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White Matter Development and Executive Outcomes Following Pediatric Brain Tumor Treatment

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ABSTRACT

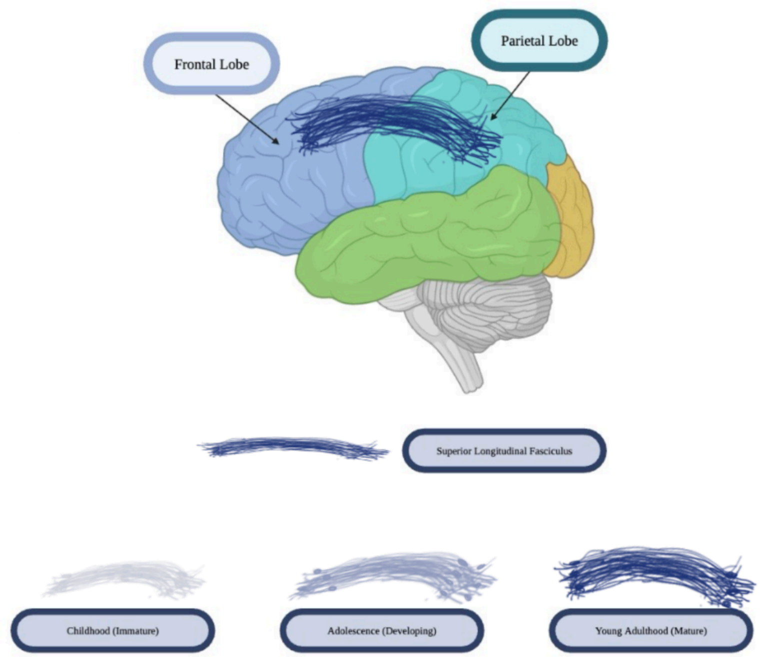
Advances in cancer treatments have significantly improved survival rates for childhood cancers. However, many survivors experience persistent neurocognitive difficulties. Rapid brain development during childhood involves the maturation of cerebral white matter, which is essential for executive functions. Although pediatric cancer treatments are known to impact the developing brain, the influence of developmental timing on long-term outcomes is unclear. It is not well understood how age at exposure to cancer treatments affects white matter and executive function development. The general problem addressed here is whether treatment during early stages of brain maturation leads to greater and more persistent neurocognitive disruption. Younger age at exposure to pediatric cancer treatments is associated with greater alterations in white matter and executive function outcomes. Across numerous studies, early treatment has been linked to disruption of frontal and fronto-parietal white matter pathways, which are critical for cognition. These findings suggest that while developmental neuroplasticity allows for some functional compensation, it does not fully prevent long-term changes to cognitive decline. Together, these results emphasize the importance of developmental timing in pediatric cancer survivors.

INTRODUCTION

Due to the advances made in the treatment of children with brain tumours, such as improved chances of survival, there is now an increasing number of survivors of childhood brain tumours who will face long-term neurocognitive deficits. Regardless of tumour type, such as medulloblastoma, ependymoma, or astrocytoma, or treatment modality, for example, chemotherapy, cranial radiation, or proton therapy, survivors exhibit deficits in processing speed, attention, working memory, and executive function (Patel et al., 2025; Sleurs et al., 2023). Due to their impact on the development of age-appropriate cognitive abilities, neurocognitive deficits can undermine a child's academic, social, and physical independence by creating gaps in performance on academic testing, in decision-making, and in overall independence. Children who have been treated for brain tumours fall further behind their peers over time as a result of these deficits, leading to greater difficulty completing multi-step tasks in the classroom, logically organizing information, and maintaining attention during complex learning experiences.

One important feature of these results is the development of cerebral white matter, which is myelinated axonal pathways that support efficient communication among distributed parts of the brain. White matter undergoes considerable maturation as it progresses from very early childhood to early adulthood. Higher-order association pathways, the Superior Longitudinal Fasciculus, which are responsible for coordinating executive functions like regulating attention, utilizing working memory, and demonstrating cognitive flexibility, develop later than basic sensory and motor systems (Fields, 2010; West et al., 2020). The Superior Longitudinal Fasciculus connects the frontal and parietal lobes **(Figure 1)**.

Figure 1. Superior Longitudinal Fasiculus



As a myelinated fiber bundle, structuring the Superior Longitudinal Fasciculus requires a sufficient axon density and fiber coherence; thus, small developmental changes can significantly impact coordination and processing speeds across regions of the brain (Fields, 2008; Fields, 2010; Lebel & Beaulieu, 2011). Consequently, through its function as a "goal-related" behavioral pathway, the Superior Longitudinal Fasciculus enables the frontal lobe to maintain focus or attention, update working memory, or transition from one task to another based on incoming information from regions of the brain (Paus, 2005; Barnea-Goraly et al., 2005).

