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REVIEW

Neuroimaging Biomarkers and Neurocognitive Outcomes in Pediatric Medulloblastoma Patients: a Systematic Review

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Abstract

Medulloblastoma is a malign posterior fossa brain tumor, mostly occurring in childhood. The CNS-directed chemoradiotherapy treatment can be very harmful to the developing brain and functional outcomes of these patients. However, what the underlying neurotoxic mechanisms are remain inconclusive. Hence, this review summarizes the existing literature on the association between advanced neuroimaging and neurocognitive changes in patients that were treated for pediatric medulloblastoma. The PubMed/Medline database was extensively screened for studies investigating the link between cognitive outcomes and multimodal magnetic resonance (MR) imaging in childhood medulloblastoma survivors. A behavioral meta-analysis was performed on the available IQ scores. A total of 649 studies were screened, of which 22 studies were included. Based on this literature review, we conclude medulloblastoma patients to be at risk for white matter volume loss, more frequent white matter lesions, and changes in white matter microstructure. Such microstructural alterations were associated with lower IQ, which reached the clinical cut-off in survivors across studies. Using functional MR scans, changes in activity were observed in cerebellar areas, associated with working memory and processing speed. Finally, cerebral microbleeds were encountered more often, but these were not associated with cognitive outcomes. Regarding intervention studies, computerized cognitive training was associated with changes in prefrontal and cerebellar activation and physical training might result in microstructural and cortical alterations. Hence, to better define the neural targets for interventions in pediatric medulloblastoma patients, this review suggests working towards neuroimaging-based predictions of cognitive outcomes. To reach this goal, large multimodal prospective imaging studies are highly recommended.

Keywords Medulloblastoma · MRI · Neurocognitive outcomes · Innovative imaging methods · Multimodal neuroimaging · Pediatric · Systematic review · Neurocognition

Introduction

Medulloblastoma (MB) is a malign embryonic neuroepithelial brain tumor that occurs in the cerebellum [1–3]. It is a pediatric cancer that represents approximately 10–20% of brain tumors in children [1, 4–6]. Overall 5-year survival rates of pediatric MB patients rise up to 70% [4, 7–9], depending on the molecular profile [10, 11] and age at diagnosis, with younger patients being more at risk [8]. Their treatment mostly consists of surgical resection, radiation therapy (RT), and/or chemotherapy (CT). With regard to RT, standard-risk patients commonly receive a craniospinal radiation dose of 23.4 Gy with additional posterior fossa (PF) boost of 32.4 Gy, resulting in a total PF dose of 55.8 Gy [12–15]. In children younger than 3 years, RT is usually avoided or delayed as long as possible because of its damaging effect on the infant's brain [1, 16–18]. Alternative treatments in these patients make use of multiagent systemic CT [17] combined with intraventricular methotrexate (MTX) [19–21], high-dose CT with stem-cell transplantation [22–24], or local RT (radiation dose to PF with boost to primary tumor site) [25].

With increased survival rates, minimizing iatrogenic damage due to treatment increasingly received attention [7]. Survivors of childhood MB have an increased risk of neurological and psychological deficits [26, 27]. Cranial RT has a

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negative effect on processing speed (PS) and intelligence quotient (IQ) [28]. Negative effects of treatment on PS and a decline in IQ, reading, spelling, and mathematical skills have also been reported in pediatric MB patients [29–32]. IQ is more severely decreased in high-risk MB patients who received higher doses of cranial RT [29]. Pediatric MB survivors have a decreased ability to learn new information and skills, which causes them to have poorer intellectual outcomes than their healthy peers later in live [30]. Adult survivors of childhood MB seem to be less likely to obtain a college degree and to gain social independence [26]. Neurodevelopmental models have been proposed by multiple researchers, suggesting PS to be a core ability [33–35]. In short, they state that if PS is decreased after MB treatments, other cognitive outcomes would also likely be affected.

However, neuroimaging studies suggested altered structure and functioning of the brain to explain cognitive deficits more recently. 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, and with PS on the same level as other cognitive outcomes [36]. Similarly, other neurobiological models focused on microstructural alterations of the white matter to explain changes in cognition in survivors of pediatric brain cancer [34, 35, 37]. Multiple magnetic resonance imaging (MRI) modalities have been used to explore neural changes occurring in patients treated for MB during childhood [36, 38–40]. More specifically, white matter volumes [41] and microstructural organization were affected after treatment for MB [42], with most prominent effects in case of higher cranial radiation dose [18]. Microstructural alterations after treatment are not limited to white matter only. Also, cortical features (e.g., thickness [43], gray matter density [44]) can be affected after brain tumor treatments. However, what the underlying mechanisms of toxicity are, and what associations exist with neurocognitive outcomes, remain inconclusive. Hence, we aimed to pinpoint which microstructural neuroimaging features can predict neurocognitive outcomes in medulloblastoma patients specifically. In this review, we summarize all of the reported associations between neuroimaging parameters and neurocognitive outcomes in survivors of MB who received treatment during childhood, based on the literature of the last two decades regarding this topic. With regard to MR imaging, the following MR sequences were specifically investigated: T1-weighted, T2-weighted MRI, Fluid Attenuated Inversion Recovery (FLAIR), diffusion-weighted imaging (DWI), T2*-weighted gradient-recalled echo (T2* GRE), functional MRI (fMRI), arterial spin labeling (ASL). For these specific MR sequences, we hypothesized to observe more pathological findings in medulloblastoma patients with more intensive treatments (including leukoencephalopathy, microbleeds and atrophic findings, based on FLAIR/T2, T2*GRE, and T1weighted MR, respectively). In addition, oxygen and blood supply were anticipated to be affected (as measured with fMRI and ASL, respectively.).

