Memory After Tumours of the CNS in Childhood (MATCCh) Study: Long-term Memory and Forgetting in Paediatric Brain Tumour Survivors

and

Clinical Research Portfolio

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CHAPTER 1

Systematic Review

A systematic review of the literature comparing memory in paediatric brain tumour survivors with controls

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Submitted in partial fulfilment of the requirements for the degree of Doctorate in Clinical Psychology (D.Clin.Psy)

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Abstract

Background and Objectives There is evidence that paediatric brain tumour survivors show impaired memory when compared to normative data (Robinson et al., 2013), however differences may be due to confounding factors. The current review assessed memory outcomes in brain tumour survivors relative to matched controls.

Data Sources PsycINFO, CINAHL, MEDLINE, EMBASE, and Web of Science.

Study Eligibility Quantitative articles comparing memory (assessed with standardised measures) in paediatric brain tumour survivors and healthy or non-CNS cancer controls.

Study appraisal Methodological quality of studies was rated using a modified version of the SIGN Cohort Study Critical Appraisal Checklist.

Results High quality studies provided evidence of visual and verbal long-term memory impairment in survivors compared to healthy controls, and visual long-term memory impairment relative to non-CNS cancer controls. There was evidence that survivors have impaired verbal working memory compared to healthy but not non-CNS cancer controls, however most studies failed to control for IQ, therefore differences may reflect underlying cognitive deficits. There was insufficient robust evidence to determine whether visual working memory is impaired in survivors compared to controls.

Limitations The tool used to critically appraise the studies did not differentiate between the studies well and some degree of subjectivity was used. A second rater minimised the risk of bias.

Conclusions Further high quality research is required to understand the long-term effects of brain tumours on memory. The results of the current review, however, can be used to better support paediatric brain tumour survivors in educational settings and increasing early assessment and recognition of memory impairments in school and clinical settings.

Keywords paediatric brain tumour, controlled study, memory.

Introduction

Central Nervous System (CNS) tumours are among the most common paediatric cancers in the UK (Stiller, 2007). Improvements in treatments such as chemotherapy and radiotherapy have led to an increase in survival rates among this population, but there is significant evidence that survivors experience a range of long-term cognitive deficits (Robinson et al., 2010).

Most of the research exploring cognitive outcomes after brain tumours is observational and retrospective (George et al., 2003). Some studies prospectively assess cognitive outcomes in brain tumour survivors at one, or numerous, time points post-treatment. Previous reviews suggest brain tumour survivors have deficits in overall cognitive functioning, academic achievement, attention, memory, and language (Robinson et al., 2010; De Ruiter, Van Mourik, Schouten-Van Meeteren, Grootenhuis, & Oosterlaan, 2013) and that general cognitive ability significantly reduces over time (Mulhern et al., 2004). Younger age at treatment, cranial irradiation therapy, tumour size and severity, and treatment complications such as hydrocephalus have also been found to impact negatively on cognitive outcomes (Shortman et al., 2014).

Most research on memory compares outcomes in paediatric brain tumour (PBT) survivors to normative data. A recent meta-analysis reported the magnitude of impairment in paediatric and young adult survivors of PBT of the posterior fossa relative to norms using Hedges g (which represents the number of standard deviations the PBT survivors mean differed from the mean of normative samples on cognitive measures; Robinson et al., 2013). They estimated verbal and visual memory as -1.12 and -0.68, respectively,

suggesting both are significantly affected in relative to norms. Normative samples fail to match patient samples for age, educational level or gender, and often for ethnic or cultural background. It is unclear whether impairments in survivors are due to treatment and tumour factors, or demographics. Studies comparing survivors with appropriately matched controls allow stronger conclusions to be made regarding cognitive deficits. Memory deficits in young people have significant implications for future learning and academic achievement, as well as quality of life (Waber et al., 2006; Ullrich & Embry, 2012).

A systematic review of controlled studies comparing cognitive function in adult survivors has been conducted (Gehrke, Baisley, Sonck, Wronski, & Feuerstein, 2013), but one in paediatric survivors has not. The current systematic review aims to critically examine studies comparing memory outcomes in PBT survivors with an appropriately matched control group. The literature on brain tumour survivors includes a range of tumour and treatment factors, which are all included in the review, in line with previous meta-analyses (Robinson et al., 2010; Gehrke, et al., 2013).

Aim

The aim is to systematically review the literature and compare memory in PBT survivors with appropriately matched controls.

Research Questions

Are Working Memory (WM) and Long-Term Memory (LTM) functions significantly impaired in PBT survivors compared to healthy or non-CNS cancer controls?

Methods

Search Protocol

When considering search terms, a PICOS Model, outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009), was utilised. *Participants* were paediatric brain tumour survivors; *Intervention* related to the diagnosis of brain tumour; *Comparison* related to an appropriate control group (healthy or non-CNS cancer controls); *Outcome* related to memory; *Study Design* was comparative. Once search terms were allocated to each factor, Pubreminer was utilised to explore alternative search terms that may be used in articles. Previous systematic reviews (Gehrke et al., 2013; Robinson et al., 2010) were used for comparison.

The following electronic databases were searched: PsycINFO (EBSCO), CINAHL (EBSCO), MEDLINE (OVID), EMBASE (OVID), and Web of Science. These were chosen because they are routinely used in reviews in neuropsychology (Gehrke et al., 2013; Robinson et al., 2010). The search took place on the 31st January 2015 for all databases. An initial search included an exhaustive list of paediatric brain tumour diagnoses and neurocognitive processes, but this resulted in a number of irrelevant articles. Only the main six brain tumour diagnoses and memory-related terms were included. The search time frame covered all available years indexed by each database until the date the search was performed.

Final Search

1. intracranial OR brain OR cerebr* OR cerebell* OR cranial

AND

2. tum?r OR neoplasm* OR cancer*

OR

3. astrocyt* OR glioma* OR glioblastoma OR ependymoma OR medulloblastoma* OR craniopharyngioma*

AND

4. Paediatric OR child*

AND

5. memory OR recall OR retention OR long-term memory OR short-term memory OR working memory

Search Results:

PsychINFO (EBSCO): 161

CINAHL (EBSCO): 90

MEDLINE (OVID): 436

EMBASE (OVID): 908

Web of Science: 706 (limited to English articles)

Inclusion and Exclusion Criteria

Figure 1 provides a flowchart summary of inclusion and exclusion criteria and the process of article selection in line with the PRISMA guidelines (Liberati et al., 2009).

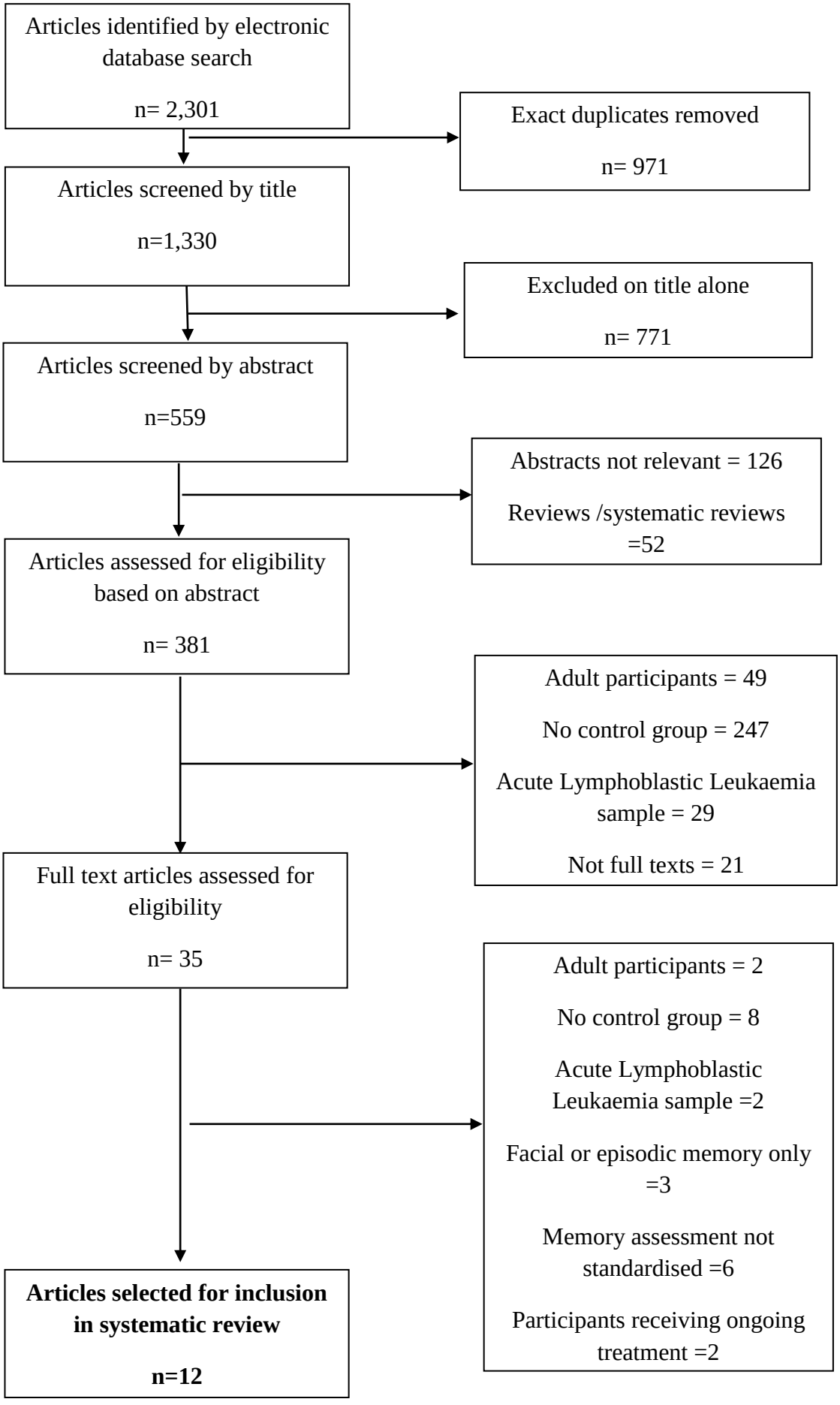
Inclusion Criteria

- Articles comparing memory in PBT survivors and healthy or non-CNS cancer controls
- Articles assessing memory using standardised and valid tools
- Quantitative articles with a cross-sectional or longitudinal design
- All brain tumour diagnoses, tumour grades, locations, or treatment modalities
- Articles published in a peer-reviewed journal, in English

Exclusion Criteria

- Articles that included brain tumour survivors in the control group
- Articles that did not include a control group and compared PBT survivors to normative data
- Articles that included only samples of Acute Lymphoblastic Leukaemia
- Articles that included participants who had received cognitive rehabilitation
- Memory assessments that are not standardised or validated with young people
- Articles including only the assessment of facial or episodic memory
- Samples receiving ongoing treatment with radiotherapy or chemotherapy for a brain tumour or a secondary cancer
- Articles including only adult samples, in which all participants are above the age of 18
- Dissertations, theses, conference abstracts and review articles

Figure 1. PRISMA Flow Chart



Results

Study Characteristics

The systematic search resulted in twelve articles which assessed memory in PBT survivors against a control group that was either healthy or had survived a non-CNS cancer. Three studies were produced by the same research group (Horska et al., 2010; Horska et al., 2014; Redmond et al., 2013) and there was an overlap in their PBT survivor samples. The Redmond et al. (2013) study included most of the participants in the Horska et al. (2010; 2014) studies, therefore results for the Redmond et al. (2013) will be reported. Two further studies were produced by similar research groups (Law et al., 2011; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008) and there the samples of PBT survivors likely overlapped. The studies utilised different memory assessments and different control groups, therefore each contributed novel information and were both included in the review. Table 1 summarises the demographic and clinical characteristics of tumour and control samples the ten studies included in the review. In seven studies, the primary aim was to assess general cognitive functioning, including memory, in groups; one study exclusively assessed memory (Conklin et al., 2012); two studies explored the degree to which changes in brain structure in PBT survivors were associated with cognitive outcomes (Law et al., 2011; Robinson et al., 2014)

Table 1. Demographic and clinical characteristics of participants in each of the articles

