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Limited research investigating the value of MRI in predicting future cognitive morbidity in survivors of paediatric brain tumours: A systematic-review and call to action for clinical neuroimaging researchers

Daniel J. Griffiths-King[1], **Christopher Delivett**[1], **Andrew Peet**[2,3], **Jane Waite**[1], **Jan Novak**[1]*

1 Aston Institute of Health and Neurodevelopment, Aston University, Birmingham, United Kingdom, **2** Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom, **3** Birmingham Women's and Children's Hospital NHS Foundation Trust, Institute of Child Health, Birmingham, United Kingdom

* j.novak@aston.ac.uk

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Abstract

Survivors of pediatric brain tumours are at a high risk of cognitive morbidity. Reliable individual-level predictions regarding the likelihood, degree, and affected domains of cognitive impairment would be clinically beneficial. While established risk factors exist, quantitative MRI analysis may enhance predictive value, above and beyond current clinical risk models. This systematic review addresses the question: "Do MRI markers predict future cognitive functioning in pediatric brain tumour survivors?" We conducted a comprehensive search for studies published up to March 2024 that assessed MRI variables as predictors of later neuropsychological outcomes in pediatric brain tumour patients. Only studies that acquired MRI scans at an earlier timepoint to predict subsequent cognitive test performance were included. Surprisingly, few studies met these criteria, with identified research focusing primarily on MRI measures of cerebellar and white matter damage as features in predicting cognitive outcomes. Ultimately, this review reveals a limited literature, characterized by small sample sizes and poor-quality studies, placing findings at high risk of bias. Consequently, the quality and conclusions drawn from the existing research are constrained, especially in the context of prediction studies. Given the significant implications for this clinical population, this review highlights the urgent need for further investigation and a 'call to action' for medical imaging researchers in pediatric neuro-oncology.

Introduction

Individual outcomes for childhood brain tumour patients

Survival from cancer in childhood has seen great improvement in recent decades [1]. Consequently, there is an increasing population of adult survivors [1, 2], with approximately 1 in 530

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young adults between the ages of 20 and 39 being a survivor of childhood cancer [3]. This is especially true in pediatric brain tumours, the most common solid tumours in children (roughly 20%) [4], where survival is now estimated at around 95% for cerebellar pilocytic astrocytoma, and 60–80% for medulloblastoma [5–8]. Thus, there is an ever increasing need to focus on ensuring quality of life for the future of these children.

Many children with brain tumours experience neurocognitive effects at some point in their disease course, resulting in dysfunction in domains of cognition, emotion, and behaviour. The estimated risk for children with brain tumours of having emotional, psychosocial, and attention problems are 15%, 12% and 12% respectively, according to a recent meta-analysis [9]. Even at 10-year survival, these patients still demonstrate neuropsychological and psychosocial impairment across multiple domains [10]. Recent, large-scale, longitudinal studies have suggested an increased risk of continuing neurocognitive decline for these patients, irrespective of treatment type [11]. Performance over time demonstrates an inability to acquire new skills and cognitive abilities at the same rate as healthy peers, rather than a loss of previously acquired abilities [12]. This may explain why these difficulties are likely to persist long-term and are non-transient. The number of post-cancer life-years is greater for pediatric rather than adult survivors, and these years include important milestones such as education and interpersonal relationship development [13]. Long-term difficulties could profoundly affect participation for these children, at home, school and later in the workplace, likely resulting in poorer long-term educational and employment outcomes [14, 15]. This represents a persistent burden for patients, families and healthcare systems [16]. Whilst survival must always be the utmost priority, research aimed at limiting cognitive morbidity in this group is now needed to ensure likelihood of reaching their potential, despite their illness [17].

Whilst disease and treatment will inevitably place all pediatric brain tumour patients at some level of risk for poor cognitive outcomes, knowing individualised risk, an estimate of the severity of difficulties and specific domains likely to be impacted, will influence clinical practice. There is significant variability in outcomes at the individual patient-level, but this is currently understudied [16]. Person-centred analytical approaches across a large longitudinal sample of paediatric brain tumour patients, show distinct classes / phenotypes with unique profiles in social, cognitive, and attentional difficulties over time [18], with similar subgroups identified in cross-sectional data [19]. Percentages of individuals scoring in the 'impaired range' was between 28–55% across domains in a recent longitudinal study, at around 6yrs post diagnosis [11]–highlighting, within a 'cutoff' driven framework of cognitive impairment, the presence of a classification task for identifying/labelling individual cases of impairment. Thus, there is scope for developing individualised models of risk and resilience, which hold predictive validity.

Clinical benefits from prediction of cognitive outcomes

Prediction of individual-level neurocognitive outcomes would enable timely and tailored input from school and allied health services, promoting outcomes for these children, with limited healthcare resources being efficiently prioritised for those most at risk. It would also help healthcare professionals counsel and educate patients for these difficulties and help reduce uncertainty about the future for families. Individual models of risk would also impact treatment planning. In children where treatment of their brain tumour is more difficult, adjuvant therapy may include radiotherapy, which is known to have significant impact on a child's neurodevelopment. This is due to brain injury from the primary and secondary effects of radiotherapy, especially in paediatrics where there is specific vulnerability (e.g., due to younger children not yet having reached peak myelin maturity) [20, 21]. Whilst developments in

treatment have mitigated some neurocognitive toxicity (e.g. proton beam radiotherapy [22]), there is still need for clinicians to navigate treatment decisions in terms of risk to QoL based upon known disease and age related risk factors [20, 21]. More accurate prediction of individual-level risk of cognitive morbidity (even across domain and severity), would enable clinicians to further adapt and personalise treatment schedules with a greater focus on risk to quality-of-life whilst maintaining treatment efficacy [23]. Overall, there is clinical benefit for a range of patients in knowing individualised prediction of neurocognitive outcomes, and the development of these methods for deployment to a clinical setting.