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 was executed in March 2020: *Medulloblastoma AND (growth OR neurological OR mental OR cognition OR cognitive dysfunction OR neurocognitive OR neurocognition OR "intelligence quotient" OR "long-term symptoms" OR (treatment AND symptoms) OR development OR retardation) AND (fMRI OR "functional magnetic resonance imaging" OR "diffusion-weighted mri" OR dMRI OR DWI OR DTI OR "diffusion tensor imaging" OR "arterial spin labelling" OR ASL OR "MRI neuroimaging" OR GRE OR "gradient-echo")*, filtered for English language. Based on this search string, we found 649 articles. The inclusion criteria were as follows: (1) inclusion of medulloblastoma patients (2) who were cognitively assessed and (3) scanned. Articles were excluded in case they were case reports ($n < 5$), older than 1998, not related to specific treatment of medulloblastoma, did not provide cognitive data, did not provide imaging data, or if no full text was available. A meta-analysis was additionally performed on the available intelligence scores of included studies. More specifically, mean scores and standard deviations of full-scale intelligence quotient (FSIQ), verbal IQ (VIQ), and performance or perceptual IQ scores (PIQ) were tested in a fixed effects model of weighted mean differences, with a 95% confidence interval in Review Manager v5.3. Given the standardized mean value of IQ scores of 100, deviations from this value were depicted in a forest plot. I^2 tests of heterogeneity were conducted to test for heterogeneity between the included studies.

Results

After reviewing the titles, 163 manuscripts were withheld (see Fig. 1). At abstract stage, 129 articles were excluded. Of the 34 full-text manuscripts we reviewed, 20 were included. Two additional articles [45, 46] were identified by manual reference tracking, bringing the number of included studies to 22. Included studies were divided into categories according to MRI-modalities (anatomical investigations, DWI, GRE, and fMRI and ASL). Detailed information about the imaging data can be found in Table 1. Sample sizes of the included studies ranged between $n = 6$ and $n = 92$. Age at diagnosis ranged from 2.2 to 21.6 years, with time intervals between diagnosis and participation between 6 months and 17.2 years. The majority of studies closely matched the timepoints of test assessments and neuroimaging acquisition, but three studies had an interval of up to

Table 1 Overview of included studies

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequences	Cognitive assessments (*)	Mean age at diagnosis (SD) (**)	Mean age at MRI-scan(SD) (**)	Mean age at neurocognitive testing (SD) (**)	Findings
Anatomical investigations									
(Mulhern et al., 1999) [47]	Cross-sectional	36 pts. - 18 MB pts. - 18 LGA pts.	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) [48]	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)	13.4 y (4.2)	13.4 y (4.2)	- NWM is positively correlated with FSIQ (after controlling for time since RT) ($R^2 = 0.253$; $p = 0.001$)
(Riva et al., 2002) [49]	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 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.
(Fouladi et al., 2004) [50]	Longitudinal, prospective	21 pts. with WML - 20 MB pts. - 1 supratentorial PNET pts. 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

Table 1 (continued)

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequences	Cognitive assessments (*)	Mean age at diagnosis (SD) (**)	Mean age at MRI-scan(SD) (**)	Mean age at neurocognitive testing (SD) (**)	Findings
									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)
(Riggs et al., 2014) [44]	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) [51]	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; 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 organization ($p = 0.023$) - higher distractibility ($p = 0.013$) worse outcomes in VMI ($p = 0.014$)
(Glass et al., 2017) [52]	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 36 m 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 ($p = 0.025$)
(Decker et al., 2017) [53]	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 ($p = 0.05$)

Table 1 (continued)

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequences	Cognitive assessments (*)	Mean age at diagnosis (SD) (**)	Mean age at MRI-scan(SD) (**)	Mean age at neurocognitive testing (SD) (**)	Findings
									(NOTE: NS after excluding 2 pts. with IQ < 60.) - No correlations between FSIQ, VIQ or PS and hippocampal subfields.
(Szychot et al., 2017) [54]	Longitudinal, retrospective	14 pts. - 9 MB - 4 supratentorial PNET - 1 metastatic pineoblastoma pts.	SR + pre-RT CT (MTX + Vcr + VP-16 + Cyclo + Carbo) + RT (CSI: 31.2 or 39 Gy / total dose to primary site 59.2–60 Gy) + post-RT CT (maintenance Vcr + lomustine / thiotepa + stem cell rescue) Note: no information available about 1 MB patient	T1; T2; FLAIR; DWI	Lansky Scale (performance status)	Median age: 7.6 y Range: 3–13 y	3 m interval for 1 y, 6 m interval thereafter	Pts. were scored retrospectively	- No correlation between brain volume loss and Lansky performance status - Pts. with severe neuroparenchymal volume loss vs. pts. with mild neuroparenchymal volume loss: higher CC volume loss ($p = 0.024$)
(Hoang et al., 2019) [55]	Cross-sectional, case-control	8 MB pts. n-1 and n-2 back fMRI study (subset out of 11 MB pts.) 8 ctrls. n-1 back fMRI study 9 ctrls. n-2 back fMRI study	SR ($n = 11$) + CT ($n = 8$) + RT ($n = 11$)	fMRI (n-1 back and n-2 back studies; auditory verbal, auditory non-verbal, visual verbal, and visual non-verbal); T2*GRE; T1	IQ; attention (Trail-Making-Test); working memory (D'Alboy working memory procedure, French version)	/	13.1 y (1.4)	Mean time between end-of--treatment and testing: 44 m (15 m) Mean time between testing and fMRI: 52 d (52)	- Pts. with left posterior cerebellar lobe WML vs pts. without: visuospatial or verbal working memory deficit - Ctrls.: fMRI shows posterior cerebellar lobules involvement in working memory tasks (left predominance) - n-1 back (pts. vs ctrls.) - increased mean reaction time for the visual non-verbal task ($p = 0.02$) - n-2 back (pts. vs ctrls.) - decreased accuracy rates for visual verbal ($p = 0.01$), auditory verbal ($P < 0.001$) and auditory non-verbal tasks ($p = 0.01$) - increased mean reaction time for the auditory non-verbal task ($p = 0.001$) - Pts. (vs ctrls.): lower verbal comprehension (mean: 101.18 vs 115.04; $p = 0.009$) lower perceptual reasoning (98.90 vs 109.47; $p = 0.02$) lower processing speed (84.63 vs 105.43; $p = 0.002$)
Diffusion-weighted MRI									
(Aukema et al., 2009) [56]	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	- CC splenium FA is correlated with PSF: $r = 0.53$ ($p = 0.03$) - CC body FA is correlated with PSF: $r = 0.52$ ($p = 0.03$) - Right IFO FA is correlated with MS: $r = 0.49$ ($p = 0.045$)