Study	Study design	Tumour Sample	Gender	Mean age in years	Mean age diagnosis /treatment	Diagnoses in Clinical Group	Location of tumour	Surgical resection	Treatment in clinical group		Control Group(s)
									CT	RT	
Conklin et al. (2012)	Cross Section	n=50	M=25 F=25	13.18 (±0.41)	6.38 (± 0.37)	Ependymoma (n=22) low grade glioma (n=12) craniopharyngioma (n=16)	Infratentorial (n=22) Supratnetorial (n=28)	Biopsy/ STR n=25 NTR/GTR n=25	n=6	CRT n=50	Healthy Siblings (n=40) Non-CNS Cancer (n=40)
Garcia-Perez et al. (1994)	Cross Section	n=25	Not Specified	11.76 (range 6-25)	8.04	Medulloblastoma (n=7) Oligodendroglioma (n=1) Astrocytoma (n=5) Glioma (n=7) Pineal Tumour (n=1) Ependymoma (n=4)	Anterior fossa (n=4) Middle fossa (n=7) Posterior fossa (n=14)	Not specified	n=25	Involved RT (n=25) WBR (n=14)	Chronic disease (n=25) Non-CNS Cancer (n=25)
Law et al. (2011)	Cross Section	n=29	M=16 F=13	11.36 (±3.74)	7.63 (SD 3.20)	Ependymoma (n=5) Medulloblastoma (n=23) Germinoma (n=1)	Posterior Fossa (n=29)	Biopsy (n=7) 50-95% resection (n=6) Over 95% resection (n=16)	n=23	Cranio-spinal (n=23) Focal (n=6)	Healthy Children (n=26) Surgery only BT (n=12)
Mabbott et al. (2008)	Cross Section	n=32	M=18 F=14	11.44 (SD 2.99)	6.85 (SD 2.66)	Medulloblastoma (n=22) Ependymoma (n=5) Glioma (n=4) No Information (n=1)	Posterior Fossa (n=32)	50-95% resection (n=8) Over 95% resection (n=24)	n=21	Cranio-spinal (n=23) Focal (n=9)	Non-CNS Survivors (n=10) Surgery only BT (n=30)

Study	Study design	Tumour Sample	Gender	Mean age in years	Mean age diagnosis/ treatment	Diagnoses in Clinical Group	Location of tumour	Surgical resection	Treatment in clinical group		Control Group(s)
									CT	RT	
Ozyurt et al. (2014)	Cross Section	n=15	M=9 F=6	19.38	11.7	Craniopharyngioma n=15 n	Intrasellar (n=5) Extrasellar (n=10)	Complete (n=7) Incomplete (n=8)		GK (n=1) EPT (n=4)	Healthy controls (n=24)
Quintero-Gallego et al. (2006)	Cross Section	n=18	M=6 F=12	12.16	8.08 (SD 3.19)	Astrocytoma (n=11) Medulloblastoma (n=7)	Posterior fossa (n= 18)	Not specified	n=7	n=7	Healthy controls (n=12)
Redmond et al. (2013)	Longitudinal	Total n=19 (15m FU n=14) (27m FU n=10)	M=12 F=7	12.11	11.8 (range 1.1-18.6)	Glioma (n=4) Medulloblastoma/ PNET (n=5) Germinoma (n=3) Leukemia (n=2) Nongerminoma germ cell tumour (n=2) Pineoblastoma (n=1) Craniopharyngioma (n=1) Ependymoma (n=1)	Infratentorial (n=5) Supratentorial (n=14)	Not specified	n=8	Cranio-spinal (n=8) WBR (n=3) IMRT (n=8)	Healthy controls (n=55) (27m FU n=37)
Riva et al. (2002)	Cross Section	n=21	M=11 F=10	Median =12:9	3-10 yrs (n=12) >10 yrs (n=9)	Medulloblastoma (n= 21)	Cerebellum (n=21) Vermis (n=8) Vermis /Fourth Ventricle (n=9) Lateral Recesses (n=1) Right Hem. (n=3)	Incomplete resection (n=8) Complete resection (n=13)	n=21 ITM (n=11) No ITM (n=10)	Cranio-spinal (n=21)	Siblings and cousins controls (n=20)

Study	Study design	Tumour Sample	Gender	Mean age in years	Mean age diagnosis/ treatment	Diagnoses in Clinical Group	Location of tumour	Surgical resection	Treatment in clinical group		Control Group(s)
									CT	RT	
Robinson et al. (2014)	Cross Section	n=17	M=7 F=10	12.60 (SD 2.48)	6.94 (SD 2.41)	PA (n=9) Medulloblastoma (n=4) Dysembryoplastic neuroepithelial tumour (n=3) Craniopharyngioma (n=1)	Posterior Fossa (n=13) Parietal Lobe (n=2) Temporal Lobe (n=1) Pituitary Gland (n=1)	n=17	n=5	n=5	Healthy control group (n=15)
Shortman et al. (2014)	Longidtudinal	12m FU n=25	M=14 F=15	12m FU: Mean age 11.26	Median age 9.4	Low grade astrocytoma (n=14) High grade astrocytoma (n=3) Craniopharyngioma (n=2) Germ cell tumour (n=3) Ependymoma (n=2) PNET (n=4) Meningioma (n=1)	Supratentorial (n=15) Infratentorial (n=14)	No information	n=7	n=29	Best friends control group (n=23 at 12m FU)

Key

ALL= Acute Lymphoblastic Leukaemia
BT= Brain Tumour
CNS= Central Nervous System
CRT= Conformal Radiation Therapy
CT= Chemotherapy
EPT= External Photon Therapy
F=Female
FU= Follow-up
GK= Gamma Knife
GTR= Gross Total Resection
ITM= Intrathecal Methotrexate
IMRT= Intensity-Modulated Radiotherapy
M=Male
MT= Medial Temporal
NTR= Near Total Resection
PA= Pilocytic Astrocytoma
PNET= Primitive Neuroectodermal Tumour
RT= Radiotherapy
SD= Standard Deviation
STR= Sub-Total Resection
WBR= Whole Brain Radiation

Methodological Quality and Risk of Bias

Quality was evaluated using an adapted version of the SIGN Cohort Study Checklist, (Appendix 1.2), commonly used to assess methodological quality in articles. The checklist includes 17 items related to selection, performance, detection and attrition bias, and an overall quality rating. Exposure status related to having had a brain tumour, and outcome related to memory.

The articles were appraised according to the SIGN checklist and overall quality ratings assigned. A 'High Quality' rating was given to studies with a robust design, minimising the risk of bias and controlling for the majority of confounding factors, specifically either IQ or psychological factors had be matched between groups to receive this rating; an 'Acceptable' rating given to studies that minimised some bias, but included some design limitations which would increase the risk of bias, such as not matching groups for IQ or psychological factors; an 'Unacceptable' rating, suggestive of a high likelihood of bias, was not given to any articles under review. Eight articles were further rated by an independent rater. Percentage agreement between ratings was 87.5 percent. Items rated differently were discussed and given an agreed rating. The overall quality rating for each study is shown in Tables 2, 3 and 4, and a breakdown of each item is shown in Appendix 1.3.

Definition of Memory Terms

The literature includes a number of memory theories and the terms 'short-term memory', 'working memory' and 'long-term memory' are not used consistently. Andrade (2001) believes the most widely used memory model is that of Baddeley and Hitch (1974), which suggests memory is made up of two systems, working memory (a multi-component system

that includes the temporary storage and manipulation of information) and long-term memory (a long-term store that has a very large capacity).

Some articles refer to the temporary storage of information within the working memory system as 'short-term memory' and only use 'working memory' to refer to the process of temporarily holding information whilst simultaneously performing cognitive processes on it (Daneman and Carpenter, 1980). Aben, Stapert and Blokland (2012) acknowledge that both terms are often used interchangeably in the literature. Recent research has found that performance in assessments which measure only short-term storage (simple serial recall tasks) do not correlate as highly with intellectual functioning as performance in those that require both storage and processing (Conway et al., 2005 and Engle, Tuholski, Laughlin & Conway, 1999), suggesting different memory functions. Another explanation for this finding, suggested by Cowan (2008), proposes that working memory includes an attentional mechanism and an executive function which affects manipulation. This may account for the variability in the relationship between working memory and cognitive ability. Cowan (2008) suggests the attentional aspect is akin to the episodic buffer, a mechanism within working memory that was added by Baddeley to his original model in 2000.

Given the variation in the literature, within the current review, 'working memory' will be used to refer to both the temporary storage and the manipulation of information. In line with current findings, working memory tasks that include the manipulation of temporarily stored information, such as backward digit span tasks, will be reported separately to those that only require only the temporary storage of information, such as forwards digit span tasks. Most results collate performance in such tasks, however, giving a standardised

working memory score, such as in the Digit Span subtest of Wechsler Scales, which therefore include both the storage and manipulation of information.

Long-term memory is generally agreed within the literature to refer to information that is rehearsed for longer than a few seconds and enters the long-term store. If information is repeated until learned, it has therefore entered the long-term store. Some memory assessments refer to the immediate recall of learned items as 'short-term memory' and delayed recall (usually after half an hour) as 'long-term memory', however both require retrieval from long-term store. Within the current review, measures that include learning trials will be categorised as long-term memory measures, however immediate and delayed recall will be discussed separately.

Data Extraction and Analysis

In order to answer the question of whether memory is significantly impaired in PBT survivors relative to controls, relevant data regarding memory assessments and results were extracted and summarised in Tables 2, 3 and 4. Authors of articles that did not report memory results were contacted via email and asked to provide this data (indicated with an asterisk in Tables 2, 3 and 4). As non-CNS cancer controls share additional cancer and treatment-related factors with PBTS that healthy controls do not, results were categorised by control group. Data on further variables matched across groups were extracted. Effect sizes of group differences were calculated for the parametric data using Cohen's d equation (Cohen, 1977). There was insufficient information to calculate non-parametric effect sizes. Negative effect sizes indicate the PBT group performed worse than the controls, positive indicate the PBT group performed better. Because outcome measures and designs varied across studies, the results, their limitations and applicability have been described in a narrative synthesis rather than a meta-analysis.

Table 2. Working memory in paediatric brain tumour survivors compared to healthy controls.

Study	Outcome Measure and Subtest	Memory Function	Outcome Score	Group Analysis	Mean Result Clinical group (SD)	Mean Result Control group (SD)	Statistical Test and significance	Effect Size	Variables Matched Across Groups	Quality Rating
Robinson et al. (2014) *	**WISC** DS/ LNS	Verbal WM	Standardised WM Index (M 100/ SD 15)		90.94 (12.47)	101.93 (8.92)	t-test **(p=0.008)**	d= -1.01	Age, gender, SES, psychological problems IQ not matched	High quality
Riva et al. (2002)	**WISC** DS	Verbal WM	Standardised	**Clinical subgroups**	ITM Group		MWU	IDC	Age, SES and family factors	High quality
				3-10 at diag.	5.17 (2.4)	8.83 (2.48)	**(p=0.036)**			
				>10 at diag.	5.6 (2.07)	10.25 (1.5)	**(p=0.014)**		IQ matched on all comparisons except PBT survivors under 10 who received ITM and controls under 10	
					No ITM Group					
				3-10 at diag.	7.33 (3.5)	8.67 (2.58)	Not sig			
				>10 at diag.	7 (0.82)	7.5 (1.73)	Not sig			
	BVRT Multiple Choice Task	Visual WM	Raw scores		ITM Group		MWU	IDC		
				3-10 at diag.	8.83 (2.79)	13.1 (1.34)	**(p=0.016)**			
				>10 at diag.	12.3 (3.11)	13.88 (1.32)	Not sig			
					No ITM Group					
				3-10 at diag.	10.42 (2.62)	13.25 (1.94)	Not sig			
				>10 at diag.	12.75 (0.5)	13.25 (0.5)	Not sig			
Law et al. (2011)	**WISC** DS/ LNS	Verbal WM	Standardised WM Index (M 100/SD 15)	Clinical subgroups			ANCOVA		Age, gender and parental education IQ not matched	Acceptable Quality
				RT	88.37 (14.93)	102.24 (10.13)	**(p=0.04)**	d= -1.09		
				SO	98.27 (14.85)	102.24 (10.13)	Not sig	d= -0.31		
Conklin et al. (2012)*	**WISC/ WAIS** DSB/ DSF	Verbal WM	z-scores				ANOVA	IDC	Family factors, age, gender, IQ not matched	Acceptable quality
					DSB: -0.1228	DSB: 0.5663	**p=0.01**			
					DSF: NR	DSF: NR	Not sig			

Study	Outcome Measure and Subtest	Memory Function	Outcome Score	Group Analysis	Mean Result Clinical group (SD)	Mean Result Control group (SD)	Statistical Test and significance	Effect Size	Variables Matched Across Groups	Quality Rating
Redmond et al. (2013) *	**SBIS** BMT	Visual WM	z- score	15month FU 27month FU	22.71 (7.18) 21.4 (6)	26.89 (4.94) 28.03 (4.68)	LME **Sig** **Sig**	 d= -0.68 d= -1.23	Matching of controls not discussed	Acceptable Quality
	WJ AWMT	Verbal WM	Standard	15month FU 27month FU	Not reported	Not reported	Not sig Not sig	IDC IDC		
Quintero - Gallego et al. (2006)	**CVLT-C** Learning trial 1	Verbal WM	Raw Score	Clinical Subgroups Medullo-blastoma	6.42 (1.13)	7.33 (1.43)	MANOVA Not sig	 d= -0.71	IQ not controlled for	Acceptable Quality
				Astrocytoma	7.27 (1.55)	7.33 (1.43)	Not sig	d= -0.04		

Key
ANOVA= Analysis of Variance
AWMT= Auditory Working Memory Test
BMT= Bead Memory Test
BVRT= Benton Visual Retention Test
CVLT-C= California Verbal Learning Test Child
DS= Digit Span
DSF= Digit Span Forward
DSB= Digit Span Backward
FU= Follow-up
GLM= General Linear Modelling
IDC= Insufficient Data to Calculate Effect Size
ITM= Intrathecal Methotrexate
LME= Linear Mixed Effect Regression
LNS= Letter-Number Sequencing
M= Mean
MANOVA= Multivariate Analysis of Variance
MWU= Mann-Whitney U
NR= Not reported
RT= Radiotherapy
SBIS= Stanford-Binet Intelligence Scale
SD= Standard Deviation
SO= Surgery Only
SES= Socio-Economic Status
WAIS= Wechsler Adult Intelligence Scale
WISC= Wechsler Intelligence Scale Children
WJ= Woodcock Johnson Test of Achievement
WM = Working Memory