Predicting cognitive outcomes

There are many established risk factors for poor long-term neuropsychological outcome that need to be understood to provide a comprehensive risk profile at the individual child level [24]. Recent neurodevelopmental models based on known risk factors have been proposed to explain outcomes for brain tumour survivors, specifically in medulloblastoma [25–27], taking into consideration the complex disease-, treatment- and host-related factors that may influence these outcomes. Many aspects can result in neurodevelopmental insults to the developing brain which may explain and underpin these neurobehavioral morbidities [28, 29] and thus are significant risk factors for these poor outcomes [24]. These range from physical factors such as treatment effects (i.e. resection and/or adjuvant therapy [20, 30]) and individual differences (e.g. age at diagnosis [30], cognitive reserve), but also psychological factors (i.e. Early Childhood Adversity, threat exposure) and environmental factors (i.e. Socioeconomic Status (SES) and social support) [28]. See [24] for a model of cognitive risk in pediatric brain tumour survivors. Essentially, neurocognitive outcomes are complex and are dependent on several interacting factors [13].

Risk-based and exposure-related guidelines and models have been developed to manage these neurocognitive late-effects of pediatric brain tumours [24, 31]. Neurobehavioral morbidities are predicted by clinical variables such as radiotherapy, chemotherapy, neurosurgery, and parental education but less-so age at diagnosis, gender, or time since diagnosis [13, 14, 20, 32–35]. A number of these complex risk factors can be either difficult to measure or qualitative in their assessment and therefore can inform decisions but do not make individual predictions. The Neurological Predictor Scale (NPS) was designed as an ordinal scale to quantitatively capture the cumulative effect of several risk factors on outcomes, and somewhat predicts IQ, adaptive functioning and processing speed and working memory, at both short- and long-term follow-up [34, 36–39]. This cumulative measure captures unique variance, above and beyond the individual predictors.

MRI as a novel predictor of outcomes

This systematic review posits that magnetic resonance imaging (MRI) measures are likely to be a good proxy of the burden of brain tumours and their treatment thus, are likely to be predictive of cognitive impairment at the individual patient-level. Qualitative reporting of MRI does predict outcomes, with brainstem invasion, midline location of the tumour, and tumour type predicting post-operative cerebellar mutism syndrome, a (typically) transient, neurological morbidity seen in this population [40]. Quantitative alterations to the brain's structure and function, specifically microstructural changes to the white matter (WM) of the brain, during the developmental period, could be the common neuroanatomical substrate of poor neurocognitive outcomes [25, 27]. See [23, 41] for a review of MRI in pediatric brain tumours. Recent successes and interest in using MRI to predict neurodevelopmental outcomes in premature infants [42], or even decline in neurocognitive functioning in older adults [43] highlights the

potential opportunities offered by MRI. There is also a relative abundance of MRI data in these patients, acquired as part of standard of care and most research protocols. Therefore, MRI is likely to provide highly relevant features which provide 'added-value' in predicting outcomes beyond clinical risk factors alone.

There is extensive research establishing associations between MRI variables and neurocognitive outcomes in pediatric brain tumour patients, distilled across multiple systematic reviews [23, 41]. However, it is currently unclear whether these studies translate into the mode of predictive studies. No current systematic review has focussed solely on predictive studies in these cohorts, with specific restrictions on the timing of MRI scanning and outcome assessment. This systematic review specifically investigates existing literature using MRI scans, taken at any point in the disease course, to predict non-contemporaneous, later neuropsychological outcomes in survivors of pediatric brain tumours.

Whilst there is existing literature of existing established clinical predictors of cognitive late effects in this population, this review aims to assess studies using MRI as a predictive modality, with the goal of assessing whether quantitative analysis of MRI provides 'added-value' in these risk models.

Materials and method

We conducted this systematic review in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [44], an overview of which is reported in Fig 1. Initially, a limited search of the Web of Science database was undertaken in June 2022 for the purpose of refining the search terms. Due to the wide-ranging classifications of central nervous system (CNS) tumours, as well as generic tumour-focussed terms, we also included terms pertaining to the most common paediatric histological diagnoses accounting for 85% of total incidence rates (Central Brain Tumour Registry of United States, 2014–2018 [45]). Search terms can be found in supporting materials (S1 Table). Based on our initial search, we pre-registered our review protocol through the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42022343161).

A comprehensive search of Embase, MEDLINE, PsycINFO, Scopus and Web of Science was conducted in July 2022 using the designed search, resulting in 8,632 records (see supporting materials S1 Fig). Searches were rerun and results updated in March 2024, resulting in an

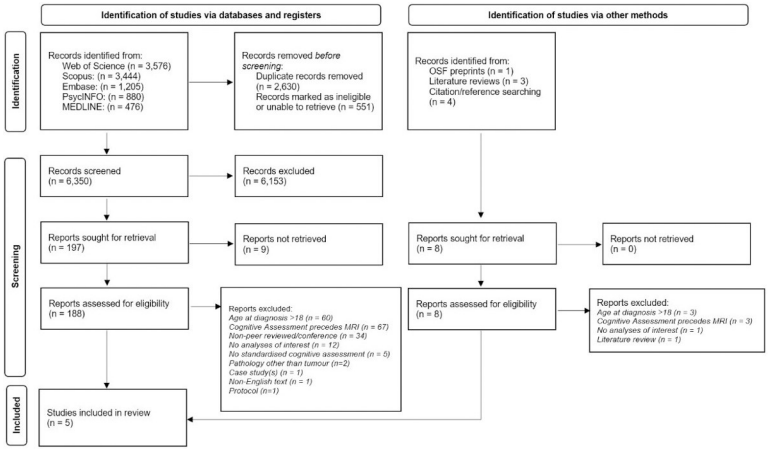

Fig 1. PRISMA flow diagram. Results of the search conducted in March 2024.

