incompatible programmable shunts (n=2; patients), or declined the MRI portion of the study (n=1; patient).

4.5.8 Tract based spatial statistics (TBSS)

Voxelwise analyses were conducted with TBSS (Smith et al., 2006). All participants’ FA data were aligned into a common space (MNI152; Montreal Neurological Institute, McGill, Montreal, Canada) using the nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b). Then, a cross-subject mean FA image was created and used to generate a skeleton FA map representing the center common to all tracts, thresholded at FA>0.20. Finally, participant-specific FA and RD maps were aligned with the skeleton, and values along the width of each tract were considered in the cross-subject voxelwise statistics.

4.5.9 Analytic plan

4.5.9.1 Hypotheses 1 and 2

(1) Emotional faces will capture attention: children in all groups will exhibit an orienting preference to the emotional face and (2) children treated for brain tumours will have difficulty regulating this attentional capture, and will continue to attend to the emotional face despite being instructed not to

Eye-movement analyses were performed with respect to interest areas corresponding to the locations of the two faces in the display (Figure 4.2b; blue circles). To evaluate attentional orienting, the mean probability of first fixation and the average time to first fixation (i.e., first fixation latency), to each interest area, were used. To evaluate attentional engagement, the number of fixations and total dwell time, to each interest area, were used. For each eye-tracking condition (baseline: hypothesis 1; regulate: hypothesis 2), a mixed design analysis of variance (ANOVA) was conducted for the abovementioned eye-tracking metrics, as follows: 3 (group: healthy control, radiation, surgery) x 2 (face: emotional, neutral). Significant main effects and interactions were further investigated to determine response patterns. All analyses were corrected for multiple comparisons with Bonferroni correction.
4.5.9.2 Hypothesis 3

Children treated for brain tumours will have worse emotional control, and will experience more symptoms of anxiety and depression than typically developing children

Age-standardized scores from the BRIEF (emotional control scale), the CDI-2 (all scales), and scores from the SCARED (all scales) were compared between the healthy control, surgery and radiation groups, using three separate ANOVAs. To evaluate if the proportion of children with mildly to clinically elevated scores differed between patients and healthy controls, we conducted three Chi-square analyses. A T score of $\geq 60$ was used as the cutoff from the BRIEF and CDI-2, and a score of $\geq 25$ was used as a cutoff for the SCARED. The SCARED does not have age-norms, which is why T scores were not used; however a score of $\geq 25$ may represent an anxiety disorder (Birmaher et al., 1999).

4.5.9.3 Hypothesis 4

Our eye-tracking measure of emotion regulation will relate to emotional control in daily life

For the directed-viewing (regulate) condition, an emotion regulation score for each trial was calculated. It was calculated by subtracting the time to first fixation on the target face (i.e., the neutral face) from the time to first fixation on the non-target emotional face (i.e., angry, happy or sad face). Thus, values below zero indicate a greater ability to override the attentional capture of emotional faces, following the instruction to look at the non-emotional face. This emotion regulation score was created for two reasons: first, to prevent individual differences in latency of first fixation from influencing the eye-tracking emotion regulation score, and second, to obtain a single score to correlate with the emotional control score from the BRIEF, and with WM microstructure throughout the brain (detailed in section 4.5.9.4 below).

Across all children, the eye-tracking emotion regulation score was correlated with the parent-reported emotional control score from the BRIEF, using a Pearson correlation.

4.5.9.4 Exploratory aim

We took an unbiased voxelwise approach to evaluate the association between WM and our eye-tracking measure of emotion regulation
Using TBSS, we assessed if RD and FA in any voxels throughout the brain correlated with our eye-tracking emotion regulation score, in healthy control and patient groups considered separately. Age at testing was included as a covariate. A mask was made for each significant cluster of > 100 voxels, and the anatomic extent of each mask was labeled with reference to the JHU White-Matter Tractography Atlas (Hua et al., 2008). TBSS controls for family-wise errors using a permutation methodology; the null distribution of the cluster-size statistic was built up over 5000 random permutations. Cluster size was thresholded at $p < 0.05$, which was corrected for multiple comparisons.
Chapter 5

5 Contributions, challenges, opportunities and concluding remarks

This thesis examined how WM microstructure and emotional functioning are affected in children treated for PF tumours, and evaluated if alterations to WM microstructure are associated with poor emotional functioning; to achieve this, a combination of methodological approaches including DTI, eye-tracking, and standardized measures of cognitive and emotional functioning were utilized, in children treated for PF tumours and typically developing children.

Specifically, this thesis evaluated if treatment with the lowest intensity CSI protocol spares WM in children treated for medulloblastoma, and directly assessed the effect of increasing CSI dose on WM indices (Chapter 2). This thesis also used novel eye-tracking approaches in children treated for PF tumours and typically developing children to investigate two fundamental components of emotional functioning: facial emotion recognition (Chapter 3) and emotion regulation (Chapter 4). By implementing an eye-tracking version of a computerized facial emotion recognition task (e.g., the DANVA2), and developing a novel eye-tracking task of emotion regulation, this thesis evaluated if there is evidence of facial emotion recognition deficits (Chapter 3), and/or challenges with emotion regulation (Chapter 4). The goal of relating WM compromise to emotional functioning was addressed by determining if specific tracts implicated in facial emotion recognition, namely the ILF, IFOF and UF, and/or distributed WM explain their facial emotion recognition abilities (Chapter 3), and by evaluating if WM throughout the brain is associated with emotion regulation, measured with the eye-tracking emotion regulation task (Chapter 4).

