KU LEUVEN

FACULTY OF MEDICINE

The association between neuroimaging and neurocognition in pediatric medulloblastoma patients: a systematic review

Master Thesis proposed to achieve the degree of master in medicine by

WAUTERS Maarten

Unit: Pediatric Hematology and Oncology

Department: Pediatrics

Promotor: Prof. dr. JACOBS Sandra
Mentor: SLEURS Charlotte

Leuven, 2018-2019

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COVER LETTER

Dear members of the editorial board,

We wish to submit our manuscript “The association between neuroimaging and neurocognition in pediatric medulloblastoma patients: a systematic review” for publication in your journal.

With increasing life expectancy of pediatric medulloblastoma patients, the impact that treatment has on their lives is becoming more relevant. Neurocognitive impairment, seen in medulloblastoma survivors, is often attributed to the therapy they received. Optimization and personalization of therapy to limit cognitive damage in medulloblastoma survivors is crucial to improve functional outcome and quality of life of these patients (and their families).

Previously, several authors have published neurodevelopmental models trying to explain the mechanism by which neurocognition of pediatric brain cancer patients is influenced. Also, more studies have been conducted using magnetic resonance imaging to investigate changes in neuroanatomy in survivors of medulloblastoma and other brain tumors.

With this systematic review we summarize results of the published studies that search for associations between neuroimaging and neurocognition in patients that were treated for childhood medulloblastoma.

We are of the opinion that our manuscript deserves to be published in your journal for multiple reasons: (1) We are, as far as we know, the first to produce a systematic review of the current literature available on associations between imaging and cognition in this patient population. (2) This manuscript provides a summarization of the current known information on medulloblastoma, it’s treatment, the influence of treatment on neurocognition and the role of neuroimaging. (3) We deliver evidence in support of a neurodevelopmental model that uses neuroanatomical changes to explain the mechanism by which cancer treatment causes cognitive damage in children. (4) With this paper, we provide support for further research on the role of neuroimaging parameters in predicting cognitive outcome of patients and on new possible points of intervention to limit neurocognitive damage.

With this systematic review, we want to contribute to future development of more personalized therapy to further improve the care for pediatric medulloblastoma patients.

We declare that this is a unique work, which was not published or sent in for publication elsewhere. We have no conflict of interest or financial interest to report. The writing of this review was approved by the Ethics Committee of the University Hospital of Leuven, Belgium.

We hope you will enjoy reading this manuscript and that you are willing to consider it for publication in your journal.

Yours sincerely,

Maarten Wauters

ABSTRACT

Medulloblastoma is a malign posterior fossa brain tumor, mostly occurring during childhood. Improving survival rates have caused functional outcome of medulloblastoma patients to gain in importance. The therapy these children receive can be harmful to their developing brains. This review summarizes the relevant literature on associations between neuroimaging and neurocognitive changes in patients that were treated for pediatric medulloblastoma. This is useful (1) to identify underlying neuroanatomical processes that explain neurocognitive changes caused by medulloblastoma treatment, (2) to work towards the use of neuroimaging to estimate cognitive outcome of medulloblastoma patients and (3) to explore possible points of intervention that improve cognitive functioning.

We searched the PubMed/Medline database with search terms belonging to three categories: medulloblastoma, neurocognition and imaging. After selection and manual reference tracking, we included 20 articles that fitted the aim of our review.

White matter macro- and microstructure disruption, investigated by anatomical and diffusion-weighted magnetic resonance imaging, plays a crucial role in the development of cognitive deficits in childhood medulloblastoma survivors. This supports the earlier published neurodevelopmental model by Wolfe that states that changing white matter is the neuroanatomical mechanism by which brain cancer treatment causes cognitive damage in the developing child. Also, diffusion-weighted imaging is potentially useful to predict processing speed and other cognitive outcomes. This can help in personalizing therapy to improve neurocognition of childhood medulloblastoma survivors.

In the future, large prospective studies, using diffusion-weighted imaging, should be performed to further investigate possible neuroimaging parameters with predictive value and intervention opportunities in pediatric medulloblastoma patients.

NEDERLANDSTALIGE SAMENVATTING

Medulloblastoma is een maligne fossa posterior hersentumor die vooral voorkomt bij kinderen. Verbeterde overleving van medulloblastoma-patiënten heeft ervoor gezorgd dat hun functionele uitkomst belangrijker geworden is. De kankerbehandeling die deze kinderen krijgen kan schadelijk zijn voor hun zich ontwikkelende hersenen. Deze literatuurstudie vat de relevante studies over associaties tussen neurobeeldvorming en neurocognitieve veranderingen bij patiënten die behandeld werden voor pediatrische medulloblastoma samen. Dat is nuttig (1) om onderliggende neuro-anatomische processen te identificeren die de neurocognitieve veranderingen, veroorzaakt door medulloblastoma-behandeling, verklaren, (2) om te werken naar het gebruik van beeldvorming om cognitieve uitkomst in te schatten en (3) om interventiepunten te ontdekken die het cognitief functioneren van medulloblastoma-overlevenden verbeteren.

Wij zochten in de PubMed/Medline database met zoektermen die behoren tot drie categorieën: medulloblastoma, neurocognitie en beeldvorming. Na selectie en het manueel doorzoeken van referenties, includeerden we 20 artikels die binnen onze onderzoeksvraag pasten.

Verstoring van de macro- en microstructuur van witte materie, onderzocht met anatomische en diffusie-gewogen kernspintomografie, speelt een cruciale rol in de ontwikkeling van cognitieve tekorten in patiënten die medulloblastoma doormaakten in hun kindertijd. Dit ondersteunt het eerder gepubliceerde neuro-ontwikkelingsmodel van Wolfe dat stelt dat veranderende witte materie het neuro-anatomische mechanisme is via hetwelk hersenkankerbehandeling cognitieve schade veroorzaakt in het zich ontwikkelende kind. Het is ook zo dat diffusie-gewogen beeldvorming mogelijk nuttig is om verwerkingssnelheid en andere cognitieve uitkomsten te voorspellen. Dit kan helpen in de personalisatie van therapie om neurocognitie van medulloblastoma-overlevenden te verbeteren.

In de toekomst zouden grote prospectieve studies, die diffusie-gewogen beeldvorming gebruiken, moeten worden uitgevoerd om verder onderzoek te voeren naar mogelijke neurobeeldvorming-parameters met voorspellende waarde en interventiemogelijkheden in pediatrische medulloblastoma-patiënten.

INTRODUCTION

Epidemiology

Medulloblastoma (MB) is a malign embryonic neuroepithelial brain tumor that occurs in the cerebellum[1–3]. It is a mostly pediatric cancer that represents approximately 10% of brain tumors in children[1,4]. Overall incidence rate is estimated at 1.58 per million per year and is highest in 1–9 year-olds[5]. Overall survival rates of pediatric MB patients have been reported around 70% and 63% for 5-year and 10-year survival respectively[4,6–8]. Survival is influenced by many factors, one of these factors being age at diagnosis. Patients who are older when diagnosed with MB have higher 5-year survival rates compared to those who are younger (47.4% (<1 year), 64.5% (1–4 years), 74.2% (5–9 years), 81.5% (10–19 years))[7].

In studies and in deciding on a treatment strategy, patients are often divided in a standard-risk and a high-risk group. Patients aged over 3 years with residual tumor <1.5 cm² post-surgery and without metastasizes are categorized as standard-risk patients. Sometimes, patients with M1 disease are also considered to be part of the standard-risk group. Patients with larger residual tumor after resection or metastatic disease are considered to be part of the high-risk group[9,10]. There is a significant difference in survival between patients with standard-risk and high-risk disease. In standard-risk MB patients, a 5-/10-year overall survival rate of 87.91%/54.77% was reported versus 66.17%/36.76% in a group of non-metastasized high-risk patients with residual tumor and 39.22%/33.61% in patients categorized as high-risk with M2 or M3 disease[11]. In other studies, long term survival was estimated around 85% for standard-risk patients and 70% for high-risk patients[1,12].

Histological classification also has an influence on survival. Large cell/anaplastic MB patients have a considerably poorer prognosis than classic MB patients[8,13–16]. Their 5-year overall survival is estimated at 57% versus 94% in average-risk patients with classic MB[8].

More recently, MB has been found to exist of four molecular subgroups: wingless (WNT), sonic hedgehog (SHH), group 3 and group 4[17,18]. SHH-driven tumors mostly appear in infants and adults, while group 3 tumors are seldom found in patients older than 10 years old. WNT and group 4 MB have a wider age-distribution with a median age of around 9 to 10 years old[17,19]. WNT tumors have a very good prognosis. Multiple studies have reported 5- and 10-year overall survival rates of 90-95% in children[19–21]. Group 3 patients have the worst prognosis with a 5-year overall survival of 45% in infants and 58% in children[17–19]. Because of this, it has been proposed to include group 3 MB in the high-risk group, independent of other factors[22].

Treatment

Treatment of MB exists of surgical resection, radiation therapy (RT) and chemotherapy (CT). Maximal safe surgical resection is a vital part of MB therapy because the extent of excision is an important prognostic factor[23–25]. If it implicates a high risk of neurological morbidity, removal of small residual portions is not indicated. A study on this subject did not show a difference in overall survival between gross total and subtotal resection[26].