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additional 899 records. Alterations were made to the search terms for each database to account for differing Boolean operators (see Supporting Materials S1 Table). Additionally, we also searched the Open Science Framework (OSF) preprints archive for relevant articles that had not otherwise appeared as published texts in our main search. We included any longitudinal study concerning patients diagnosed with a brain tumour before the age of 18, who had MRI data that clearly preceded an age-appropriate, standardised test of cognitive ability (e.g., intellectual ability assessed with Weschler Intelligence Scale for Children—WISC-V [46]). Central to our main research aim, we included those studies that explicitly reported an association between future cognitive outcomes based on prior MRI. Meta-analyses and literature reviews that did not report new data were excluded, however, reference lists were searched for additional studies of interest. Search results were not restricted by publication date but were limited to those written in English. In addition to our pre-registered exclusion criteria, we also excluded patients with CNS tumours secondary to neurofibromatosis, tuberous sclerosis, or acute lymphoblastic leukaemia as these were considered significant confounds for predicting cognitive outcomes. We also excluded non-peer reviewed articles, such as conference abstracts and theses. Inclusion/exclusion criteria are further detailed in Table 1.

Identified records were first imported into MS Excel and duplicates removed. Following a short pilot, two independent reviewers (CD + DGK) screened the titles and abstracts of all the identified papers against the inclusion criteria. Full texts of suitable papers were subsequently retrieved and screened by both reviewers for final inclusion in the review. For completeness, the reference lists and citations of those papers marked for inclusion were reviewed for additional studies that may have been missed. At each stage of the process, disagreements were discussed until consensus was met. Per our pre-registration, data extraction was completed by one reviewer (DGK), whilst a second reviewer evaluated data extraction of all papers for correctness (JN). The data extraction tool was initially developed for this research protocol and was later refined based upon the findings of the search results. This was not based on an existing tool, and items were selected based on discussion within the research team. Data from each study included: (1) year of publication, (2) study aims and/or hypotheses, (3) study location (i.e., country, recruiting hospital), (4) number of patients, (5) patient characteristics (i.e., years recruited, diagnoses, treatments, cognitive outcomes, age at diagnosis/MRI/neuropsychological evaluation), and (6) statistical analyses.

We had initially registered our intention to assess the validity of the included studies using the Transparent Reporting of a multivariate prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines; however, this was deemed unsuitable given that none of the studies reported using predictive modelling in their approach. Instead, studies were reviewed

Table 1. Inclusion and exclusion criteria for identifying publications for the systematic review.

Inclusion Criteria	Exclusion Criteria
• Participants are patient group of primary central nervous system (CNS) tumour • Participants have any diagnosis of pediatric brain tumour, between ages of 0–18 • Reported data include brain MRI (of any modality) and age-appropriate, standardised neuropsychological evaluation. • Reported MRI must precede neuropsychological testing, by any period of time. • Report analyses of an association between or prediction of, prospective cognition from MRI. • Written in English	• Patient groups where CNS tumours may be present but secondary to other disease (i.e. NF1) • Case studies • Meta-analyses and systematic reviews • Pre-prints where subsequent publication is already included • Not written in English • Conference Abstracts and Theses

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(by DGK) using the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) checklist [47, 48], a checklist for assessing reporting quality specific to the domain of oncology. Whilst designed for marker/assay testing, the domain relevance and prognostic nature renders this a relevant tool. We considered the MRI measures as the 'marker' under investigation and the neuropsychological assessment as 'endpoints' for the purposes of the checklist.

Results

After reviewing titles and abstracts, 197 records were selected (see Fig 1), and 188 full-text articles were assessed for eligibility. Of those, five studies were included. Manual reference and citation checking of these selected articles (and identified literature reviews deemed to be relevant), identified no additional studies. Detailed information about the included studies can be found in Table 2.

Study characteristics and reporting quality

Many studies were excluded because the MRI did not precede neuropsychological assessment (for instance because of the matched timepoints of neuroimaging acquisition and test assessment), thus not defining them as 'predictive' studies. In a small number of cases, the text was ambiguous to the order of testing (i.e., [49–54]) but did not refer to prediction or other details suggestive of the order, and thus were not included. For other studies, data including MRI which preceded a later neurocognitive assessment existed, due to the inclusion of multiple timepoints, however it was ambiguous in the analyses of interest as to the time points being referred to and so these studies were not included [55, 56].

For the selected studies, sample sizes were small and ranged between n = 7 and n = 61; altogether (notwithstanding dataset overlap) only n = 118 pediatric brain tumour patients and n = 37 healthy controls were included across the reviewed studies. The most common tumour type across studies was medulloblastoma (n = 96), then astrocytoma (n = 17) with relatively few ependymoma and choroid plexus papilloma (n = 3 & 1 respectively). Age at diagnosis across the studies ranged from 2.2 years to 15.6 (based on ranges and inter quartile range (IQR)). All studies selected associative statistical approaches (i.e., correlational analyses), with one also adopting a mediation approach.

Using the REMARK checklist, studies were assessed against each reporting item (*Item 1–20*), and here we report items where reporting was limited across the studies (i.e. one or less studies reported the item). No studies gave a rationale for sample size (Item 9, 0/5 studies), likely due to the limited samples in each study, however it was unclear as to whether these were the entirety of eligible patients within the given timeframe (as only 1 study gave a full accounting of the flow of patients in the study, *Item 12*, 2/5 studies) In terms of "Analysis and presentation", studies performed poorly for a number of items (*Item 15*, *16*, *18*, all 1/5 studies, and *Item 17 0/5* with no studies completing the item to be reported). Firstly, only one study presented an effect size for the predictive analysis (*Item 15*, 1/5 studies). Further, included studies did not conduct analysis of added value, including the MRI marker and 'standard prognostic variables' which are established (*Item* 17, 0/5 studies) nor sensitivity analysis/validation although one study confirmed statistical/theoretical assumptions (*Item 18*, 1/5 studies).