As pathways like the Superior Longitudinal Fasciculus are undifferentiated and developing through maturation of myelination and structural refinement between the ages of five and twenty-five, the development in these pathways is especially vulnerable to threats from chemotherapy, which targets rapidly developing neural tissues (Reddick et al., 2006). For example, damaging oligodendrocytes or disrupting myelination decreases the speed and efficiency of transmission of neural signals among various brain areas that contain goal-directed behavior.

The study of neuroimaging has proven the correlation between treatments received throughout life and the structural integrity of the white matter in the brain after many years post treatment. Using diffusion tensor imaging to assess the micro-level structure of the white matter in the brain, studies have shown a lower level of fractional anisotropy and less connectivity within some of the major areas of white matter in those who have survived a childhood brain tumor (Brinkman et al., 2012; Reddick et al., 2006). Other studies have used functional magnetic resonance imaging to demonstrate that the prefrontal regions of the brain became more activated to complete tasks involving working memory and attention than in other individuals without significant illnesses (Robinson et al. 2010). This over-activation may allow children to complete tasks such as recalling memories, such as, items to bring to school or the store, or to follow single-step instructions, but they are unable to sustain this level of activity when asked to complete multiple tasks at once, think outside of what they have learned, or show sustained attention over time (Kesler et al. 2023).

There has been progress made regarding the understanding of the effects of treatment upon brain structure and function, but there is still a gap in understanding the role of the timing of development on the outcomes of these treatments. Younger age of treatment continues to be associated with more severe and long-term impairments; however, the exact mechanisms by which early versus later exposure leads to disruption of the normal maturation of white matter and resulting long-term impact on executive function are still not well understood. Of particular concern is how treatment during sensitive periods of myelination and formation of networks affects the development of important pathways, such as the superior longitudinal fasciculus, and the way in which those structural disruptions may lead to functional limitations for more complex, real-world cognitive tasks, including multitasking, problem solving, and sustained attention.

This review investigates how the age of exposure to pediatric brain tumor treatment affects white matter development and long-term executive functioning, based on the question: How does age at exposure to pediatric cancer treatments influence white matter development and long-term executive function outcomes? In doing this, it includes all structural and functional neuroimaging data in addition to psychological factors like distress from the traumatic experience of cancer treatment, in combination with structural and functional brain data, to provide an understanding of the recovery. This paper will help clarify the effect of the disruption to brain networks developing through age and emotional and cognitive processes on long-term outcomes by combining research from multiple studies on tumors at different developmental stages with different treatment techniques. The goal of this review is ultimately to better inform how to identify those patients who are at risk for developing problems associated with their tumor by providing a basis for establishing specific interventions and tracking quality of life improvements through targeted intervention strategies.

Executive Function Development

Mental skills such as holding thoughts briefly, focusing, shifting ideas, and organizing steps grow stronger as parts near the brain's cortex develop links to deeper striatal and thalamic areas. The frontal lobe, at the front of the brain, supports decision-making, inhibitory control, and planning, while the parietal lobe, located behind the frontal lobe, integrates sensory information and guides spatial attention. Signals moving through tracts, such as the superior longitudinal fasciculus or loops tied to movement centers, enable coordination essential for advanced thinking. Without smooth traffic across these routes, integration slows down (Kesler et al., 2023; Brinkman et al., 2012).

Among children who survive cancer, problems with mental control processes occur frequently. Following treatment for medulloblastoma or growths in the back of the brain, delays in thinking pace emerge alongside weaker short-term recall and challenges with steady focus (Mulhern et al., 2010; Robinson et al., 2023). When confronted with intense memory demands, scans show unusual surges of activity in outer frontal zones, a sign that the mind works harder due to disrupted signal routes beneath the surface. Because communication channels lack efficiency, extra areas are activated just to keep up. Though such adjustments support basic operations, they falter under advanced requirements, revealing hidden weaknesses long before outward signs appear (Kesler et al., 2023; Kesler et al., 2024).

Critical for executive function connections between frontal and parietal areas, the superior longitudinal fasciculus, along with circuits linking the cerebellum to frontal regions. When affected by tumors, surgical intervention, or radiation exposure, these zones may lead to lasting cognitive challenges through later developmental stages. Located in the fourth ventricle or posterior fossa, a tumor might delay maturation of distant neural systems, showing consequences that reach farther than visible injury points (Brinkman et al., 2012; West et al., 2020; Tanedo et al., 2022).