Table 3. Working memory in paediatric brain tumour survivors compared with non-CNS cancer controls

Study	Outcome Measure and Subtest	Memory Function	Outcome Score	Group Analysis	Mean Result Clinical group (SD)	Mean Result Control group (SD)	Statistical Test and significance	Effect Size	Variables Matched Across Groups	Quality Rating
Garcia-Perez et al. (1994)	**WISC** DS	Verbal WM	Standard score (M=10, SD=3)	Clinical vs Non-CNS cancer controls	9 (3.27)	10.63 (2.43)	MWU (Not sig)	IDC	Age, parental SES, psychological impact of illness, cognitive ability	High quality
	WISC DS	Verbal WM	Standard score (M=10, SD=3)	Clinical vs chronic disease controls	9 (3.27)	10.14 (2.63)	MWU Not sig	IDC		
Mabbott et al. (2008)	**WJ** AWMT	Verbal WM	Standard score		101.79 (2.93)	102.10 (5.16)	MANOVA Not sig	d= -0.07	Age, psychological impact of illness, RT dose. IQ not matched	Acceptable quality
	WISC/WAIS DS	Verbal WM	Scaled score		9.29 (0.49)	8.70 (0.86)	Not sig	d= 0.84		
	WISC/WAIS Spatial Span	Visual WM	Scaled score		8.84 (0.58)	8.80 (1.02)	Not sig	d= 0.05		
Conklin et al. (2012) *	**WISC/WAIS** DSF DSB	Verbal WM	z-score		DSF: not reported DSB= 0.1228	DSF: not reported DSB= 0.4500	Not sig ANOVA **(p=0.01)**	IDC	Age, family, psychological impact of illness. IQ not matched	Acceptable quality

Key

DS= Digit Span
DSB= Digit San Backwards
DSF= Digit Span Forwards
IDC= Insufficient Data to Calculate Effect Size
M= Mean
MANOVA= Multivariate Analysis of Variance
MWU= Mann-Whitney U
RT= Radiotherapy
SD= Standard Deviation
SES= Socio-Economic Status
WAIS= Wechsler Adult Intelligence Scale
WISC= Wechsler Intelligence Scale Children
WM= Working Memory

Table 4. Long-term memory in paediatric brain tumour survivors compared with healthy (current page) and non-CNS cancer controls (next page)

Study	Outcome Measure and Subtest	Memory Function	Outcome Score	Group Analysis	Mean Result Clinical group (SD)	Mean Result Control group (SD)	Statistical Test and significance	Effect Size	Variables Matched Across Groups	Quality Rating
Ozyurt et al. (2014)	**VMLT** Full	Verbal Learning Delayed Recall Loss after delay LT Recognition	T Scores		Median (IQR) 46 (14) 44 (15) 55 (16) 53 (6)	Median (IQR) 60 (9) 58 (4.5) 63 (7) 54 (1)	MWU **(p=0.02)** **(p=0.001)** **(p=0.001)** Not sig	IDC	Age, IQ, anxiety, depression	High quality
Shortman et al. (2014)	**CMS** (5-16) All Subtests **WMS** (over 16) All Subtests	Immediate Verbal LTM	Composite scores		98.8 (20.8)	116.2 (16.7)	ANOVA **(p=0.018)**	d= -0.92	SES, age, gender, educational attainment. Some survivors still being treated	High quality
		Immediate Visual LTM	Composite scores		102.6 (24.5)	120.3 (12.9)	ANOVA **(p=0.003)**	d= -0.90		
		Delayed Visual LTM	Composite scores		109.2 (22)	118.4 (13.9)	ANOVA Not sig	d= -0.5		
		Delayed Verbal LTM	Composite scores		100.4 (19.7)	113.8 (15)	ANOVA Not sig	d= -0.77		
		General LTM	Composite scores		104.3 (25.2)	124.1 (15.2)	**(p=0.021)**	d= -0.95		
Redmond et al. (2013)	**WJ** Memory for Words Test	Immediate Verbal LTM	Raw score	15month FU 27month FU	16.29 (2.95) 16.6 (3.03)	17.55 (1.7) 18.3 (1.93)	LME Not sig Not sig	d= -0.50 d= -0.67	Matching of controls not discussed	Acceptable quality
Quintero - Gallego et al. (2006)	**CVLT-C** Learning trial 5	Immediate Verbal LTM	Raw Score	Clinical subgroups Medullo-blastoma	11.28 (3.72)	13.58 (1.37)	MANOVA Not sig	d= -0.82	IQ not matched	Acceptable quality
				Astrocytoma	12.36 (2.06)	13.58 (1.37)	Not sig	d= -0.70		

Study	Outcome Measure and Subtest	Memory Function	Outcome Score	Group Analysis	Mean Result Clinical group (SD)	Mean Result Control group (SD)	Statistical Test and significance	Effect Size	Variables Matched Across Groups	Quality Rating
Garcia-Perez et al. (1994)	**Spreen Benton** Sentence Repetition	Immediate Verbal LTM	Raw (out of 26)	Clinical vs Chronic disease	22.17 (3.46)	23.92 (2.91)	ANOVA (Not sig)	d= -0.56	Age, parental SES, psychological impact of illness, cognitive ability	High quality
	RCFT	Immediate Visual LTM	Standard score (M=50, SD=10)	Clinical vs Chronic Disease	45.80 (14.46)	54.66 (10.08)	MWU **(p=0.022)**	IDC		
	Yuste Memory Test	General Long-term memory	Standard score (M=50, SD=10)	Clinical vs Chronic Disease	37.29 (9.85)	51.92 (10.46)	ANOVA **(p=0.05)**	d= -1.44		
	Spreen Benton Sentence Repetition	Immediate Verbal LTM	Raw (out of 26)	Clinical vs Non-CNS Cancer	22.17 (3.46)	23. 62 (2.65)	ANOVA Not sig	d= -0.47		
	RCFT	Immediate Visual LTM	Standard score (M=50, SD=10)	Clinical vs Non-CNS Cancer	45.80 (14.46)	55.66 (8.50)	MWU **(p=0.008)**	IDC		
	Yuste Memory Test	General Long-term memory	Standard score (M=50, SD=10)	Clinical vs Non-CNS Cancer	37.29 (9.85)	49.01 (8.06)	ANOVA **(p= 0.05)**	d= -1.30		

Key
ANOVA= Analysis of Variance
CMS= Children's Memory Scale
CNS= Central Nervous System
CVLT-C= California Verbal Learning Test- Child
FU= Follow-up
IQR= Inter Quartile Range
IDC= Insufficient Data to Calculate effect size
LME= Linear Mixed Effect Regression
LT= Long Term
LTM= Long-term memory
MANOVA= Multivariate Analysis of Variance
MWU= Mann-Whitney U
RCFT= Rey Complex Figure Test
SD= Standard Deviation
SES= Socio-Economic Status
VLMT= Verbaler Lern und Merkfahigkeitstest
WMS= Wechsler Memory Scale
WJ= Woodcock Johnson Test of Achievement

Working Memory

Verbal Working Memory in Paediatric Brain Tumour Survivors in Comparison to Healthy Controls

High quality studies (Robinson et al., 2014; Riva et al., 2002) found evidence of significant differences in verbal WM between PBT survivors and healthy controls. Both studies had moderate small sample sizes, which may not have been representative of the PBT survivor population, however. IQ was not matched the study by Robinson et al (2014) or in all group comparisons within the Riva et al. (2002) study. As IQ is known to significantly correlate with working memory (Cowan, 2008), results may be due to underlying cognitive differences between groups. Psychological factors, which may affect performance on memory assessments, were matched within the Robinson et al., (2014) study, and Riva et al. (2002) used sibling controls, matching for social and family factors, strengthening the evidence for WM impairment in PBT survivors. Studies of acceptable quality reported varied results. Studies finding evidence of significant verbal WM impairments in PBT survivors compared to healthy controls (Law et al., 2011; Conklin et al., 2012) did not match for IQ, depression or anxiety, hence group differences may be a result of underlying cognitive and psychological variables. Redmond et al. (2013) found no group differences, but did not minimise the risk of bias through group matching or controlling for treatment and tumour effects. Collectively, these studies suggest verbal WM is impaired in PBT survivors compared to healthy controls but this may reflect underlying cognitive and psychological differences between groups.

Certain treatments were associated with poorer WM in studies; PBT survivors treated with radiotherapy had poorer WM outcomes than those treated with surgery alone (Law et al., 2011), as did those treated with Intrathecal Methotrexate (ITM) compared to those treated

without (Riva et al., 2002). No strong conclusions can be made regarding treatment effects on PBT survivors' WM, however. There was also some evidence that working memory assessments that required both the temporary storage and manipulation of information were more impaired in PBT survivors relative to controls (Conklin et al., 2012; Quintero-Gallego et al., 2006), suggesting that PBT survivors may be able to temporarily store, but not manipulate, information as well as healthy controls. Definitive conclusions cannot be drawn from the results as studies failed to minimise selection and detection biases.

Verbal Working Memory in Paediatric Brain Tumour Survivors in Comparison to Non-CNS Cancer Controls

A high quality study comparing verbal WM in PBT and non-CNS cancer survivors found no differences between groups (Garcia-Perez, Sierra-Sesumaga, Narbona-Garcia, Calvomanuel and Aguirre-Ventallo, 1994). Although there was variability in 'time since treatment' (six months to ten years) and the level of radiation received within the brain tumour group, which may have influenced outcomes, cognitive ability was matched between groups, strengthening the conclusion. They also compared PBT survivors to young people who have a chronic disease and found no group differences in WM scores. Of the two studies of acceptable quality (Conklin et al., 2012; Mabbott et al., 2008), only one found differences in verbal WM between PBT and non-CNS cancer survivors, and only for a task involving both storage and manipulation of information. Collectively, these studies suggest that there may be generic illness and treatment factors that may affect verbal working memory in young people, however small sample sizes and heterogeneous PBT samples in the studies make generalising results to the PBT survivor population difficult.

Visual Working Memory in Paediatric Brain Tumour Survivors in Comparison to Healthy Controls

Two studies, one of high quality (Riva et al., 2002) and one of acceptable quality (Redmond et al., 2013), found significantly poorer visual WM performance in PBT survivors than healthy controls, suggesting an impairment in visual in PBT survivors. Riva et al. (2002) only found differences in PBT survivors treated with ITM under the age of eleven, and healthy controls of the same age, which is not representative of the PBT survivor population. Furthermore, neither study matched groups for IQ in all groups, therefore differences may reflect cognitive ability rather than visual WM, reducing the strength of the conclusions. The multiple-choice version of the Benton Visual Retention Test (BVRT; Benton, 1950) utilised by Riva et al. (2002) had poor internal consistency in children (Wagner, 1992, cited in Strauss, Sherman & Spreen, 2006), further reducing the strength of conclusions that can be made regarding the data.

Visual Working Memory in Paediatric Brain Tumour Survivors in Comparison to Non-CNS Cancer Controls

A single study of acceptable quality found no significant differences in spatial WM on in PBT and non-CNS cancer survivors (Mabbott et al., 2008). The brain tumour group only included survivors of posterior fossa tumours and results cannot be generalised to survivors of tumours in other locations, however this provides tentative evidence that spatial WM is not impaired in PBT compared to non-CNS cancer survivors.

Long Term Memory

Verbal and Visual Long-Term Memory in Paediatric Brain Tumour Survivors in Comparison to Healthy Controls

Two high quality studies comparing LTM in PBT survivors and healthy controls using sensitive and reliable assessments found PBT survivors were significantly impaired in verbal LTM relative to controls (Shortman et al., 2014; Ozyurt et al., 2014). Shortman et al. (2014) found evidence of impairment in immediate LTM recall following learning, but not after a 30-minute delay. Ozyurt et al. (2014) found evidence of delayed verbal LTM impairment after 30 minutes, however. Shortman et al. (2014) report that their study was underpowered due to the small sample size (although 25 in each group is moderate), which could have contributed to the null result after a delay. This is corroborated by the large effect size for group differences in verbal recall after a delay (-0.75).

Shortman et al. (2014) also found evidence of visual LTM impairment in PBT survivors compared to healthy controls; again, group differences were significant for immediate and not delayed recall, however this may also be the result of the study being underpowered. As some PBT survivors had not yet or had only recently completed treatment in the Shortman et al. (2014) study, the sample may not be representative of the PBT survivor population, making results less generalizable and difficult to compare with the Ozyurt et al. (2014) study, which included survivors that had completed treatment years previously.

The two studies of acceptable quality failed to find differences in immediate verbal recall in PBT survivors and healthy controls (Redmond et al., 2013; Quintero-Gallego et al., 2006). Both studies failed to minimise the risk of bias by matching groups and included small sample sizes, which, they acknowledge, may mean the studies lacked the power to

detect group differences. Therefore strong conclusions cannot be drawn from them. Collectively, the studies suggest verbal and visual LTM are impaired in PBTS, corroborated by significantly lower global LTM scores in PBT survivors compared to controls (Shortman et al., 2014). Ozyurt et al. (2014) also found evidence that PBT survivors learned significantly fewer words during learning trials than the control group, and showed no impairment in recognition, suggesting words were stored but not retrieved.