White matter (WM) predictors

Of the studies assessed, three utilised diffusion tensor imaging (DTI) to image white matter as a predictor of outcomes. Liguoro et al. measured the fractional anisotropy (FA) and volumetry of spinocerebellar (SC), dentorubrothalamocortical (DRTC) and corticopontocerebellar tracts

Table 2. Details of included studies.

Reference	Study Variables				Medical Variables		
	Recruitment Hospital	Years of Recruitment	Number of participants	Healthy controls?	Age at Diagnosis	Tumour Type	Treatment
Zilli et al. [61]	Azienda Sanitaria Universitaria Integrata di Udine, Italy	2012–2019	7 (5 males, 2 females)	NA	Med. 5.3y (IQR 2.2–8.1)	PA n = 5, MB n = 2	Surgery (7, 100%), Radical surgery (7, 100%), CT (2, 29%), CRT (1, 14%), PT (1, 14%)
Partanen et al. [58]	Hospital for Sick Children, Alberta Childrens Hospital, British Columbia Childrens Hospital, Canada	2007–2011	CSR Group 12 (7 males, 5 females), Local therapy 10 (5 males, 5 females)	24 (12 males, 12 females), Mean age at testing 10.51y (range 5.81–14.93)	CSR Group: Mean 9.32y (sd 2.69, range 5.96–15.26), Local Group: Mean 9.59y (sd 3.62, range 5.77–15.63)	CSR group: MB n = 12, Local group: Astrocytoma n = 6, EP n = 3, Choroid Plexus papilloma (4th Ventricle) n = 1	CSR group: surgery (12), CSR (12) and focal radiation to tumour bed (12), chemotherapy (12), Local therapy group: surgery only (7), surgery and focal radiation to the tumour bed (3), chemotherapy (1).
Liguoro et al. [57]	NR	2013–2017	7 (4 males, 3 females)	NA	Med. 63 months (IQR 39–80)	PA n = 5, MB n = 2	Only surgery (5, 72%), Surgery + RT + CT (2, 28%)
Riggs et al. [59]	Hospital for Sick Children, Alberta Childrens Hospital, British Columbia Childrens Hospital, Canada	2007–2011	20 (13 males, 7 females)	13 (8 males, 5 females), Mean age at test 12.5y (range 8.1–17.2)	Mean 7.2y (range 4.3–12.8)	Recurrent Astrocytoma n = 1, MB n = 19	surgery (20, 100%), CRT (20, 100%), CT (NR)
Wang et al. [60]	NR	NR	AR Group 43 (29 males, 14 females); HR Group 18 (10 males, 8 females)	NA	AR Group: Mean 14.85yr (sd 4.54); HR Group: Mean 13.31 (sd 4.06)	MB n = 61	CRT plus CT (AR Group: Lower CRT dosage (70%), HR Group: Higher CRT dosage (30%))

Reference	MRI Variables				Neuropsychology Variables			Statistical Variables	
	Age at MRI	MRI Timepoint	Sequence	MRI Measure	Age at Assessment	Measure	Time between MRI and Assessment	Statistical Approach	Statistic of association/ prediction
Zilli et al. [61]	NR	Post-surgery	1.5T T1w, T2w, FLAIR	sMRI—VOI of i) lesion, ii) frontal insertion of VPS and iii) ventricular volume, achieved extent of resection.	Med. 7.3y (IQR 6.0–10.8)	NEPSY-II, BVL_4–12	Med. 5.0 months (IQR 0.0–11.0)	Lesion symptom mapping	NA
Partanen et al. [58]	CSR Group: Mean 9.59y (sd 2.66, range 6.27–15.41), Local Group: Mean 9.88y (sd 3.65, range 6.01–16.07)	During and Post-Treatment (3m post diagnosis)	1.5T T1w, DTI	dMRI—FA, MD, RD, AD	NR—Multiple assessment timepoints (3, 12, 24, and 36 months post diagnosis),	WISC-IV or WAIS-IV	NR—Multiple assessment timepoints (3, 12, 24, and 36 months post diagnosis),	Correlational analyses	Pearson's r
Liguoro et al. [57]	NR	NR (post-resection)	1.5T T1w, T2w, FLAIR, DTI	Fibre tract volume, FA, RA, SI, PI, LI (cerebellar connections)	Med. 88m (IQR 74.5–129.5)	NEPSY-II WISC-IV	Med. 5m (IQR 0–8.5)	Correlational analyses	Spearmans Rank
Riggs et al. [59]	NR	Chronic post treatment (5yr-post diagnosis)	1.5T T1w, DTI	Whole brain volumes, Unicate Fasciculus (FA), hippocampal volume.	NR	CMS	n = 10 assessed, n = 7 <2 months of MRI, n = 3 <19 months of MRI	Correlational analyses	NR

(*Continued*)

Table 2. (Continued)

Wang et al. [60]	NR	Post-CRT	DTI	Voxel-wise, Tract-Based Spatial Statistics measured with FA	NR	Working Memory score from WJ-III	NR–Assessment was change in score between baseline and 36m	Mediation/ Correlational analyses	NR

N.B. NA = Not Applicable, PA = Pilocytic Astrocytoma, MB = Medulloblastoma, CT = Chemotherapy, CRT = Cranial Radiation Therapy, PT = Proton Therapy, AR = Average Risk*, HR = High Risk*, NR = Not Reported, Med = Median, sd = standard deviation.