How The Brain Adapts And Heals

A child's brain has a strong ability to change its structure and operation, called neuroplasticity. Because of processes like the removal of extra synapses, insulation of nerve fibers, and creation of backup connections, thinking systems become more effective over time. Even so, neuroplasticity has limits. Damage to key white matter routes at vital times in growth may disrupt how networks form, staying present into later years as difficulties with planning and control (Brinkman et al., 2012; Kesler et al., 2024).

Overactivation in the prefrontal region signals adaptation, not full restoration. Compensation emerges under pressure. When tasks grow more complex, earlier gains falter, exposing weaknesses within control systems (Kesler et al., 2023). Support introduced early, cognitive exercises, focus drills, and organized learning may support neuroplasticity. Neuroplasticity is able to compensate, which helps with increased activity, but it does not fully support it. This is especially relevant in phases of expanding white matter development, aiding long-term function (Robinson et al., 2023; West et al., 2020).

Past Research About Children's Cancer and Thinking

Research clearly links childhood cancer therapies like chemotherapy and brain radiation to disrupted white matter growth plus weakened thinking skills. Though once viewed as gentler, drug-only treatments may still harm brain structure, especially when doses rise or patients are very young. Even advanced forms of radiation, such as proton approaches, extend life yet fail to fully protect neural tissue. The earlier a child receives these interventions, the greater the long-term mental challenges tend to be (Mulhern et al., 2010; Lassaletta et al., 2023).

Where a tumor is found plays a role in how things turn out. When growths sit in the posterior fossa, they risk interfering with connections between the cerebellum and frontal areas, pathways needed for focus, planning, and time perception. Such interference shows that damage might be seen throughout brain networks without touching the frontal lobe directly (West et al., 2020; Tanedo et al., 2022). Evidence from structural mapping hints at hidden weaknesses in communication across regions, possibly explaining thinking difficulties despite clean Magnetic resonance imaging results (Tanedo et al., 2022; Robinson et al., 2023).

Signs of trauma-related distress can worsen mental processing speed even without visible brain damage, showing how biological and social influences jointly shape results. Although knowledge has advanced, certain shortcomings persist. Long-term observations linking white matter changes to thinking skills are rare, while broad studies combining physical, neurological, and emotional data across varied child populations are scarce. Closing such divides becomes necessary if support strategies are to improve the thought abilities of vulnerable youth at key growth stages.

Genetics and Tumor Formation

To understand the relationship between genetic regulation and the distinct structural organization of the brain, and to comprehend why treatments for pediatric brain tumors are so harmful. Fundamentally, cancer is a disorder of unchecked cell proliferation in which the regular cell cycle, which is controlled by "checkpoints" that guarantee accurate DNA copying, is disturbed (Hanahan & Weinberg, 2011). By stopping the cell cycle at the checkpoint to permit DNA repair or inducing apoptosis if the damage is irreversible, the p53 gene acts as the main tumor suppressor (Vousden & Prives, 2009). Gliomas that originate from glial cells form when cells avoid these checkpoints due to mutations or loss of p53 or related genetic components. These tumors press against vital organs like the brainstem and cerebellum after they develop, especially in common pediatric locations like the posterior fossa or fourth ventricle. This impairs motor coordination. The majority of neurons in the adult brain do not regenerate, in contrast to skin or liver cells; neurogenesis is strictly restricted to small areas such as the olfactory bulb and hippocampus (Gage, 2000). Therefore, damage to the brain's "wiring" is frequently irreversible when radiation or chemotherapy kills neurons or the oligodendrocytes that form the myelin sheath. White matter tracts such as the Superior Longitudinal Fasciculus, which connects the frontal and parietal lobes. This pathway is crucial for combining sensory information with decision-making, so when it is disrupted, survivors experience the typical loss of executive function, which includes multitasking and planning.

Tumor Type, Location, Treatment Impact

Brain tumor kinds differ among children, and location matters too; both combine with therapy choices to affect brain development results. Take medulloblastoma, it typically forms inside the fourth ventricle, a space filled with fluid nestled beneath the cerebellum, which handles movement control and mental rhythm, and above the brainstem relaying body signals back and forth. Growth here presses on those areas, disturbing connections between cerebellum and front parts of the brain, along with links across parietal and frontal zones needed for focus, planning, and short-term recall (Stoodley et al., 2012; Tanedo et al., 2022). Removing such tumors by surgery, followed sometimes by radiation aimed at the head, damages still-maturing fiber bundles like the Superior longitudinal fasciculus and the corpus callosum because of how fast-growing cells respond to treatment, leading to delays in nerve communication plus weaker performance in thinking speed and holding thoughts briefly (Mulhern et al., 2010; Lassaletta et al., 2023).