Verbal and Visual Long-Term Memory in Paediatric Brain Tumour Survivors Compared to Non-CNS Cancer Controls

A high quality study comparing PBT and non-CNS cancer survivors found significant group differences in immediate visual LTM, but not immediate verbal LTM, although the effect size was medium (0.47) suggesting the study may not have had the power to detect group differences (Garcia-Perez et al., 1994). They found similar results when comparing PBT survivors with chronic disease controls, suggesting general illness or treatment factors (such as the psychological impact of illness and time away from school) may affect verbal LTM, and brain tumour and treatment factors may affect visual LTM. General LTM was also impaired in PBT survivors relative to non-CNS and chronic disease controls.

Discussion

Main Findings

Is there a significant working memory impairment in paediatric brain tumour survivors compared to controls?

There was some robust evidence for verbal WM impairment in PBT survivors compared to healthy controls, but insufficient robust evidence of visual WM impairments. The lack of matching for IQ in all studies means group differences may be due to underlying cognitive ability, reducing the strength of conclusions made about WM in PBT survivors. It was unclear whether specific treatment modalities, age at treatment or time since treatment were associated with WM impairment. There was some evidence to suggest that tasks involving both the short-term storage and manipulation of information were more adversely affected in PBT survivors than tasks requiring simple serial recall, however further research is necessary to confirm this hypothesis. There was robust evidence that WM is not impaired in PBT compared to non-CNS cancer survivors, suggesting cancer treatment (chemotherapy or radiotherapy) may affect WM in young people, however this may be due to more general illness and treatment factors (fatigue, time off school, the psychological impact of illness) given the similarity in verbal WM scores between PBT survivors and young people with a chronic disease.

Is there a significant impairment in long-term memory in paediatric brain tumour survivors compared to controls?

Although there was variation across studies, high quality studies found significant impairments in immediate visual, and immediate and delayed verbal LTM in PBT survivors compared to healthy controls. Two studies of acceptable quality found no group differences in LTM, but they failed to control for confounders, reducing confidence in their

overall negative findings. There was robust evidence of immediate visual but not verbal LTM impairment in PBS survivors relative to non-CNS cancer and chronic disease controls. Collectively, the results suggest specific brain tumour and treatment factors may impact visual LTM in survivors of PBT.

Other findings

Radiotherapy in combination with surgery or chemotherapy may result in greater memory impairment in PBT survivors (Riva et al., 2002; Law et al., 2011). Mabbott et al. (2008) did not find any differences in WM outcomes in those treated with standard compared to reduced-dose radiation, although they included a non-CNS cancer control group rather than a healthy one, who also received cancer treatments. Overall, definite conclusions cannot be made regarding which variables have an impact on memory in this population.

Methodological Quality and Risk of Bias

The SIGN Checklist for Cohort studies identified that methodological quality varied across studies in the review. Five studies matched tumour and control groups for IQ or psychological factors, reducing selection bias and ensuring effects on memory are due to the brain tumour rather than other confounders. All the longitudinal studies reported participant drop-out between assessments, but none compared them with completers. If these groups differ significantly in confounding factors, it causes attrition bias and decreases the generalisability of study results. No studies reported whether assessors were blinded to group status of participants, which could have led to bias when delivering and marking assessments (detection bias). All outcomes were clearly defined, reliable and valid, and all studies reported using similar procedures for collecting data in both groups,

minimising further detection bias. Overall, articles controlled for age, gender and treatment factors well, but not intelligence and psychosocial factors.

Context of Main Findings

The results of the review correspond to the literature, which suggests impaired memory outcomes in brain tumour survivors when compared to normative data (Benesch et al., 2009). Robinson et al. (2010) found larger mean effect sizes for verbal than visual memory outcomes, in line with working memory outcomes in the current review. Fewer studies in the current review assessed visual memory, however, which may be due to certain assessments being more popular, such as digit spans. The current review highlighted the lack of research assessing visual memory; future research should explore this in order to better understand which aspects of memory are most affected and how to best support survivors.

The reviewed studies mainly included survivors who had completed treatment some years previously (Ozyurt et al., 2014), although one included survivors who had recently completed, or were still completing, treatment (Shortman et al., 2014). Previous longitudinal studies suggest that cognitive outcomes worsen in PBT survivors over time (Mulhern et al., 2004), and this may explain differences in findings between studies. The longitudinal articles in the current review did not all report deterioration in memory outcomes across time points, specifically between 15 and 27 months post-treatment. This does not contradict the literature as these time points are shorter than those normally reported in studies assessing long-term neurocognitive outcomes in PBT survivors.

Relevant Implications

These results suggest memory should be clinically monitored in young people who have survived a brain tumour, as they may have significant impairments. The results would also be relevant to educational settings; educators should be aware that survivors may have difficulties retaining information and provide appropriate support to those that require it. There is currently more evidence to suggest verbal working and long-term memory are impaired in survivors relative to peers, therefore visual memory aids may be beneficial. The lack of articles comparing memory in PBT survivors and controls suggests the need for further research in this area. The evidence base would benefit from better designed studies that controlled for potential confounders such as IQ, treatment, tumour and psychosocial factors, and included larger sample sizes to improve the validity of results. Establishing a consensus in memory terminology and the functions assessed in different assessments would also increase the validity of conclusions drawn from the literature and allow comparisons between studies to be more easily made. For example, the use of the term 'short-term memory' in relation to immediate recall following learning trials is disputed and this could be addressed in future.

Strengths and Limitations of the Review

The methodological quality tool developed by SIGN is standardised and validated and was a good assessment of methodological quality in the reviewed studies. It did not differentiate between studies very well, therefore specific confounders deemed to be significant were used to identify high and acceptable quality studies. As this was somewhat subjective, the quality ratings may have negatively affected the reliability, although this was minimised by the use of a second rater.

There are general challenges in reviewing literature from this population. Samples are often small and heterogeneous due to the small population. Data are often collected as part of treatment protocol studies, thus battery of assessments could be included in the protocols to collect more extensive data on cognitive outcomes in survivors. The current review included studies between 1994 and 2014, during which time treatments for cancer have developed and become less damaging to the brain. The reviewed articles also varied in tumour diagnoses and locations. The synthesis of the findings would have been more valid if these factors had been reviewed separately. This could not be accomplished due to the small sample sizes within articles. The review included only articles with paediatric populations. Research into cognitive late-effects suggests some functions deteriorate with time following treatment, so including studies with adults who had survived a paediatric brain tumour may have delivered more robust results. The review focused on memory only and executive functions may affect memory performance. Including executive functions in the review may have improved the strength of conclusions. A publication bias towards the publication of significant findings only may also account for some of the results, influencing how meaningful they are.

Conclusions

There is robust evidence of verbal working memory and verbal and visual long term memory impairments in paediatric brain tumour survivors compared to healthy controls. There was insufficient robust evidence to make conclusions regarding visual working memory. Memory can affect both educational and everyday functioning in PBT survivors. The results of the current review could therefore be used to better support this group of young people, both in educational and home settings. Systematic assessment on return to school and subsequent follow-up assessments every six months could be included in routine follow-up. Results are also applicable clinically, confirming the importance of memory assessments in PBT survivors in order to recognise impairments early and provide support as quickly as possible.

The lack of high-quality articles comparing tumour and control groups means further research is required to understand the long-term effects of brain tumours and their treatment on memory in young people, in order to improve understanding of which memory functions are most impaired in survivors.

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CHAPTER 2

Major Research Project

Memory After Tumours of the CNS in Childhood (MATCCh) Study: Long-term Memory and Forgetting in Paediatric Brain Tumour Survivors

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Plain English Summary

Background Some children and young people who have survived a brain tumour have poor memory. They report finding it difficult to remember information they learned at school for exams, which may be because they forget more information than other people of their age. Poor sleep, depression and anxiety can affect how well you remember things and can be common in young people who have had a brain tumour.

Aims To explore whether young people who have survived a brain tumour can learn and remember information as well as their siblings, cousins or best friends. A second aim is to explore whether memory is related to sleep quality, depression and anxiety in young people who have survived a brain tumour.

Method Young people between the ages of 11 and 24 who had survived a brain tumour were taught a list of words and a shape. They were asked to remember as much as they could 30 minutes later and again after a week. They also filled in questionnaires about their mood and wore an Actiwatch for one week, which measured how well they slept.

Results Young people who survived a brain tumour found it more difficult to learn the word list than their siblings/cousins/best friends. Some of the brain tumour survivors found it very difficult to remember the words and shape, especially after a week, but others remembered them as well as their friends or family. Brain tumour survivors may have different memory abilities because there was a range of different brain tumour diagnoses and treatments in the group. The results suggest that schools and hospitals should monitor survivors to make sure they get support if they do have these difficulties. Memory was not associated with sleep, depression or anxiety in the survivors, but the study was small so more studies are needed to look at which groups of brain tumour survivors have poor memory and how their sleep and mood affects this.

Abstract

Background The literature suggests that working and long-term memory are impaired in paediatric brain tumour survivors (Robinson Fraley, Pearson, Kuttesch & Compas, 2013; Robinson et al., 2014). Survivors report difficulties remembering information they learned days before, including for school exams. Sleep and psychological problems can affect memory performance and may exacerbate memory difficulties in this population.

Aims Assess learning and long-term memory in paediatric brain tumour survivors relative to healthy controls, and explore associations between memory, sleep and mood.

Method A learning paradigm was used to teach verbal and visual material to an 80 percent criterion in ten young brain tumour survivors and ten matched healthy controls (sibling, cousin or best friend) aged between 11 and 24. A between-subjects design compared recall between groups at delays of 30 minutes and one week. Sleep quality (measured by Actigraphy), anxiety and depression were also assessed.

Results Verbal learning was significantly impaired in brain tumour survivors relative to controls. There was very tentative evidence of increased visual forgetting in the tumour group, however definitive conclusions could not be drawn from results due to the study lacking power. Some participants had significant impairments in verbal learning or verbal and visual long-term memory, and others did not. Memory was not associated with sleep or psychological variables in the tumour group, although this may be due to the study lacking power.

Discussion The variability in memory within the tumour sample emphasises the heterogeneity in the brain tumour population and the need for memory to be monitored in individuals. Education and occupational settings could offer further support to those that require it. Future research should assess memory after delays longer than 30 minutes and further explore how tumour, treatment, sleep and mood variables affect memory.

Introduction

In the United Kingdom, 24.5 percent of all new cancer diagnoses in children below the age of 14 are due to central nervous system tumours (Stiller, 2007). The most common diagnoses of paediatric brain tumour (PBT) are medulloblastoma (a high grade, fast growing tumour), pilocytic astrocytoma and craniopharyngioma (low grade tumours). Survival rates in young people with brain tumours have improved drastically over the past twenty years as a result of treatment advances, however the treatments can be damaging to healthy tissue, such as through neurosurgical resection, and chemotherapy and/or radiotherapy, which can be neurotoxic (Turner, Rey-Casserly, Liptak, & Chordas, 2009).

Children and young people who have been treated for a brain tumour can experience cognitive deficits including memory and language (Robinson et al., 2010). In addition, children may miss months or even years of school and have ongoing educational interruptions during treatment, which could have a further negative effect on learning.

Memory

Baddeley and Hitch (1974) suggest memory is made up of two systems that interact: working memory and long-term memory (LTM). Working memory is a multi-component system that includes the temporary storage and manipulation of information and LTM includes the long-term storage of information. The Standard Consolidation Model (Hasselmo and McClelland, 1999) suggests that information from working memory is encoded in the hippocampus then consolidated to the long-term store within the neocortex, creating new neural pathways between the hippocampus and neocortex. Standard memory assessments measure LTM immediately following learning trials for a stimulus, and after a

thirty minute delay. PBT survivors were found to have poorer delayed than immediate recall of verbal and visual information, suggestive of impaired consolidation (Carpentieri et al., 2001).

There is evidence that the process of consolidation can take several days, and is vulnerable to disruption. Children with epilepsy forget a higher proportion of information than healthy controls after a week, a phenomenon called 'accelerated forgetting', suggesting seizures may be affecting consolidation (Davidson, Dorris, O'Regan and Zuberi (2007). Chemotherapy and radiotherapy can damage the development of white matter in the brain (Reddick et al., 2003), which may affect the integrity of the neural pathways between the hippocampus and neocortex. This may affect consolidation in PBT survivors, therefore standard measures may not be appropriate to assess consolidation in this population.

Anecdotal evidence from studies suggests that PBT survivors have difficulty remembering information over longer time periods, including for school exams (Waber et al., 2006). Parents have also reported their children having difficulty *applying* information they had previously learned (Ondrucht, Maryniak, Kropiwnicki, Roszkowski, & Daszkiewicz, 2011). Collectively, this suggests brain tumour survivors may have difficulty retrieving material previously encoded into LTM, or may forget more rapidly than peers. As this would significantly affect learning, longer term memory retention should be explored in this population.