Novel to the literature, this thesis demonstrated that treatment with reduced dose CSI and a restricted tumour bed boost spared WM in a large portion of temporal lobe WM in patients diagnosed with medulloblastoma (Chapter 2). It also revealed that cognitive, social and affective functioning is largely preserved in children treated with less intensive protocols (Chapters 3 and 4). In a field dominated by findings that characterize negative sequelae, this thesis highlights the possibility of better outcomes for patients with PF tumours who are eligible for treatment with
lower intensity protocols. However, experimental tasks of emotional functioning revealed that some deficits persist; children treated for PF tumours have difficulty recognizing facial emotions, despite attending to the photographs throughout the task (Chapter 3), and they have difficulty regulating their initial attention away from emotional faces (Chapter 4).

This thesis also revealed that the relations between WM microstructure and emotional functioning can diverge in the injured and uninjured brain. Namely, WM microstructure predicted facial emotion recognition in typically developing children only (Chapter 3), whereas WM of the splenium of the corpus callosum was associated with emotion regulation in patients treated for PF tumours only (Chapter 4).

Furthermore, this thesis confirmed that it is possible to successfully utilize eye-tracking technology in the paediatric brain tumour population (Chapters 3 and 4). It also revealed that a novel eye-tracking paradigm of attention to emotional faces detected emotion regulation capabilities that relate to emotional control in daily life (Chapter 4).

In this final chapter, the clinical, theoretical and methodological contributions of this work are discussed, some challenges are detailed, and opportunities for future research are suggested.

5.1 Contributions

Through integrating the results from all chapters, several overarching themes that contribute novel clinical, theoretical and methodological information have emerged; these contributions include: clarifying the effect of decreasing treatment intensity in children treated for PF tumours, providing novel information regarding brain-behaviour relations in the injured and uninjured developing brain, and detailing the utility of eye-tracking technology to evaluate emotional functioning. These contributions are discussed in turn, in the sections that follow.

5.1.1 Clinical: the effect of decreasing treatment intensity in children treated for PF tumours

Decreasing treatment intensity has improved, but not eradicated, deficits in children treated for PF tumours. This thesis demonstrated that children treated with lower intensity protocols for PF had evidence of less WM compromise, and largely preserved cognitive, social and affective functioning. Despite these improvements, some deficits remained; WM was still compromised in
many regions throughout the brain, and their emotional functioning differed from typically developing children.

Although it is well documented that CSI damages WM (Mabbott et al., 2006; Nagesh et al., 2008; Reddick et al., 2005), the effect of different clinically relevant dose and boost volumes on WM microstructure had not been investigated directly in children treated for medulloblastoma. This thesis demonstrated that treatment with a reduced dose CSI and a focal conformal boost the tumour bed (i.e., the lowest intensity CSI protocol), was associated with preserved WM microstructure in some brain regions; the most striking region of preserved WM microstructure was in the temporal lobe (Chapter 2; Moxon-Emre et al., 2016). Furthermore, by combining radiation dosimetry maps with DTI data, this thesis demonstrated that radiation dose and age at diagnosis predicted WM indices in the temporal lobe; higher doses and younger ages at diagnosis were associated with lower FA.

It is well established that treatment with CSI is associated with cognitive dysfunction (Jain et al., 2008; Kieffer-Renaux et al., 2000; Mabbott et al., 2006; Mabbott et al., 2008; Mabbott et al., 2005; Mulhern & Butler, 2004; Mulhern et al., 1998; Palmer et al., 2007; Ris et al., 2001; Spiegler et al., 2004). A recent study revealed that children treated for medulloblastoma with the lowest intensity CSI protocol had preserved intellectual function over time, whereas patients treated with higher intensity protocols declined over time (Moxon-Emre et al., 2014). Although not assessed directly in this thesis, it is certainly possible that intact WM microstructure of the temporal lobe contributed to the better intellectual outcomes in children treated for medulloblastoma with the lowest intensity CSI protocol. Unexpectedly, 74% of the children that comprised the radiation group in Chapters 3 and 4 were treated with lower intensity radiation protocols; perhaps not surprisingly, IQ scores in this group were less than 1 standard deviation from the population mean. Moreover, the surgery group had comparable IQ scores that were also within the normal range for the population. It appears that reducing treatment intensity preserves intellectual functioning in children treated for PF tumours, when the normative population mean is the comparative benchmark.

Despite the apparent preservation of intellectual function in children treated for PF tumours with and without radiation, both the surgery and radiation groups in this thesis had significantly lower scores than the control group in. It is noteworthy that the control group had a mean IQ score that
was greater than 1 standard deviation above the normative mean; this may indicate that the control sample overrepresented children with higher intellectual functioning, despite the attempt that was made to recruit siblings of brain tumour patients (i.e., 56% of controls were related to brain tumours patients) in order for the control group to represent a comparable sample of children. Other interpretations of this finding are discussed in section 5.2.