Found in proximity to the fourth ventricle or within the spinal canal, ependymoma carries comparable consequences. As these masses expand, followed by intervention through excision, pathways linking upper brain regions with deeper nuclei may become compromised, resulting in impaired movement control, altered perception-handling, and diminished complex thinking abilities (Robinson et al., 2023). When radiation follows resection, damage to insulated nerve fibers intensifies, especially among young patients whose neural insulation remains incomplete. Despite treatment intent, structural vulnerability persists during developmental stages.

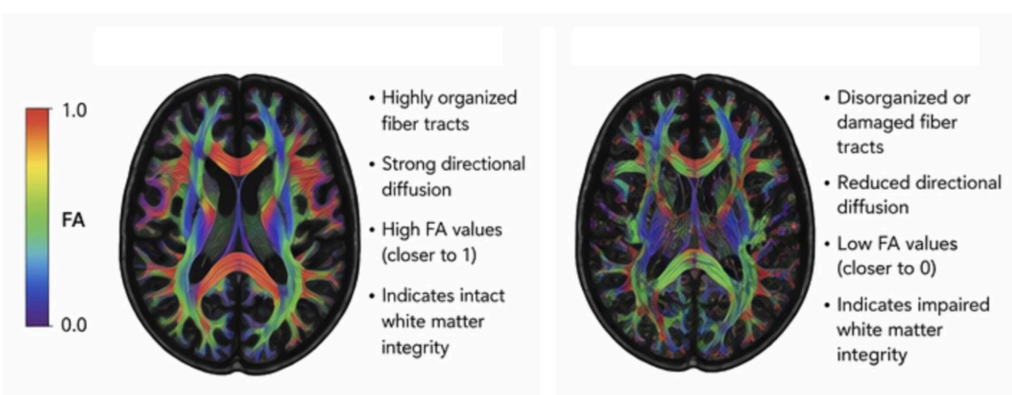
Brain Structure and White Matter

Unlike others, astrocytomas tend to appear in the cerebellum or areas above the tentorium, including parts like the frontal or parietal cortex. Although such growths usually involve specific brain zones, interventions involving radiation to the head or chemical agents delivered systemically or into the spinal fluid might lead to widespread damage in white tissue. Such changes disrupt neural pathways needed to link activity between distant sites, impairing complex mental functions like focus control and organizing actions forward in time (Reddick et al., 2006).

White matter changes following treatment change as much on the developmental stage as they do on the technique type. During childhood, when insulation of nerve fibers continues, harm to these regions interferes with core circuits shaping future thinking skills. Rather than assuming effects, medical strategies now tailor radiation levels using both patient age and disease seriousness, which lowers risk yet still leaves growing pathways exposed (Mulhern et al., 2010). Among those surviving medulloblastoma, earlier intervention correlates strongly with lasting slowdowns in thought pace, short-term recall issues, and wider mental control weaknesses (Lassaletta et al., 2023; Robinson et al., 2023).

Consequences

Figure 2. Diffusion Tensor Imaging: Fraction Anisotropy



Evidence from brain scans increasingly supports these observations. Where diffusion tensor imaging detects lower fractional anisotropy alongside higher radial diffusivity, especially within frontal white matter, the Superior longitudinal fasciculus, and connections linking the cerebellum to frontal regions, a breakdown in myelin integrity and fiber alignment becomes evident **(Figure)**. Structural anomalies seen through diffusion tensor imaging gain context from functional Magnetic resonance imaging data; such studies record heightened activity in prefrontal areas during working memory exercises, a pattern hinting at effortful compensation due to weakened signal transmission across neural tracts (Brinkman et al., 2012; Reddick et al., 2006; Tanedo et al., 2022; West et al., 2020). Despite unremarkable results on basic behavioral tests, altered activation patterns imply diminished processing ease. Under heavier mental loads, particularly later in life, previously concealed weaknesses may surface.

METHODS

A systematic review of the current academic literature was performed to investigate the impact of childhood brain cancer treatments on white matter development and advanced cognitive functioning. The search included a set of keywords **(Table 1)** and occurred from December 2025 to April 2026, with studies published from 2000 to 2025 to include both research and developments in neuroimaging and survivorship outcomes. Sources were primarily identified through PubMed/MEDLINE.