RT is part of the standard-of-care therapy in children older than 3 years. Better overall survival rates are seen compared to patients who are not treated with RT[7]. For children with standard-risk disease, a craniospinal radiation dose of 23.4 Gy with additional posterior fossa (PF) boost of 32.4 Gy, bringing the total PF dose to 55.8 Gy, is the common treatment[10,27–29]. Maintenance CT is usually added after RT[28]. A combination of lomustine, vincristine and cisplatin is widely used[10]. An alternative combination of cisplatin, vincristine and cyclophosphamide gives similar outcomes[27,29].

There is no clearly defined standard-of-care practice in the management of high-risk MB disease. A RT schedule used for high-risk patients exists of craniospinal doses of 36 Gy for M0-1 patients and 39.6 Gy for M2-3 patients with a boost on the primary tumor bed, bringing the total dose there to 55.8 Gy[12]. The schedule with 36 Gy as craniospinal dose was used for all high-risk patients in the 2012 Children's Oncology Group (COG) study[30]. Hyperfractionated RT has been discussed as an alternative treatment option for patients with high-risk disease[31,32]. No significant differences in overall intelligence were found compared to patients treated with standard RT[33]. Different CT schedules have been described, including carboplatin as radiosensitizer (in metastasized disease) and a maintenance schedule with cyclophosphamide and vincristine (and sometimes cisplatin)[30].

In children younger than 3 years, RT is avoided or delayed as long as possible because of its damaging influences on the infant's brain[1,34,35]. Three different treatment strategies are described as alternatives in this population[35]. All of them make use of multiagent systemic CT, respectively combined with: (1) intraventricular methotrexate (MTX)[36–38], (2) high-dose CT with stem-cell transplantation[39–41] (sometimes only used as salvage therapy at relapse)[42] and (3) local RT (radiation dose to PF with boost to primary tumor site)[43].

Effects on neurocognition

With increased survival of pediatric MB patients, due to improved treatment strategies, quality-of-life has gained more importance[44,45]. Minimizing iatrogenic damage on the patients' functioning plays an important role in this[6]. Survivors of childhood MB have increased risk of many neurological and psychological defects[46,47]. In this paper, we will focus on the harmful effects of MB treatment on cognitive functioning.

Cranial RT has a negative effect on processing speed (PS) and intelligence quotient (IQ)[48]. Negative effects of treatment on PS and a decline in IQ, reading, spelling and mathematical skills have also been reported in pediatric MB patients[49–52]. IQ is more severely decreased in high-risk MB patients who received higher doses of cranial RT[49]. Pediatric MB survivors have a decreased ability to learn new things, which causes them to have poorer intellectual outcomes than their healthy peers later in live[50]. Adult survivors of childhood MB seem to be less likely to obtain a college degree and to gain social independence[46].

In 2008, Palmer SL published a conceptual model for neurodevelopmental impacts of treatment on pediatric patients with MB **(figure 1)**[53]. Processing speed has a central role in this model, which is largely based on the *developmental cascade model* of normal development[53–55].

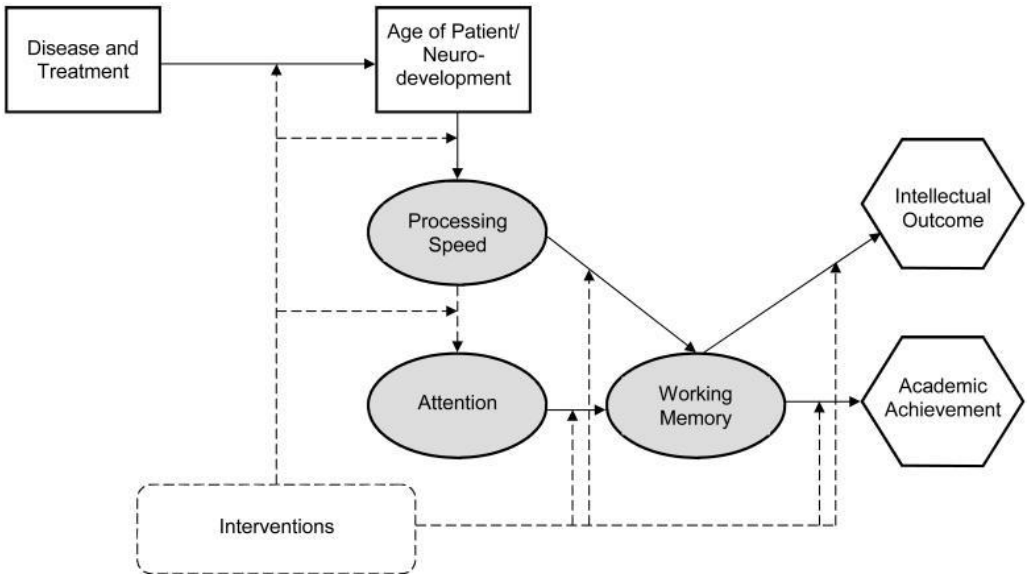

Figure 1: *Proposed developmental cascade model by Palmer*
Note. *Proposed conceptual model to understand neurodevelopmental impacts of diagnosis and treatment of pediatric MB. Solid lines indicate associations derived from review of the present literature. Broken lines indicate suggested areas of future research*[53].

Wolfe et al. (2012) developed a model for childhood PF tumors in which white matter is implemented as a neuroanatomical substrate, influenced by tumor and treatment related factors and age, gender and neurodevelopment **(figure 2)**. They did not give PS a primary role in their theory but consider it to be on the same level as the other core cognitive abilities: attention, working memory and general executive functions (EFs)[56].

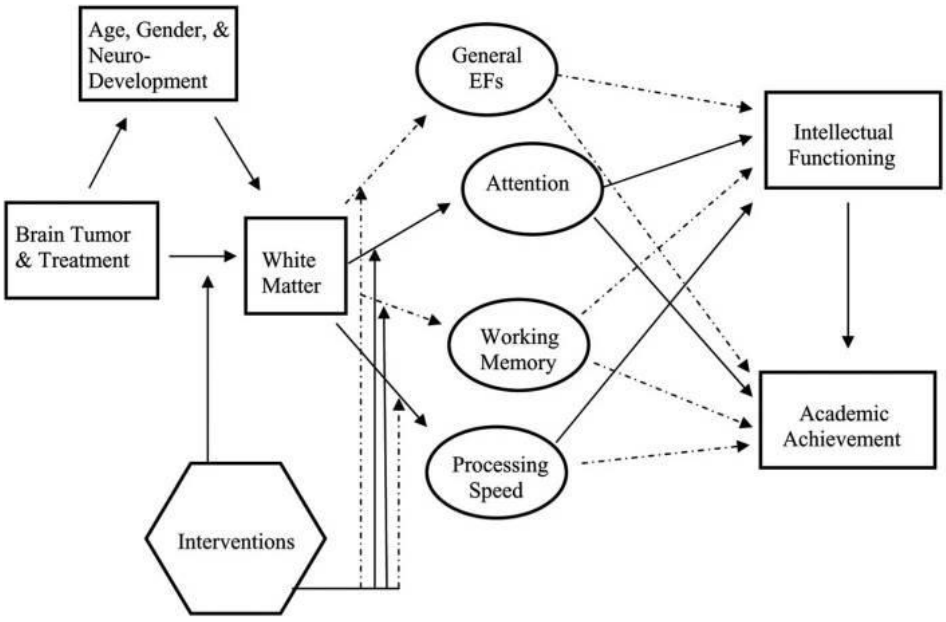

Figure 2: *Proposed neurodevelopmental model by Wolfe.*
Note. *A theoretical model of the effects of pediatric brain tumor and its treatment on intellectual functioning and academic achievement. Solid lines represent findings from studies with pediatric brain tumor survivors. Dotted lines represent relationships that are theoretically plausible but have yet to be investigated in the literature*[56].

Recently, King et al. (2017) constructed a new neurodevelopmental model, combining Palmer's and Wolfe's theories **(figure 3)**. In this model, processing speed is the central cognitive ability that

influences the others, although all three core cognitive skills examined in this study make unique contributions to intelligence and academic achievement[55]. Neuroanatomical factors were not included in this model. In contrast to the other models, the revised model by King was developed for all pediatric brain tumor patients and not solely for those with MB (Palmer's model) or PF tumors (Wolfe's model)[53,55,56].

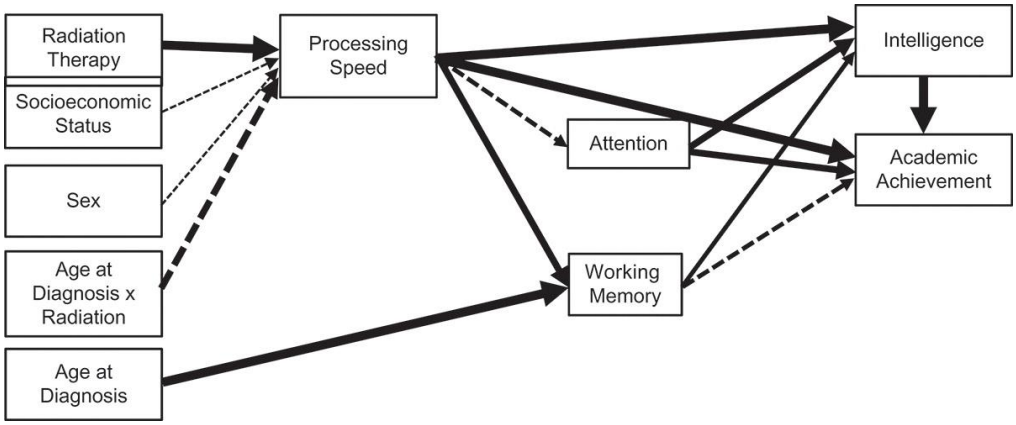

Figure 3: *Revised neurodevelopmental path model by King.*
Note. *Arrow thickness indicates the strength of the relationship based on standardized effect sizes. Small effects have thinner lines and larger effects have thicker lines. Solid arrows indicate significant effects; dotted arrows signify relationships that should be explored in future research due to possible underpowered relationships[55].*

Considering our aim, Wolfe's model **(figure 2)** is the most relevant one for this review, because it includes a neuroanatomical factor, namely changing white matter, in explaining the influence of brain cancer treatment on cognition.