The literature has also demonstrated that children treated for PF tumours, in particular those treated with CSI, are at risk for social and affective problems (Beebe et al., 2005; Bonner et al., 2008; Brinkman et al., 2012; Moitra & Armstrong, 2013; Schultz et al., 2007; Zeltzer et al., 2009). In contrast with these reported findings, no evidence of social or affective problems were detected; there were no significantly elevated scores in either the radiation or surgery group. Furthermore, with the exception of a few instances where the control group exhibited more (non-clinically significant) problems than the patient groups, no differences between the control and patient groups emerged. It is certainly possible that decreases in treatment intensity contributed, at least in part, to the apparent preservation of social and affective functioning in children treated for PF tumours.

Taken together, treatment intensity decreases appear to be associated with more favourable WM microstructure, cognitive and social outcomes in children treated for PF tumours, yet some deficits remain. Although WM microstructure was preserved in much of the temporal lobe in children treated with the lowest intensity CSI protocol, widespread alterations to WM microstructure were still evident; there were thousands of voxels of WM that differed from typically developing children, albeit fewer than half the number that differed in children treated with higher intensity protocols (Chapter 2; Moxon-Emre et al., 2016). Although it is tempting to attribute this remaining WM compromise to the radiation that patients treated with the lowest intensity CSI protocol were still exposed to, results from Chapters 3 and 4 raise the possibility that this compromise would have been present in the absence of radiation altogether. The surgery and radiation groups in Chapters 3 and 4 had comparable WM compromise, and the pattern of compromise was similar to the reduced dose CSI and tumour bed boost group from Chapter 2; namely, much of the corpus callosum, superior longitudinal fasciculus (SLF), cingulum, and portions of the corticospinal tract (CST), ILF, IFOF and UF differed from the control group. A handful of studies have documented WM compromise in children treated for PF tumours without radiation (Liu et al., 2015; Partanen et al., 2018; Rueckriegel et al., 2010); however, its striking
similarity to the compromise detected in children treated with lower intensity radiation protocols had not yet been noted. Given these similarities, it is a challenge to pinpoint what underlies WM compromise in children treated for PF tumours. Although it cannot be stated that radiation does not contribute, it can be stated that similar WM compromise can be observed in the absence of radiation altogether.

The surgery and radiation groups also had comparable emotional functioning; compared to controls, both facial emotion recognition and emotion regulation was compromised in patients. Specifically, patients treated for PF tumours had more difficulty recognizing facial emotions than controls, and patients were unable to override the attentional capture of emotional faces when instructed to do so. Patients also had significantly higher scores than controls on the emotional control scale of the BRIEF, indicative of worse functioning. Although the patient group had a mean emotional control score that was within the normative range, 19% of patients had clinically elevated scores, whereas no elevated scores were found in controls. Given that emotional functioning deficits were observed in children treated for PF tumours using experimental paradigms, this suggests that experimental tasks may have a unique ability to detect deficits even when cognitive and affective functioning – based on standardized normative tests - is within the normal range. Novel tasks may become increasingly important in the assessment of children treated for brain tumours, in particular for children who are treated with lower intensity protocols and for whom deficits may be overlooked if they are assessed exclusively with standardized measures.

Together, these findings indicate that although decreases in treatment intensity have improved functioning in children treated with radiation for PF tumours, comparable deficits in patients treated with and without radiation remain. The similarities in WM microstructure, cognitive function and emotional functioning in both patient groups raises the possibility that treatment with lower intensity radiation protocols may not render children more susceptible to deficits than treatment without radiation. Conversely, these findings highlight that treatment without radiation is not inert, and emphasizes that all children treated for PF tumours warrant close attention, regardless of how they are treated.

In light of the similarities that were observed in patients treated with and without radiation across neuroimaging, cognitive and emotional functioning measures, all patients treated for PF tumours
were considered together for analyses that evaluated associations between WM microstructure and emotional functioning. The patterns of these associations, and how they differed between children with and without injury to the brain as a result of their PF tumour and treatment, are discussed in the following section.

5.1.2 Theoretical: brain-behaviour relations in the injured and uninjured brain

A divergence of brain-behaviour relations between typically developing children and children that sustain a brain injury as a result of their PF tumour and treatment was documented in Chapters 3 and 4. This divergence of brain-behaviour associations was evident in both directions. Namely, distributed WM throughout the brain predicted facial emotion recognition in typically developing children, yet this was not observed in children treated for PF tumours. Conversely, WM of the splenium of the corpus callosum was associated with performance on the emotion regulation eye-tracking task in children treated for PF tumours, yet no associations were detected in typically developing children. The presence of a brain-behaviour relation in one group and not another may have different meanings depending on the nature of the association, and on the group in which it is detected.