*Defined by the SJMB03 phase III risk-adapted trial (ClinicalTrials.gov identifier: NCT00085202)

N.B. PA = Pilocytic Astrocytoma, MB = Medulloblastoma, EP = Ependymoma, CT = Chemotherapy, CRT = Cranial Radiation Therapy, PT = Proton Therapy, NR = Not Reported, sMRI = structural MRI, dMRI = Diffusion MRI, VOI = Volume of Interest, FA = Fractional Anisotropy, MD = Medial Diffusivity, RD = Radial Diffusivity, AD = Axial Diffusivity, Med. = Median, BVL = Battery for the Assessment of Language in Children aged 4–12, WJ-III = Woodcock-Johnson III Tests of Cognitive Abilities, CMS = Children's Memory Scale, CSR = Cranial-Spinal Radiation, m = months, NA = Not applicable.

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(frontopontocerebellar (FPC), parieto-pontocerebellar (PPC), occipitopontocerebellar (OPC), and temporo-pontocerebellar (TPC)) [57]. Significant relationships were found between tracts relevant to cerebellar connectivity, and the Developmental Neuropsychology Assessment (NEPSY) and full-scale IQ (FSIQ) measured approximately 5 months later [57]. Specifically, FSIQ correlated significantly with spherical and planar indices of the right PPC ($r = -1$, $p = 0.017$ and $r = 0.886$, $p = 0.033$), with increases to planar index and decreases in spherical index associated with IQ [57]. Liguoro et al. also found significant correlations between specific fibre tract characteristics and tasks measuring attention, memory, sensorimotor, social perception, and visuospatial processing domains. However, only visuospatial processing showed convergent validity with significant correlations across two different tasks measuring this same domain [57]. In this study, the bilateral PPC and SC tracts were most commonly correlated with the neuropsychology tasks [57].

Partanen et al., used MRI from the treatment period 3 months after diagnosis (including during and after treatment) to predict change in intellectual functioning over a 36 month period after diagnosis. A significant reduction in FSIQ over time was found but this was not related to diffusion measures (FA, mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD)) for the cortical spinal tract (CST), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), optic radiations (OR), and uncinate fasciculus (UF) [58]. Partanen et al. did however show that declines over time in processing speed index, observed only in a subgroup of patients experiencing local therapy (i.e., focal radiation) versus cranial spinal radiation, was predicted by baseline anisotropy in left inferior fronto-occipital fascicle (IFOF), with lower FA being related to greater decline [58]. Neither patient groups showed a difference in the left IFOF for diffusions measures compared to controls.

Riggs et al. [59] utilised chronically acquired MRI (approximately 5 years post diagnosis) investigated correlations between whole brain WM volume, FA of both the left and right UF and the general memory index of the Childhood Memory Scale (CMS) (in a subset of $n = 10$ patients, outcomes measured between 2 and 19 months after MRI). Only FA of the left UF was significantly associated to memory ($R = .64$, $p = .045$), not the right uncinate fasciculus or total WM volume (as measured by structural MRI), with increased FA related to increases in memory performance. The volume of the PPC tract also positively correlated with memory performance ($R = .71$, $p = .045$) in Parten's study [58].

Wang et al. [60] used a high-dimensional mediation model to estimate microstructural damage to brain WM that mediates the negative treatment effects craniospinal radiation has on declining working memory outcomes over a 36month period. Post-treatment DTI was

used to estimate FA tract-based spatial statistics (TBSS) across tracts within a white-matter atlas. Larger FA was associated with better working memory outcome, across multiple WM tracts including the cerebral peduncle, corpus callosum, splenium and corona radiata. Specifically, Wang et al [60] found that there was a significant negative mediation effect of the WM microstructure between radiation treatment (average risk / lower dose vs high risk / higher dose) and the change in working memory over 36 months. This study therefore demonstrated the causal effect of radiation-related damage to white matter predicting long-term working memory in these children, accounting for around 43% of the overall impact of treatment on long-term working memory decline.

Strength of correlational relationship between indices of white matter integrity and neuropsychological outcome were large (according to Cohen's criteria) ranging from $|r| = .64 - |r| = 1$. However, the very limited sample sizes (n = 10 & n = 7) from which these were drawn gives reason for concern over the interpretation of these estimates.

Grey matter (GM) predictors

In Riggs et al., no correlation was found between total GM volume or left hippocampus with the general memory index of the CMS, but the right hippocampal volume, measured at a chronic timepoint, showed significant positive correlation with memory outcomes 2–19 months after MRI ($R = .71$, $p = .02$) [59]. It is important to note in this study, that the right hippocampus, rather than the GM volume and left hippocampus, was significantly smaller in the patient group compared to healthy controls.

Lesion predictors

Zilli et al. [61] used a lesion-symptom mapping approach, to investigate the overlap of lesions in children with versus without psychological impairment. The lesions investigated where tumour lesions, frontal insertion of ventriculoperitoneal drainages and ventricular volumes, as drawn on the T1w MRI. They found the greatest tumour lesion overlap and therefore greatest damage was found in median cerebellar, specifically paravermal and vermal regions. Regions of interest for the lateral ventricles also overlapped in impaired children, suggesting hydrocephalus as additional cause of future impairment.

Meta-analysis

Despite registering our intention, reviewed studies were not of sufficient quality to conduct any form of meta-analysis due to varying measurement strategies, gaps in reported descriptive variables, and low statistical power (due to small sample sizes).

Discussion

Review of the state of research

The current systematic review aimed to investigate existing literature using MRI to predict later, and non-contemporaneous neuropsychological outcomes in children with brain tumours. No studies reviewed here set out the rationale for and/or aimed to predict future outcomes using model development and validation approaches. The lack of scientific attention given to this topic is surprising given the dearth of literature advocating for such research. The papers identified and reviewed here, did in fact conduct analyses to this effect, but only due to the fortuitous nature of the selected timepoints, and intervals between the activities of MRI scanning and neuropsychological testing. Despite an extensive search strategy, evidence with which to answer the current research question was extremely limited, with the major finding

being a severe lack of studies in this area. The primary result of the review must therefore be viewed as a need for further research in this very important research area, with study designs that directly tackle the need for outcome prediction in these cohorts.