Neuroimaging

Several authors have suggested neurobiological models focusing on white matter to explain changes in cognition in survivors of pediatric brain cancer[56,57]. Finding neurobiological mechanisms that relate to the impact of pediatric MB treatment on normal brain functioning can contribute to the development of therapeutic or preventive interventions[55,58]. Neuroimaging can be used to investigate which anatomical changes are caused by MB treatment and which of them are associated with certain cognitive outcomes[45,53,55].

Multiple magnetic resonance imaging (MRI) modalities have been used to explore changes occurring in patients treated for MB during childhood. White matter changes have been regularly linked to treatment of children with MB (and children with other brain tumors)[56,59–61]. For example, normal white matter volume decreases after treatment for MB and decreases faster if the cranial radiation dose is higher[58]. These white matter changes have been proposed as a possible anatomical substrate for negative influences of brain tumor treatment on cognition[56] **(figure 2)**.

Anatomical MRI investigations (T1- and T2-weighted imaging) can be used to evaluate changes of normal white matter volume or white matter lesions[62]. Fluid attenuated inversion recovery (FLAIR) is an MR sequence which can be used to evaluate white matter lesions, especially when these are located in the periventricular brain area[63].

To investigate certain changes in brain structures that the earlier mentioned techniques cannot visualize, diffusion-weighted imaging (DWI) can be used. With diffusion-weighted MRI, information about tissue can be obtained through the amount of motion of water within the tissue[64]. The apparent diffusion coefficient (ADC) can be calculated and used to create ADC maps to visualize diffusion in brain tissue[65]. ADC indicates the magnitude of diffusion within a voxel. A high ADC-value means that tissue

has free diffusion. A low value means restricted diffusion[64]. In areas of normal white matter, ADC is rather low because of restriction of water diffusion by the fiber tracts[64,65]. In patients with that received RT, white matter tracts are damaged and higher ADC-values are seen[66].

Diffusion-tensor imaging (DTI) is an extension of DWI that allows us to measure the preferential direction of water diffusion. The direction of diffusion is associated with the orientation of white matter fibers[67]. Because of this, DTI can be used to estimate changes in white matter fiber organization quantitatively and to visualize connections between different regions of the brain (DTI tractography) [45,62]. Fractional anisotropy (FA) is a parameter that gives information about the amount of distortion of diffusion within a voxel. If FA is low (close to 0), diffusion is more isotropic (random, without a net direction). A value that is high (close to 1), indicates that diffusion happens more in one direction, that water diffusion is restricted[64]. FA is thus used in research to estimate the influence of brain cancer treatment on the microstructure of white matter fiber tracts. Multiple studies have shown a decreased FA in patients compared to controls, indicating damage to white matter tracts in the brain[59,68].

Focal hemosiderin deposition (FHD) lesions seen on MRI are a frequently occurring finding after RT for pediatric brain cancer[69]. FHD lesions exist of microbleeds and cavernomas. These lesions can indicate small vessel disease[70], which is known to be related with RT in childhood brain tumor survivors[70,71]. Often the term cerebral microbleed (CMB) is used for these lesions[72]. It appears that CMBs observed with MRI can correspond with multiple histopathological conditions such as vasculopathy, erythrocytes and hemosiderin-laden macrophages[72,73]. CMBs can be detected with T2*-weighted gradient-recalled echo (GRE) imaging and with susceptibility-weighted imaging (SWI)[74,75]. SWI is currently seen as a superior investigation compared to T2* GRE[76].

Functional MRI (fMRI) is a technique that is used to see which brain regions are activated during a certain task, performed by the examined subject, by comparing changes in blood-oxygen level dependent (BOLD) signal during this activity[77]. Functional MRI uses deoxyhemoglobin concentration as a tool to estimate oxygen consumption by neurons, reflecting the neuronal activity of a certain part of the brain during a certain moment in time[78,79].

Arterial spin labeling (ASL) is a quantitative MRI technique that is used to map brain perfusion, which is well correlated with brain metabolism. With series of radiofrequency pulses the magnetization of blood is inverted and labelled. Blood perfusion can be visualized and quantified by subtracting the labelled images from control images[80].

Aim

The aim of this review is to identify and summarize associations between neuroimaging parameters and neurocognitive outcome in survivors of MB who received treatment during childhood. We searched and summarized the relevant literature of the last two decades regarding this topic.

METHODS

We used the PubMed search engine to screen the Medline database for relevant publications. The search input exists of three components: (1) medulloblastoma, (2) neurocognition and (3) imaging. The complete search input and algorithm is summarized in **figure 4**. With a systematic working method, we selected the articles that were most relevant for this review.

We found 429 articles using this search strategy. After reviewing the titles, 153 papers were withheld. At abstract stage, 123 articles were excluded for reasons listed in **figure 4**. Of the 30 full-text manuscripts we reviewed, 18 were included. Two additional articles (Palmer et al. (2010)[81] and Palmer et al. (2012)[82]) were identified by manual reference tracking, bringing the amount of included publications to 20.

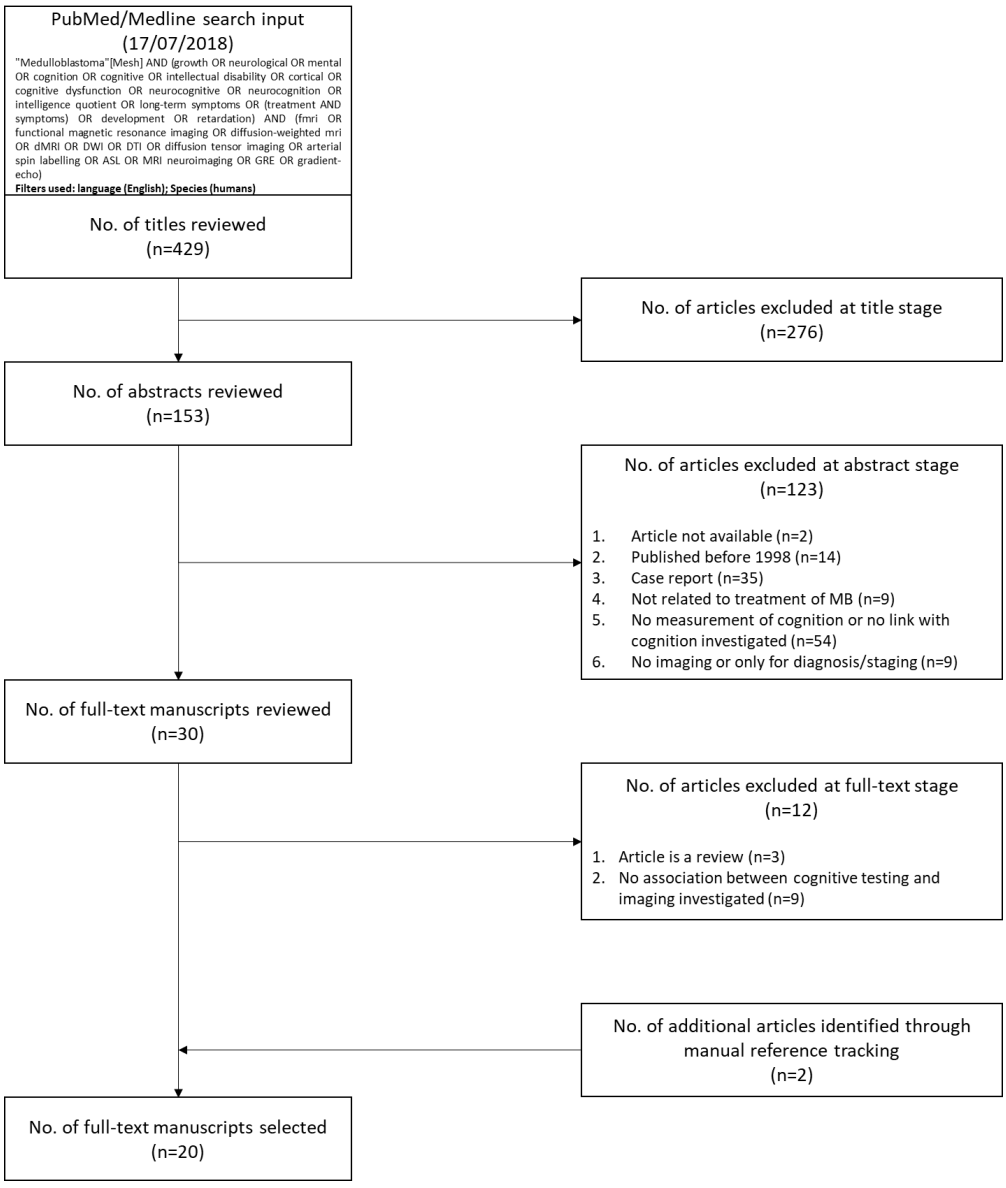

Figure 4: *Flowchart showing the search algorithm and selection process used for this review.*

Included studies were divided into categories according to MRI-modalities (anatomical investigations, diffusion weighted imaging, GRE and fMRI and ASL). In the results section we will describe the most relevant findings of the included papers and our conclusions. More detailed information about the articles can be found in **supplementary table 1**.