Detecting an association exclusively in a typically developing population may not mean that the association is absent altogether in the clinical group; rather, the association may be overshadowed or muted by factors that are unique to the clinical group. Given the wealth of studies that have implicated specific WM tracts with facial emotion recognition abilities in adults (Coad et al., 2017; Crespi et al., 2014; Genova et al., 2015; Philippi et al., 2009; Unger et al., 2016), it was not surprising that WM predicted facial emotion recognition in typically developing children (Chapter 3). Conversely, the absence of an association in children treated for PF tumours may have resulted from their unique and multifaceted brain injury. Although WM may still be important for facial emotion recognition abilities in children treated for PF tumours, factors associated with their diagnosis and treatment may also influence facial emotion recognition abilities; such factors may include the location/size of the tumour within the cerebellum, or the development of postsurgical complications such as hydrocephalus and/or mutism. Notably, there is increasing evidence that the cerebellum is involved in emotion recognition abilities (reviewed in Clausi et al., 2017).
Although WM pathways that have been implicated in facial emotion recognition (i.e., the ILF, IFOF and UF) did not differ in their entirety between the patient and control groups, voxelwise analyses revealed some regions along these specific tracts where WM differed between patient and control groups. Thus, the degree to which alterations are present in these tracts may be variable across patients. For this reason, and due to the variability in treatment and post-surgical complications that can occur, the PF tumour population may be heterogeneous regarding the factors capable of influencing facial emotion recognition abilities. As a result, associations that underlie facial emotion recognition deficits in one subgroup of patients may not be directly relevant to another subgroup of patients. If this is indeed the case, it may be more challenging to detect an association between WM and facial emotion recognition at a group-wide level in patients treated for PF tumours. Finding that medical variables predicted facial emotion recognition abilities in children treated for PF tumours, and that this composite included treatment intensity and complications, lends support to this possibility.

The absence of an association in a clinical group, when it is detected in a typically developing control group, has been documented previously; for example, a recent study by Young and colleagues (2018) found no association between DTI metrics and neurodevelopmental outcomes in children born very preterm, whereas FA was associated with intellectual outcome in term-born children. In discussing potential reasons for their findings, the authors indicate that children born very preterm had more variable DTI and outcome measures (Young et al., 2018); this type of variability is often observed in the brain tumour population as well, and could help explain the lack of an association. Namely, the extent of WM damage, and intellectual outcome measures, may vary considerably among brain tumour survivors according to their age at treatment, how intensely they were treated, and whether postsurgical complications were experienced.

On the other hand, it is possible for a brain-behaviour association to be observed exclusively in a clinical population. This thesis detected an association between WM microstructure of the splenium of the corpus callosum and emotion regulation in children treated for PF tumours, yet this association was absent in controls (Chapter 4). A handful of studies have documented similar phenomena. For instance, Dennis and colleagues (2016) found evidence of a negative relation between reaction time measures and several brain regions, including the corpus callosum (CC), in children with spina bifida myelomeningocele (SBM) yet not controls; the authors suggested this association was functionally significant as the CC is consistently abnormal in
SBM, and because reaction time is important for numerous cognitive tasks. In a longitudinal study, Treit and colleagues (2013) documented that greater MD reductions in the superior longitudinal and superior occipital fasciculi were associated with larger reading performance gains in children with fetal alcohol spectrum disorders (FASD), yet no association was found in controls; the authors suggest that changes to MD in these tracts are functionally relevant in FASD.

Detecting a brain-behaviour association in a clinical group, and not in a control group, may provide different information than when the association is reversed. Given the previously mentioned heterogeneity and complexity of insults to the brain sustained by patients treated for PF tumours, detecting an association in a clinical group may speak to its robustness or functional relevance. Of note, corpus callosum damage is ubiquitous in PF tumour patients; altered microstructure of the corpus callosum has been previously documented (Liu et al., 2015; Mabbott et al., 2006; Moxon-Emre et al., 2016; Palmer et al., 2012; Rueckriegel et al., 2010), and was detected in both the surgery and radiation groups throughout this thesis. Consistent alterations to WM in the corpus callosum may allow for deficits that are associated with corpus callosum dysfunction to be detected more readily. Moreover, perhaps unlike what was proposed for facial emotion recognition abilities, damage to other brain regions and post-surgical complications in children treated for PF tumours may not influence performance on this task, rendering this association easier to detect as a result.

It is also important to consider the meaningfulness of the directionality of DTI indices when associations with behavioural outcomes are detected. Given that lower FA and higher MD, AD and RD have been shown to reflect myelin sheath damage and axonal degeneration (Beaulieu, 2002; Song et al., 2002), lower FA is though to reflect WM damage. Throughout this thesis, FA within the corpus callosum was consistently lower in the patient groups compared to the control group. Within the context of this lower group-wise FA in patients, an increase in FA within the splenium of the corpus callosum was associated with worse performance on the eye-tracking emotion regulation task. This is a surprising finding if higher FA is exclusively assumed to reflect less WM damage, as it would suggest that patients who have less damage to the splenium are better able to perform the emotion regulation eye-tracking task. However, it is important to consider that diffusivity can be influenced by various aspects of brain structure, including axon coherence, membrane permeability, cell density and water content (Beaulieu, 2002). It is thus
possible for FA to be confounded by factors that do not reflect WM microstructure; a phenomenon that may be particularly relevant for DTI indices obtained from a population that sustained brain injury. Furthermore, higher FA has not exclusively been associated with better behavioural performance on social cognition tasks, and linearly relating FA to behavioural performance has been cautioned against as a result (Wang et al., 2018).

Taken together, it is possible that the meaning of a brain-behaviour association detected in one group and not another, may depend on whether the association is found the clinical group or in the typically developing control group, and on the broader context of brain pathology experienced by the clinical group. A possible approach for probing brain-behaviour associations that may be muted in clinical populations is detailed in section 5.3.