Memory, Sleep and Psychological Factors

Good sleep is important for memory consolidation (Maquet, 2001) and PBT survivors experience sleep problems in initiating and maintaining sleep, hypersomnia and fatigue

(Verberne, Maurice-Stan, Grootenhuis, Van Santen, & Schouten-Van Meeteren, 2012). Impaired working memory was associated with poorer sleep quality and increased sleepiness in adult survivors of childhood cancer, after controlling for age, gender and treatment (Clanton et al., 2011). Depression and anxiety have been associated with poor academic performance in healthy children (Owens, Stevenson, Hadwin, & Norgate, 2012) and brain tumour survivors can have significantly higher levels of distress and depression than sibling controls (Zebrack et al., 2004), which may exacerbate memory difficulties. Should these factors be associated with memory, evidence-based interventions for children to ameliorate low mood, anxiety and sleep quality, and cognitive rehabilitation techniques, may enhance memory (Compton et al., 2004; Kesler, Lacayo and Jo, 2011).

The Current Study

This study explored memory and its relationship to sleep, anxiety, and depression on in PBT survivors. It was hypothesised that PBT survivors have impaired retention of learned information after a delay of days or weeks that may not be evident in a delay of half an hour, therefore memory was assessed at a 30 minute and one week delays in PBT survivors and healthy controls. There is evidence to suggest several factors affect cognitive functioning in brain tumour survivors, such as age at diagnosis, severity of tumour, treatment received and location of tumour. Due to the time and recruitment limitations in the scope of the study, these factors were not controlled for, but tumour and treatment factors are described (Table 1).

Hypotheses

1. PBT survivors have significantly lower scores on working memory tests than healthy controls

2. PBT survivors require significantly more trials to learn verbal and non-verbal information than healthy controls.
3. PBT survivors have lower recall and recognition scores after a 30 minute delay and *significantly* lower recall and recognition scores after a one week delay than healthy controls.
4. PBT survivors forget a significantly greater proportion of learned verbal and visual information between 30 minute and one week delays than healthy controls.
5. Better memory performance is associated with better sleep quality and lower self-reported anxiety and depression in PBT survivors.

Method

Design

A prospective, within and between-subjects design compared LTM in PBT survivors and healthy age-matched sibling, cousin or best friend controls.

Participants

Inclusion Criteria

Young people who had received treatment for a brain tumour at the Royal Hospital for Sick Children (RHSC) in Edinburgh between the ages of 11 (the age secondary education commences) and 24 years (the age to which paediatric oncology reviews continue) at time of recruitment were eligible. Exclusions were not made on the basis of tumour type or location, or treatment type. Treatment had to have been completed at least six months prior to recruitment. Healthy siblings, cousins or best friends of tumour participants aged

between 11 and 24 were recruited as controls for psychosocial, family and environmental factors. All participants had to be fluent in English.

Exclusion criteria

PBT survivors were excluded if they had a secondary cancer for which they were receiving chemotherapy or radiotherapy. Controls were excluded if they had a history of cancer or other neurological diagnoses (including head injury and neurological infection) or had been admitted to hospital in the 6 months previous. Young people were excluded if they had a diagnosis of a developmental disorder, such as Autistic Spectrum Disorder or Learning Disability, were being treated for a mental health disorder, or had received a recent cognitive assessment.

Sample size

No studies assessing longer-term memory have been conducted in PBT survivors, so an a priori sample size calculation was based on Davidson et al. (2007) as it most closely resembled the current design. They found significant differences in recall on the Stories Subtest of the Children's Memory Scale in 21, 6-16 year olds with epilepsy and 21 healthy controls matched for age and IQ, after a one week delay. G-power was used to calculate the sample size required for an independent t-test (epilepsy group: M= 75.8 (SD=13.8); control group: M= 84.4 (SD= 6.8)). Assuming a normal distribution, two-tailed analyses, a significance level of 0.05 and power at 0.80, a sample size of 27 in each group was estimated to find a large effect size[1]. As the current study used sibling controls, paired t-

[1] The sample size calculation differed from that in the proposal following consultation with a statistician.

tests would be used, which have higher power to detect any effects, therefore a smaller sample would be required. A sample of 20 in each group was the target for recruitment.

Recruitment Procedure

Approval was obtained from West of Scotland NHS Research Ethics Service and NHS Lanarkshire and NHS Lothian Research and Development (Appendices 2.2, 2.3, 2.4). The Research Oncology Nurse identified and contacted 53 brain tumour survivors eligible for recruitment. Young people who had survived a Medulloblastoma were recruited first, but as the response rate was low, Pilocytic Astrocytoma and Craniopharyngioma survivors were also recruited.

Potential participants (or parents of those under 16) were sent information regarding the study by post. Those that were interested were asked to contact the Research Oncology Nurse, or to return the consent form. Consultant Oncologists were available to answer questions within clinical review appointments. Posters were displayed in hospital waiting areas to aid recruitment. Control subjects were recruited through PBT survivors or their parents. Twelve PBT survivors consented to be contacted, a response rate of 23 percent. They were contacted by the researcher for initial screening and to organise assessment sessions. Two PBT survivors and their controls failed to attend. Of the remaining ten, two participants in the tumour group did not have an appropriate control; for these participants, unrelated healthy controls were recruited through the researcher's work colleagues and were matched to PBT survivors based on their age only. In total, ten PBT survivors and ten controls participated.

Research Procedure

Each participant attended two sessions, one week apart. In the first session, cognitive and memory assessments were completed, in the second, memory assessments were re-administered and mood and sleep questionnaires completed. All sessions were conducted in an outpatient hospital setting or a local health centre if more convenient for families. Written assent was obtained for 11 year olds, and consent for those 12 years and above. Further consent was obtained from parents of participants under sixteen. Participants were given an Actiwatch to wear over the week. Participants were asked not to discuss the assessments with their control during the week between assessments and were not aware they would be asked to recall information after one week. Data collection occurred between February and June 2015.

Measures and Equipment

Intellectual Functioning

The two-subtest version of the Wechsler Abbreviated Scale of Intelligence- Second Edition (WASI-II; Wechsler, 2011) was used to estimate full-scale IQ. It comprises Matrix Reasoning (a measure of visual abstract reasoning) and Vocabulary (a measure of verbal comprehension) subtests. It is standardised for ages 6-90 years. An IQ score was calculated for each participant (WASI IQ scores have a mean of 100 and standard deviation of 15).

Working Memory

Working memory was estimated using the Digit Span subtest of either the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2003) for those aged 11-15 years, or the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV;

Wechsler, 2008) for those aged 16 to 24 years. The totals of raw scores for backward and forward digit span were calculated for each participant.

Long-Term Memory

The Rey Auditory Verbal Learning Test (RAVLT; see Lezak, Howieson, & Loring, 2004) was used to assess auditory verbal memory. The 15 word list was read aloud by the researcher and participants were asked to recall the words. The normal testing procedure includes five learning trials. This was changed for the purpose of this research and a learning paradigm was employed. Participants received learning trials repeatedly until they achieved a learning criterion of 80 percent accuracy (12/15 words). If participants did not achieve this criterion, the number of trials they were given before they asked to stop was recorded. This replicates the learning procedure used by Davidson et al. (2007). Participants were then assessed on free recall at 30 minute and one week delays, and recognition from a list of 50 words.

The Rey Complex Figure Test (RCFT; Meyers & Meyers, 1996) was given to assess visuo-spatial memory. Participants were shown the design and asked to copy it, the design was then obscured and participants were asked to recall it from memory. The normal procedure was altered and a learning paradigm was employed (as above). Recall was assessed after 30 minute and one week delays, followed by recognition of 12 elements within the Rey Complex Figure from 24 items (converted into a percentage).

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used to measure anxiety and depression symptoms. Although originally normed against an adult population, it has been validated in a sample of children aged between 12 and 17 (White, Leach, Sims, Atkinson, & Cottrell, 1999). They found the HADS to have reasonable test-retest reliability (r=0.62 for depression subscale and 0.74 for anxiety) and to discriminate between adolescents with and without diagnoses of anxiety or depressive disorders.

Sleep

Actigraphy has been found to be an objective measure of sleep quality (Sadeh & Acebo, 2002). Participants wore an 'Actiwatch' AW4 series (produced by CamNtech in 1996), which is a watch-like device that measures activity levels during sleep on their non-dominant wrist. The Actiwatch was worn for one week, adhering to recommendations of five week nights for reliably calculating sleep efficiency in children (Acebo et al., 1999). Participants were asked to press the Actiwatch button when they turned off the lights at night, to record this time point for analysis. Actiwatch Sleep 7 software was used to calculate sleep efficiency (total time asleep divided by total time in bed multiplied by 100, indicative of the proportion of time you are asleep when trying to sleep), sleep latency (how many minutes it takes to fall asleep), percentage of time in 'immobile sleep' (number of immobile minutes divided by number of minutes of assumed sleep, which indicates the proportion of deep sleep), and the Fragmentation Index (the proportion of movement within sleep, which is an indication of increased restlessness in sleep; The Actiwatch User Manual V7.2; CamNtech, 2008). Participants also completed a sleep diary (see Appendix 2.5 for details), to provide corroboration of Actiwatch data and allow the sleep factors to be calculated more accurately.

The Sleep Self-Report (SSR; Owens, Spirito, McGuinn, & Nobile, 2000), a retrospective, self-rated measure of sleep habits, problems falling asleep, sleep duration, night waking and daytime sleepiness was used to measure sleep subjectively. It comprises 18 questions and higher scores represent greater sleep disturbance (Owens, Spirito, McGuinn, & Nobile, 2000). It shows good psychometric reliability (internal consistency estimated at 0.71; Lewandowski, Toliver-Sokol and Palermo, 2011) and although created for children between 7 and 12 years, it has been used with adolescents (Sumpter et al., 2013). Permission to use the tool was granted by the author (Appendix 2.6). The Fatigue Scale-Adolescent (Hinds et al., 2007; Mandrell et al., 2011) is a 13 item self-report measure for fatigue for 13 to 18 year olds with cancer. It was found to have good reliability (internal consistency 0.87) and identify patients with high and low fatigue with adequate sensitivity (Mandrell et al., 2011). The first part of the scale was used, as the second relates specifically to current cancer and treatment factors. Permission to use the tool was given by the author (Appendix 2.6).

Data Analysis

The distributions of the data were analysed for normality based on histograms, Q-Q Plots and the Shapiro-Wilk test for normality. Only the data in two variables were normally distributed, and paired samples t-tests were used to compare groups. Paired-samples Wilcoxon signed rank tests (WSRT) were used to compare groups where distributions were not normally distributed and not appropriate for transformation, as most controls were related in some way to the tumour group. Effect sizes for non-parametric data were calculated as follows (Rosenthal, 1994):

$r = Z/\sqrt{n}$.

Rosenthal (1994) suggests an effect size for *r* of 0.1 is small, 0.3 medium and 0.5 large. Participants who did not reach learning criterion on memory assessments were assigned a valued based on the number of trials they completed before asking to stop the assessment, in order for them to be included in the analyses. It was not appropriate to apply regression models due to the data not meeting parametric assumptions, therefore relationships between memory, anxiety, depression and sleep quality were analysed using non-parametric Spearman correlations.

Results

Participant Characteristics

The clinical characteristics of the ten PBT survivors (five male, five female) are summarised in Table 1. The ten control participants (four male, six female) comprised five siblings, one cousin and two friends of the tumour group, and two unrelated healthy controls. The tumour group was aged between 13 years and one month and 25 years at time of assessment; median age was 17 years and 5 months (interquartile range (IQR) 5). Five were in full-time education (of these, two were on study leave), two were in full-time employment and three were unemployed. The control group were aged between 11 years 5 months and 23 years 7 months. Median age was 17 years (IQR 8). The groups did not differ in age (WSRT; W=19, Z= -0.867, p=0.386, effect size -0.19). Six controls were in full-time education (of these, three were on study leave), two were in full-time employment and two were unemployed. Socio-economic status was estimated using the Scottish Index of Multiple Deprivation (SMID; Scottish Government, 2012), and was calculated for each participant using their home address, through the Scottish

Neighbourhood Statistics website. Eight PBT survivors and seven controls had SIMD scores indicating they are not in disadvantaged areas; one PBT survivor had an SIMD score indicating they were within the most deprived 20-25 percent in Scotland, and one PBT survivor and one control were in the most deprived five percent in Scotland. Home addresses were not available for two controls; although one had recently moved out of the family home. The tumour group had an estimated median IQ of 103.5 (IQR 15) and the control group of 108 (IQR 16). Groups did not differ in estimated IQ (WSRT; W=42.5, Z=1.53, p=0.126, effect size -0.34).

