

Neuropsychological Comparison of Pediatric Medulloblastoma and Pilocytic Astrocytoma: Existing Knowledge and Future Directions

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This paper reviews existing knowledge regarding neuropsychological late effects of pediatric medulloblastoma and cerebellar pilocytic astrocytoma, with the goal of highlighting areas for future research. Comparison of these two tumors, which occupy the same region of the brain, is arguably the ideal method for researching the late effects of craniospinal radiation, as medulloblastoma patients receive radiation, while cerebellar pilocytic astrocytoma patients do not. Such comparative research, which has yet to be extensively conducted, has the potential to enhance targeted neuropsychological interventions and help neuro-oncologists make treatment decisions regarding use, frequency, duration, and dose of radiation. A discussion of cognitive fluency is included, detailing the importance of researching this overlooked construct in these two tumor groups. Existing knowledge of differential processing speed deficits in these populations, which appears to be strongly related to administration of craniospinal radiation, provides a rationale for such investigation.

Keywords: medulloblastoma, pilocytic astrocytoma, neuropsychological late effects, cognitive fluency, craniospinal radiation, executive function, cognition

Brain tumors are the second most common form of cancer during childhood, accounting for 16.6% of all cancers diagnosed among children younger than 15 years old (Gurney, Wall, Jukich, & Davis, 1999; Horner et al., 2009). In the United States, an estimated 2,900 children and adolescents are diagnosed with a brain tumor annually (Horner et al., 2009). Although tumors in the posterior fossa (PF) area comprise less than 1% of all adult brain tumors (Hubbard et al., 1989), they account for two-thirds of all brain tumors in children (George et al., 2003). Posterior fossa refers to the cerebellum and brain stem area, near the base of the skull. Common PF tumors include pilocytic astrocytoma (PA) and medulloblastoma (MB). Standard of care for PF tumors depends primarily on histopathological diagnosis of tumor type. Treatment options generally include surgery, radiation, and chemotherapy (Evans et al., 1990).

Late effects of cancer and its treatment are defined as any medical, psychological, or cognitive effects developing months or years following diagnosis. There is a broad, long-term, neurocognitive impact of PF tumors, with deficits in areas ranging from language to executive functioning (Arsen et al., 2009;

Butler & Haser, 2006; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Palmer, 2008; Palmer & Leigh, 2009; Palmer, Reddick, & Gajjar, 2007; Reeves et al., 2006; Riva & Giorgi, 2000; Steinlin et al., 2003; Vaquero, Gomez, Quintero, Gonzalez-Rosa, & Marques, 2008; Zuzak et al., 2008). Some studies have noted a cumulative progression of these late effects starting with deficits in processing speed, followed by memory and attention deficits, then visuospatial difficulties, and finally deficits in abstract thought and vocabulary (Palmer, 2008; Garcia-Perez, Sierrasesumaga, Narbona-Garcia, Calvo-Manuel, & Aguirre-Ventillo, 1993). These late effects impact academic performance. Indeed, one study found that although 60% of PF tumor patients were in need of special education programs, only 26% were actually enrolled in such programs (Hoppe-Hirsch et al., 1995).

Neuropsychological comparison of childhood MB survivors and cerebellar PA survivors is arguably the ideal method for researching the late effects of craniospinal radiation. These two groups share a tumor site, the posterior fossa, and both undergo medical treatment involving surgery and chemotherapy.

However, standard of care for MB also involves craniospinal radiation, whereas this is not the case for cerebellar PA, making the latter an ideal control group. Since there are few significant, long-term cognitive effects associated with chemotherapy (Ahles & Saykin, 2007; Reddick et al., 2005; Rutkowski et al., 2005), studies comparing the two groups have the potential to reveal cognitive effects specific to craniospinal radiation with a relatively high degree of confidence. Such research, which has yet to be extensively conducted, could not only greatly enhance understanding of the neuropsychological outcomes of craniospinal radiation but also help neuro-oncologists make treatment decisions regarding use, frequency, duration, and dose of radiation.

Medulloblastoma

Approximately 20% of all pediatric brain tumors are medulloblastomas, making them the most common brain tumor in children (Blaney et al., 2006; Gottardo & Gajjar, 2006). MBs are typically comprised of poorly differentiated epithelial cells arising from the fourth ventricle (Ris & Abbey, 2010). “Standard-risk” MB describes such a tumor occurring in children older than 3 years, with near total resection, and no evidence of dissemination, which is often a precursor to metastasis (Ris & Abbey, 2010).

Acute symptoms of MB typically include headaches and vomiting due to increased intracranial pressure, as well as gait disturbances due to the cerebellum’s role in motor functions. Identification of the tumor is conducted by CT scan or MRI. Standard of care is surgical resection coupled with craniospinal irradiation and chemotherapy (Evans et al., 1990).

Due to the use of radiation and chemotherapy in treating MB, the five-year survival rate has improved from around 0–10% to 70–85% (Palmer, 2008). Simultaneously, increased awareness of the myriad neurocognitive late effects of radiation has led to efforts to reduce the standard radiation dose in treating MB. Despite these efforts, the majority of children treated for MB still show a wide range of moderate to severe cognitive, academic, and psychosocial deficits.