5.1.3 Methodological: evaluating emotional functioning with eye-tracking

Research into emotional functioning of children treated for PF tumours has typically relied upon self- or parent-report measures, which as detailed in Chapter 1, have limitations; they were not designed for use in a clinical population and they lack objectivity. To begin overcoming these limitations, this thesis utilized eye movement monitoring during two tasks designed to evaluate components of emotional functioning: a facial emotion recognition task and an emotion regulation task. Eye-tracking technology is being used increasingly in developing and psychiatric populations (Armstrong & Olatunji, 2012; Karatekin, 2007). Its power lies in its ability to shed light on processes, governed by brain function, which cannot be gleaned by self- or parent-report measures.

This thesis provided direct evidence that eye-tracking is feasible in children treated for PF tumours; Chapters 3 and 4 represent the first two studies that utilized eye-tracking technology in this clinical population. Given the role of the cerebellum in oculomotor function, in particular the flocculus/paraflocculus for gaze holding, and the dorsal oculomotor vermis for saccades (Kheradmand & Zee, 2011), it is not surprising that patients treated for PF tumours can suffer from ocular motor abnormalities such as nystagmus and strabismus (Peeler et al., 2017). As a result, it was occasionally more challenging to calibrate the eye-tracking system in patients, using the standard 9-point grid prior to the start of the experiment. Namely, the spatial resolution of fixations were sometimes less precise than in typically developing children; however, the system could still be calibrated, and the eyes tracked reliably as a result. That a single eye was
used for tracking helped overcome this technical challenge, as patients often had one eye that was easier to track than the other. Moreover, the eye-tracking tasks used in this thesis were designed with the expectation of such challenges in mind. For instance, ROIs that were used to determine whether a fixation was made to a particular image were deliberately kept large, so that small differences in spatial resolution would not influence the results. Detailed spatial analyses, such as evaluating attention to specific features within the face would have been more challenging with less accurate calibrations, and were not attempted in this thesis as a result.

A range of information of varying complexity can be gleaned from eye-tracking studies. Chapter 3 utilized a basic function of this technology to ensure that participants attended to the stimuli in the task; in this way, results from the facial emotion recognition task could be interpreted with the confidence that stimuli were attended. Chapter 4 on the other hand, capitalized on the detailed information that can be obtained from eye-tracking, in order to deconstruct a process of controlling eye-movements during an emotion regulation task.

The emotion regulation task designed and tested in Chapter 4 built on a task that evaluated eye-movements to emotional stimuli (Nummenmaa et al., 2006). Nummenmaa and colleagues (2006) showed participants emotional and neutral images (scenes), side-by-side, and found that the emotional image consistently captured attention, even when participants were instructed to look at the neutral scene only. Although similar in theoretical design, the task used in this thesis differed from the task used in Nummenmaa and colleagues (2006) in several notable ways. First, by presenting the same actor displaying different emotions side-by-side, the possibility for featural differences in the images to influence attention was removed. Although Nummenmaa and colleagues (2006) controlled for the complexity and luminance of their images, the only way to fully remove the potential for viewing biases is to use two images that are identical. This fundamental difference in the tasks may partially explain why healthy controls in our task could regulate their initial attention away from the emotional face when instructed to, whereas this was not the case in their study (Nummenmaa et al., 2006). Second, by using images of children and adults of various ethnicities, potential biases in viewing patterns based on age and ethnicity (Elfenbein & Ambady, 2002) were minimized. Third, several steps were taken to ensure that the task was carefully controlled; namely, the positioning of faces were counterbalanced and faces were warped to be identical in size and position. Collectively, these measures ensured that any differences in viewing could be directly attributed to the expression of the face.
It is well documented that emotional stimuli capture attention (reviewed in Carretie, 2014); results from Chapter 4 provided the first evidence that children treated for PF tumours are no exception in this regard. That emotional faces captured attention in patients treated for PF tumours suggests the automatic emotion regulation component, where emotionally arousing stimuli are encoded without awareness (Gyurak et al., 2011), continues to occur in an obligatory manner in this clinical population. Results from this study thus raise the possibility that the coordinated set of processes that underlie this automatic response is unaffected by treatment for PF tumours. It is notable however, that children in the radiation group made slower eye-movements overall, suggesting the presence of underlying differences, perhaps with processing speed; however, within the context of their slower eye-movements, their pattern of responding paralleled that of the other groups.