Table 1 (continued)

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequences	Cognitive assessments (*)	Mean age at diagnosis (SD) (**)	Mean age at MRI-scan(SD) (**)	Mean age at neurocognitive testing (SD) (**)	Findings
								MRI: 0.0–3.5 m	*(also significant in control group)* - Correlations involving FSIQ: NS - Correlations involving mean FA: NS
(Khong et al., 2006) [57]	Cross-sectional, case-control	30 pts. - 12 MB pts. - 18 ALL pts. 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 FA is correlated with: - FSIQ (adjusted $r^2 = 0.439$; $p < .001$) - VIQ (adjusted $r^2 = 0.237$; $P < .028$) PIQ (adjusted $r^2 = 0.491$; $P < .001$) *(NOTE: after adjusting for age at treatment, radiation dose and time interval from treatment)*
(Palmer et al., 2010) [45]	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)*
(Palmer et al., 2012) [46]	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 ($p = 0.010$) - CC genu FA: r = 0.31 (0.050) - CC body FA: r = 0.38 (0.016) - CC splenium FA: r = 0.37 (0.018) - Post thalamic radiation FA: r = 0.33 ($p = 0.042$) - External capsule FA: r = 0.37 ($p = 0.022$)
(Mabbott et al., 2006) [58]	Cross-sectional, case-control	8 MB pts. 8 controls	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	- ADC is negatively correlated with IQ (r = −0.60, p = 0.01) - FA is positively correlated with IQ (r = 0.65, $P < 0.01$)

Table 1 (continued)

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequences	Cognitive assessments (*)	Mean age at diagnosis (SD) (**)	Mean age at MRI-scan(SD) (**)	Mean age at neurocognitive testing (SD) (**)	Findings
								(range: 1.02–5.22 y)	- 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)*
(Khong et al., 2003) [59]	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 (1 pt.): 46.2%
(Rueckriegel et al., 2015) [60]	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 FA and cognitive tests
(Law et al., 2017) [61]	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 RD in left cerebello-thalamo-cortical pathway: R^2 = -0.110 Indirect effect explains 1.7% of variance in working memory
(Li et al., 2017) [62]	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: 1 pt only received RT to	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,

Table 1 (continued)

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequences	Cognitive assessments (*)	Mean age at diagnosis (SD) (**)	Mean age at MRI-scan(SD) (**)	Mean age at neurocognitive testing (SD) (**)	Findings
			PF: 50.4 Gy)) + CT (Vcr + CDDP and/or carbo + cyclo and/or lomustine (+ VP-16))						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
(Brinkman et al., 2012) [63]	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: - RD 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) - RD and shifting attention: left: r = −0.63 ($p = 0.003$); right: r = −0.55 (p = 0.01) Temporal lobes: - RD and shifting attention: right: r = −0.63 (p = 0.003); left: r = −0.69 ($p = 0.0008$) - RD 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 ($p = 0.007$)
Hemosiderin deposits and microbleeds									
(Yeom et al., 2013) [64]	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
Oxygenation									
(Zou et al., 2016) [65]	Longitudinal, case-control, prospective	40 MB pts. - 19 reading--intervention	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)	Age at first fMRI: Reading intervention group: 11.7 y	Age at first reading evaluation: Reading intervention group:	- Reading-intervention group (vs standard-of-care group): higher Sound Awareness scores at time of fMRI ($p = 0.046$)

Table 1 (continued)

Reference (year)	Study type	Patients (and control subjects)	Treatment	MRI sequences	Cognitive assessments (*)	Mean age at diagnosis (SD) (**)	Mean age at MRI-scan(SD) (**)	Mean age at neurocognitive testing (SD) (**)	Findings
		- 21 standard-of-care 21 ctrls.				Standard-of-care group: 9.5 y (0.6)	(0.6) Standard-of-care group: 12.1 y (0.6) (+ 2 more fMRI examination at 1 y intervals)	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: 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

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 leukemia; *ANT*, Amsterdam Neuropsychological Tasks; *AUNV*, auditory non-verbal; *AUVE*, auditory verbal; *babyPOG*, baby Pediatric Oncology Group protocol (Vcr, Cyclo, CDDP and VP16); *BMCT* Benton Multiple Choice Test (used for spatial memory testing); *Carbo*, carboplatin; *CC*, corpus callosum; *CCV*, CCNU, cisplatin, and vincristine; *CDDP*, cisplatin; *CERQ(-k)*, Cognitive Emotion Regulation Questionnaire for Children (under 12 years 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; *RD*, 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; *VINV*, visual non-verbal; *VIQ*, verbal intelligence quotient; *VIVE*, visual verbal; *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); *FA*, 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/IV 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

1 month [55], 3 months [56], 6 months [47], and 19 months [44]. All patients were treated with multimodal treatment including craniospinal RT (23.4–41.4 Gy), RT boost to the posterior fossa (50.4–68 Gy), and chemotherapeutic agents (cyclophosphamide, vincristine, lomustine, VP-16, carboplatin, cisplatin, (intrathecal) methotrexate, thiothepa, placlitaxel). Based on the neurobehavioral meta-analysis, strong overall effects were encountered with regard to decreased IQ scores in MB patients compared to healthy controls (see forest plot, Fig. 2). More specifically, total IQ, verbal IQ, and performance IQ were 14.27, 13.70, and 13.74 points lower on average in MB patients compared to controls (overall Z tests > 7, $p < .00001$). These effects showed low heterogeneity ($I^2 < 50\%$, $p > .05$).