RESULTS

Anatomical investigations

1. Normal white matter (NWM) volume

Two publications, with populations of 18 and 42 MB patients, report that lower NWM is associated with lower full-scale intelligence quotient (FSIQ)[83,84]. Another paper, with a bigger study population (n=92) shows that NWM volume at 36 months post-diagnosis is correlated with working memory[85]. Two studies, with smaller study populations (n=20 and n=10) did not find any significant associations with respectively EFs and the general index of Children's Memory Scale (CMS)[86,87].

The first study reported that MB patients have less NWM, lower FSIQ and lower performance intelligence quotient (PIQ), compared to low-grade astrocytoma (LGA) patients (n=18). This suggests an important role for the non-surgical treatment of MB on neuroanatomy and neurocognitive functioning, because in this article, LGA patients are treated with surgery only[83].

2. Normal gray matter volume

No significant associations are reported with regards to normal gray matter volume[84].

3. White matter lesions (WML)

One paper states that WML are correlated with a negative impact on visuospatial planning, common sense judgement and arithmetic reasoning in MB patients who receive intrathecal MTX as part of their treatment (n= 11), which is not the case in patients not treated with intrathecal MTX (n=10)[88]. Another publication reports a significant decline in IQ and mathematical scores in 21 brain tumor patients with WML, including 20 MB patients, versus patients without WML (n=93)[89]. A third article reports a correlation between WML and worse PS, worse perceptual organization, higher distractibility and worse visual motor functioning in a subset of 17 MB patients[90].

4. Brain atrophy

Cerebellar atrophy is correlated with higher distractibility and supratentorial atrophy with low verbal comprehension scores[90].

Reference	**Number of MB pts.**	**Number of non-MB pts.**	**Correlation between** Neuroimaging	Neurocognition	**Results (correlations / significancy)**
Mulhern et al. (1999)[83]	18	/	NWM	FSIQ	R=0.56 (p<0.05)
				VIQ	R=0.49 (p<0.05)
				PIQ	NS
Mulhern et al. (2001)[84]	38	/	NWM	FSIQ	R^2=0.253 (p=0.001) (after controlling for time since RT)
	20			Verbal memory	NS
	25			Sustained attention	NS
	42		NGM	All neurocognitive variables	NS
Riva et al. (2002)[88]	11 / 10	/	WML (PVL)	EFs: - Arithmetic - Comprehension - Block design - TMT B, picture arrangement, object assembly, coding	 p=0.02 / NS p=0.02 / NS p=0.05 / NS NS

				Attention, visual perception, short-term memory, intelligence	NS
Fouladi et al. (2004)[89].	20	1	WML	IQ	Mean decline: -2.46 points/y (p=0.03) Vs. NS in pts. without WML
				WIAT: Math scores	Mean decline: -4.49 points/y (p=0.003) Vs. NS in pts. without WML
				Spelling scores	Mean decline: -4.31 points/y (p=0.0001) Vs. -2.86 points/y in pts. without WML (p=0.002)
				Reading scores	Mean decline: -3.59 points/y (p=0.0001) Vs. -2.42 points/y in pts. without WML (p=0.003)
Brinkman et al. (2012)[86]	20	/	NWM	EFs	NS
Riggs et al. (2014)[87]	10	/	NWM	Learning and memory (CMS)	NS
Khajuria et al. (2015)[90]	17	/	Cerebellar atrophy	Distractibility	Significantly correlated
				Attention, verbal memory, visual-motor function	NS
			Supratentorial atrophy	Verbal comprehension	p=0.039
				IQ, attention, verbal memory, visual-motor function	NS
			WML: supratentorial leukoencephalopathy	PS	p=0.007
				Perceptual organization	p=0.023
				Distractibility	p=0.013
				Visual-motor function	p=0.014
				Attention, verbal memory	NS
Glass et al. (2017)[85]	92	/	NWM	Working memory	p=0.026 (after adjusting for age)
				PS, broad attention, general intellectual ability	NS

***Table** 1: Overview of results of anatomical investigations.*
***Abbreviations:** "CMS" = Children's Memory Scale; "EFs" = executive functions"; "FSIQ" = full scale intelligence quotient; "IQ" = intelligence quotient; "NGM" = normal gray matter volume; "NS" = not significant; "NWM" = normal white matter volume; "PIQ" = performance intelligence quotient; "PS" = processing speed; "pts." = patients; "PVL" = periventricular leukomalacia; "RT" = radiotherapy; "TMT B" = form B of the Trail-Making Test; "VIQ" = verbal intelligence quotient; "Vs." = versus; "WIAT" = Wechsler Individual Achievement Test; "WML" = white matter lesions; "y" = year(s).*

5. Hippocampal subfield volumes

The only article that considers hippocampal subfield volumes reports that smaller volumes of several hippocampal subfields are correlated with poorer verbal associative memory in 11 brain tumor patients, including 10 MB patients[91].

Another study reports a correlation between right hippocampus volume and learning, attention and memory, tested using the CMS, in 10 MB patients[87].

White matter microstructure (diffusion-weighted imaging)

1. Apparent diffusion coefficient (ADC)

In one of the included studies, significantly lower median ADC-values are seen in the hippocampi of 21 MB patients compared to a control group (n=64)[92]. Together with the earlier mentioned studies regarding hippocampal (subfield) volumes[87,91], this suggests a role for disturbed hippocampal structure in poorer memory performance in patients treated for MB.

Two articles report associations between higher white matter ADC-values and lower IQ in a population of 8 MB patients and a subset of 12 patients, including 9 MB patients[92,93]. The first one also reports a significantly lower IQ compared to control subjects. This difference in IQ becomes non-significant after correction for mean ADC[93]. The second article additionally reports associations between ADC in other brain structures, like the cerebral cortex, and IQ[92]. A third study, with a population of 20 MB patients, does not report any significant correlations between ADC of separate brain lobes and multiple EFs[86].

In a group of 6 MB and 11 ALL patients, higher radial diffusivity (RAD), which is a component of ADC, in the left cerebello-thalamo-cortical pathway partly explains the negative effect of MB treatment on working memory[94]. A study with in 20 MB patients shows associations between RAD in several brain lobes and shifting attention and cognitive flexibility[86].

These findings suggest that disrupted white matter tract organization, which causes increased free diffusion is, at least partially, responsible for the influence of therapy on intelligence in MB patients.

Reference	Number of MB pts.	Number of non-MB pts.	Correlation between			Results (correlations / significancy)
			Neuroimaging		Neurocognition	
Khong et al. (2003) [95]	9	/	FA: mean reduction in supratentorial FA		Deterioration in learning capacity: mild/moderate/severe	7% / 20% / 46.2%
Khong et al. (2006) [96]	12	18	FA: difference in WMFA		FSIQ	Adjusted R^2 =0.439 (p<0.001)
					VIQ	Adjusted R^2 =0.237 (p<0.028)
					PIQ	Adjusted R^2 =0.491 (p<0.001)
Mabbott et al. (2006) [93]	8	/	ADC		FSIQ	R=-0.60 (p=0.01)
			FA			R=0.65 (p<0.01)
Aukema et al. (2009) [97]	6	11	Mean WMFA		FSIQ, PSF, MS	NS
			sCC WMFA		PSF	R=0.53 (p=0.03)
			bCC WMFA		PSF	R=0.52 (p=0.03)
			All other correlations between CC WMFA and FSIQ, PSF and MS			NS
			Right IFO WMFA		MS	R=0.49 (p=0.045)
			All other correlations between IFO WMFA and FSIQ, PSF and MS			NS
Palmer et al. (2010) [81]	49	3	FA of 8 clusters		Reading decoding skill (WJ: Word Attack raw score)	R^2=0.516-0.576 (p<0.001)
Brinkman et al. (2012) [86]	20	/	FA	Frontal lobes	All EF	NS
				Parietal lobes (right/left)	Working memory	r=0.52 (p=0.017) / r=0.54 (p=0.01)
				Temporal lobes (right/left)	Cognitive fluency	r=0.58 (p=0.007) / r=0.65 (p=0.002)
			RAD		Shifting attention	r=-0.64 (p=0.002) / r=-0.67 (p=0.001)

				Frontal lobes (right/left)	Cognitive flexibility	r=-0.54 (p=0.01) / r=-0.56 (p=0.01)
				Parietal lobes (right/left)	Shifting attention	r=-0.55 (p=0.01) / r=-0.63 (p=0.003)
				Temporal lobes (right/left)	Shifting attention	r=-0.63 (p=0.003) / r=-0.69 (p=0.0008)
					Cognitive fluency	r=-0.52 (p=0.017) / r=-0.56 (p=0.01)
			All other correlations between FA/RAD and examined EFs			NS
Palmer et al. (2012) [82]	38	2	CC	CC	PS	R=0.41 (0.010)
				gCC		R=0.31 (0.050)
				bCC		R=0.38 (0.016)
				sCC		R=0.37 (0.018)
			Post thalamic radiation			R=0.33 (0.042)
			External capsule			R=0.37 (0.022)
			Cerebral peduncle, internal capsule, corona radiata, sagittal stratum, cingulum, superior longitudinal fasciculus			NS
Riggs et al. (2014) [87]	10	/	Uncinate fasciculus FA (right/left)		Learning and memory (CMS)	NS / r=0.64 (p=0.045)
Rueckriegel et al. (2015) [98]	18	14	FA of skeletonized tracts		FSIQ	r=0.44 (p=0.008)
					ANT baseline speed	r=-0.37 (p=0.028)
					ANT shifting attention	r=-0.34 (p=0.045)
			WM/GM+CSF ratio		FSIQ	r=0.519 (p=0.002)
					ANT baseline speed	r=0.356 (p=0.04)
					ANT shifting attention	r=0.51 (p=0.004)
			Frontocerebellar tract volumes		FSIQ	r=-0.49 (p=0.011)
					ANT baseline speed	NS
					ANT shifting attention	NS
			Mean WMFA		All tests	NS
Glass et al. (2017) [85]	92	/	Baseline FA		PS (at 36m)	p=0.014
					Broad attention	p=0.025
			All associations with working memory and general intellectual ability			NS
Law et al. (2017) [94]	24	/	RAD left cerebello-thalamo-cortical pathway		Working memory	R^2=-0.110 (p<0.05)
			FA, AD, RAD of CTC and CPC pathways		EF	NS
Li et al. (2017) [92]	9	3	ADC of multiple regions (cerebral white matter, cerebral cortex, caudate, putamen, globus pallidus, hippocampus, amygdala, nucleus accumbens)		FSIQ	r^2=0.37-0.75 (adjusted p<0.05)
			ADC of thalamus			NS (R^2=0.33, adjusted p=0.052)