Table 1. Clinical Characteristics of the Tumour Group

Participant	Age at Diagnosis (years)	Age at Treatment (years)	Time Since Treatment (years)	Age at Assessment (years)	Tumour Diagnosis	WHO Tumour Grade	Location of Tumour	Extent of Surgical Resection	Radiotherapy Treatment	Chemotherapy Treatment
1	11	11-12	5	17	Craniophary ngioma	1	Pituitary Fossa	Tumour drainage and surgical debulking	Focal Photon	
2	8	8	6	14	Pilocytic Astrocytoma	1	Posterior Fossa and Fourth Ventricle	Incomplete resection and surgical debulking		
3	2	Watch and wait for 10 years 12-16	2	18	Pilocytic Astrocytoma	1	Suprasellar	Incomplete resection and surgical debulking	Focal Photon	Carboplatin and Vincristine
4	5	5	8	13	Pilocytic Astrocytoma	1	Posterior Fossa	Complete resection		
5	4	4	13	17	Pilocytic Astrocytoma	1	Posterior Fossa	Complete resection		
6	14	15	3	18	Pilocytic Astrocytoma	1	Suprasellar located in hypothalamus	Surgical debulking	Focal Photon	Vinblastine
7	11	11	12	23	Cranio-pharyngioma		Pituitary Fossa	Surgical debulking	Focal Photon	
8	10	10	5	15	Medullo-blastoma	4	Right Cerebellum	Incomplete resection	Cranio-spinal	Vincrtistine followed by Packer Chemotherapy
9	14	14	4	18	Pilocytic Astrocytoma	1	Left Occipital and Parietal	Incomplete resection		
10	11	12	13	25	Pilocytic Astrocytoma	1	Optic Chiasm, Suprasellar extension	Not specified	Focal Photon	

Memory (see Table 2)

Working Memory

There were no significant differences in total raw scores on the forward and backward digit span tasks between groups; hypothesis 1 was not supported.

Learning and Encoding

Hypothesis 2 was supported for verbal but not visual material.

Visual Memory

The RCFT was not administered to one participant in the tumour group who was visually impaired. The number of trials required to learn the shape to the 80 percent criterion did not differ between groups.

Verbal Memory

Three participants in the tumour group did not reach the 80 percent learning criterion on the RAVLT; one asked to stop after seven and two after eleven trials (used as coding values for analyses). When included in analyses, the tumour group required significantly more learning trials to learn verbal material than the control group (significance remained after a Bonferroni Correction was applied). When those that did not reach criterion were excluded from analyses, the number of learning trials required to reach criterion did not differ significantly between groups.

Table 2. Summary of results and statistical analyses comparing tumour and control groups

Measure		Tumour Group Mean (SD) Median (IQR)	N	Control Group Mean (SD) Median (IQR)	N	Statistical Analysis	n in analysis	Test statistics	Significance	Effect size
WAIS/ WISC	Digit Span Forward and Backward (Raw score)	16 (4)	10	19 (7)	9	RSWSRT	18	W= 23 Z= 1.521	p= 0.128	r= -0.36
RCFT	Number of Learning Trials to Criterion	3 (3)	9	2.5 (2)	10	RSWSRT	18	W= 16 Z=-0.778	p= 0.436	r= 0.18
	30 Minute Recall (Raw score)	29.5 (2.5)	9	30.75 (5.1)	10	RSWSRT	18	W= 25.5 Z= 0.356	p=0.722	r= -0.08
	30 Minute Recognition (Percentage)	91.67 (16.67)	7	91.67 (14.59)	8	RSWSRT	14	W= 6.5 Z= -0.271	p= 0.786	r= 0.07
	1 Week Recall (Raw score)	24 (4.3)	9	27.5 (5.3)	10	RSWSRT	18	W= 38 Z= 1.843	p= 0.065	r= -0.43
	1 Week Recognition (Percentage)	91.67 (8.34)	7	83.33 (20.84)	6	RSWSRT	10	W= 1 Z= -0.447	p= 0.655	r= 0.14
	Forgetting (Percentage)	15.09 (13.03)	9	8.24 (5.65)	10	RSWSRT	18	W=7 Z= -1.836	p=0.066	r= 0.43
RAVLT	Number of Learning Trials to Criterion	5 (5)	10	3 (0)	10	RSWSRT	20	W=2 Z=-2.254	p= 0.024	r= 0.50
	30 Minute Recall (Raw score)	10 (6)	10	9.5 (4)	10	RSWSRT	20	W= 31.5 Z= 0.409	p= 0.683	r= 0.09
	30 Minute Recognition (Percentage)	100 (13.33)	10	96.67 (8.34)	10	RSWSRT	20	W= 16.5 Z=0.431	p= 0.666	r= -0.10
	1 Week Recall (Raw score)	7 (5)	10	7.5 (3)	10	RSWSRT	20	W= 33.5 Z= 1.310	p= 0.190	r= -0.29
	1 Week Recognition (Percentage)	93.33 (13.33)	10	93.33 (11.66)	8	RSWSRT	16	W=13 Z= 0.530	p= 0.596	r= -0. 13
	Forgetting (Percentage)	20 (26.52)	9	12.5 (25.82)	10	RSWSRT	18	W= 8 Z= -1.40	p=0.161	r= 0.33

Key
RAVLT= Rey Auditory Verbal Test
RCFT= Rey Complex Figure Test
RSWSRT= Related Samples Wilcoxon Signed Rank Test
SD= Standard Deviation
WISC= Wechsler Intelligence Scale Children
WAIS= Wechsler Adult Intelligence Scale

Effect sizes: Positive if tumour group has higher value and negative if tumour group has lower value

Recall and Recognition

Hypothesis 3 was partly supported.

Visual Memory

Recall on the RCFT did not differ between groups at 30 minutes and there was a non-significant trend towards lower recall scores in the tumour group after a one week delay, although this did not remain following Bonferroni correction. Recognition of the visual elements of the RCFT as a percentage of the maximum did not differ between groups at either delay.

Verbal Memory

Data were analysed with the inclusion of participants that did not reach the learning criterion because excluding them would not represent the range of learning difficulty in the sample. Recall and recognition did not differ significantly between groups at either delay. There was a large variation in recall within the tumour group, however. One PBT survivor was unable to recall any words at either delay, and a further PBT survivor recalled only 4 words after 30 minutes, far below the median for the group.

Forgetting

The proportion of information forgotten between 30 minute and one week delays was calculated using the formula described by Narayanan et al. (2012):

$$\text{Percentage information forgotten} = 100 \times \frac{\text{30 minute recall} - \text{one week recall}}{\text{30 minute recall}}$$

Hypothesis 4 was partly supported. There was a trend towards greater forgetting of visual information in the tumour group than in the control group, although this did not remain following Bonferroni correction. The tumour group showed greater variability than the

control group, with three participants forgetting five to ten percent more visual information than the group median, suggesting poor visual retention. One participant was not included in the verbal forgetting data because their recall on the RAVLT was zero at both time points. Groups did not differ in the proportion of verbal material they forgot over the week and both groups showed high variability in forgetting.

Relationship Between Memory, Sleep and Psychological Factors

Actigraphy was analysed using Sleep 7 software and sleep diaries were used to infer times of lights out and lights on, between which time subjects were trying to sleep. As half of the participants were either on leave from school/college or were unemployed and had little routine during the week, it was felt that using only weekdays to calculate sleep variables would not be valid. Adherence to wearing the Actiwatches during the night was variable; four controls did not wear an Actiwatch for two or three nights, and three PBT survivors did not wear one for between two and five nights. Average sleep variables were therefore computed from all available nights for each participant, to increase reliability of the data. Further analyses on sleep and psychological variables are reported in Appendix 2.7.

Correlations (Spearman's Rho) were calculated between the memory, sleep and psychological variables in the tumour group. Correlations between memory and sleep or psychological variables were non-significant ($p>0.05$); hypothesis 5 was not supported.

Discussion

Main Findings in Relation to the Literature

Working Memory

Working memory was not significantly impaired in PBT survivors relative to healthy controls in the current study, however this result should be interpreted with caution because the study lacked the power to detect any group differences. This may be the reason it differs from the literature, which suggests that verbal working memory is impaired in PBT survivors relative to healthy controls (Robinson et al., 2014; Riva et al., 2002; Law et al., 2011, Conklin et al, 2012). Unlike the current study, many studies failed to control for IQ, which correlates with working memory, and may also explain differences in results.

Learning and Encoding

PBT survivors required significantly more trials to learn verbal (but not visual) material than controls, however there was large variability in the number of learning trials required on the RAVLT. Some PBT survivors required only a few trials but three PBT survivors felt unable to learn the word list to the criterion level, suggestive of significant verbal learning deficits. Ozyurt et al. (2014) found that survivors of craniopharyngiomas learned significantly fewer words than healthy controls matched for age and intelligence, consistent with the current study. Di Pinto et al. (2012) found that craniopharyngioma and low grade glioma survivors treated with surgery and focal radiotherapy had normal verbal learning, however they reported that survivors treated with pre-irradiation chemotherapy were more impaired. The current sample included PBT survivors who received a variety of treatments, including chemotherapy, and used a control group rather than norms to infer impairment, which may account for the differences between results.

Recall and Forgetting

As the study had a modest sample size and lacked the power to detect true effects, definitive conclusions cannot be drawn from the results regarding group differences in recall and forgetting. Although it is difficult to reliably answer whether LTM is impaired in PBT survivors, there was very tentative evidence of survivors forgetting more visual material after one week than controls (although the non-significant trend did not remain once multiple comparisons were controlled for) and of larger group differences in recall at one week than 30 minute delays. It was evident that verbal recall and visual retention abilities varied within the tumour group; some PBT survivors showed similar abilities as controls, others showed significant impairments suggestive of LTM deficits. This may be a reflection of the varied treatment and tumour factors in the sample and it emphasises the heterogeneous nature of the PBT survivor population.

Collectively, these results tentatively suggest that the consolidation of verbal and visual information may take a few days and that this may be disrupted in some PBT survivors, causing difficulty in retaining information over longer time periods. This supports the use of longer delays when assessing memory in this population.

Research comparing PBT survivors and healthy controls provides robust evidence for impairments in verbal LTM (Ozyurt et al., 2014) and visual LTM (Shortman et al., 2014). This was not found in the current study and may reflect differences in samples and measures, or the lack of power in the current study. Further research is required to explore memory retention in this population as definitive conclusions cannot be drawn from the current results.

Recognition

Recognition memory for verbal and visual information did not differ between groups, suggesting brain tumour and treatment factors had little effect on the process of identifying whether a stimulus had been encountered previously. Intact recognition in the sample is in line with previous research (Ozyurt et al., 2014).

Relationship Between Memory, Sleep and Psychological Factors

There is evidence that impaired memory is associated with poor self-reported sleep quality in adult survivors of childhood cancer (Clanton et al., 2011), and that depression and anxiety are associated with poor academic performance in healthy children (Owens, Stevenson, Hadwin, & Norgate, 2012). Memory was not associated with any sleep or psychological factors in PBT survivors in the current study, which is likely due to the study lacking power to detect significant correlations. The Actigraphy data should be interpreted with caution, as it was often difficult to interpret and contained missing data, which may have reduced its validity. It is therefore difficult to reliably answer whether sleep, psychological factors and memory are associated in PBT survivors, therefore further research is required.

Strengths and Limitations of the Research and Future Directions

The main limitation was the modest sample size, which meant definitive conclusions regarding learning and LTM impairment in PBT survivors relative to controls could not be made. There were several limitations that influenced recruitment that contributed to this, primarily the small brain tumour survivor population in Scotland and recruiting from a single centre, where only 53 potential participants were identified. Time limitations and the

high demand from participants (meeting twice, a week apart) with no incentives also affected recruitment. The low opt-in rate resulted in a heterogeneous tumour sample which may not be representative of other young people who have survived a PBT, increasing the risk of selection bias. Previous research has shown that tumour and treatment factors affect memory in survivors (Shortman et al., 2014; Robinson et al., 2013; Di Pinto et al., 2012, Riva et al. 2002), but subgroup analyses were not appropriate due to the modest sample size.

Another limitation was the validity of the Actigraphy data. Actigraphy has been found to be an objective measure of sleep (Sadeh & Acebo, 2002), but it has also been criticised for not reliably distinguishing still wakefulness and sleep (Sadeh and Acebo, 2002). Similar to the current study, previous research including adolescents reported low compliance in Actiwatch use (Acebo et al., 1999). Data from less than five nights has poor reliability (Acebo et al., 1999), suggesting some of the current data are unreliable. The sleep diaries were subjective in nature and often did not correspond to the data from the Actiwatches, it was unclear whether they had been filled in accurately and whether the sleep data is in fact valid. The results of the sleep data must therefore be interpreted with caution, making it difficult to draw robust conclusions about its association with memory. In future, creating a more simplistic diary and using memory aids, such as alarms, to remind participants to press the Actiwatch button may improve the accuracy of reporting. Including parent-reports to corroborate information may also improve the reliability of the sleep data.

A strength of the study is that it is the first to assess LTM after a delay longer than 30 minutes in PBT survivors. The current study followed the learning paradigm described by Davidson et al. (2007), however they excluded children unable to reach learning criterion

after ten consecutive learning trials. The current study did not exclude these participants because this would have removed data from the most impaired individuals and would not have represented the sample, reducing the generalisability of results.

The use of sibling and cousin controls minimised the environmental, parental and biological differences between groups. Paired analyses have more statistical power than independent-samples analyses (Lakens, 2013), somewhat improving the power of the study to detect differences. Groups were matched for age, IQ and socioeconomic status, controlling for potential effects of general cognitive ability and developmental differences between groups.