Risk Factors

Several variables that represent risk factors for worse neurocognitive and psychosocial outcome from pediatric MB have been identified. Younger age at diagnosis is the most widely documented risk factor (Dennis, Spiegler, Hetherington, & Greenberg, 1996; George et al., 2003; Hoppe-Hirsch et al., 1990; Kao et al., 1994; Kimmings, Kleinlugtebeld, Casey, & Hayward, 1995; Palmer, 2008; Radcliffe, Bunin, Sutton, Goldwein, & Phillips, 1994; Ris & Abbey, 2010; Silverman et al., 1984; Todd & Ruge, 1999). This may be due to the fact that radiation interferes with neuronal development, consequently impacting less developed brains more severely (Monje, Mizumatsu, Fike, & Palmer, 2002). Additionally, the effects of the tumor and resection may impact younger children more severely because, according to the vulnerability theory, they have less developed basic skills and thus face a greater challenge in developing further cognitive abilities (Mitby et al., 2003). However, Levisohn, Cronin-Golomb, and Schmahmann (2000) saw fewer cognitive and affective deficits in younger children among their sample. They offer that this may be due to either neural plasticity, lack of sensitivity in testing, or the fact that the functional domains in which older children show deficits are not significantly developed until at least age 7.

While males are diagnosed with MB at almost twice the rate as females (Gottardo & Gajjar, 2006; Horner et al., 2009), some studies have suggested that female MB survivors are at higher risk for worse neurocognitive outcomes (Butler & Haser, 2006; Nagel et al., 2004; Palmer et al., 2007; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001). Other studies, however, have failed to replicate this finding (Hardy, Bonner, Willard, Watral, & Gururangan, 2008; Mabbott et al., 2005, 2008; Maddrey et al., 2005). Other risk factors for poor neurocognitive outcome include low socioeconomic status and high stress levels (Palmer, 2008), postoperative complications (Maddrey et al., 2005), and hydrocephalus (Hardy et al., 2008; Kao et al., 1994).

Pilocytic Astrocytoma

Approximately 10–20% of all pediatric brain tumors (Hildebrand & Baleriaux, 2002) and 30–40%

of all PF tumors (Packer, Friedman, Kun, & Fuller, 2002) are cerebellar pilocytic astrocytomas, making them the second most common cerebellar tumor in children. About 80–85% of cerebellar astrocytomas are pilocytic, so called because when viewed under a microscope, the tumor cells appear fibrous (Cohen & Duffner, 1994).

Like MB, acute symptoms of cerebellar PA typically include headaches, vomiting, and gait disturbances, and tumor identification is conducted by CT scan or MRI. Standard of care is surgical resection (Hildebrand & Baleriaux, 2002). Since cerebellar PAs are less invasive than MBs, radiation and chemotherapy are generally unnecessary, and approximately 90–95% of children require no further treatment post-surgery (Cohen & Duffner, 1994; Packer et al., 2002).

With a 10-year survival rate of 94% (Callu et al., 2009), PAs have the best medical prognosis of any pediatric intracranial tumor. Although radiation and chemotherapy are not standard of care for cerebellar PA, as for MB, survivors of PA also show a wide range of cognitive, academic, and psychosocial deficits (Cohen & Duffner, 1994; Hildebrand & Baleriaux, 2002).

Risk Factors

As with MB, younger age at diagnosis represents the strongest risk factor for worse neurocognitive and psychosocial outcomes from PA (Aarsen et al., 2009; Mitby et al., 2003; Taylor & Alden, 1997). A possible explanation for this is provided by vulnerability theory, which states that the effects of the tumor and surgical resection may impact younger children more severely because they have not learned as many basic skills and thus face a greater challenge in developing further cognitive abilities (Mitby et al., 2003). Neuropsychological functioning appears to worsen with increased time since diagnosis, likely due to the fact that these children “grow into” functional deficits (Aarsen et al., 2006, 2009). That is, their deficits do not become plainly evident until they progress further in school and are expected to perform at a higher cognitive level. However, other studies have failed to find a relationship between neuropsychological functioning and age at diagnosis,

as well as gender, ethnicity, and parental education of pediatric cerebellar PA survivors (Ater et al., 1996; Beebe et al., 2005; Mabbott et al., 2008; Ronning, Sundet, Due-Tonnessen, Lundar, & Helseth, 2005; Sherwood et al., 2010).

With regard to tumor-related variables, most studies indicate that there is no correlation between tumor location and neurocognitive outcomes (Aarsen, Van Dongen, Paquier, Van Mourik, & Catsman-Berrevoets, 2004; Beebe et al., 2005; Daszkiewicz, Maryniak, Roszkowski, & Barszcz, 2009). Aarsen and colleagues (2004) also noted that there seem to be no lateralization effects, suggesting that the lateralization of cerebro-cerebellar pathways may not be fully developed in young children. However, some studies have found location-specific effects, particularly indicating that PAs affecting the cerebellar vermis result in permanent neurological deficits (e.g., paresis, ataxia, epilepsy) and emotional dysfunction (Daszkiewicz et al., 2009; Levisohn et al., 2000; Riva & Giorgi, 2000). Larger residual tumor size appears to be correlated with worse cognitive outcomes (Aarsen et al., 2009). Pre-operative hydrocephalus severity (but not duration) may be associated with worse visuospatial skills post-treatment (Aarsen et al., 2004).

Comparison of Neuropsychological Late Effects

Intellectual Functioning

Many studies have found that childhood MB survivors have worse intellectual outcomes than childhood PA survivors, likely due to the non-linear decline in IQ associated with cranial radiation (Fuss, Poljanc, & Hug, 2000; Hoppe-Hirsch et al., 1995; Kieffer-Renaux et al., 2005; Lafay-Cousin et al., 2009; Palmer et al., 2003; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004). Spiegler et al. (2004) explain that losses of 2 to 4 points in IQ scores appear to occur annually in radiated PF (i.e., MB) patients, although the losses are generally steeper in the first few years after radiation. In contrast, Steinlin and colleagues (2003) found that PA survivors performed within normal limits on measures of verbal, performance, and full-scale IQ (FSIQ), replicating the finding of Riva, Pantaleoni, Milani,

and Belani (1989). Additionally, Copeland, Demoor, Moore, and Ater (1999) found that the verbal IQ of survivors of cerebellar PA does not appear to decline over time. Another study has suggested that verbal IQ may be more impaired than performance IQ in this population, contrary to the general findings for MB survivors (Reimers et al., 2003), however, this study also reported that the mean FSIQs of non-irradiated benign tumor (i.e., PA) patients were well within the normal range.