Table 1. Literature Search Strategy for Pediatric Brain Tumor Neurocognition

Literature Search Strategy and Criteria Used to Identify Studies on Pediatric Brain Tumors and Neurocognitive Outcomes

Category	**Search Terms**
Tumor Type & Location	"medulloblastoma" OR "ependymoma" OR "astrocytoma" AND "fourth ventricle" OR "posterior fossa" OR "supratentorial"
Treatment	"chemotherapy" OR "cranial radiation" OR "proton therapy" AND "pediatric brain tumor"
Cognitive Outcomes	"executive function" OR "working memory" OR "attention" OR "processing speed"

Imaging	"white matter" OR "fractional anisotropy" OR "diffusion tensor imaging" OR "structural connectivity"
Study Type	"observational study" OR "clinical trial" OR "systematic review" OR "meta-analysis"

Inclusion

The review focused on pediatric populations diagnosed with brain tumors commonly associated with disruption of developing neural pathways, including medulloblastoma, ependymoma, astrocytoma, and other posterior fossa tumors. These conditions were emphasized because of their proximity to structures such as the cerebellum, brainstem, and major white matter tracts that support communication between posterior and frontal brain regions. Particular attention was given to treatments frequently used in these populations, including chemotherapy, cranial radiation, and proton-based radiation therapy, due to their potential to affect myelination and long-term brain network organization during periods of active development.

Studies that looked at pediatric patients who had recovered from brain tumors that started in childhood and reported results pertaining to white matter integrity, brain connectivity, or neuroimaging markers like functional imaging, diffusion tensor imaging, or magnetic resonance imaging were accepted. Measures of cognitive or executive functioning, such as working memory, attention, processing speed, or organizational abilities, had to be included in studies.

Exclusion criteria

Research that focused on adult brain tumors exclusively is not considered in this review since it looks at treatment outcomes during the period of active brain development, ages 0-18. Studies were removed from the analysis if they did not have neuropsychological outcome measures, such as executive functioning, working memory, attention, or processing speed measured by neuropsychological testing, or had no neuroimaging results related to white matter integrity, including diffusion tensor imaging, magnetic resonance imaging, and functional magnetic resonance imaging. In addition, case studies without full-text access were removed due to a lack of sufficient evaluation and replication. Any study that did not define participant characteristics, treatment age, type of tumor, treatment characteristics, chemotherapy, cranial radiation, proton therapy, or define outcome with quantitative data was also not included.

Study Process

Only meta-analyses, systematic reviews, and peer-reviewed studies that offered adequate methodological detail and understandable outcome data were kept for analysis. Thirteen studies were included in the final synthesis after completing a full-text review and meeting all inclusion criteria. Backward reference searching was used to find more supporting publications, which helped identify important foundational research.

The relationship between treatment timing and ongoing maturation was emphasized throughout the chosen literature. Disruption of myelin-producing cells, changes in white matter tract integrity, and modifications to large-scale brain connectivity were the main focus of the evidence. To identify consistent patterns linking stronger executive functioning to white matter organization, structural imaging results were considered alongside performance. The effects of different tumor types, treatment approaches, and developmental stages at the time of intervention were also looked at. By combining imaging, behavioral, and clinical data, this method made it possible to understand the potential long-term effects of pediatric brain tumor treatments on attention, planning, working memory, and self-regulation.

RESULTS

Table 2. White Matter Outcomes in Pediatric Brain Tumor Survivors

Summary of White Matter Integrity Results From Pediatric Brain Tumor Survivor Neuroimaging Studies

Study Population	**Sample Characteristics**	**Brain Regions Examined**	**Key White Matter Findings**
Childhood cancer survivors	17 survivors, mean age ≈14 years	Inferior fronto-occipital fasciculus; corpus callosum	Slower processing and motor speed
Long-term survivors by radiation type	43 survivors, ≥7 years post-treatment	Multiple association tracts	Higher white matter integrity following proton therapy compared to photon therapy

Pediatric survivors	26 children, ages 9–14 years	Superior longitudinal fasciculus; anterior corona	Reduced integrity linked to attention and processing speed deficits

White Matter Outcomes

Young people who survived brain tumors often show weaker structure in their wiring when measured against those without such medical histories. One study looked at 17 children once treated for cancer, six who had medulloblastoma, and matched them by age with 17 others, average age near 14, using an advanced scan called diffusion tensor imaging. This technique reveals fine details within white tissue; results indicate diminished coherence in key connections like the path joining vision and thinking areas and the forward bridge between brain hemispheres (Reddick et al., 2006; Brinkman et al., 2012) **(Table 2)**. Where signal transmission proved less efficient, tasks involving thought pace and movement took longer, suggesting form affects function. Though ages varied from under nine to nearly seventeen, patterns remained similar across participants (Reddick et al., 2009).