Table 2: *Overview of the results of diffusion weighted imaging.*

Abbreviations: *"AD" = axial diffusivity; "ADC" = apparent diffusion coefficient; "ANT" = Amsterdam Neuropsychological Tasks; "bCC" = body of corpus callosum; "CC" = corpus callosum; "CMS" = Children's Memory Scale; "CPC" = cerebro-ponto-cerebellar; "CSF" = cerebrospinal fluid; "CTC" = cerebello-thalamo-cerebral; "EFs" = executive functions; "FA" = fractionated anisotropy; "FSIQ" = full scale intelligence quotient; "gCC" = genu of corpus callosum; "GM" = gray matter volume; "IFO" = inferior fronto-occipital fasciculus; "MS" = motor speed; "NS" = not significant; "PIQ" = performance intelligence quotient; "PS" = processing speed; "PSF" = processing speed factor; "RAD" = radial diffusivity; "sCC" = splenium of corpus callosum; "VIQ" = verbal intelligence quotient; "WJ" = Woodcock-Johnson tests of cognitive abilities; "WM" = white matter volume; "WMFA" = white matter fractionated anisotropy.*

2. Fractionated anisotropy (FA)

Two papers report that low global white matter FA-value is correlated with low IQ. One uses a mixed population of 12 MB and 18 acute lymphocytic leukemia (ALL) survivors, the other included 8 MB patients[93,96]. It is important to note that multiple studies do not confirm this association[97,98]. One of these studies reports correlations between FA of white matter tracts and IQ in a mixed population of 18 MB and 14 pilocytic astrocytoma (PA) patients. A ratio of NWM over gray matter and cerebrospinal fluid, calculated using FA, is correlated with IQ. Both this ratio and FA of white matter tracts are correlated with PS[98].

In another study, with a population of 6 MB and 11 ALL patients, an association between low FA-value of the splenium and body of the corpus callosum and decreased PS is reported[97]. This association between FA of the corpus callosum and PS is confirmed in a bigger study, with a population of 38 MB and 2 atypical teratoid rhabdoid tumor patients. FA of the post thalamic radiation and the external capsule are also associated with PS[82]. In another article, with a study population of 92 MB patients, baseline global FA is associated with PS, as well as with broad attention, measured 36 months later[85].

Other articles also report several different correlations involving EFs. Low FA in the parietal lobes is correlated with poorer working memory and low FA in the temporal lobes with poorer cognitive fluency, coming from measurements in a subset of 10 MB patients in an earlier mentioned study[86].

Two studies with small populations, respectively 9 and 10 MB patients, investigated associations between FA and learning[87,95]. The first one reports more reduction in supratentorial FA in patients with more severe deterioration in learning capacity. Because of small sample size and no quantitative measuring, no conclusions should be drawn of this study[95]. The other article reports an association between FA of the left uncinate fasciculus and CMS-score, which measures learning and memory performance[87].

FA scores of multiple brain regions measured around one year post-diagnosis, are correlated with reading decoding skills in patients that were diagnosed with MB (n=49) and other embryonal tumors (n=5)[81].

Oxygenation (fMRI) and blood flow (ASL)

Based on improvement of Sound Awareness scores, a case-control fMRI study on 19 reading intervention and 21 standard-of-care MB patients, concludes that prophylactic reading intervention has long-term positive effects on pediatric MB patients. This study also reports a normative trend of the differences in group activation patterns under the influence of reading-intervention[99].

We included one study, with 12 patients, including 9 MB patients, that uses ASL to investigate the relationship between CBF and IQ. No significant correlation is reported[92].

Hemosiderin deposits, microbleeds (GRE)

The only included study that discusses FHD incidence does not report any significant associations with IQ or need for special education, which are available for respectively 10 and 30 patients. Also, no significant correlation with radiation dose is observed in the total population of 41 MB patients. There

are however significantly more FHD lesions present in patients who received RT at later age (7-21 years old), compared to patients who were 6 years or younger when they were treated[100].

LIMITATIONS

A first limitation that needs to be mentioned arises from the fact that few studies on this subject were published. Ideally, we want to include studies that have homogenous outcome parameters, which we can directly compare with each other and from which we can pool the results to create a meta-analysis. Because of this limitation in number of available articles that discuss this topic, we opted for a slightly broader research question to summarize the current available data. This, however, turns this into a review that discusses very heterogenous studies. They are heterogenous with respect to design, sample size, age at diagnosis, treatment schedules, time of imaging, time of cognitive measurement, MRI-parameters and cognitive parameters. Because of this, it is rather difficult to draw definite conclusions out of this review.

Second, there is a lack of prospective studies on this subject. Of the twenty included articles, only three have a prospective study design[85,89,99]. It would be interesting to collect more data on associations between imaging and long-term cognitive outcome of patients, for which a large prospective study would be ideal. This would be useful to predict long-term cognitive outcome using neuroimaging and to introduce extra preventive measures in certain subpopulations of MB patients.

Furthermore, multiple studies don't confirm correlations found by others (for example the correlation between NWM and EFs and the correlation between global WMFA and IQ). A possible explanation for these inconsistencies could be the earlier discussed heterogeneity in this review. Especially relevant are the differences in treatment schedules and time of imaging and measurement.

Fourth, multiple studies report results for a mixed brain cancer patient population, meaning that they don't report results for MB patients separately. We decided not to exclude these studies, because we think that these mixed populations can still lead to relevant information for our research, especially seen that many of the other brain cancer patients that were included, received similar treatment as MB patients. This however further complicates drawing conclusions for MB pts exclusively. Also, we conclude that this review supports Wolfe's model in MB patients, but this model was designed for all posterior fossa patients.

DISCUSSION

The aim of this review was to summarize the currently existing literature discussing associations between neuroimaging and neurocognition in pediatric MB survivors. The purpose of this being (1) to identify neuroanatomical processes that explain the adverse effects of brain tumor treatment on neurocognitive functioning of pediatric MB patients, (2) to find possible prediction parameters for cognitive outcome and (3) to explore possible targets for medical interventions.

Medulloblastoma treatment, especially radiotherapy, has a negative impact on intellect of patients[49–51]. Changes in white matter can be seen in MB (and other brain cancer) survivors[56,59–61]. In this review we report findings that connect these white matter changes, investigated by both anatomical and diffusion-based neuroimaging, with the impact on multiple cognitive outcomes, one of them being intelligence. We show that lower intellect is correlated with both lower NWM volume and higher amount of WML[83,84,89]. Two articles don't confirm this, which could be explained by the fact that one of them uses another way of testing intelligence than IQ, namely the Woodcock-Johnson tests of cognitive abilities, and that the other article only considers periventricular leukomalacia (PVL) instead of all WML[85,88].

Compared to LGA patients who were treated by surgical resection only, MB patients have less NWM, lower FSIQ and lower PIQ, suggesting that non-surgical treatment modalities have a negative impact on the neuroanatomy and intellect of patients[83]. Lower IQ is correlated with disorganized white matter on microstructure level, indicated by higher ADC and lower FA-values[92,93,96,98]. Two studies did not confirm the correlations with some of these FA-values[97,98]. One study reports some correlations but not with global WMFA and both included non-MB patients, who received treatment schedules that differed more from the MB-treatment than in the studies that report significant results **(supplementary table 1)**.

The neurodevelopmental model by Palmer gives a central role to PS in the process of cognitive damage in MB survivors **(figure 1)**[53]. In Wolfe's model a connection with white matter changes is described **(figure 2)**[56]. Multiple papers describe findings that support a role for disorganized white matter (micro)structure in deterioration of PS after receiving MB treatment[82,85,90,97,98]. Two of these articles find that microstructural changes in the corpus callosum (CC) are correlated with lowering of PS[82,97]. This association between CC structure and PS performance has also been reported before, in other clinical contexts[101–103].

A prospective study reports that low FA post-surgery is correlated with lower PS (and broad attention) three years later[85]. It is often difficult to estimate to what extent findings in MB survivors can be attributed to treatment. In this study, low FA can clearly only be attributed to the disease and/or surgical resection and not to CT or RT. This is somehow contradicting that MB treatment is influencing cognitive functioning negatively by causing white matter tract disruption. Nevertheless, it is useful to know that FA immediately post-surgery could potentially be used to predict cognitive outcome. Now, choice of therapy is mainly chosen in function of risk of the disease and age of the patient. Predicting cognitive outcome immediately post-surgery could provide an opportunity to further personalize CT and/or RT schedules. It would be interesting to see if this and other findings could be used to construct a score system to estimate the risk on worse cognitive outcome in MB patients. This fits perfectly in the shift that has happened from focusing on survival, to a more quality-of-life-based approach.