In terms of the dose-effect relationship, Kieffer-Renaux et al. (2005) found that patients treated with focal PF radiation alone did not demonstrate declines in IQ, whereas patients receiving full craniospinal radiation of varying dosages all displayed progressive intellectual deficits over a four-year period. In contrast, Grill et al. (1999) indicated that at one year post-radiation, most pediatric PF patients displayed long-term cognitive impairment, even after focal PF radiation alone, with a significant correlation between the FSIQ and the dose of cranio-spinal irradiation. The differences between the findings of these two studies are most likely an artifact of small sample sizes, and this limitation leaves both findings in question. Clarifying the dose-effect relationship, a study with a much larger sample size showed that at 10-year follow-up only 10% of full-cranial irradiated MB patients had an FSIQ above 90, whereas 60% of PF-only radiated ependymoma patients met this criterion (Hoppe-Hirsch et al., 1995). It is generally accepted that, at equal dose levels, partial brain radiation is less damaging than whole brain radiation. However, Mabbott et al. (2005) found that academic and behavioral outcomes were not related to radiation dose, extent of surgery, or treatment with chemotherapy. This contradictory finding, though unexplained by the researchers, is further evidence of the need for comparative research examining the long-term effects of radiation on developing brains.

Age at time of radiation treatment has a well-established role in determining cognitive outcomes: the younger the child, the more pronounced the decline in intellectual ability as a result of radiation. In general, there appears to be a steeper decline both for patients with higher baseline IQ and for younger patients (George et al., 2003; Hoppe-Hirsch et al.,

1990; Palmer et al., 2003; Radcliffe et al., 1994; Reimers et al., 2003; Ris et al., 2001; Roncadin, Dennis, Greenberg, & Spiegler, 2008). For children younger than age 8 at diagnosis, intellectual deficits may be immediate, whereas older children's deficits may appear only after a two-year delay (Palmer et al., 2003).

Academic Performance

Although survivors of childhood MB display limited awareness of their cognitive deficits, self-reports regarding their academic performance are often accurate (Maddrey et al., 2005, O'Donnell, De Soto, & De Soto, 1993). This may be due to earning poor grades, feedback from parents, or awareness of being enrolled in special education programs. Likely related to declines in IQ and other cognitive functions, survivors of childhood MB exhibit significant declines in academic performance (Dennis et al., 1996; Palmer et al., 2001; Palmer et al., 2007; Ris et al., 2001). Children who receive cranial radiation, such as MB patients, are seven times more likely to require special education services compared to survivors of childhood cancers who do not receive cranial radiation, such as PA patients (Mitby et al., 2003; Palmer, 2008). Ten years after diagnosis, 80% of MB survivors may require special education services (Hoppe-Hirsch et al., 1995). Furthermore, survivors of childhood MB are significantly less likely than their healthy peers to finish high school (Mitby et al., 2003). Despite these statistics, the academic functioning of this population has not been adequately studied.

Limited research in the realm of academic achievement testing with pediatric MB survivors shows that these children display deficits in reading, spelling, and mathematics (Beebe et al., 2005; Mabbott et al., 2005; Mulhern et al., 2005; Reeves et al., 2006). Furthermore, even when accounting for declines in IQ, survivors of childhood MB exhibit significant continuing declines in spelling and arithmetic at a mean of five years post-diagnosis (Mabbott et al., 2005). Declining parent and teacher ratings of academic ability corroborate the ecological validity of these findings (Mabbott et al., 2005). Controlling for IQ, academic declines appear to be

at least in part due to additional factors, potentially related to other neurocognitive late effects. Although there does not appear to be a significant difference in academic performance based on radiation dose, patients younger than seven years at diagnosis experience significantly worse declines in reading (Mabbott et al., 2005; Mulhern et al., 2005). This is hypothesized to be a result of impairments in more fundamental language skills such as orthographic and phonologic analysis (Mulhern et al., 2005). Overall, however, research suggests that children diagnosed with MB at any age typically exhibit deficits in most, if not all, areas of academic achievement testing.

In general, survivors of pediatric cerebellar PA have better academic outcomes than survivors of pediatric MB. However, PA survivors still display an elevated risk for cognitive and academic deficits (Beebe et al., 2005). Estimates of the incidence of academic difficulties in cerebellar PA survivors range from 30% to 60% (Aarsen et al., 2006, 2009). Daszkiewicz and colleagues found that 86% of childhood cerebellar PA survivors in their sample were able to continue in regular education, with only 3% being enrolled in special education programs. Relapse and younger age at diagnosis seem to be risk factors for necessitating special education services (Aarsen et al., 2009). However, the majority of pediatric cerebellar PA survivors do not have significant academic difficulties, unlike survivors of childhood MB.

Executive Functioning

The exact role of the cerebellum in executive functioning is unclear. Some studies have found deficits in such functions (e.g., planning, organization, problem-solving) in children and adults with cerebellar pathology (Exner, Weniger, & Irle, 2004; Gottwald, Wilde, Mihajilovic, & Medhorn, 2004; Karatekin, Lazareff, & Asarnow, 2000; Malm et al., 1998), while others have found that executive function is intact in such patients (Bracke-Tolkmitt et al., 1989; Daum et al., 1993; Fiez, Petersen, Cheney, & Raichle, 1992). However, a growing body of evidence suggests that survivors of pediatric MB have difficulties with executive functioning (Aarsen et al., 2004; Levisohn et al., 2000; Maddrey et al.,

2005; Riva & Giorgi, 2000; Spiegler et al., 2004; Vaquero et al., 2008). One study found that childhood MB survivors have significantly more executive dysfunction than survivors of childhood cerebellar PA (Vaquero et al., 2008). Furthermore, Schmahmann and Sherman (1998) have described a “cerebellar cognitive affective syndrome” commonly seen in cerebellar lesion patients. This syndrome includes impairments in executive functions, such as planning, cognitive flexibility, and abstract reasoning.