Anatomical Investigations (T1- and T2-Weighted MRI)

Anatomical MRI investigations (T1- and T2-weighted MR imaging) can be used to evaluate changes of normal gray and white matter volume, or white matter lesions [48]. FLAIR is an MR sequence which can be used to evaluate white matter lesions, especially when these are located in the periventricular brain area [66].

Normal White Matter and Gray Matter Volume

Two studies reported that NWM 3–13 years after diagnosis was positively correlated with FSIQ [47, 67] and one larger study (n = 92) showed an association with working memory 3 years after diagnosis [52]. MB patients appeared to have less NWM, lower FSIQ, and lower performance intelligence quotient (PIQ), compared to low-grade astrocytoma (LGA) patients (n = 18). This suggests an important neurotoxic role of the non-surgical treatment constituents of MB (i.e., chemotherapy and radiotherapy) on neuroanatomy and neurocognitive functioning, since LGA patients are generally treated with surgery only [47]. Corpus callosum (CC) volume loss was more pronounced in patients with severe atrophy of the neuroparenchyma compared to those who were only mildly affected in a small retrospective study [54]. Still, two studies with smaller study populations (n = 20; n = 10) did not encounter any significant associations with executive functioning or the Children's Memory Scale (CMS) [44, 63].

Finally, no significant associations were reported with regard to normal gray matter volume [67].

White Matter Lesions (WMLs)

One study stated that WMLs were associated with decreased visuospatial planning, common sense judgment, and arithmetic reasoning in MB patients who received intrathecal MTX as part of their treatment (n = 11), which was not the case in patients not treated with intrathecal MTX (n = 10) [49]. Another investigation reported a significant decline in IQ and mathematical scores in MB patients with WMLs (n = 21), but not in non-lesioned patients (n = 93) [50]. WMLs in the posterior left cerebellar lobe were associated with worse working memory in these MB patients compared to patients without such lesions [55]. Finally, a correlation was demonstrated between WMLs and decreased PS, perceptual organization and visual motor functioning, and increased distractibility in a subset of 17 MB patients [51].

Gray Matter Atrophy

Cerebellar atrophy was related to higher distractibility and supratentorial atrophy with low verbal comprehension scores [51]. The only article that considered hippocampal subfield volumes reported that smaller volumes of several hippocampal subfields were correlated with poorer verbal associative memory in 11 brain tumor patients, including 10 MB patients [53]. Another study reported a correlation between the right hippocampal volume and learning, attention, and memory, using the CMS, in 10 MB patients [44].

White Matter Microstructure (Diffusion-Weighted MR Imaging)

To investigate certain microstructural white matter changes which cannot be estimated using the previously discussed anatomical MR scans, DWI can be used. With DWI, information about tissue compartments can be obtained through the amount of motion of water within the tissue [68]. The apparent diffusion coefficient (ADC) can be calculated and used to visualize diffusion in brain tissue [69]. ADC indicates the mean diffusion across the three orthogonal directions within a voxel. A high ADC value means that tissue has free diffusion. A low value means restricted diffusion [68]. In areas of normal white matter, ADC is rather low because of restriction of water diffusion by the fiber tracts [68, 69]. In patients with that received RT, white matter tracts are damaged and higher ADC values are seen [70].

Diffusion tensor imaging (DTI) is specific model applied to DWI scans, which allows us to quantify the preferential direction of water diffusion. The direction of diffusion is associated with the orientation of white matter fibers [71]. Consequently, DTI can be used to estimate changes in white matter fiber organization quantitatively and to visualize the fiber bundles connecting different brain areas (DTI tractography) [37, 48]. 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 higher FA value (close to 1) indicates that water diffusion is restricted according to the principal direction of a fiber bundle [68]. FA is thus used as a value to investigate the influence of cancer and its treatment on the microstructure of white matter fiber tracts. Multiple studies have shown decreased FA in patients compared to controls, indicating damage to white matter tracts in the brain [38, 72–74]. A correlation between RT dosage and decreases in FA has also been reported [18].