The reason for this limited number of research studies is unclear. Whilst our systematic search strategy was extensive, there were also difficulties in identifying papers due to poor reporting practices. For instance, in some studies, the timing of MRI in relation to assessment was ambiguous or unclear [49–52, 56]. Another potential cause of limited research could be previous focus on survival, where increasing survival rates are now placing a greater need for research on late effects. It is important to also consider that neurocognitive effects are also only one of many potential late effects experienced by this population [62, 63].

Quantity of research in this area may also be impacted by the availability of clinical data with which to carry out this research. For children with pediatric brain tumours, there is an abundance of clinical MRI, with medical imaging required for vital for tumour detection and diagnosis, surgical and radiotherapy planning, and monitoring of treatment response and recurrence of disease. But this is not necessarily echoed in access to neurocognitive assessment; testing is performed based upon clinical need or clinical trial protocol. This potentially limits available retrospective datasets. This data also comes from a heterogeneous cohort, with these children facing heterogenous brain injuries as a result of their disease and treatment. Identifying homogenous patient groups inevitably results in the smaller sample sizes seen in the current studies. Overall, these factors are liable to impact the quantity of research studies in this field.

Whilst number of studies was limited, the quality of existing studies was also a significant limiting factor for the usefulness of research studies in this area. In the reporting quality assessment (using the REMARK checklist [47, 48]) identified studies did not meet important criteria for development of prognostic markers. Specifically, studies failed to conduct additional analyses necessary for this development, such as sensitivity or 'added-value' analyses–although this was likely due to limited sample sizes, therefore lacking statistical power necessary for these additional analyses. To note, the checklist also comments on several items pertaining to model building and multivariate analyses, which were not conducted in the current studies.

Studies are typically involving "retrospective, monocentric study investigating a pediatric disease with low annual incidence" [61] however future work will require larger sample sizes than those of the studies presented here. This is especially true as the field of medical imaging further utilises machine learning approaches that require greater sample sizes to learn high dimensional patterns in the data that can predict an outcome variable. In the context of predictive studies, larger sample sizes will also be needed to suitably split data to conduct model validation using approaches such as cross-fold validation)–prediction requires the ability to generalise to new data scenarios [64, 65]. Not only will continued small sample sizes limit the statistical power with which to discover relevant associations between neuroimaging variables and long-terms outcomes, but they will prevent the field from providing best-practice evidence for prediction.

Overall, the findings from the reviewed research are limited–they have limited sample sizes and are rated as low quality in terms of prediction studies. Without proper validation and replication, the quality and impact of any conclusions must be viewed as limited and/or potentially spurious. However, the findings are briefly discussed here in terms of wider literature. This should be seen in the context of guiding hypothesis-driven future research and/or promoting future validation and/or replication of these findings.

Summary of findings of reviewed studies

Cerebellar damage. Given common posterior fossa presentation in pediatric brain tumours, it is unsurprising that multiple studies in this review a-priori selected regions of

interest within cerebellar structures and related fibre projections from this anatomical structure. Damage to these circuits predicted outcomes [57], with lesions to the median cerebellar regions common in cognitively impaired patients [61]. Studies of contemporaneous MRI and neuropsychology measures have found similar. Horská and colleagues [66] found a decrease in vermis volumes over a 6-month period were significantly related to radiation dose, and final volume after this period related to neuropsychological measures of motor speed. Significant recent evidence suggests that the posterior cerebellar lobes are key in maintain cognitive performance [67], and animal models suggest that intact cerebellar activity is required to enable typical developmental trajectories of cognitive abilities (in mice) [68]. Essentially, the cerebellum plays as an integral node in many distributed neural circuits that underpin multiple cognitive functions [69, 70]. Radical cerebellar resection has also been associated with extensive WM microstructure changes across the brain [71]. Overall, it is unsurprising that damage to cerebellar regions (through injury and treatment effects) may lead to and/or predict multiple cognitive morbidities.

WM damage. Riggs et al [59] argued that global measures of WM may be indicative of general injury and thus correlate well with general ability, however, integrity of discrete tracts (such as the UF) may be a better predictor of specific cognitive abilities–in this case memory. Previous reviews of cross-sectional research suggests a model where disorganised WM microstructure is related to poorer cognitive abilities, especially processing speed and memory deficits [23], by indicting that this 'damage-related impairment' is established early, and therefore WM microstructure is a potential biomarker to predict later impairment. Both preclinical and patient studies suggest a loss of both GM and WM volume, and failure of normal WM gain in pediatric brain tumour survivors [16]. There are multiple mechanisms of WM damage; hydrocephalous having direct neurotoxic effects on periventricular WM due to decreased perfusion and oedema [72] or intragenic effect of adjunct therapy (chemo and radiotherapy) as measurable by reduced volume and alterations to microstructural properties and failure of expected WM development [51, 73]. WM damage is likely non-transient; for instance, in non-irradiated patients 15 years after diagnosis, FA measures are reduced and are associated with impaired cognitive flexibility [74]. What is apparent is that, across treatment and disease effects, the subsequent WM injury is relevant to poor outcomes, across emotion, cognition, and behaviour [14, 51, 75].

Specific issues with current research

Limited longitudinal studies. The biggest limitation of the current research field is the lack of longitudinal research answering this research question. Whilst there have been multiple studies understanding the contemporaneous neuroanatomical substrates of poor neuropsychological outcomes in pediatric brain tumours, from acutely post treatment to very long-term survivors, these have not translated into similarly large body of work understanding long-term risk (as highlighted by our findings) of cognitive morbidity. Further longitudinal research is needed to assess whether the contemporaneous neuroanatomical substrates of long-term impairment are in fact predictive in the context of longitudinal studies.