Among survivors observed years after treatment, differences emerged based on radiation usage. Children exposed to standard X-ray therapy showed reduced white matter health alongside weaker cognitive results when compared to unaffected peers and those receiving proton beams. Years post-intervention, brain imaging revealed structural patterns in the proton group closer to normal development. Where photons were used, impairments persisted over time. Survivors given protons performed better on thinking tests, aligning more with typical functioning. One study notes these findings point toward less disruption in neural tissue with proton use. Long-term data support this trend without confirming causation.

A different investigation involving young people between nine and fourteen showed microstructural disruptions to key brain connections, including the superior longitudinal fasciculus and the anterior corona radiata, when set against those without prior trauma **(Table 2)**. Although intact function often depends on these neural routes, they help bridge forward-thinking parts of the cortex with zones managing focus and decision coordination. Slower performance emerged among children here regarding how fast information was handled, the ability to manage multiple inputs at once, and mental flexibility during task transitions. Where shifts occurred in tissue detail, patterns appeared across readings tied to molecular spread, seen by some as a signpost for insulation quality in nerve fibers (Glazer et al., 2023).

Executive Function Outcomes

Looking more closely at executive abilities brings into focus how white matter damage affects daily thinking. In an observation of adults who had childhood medulloblastoma, tested around age 29, roughly 18 years post-diagnosis, it emerged that three out of four showed weaknesses in areas such as switching focus or adapting thought patterns. Such challenges are tied back to subtle changes in the brain's front-region wiring structure. Evidence suggests early disturbances may echo through mental performance across decades (Brinkman et al., 2013).

Evidence gathered through structured research summaries backs these trends. Collections of investigations involving many young individuals between 1 and 20, those receiving proton therapy often maintained stronger mental performance than peers given photon treatment. While similarities appeared in some areas, abilities such as overall intellect and visual problem solving stood out more favorably among proton recipients. These findings highlight a steady link between preserved brain tissue structure and stable cognitive function throughout growth stages(Lassaletta et al., 2023; Patel et al., 2025).

Metastasis and spread of brain tumors

Brain tumors fall into two classifications, primary and metastatic. Primary tumors begin in the central nervous system, while metastatic tumors are formed when cancer cells travel to the brain from a different area in the body through the blood circulation. Adults develop distant tumors more frequently than children do; distant tumors typically spread through blood vessels and gain entry into the brain through an arterial route (Johns Hopkins Medicine, n.d.). After traveling in the blood to the brain, many metastatic tumor cells will settle in the brain, where they form secondary tumors that will compress and disrupt the surrounding neural structures.

Most pediatric brain tumors are primary brain tumors; however, it is important to understand how primary tumors may have varying levels of structural vulnerability depending on past factors, such as the degree of development before tumor formation. Whether the tumor develops in the brain or gains entry into the brain through blood circulation, its size will exert force on adjacent white matter tracts; it is also possible for the development and expansion of a tumor to compromise blood flow to the adjacent white matter tracts or interfere with ongoing myelination of those tracts. This is of particular concern in pediatric patients, where the white matter pathways, such as the superior longitudinal fasciculus and corpus callosum, are still developing (Caris Life Sciences, 2026). Understanding of these processes will help to explain how critical the time in development is to long-term executive functioning.

Long-Term Patterns and Consequences

Looking back across growth patterns, earlier therapy was linked to stronger breaks in brain wiring plus harder thinking struggles. Though young patients got care fast, those receiving standard radiation usually faced lasting delays in thought pace, along with planning issues. In one case, children surviving medulloblastoma showed weaker signal flow behind the brain when set beside peers with different cancers, a gap that stayed firm even later on (Mulhern et al., 2013).

Yet years later, those receiving advanced methods such as proton radiotherapy displayed white matter structure resembling that of unaffected individuals, hinting at limited damage whenever normal neural areas were protected (Mash et al., 2023). Still, within these cases, slight difficulties in higher-order thinking persist for certain people, implying that adaptive rewiring, where neural pathways shift following harm, does not always recover standard growth patterns, particularly across intricate mental systems.

Younger patients often show weaker white matter integrity after tumor treatment when compared to their older peers, a pattern that coincides with sharper challenges in decision-making and planning tasks. Closer observation from the start may support better outcomes as these children develop, especially where thinking skills and brain structure are concerned.