In a study of long-term survivors of childhood cerebellar PA, only 17% were found to have difficulties with executive functions such as planning and cognitive flexibility (Aarsen et al., 2004). A study of short-term outcomes in this population found that executive dysfunction was more common, yet parents of these children did not discuss this as a primary concern (Karatekin et al., 2000). Children treated for PA prior to age 3 may exhibit more severe executive dysfunction post-treatment than those who are diagnosed and treated when older (Ward, Phipps, De Sousa, Butler, & Gumley, 2009). However, overall, survivors of pediatric cerebellar PA display less executive dysfunction than survivors of MB (Vaquero et al., 2008).

Language

Deficits in language production, particularly with regard to prosody, grammar, and word-finding abilities (mild anomia), have been documented among MB survivors (Dennis et al., 1996; Levisohn et al., 2000; Maddrey et al., 2005; Riva & Giorgi, 2000). This is not one of the more common findings among survivors of childhood MB. In fact, language appears to be the least impaired neurocognitive domain (Maddrey et al., 2005). However, it is estimated that up to 58% of pediatric MB survivors display some sort of language deficit (Maddrey et al., 2005).

Relative strengths in language skills among childhood MB survivors are reflected in verbal IQ typically being higher than performance IQ (Dennis et al., 1996; Hardy et al., 2008; Kieffer-Renaux et al., 2000; Maddrey et al., 2005; Mulhern et al., 1998; Riva, Milani, Pantaleoni, Ballerini, & Giorgi, 1991; Silverman et al., 1984). This can cause others to overestimate these individuals' abilities,

which is particularly problematic in educational and occupational settings (McCabe, Getson, Brasseux, & Johnson, 1995).

Even without radiation or chemotherapy, survivors of pediatric cerebellar PA often display language problems ranging from “cocktail party speech” (fluid, prolific speech lacking logical meaning) to word-finding difficulties (Aarsen et al., 2004). This may be an example of cerebellar cognitive affective syndrome, which can cause difficulties with language production, particularly prosody, grammar, and word-finding abilities (Schmahmann & Sherman, 1998). However, as with survivors of childhood MB, language difficulties are typically rare and short-lived, if present; they do not represent a significant aspect of the neurocognitive profile of deficits in this population.

Visuospatial

Impairments in visuospatial skills have been widely noted in survivors of childhood medulloblastoma (Levisohn et al., 2000; Maddrey et al., 2005; Spiegler et al., 2004; Steinlin et al., 2003). These visuospatial difficulties may be a consequence of executive function deficits, particularly related to planning and organization (Levisohn et al., 2000). MB patients with a history of receiving a shunt due to hydrocephalus display even more severe visuospatial deficits than those who do not require a shunt (Hardy et al., 2008). Notably, visuospatial impairments in MB survivors have been observed independent of motor skills (Maddrey et al., 2005).

Regarding cerebellar PA survivors, one estimate is that visuospatial deficits are seen in about 22% of this population at a mean of three years post-treatment (Aarsen et al., 2004). Intracranial pressure appears to play a significant role in the development of these deficits, as there was a significant association between severity of preoperative hydrocephalus and persisting visuospatial impairment (Aarsen et al., 2004). However, brain tumor patients who receive radiation (e.g., MB patients) display worse visuospatial skills than PA patients or other surgery-only brain tumor populations (Copeland et al., 1999; Spiegler et al., 2004).

Motor

Survivors of childhood MB often display motor

skills deficits (Grill et al., 2004; Jain, Krull, Brouwers, & Chintagumpala, 2008). As measured by a finger-tapping task, such deficits are seen in up to 77% of the population (Maddrey et al., 2005) and can cause difficulties in performing a number of recreational and vocational tasks, from driving a car to typing. In a general population of PF patients, it has been found that surgical resection of the tumor may be the primary cause of these motor deficits (Aarsen et al., 2004; Levisohn et al., 2000; Steinlin et al., 2003). This is supported by the finding that motor deficits remain constant over time, neither worsening nor improving (Dennis et al., 1996; Hoppe-Hirsch et al., 1990; Packer et al., 1989). Peripheral neuropathy, often linked to chemotherapy agents such as vincristine and cisplatin, is another potential cause of late motor deficits in pediatric MB survivors, although this is rare (Hockenberry et al., 2006; Packer et al., 1994; Quastoff & Hartung, 2002).

With regard to motor deficits among childhood cerebellar PA survivors, Beebe et al. (2005) reported larger effect sizes associated with measures requiring motor responses, such as performance IQ and spelling, in addition to measures of adaptive motor skills. However, a test of fine motor coordination did not indicate deficits in this sample. Motor functioning difficulties in survivors of cerebellar PA have been confirmed by parent report (Aarsen et al., 2006; Beebe et al., 2005) and become more pronounced with time (Aarsen et al., 2006). However, survivors of cerebellar PA generally have better motor functioning than survivors of MB (Callu et al., 2009; Copeland et al., 1999).