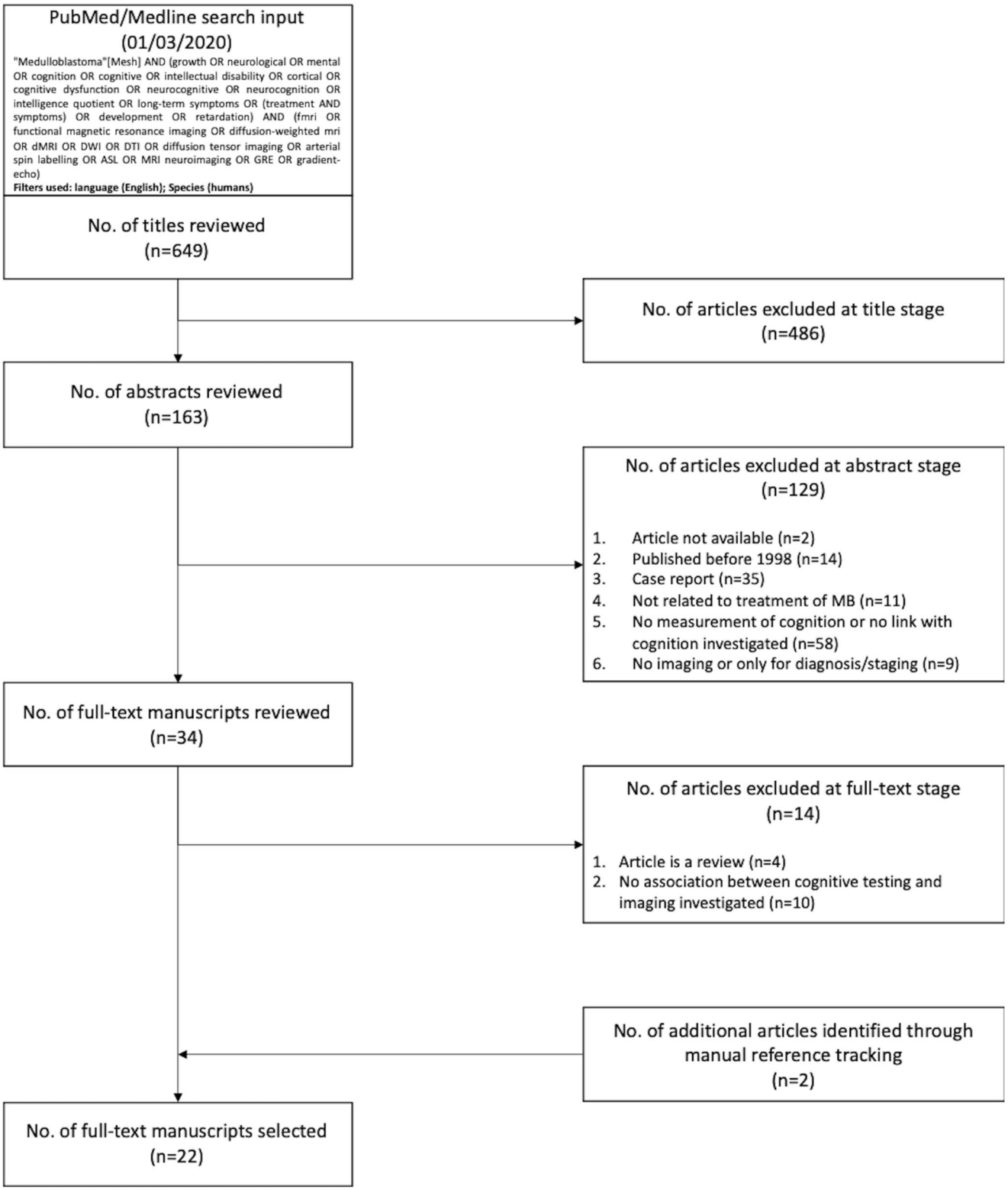

Fig. 1 Flowchart showing the search algorithm and selection process used for this review

Apparent Diffusion Coefficient (ADC)

In one of the included studies, significantly lower ADC values were seen in the hippocampi of 21 MB patients compared to a control group ($n = 64$) [62]. In addition to the abovementioned studies regarding hippocampal volumes [44, 53], this study suggested a disturbed hippocampal microstructure resulting in poorer memory performance in patients treated for MB.

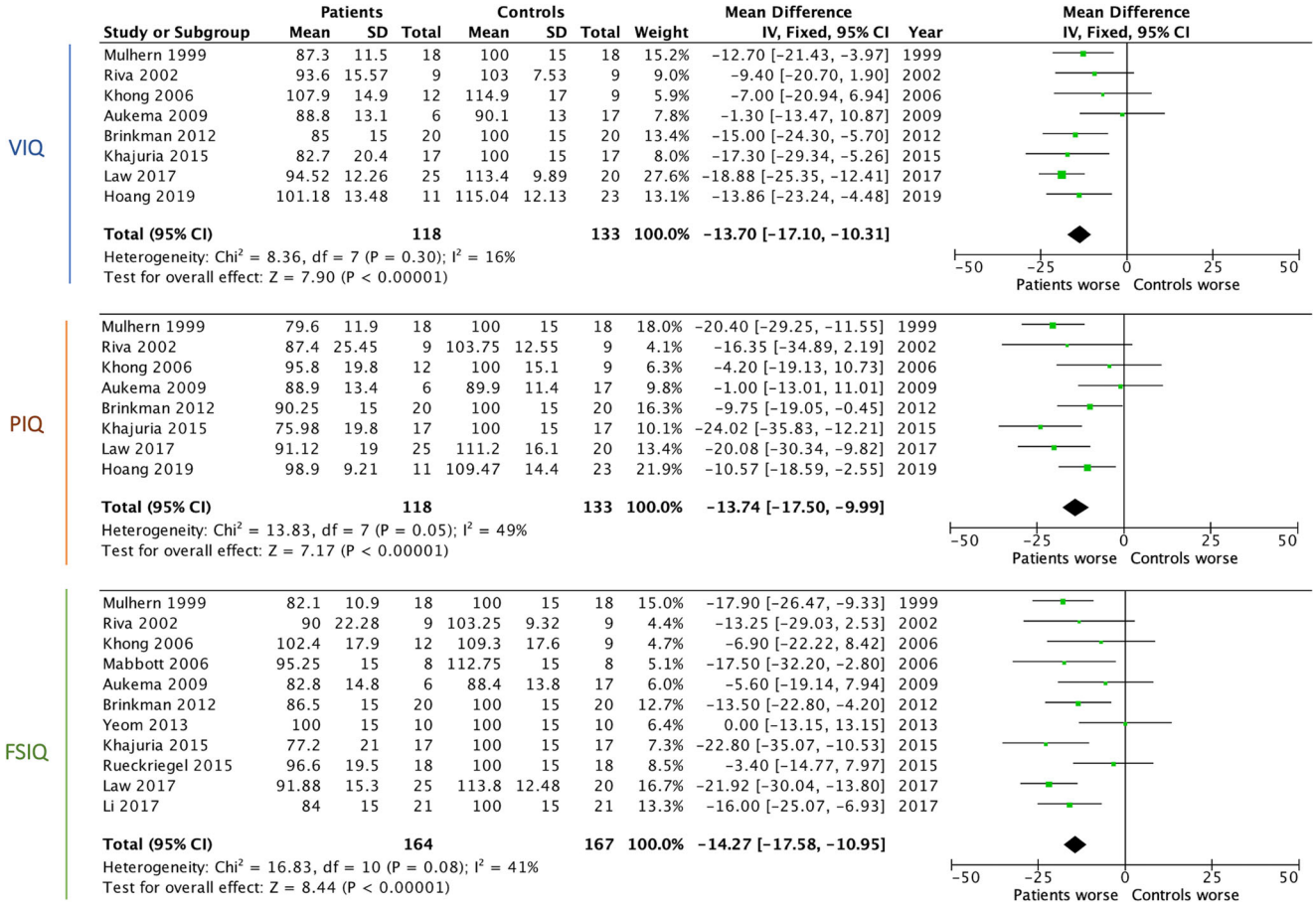

Fig. 2 Forest plots for IQ scores in included studies. Note. PIQ = performance intelligence quotient, VIQ = verbal intelligence quotient, FSIQ = full-scale intelligence quotient. In case of adult assessments, the total scale scores of perceptual reasoning and verbal component scores were used as equivalent. If healthy control data were not available in the specific study, the normative IQ values with mean = 100 and SD = 15 were used instead