In contrast, results from Chapter 4 revealed that the deliberate control over the earliest component of the visual response was impaired in children treated for PF tumours. That this response occurred within the first few hundred milliseconds highlights the value of deconstructing the time course of a response. It is particularly noteworthy that this early eye-tracking measure was associated with emotional control, across all children. That the earliest components of eye-movements to emotional stimuli can be related to complex behaviour in daily life has powerful implications, and suggests there is a direct relationship between emotion regulation and attentional processes. In fact, it has been proposed that affect-biased attention is a fundamental component of emotion regulation (Todd et al., 2012; Wadlinger & Isaacowitz, 2011). Notably, Todd and colleagues (2012) developed an extended model of emotion regulation that was built upon the dual-process model detailed in Chapter 1; the authors argue that the unfolding of cognition-emotion interactions in real time, over milliseconds to minutes, and throughout development more broadly, involves increasingly effortful strategies to reprocess information from responses that may initially be rapid and habitual (Todd et al., 2012). From this viewpoint, affect-biased attention precedes the evaluation of events and regulation of responses, and consequently both shapes, and is shaped by, reprocessing of emotional information (Todd et al., 2012). That our emotion regulation eye-tracking task of attention to emotional stimuli detected an implicit emotion regulation response, and demonstrated that ability to regulate this response was correlated with behaviour in daily life, lends support to the importance of affect-biased attention in emotion regulation, as proposed by Todd and colleagues (2012).
The work presented in Chapters 3 and 4 of this thesis represent the first objective evaluations of emotional functioning in children treated for PF tumours. By demonstrating that eye-tracking is feasible in this clinical population, and that it can be used to detect subtle differences in emotion regulation, indicates this technology may have tremendous utility in children treated for PF tumours. For instance, by helping to uncover how a process unfolds in real time, it has the potential to provide unparalleled information for designing effective interventions to improve functioning. Potential approaches for the development of interventions will be discussed in section 5.3. Although the emotion regulation task developed and tested in Chapter 4 was designed to evaluate emotion regulation in children treated for PF tumours, its foundation is based on fundamental principles of emotion regulation that are not unique to PF tumour patients, and may have utility beyond the brain tumour population as a result; namely, for typically developing children who may be at risk for emotional problems, and/or for a variety of children with neurodevelopmental and psychiatric conditions that may have limited self-insight and that may not have the capacity or willingness to communicate verbally.

5.2 Challenges: study limitations

There are several limitations to the work presented in this thesis that warrant discussion. A limitation across Chapters 2, 3 and 4 is that these studies were cross-sectional, and therefore cannot provide information about changes over time, or insights into how current deficits influence future functioning. For instance, although WM sparing was documented in children treated with the lowest radiation intensity protocol (Chapter 2), this was characterized by demonstrating that WM did not differ from typically developing controls; however, because pre-treatment MRI scans were not acquired as part of this study, it is not possible to determine whether WM microstructure within these ‘spared regions’ of individual patients remained unaltered following treatment. Moreover, although emotional functioning deficits were observed in children treated for PF tumours, their cognitive, social and affective functioning were within normal limits (Chapters 3 and 4). It is certainly possible that current emotional functioning deficits could negatively influence social and affective functioning at a later date, especially given that the dynamics and demands of social relationships change over adolescence and adulthood, and that social factors have been shown to be involved in both the pathogenesis and consequences of affective disorders (Kupferberg, Bicks, & Hasler, 2016). Moreover, given that treatment with the least intensive CSI protocol reflects a relatively recent treatment change,
literature on adult survivors of children treated with this protocol has yet to emerge; it is currently unknown if they will experience fewer deficits than adult survivors reported on to date.

Another limitation relevant to Chapters 2, 3 and 4, and to research conducted with children treated for rare medical disorders more broadly, is the challenge associated with recruiting a large and homogenous sample size. For instance, patients treated with radiation for PF tumours included in this thesis received different dose and boost volume combinations according to when they were treated, and whether they were diagnosed with medulloblastoma or ependymoma; both receive radiation, but differ in that ependymoma patients only received focal radiation to the tumour site. Furthermore, patients treated for pilocytic astrocytoma serve as an ideal control group because they do not receive radiation; however, as some patients received chemotherapy, outcomes in this group could not be attributed to surgery alone. The within-group heterogeneity is further exacerbated by the array of medical and post-surgical complications known to influence functional outcomes, such as mutism and hydrocephalus. Further subdividing each patient group into those that did and did not experience such complications was unfortunately not possible with the sample size recruited in this thesis. Moreover, because the surgery and radiation groups in Chapters 3 and 4 did not differ in any of their WM indices, or in their emotional functioning, they were grouped together for analyses to evaluate brain-behaviour relations. With larger sample sizes, this approach would have been avoided.

A limitation restricted to Chapter 2 was that MRI data were acquired from two different scanners, one at 1.5T and the other at 3T. It has been suggested that using both 1.5T and 3T data together does not compromise the validity of group analyses (Han & Talavage, 2011); however, given that the signal-to-noise (SNR) is increased, and that the partial volume effect is reduced, meaning there is a decrease in the signal constituting a mixture of signals from different tissue types, at 3T compared to 1.5T (Voss, Zevin, & McCandliss, 2006), combining data from mixed field strengths is not ideal. As a result, scanner was included as a covariate in all analyses, and groups were matched as best as possible for the number of children scanned with each. For Chapters 3 and 4, a decision was made to only include data from the 3T scanner. However, it is noteworthy that children in the radiation group in Chapters 3 and 4, comprised mostly of children treated with reduced dose CSI and a boost to the tumour bed, had (qualitatively) comparable patterns of WM compromise to patients treated exclusively with this protocol in Chapter 2;
suggesting that utilizing data acquired from two different scanner strengths did not alter the ability to detect WM compromise.