Working memory is prominent in all three models mentioned earlier (**figures 1-3**)[53,55,56]. Furthermore, Wolfe's model considers an association between white matter changes and working memory as theoretically plausible[56]. With this review we summarize data that support the existence of this association. Decreased working memory is associated with microstructural white matter changes, shown by low FA-values and high RAD-values in different brain regions[86,94], and with macrostructural change in the form of reduced NWM volume as reported by one study[85]. This last association is not confirmed by another article with a smaller study population[88].

Other cognitive outcomes are also associated with white matter changes. Disorganization of several white matter microstructures is correlated with shifting attention and cognitive flexibility[86,94] and more WML are seen in patients with worse visuospatial planning, common sense judgement, arithmetic reasoning, math scores, perceptual organization, distractibility and visual motor functioning[88–90]. In a study comparing two treatment protocols, the correlation between EFs and WML was only significant in the patients that received intrathecal MTX[88]. Worse cognitive outcomes were seen compared to the patients that did not receive intrathecal MTX[88], thus providing an argument for the role of (intrathecal) CT in cognitive deterioration in MB patients.

The negative impact that MB treatment has on a child's development can be seen in the deterioration in learning capacity and poorer learning and memory performance[87,95]. This is correlated with lower FA-values, equivalent with damaged white matter microstructures[87,95]. Disrupted hippocampal structure has a role in poorer memory performance in patients that were treated for MB[87,91,92]. It has been stated earlier that poor intellectual outcomes in pediatric MB survivors are no so much because of deterioration of existing intellectual capacities but rather because of a decreased ability to learn new things[50]. This makes these associations between anatomical changes and learning and memory performance even more relevant.

MB patients have a clear decline in spelling and reading scores compared to control subjects[89]. Worse reading decoding is correlated with higher FA-values in several brain structures[81]. This means that reading practice could potentially be beneficial for MB survivors. A reading intervention was designed in game-like format to try to limit the negative influences of MB treatment in children[104]. This program appears successful: long-term positive effects of the prophylactic reading intervention can be seen in pediatric MB patients[99].

From multiple studies, mainly using anatomical investigations and DWI, we conclude that both macrostructural and microstructural white matter changes play an important role in the effects of therapy on cognitive functioning of childhood MB survivors. This provides, at least partly, support for the neurodevelopmental model of Wolfe (**figure 2**)[56].

In the future, a large prospective study with long-term follow-up should be performed. Ideally, patients would be categorized in age-groups and according to the (molecular) typing and staging of their disease and the treatment they received. They should undergo both baseline imaging and cognitive testing, as well as imaging and testing in follow-up on certain points in time that are determined in advance. Use of DWI would be invaluable to this study, because it seems that it often is the case that only microstructural changes are detected, without there being a clear change in white matter on anatomical investigations. Special attention should go to further examining the predictive value of MRI parameters, which could potentially contribute to a prediction tool for further individualization of therapy schedules focusing more on cognitive outcome. This, and the search for more points of intervention are invaluable to keep on improving cognitive functioning of survivors of childhood medulloblastoma.

CONFLICT OF INTEREST

None.

FINANCIAL DISCLOSURE

None.

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SUPPLEMENTARY TABLE

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequence(s)	Cognitive testing (*)	Mean age at diagnosis / start of treatment (SD) (**)	Mean age at MRI-scan (SD) (**)	Mean age at neurocognitive testing (SD) (**)	Most relevant correlations / results
Mulhern et al. (1999)[83]	Cross-sectional	36 pts. - 18 MB - 18 LGA	**MB:** SR + RT (CSI: 23.4 or 36 Gy / total dose to PF: 49.0-54.0 Gy) + CT (CDDP/VP-16, Carbo/VP-16 + Cyclo/Vcr, CDDP/ VP-16 + Cyclo/Vcr, Carbo/Cyclo/VP-16 or MOPP) **LGA:** SR	T1; T2; PD	VIQ; PIQ; FSIQ	*< 21 y (mean age difference between MB and LGA: 3.7 months)*	*Mean interval between diagnosis and MRI-scan:* ***MB:*** *3.8 y (SD = 2.6)* ***LGA:*** *2.6 y (SD = 1.1)*	*Within 6 months of MRI-scan*	- **MB:** NWM is positively correlated with FSIQ (R=0.56) and with VIQ (R=0.49) (p<0.05) - **MB:** NWM accounts for 30.8% of the variance in FSIQ - **MB (vs LGA):** less NWM (p<0.01), lower FSIQ (mean: 82.1 vs 92.9; p<0.05), lower PIQ (mean: 79.6 vs 92.9; p<0.01)
Mulhern et al. (2001)[84]	Cross-sectional	42 MB pts.	**13 pts.:** SR + RT (CSI: 23.4 or 36 Gy / total dose to PF: 49.0-54.0 Gy) **29 pts.:** SR + RT (CSI: 23.4 or 36 Gy / total dose to PF: 49.0-54.0 Gy) + CT (CDDP/VP-16, Carbo/VP-16 + Cyclo/Vcr, CDDP/ VP-16 + Cyclo/Vcr, Carbo/Cyclo/VP-16 or MOPP)	T1; T2; PD	FSIQ (38 pts.); verbal memory (CVLT) (20 pts.); sustained attention (CPT) (25 pts.)	8.2 y (3.8 y)	*Within 6 months of testing*	13.4 y (4.2 y)	- NWM is positively correlated with FSIQ (after controlling for time since RT) (R^2=0.253; p=0.001)
Riva et al. (2002)[88]	Cross-sectional	21 MB pts. - 11 with intrathecal MTX - 10 without intrathecal MTX	**Protocol 1:** SR + pre-RT CT (Vcr , MTX, intrathecal MTX + RT (CSI: 20 Gy (pts.<10y) or 35 Gy (pts.>10y) / total dose to PF: 54 Gy) + post-RT CT (Vcr + lomustine) **Protocol 2:** idem, except no intrathecal MTX	T1; T2	- Intelligence: FSIQ, VIQ, PIQ - EFs: TMT B, arithmetic, picture arrangement, block design, object assembly, coding - Attention: TMT A - Visual perception: picture completion - Short-term memory: digit span, BMCT	*Median age:* - ***Treatment protocol 1:*** *12 y 10 m (range: 6 y 11 m – 17 y 11 m)* - ***Treatment protocol 2:*** *12 y 8 m (range: 7 y – 17 y 10 m)*	*MRI was performed every 6 m*	*Mean time between end-of-treatment and neuropsychological testing:* - ***Treatment protocol 1:*** *3 y 1 m (range: 2 y 1 m – 5 y 10 m)* - ***Treatment protocol 2:*** *3 y 9 m (range: 2 y 11 m - 5 y 8 m)*	- **Protocol 1 (with intrathecal MTX):** Extent of PVL is negatively correlated with performance on Arithmetic (p=0.02), Comprehension (p=0.02), and Block Design (p=0.05) test. - **Protocol 2 (without intrathecal MTX):** no correlations between the extent of PVL and performance in any test item.

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequence(s)	Cognitive testing (*)	Mean age at diagnosis / start of treatment (SD) (**)	Mean age at MRI-scan (SD) (**)	Mean age at neurocognitive testing (SD) (**)	Most relevant correlations / results
Khong et al. (2003)[95]	Cross-sectional	9 MB pts.	SR + RT (CSI: 30.6–40 Gy / total dose to PF: 50.4-54 Gy) + CT (babyPOG or CCV protocol)	DWI	Severity of deterioration in learning capacity: mild, moderate or severe (according to school performance + need for special school placement / achievement of developmental milestones)	7.8 y *Range: 3 – 19 y*	10.8 y *Range: 3 – 14 y* *Mean time interval between treatment and MRI: 3.6 y (range: 1 – 6y)*	/	Mean reduction in supratentorial FA: - mild deterioration (2pts.): 7% - moderate deterioration (6pts.): 20% - severe deterioration (1pt.): 46.2%
Fouladi et al. (2004)[89]	Longitudinal, prospective	21 pts. with WML - 20 MB - 1 supratentorial PNET 93 pts. without WML (risk- and age-matched)	SR + RT (CSI: 23.4, 36 or 39.6 Gy / total dose to PF: 36 or 39.6 Gy / total dose to tumor bed: 55.8 Gy) + CT (CCV protocol)	T1; T2; PD; FLAIR	IQ; tests of academic achievement (WIAT)	/	/	/	- **IQ decline** in pts. with WML (mean: -2.46 points/y; p=0.03) vs NS in pts. without WML - **Decline in math scores** in pts. with WML (mean: -4.49 points/y; p=0.003) vs NS in pts. without WML - **Decline in spelling scores** in pts. with WML (mean: -4.31 points/y; p=0.0001) and without WML (mean: -2.86 points/y; p=0.002) - **Decline in reading scores** in pts. with WML (mean: -3.59 points/y; p=0 .0001) and without WML (mean: -2.42 points/y; p=0.003)
Khong et al. (2006)[96]	Cross-sectional, case-control	30 pts. - 12 MB - 18 ALL 55 ctrls.	**12 MB pts.:** SR + RT (CSI: 23.4, 30.6, 36 or 40 Gy / total dose to PF: 50-55.8 Gy) + CT (babyPOG or CCV protocol) **9 ALL pts.:** CT (MTX intrathecal and systemic + HKALL93 protocol or HKALL97 protocol) **9 ALL pts.:** idem + RT (cranial: 12, 18 or 24 Gy)	DWI	FSIQ; VIQ; PIQ	**MB:** 8.52 y (3.57) **ALL without RT:** 6.68 y (6.32) **ALL with RT:** 6.47 y (4.35)	**MB:** 11.75 y (4.87) **ALL without RT:** 13.06 y (4.00) **ALL with RT:** 14.83 y (4.67)	/	Difference in WMFA is correlated with: - FSIQ (adjusted r^2=0.439; p<.001) - VIQ (adjusted r^2=0.237; P<.028) - PIQ (adjusted r^2=0.491; P<.001) *(after adjusting for age at treatment, radiation dose and time interval from treatment)*
Mabbott et al. (2006)[93]	Cross-sectional, case-control	8 MB pts. 8 ctrls.	SR + RT (CSI: 23.4, 36.0 or 36.6 Gy / total dose to PF: 55.4 Gy) + CT (babyPOG or CCV protocol)	DWI	FSIQ	7.48 y (3.87)	9.98 y (2.90)	/ *Mean time from diagnosis to testing: 2.38 y (range: 1.02-5.22 y)*	- ADC is negatively correlated with IQ (r=-0.60, p=0.01) - FA is positively correlated with IQ (r=0.65, P<0.01) - Difference in mean IQ between MB (87.50) and ctrls. (112.75): F=9.53 (P<0.01) *(NS when controlling for overall mean FA (with the outlier removed) or ADC)*