DISCUSSION

White matter disruption and developmental timing

Age at treatment is an important value when it comes to long-term white matter integrity and executive function outcomes in survivors of pediatric brain tumors. Research shows that earlier exposure to chemotherapy or radiation significantly impacts the integrity of large white matter tracts over time (Mulhern et al., 2005; Palmer et al., 2001). All studies reported that receiving chemotherapy or radiation at a younger age was associated with significantly lower integrity of several white matter tracts identified in a systematic review: superior longitudinal fasciculus, corpus callosum, inferior fronto-occipital fasciculus, and anterior corona radiata (Reddick et al., 2003; Mabbott et al., 2006) **(Table 2)**.

For instance, measures of cognitive function at the basic level, such as simple reaction time, responding to a light, step 1 instruction, recalling one item, and executing one step, were reported to be intact or showed to be of least difficulty in many survivors (Butler & Haser, 2006). However, measures requiring greater amounts of executive function showed a strong level of impairment, such as multi-step working memory tasks, repeating a sequence of numbers backward while simultaneously tracking changing visual details, cognitive flexibility tasks, sustained attention tasks, and continuous performance testing of an event for an extended period with no errors. These measures rely on coordination between the frontal and parietal networks, which depend heavily on the superior longitudinal fasciculus (Mabbott et al., 2009).

Disruption in the function of these pathways has impacted or limited the brain's ability to integrate information across different areas of the brain. This has resulted in decreased ability to process information at an appropriate rate or with appropriate accuracy when task-related demands increase. The reduction seen in these tracts is correlated with worse attention and a slower rate of processing for survivors of childhood brain injury **(Table 2)**.

Functional consequences of white matter disruption

The available research suggests that white matter damage does not eliminate cognition but rather changes the efficiency of processing under greater higher-order cognitive demand workloads. This trend is especially prominent when examining tasks similar to those people would encounter in a normal daily situation. Yet the fact that the same is not true for similar tasks reflects preserved basic function but impaired network integration.

This over-activation represents efforts by the brain to recruit more resources to sustain performance (Robinson et al., 2010), but such efforts are limited and break down with increasing task demand, especially when tasks require sustained attention or flexible switching rules (Kesler et al., 2023).

Table 3. Executive Function Outcomes in Pediatric Brain Tumor Survivors

Executive Functioning Outcomes Reported in Pediatric Brain Tumor Survivors From Studies

Study Population	Sample Characteristics	Cognitive	Executive Function Outcomes
Adult survivors of childhood medulloblastoma	50 adults, mean age ≈29 years	Cognitive flexibility; executive control	75% impaired in at least one executive domain; linked to frontal white matter
Systematic review and meta-analysis	Hundreds of patients, ages 1–20 years	Intelligence; processing speed; reasoning	Proton therapy is associated with better cognitive preservation than photon therapy

Approximately 75% of adult survivors of childhood medulloblastoma demonstrate some degree of impairment in one or more regions of executive function, particularly related to cognitive flexibility and inhibitory control **(Table 3)**.

Role of treatment type and radiation exposure

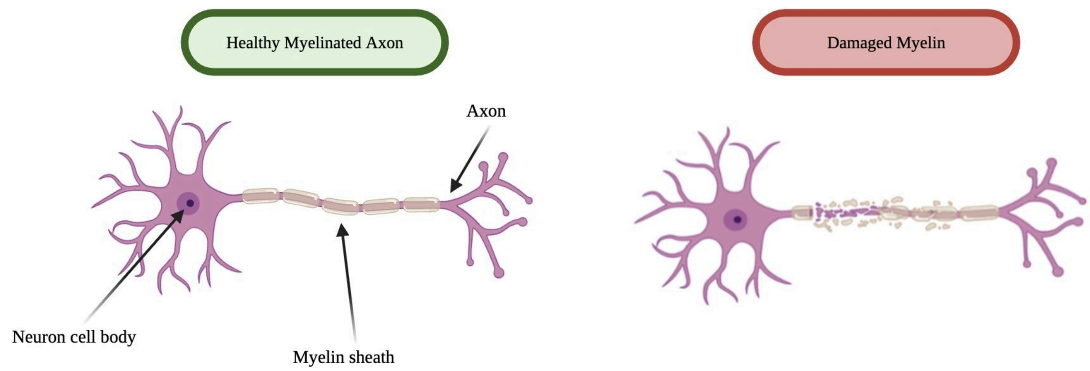
Table 4. Age at Treatment and Neurocognitive Outcomes

Relationship Between Age at Treatment Exposure and Long-Term Neurocognitive and Executive Functioning Outcomes