As detailed in section 5.1.1, patients had preserved cognitive function, and controls had superior functioning. However, because characterizing intellectual functioning was not the focus of this thesis, a brief measure was used, and it is important to consider the limited interpretability of results acquired with such an approach. Specifically, the two-subtest IQ from the Wechsler Abbreviated Scale of intelligence (WASI-II; Wechsler, 2011) was used to assess intellectual functioning; the two subtests include vocabulary and matrix reasoning. The vocabulary subtest measures word knowledge and degree of language development, and the matrix reasoning subtest measures spatial ability and perceptual organization. Although correlations between the WASI-II and other IQ measures including the full scale IQ acquired from the complete Wechsler Intelligence Scale for Children (WISC-IV) range from acceptable to excellent (McCrimmon & Smith, 2012), it lacks the sensitivity to detect the full range of possible deficits experienced by children treated for PF tumours. For instance, processing speed and working memory measures are not included, and children treated for PF tumours have documented deficits in both these domains (Conklin et al., 2012; Law et al., 2011; Mabbott et al., 2008; Moxon-Emre et al., 2014).

It should also be noted that the eye-tracking emotion regulation task developed and implemented in Chapter 4 did not include an equivalent condition with non-emotional stimuli. Previous studies have shown that different brain regions are activated during emotional and non-emotional versions of conflict tasks that are based on the Stroop paradigm (Gyurak et al., 2011), indicating that inhibitory control of emotional and non-emotional content are processed differently in the brain. It is certainly possible that the eye-tracking emotion regulation task captured a response specific for emotional content; however, in the absence of a direct comparison to a non-emotional version of this task, the possibility that a similar response patterns (e.g., attentional capture) would have been detected using non-emotional content cannot be ruled out.

5.3 Opportunities: suggestions for future research

This thesis provides several opportunities for future research into WM and emotional outcomes in children treated for PF tumours.
First, given that WM microstructure of the temporal lobe was spared in children treated for medulloblastoma with the lowest intensity CSI protocol (Chapter 2; Moxon-Emre et al., 2016), and that preserved intellectual functioning was documented in a separate cohort of patients treated with this protocol (Moxon-Emre et al., 2014), future studies should evaluate if there is a direct relationship between the two findings; this could be achieved by combining DTI, radiation dosimetry and cognitive data. Using path analyses, this combination of data could help clarify if WM sparing of the temporal lobe, as a direct result of lower radiation exposure, contributes to preserved intellectual outcome in children treated the lowest intensity CSI protocol.

Second, the emotional functioning deficits detected in children treated for PF tumours warrant further investigation; such research is needed to better understand why these deficits arise, and to develop strategies to overcome them.

Future studies are required to better understand the factors that contribute to facial emotion recognition deficits. Although children treated for PF tumours attended to the photographs during the facial emotion recognition task, it is noteworthy that the photographs were only shown for two seconds. It is possible that accuracy would have increased had the photographs remained on the screen for a longer time, or indefinitely, until a response was selected. Manipulating the photograph presentation time would be a straightforward yet revealing way to evaluate if the relatively short timing contributed to their worse performance. It is certainly possible that children treated for PF tumours require more time to decode facial emotions than typically developing children, especially in light of their documented processing speed deficits (Mabbott et al., 2008; Moxon-Emre et al., 2014); to directly evaluate this, future studies would benefit from including a measure of processing speed to relate to performance on this task. It is also noteworthy that children treated with radiation made slower eye-movements (Chapter 4), thus the speed with which they scan the images may have also influenced their performance. Moreover, for reasons mentioned in section 5.1.3, detailed spatial analyses of viewing patterns to specific regions of the face were not assessed. If the facial stimuli were made considerably larger, such analyses could be performed reliably. However, the photograph sizes were kept identical to the original task so that results could be directly comparable to previous studies that have utilized this task in children treated for brain tumours (Bonner et al., 2008; Willard et al., 2009). Furthermore, it is notable that medical variables, consisting of treatment type, intensity and complications, directly predicted facial emotion recognition deficits. Future studies with
larger sample sizes will be required to directly assess the impact of treatment and post-surgical complications on facial emotion recognition abilities. For instance, it would be interesting to evaluate if damage to the vermis, or the development of mutism, directly predict facial emotion recognition difficulties.

To better understand emotion regulation in children treated for PF tumours, additional studies are required to further validate the task, and to better understand the neural circuitry associated with performance on this task. As mentioned in section 5.2, a non-emotional control task was not included in the eye-tracking emotion regulation paradigm. Future studies should consider including such a comparison to clearly demonstrate that this task is specific for emotional content. It would also be important to validate this task in other clinical populations that experience emotion dysregulation, to determine if this task is a broadly applicable behavioural marker of emotion regulation. In addition, novel statistical approaches, such as machine learning, would be helpful in determining whether this task is capable of reliably classifying and predicting those children with poor emotion regulation, rather than relying on correlational analyses.

Given that eye-movements, and emotion regulation more broadly, are governed by brain function, future work would benefit from conducting this task with concurrent neuroimaging techniques that provide a temporal component and functional connectivity measures, such as function MRI (fMRI) and magnetoencephalography (MEG). For instance, it would be valuable to characterize the neural circuits involved during implicit emotion regulation, which was unimpaired in children treated for PF tumours, and to explicit emotion regulation, where deficits were detected. In this way, the neural regions/systems that are responsible for driving eye-movement behaviours during both conditions could be evaluated, and differences between the populations that underlie these outcomes could be characterized more thoroughly. That the splenium of the corpus callosum was associated with emotion regulation in children treated for PF tumours only, suggests the underlying neural circuitry may differ from typically developing children. Furthermore, combining such neuroimaging approaches with the inclusion of a non-emotional variant of this task would help solidify the neural specificity of this task for detecting the regulation of emotions.
Moreover, as discussed in section 5.1.2, it can be a challenge to detect and evaluate brain-behaviour relations in heterogeneous clinical populations. To overcome this, novel data-driven approaches are increasingly being used in such populations as schizophrenia spectrum disorders (SSDs) and autism spectrum disorders (ASDs) (Stefanik et al., 2018). For instance, similarity network fusion (SNF) is a data-driven approach that clusters individuals based on their brain imaging and behaviour data profiles, rather than grouping based on diagnoses (Wang et al., 2014). Such an approach may be worthwhile to consider in the brain tumour population; it may help reveal associations that are muted by the heterogeneity resulting from differences in the tumour itself, its treatment, and any associated complications.