The study tested each hypotheses with more than one statistical test, increasing the likelihood of finding a significant result by chance. Therefore a Bonferroni correction was applied to significant results or non-significant trends. It has been argued that effect sizes calculated for paired samples are overestimations of true effect sizes (Dunlap, Cortina, Vaslow & Burke, 1996), therefore reported effect sizes should be interpreted with caution. Due to the modest sample size and the data not meeting parametric assumptions, the association between variables was assessed using correlational analyses, which only assesses for strength of association. Future research could recruit larger samples by using a multi-centre design, which would allow a regression model to be used to further explore how much variability in memory is accounted for by different factors.

Clinical and Educational Implications

The results provide evidence that some PBT survivors have significant impairments in verbal learning and long-term visual and verbal retention, and others do not, confirming

the heterogeneous nature of the paediatric brain tumour population. These results suggest that learning and memory should be monitored in this population, but emphasises the importance of individual management plans. Schools should be aware that learning and retention can be impaired in PBT survivors who return to school following treatment, and that these individuals may require additional support. Three participants showed significant difficulty learning novel verbal information, which would likely have a substantial negative affect on their ability to secure meaningful employment, corroborated by the fact that these participants were unemployed. Studies of adult survivors also show that brain tumour survivors have difficulty securing and maintaining jobs (De Boer, Verbeek & Van Dijk, 2006), further indicating the need for support in this area.

Intact memory in some PBT survivors may have been related to fewer risk factors; many PBT survivors only received surgery or focal radiotherapy, which are less damaging to the brain than whole-brain or cranio-spinal radiotherapy (Di Pinto et al., 2012). Although the study was small and future research is required to fully understand the relationship between different risk factors, the results from the current study are encouraging as they suggest not all PBT survivors experience memory difficulties post-treatment. This may give reassurance to young people and their families who post-diagnosis and may influence the choice of treatment in this group.

The results regarding the association between memory and anxiety, depression and sleep variables were inconclusive and an association may exist. Therefore the screening of PBT survivors for sleep and psychological difficulties should still occur. As the scales used in the current study are quick and easy to administer, they would be appropriate tools for this.

Conclusions

Results clearly demonstrated the variability in verbal learning and long-term verbal and visual retention in PBT survivors; some had significant impairments whilst others had none. This highlights the heterogeneity in the PBT population and the need for clinical monitoring to be conducted on a case-by-case basis. There was evidence of verbal learning impairment in PBT survivors relative to healthy controls, however, due to the modest sample size within the study, it was difficult to draw robust conclusions about the level of long-term memory impairment of PBT survivors as a group. As results suggest memory is not impaired in all PBT survivors, it may influence on clinical decisions regarding the choice of treatment for PBT. Within education and occupational settings, an awareness of the difficulties some of the young people may face could encourage services to give appropriate support to PBT survivors, to improve learning and secure meaningful employment. Results tentatively suggest memory consolidation may be impaired in PBT survivors, indicating the importance of longer delays to assess long-term memory in this population. This study will hopefully promote further high-quality, multi-centre research exploring the various risk and protective factors associated with memory in homogeneous PBT survivors.

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CHAPTER 3

Advanced Clinical Practice I

Reflective Account (Abstract)

Managing Client Disengagement

Frances Kessler Brown*

Submitted in partial fulfilment of the requirements for the degree of Doctorate in Clinical Psychology (D.Clin.Psy)

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Prepared in accordance with guidelines for submission: Neuropsychology (Appendix 1.1)

Abstract

A core competency for psychological therapists is the ability to engage clients using a range of skills to build and maintain active involvement of clients, communicate effectively with clients and respond to challenges in engagement (Core competence Framework for working in Child and Adolescent Mental Health Services; Roth, Calder and Pilling, 2011; 10 Essential Shared Capabilities for psychological therapies work, NHS Education for Scotland, 2011). Throughout the training programme, I have had a number of clients disengage with therapy and have found these unplanned endings difficult, affecting both my beliefs about myself and my confidence in my clinical skills. I have used the Kolb Experiential Learning Cycle (1984) to structure reflections about three clients whose disengagement I found particularly challenging and the Integrated Developmental Model of Supervision (Stoltenberg, McNeill, and Delworth, 1998) to contextualise each case in terms of my level of training and development. Not only have the experiences allowed me to develop clinically and learn how to better manage challenges in the future, but the reflective process facilitated my understanding and acceptance of myself and my limitations.

CHAPTER 4

Advanced Clinical Practice II

Reflective Account (Abstract)

Working in Multidisciplinary Teams

Frances Kessler Brown*

Submitted in partial fulfilment of the requirements for the degree of Doctorate in Clinical Psychology (D.Clin.Psy)

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Prepared in accordance with guidelines for submission: Neuropsychology (Appendix 1.1)

Abstract

New legislation and government drivers have had an impact on the way mental health services are run. As a result, a range of professionals work together in mental health teams to provide effective and efficient services. The British Psychological Society (2007) suggest clinical psychologists should be involved in delivering consultation and supervision to other team members, to ensure evidence-based psychological interventions are being delivered effectively, and in service development, by taking on leadership and managerial roles. Throughout my training, I have had a number of experiences that have made me reflect on my role and contribution to team functioning, from which I have learned a lot. I have used the Integrated Developmental Model of Supervision (Stoltenberg, McNeill, and Delworth, 1998) to contextualise the development of my awareness of multidisciplinary team functioning and my contribution to team working throughout the training. I used the Reflective Cycle (Gibbs, 1988) to guide and structure reflections about specific experiences, such as my involvement in team activities, contributing to team supervision and sharing personal reflections, and being part of challenging team experiences. Through these reflections, I have learned the importance of being an integrated member of a team as well as my role, such as encouraging team working and decision-making, and facilitating the resolution of difficult team dynamics by encouraging reflection in team supervision. The reflection has also developed my awareness of the challenges that I may face in the future and how I will manage them in a constructive way.

Appendix 1

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After the abstract, please supply three to five keywords.

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Nonstandard abbreviations should be introduced by placing the abbreviation in parentheses after the first occurrence of the term being abbreviated in both the abstract and the text. The metric system should be followed for all volumes, lengths, weights, and so on. Temperatures should be expressed in degrees Celsius (centigrade). Units should conform to the International System of Units (SI; see the *Publication Manual*).

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Whenever appropriate, statistical analyses should include effect sizes and confidence intervals and figures should include error bars. Authors are strongly encouraged to read the

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Appendix 1.2 SIGN Methodology Checklist for Cohort Studies

SIGN	**Methodology Checklist 3: Cohort studies**

Study identification (*Include author, title, year of publication, journal title, pages*)		
Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

SECTION 1: INTERNAL VALIDITY

In a well conducted cohort study:		***Does this study do it?***
[i]1.1	The study addresses an appropriate and clearly focused question.	Yes □ No □ Can't say
SELECTION OF SUBJECTS		
[ii]1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ Does not apply □
[iii]1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ No □ Does not apply □
[iv]1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Yes □ No □ Can't say □ Does not apply □
[v]1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	
[vi]1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ No □ Can't say □ Does not apply □

ASSESSMENT			
[vii]1.7	The outcomes are clearly defined.	Yes □ Can't say □	No □
[viii]1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	No □ Does not apply □
[iv]1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes □ Can't say □	No □ □
[x]1.10	The method of assessment of exposure is reliable.	Yes □ Can't say □	No □
[xi]1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes □ Can't say □	No □ Does not apply□
[xii]1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ Can't say □	No □ Does not apply □
CONFOUNDING			
[xiii]1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes □ Can't say □	No □
STATISTICAL ANALYSIS			
[xiv]1.14	Have confidence intervals been provided?	Yes □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
[xv]2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ Acceptable (+) □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes Can't say	No
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.		

Appendix 1.3 Summary of ratings for each item on SIGN Checklist.

Questions from the adapted checklist for appraising methodology	Conklin et al. (2012)	Garcia-Perez et al. (1994)	Law et al. (2011)	Mabbott et al. (2008)	Ozyurt et al. (2014)	Quintero-Gallego et al. (2006)	Redmond et al. (2013)	Riva et al. (2002)	Robinson et al. (2014)	Shortman et al. (2014)
1.1 The study addresses an appropriate and clearly focused question.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	N	Y	N	Y	Y	N	N	Y	Y	Y
1.3 The study indicates how many of the people asked to take part did so, in each of the groups being studied.	N	N	N	Y	N	N	N	Y	Y	Y
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account.	N	N	N	N	N	N	N	N	N	N
1.5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	NA	NA	NA	NA	NA	NA	Y	NA	Y	Y

	Conklin et al. (2012)	Garcia-Perez et al. (1994)	Law et al. (2011)	Mabbott et al. (2008)	Ozyurt et al. (2014)	Quintero-Gallego et al. (2006)	Redmond et al. (2013)	Riva et al. (2002)	Robinson et al. (2014)	Shortman et al. (2014)
1.6 Comparison is made between full participants and those lost to follow up.	NA	NA	NA	NA	NA	NA	N	NA	N	N
1.7 The outcomes are clearly defined.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
1.8 The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	N	N	N	N	N	N	N	N	N	N
1.9 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	N	N	N	N	N	N	N	N	N	N
1.10 The method of assess. of exposure is reliable.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
1.11 Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

	Conklin et al. (2012)	Garcia-Perez et al. (1994)	Law et al. (2011)	Mabbott et al. (2008)	Ozyurt et al. (2014)	Quintero-Gallego et al. (2006)	Redmond et al. (2013)	Riva et al. (2002)	Robinson et al. (2014)	Shortman et al. (2014)
1.12 Exposure level or prognostic factor is assessed more than once.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
1.13 The main potential confounders are identified and taken into account in the design and analysis.	N	Y	N	Y	Y	N	N	Y	Y	Y
1.14 Have confidence intervals been provided?	N	N	N	N	N	N	N	N	Y	N
2.1 How well was the study done to minimise the risk of bias or confounding?	+	++	+	+	++	+	+	++	++	++
2.2 Taking into account clinical considerations, your evaluation of the methodology used, statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Can't say	Y	Y	N	Y	Can't say	Can't say	Y	Y	N
2.3 Are the results of this study directly applicable to the patient group targeted in this guideline?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Appendix 2

Appendix 2.1 Major Research Project Proposal

Proposal for Memory After Tumour of the CNS in Childhood (MATCCh): Long-Term Memory Retention in Paediatric Brain Tumour Survivors

Abstract

Background

There is evidence that paediatric brain tumour survivors have impaired long-term memory (Benesch et al., 2009; Maddrey et al., 2005). Research has focussed on 30-minute memory retention, which may not be representative of everyday memory requirements. Anecdotal evidence from the literature suggests that brain tumour survivors have difficulties with memory retention and applying learned information (Waber et al., 2006; Ondrucht et al., 2011), which suggests that learned information is vulnerable to loss. Sleep difficulties, anxiety and depression are frequently reported by brain tumour survivors, and may be exacerbating memory deficits.

Aims

The primary aim is to explore whether young people (11-24 years) who have survived a brain tumour show impaired learning, recall and recognition of verbal and non-verbal information compared to controls, at 30 minute and one week delays. A secondary aim is to explore to what extent sleep, anxiety and depression account for memory differences between survivors and controls.

Methods

An experimental learning paradigm, in which participants learn verbal and nonverbal information until an 80 % criterion, will be adopted. A prospective, within and between-subjects design will be used to compare memory scores between brain tumour survivors

and healthy sibling controls, at two times points (30 minutes and 1 week). The extent to which Sleep Efficiency (measured by actigraphy), anxiety and depression (measured by self-report questionnaires) account for memory differences between the groups will also be analysed.

Applications

If there is evidence that brain tumour survivors have impaired long-term memory retention, it would support the use of memory-based interventions and additional school supports within this population. Results will build on existing knowledge of the psychological factors associated with neurocognitive functioning in this population.

Introduction

In the United Kingdom, 24.5 percent of all new cancer diagnoses in children below the age of 14 are due to central nervous system tumours (Stiller, 2007). The World Health Organisation Classification of Tumours of the Central Nervous System (Louis et al., 2007) classifies tumours based on their area and tissue of origin and grades tumour severity (Grades I to IV) based on the abnormality of cell growth. Higher grades suggest faster cell growth, worse prognosis and more intensive treatments. The most common diagnoses in young people are pilocytic astrocytoma, craniopharyngioma and medulloblastoma.

The main treatments for brain tumour include neurosurgical resection, followed by chemotherapy and/or radiotherapy treatments. Survival rates in young people with brain tumours have improved drastically over the past twenty years, but evidence suggests both tumour and treatment factors can lead to long-term neurological damage (Di Pinto et al., 2013). Tumours and surgical resection can damage healthy brain tissue, and chemotherapy and radiotherapy treatments can be neurotoxic to the brain (Turner et al., 2009). There is

evidence that chemotherapy and radiotherapy treatments damage the development of cortical and subcortical white matter in the brain, affecting neurocognitive function (Reddick et al., 2003). As full myelination is not complete until adulthood, children are particularly vulnerable to cognitive impairments if white matter is damaged or its growth is affected (Askins and Moore, 2008).