Memory

Pediatric MB survivors display a wide variety of memory deficits (George et al., 2003; Hardy et al., 2008; Maddrey et al., 2005; Nagel et al., 2006; Palmer, 2008; Palmer et al., 2007; Roman & Sperduto, 1995; Steinlin et al., 2003; Timmann & Daum, 2007). The past two decades of research have illuminated the cerebellum’s role in verbal working memory, a function often impaired among childhood MB survivors (Timmann & Daum, 2007). Verbal memory deficits in survivors of childhood MB are likely due to poor encoding of information rather

than difficulties in storage or retrieval (Levisohn et al., 2000; Maddrey et al., 2005). However, Nagel et al. (2006) report both retrieval and recognition deficits in this population, while other studies indicate no evidence of verbal memory decline, rather only visual memory deficits (Johnson et al., 1994; Spiegler et al., 2004). Hardy et al. (2008), on the other hand, found both verbal and visual memory to be impaired in childhood MB survivors. Within the realm of short-term memory, research has suggested that verbal short-term memory is more frequently impaired in this population than visual short-term memory (Riva & Giorgi, 2000; Steinlin et al., 2003).

Overall, the findings that suggest verbal memory impairments in this population are more clear and consistent than findings regarding visual memory impairments, with most studies indicating some form of verbal memory deficit (George et al., 2003; Hardy et al., 2008; Levisohn et al., 2000; Maddrey et al., 2005; Nagel et al., 2006; Palmer, 2008; Palmer et al., 2007; Riva & Giorgi, 2000; Steinlin et al., 2003; Timmann & Daum, 2007). The inconsistency of findings on visual memory in survivors of pediatric MB may be due to the methodology of visual memory testing. For example, Steinlin et al. (2003) note that performance on the Rey-Osterrieth Complex Figure, used to test visual-spatial memory, can be affected by difficulties with planning and organization, which their study found to be the source of the apparent visuospatial memory deficits in childhood MB survivors.

Additionally, neural damage may impact variations in memory deficits among survivors of childhood MB. Imaging research has shown that survivors of childhood MB, especially females, experience hippocampal atrophy, possibly due to cranial radiation (Nagel et al., 2004). Cranial radiation dose has been found to be negatively correlated with both verbal and nonverbal memory functions (Roman & Sperduto, 1995), although findings specific to these two domains have been inconsistent (Konczak, Schoch, Dimitrova, Gizewski, & Timmann, 2005; Spiegler et al., 2004; Timmann & Daum, 2007). Some studies have suggested that radiation-induced deficits in processing speed, which impact learning and retrieval, may be at the core of memory impairments in childhood MB survivors (Mabbott et al., 2008; Palmer, 2008).

In contrast to the findings regarding survivors of pediatric MB, Roncadin and colleagues (2008) have suggested that survivors of pediatric cerebellar PA generally have intact memory functioning. However, these researchers note that younger age at diagnosis and more medical events (e.g., shunt infection, seizures) in the first five years following surgery are associated with more severely impaired memory in this population. Other studies suggest that memory deficits, particularly in verbal memory, are common in cerebellar PA survivors (Aarsen et al., 2004, 2009; Kirschen et al., 2008; Levisohn et al., 2000; Steinlin et al., 2003; Vaquero et al., 2008). However, Levisohn and colleagues caution that some findings of verbal memory deficits among cerebellar PA survivors may simply be representative of difficulties with sequencing and planning verbal output (Levisohn et al., 2000). In general, survivors of pediatric cerebellar PA display less severe memory deficits than survivors of pediatric MB (Copeland et al., 1999; Konczak et al., 2005; Ronning et al., 2005). This is particularly true with regard to visual and working memory, which often are not impaired in survivors of PA (Copeland et al., 1999; Konczak et al., 2005).

Attention

Deficits in attention are common among childhood MB survivors. Research indicates up to 92% of these patients have difficulties with simple attention (Maddrey et al., 2005), and teachers report increasing attention deficits in this population over time (Mabbott et al., 2005). Specifically, MB survivors often exhibit deficits in both selective and sustained attention (Dennis, Hetherington, & Spiegler, 1998; Mulhern et al., 2004; Reddick et al., 2003; Roman & Sperduto, 1995; Steinlin et al., 2003). In this population, impaired attention is particularly problematic due to its negative impact on the development of cognitive abilities and academic achievement (Briere, Scott, McNall-Knapp, & Adams, 2008; Dennis et al., 1998; Maddrey et al., 2005; Palmer, 2008; Palmer et al., 2007; Roman & Sperduto, 1995).

Dennis et al. (1998) note that "it is not the presence of a tumor as such that appears to place the child at risk for poor attention but, rather, the combination of a tumor and adjuvant radiation treatment" (p. 31).

This has been replicated in other studies (Butler, Kerr, & Marchand, 1999; Garcia-Perez, Sierrasesumaga, Narbona-Garcia, Calvo-Manuel, & Aguirre-Ventalló, 1994; Merchant et al., 2002; Reeves et al., 2006). Increased time since radiation may be associated with worsening attention problems (Briere et al., 2008; Palmer et al., 2001, 2003; Reeves et al., 2006; Spiegler et al., 2004). Attention deficits are particularly pronounced in patients less than 8 years of age at diagnosis and in patients who receive higher doses of radiation (Mulhern et al., 1998).

This finding also suggests that radiation again plays a large role in exacerbating neurocognitive deficits. Indeed, the primary consequence of reduced normal-appearing white matter as a result of cranial radiation appears to be decreased attention abilities (Mulhern et al., 2004). Just as in the domain of memory, researchers have suggested that attention difficulties in childhood MB survivors may be due to processing speed deficits thought to be caused by radiation-induced white matter damage (Mabbott et al., 2008; Palmer, 2008).

Regardless of tumor location, Aarsen et al. (2004, 2009) found that all pediatric PA patients exhibit deficits in attention. However, this group's findings indicated that attention deficits improve over time, as suggested by an earlier study (Riva & Giorgi, 2000), while Zuzak et al. (2008) found that only 33% self-reported attention deficits. Dennis and colleagues (1998) found that patients treated with craniospinal radiation (e.g., MB patients) have worse selective attention than those treated with surgical resection alone (e.g., PA patients). Another study found that even patients treated with surgical resection alone have deficits in selective attention (Mabbott, Snyder, Penkman, & Witol, 2009). Unlike survivors of childhood MB, however, these patients do not display sustained attention deficits (Mabbott et al., 2008; Steinlin et al., 2003). Overall, it is clear that MB survivors have more significant attention deficits than survivors of PA, likely due to the use of radiation in the treatment of MB (Butler et al., 1999; Mabbott et al., 2008; Merchant et al., 2002; Reeves et al., 2006; Ronning et al., 2005).