In addition to providing novel information about emotional functioning, this thesis provides the foundation for interventional studies to improve emotion regulation in children treated for PF tumours. Several intervention programs have been applied and investigated in children treated for cancer; these included pharmacologic treatments to improve attention, nonpharmacologic rehabilitation programs to improve behavioural skill acquisition, and physical activity approaches to promote neuroplasticity (reviewed in Krull et al., 2018). The eye-tracking emotion regulation task detailed in Chapter 4 revealed differences in the real-time regulation of attention to emotional stimuli that may contribute to poor emotional control in daily life. As such, intervention programs designed to improve attentional control to emotional stimuli may have positive effects on behaviour. Attention training has been proposed as a valuable technique to improve emotion regulation; although attentional training methods require effort to acquire initially, it has been suggested that repeated practice of attentional processes may become automated over time, and eventually require less effort to execute (reviewed in Wadlinger & Isaacowitz, 2011). Thus, an intervention program designed to train the control of initial attention away from emotional faces may enhance control over this process. Similarly, given that working memory capacity has been associated with the ability to override attentional capture (Fukuda & Vogel, 2009), it may be worthwhile to evaluate if recently developed intervention programs designed to improve working memory in children treated for brain tumours (Conklin et al., 2017; Conklin et al., 2015) can lead to improvements in the eye-tracking emotion regulation task tested in Chapter 4. Another type of intervention training that has yielded positive effects on emotion regulation is mindfulness training (Kaunhoven & Dorjee, 2017; Wadlinger & Isaacowitz, 2011). Mindfulness combines the self-regulation of attention with an accepting orientation towards
current moment experiences (Bishop et al., 2004). It has been suggested that mindfulness training may enhance emotion regulation and executive control in children with self-regulatory difficulties by altering neural activity; for example, training may influence the N2 event related potential (ERP) amplitude, a component of response inhibition commonly measured during tasks involving inhibition of a pre-potent response (reviewed in Kaunhoven & Dorjee, 2017). Mindfulness training may represent a non-invasive way to harness neural systems that improve emotional control in children treated for PF tumours. It would be valuable to evaluate children treated for PF tumours on the eye-tracking emotion regulation task prior to, and following attentional, working memory and mindfulness based interventions.

5.4 Concluding remarks

The present thesis represents the first account of combining DTI, eye-tracking and standardized measures of cognitive and emotional functioning in children treated for PF tumours, to characterize outcomes related to decreasing treatment intensity, and to objectively evaluate their emotional functioning. This powerful convergence of methods has yielded several novel findings and contributions. Namely, treatment with the least intensive CSI protocol is associated with better WM, affective and cognitive outcomes, but subtle deficits in emotional functioning persist. Moreover, it is now known that eye-tracking can be used to objectively evaluate emotional functioning in children treated for PF tumours. Children treated for PF tumours have difficulty with facial emotion recognition and the early attentional component of emotion regulation. The work presented in this thesis has laid the foundation for future studies to better understand why these deficits persist, and to the development of interventions to overcome them. Although the future is certainly brighter for children who are diagnosed and treated for PF tumours today, some challenges remain and there are still gains to be made. Future research into emotional functioning in children treated for PF tumours would benefit from a combination of carefully constructed objective measures to evaluate how emotional processes are altered in real-time, followed by the development of intervention programs designed to target altered processes. This thesis detailed one such objective measure of emotion regulation, and detected an oculomotor response that may warrant interventional follow-up. Hopefully the work presented in this thesis will serve to motivate and inspire researchers who work with children treated for brain tumours to build upon this work to further improve their quality of life.
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Supplementary Figure 4.1 Attentional orienting to emotional faces

**a** and **b**. Boxplots showing all data points with the mean (white diamond) and median (black line) for the **a** time to first fixation, and **b** probability of first fixation to the **i** angry vs. neutral face, the **ii** happy vs. neutral face, and the **iii** sad vs. neutral face in the baseline (top panel) and regulate (bottom panel) conditions.
Supplementary Figure 4.2 Attentional engagement of emotional faces

a-b. Boxplots showing all data points with the mean (white diamond) and median (black line) for the (a) number of fixations, and (b) dwell time to the i. angry vs. neutral face, the ii. happy vs. neutral face, and the iii. sad vs. neutral face in the baseline (top panel) and regulate (bottom panel) conditions, over the course of the full trial (5 seconds).

Note: although patients in the radiation group made fewer fixations than healthy controls and patients in the surgery groups, during both the baseline and regulate conditions, they did not differ in their dwell times, indicating they spent equivalent time viewing the faces despite making fewer fixations.