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequence(s)	Cognitive testing (*)	Mean age at diagnosis / start of treatment (SD) (**)	Mean age at MRI-scan (SD) (**)	Mean age at neurocognitive testing (SD) (**)	Most relevant correlations / results
Palmer et al. (2010)[81]	Cross-sectional	54 pts. - 49 MB pts. - 3 atypical teratoid rhabdoid tumor pts. - 2 pineoblastoma pts.	SR + RT (CSI: 23.4 Gy or 36-39.6 Gy / total dose to primary site: 55.8-59.4 Gy) + CT (cyclo, CDDP, Vcr)	DWI	Reading decoding skill (WJ: word attack subtest)	9.8 y (3.8)	*<12 m post-diagnosis*	10.67 y (3.8)	- Reading decoding is correlated with: - left pons-medulla oblongata FA: r^2=0.526 - right pons FA: r^2=0.566 - left and right posterior limb of the internal capsule FA: r^2=0.531 and r^2=0.555 - right knee of the internal capsule FA: r^2=0.576 - left inferior parietal lobe FA: r^2=0.565 - right occipital lobe FA: r^2=0.567 - left temporal occipital cluster FA: r^2=0.516 *(NOTE: after accounting for age at the time of evaluation and risk)*
Aukema et al. (2009)[97]	Cross-sectional, case-control	6 MB pts. 11 ALL pts. 17 ctrls.	**MB:** SR + RT (CSI: 25.2-34.5 Gy / total dose to PF: 53.3-55.4 Gy) + CT (CCV protocol) **ALL:** MTX	DWI	FSIQ; PSF; MS	5.2 y (3.1)	14.0 y (2.5)	/ *Range of interval between neurocognitive testing and MRI: 0.0 - 3.5 m*	- sCC WMFA is correlated with PSF: r=0.53 (p=0.03) - bCC WMFA is correlated with PSF: r=0.52 (p=0.03) - Right IFO WMFA is correlated with MS: r= 0.49 (p=0.045) (*also significant in control group)* - Correlations involving FSIQ: NS - Correlations involving mean WMFA: NS
Brinkman et al. (2012)[86]	Cross-sectional	20 MB pts.	SR + RT (CSI: 23,40–61,60 Gy / boost given to PF: 11,00–32,40 Gy) + CT (in 15 pts., protocol not mentioned)	DWI; T1; T2	EFs (Wisconsin Card Sorting Test; Rey-Osterrieth Complex Figure; Stroop Color Word; Trail Making Test, Part B; WAIS III–Digits Backward; Controlled Oral Word Association Test)	*Range: 2-17 y*	*Interval between testing and MRI was 0-9 days*	29 y *Range: 21-36 y*	Correlations between: **Frontal lobes:** - RAD and shifting attention: left: r=-0.67 (p=0.001); right: r=-0.64 (p=0.002) - and cognitive flexibility: left: r=-0.56 (p=0.01); right: r=-0.54 (p=0.01) **Parietal lobes:** - FA and working memory: right: r=0.52 (p=0.017); left: r=0.54 (p=0.01) - RAD and shifting attention: left: r=-0.63 (p=0.003); right: r=-0.55 (p=0.01) **Temporal lobes:** - RAD and shifting attention: right: r=-0.63 (p=0.003); left: r=-0.69 (p=0.0008) - RAD and cognitive flexibility: right: r=-0.52 (p=0.017); left r=-0.56 (p=0.01) - FA and cognitive fluency: left: r=0.65 (p=0.002); right: r=0.58 (p=0.007)

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequence(s)	Cognitive testing (*)	Mean age at diagnosis / start of treatment (SD) (**)	Mean age at MRI-scan (SD) (**)	Mean age at neurocognitive testing (SD) (**)	Most relevant correlations / results
Palmer et al. (2012)[82]	Cross-sectional	40 pts. - 38 MB pts. - 2 atypical teratoid rhabdoid tumor pts.	SR + RT (CSI: 23.4 Gy or 36-39.6 Gy / total dose to primary site: 55.8-59.4 Gy) + CT (cyclo, CDDP, Vcr)	DWI	Information PS (WJ-III) (subsets: decision speed and overall processing)	9.9 y (4.3)	*<36 m post-diagnosis*	12.8 y (4.4)	- Overall PS is correlated with: - Corpus callosum FA: r=0.41 p=0.010) - gCC FA: r=0.31 (0.050) - bCC FA: r=0.38 (0.016) - sCC FA: r=0.37 (0.018) - Post thalamic radiation FA: r=0.33 (p=0.042) - External capsule FA: r=0.37 (p=0.022)
Yeom et al. (2013)[100]	Longitudinal, retrospective	40 MB pts. (subset out of 41 MB pts.) - 10 pts. with IQ available - 30 pts. with information about special education	SR + RT (CSI: 18,0-23.4 Gy or 29.2-39,6 Gy / total dose to PF: 18.0-23.4 Gy or 54,0 Gy) + CT (protocol not mentioned)	GRE T2* (FHD)	IQ (10 pts.); special education or not (30 pts. of which 21 pts. with special education)	8.1 y (4.5)	/ *Mean follow-up: 5.0 y (3.1)*	/	- 10 pts.: No significant correlation of FHD incidence with IQ - 30 pts.: No significant correlation of FHD incidence with the need for special education
Riggs et al. (2014)[87]	Cross-sectional, case-control	10 MB pts. (subset out of 20 pts.) 13 ctrls.	SR + RT (CSI: 23.4-41.4 Gy / total dose to PF: 54.0-59.4 Gy or *in 2 pts.: 36.0 and 50.4 Gy (with total dose to tumor bed: 54.0 or 55.8 Gy)*) + CT (various combinations of CDDP, Vcr, VP-16, ifosfamide, carbo and cyclo)	T1; DWI	Learning and memory (CMS)	7.2 y *Range: 4.3-12.8 y*	12.4 y *Range 7.2-17.2 y*	/ *7 pts.: within 2 m of imaging* *3 pts.: within 19 m of imaging*	- Left UF FA is correlated with general index of CMS: r=0.64 (p=0.045) - Right hippocampus volume is correlated with general index of CMS: r=0.71 (p=0.02) Correlation between total white matter volume and general index of CMS: **NS**
Khajuria et al. (2015)[90]	Cross-sectional	17 MB pts. (subset out of 34 pts.)	SR + RT (CSI: 36 Gy / total dose on tumor bed: 54-56 Gy (2 pts: 68 Gy / 1 pt: 49 Gy / 1 pt: 50 Gy)) + CT (carbo, Vcr, CCNU and VP-16)	T1; T2; FLAIR; PD	FSIQ (WISC-III); attention (Test battery for Attentional Performance); verbal memory (Test of Verbal Learning and Memory); visual motor function (VMI)	7.6 y *Range: 2.2-16.6 y)*	/	13.2 y *Range: 7.8-20.6 y*	Correlations between: - Cerebellar atrophy and: - higher distractibility - Supratentorial atrophy and: - lower scores in verbal comprehension (p=0.039). - Supratentorial leukoencephalopathy and… - lower scores in PS (p=0.007) - perceptual organisation (p=0.023) - higher distractibility (p=0.013) - worse outcomes in VMI (p=0.014)
Rueckriegel et al. (2015)[98]	Cross-sectional	32 pts. - 18 MB pts. - 14 PA pts.	**MB:** SR + RT (CSI: 24-32 Gy / additional boost to PF: 18-30 Gy) + CT (CCNU, carbo, Vcr, cyclo, PTX, VP-16) **PA:** SR	T2; T1; DWI	FSIQ (30 pts.); PS (ANT): - Baseline speed (27 pts.) - Shifting attention (26 pts.)	**MB:** 11.2 y (3.7) **PA:** 9.9 y (4.4)	/	**MB:** 15.2 y (4.9) **PA:** 12.6 y (5.0)	- FA of skeletonized tracts is correlated with: - FSIQ: r=0.44 (p=0.008) - ANT baseline speed: r=-0.37 (p=0.028) - ANT shifting attention: r=-0.34 (p=0.045) - WM/GM+CSF ratio is correlated with: - FSIQ: r=0.519 (p=0.002) - ANT baseline speed: r=0.356 (p=0.04) - ANT shifting attention: r=0.51 (p=0.004) - Frontocerebellar tract volumes are correlated with FSIQ (p=0.011) - No significant correlation between global mean WMFA and cognitive tests