Processing Speed

Several studies have noted deficits in processing

speed in survivors of pediatric MB (Dennis et al., 1998; Kieffer-Renaux et al., 2000; Mabbott et al., 2008; Mulhern et al., 2004; Nagel et al., 2006; Riva & Giorgi, 2000; Reeves et al., 2006; Schatz, Kramer, Ablin, & Matthay, 2000; Spiegler et al., 2004; Vaquero et al., 2008). A review by Palmer (2008) has suggested that in this population, processing speed deficits are first to emerge post-treatment. In a comparison of radiated and non-radiated PF tumor survivors, the only significant difference observed was poorer processing speed among radiated patients (Mabbott et al., 2008). Furthermore, MB patients younger than 12 years of age show decreased reaction times after radiation therapy (Merchant et al., 2002). These findings suggest that radiation may play a large role in the processing speed deficits seen in childhood MB survivors.

The presence of processing speed deficits in childhood MB survivors may be due to the tumor's close proximity to the ascending reticular activating system of the brainstem (Riva et al., 1989). Another hypothesis, proposed by Riva and Giorgi (2000), is that slow processing speed is reflective of a disruption of the intrinsic structure of the cerebellum, "which is constituted in a crystalline manner by a micromodular structure that works in parallel" (p. 1057). Thus, Riva and Giorgi have posited, any lesion to this cerebellar network reduces the speed at which cerebellar modules may be recruited, in turn reducing the cerebellum's ability to accelerate cognitive processes (Ito, 1984; Kandel, Schwartz, & Jessell, 2000). One of the most prominent deficits associated with any sort of cerebellar damage is decreased processing speed (Aarsen et al., 2009; Butler & Haser, 2006; Mabbott et al., 2008; Palmer, 2008; Palmer & Leigh, 2009; Palmer et al., 2007; Reeves et al., 2006; Riva & Giorgi, 2000; Steinlin et al., 2003; Vaquero et al., 2008; Zuzak et al., 2008). The larger the lesion, the more cognitive processes may be slowed.

Processing speed likely is impaired by the reduced functionality of cerebral white matter pathways, as damage to these neural tracts is another known effect of cranial radiation (Khong et al., 2006; Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006; Mulhern et al., 1999; Palmer, 2008; Reddick et al., 2000). Briere et al. (2008) hypothesize that

radiation-induced cerebral white matter damage impairs processing speed by disrupting development of the brain's overall structural network. White matter damage specific to the cerebellum, caused by PF radiation, can have widespread effects due to the extensive reciprocal connections between the cerebellum and the frontal lobe (Leiner, Leiner, & Dow, 1986). Thus, it may be inferred that the damaging effects of radiation on white matter in both the cerebrum and the cerebellum contribute to childhood MB survivors' significant deficits in processing speed.

Several studies have indicated that survivors of childhood PA often have deficits in processing speed, regardless of the tumor location (Aarsen et al., 2009; Steinlin et al., 2003; Zuzak et al., 2008). However, their deficits are not as severe as those of survivors of pediatric MB (Mabbott et al., 2008; Palmer & Leigh, 2009). Indeed, deficits in processing speed appear to be positively correlated with radiation dose (Kieffer-Renaux et al., 2000). Treatment with surgical resection alone, as is standard for PA, has not been documented to significantly impact processing speed (Mabbott et al., 2008). Therefore, although there have not yet been studies explicitly addressing this question, available evidence suggests that survivors of childhood MB would have greater deficits in cognitive fluency than survivors of cerebellar PA.

Cognitive Fluency

It has been proposed that the ability to perform complex cognitive operations quickly and accurately (i.e., cognitive fluency) enables minimization of resource allocation and maximization of performance (Rypma et al., 2006). From a developmental perspective, cognitive fluency appears to govern improvements in task performance (Kail, 1986, 1988, 1991; Keating & Bobbitt, 1978). In terms of the Cattell-Horn-Carroll theory, cognitive fluency—a measure of ease, speed, and accuracy in performing complex cognitive processes that rely more on long-term knowledge acquisition than short-term memory—is a combination of *Gs*, or processing speed, and *Gl_r*, or long-term retrieval (Mather & Woodcock, 2001; McGrew & Woodcock, 2001). Thus, cognitive fluency is distinguished from

cognitive efficiency, which is a combination of *Gs* and *Gsm*, or working memory. Processing speed is a necessary, but not sufficient, component of cognitive fluency. In addition to short-term memory, other cognitive abilities, such as visuospatial skills and attention, may also be needed to complete a given task quickly and accurately. Many such components of cognitive fluency are often significantly impaired following treatment for childhood MB.

Studies of both development and aging suggest that one determinant of cognitive fluency is axonal maturation of the prefrontal cortex (Gomez-Perez, Ostrosky-Solis, & Prospero-Garcia, 2003; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Fisk, Fisher, & Rogers, 1992; Medina et al., 2006; Rypma, Berger, Genova, Rebbecki, & D'Esposito, 2005; Rypma, Prabhakaran, Desmond, & Gabrieli, 2001; Rypma & D'Esposito, 1999; Salthouse, 1992; Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002; Small, Kemper, & Lyons, 2000; West, 1996). However, the cerebellum also has been shown to play a large role in cognitive fluency (Ackerman et al., 2004; Desmond, 2001; Ivry & Baldo, 1992; Leiner et al., 1986; Leiner, Leiner, & Dow, 1989; Schmahmann & Sherman, 1998; Weaver, 2005). Leiner and colleagues (1989) mention that "increased speed and skill in the control of mental manipulation" (p. 1005) is the primary impact of the cerebellum on the prefrontal cortex, enhancing the efficiency of many cognitive functions.