These longitudinal studies would also provide an opportunity to disentangle the developmental and age-related effects on this prediction-task. For several of the measures highlighted in this review (FA/MD etc.) there are known developmental trajectories [76] which will necessarily interact with disease-related changes. There is also likely to be unique effects of brain insult, across tumour growth, and treatment related injury at different ages, resulting in varying levels of long-term impairments [77]. The field will need to rely upon longitudinal studies

(with sufficient sample size/statistical power) that can sufficiently disentangle these interactions.

Study variables: Timing. The current systematic review includes studies that use MRI from any point in the disease course. The timepoint of the MRI used for the purposes of prediction in the reviewed studies were most commonly post some form of treatment (surgical or post radiation therapy, e.g. [59, 60] respectiverly) other than 57 which included MRI during treatment. Given the limited research available, this was done to assess the entire literature, but results from different timepoints in the disease to conduct prediction will undoubtedly have varying interpretations. For instance, post-treatment MRI may identify insult-related factors which are related to later decline–as demonstrated by the study by Wang and colleagues [60]. Pre-treatment MRI may allow us to identify specific vulnerabilities to the longer-term neurocognitive effects–for instance Zheng and colleagues [78] propose that functional network plasticity pre-treatment may mediate the impact of surgery on later cognitive ability. However, any MRI timepoint is likely to capture a mixture of these two influences, vulnerability, and insult factors, which may contribute towards prediction.

Overall, there is no consensus on the optimal timing of MR imaging to use for predictive purposes. Selection of which MRI is likely to be most predictive (in terms of reliability, accuracy etc.) will not be trivial for future research. We propose that for future research, selection of MRI timepoints with which to test predictive validity should be guided by two principals–a) clinical need, and b) evidence-based theoretical grounds. For instance, in terms of clinical need, if the most useful purpose of these models is to aid/supplement treatment management decisions, then an early, pre-treatment MRI will be necessary. In terms of guiding MRI timing based upon existing evidence a strong example of this is the study by Wang and colleagues [60] which suggests there is a treatment related 'injury' which mediates radiotherapy—related working memory impairment, suggesting post treatment MRI would have benefit. Timing is an even greater consideration in this patient group compared to adult brain tumour patients due to the likely interaction also with ongoing brain development over time for these patients.

These children undergo MRI scanning at a number of timepoints in their disease course (e.g. diagnostic imaging, pre- and post-surgical evaluation, progression monitoring etc), and so there is significant data for potential retrospective studies to investigate effect of MRI timing on prediction. Direct comparisons between models using MRI from different timepoints will be meaningful to understand variation on predictive validity over time, and further inform designs for prospective predictive studies.

Timing of neuropsychological assessment is also not to be overlooked. To develop predictive models, a given endpoint will need to be set (for instance a given number of years post diagnosis). Overall neurocognitive trajectory is "idiosyncratic" over time, with longitudinal studies suggesting an injury-related early impact, followed by a decline or failure to meet the normal developmental trajectory and potential long-term plateauing [11, 18]. Therefore, the endpoint of interest, may also inform the timing of MRI which may be more predictive of longer-term outcomes.

Added value of MRI. A major limitation of the current state of the research literature in this field is that the added value of MRI in prediction has not been established, above and beyond existing approaches. No reviewed studies assessed existing risk factors in a multivariate analysis to test the relative contributions, and therefore added value, of early MRI in predicting future neurobehavioral morbidities. However, Partanen et al. reported that none of the medical or treatment variables that they tested predicted change in IQ scores over time [58]. This is despite these medical variables (Neurological Predictor Scale and presence of cerebellar mutism syndrome) predicting acute/contemporaneous neuropsychology outcomes, and MRI-derived measures of baseline WM injury being significantly related with outcomes [58]. This is

limited evidence to support the incremental validity of MRI as a predictor of long-term outcomes.

The current systematic review selected MRI as the proposed predictor of long-term outcomes, over other potential predictive tools. The reason for this is two-fold. Firstly, quantitative analysis of MRI imaging provides a more detailed, less reductionist approach to assessing medical imaging compared to typical radiological reporting of these. Alternatively, MRI also provides a quantitative proxy for the 'burden' of many of the complex risk factors that have been proposed in models of neurocognitive outcomes including those which are either hard to measure reliably or non-subjectively (for instance early childhood adversity [28]).

Therefore, future research should assess both added value, but also concurrent validity, against current clinical prediction approaches, such as the Neurological Predictor Scale. Given the additional computational and resource burden in conducting these types of quantitative image analysis for the purposes of prediction, it is important for future studies to test for unique and additional predictive power offered by quantitative MRI variables.

Study variables: Approach to ROIs. Across the studies reviewed here two conducted analyses in regions-of-interest (ROIs) directly related to sites of brain insult in these patients [57, 58], one in ROIs related to the cognitive comorbidity under investigation [59], and only one investigating characteristics of the lesion itself [61]. This does not consider how the wider brain network may be influenced by the brain tumour, and this information may explain/predict additional variance in outcomes. For instance, in paediatric neurological disorders/syndromes, differences in brain morphometry or connectivity have been found beyond the site of pathology (i.e. paediatric epilepsy [79]) or in the absence of frank pathology (i.e. mild paediatric TBI [80], MRI-negative epilepsy [81]). Disconnectome symptom mapping, shows that non-homologous lesions to the same brain network can generate the same cognitive sequalae in terms of deficits [82]. Many compensatory and 'rerouting' models of functional brain activity post injury suggest that regions beyond the focal lesion may explain some sparing of cognitive abilities (another important factor in predicting endpoint neurobehavioral morbidities). These findings all show that disparate, diffuse, and non-lesioned changes to the brain, including tissue which may be typically thought of as 'spared', could also explain variance in neurobehavioral morbidities. Connectivity approaches to MRI have shown utility in contemporaneous measurements of MRI and neuropsychology [83, 84]. These neurobiological effects of injury beyond the focal lesion may provide further prognostic information towards the aim of a predictive model, however, to test a greater number of regions larger sample sizes will be necessary to accurately estimate statistical models across many more ROIs. This highlights one of the key challenges for future studies in this field being data collection.