Second, two investigations reported associations between white matter ADC values and lower IQ in a population of 8 MB patients and a subset of 12 patients, including 9 MB patients [58, 62]. One of these also reported a significantly lower IQ compared to control subjects. However, this difference in IQ became non-significant after correction for average ADC values [58]. The other researchers additionally reported associations between ADC in other brain areas (such as the cortex) and IQ as well [62]. These studies thus suggest that altered ADC after MB treatment could partly explain the observed decreases in IQ scores. By contrast, Brinkman and colleagues did not report any significant correlations between ADC and multiple executive functioning tasks in a population of 20 MB patients [63].

Besides ADC, higher radial diffusivity (RD) (i.e., diffusivity perpendicular to the axons) was detected in the left cerebellar-thalamic-cortical pathway in a group of 6 MB and 11 ALL patients. This was associated with working memory [61]. Similarly, one study in 20 MB patients showed associations between RD in several brain areas and shifting attention and cognitive flexibility [63].

In summary, these findings suggest that altered white matter tract organization, resulting in increased free diffusion could, at least partially, account for therapy-related decreases in intelligence in MB patients.

Fractional Anisotropy (FA)

Two studies reported that low global white matter FA was correlated with low IQ, of which one used a mixed population of 12 MB and 18 acute lymphocytic leukemia (ALL) survivors and the other included 8 MB patients only [57, 58]. It is important to note that some remaining studies did not necessarily confirm this association [56, 60].

Other studies focused on more specific tracts and PS. One study reported that both relative NWM (over gray matter and cerebrospinal fluid) and FA of specific white matter tracts were positively correlated with PS in a mixed population of 18 MB and 14 pilocytic astrocytoma (PA) patients [60]. 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 CC and decreased PS was reported [56]. This

association between FA of the CC and PS was confirmed in a larger study, with a population of 38 MB and 2 atypical teratoid rhabdoid tumor patients. FA of the posterior thalamic radiation and the external capsule were also associated with PS [46]. In another article, with a study population of 92 MB patients, baseline global FA was associated with PS, as well as with broad attention, measured 36 months later [52].

Other articles also reported several correlations involving EFs. Low FA in the parietal lobes was correlated with poorer working memory and low FA in the temporal lobes with poorer cognitive fluency, in a subset of 10 MB patients [63].

Two studies with small populations, respectively 9 and 10 MB patients, investigated associations between FA and learning [44, 59]. The first study reported more reduction in supratentorial FA in patients with more severe deterioration in learning capacity. Because of the small sample size and no quantitative assessments, these findings require cautious interpretations [59]. The other article reported an association between FA of the left uncinate fasciculus and learning and memory performance [44].

FA scores of multiple brain regions measured around 1 year post-diagnosis were correlated with reading decoding skills in patients that were diagnosed with MB ($n = 49$) and other embryonal tumors ($n = 5$) [45].

Oxygenation (fMRI) and Blood Flow (ASL)

Functional MRI (fMRI) is a neuroimaging technique to specify brain regions that are activated during a certain task, through changes in blood-oxygen level-dependent (BOLD) signal [75]. As this signal depends on deoxyhemoglobin concentrations, functional MRI estimates oxygen consumption by neurons, reflecting the neuronal activity throughout time [37, 76].

First, a case-control fMRI study was conducted in MB patients who received a reading intervention ($n = 19$) or standard-of-care ($n = 21$). These researchers concluded that a prophylactic reading intervention has long-term positive effects in pediatric MB patients. This study also reported increased activation during reading tasks in the reading-intervention group [65]. In another study, fMRI showed posterior cerebellar lobules involvement in working memory tasks with a left lobe predominance in control participants. Patients in the same study scored significantly worse in multiple working memory tasks and showed lower PS, lower verbal comprehension, and lower perceptual reasoning compared to control subjects [55].

Second, 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 labeled. Blood perfusion can be visualized and quantified by subtracting the labeled images from control images [77]. One study investigated CBF in 9 MB patients using ASL. They reported a lack of associations between CBF and IQ [62].

Hemosiderin Deposits, Microbleeds (T2*-Weighted GRE or SWI)

Focal hemosiderin deposition lesions seen on MRI are a frequently occurring finding after RT for pediatric brain cancer [78]. Such observations can be caused by underlying cerebral microbleeds (CMB) and cavernomas, and could be referred to as small vessel disease [79–81]. CMBs can be detected with T2*-weighted gradient-recalled echo (GRE) imaging or susceptibility-weighted imaging (SWI) [82, 83].

The only study that discussed CMB incidence ($n = 41$) demonstrated more lesions in patients who received RT at later age (7–21 years old), compared to younger patients. They did not report any significant associations with IQ or need for special education. Also, no significant correlation with radiation dose was observed [64].

Limitations and Recommendations

A first limitation that needs to be mentioned is the heterogeneity in the applied methods across the studies. The included studies are heterogeneous with respect to design, sample size ($n = 6$–92), age at diagnosis (2.2–21.6 years), treatment schedules, time of imaging (6 months−17.2 years after diagnosis), time of cognitive measurement (0–19 months after MR-scan), MRI parameters, and cognitive test assessments. This is related to the fact that only a small number of studies on this subject were published. Ideally, studies would use standardized, homogenous outcome parameters, which can directly be compared, and data can be pooled for large sample size studies or meta-analyses.