While processing speed is a basic cognitive function referring to the speed at which a person can perform automatic, over-learned tasks, cognitive fluency is conceptualized as speed of performance on more complex cognitive tasks. Thus, deficits in these two areas most likely contribute to the declines in IQ and academic performance observed in childhood MB survivors. While deficits in processing speed have been clearly documented in survivors of childhood MB, specific studies of cognitive fluency in this population have not been conducted previously.

In a study of working memory, sustained attention, and processing speed among radiated and non-radiated PF patients, only processing speed was significantly more impaired in radiated patients (Mabbott et al., 2008). Furthermore, MB patients

younger than 12 years of age showed decreased reaction times after radiation therapy (Merchant et al., 2002). This is most likely due to the negative effects of radiation on white matter (Mabbott et al., 2006; Mulhern et al., 1999, 2001, 2004; Palmer et al., 2002; Reddick et al., 2000, 2003). White matter is particularly crucial to cognitive fluency, due to its role in facilitating the rate of signal transmission (Schmithorst, Wilke, Dadzinski, & Holland, 2002). It is theorized that impaired processing speed, a consequence of radiation damage to white matter, is responsible for poor acquisition of skills and knowledge in childhood MB survivors (Mabbott et al., 2008). This theory may be extended to include the impact of impaired cognitive fluency. However, specific studies of cognitive fluency in childhood MB survivors have not been conducted.

Discussion

Current knowledge regarding the neuropsychological outcomes of childhood MB and PA is expansive in certain areas. Specifically, executive functioning appears to be more impaired in childhood MB survivors than in PA survivors (Vaquero et al., 2008). Processing speed is another area in which MB survivors display deficits of greater severity than those of PA survivors (Palmer & Leigh, 2009). This also appears to be true for attentional abilities (Mabbott et al., 2008). Additionally, it is generally agreed that radiation is more devastating to attention and processing speed than the tumor itself (Palmer, 2008). Studies have consistently shown that childhood MB survivors display a failure to make typical intellectual gains post-treatment, potentially for at least a decade (Hoppe-Hirsch et al., 1990, 1995; Kieffer-Renaux et al., 2005; Lafay-Cousin et al., 2009; Palmer et al., 2003; Spiegler et al., 2004; Ris et al., 2001; Riva et al., 1989), likely resulting from both the aforementioned deficits and radiation-induced white matter damage. Psychosocial outcomes also are consistently found to be negatively impacted in both MB and PA survivors, although this research is limited. For example, one study showed that five years post-surgery, 47% of childhood medulloblastoma survivors exhibit symptoms of an emotional or behavioral disorder, and this percentage

increases with time: Ten years post-surgery, 78% of the sample had some sort of psychopathology (Hoppe-Hirsch et al., 1990). Further research also is needed regarding the nature of visuospatial deficits in MB survivors. While such deficits are common in this group (Levisohn et al., 2000; Spiegler et al., 2004; Steinlin et al., 2003; Maddrey et al., 2005), it is unclear whether these deficits are primarily related to executive dysfunction, motor difficulties, or disruption of visual-perceptual neural pathways.

Other aspects of cognitive functioning in these two groups have been fairly extensively researched, but no consensus has been reached. The intellectual functioning of PA survivors is a divisive topic, with some research suggesting these children display significant deficits (Aarsen et al., 2004; Beebe et al., 2005), while other studies have found no impairments (Karatekin et al., 2000; Reimers et al., 2003; Steinlin et al., 2003). Language skills have generally been thought to be preserved in both populations, although a recent study estimated that nearly 60% of pediatric MB survivors display some sort of language deficit (Maddrey et al., 2005). The extent to which motor functioning is impaired in childhood PA survivors is also unclear, with one study suggesting that affected patients have deficits in adaptive motor skills but intact fine motor coordination (Beebe et al., 2005). The memory functioning of childhood MB survivors, however, is perhaps most controversial. Although current research has reached the consensus that memory is impaired in this population, there is conflicting evidence regarding outcomes related to specific verbal, visual, short-term, and long-term memory modalities. Certainly, there is a great need for further investigation in this area.

Finally, some aspects of the neuropsychological outcomes of these two tumor groups simply have not been sufficiently researched, notably cognitive fluency and academic performance. With regard to the latter, studies have shown that childhood MB survivors have poorer academic outcomes than both their healthy peers and cerebellar PA survivors (Aarsen et al., 2006, 2009; Dennis et al., 1996; Hoppe-Hirsch et al., 1995; Mitby et al., 2003; Palmer et al., 2001; Palmer et al., 2007; Ris et al., 2001). Despite this finding, only four studies to date have investigated the

performance of these two tumor groups on measures of academic achievement (Beebe et al., 2005; Mabbott et al., 2005; Muhern et al., 2005; Reeves et al., 2006). Thus, more research on the precise nature of these academic deficits is warranted. A pilot study by Stavinoha and Burrows (2004) found no deficits in the academic skills of childhood MB survivors, but significant deficits in academic fluency. Thus, real-world academic difficulties may be due to processing speed deficits, which are typically worse in childhood MB survivors than in PA survivors (Mabbott et al., 2008; Palmer & Leigh, 2009).