Tumor Type	Age at Treatment	Treatment	Long-Term Outcome Pattern
Medulloblastoma and related tumors	3–12 years	Photon radiotherapy	Younger age is linked to persistent white matter disruption and executive deficits
Mixed pediatric brain tumors	Childhood	Proton therapy	Partial preservation of white matter; milder long-term cognitive effects

Children who received proton therapy had greater preservation of white matter integrity than those who received photon-based radiotherapy because radiation from protons is delivered more precisely and limits exposure to developing neural tissues **(Table 2; Table 4)**. On the other hand, photon-based radiation consistently resulted in more significant disturbances to developing association pathways. Children treated between the ages of 3 and 12, a period of high rates of myelination, exhibited the most persistent executive function and processing speed impairments **(Table 4)**.

Figure 3. Myelination: Healthy vs. Damaged



The impact of timing on developing oligodendrocytes and ongoing myelination within the developing brain is a contributing factor to the vulnerability of these children during the period of treatment when neural networks continue to develop (Kahalley et al., 2020; Yock et al., 2016). While treatment impacts long-term outcomes of the patient, young patients also appear to suffer the most long-term disruptions as it relates to cognitive function, and when imaging involves some sort of disruption.

Neural efficiency and compensatory activation

The tendency for many survivors to have increased activations in the prefrontal cortex in studies utilizing imaging techniques suggests a benefit for the individual regarding their cognitive performance. However, an increase in prefrontal activation will also create less efficient neural processing and performance as opposed to enhanced function or ability (Kesler et al., 2011).

As task demands increase, cognitive-related areas become overwhelmed, resulting in slower response and reduced accuracy (Barulli & Stern, 2013).

These findings suggest that cognitive deficits are not only a reflection of an isolated area of brain damage but are a result of disruption in the communication between different cerebral systems or networks. This type of disruption is partly due to the superior longitudinal fasciculus, because of its importance as a communication pathway.

Integrating structural, functional, and developmental evidence

Observations made based on various types of imaging and cognitive testing lead to a similar conclusion. There was a significant correlation with reduced white matter in association with executive impairment, strongly affected by age at the time of treatment.

The greatest long-term negative effects occur in those being treated when they are still relatively young due to the fact that treatments affect the processes of the formation of active myelin and networks. Older children and adolescents experience partial sparing of the white matter pathways and improved executive functioning; however, they may still show subtle deficits (Mulhern et al., 2005).

Physiological Stress Effects

When it comes down to the effect of white matter development, it is also important to understand the psychological effects. Children who are being treated for brain cancer have reported having a lot of stress due to their long periods in the hospital, undergoing many traumatic experiences, and uncertainty about what might happen once they get better. This prolonged stress and traumatic experiences would typically indicate the development of Post Traumatic Stress Symptoms, and they have also recently been linked to a decrease in cognitive abilities, such as the ability to concentrate and to process information quickly (Leenders et al., 2024). Post-Traumatic Stress Symptoms may not alter a person's brain structure; however, they do affect cognitive functioning by impairing attention control and emotion regulation. Therefore, cognitive outcomes should be considered as an outcome of the combination of biological, neurological, and psychological factors working together and not just simply a result of an injury to the brain.

Clinical Implications

The data collected highlights the importance of identifying children who have been treated early in their development as having a higher risk for long-term effects than children who are older at the time they receive treatment. Signs of neurocognitive decline, such as decreased fractional anisotropy or altered tracts, may be indicators of potential for long-term cognitive impairment.

The use of cognitive rehabilitation, school-based supports, and adaptive learning strategies is likely to have the greatest impact when commenced prior to the child reaching the age of their neural plasticity, since that would be a time when the brain is able to adapt better. The data suggest that strategies that use a lower dose of radiation to treat a child, such as proton therapy, could positively impact a child's ability to achieve optimal long-term cognitive outcomes **(Table 4)**.

CONCLUSION

Brain tumor diagnosis in children can have a long-term impact on their brain's white matter development, which will hurt their executive functioning, particularly if treatment was given during crucial brain development, as structural changes to the brain's white matter have been correlated with long-term challenges with executive functionalities. However, although children with brain tumors may have the potential for some degree of neuroplasticity to allow for some compensation during the long term, the ability for children with brain tumors to regain the efficiency of cognitive functioning will be more limited in complex tasks due to the biological and emotional stresses children may be exposed to. Overall, understanding the combined impact of treatment timing, brain structure, and psychological stress is very important for improving long-term support and interventions for pediatric survivors.

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