Second, there is a lack of prospective studies on this subject. Of the 22 included articles, only three had a prospective study design [50, 52, 65]. 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. Although a limited amount of longitudinal imaging studies evidenced deviant growth patterns of the brain in medulloblastoma patients [84, 85], no studies have been reported to date which investigate both longitudinal behavioral and imaging data. It would be useful to predict long-term cognitive outcome using neuroimaging and to introduce extra preventive measures in certain subpopulations of MB patients. We suggest a prospective design including MB patients and age-and gender-matched controls, of whom advanced MR scans and cognitive assessments should be acquired at least at the end of treatment, as well as > 2 years after treatment (to avoid possible short-term learning effects and

acute neural damage which could recover). The interval of > 2 years is also substantiated by the fact that cognitive decline might arise later due to the "growing into deficit." Hence, the required variability between patients and controls to find important associations with the neuroimaging might only occur later in time. Both MR scans and cognitive test assessments should be acquired at closely matched timepoints (i.e., in the same week as the test assessment). In case of small cohorts, data acquisition is rather recommended in adulthood in order to decrease the impact of age at acquisition on the neuroimaging analyses.

Furthermore, multiple studies demonstrate differential findings (e.g., significant versus insignificant correlations between NWM and EFs and between global FA and IQ). A possible explanation for these inconsistencies could be the abovementioned heterogeneity in methodology. Mainly, differences in treatment schedules, time of imaging, and assessments can largely influence the results. These differences between the studies (e.g., treatment, timing) were not consistently associated with clear differences in cognitive effects.

Finally, multiple studies included a mixed brain cancer patient population, meaning that they do not focus on MB patients separately. This complicates the question whether cancer type itself can also interfere with brain development. However, we decided not to exclude these studies, since many other brain cancer patients received similar treatments as MB patients.

Discussion

The aim of this review was to summarize the currently existing literature discussing associations between neuroimaging and neurocognition in pediatric MB survivors. For a schematic overview of significant associations, see Fig. 3. The purpose of this review was (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 predictive neuroimaging parameters for cognitive outcomes, and (3) to explore potential targets for medical interventions.

Medulloblastoma treatment, especially radiotherapy, has a negative impact on the intelligence scores of patients [29–31]. This review provides evidence for white matter changes, investigated by both anatomical and diffusion-weighted MR imaging, which could explain the decreases in overall intelligence scores. Based on our behavioral meta-analysis, we showed that intelligence scores of patients were significantly lower compared to healthy controls across studies. Given that overall average IQ scores of survivors almost reached a standard deviation from the norm (mean = 100, SD = 15) across studies, we conclude a clinical vulnerability of the MB patient population. Furthermore, multiple studies showed IQ scores to correlate with both lower NWM volume and a higher amount of WML [47, 50, 67]. Although two articles disconfirmed this, either another assessment was used (i.e., the Woodcock-Johnson tests) or only periventricular leukomalacia was considered in these studies [49, 52].

Compared to LGA patients who were treated by surgical resection only, MB patients have less NWM and lower IQ scores, suggesting that non-surgical treatment modalities (i.e., chemotherapy and radiotherapy) have a negative impact on the neuroanatomy and intelligence of patients [47]. More specifically, one study comparing two treatment protocols showed worse cognitive outcomes observed in patients who received intrathecal MTX [49], and only their cognitive scores correlated with WMLs, providing an argument for the role of (intrathecal) CT in cognitive deterioration in MB patients.

Besides the investigations of NAWM and WMLs, lower IQ scores were most often associated with disorganized white matter on microstructure level, indicated by higher ADC and lower FA values [57, 58, 60, 62].

However, it should be noted that more specific cognitive domains were also associated with imaging parameters, rather than overall IQ scores. In that regard, poorer intellectual outcomes in pediatric MB survivors might not necessarily be due to loss of intellectual capacities, but can rather occur because of decreased PS, working memory, ability to learn new things or memory [30], and language problems. Hence, anatomical changes that affect any of these specific cognitive domains could underlie the decreased intelligence scores that are ultimately assessed.

For instance, disorganized white matter (micro)structure was associated with deterioration of PS after MB treatment as well [46, 51, 52, 56, 60]. Two of these articles demonstrated that microstructural changes in the CC specifically were related to lower PS [46, 56], which has also been reported in other clinical populations [86–88].

One prospective study reported that low FA post-surgery was correlated with lower PS 3 years later [52]. This clearly demonstrates that not only chemotherapy and radiotherapy can cause white matter damage, but also acute damage due to surgery could cause cascade effects. Therapy is mainly chosen in function of risk of the disease and age of the patient. Hence, predicting the cognitive outcome after surgery could provide an opportunity to further personalize CT and/or RT schedules. Hence, a treatment-based risk classification system could be beneficial for such individual treatment adaptations, shifting the clinical focus towards a more quality-of-life-based approach.

Besides processing speed, working memory is a prominent cognitive function in MB patients [34–36]. Also, decreased working memory was associated with microstructural white matter changes, shown by low FA- and high RD values in different brain regions [61, 63], and with macrostructural change in the form of reduced NWM volume as reported by