Recommendations for future research

Beyond the apparent requirement for more research studies in this field, there are specific recommendations that should guide future endeavours. In many cases, due to the rarity of disease, multinational and multicentre analyses will be needed to achieve the sample sizes necessary to definitively address some of the issues in this review. To do so, a level of harmonisation amongst research groups in terms of data collection is necessary to facilitate combining of cohorts. For instance, adhering to similar imaging protocols (following guidelines for advanced MRI in pediatric CNS such as those proposed by the European Society of Pediatric Oncology (SIOPE) [85]). Harmonisation will not only allow integration of multiple datasets, but potentially reduce biases in measurements caused by differences in MRI acquisition protocols.

Additionally, harmonisation of neurocognitive assessment will also facilitate data aggregation. In the absence of a common outcome measure for these children (for instance a common data elements set as proposed by the National Institute of Neurological Disorders and Stroke (NINDS) for other neurological disease [86]) broad composite measures should be used that can capture multiple aspects of the neurocognitive morbidity experienced by these patients (for example the Wechsler Intelligence Scale for Children [46] or the NIH Toolbox Cognition Battery [87]. Neurocognitive assessment protocols are being developed for specific tumour groups (for instance in childhood ependymomas [88]) which will provide practical approaches to "strongly support the routine incorporation of neuropsychology assessments as key outcomes" to "facilitate successful global collaborations" [89]. These should be adopted wherever possible.

To facilitate future reviews such as this, and more importantly meta-analyses of said future research, greater reporting expectations should be placed on researchers–given the current review highlighted this to be a key weakness in existing research. Emphasis should be on using reporting guidelines, and quality assessment checklists (such as the REMARK checklist used in the current review [47], or the tools provided by the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network [90] such as the TRIPOD tool [91]). Transparent and full reporting will allow better assessment of the literature across the field. These recommendations will help facilitate the important goals of this research, hopefully leading to greater clinical impact.

Limitations of review

It should be noted that, despite an extensive search, no study explicitly investigated the research question of whether MRI could be used for long term prediction of neurocognitive outcomes in pediatric brain tumour patients. Described studies were reviewed here due to non-primary analyses which fulfilled inclusion criteria, and therefore it may be the case that other studies with such analyses may have been missed in the review process (for instance if these secondary analyses were not mentioned in the abstract). To address this, we erred on the side of caution in reviewing abstracts, using full-text review as a method to identify these relevant secondary analyses. This may have resulted in a greater proportion of reportedly 'low quality' studies, not because they are low quality in terms of achieving their stated aims, but low quality in relation to the question of the current review–which they did not aim to answer necessarily.

A significant limitation of the current review is that, given small sample sizes and limited quality of the studies reviewed, the synthesis of findings in the current study must be viewed with scepticism and caution, despite framing these findings within the wider literature. It is proposed that these may inspire future hypotheses or replications, but the nature of these findings must be emphasised to prevent amplification of potentially spurious findings.

Conclusion

As early as 2008, it was proposed that to truly balance the aggressiveness of treatment for childhood CNS tumours, against the relative quality of life due to cognitive impairment, an important factor is knowing the likelihood of any one individual experiencing neurocognitive impairment [13]. This individualised risk is key in purported models of monitoring and managing of neurocognitive functioning in children with brain tumours [92]. There has also been significant work in the field of pediatric brain tumours proposing developmental cognitive neuroscience models of late effects in survivors [13, 23, 93, 94]. These models, built on contemporaneous measures of cognition and brain development,

alongside cross-sectional data, are inherently limited. Knowing individualised risk of long-term cognitive morbidity ahead of time would have significant clinical impact; to inform clinical management, prioritise resources/support, and reduce uncertainty for families. Overall, there exists plenty clinical reasoning to prompt scientific enthusiasm and attention for this topic.

However, despite these early calls for prediction, and models with which to guide these predictive studies, this systematic review highlights that the number of truly predictive studies (requiring a period between predictive features and long-term outcomes) is still limited. In conclusion, given the increased number of adult survivors of childhood brain tumours, the poorer long-term cognitive, educational and employment outcomes [10, 14, 15] and the significant burden this represents to patients, families and healthcare, work now needs to be completed to integrate predictive data into these models, which will expand their explanatory value and utility to clinical practice. This will be an important next step in delivering further clinical impact for this patient group.

Given the great potential that MRI provides in investigating neurobiological effects of disease and treatment at the individual-level, the plethora of multimodal imaging available in these clinical populations and finally the positive clinical benefit this could offer, there is exciting opportunities for this type of research.

Supporting information

S1 Table. Tables outlining search strategy. Formulation of searches for the different data sources for the study, including number of results at each search point.
(DOCX)

S1 Fig. PRISMA flow diagram. Results from Original July 2022 searches.
(DOCX)

S1 Checklist. PRISMA 2020 reporting checklist for systematic reviews.
(DOCX)

Author Contributions

Conceptualization: Daniel J. Griffiths-King, Andrew Peet, Jan Novak.

Data curation: Daniel J. Griffiths-King, Christopher Delivett.

Formal analysis: Daniel J. Griffiths-King, Christopher Delivett, Jan Novak.

Funding acquisition: Daniel J. Griffiths-King, Jan Novak.

Investigation: Daniel J. Griffiths-King, Christopher Delivett.

Methodology: Daniel J. Griffiths-King, Christopher Delivett, Jan Novak.

Project administration: Daniel J. Griffiths-King.

Supervision: Andrew Peet, Jane Waite, Jan Novak.

Writing – original draft: Daniel J. Griffiths-King.

Writing – review & editing: Daniel J. Griffiths-King, Christopher Delivett, Andrew Peet, Jane Waite, Jan Novak.

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