Cognitive fluency, then, would be a natural target for future investigations into the cognitive late effects of these two tumor groups, as processing speed is a component of cognitive fluency. Although the degree of processing speed impairment already distinguishes childhood MB survivors and childhood PA survivors (Mabbott et al., 2008), it is essential to study cognitive fluency in these populations. Academic performance may be more strongly correlated with cognitive fluency than with processing speed, as cognitive fluency relies more on long-term knowledge acquisition. Both academic and cognitive fluency may be additional distinguishing features between the two tumor groups. Defining such distinguishing characteristics is an important goal for research in these populations, as inferences may then be made regarding the late effects of radiation. The ultimate goal is to improve the long-term physical and cognitive health of these children, and a more precise understanding of how radiation affects the brain could inform both neuropsychological interventions and medical treatment decisions.

Both childhood MB survivors and cerebellar PA survivors have tumors in the posterior fossa, yet the former typically receives radiation and chemotherapy treatments, and the latter most often receives only surgical interventions. Thus, pediatric cerebellar PA survivors are the ideal control group for studies attempting to identify cognitive and academic late effects of craniospinal radiation and chemotherapy. Since chemotherapy rarely is associated with significant, long-term cognitive effects (Ahles & Saykin, 2007; Reddick et al., 2005; Rutkowski et al., 2005), the degree of confidence with which any

cognitive late effects could be ascribed to radiation in such studies would be high.

Studies have attempted to compare these two tumor types in the past, but conclusions have been weakened by methodological issues. Due to the relatively low frequency of MB cases compared to cases of cerebellar PA, studies often include other types of radiated tumors, such as ependymoma (Hoppe-Hirsch et al., 1995; Spiegler et al., 2004), making it difficult to draw conclusions regarding the impact of tumor type or treatment. Additionally, many studies include all PA survivors, not just those who had a cerebellar tumor. Some studies have included PA survivors who have received treatment modalities beyond surgical resection, such as chemotherapy or radiation. Finally, a large number of existing studies of these two tumor groups feature small sample sizes, thus limiting the power of any significant findings. Future studies should attempt to address these methodological issues. Though improving study design will likely mean more time spent in data collection, the potential strength of the conclusions that could be drawn in doing so—particularly conclusions regarding the cognitive impact of craniospinal radiation, identifying at-risk areas of neuropsychological functioning and, as a result, potentially beneficial services and therapies—would certainly make this time well spent.

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Appendix
Summary of Selected Key Studies.

Study	Sample	N	Method	Major Findings
Aarsen et al. (2004)	PA	23	Prospective	Deficits in language, sustained attention, visual-spatial abilities, executive functioning, memory, and motor functioning; behavior problems
Aarsen et al. (2009)	PA	38	Prospective	Decreased quality of life; neuropsychological deficits increase with time since treatment
Aarsen et al. (2009)	PA	61	Prospective	Deficits in sustained attention, processing speed; radiation, younger age at diagnosis, and greater time since diagnosis identified as risk factors
Beebe et al. (2005)	PA	103	Prospective	Elevated risk for cognitive and adaptive deficits not associated with tumor location
Dennis et al. (1996)	MB	25	Retrospective	Performance IQ more sensitive to age at diagnosis than verbal IQ; observed “decline” is failure to make expected gains
George et al. (2003)	MB & PA	15	Retrospective	Diagnosis prior to age 6 associated with greater decline in IQ
Hoppe-Hirsch et al. (1995)	General PF	96	Prospective	Radiation associated with progressive decline in IQ
Levisohn, Cronin-Golomb, & Schmahmann (2000)	MB & PA	48	Retrospective	Deficits in visuospatial function, expressive language, sequencing, memory, and regulation of affect; younger children had fewer deficits
Mabbott et al. (2005)	General PF	53	Retrospective	Radiation associated with deficits in attention, academic functioning, and social skills
Mabbott et al. (2008)	General PF; solid tumor controls	74 (10)	Prospective	Treatment with radiation associated with lower IQ and slower processing speed
Mabbott et al. (2009)	General PF; non-clinical controls	54 (10)	Prospective	Deficit in selective attention
Maddrey et al. (2005)	MB	16	Prospective	Deficits in attention, memory, visuospatial abilities, motor functioning, language, and executive functioning; deficits in activities of daily living but normal self-reports of quality of life
Mulhern et al. (2001)	MB	42	Prospective	Younger age associated with greater deficits in all areas except verbal memory; reduced white matter post-radiation associated with decline in IQ
Mulhern et al. (2005)	MB	111	Prospective	Younger age at diagnosis identified as biggest risk factor for neurocognitive deficits; reading skills particularly affected

continued

Note: Number in parentheses indicates size of control group when applicable. In those instances, *N* reported is total sample.

Study	Sample	<i>N</i>	Method	Major Findings
Palmer et al. (2001)	MB	44	Prospective	Mean loss of 2.55 FSIQ points lost per year post-radiation; “decline” is failure to make expected gains
Palmer et al. (2003)	MB	50	Retrospective	Younger patients (mean age 5.86) demonstrate immediate decline in IQ; delay prior to decline seen in older patients (mean age 11.05)
Reeves et al. (2006)	MB	38	Retrospective	Intact verbal memory; deficits in selective attention; greater time since radiation noted as risk factor
Riva & Giorgi (2000)	General PF	26	Prospective	Right cerebellar tumors associated with deficits in auditory memory and language processing; left cerebellar tumors associated with deficits in nonverbal memory
Spiegler et al. (2004)	General PF	34	Retrospective	Radiation associated with deficits in visual-motor integration, visual memory, verbal fluency, executive function, and IQ, but not verbal memory or receptive vocabulary
Steinlin et al. (2003)	General PF	24	Retrospective	Deficits in memory, attention, visuospatial abilities, executive function; 33% had behavioral difficulties
Vaquero et al. (2008)	MB & PA; non-clinical controls	33 (12)	Prospective	More severe executive dysfunction in MB; processing speed deficits in both groups; younger age at surgery identified as risk factor

Note: Number in parentheses indicates size of control group when applicable. In those instances, *N* reported is total sample.