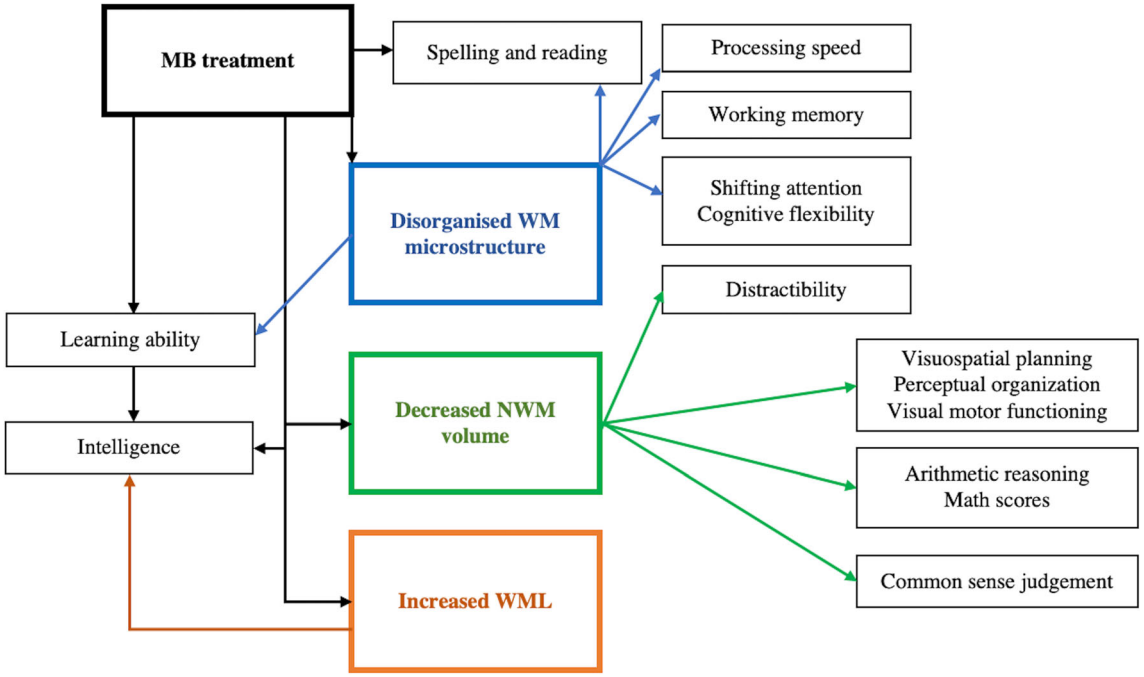

Fig. 3 Schematic overview of significant associations described in the included manuscripts. Note. WM = white matter, NWM = normal-appearing white matter, WML = white matter lesions

one study [52] and left posterior cerebellar lobe WML as reported by another study [55]. Similarly, disorganization of several white matter microstructures was correlated with shifting attention and cognitive flexibility [61, 63] and more WML are seen in patients with worse visuospatial planning, common sense judgment, arithmetic reasoning, math scores, perceptual organization, distractibility, and visual motor functioning [49–51].

The negative impact of MB treatment on a child's development is reflected in deteriorating learning capacity and poorer memory performance [44, 59]. This again was associated with lower FA values [44, 59]. Furthermore, an abnormal growth pattern was encountered for the hippocampal structure [89], which appeared to have an additional role in poorer memory performance [44, 53, 62]. In addition to changes in the hippocampal areas, cortical thinning was encountered in other gray matter areas, including the perirolandic area and the parieto-occipital lobe, as well [90].

A final cognitive domain concerns language functioning. MB patients showed a clear decline in spelling and reading scores compared to control subjects [50], which again was correlated with higher FA values in several brain structures [45].

To improve these cognitive skills, more recent studies have focused on potential intervention programs. First, a reading intervention was previously designed in a game-like format to limit the negative influences of MB treatment in children [91]. This program appeared successful with long-term positive effects on functional brain activity in pediatric MB patients [65]. Second, physical training interventions have recently also been associated with structural changes, including increased cortical thickness [92] and higher FA values [93] in pediatric brain tumor survivors. Finally, computerized cognitive trainings could result in similar effects. Conklin and colleagues demonstrated executive scores to improve and functional activation of prefrontal areas to decrease after such training sessions [94]. However, given the limited number of intervention studies including neuroimaging follow-up to date, these studies still need more validation.

Finally, one article hypothesized the possible association between CMB and lower intelligence scores [64]. However, their findings did not support this hypothesis. A more recent imaging study also confirmed a significantly higher amount of CMB in MB compared to healthy controls, but unfortunately, this study did not include cognitive assessments [95]. To which extent microvascular changes thus play a role in cognitive outcomes remains insufficiently addressed.

Based on this review paper, we conclude that both macrostructural and microstructural white matter changes can occur during or after childhood MB treatment and play an important role in cognitive functioning of these survivors. Due to the lack of prospective studies, however, the timeline of toxic mechanisms and neural damage remains inconclusive. In addition, given that all patients in the included studies received relatively similar and standardized RT doses (23.4–31.4 Gy craniospinal RT, 50.4-68Gy PF RT boost) as well as combinations of multiple chemotherapeutic agents, we currently cannot distinguish between possibly abundant cascade effects

due to the tumor itself, the remaining lesion, and specific toxic mechanisms induced by the neurosurgery, radiotherapy, or chemotherapy afterwards. In other words, it remains challenging to identify whether the long-term cognitive deterioration in this population is due to the cerebellar damage and to which extent it is due to additional treatment-associated neurotoxicity. Hence, more rodent research could further elucidate these causal associations [96]. In order to improve future treatments, clinical trials comparing multiple treatment arms would ideally include add-on comparative studies of prospective imaging and cognitive data.

In the future, large prospective studies with long-term follow-up should be performed. These ideally investigate the impact of the newly defined molecular subgroup types, and include long-term neurocognitive outcomes as well as advanced neuroimaging acquisition. Ideally, patients would be categorized in age-groups and according to the (molecular) typing and staging of their disease and the treatment they received. 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. Hence, patients ideally undergo baseline neuroimaging and cognitive testing, as well as imaging and testing in follow-up on certain points in time that are determined a priori, at least at the end of treatment, as well as > 2 years after treatment. Use of DWI would be highly recommended, as microstructural changes are often detected, without observing a clear change in white matter on anatomical investigations. Special attention should be paid to further examine 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 will be invaluable to improve cognitive functioning of survivors of childhood medulloblastoma.

Conclusion

Based on this review study, we conclude clinically affected IQ scores in medulloblastoma survivors, as well as lower white matter volumes, more frequent white matter lesions, changes in white matter microstructure, more cerebral microbleeds, and changes in functional activity in medulloblastoma patients. These alterations were associated with lower intelligence scores, working memory, and processing speed. We suggest working towards neuroimaging-based prediction of cognitive outcomes, for which large prospective studies using multimodal magnetic resonance neuroimaging are recommended. Potential interventions reducing these structural and functional brain changes are unfortunately only limitedly investigated. Hence, such studies are highly recommended in pediatric medulloblastoma patients in the future.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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