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequence(s)	Cognitive testing (*)	Mean age at diagnosis / start of treatment (SD) (**)	Mean age at MRI-scan (SD) (**)	Mean age at neurocognitive testing (SD) (**)	Most relevant correlations / results
Zou et al. (2016)[99]	Longitudinal, case-control, prospective	40 MB pts. - 19 reading-intervention - 21 standard-of-care 21 ctrls.	SR + RT (CSI: 23.4 Gy or 36-39.6 Gy / total dose to tumor bed: 55.8-59.4 Gy) + CT (cyclo, CDDP and Vcr)	fMRI: reading-related neural activation	Reading abilities: Woodcock-Johnson Reading Fluency, Word Attack and Sound Awareness subtests	Reading intervention group: 10 y (0.6) Standard-of-care group: 9.5 y (0.6)	**Age at first fMRI examination:** Reading intervention group: 11.7 y (0.6) Standard-of-care group: 12.1 y (0.6) **(+ 2 more fMRI examination at 1 y intervals)**	**Age at first reading evaluation:** Reading intervention group: 11.7 y (0.6) Standard-of-care group: 12.1 y (0.6) **(+ 2 more reading evaluations at 1 y intervals)**	- Reading-intervention group (vs standard-of-care group): higher Sound Awareness scores at time of fMRI (p=0.046) - Reading-intervention group: normative trend in patterns of brain activation for reading tasks - No association of improved Sound Awareness with generalized improvement in reading skills at time of fMRI
Decker et al. (2017)[91]	Cross-sectional, case-control	11 pts. - 10 MB pts. - 1 pineoblastoma pt. 16 ctrls.	SR + RT (dose not mentioned) + CT (various combinations of CDDP, cyclo, Vcr, lomustine, VP-16, amifostine) *(1 pt. did not receive CT.)*	T1	Short-term verbal associative memory (CMS (<16 y) or WMS-III (>16 y)); information PS (WJ-III); FSIQ and VIQ *(available for 10 pts.)*	6.66 y (2.39)	14.77 y (2.93) *MRI at same day as testing.*	14.77 y (2.93)	- Memory performance is correlated with: - bilateral volumes in hippocampal subfields (CA1: r=0.71 (p=0.01) and SRLM: r=0.61 (p=0.04)) - left DG-CA4 volume: r=0.70 (p=0.02) - left SRLM volumes: r=0.59 (p=0.05) *(NOTE: NS after excluding 2 pts. with IQ<60.)* - No correlations between FSIQ, VIQ or PS and hippocampal subfields.
Glass et al. (2017)[85]	Longitudinal, prospective	92 MB pts. (subset out of 146 MB pts.)	SR + RT (CSI: 23.4 or 36 Gy / total dose to primary site: 55.8-59.4 Gy) + CT (cyclo, CDDP, Vcr)	T1; T2; PD; FLAIR; DWI	PS; working memory; broad attention; general intellectual ability (WJ-III)	*Median age: 8.7 y* *Range: 3.2-21.6 y*	*Baseline after surgery + after completion of RT (average 85d after baseline) + 12, 18, 24, 30 and 36m after diagnosis.*	*At baseline + yearly afterward.*	- WM volume at 36 m is correlated with working memory performance at 36 m (p=0.026) (after adjusting for age) - Baseline FA is correlated with PS at 36 m (p=0.014) - Baseline FA is correlated with broad attention at 36 m (p=0.025)

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequence(s)	Cognitive testing (*)	Mean age at diagnosis / start of treatment (SD) (**)	Mean age at MRI-scan (SD) (**)	Mean age at neurocognitive testing (SD) (**)	Most relevant correlations / results
Law et al. (2017)[94]	Cross-sectional, case-control	25 MB pts. 20 ctrls. *(note: 1 pt. did not participate in MRI)*	SR + RT (CSI: 23.4-36.0 Gy / total dose to PF: 54.0-55.8 Gy) + CT (carbo, CDDP, cyclo, CCNU, Vcr) *(note: 1 pt. did not receive CT)*	T1; DWI	Executive functioning (D-KEFS, WMTB-C and CERQ(-k)): - cognitive efficiency; - planning/problem-solving; - positive cognitive emotion regulation; - working memory; - negative cognitive emotion regulation; - mixed cognitive emotion regulation	7.02 y (2.66)	13.30 y (3.47)	13.30 y (3.47)	- Total effect of MB treatment on working memory: R^2=-0.545 - Indirect effect of MB treatment on working memory mediated by higher RAD in left cerebello-thalamo-cortical pathway: R^2=-0.110 - Indirect effect explains 1.7% of variance in working memory
Li et al. (2017)[92]	Cross-sectional	12 pts. (subset out of 39 pts.) - 9 MB pts. - 3 PA pts.	**PA:** SR **MB:** SR + RT (CSI: 18-36.9 Gy / total dose to PF: 54-55.8 Gy *(note: 1pt only received RT to PF: 50.4 Gy)*) + CT (Vcr + CDDP and/or carbo + cyclo and/or lomustine (+ VP-16))	perfusion ASL; DWI	FSIQ	*Range for full study population: 1.2-16.2 y*	*Range for full study population: 5.0-20.4 y*	Subset: 13.4 y (*Range: 7.3-18 y)*	- ADC values in multiple regions (cerebral white matter, cerebral cortex, caudate, putamen, globus pallidus, hippocampus, amygdala and nucleus accumbens) are positively correlated with FSIQ: r^2=0.37-0.75 - Correlation between ADC in thalamus and FSIQ is NS - No significant correlation between CBF and IQ

Supplementary table 1: *Overview of included articles.*

Abbreviations: *"8/1" = 8 drugs in 1 day (vincristine [VCR], hydroxyurea, procarbazine, CCNU, cisplatin, cytosine arabinoside [Ara-C], high-dose methylprednisolone and either cyclophosphamide or dacarbazine); "ADC" = apparent diffusion coefficient; "ALL" = acute lymphoblastic leukaemia; "ANT" Amsterdam Neuropsychological Tasks; "babyPOG" = baby Paediatric Oncology Group protocol (Vcr, Cyclo, CDDP and VP16); "BMCT" = Benton Multiple Choice Test (used for spatial memory testing); "Carbo" = carboplatin; "CCV" = CCNU, cisplatin and vincristine; "CDDP" = cisplatin; "CERQ(-k)" = Cognitive Emotion Regulation Questionnaire for Children (under 12y of age); "CMS" = Children's Memory Scale; "cPA" = cerebellar pilocytic astrocytoma; "CPT" = Connor's Continuous Performance Test; "CSI" = craniospinal irradiation; "CT" = chemotherapy; "ctrls." = control subjects; "CVLT" = California Verbal Learning Test; "Cyclo" = cyclophosphamide; "D-KEFS" = Delis-Kaplan Executive Function System; "DTI" = diffusion tensor imaging; "DTI" = diffusion tensor imaging; "DWI" = diffusion weighted imaging; "EFs" = executive functions"; "eFSIQ" = estimated full-scaled intelligence quotient; "FA" = fractional anisotropy; "FHD" = focal hemosiderin deposition; "FSIQ" = full scale intelligence quotient; "GRE" = gradient recalled echo; "Gy" = Gray; "HD-BU-TTT" = high dose busulfan and thiotepa with peripheral blood stem cell rescue; "IFO" = inferior fronto-occipital fasciculus ; "LGA" = low-grade astrocytoma; "m" = month(s); "MB" = medulloblastoma; "MOPP" = mechlorethamine, Oncovin, procarbazine and prednisone; "MS" = motor speed score in Z-scores; "MTX" = methotrexate; "NGM" = normal gray matter; "NS" = not significant; "NWM" = amount of normal white matter; "PD" = proton density; "PF" = posterior fossa; "PIQ" = performance intelligence quotient; "PNET" = primitive neuroectodermal tumor; "PS" = processing speed; "PSF" = processing speed factor; "pt(s)." = patient(s); "PVL" = periventricular leukomalacia; "RAD" = radial diffusivity; "RT" = radiotherapy; "SD" = standard deviation; "SR" = surgical resection; "T1" = T1-weighted images; "T2" = T2-weighted images; "TMT A" = form A of the Trail-Making Test; "TMT B" = form B of the Trail-Making Test; "Vcr" = vincristine; "VIQ" = verbal intelligence quotient; "VMI" = version 4 of the American Beery-Buktenica test of Visual Motor Integration; "VP-16" = etoposide; "vs" = versus; "w" = week(s); "WIAT" = Wechsler Individual Achievement Test; "WJ(-III)" = Woodcock-Johnson tests of cognitive abilities (third edition); "WMFA" = white matter fractional anisotropy; "WML" = white matter lesions; "WMS-III" = Weschler Memory Scale-third edition; "WMTB-C" = Working Memory Test Battery for Children; "y" = year(s).*

(*) For IQ-evaluation an age-appropriate version of the Wechsler Intelligence Scale for Children–III or the Wechsler Adult Intelligence Scale–Revised or an abbreviated version of one of these scales was used unless stated otherwise.

(**) If mean age is not available, we report the relevant alternative data (in italic) mentioned in the article that indicates the moment of treatment / MRI-scan / neurocognitive testing.