Neurocognitive consequences

The literature suggests children and young people who have been treated for a brain tumour experience a range of neurocognitive deficits, including overall cognitive ability, verbal memory and language (Robinson et al., 2010). Executive function, speed of processing and attention are also likely to be impaired following brain tumour (Gehrke et al., 2013), which control and moderate abilities in new learning and memory consolidation. In addition, children may miss years of school and ongoing interruptions during treatment which could further impact learning and memory.

Memory

The term memory is used to describe the process of encoding, consolidating and retrieving information and there is evidence that all three processes are impaired in paediatric brain tumour survivors (Waber et al., 2006 and Carpentieri et al., 2001). Research suggests paediatric brain tumour survivors have deficits in visual and verbal working memory (sometimes referred to as short-term memory) and long-term memory (LTM) compared to normative data and healthy controls (Bonner and Hardy, 2009; Maddrey et al., 2005), although there is some evidence that memory ability remains stable post-treatment (Di Pinto et al., 2012).

Standardised assessments measure LTM using 30 minute delayed recall tasks, which may not be representative of everyday memory requirements (Waber et al., 2006). Several studies include anecdotal evidence of participants reporting difficulties with everyday memory suggestive of consolidation and retention deficits (Carpentieri et al., 2011; Waber et al., 2006), and parents reporting their children having difficulty *applying* information they have learned (Ondrucht et al., 2011). Anecdotally, parents and teachers report that brain tumour survivors learn information to an adequate level, but retain less than expected compared to class peers the following week. This suggests new information that has been encoded to LTM is not retrieved effectively or it is vulnerable to loss over longer time periods in brain tumour survivors. As this would significantly impact learning, longer-term memory retention should be explored in this population.

No studies have been identified that assess long-term memory over 30 minutes in brain tumours survivors, but studies of different paediatric neurological populations have adopted learning paradigms to determine the proportion of information recalled and recognised after much longer delays (usually one week). Davidson et al. (2007) taught children with idiopathic generalised epilepsy and healthy controls verbal and non-verbal information until they reached a learning criterion, and assessed memory retention after 30 minutes and one week. Children with epilepsy recalled significantly less verbal information than controls after a week, suggesting 'accelerated forgetting', or that memory consolidation takes longer than 30 minutes. Similar evidence from adult epilepsy studies suggests it can be vulnerable to disruption for four weeks (Naryanan et al., 2012). It is unknown whether paediatric survivors of brain tumours are impaired in memory consolidation and retention over a week. If such impairments are found, it would support

the use of memory-based interventions and additional support in school, in order to improve academic, occupational and social functioning in this population.

Factors influencing memory and learning

Biological Factors

Tumour and treatment

Evidence for LTM deficits exists across a range of brain tumour diagnoses, although higher-grade tumours, medulloblastomas or ependymomas, are associated with significantly worse LTM outcomes than lower-grade ones, pylocytic astrocytomas (Benesch et al., 2009). There is evidence that memory is affected by tumour location; LTM retention was found to be significantly more impaired in supratentorial tumours (within the cerebrum) than infratentorial tumours (within the cerebellum; King et al., 2004). This difference was not sustained once verbal intellectual abilities and attention were controlled for, however (Micklewright et al., 2007), which suggests memory deficits are not location-specific. The combination of both chemotherapy and cranial radiotherapy during treatment are associated with poorer neurocognitive outcomes (De Ruiter et al., 2013). Younger age at treatment and longer time since treatment are also associated with poorer cognitive outcomes (Mulhern et al., 2005), possibly because younger children are at an earlier developmental stage, so have to acquire new skills within the context of the brain tumour and potential damage to the brain.

Psychological Factors

Sleep

Good sleep is crucial for memory consolidation (Maquet, 2001) but there is evidence that survivors of paediatric brain tumours experience sleep problems, including initiating and

maintaining sleep, hypersomnia and fatigue (Verberne et al., 2012). Impaired working memory was shown to be associated with poorer sleep quality and increased sleepiness in a sample of adult survivors of childhood cancer, after age, gender and the effects of treatment were controlled for (Clanton et al., 2011). Although no research into the association between sleep and memory retention in paediatric survivors was identified, sleep may exacerbate memory difficulties in this population, which would support the use of administering evidence-based sleep interventions to those that require it, in order to improve neurocognitive and academic outcomes. The extent to which sleep accounts for differences in memory scores between brain tumour survivors and controls will therefore be explored.

Depression and Anxiety

A review of the literature suggests depression and anxiety are associated with poor academic performance in children (Owens et al., 2012) and brain tumour survivors present with significantly higher levels of distress and depression than sibling controls (Zebrack et al., 2004). If anxiety and depression were found to account for some of the differences between memory between survivors and healthy young people, it would support the use of psychological interventions to improve anxiety and mood in order to increase learning and academic achievement.

Aims and hypotheses

Aims

1. Learning and Encoding

Explore whether children and young people who have survived a brain tumour show impaired learning of verbal and non-verbal information compared to healthy controls.

2. Recall and Recognition

   Explore whether recall and recognition of verbal and nonverbal information after a 30 minute delay are impaired in brain tumour survivors compared to healthy controls.

3. Memory Retention

   Explore whether recall and recognition of verbal and nonverbal information at one week delay are impaired in brain tumour survivors compared to healthy controls.

4. Explore the extent to which sleep efficiency accounts for differences between the memory in brain tumour survivors and healthy sibling controls.
5. Explore the extent to which anxiety and depression account for differences between the memory in brain tumour survivors and healthy sibling controls.

Hypotheses

6. Brain tumour survivors require significantly more trials to learn verbal and non-verbal information.
7. Brain tumour survivors have significantly lower recall after 30 minutes delay than healthy controls.
8. Brain tumour survivors have significantly lower recall at one week delay than healthy controls.
9. Sleep efficiency (measured by actigraphy) will account for some of the memory differences between brain tumour survivors and healthy controls.

10. Depression and anxiety scores will account for some of the memory differences between brain tumour survivors and healthy controls.

Plan of Investigation

Design

Experimental learning paradigm with a prospective, within and between-subjects design comparing 30 minute and 1 week delayed recall on a verbal and nonverbal task between brain tumour survivors and healthy age-matched sibling controls. There is evidence to suggest several factors impact on neurocognitive functioning in brain tumour survivors, such as age at diagnosis, severity of tumour, treatment received and location of tumour. Due to the size of the proposed study, these factors will not be controlled for, but, in line with previous research, tumour and treatment factors will be fully described. Recruitment will also be conducted in a systematic way, recruiting participants with one tumour diagnosis first, and then expanding to the other diagnoses if participants numbers are not met. The main tumour diagnoses that will be included will be Medulloblastoma, Pilocytic Astrocytoma and Craniopharyngioma.

Participants

Participants will include young people who have survived any type of brain tumour between the ages of 11, the age they enter secondary school, and 24, the age they receive clinical reviews until. The control group will consist of healthy siblings, cousins or best friends. Sumpter et al. (2013) chose sibling controls in recent sleep study, in order to match psychosocial, family and sleep environmental factors. If the brain tumour survivor is an only child or their sibling is much older/younger, relatives or best friends will be asked to participate as controls. They will be recruited via the brain tumour survivors or their

parents, who will gain their consent to pass on contact details to the researcher, who will contact them to organise participation.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for sample of children who have survived a brain tumour:

- Not undergoing chemotherapy or radiotherapy
- Over 6 months since chemotherapy or radiotherapy were completed
- Aged between 11 and 24 years
- Fluent in English in order to complete verbal memory assessments

Inclusion and exclusion criteria for healthy controls:

- No history of cancer
- No developmental disorders or disabilities eg: Autism Spectrum Disorder.
- No history of neurological diagnoses (including head injury, brain tumour, neurological infection).
- Not receiving treatment for a mental health disorder
- No admission to hospital in the past 6 months

Measures

Intellectual Functioning

Wechsler Abbreviated Scale of Intelligence- Second Edition (WASI-II; Wechsler, 2011)

Estimates full-scale IQ using Matrix Reasoning and Vocabulary Subtests. Standardised for 6-90 years.

Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Weschler, 2011).

Digit Span subtest as an estimate of working memory for participants under 16 years.

Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Weschler, 2011).

Digit Span subtest as an estimate of working memory for participants 16 years and over.

Assessment of Memory

Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996).

Measure of auditory verbal memory which includes a list of 15 words. Good sensitivity and normed for ages 7 to 89.

Rey Complex Figure Test (RCFT; Meyers &Meyers, 1996).

Measure of visuo-spatial memory in which participants have to remember a design. It is normed for ages 7-89 and been used in previous research with paediatric populations (Micklewright et al., 2007).

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983).

Although normed with an adult population, it has been validated in a sample of children aged between 12 and 17 by White et al. (1999). There was evidence to suggest the HADS has good test-retest reliability and can discriminate between adolescents with and without diagnoses of anxiety or depressive disorders.

Sleep

Actigraphy

This in an objective measure of activity during sleep, which correlates with sleep efficiency. It will be worn by participants on non-dominant wrists every night for one week between the first and second appointments.

Sleep Self-Report (SSR; Owens et al., 2000)

A retrospective, self-rated measure of sleep habits, problems falling asleep, sleep duration, night waking and daytime sleepiness. It includes 18 questions and shows good psychometric properties. It is validated for children between 7 and 12 years, however Sumpter et al. (2013) used this measure with adolescents over the age of 12 successfully.

Sleep Diary

Participants report when they go to bed, when the lights go off, when they fall asleep, when they rise and any daytime naps during the week of actigraphy.

Fatigue Scale-Adolescent (Hinds et al., 2007)

A 14 item self-report measure for fatigue for 13 to 18 year olds. Shows moderate to strong reliability and strong validity when compared to other instruments (Hinds et al., 2007).

Sample size analysis

In order to guide recruitment, an a priori sample size calculation was conducted based on the study by Narayanan et al. (2012). They found significant differences between 15 adults with epilepsy and 17 controls on their memory performance measured by the RAVLT at a 4 week delay (epilepsy group: M= 3.71 (SD= 2.92); control group: M= 6.47 (SD= 2.48)). Assuming alpha equals 0.05 and beta equals 0.80, a sample size of 17 in each group would be necessary to find a significant difference on the RAVLT at a 4 week delay. Considering Narayanan et al. (2012) used an adult population and a longer delay than the proposed study, a larger sample size of 20 in each group would be an appropriate target for recruitment.

Research and Recruitment Procedures

Approval from NHS Lanarkshire and Lothian R&D and NHS Ethics will be sought before recruitment is commenced. Children who have undergone treatment for a brain tumour in the Royal Hospital for Sick Children (RHSC) in Edinburgh and their families will be recruited. Information about these cases will be gathered through the Oncology service. The Oncology Research Nurse, Rachel McAndrew, involved in patient care at the RHSC in Edinburgh will recruit participants. She will send information to and invite young people and families to participate by post. Potential participants will telephone or email either Rachel McAndrew or the Principle Investigator, or send back a stamped addressed card indicating whether they consent to being contacted by the Principle Investigator. Families who consent, will be contacted by telephone at which time they will complete initial screening, be fully informed about the research and organise who the control will be (if it is a relative or best friend, the brain tumour survivor or their parents will be asked to recruit the control). Both the brain tumour survivors and their relative/best friend will then be invited to attend two data collection sessions (one week apart).

The initial session last 1 hour for each child and be conducted in an outpatient hospital setting. Where possible, it will coincide with participants' review appointments at hospital (every 3-12 months). Participants below the age of 16 and their parents will be asked to sign a consent form, and young people below 12 will be asked to sign an assent form. Participants will complete the HADS before being administered the two-subtest version of the WASI-II and the Digit Span subtest of the WISC-IV or WAIS-IV (depending on the participant's age). Participants will then be taught the RAVLT and RCFT. The number of trials required for them to reach learning criterion, and immediate and 30-minute delayed

recall and recognition will be measured. Participants (and parents if under 16 years) will be given information on Actigraphy and how to use the Actiwatches, which all participants will wear for one week. Sleep diaries will also be completed during the week. Families will then be invited to another follow-up session after one week which will last 30 minutes, either at the hospital or at the family's local health centre if they have difficulty travelling to Edinburgh. Parents/participants will return the Actiwatches and be asked to fill in the sleep and fatigue measures and be assessed on their retention of both memory tasks. The researcher will aim to collect data between October 2014 and May 2015 in order to attain the necessary sample size.

The researcher will also attend team meetings and present the research at the hospital to increase staff awareness of the study, and clinicians will discuss the research with patients within review sessions to aid recruitment. A poster will be on display in the waiting areas to encourage participation and provide information. Neuro-Oncology clinicians will be available to answer questions regarding the study.

Data Analysis

A repeated-measures Analysis of Variance (ANOVA) will be used to analyse the difference in memory retention between 30 minute and one week delays, and between brain tumour survivors and healthy sibling controls. Anxiety, depression and sleep scores will be used as covariates against memory between the two groups, and an ANCOVA will be used to analyse the extent to which the covariates account for memory differences between brain tumour survivors and controls.

Settings and Equipment

All testing will be done by the researcher either at the RHSC, the Western General Hospital or in local health centres throughout Scotland. The neurocognitive measures (WASI-II, WISC-IV, RAVLT and RCFT) and Actiwatches are available within from the University of Glasgow. All other measures are not copyrighted and available from the internet.

Financial Issues

The neurocognitive assessment measures (WASI-II, WISC-IV, WAIS-IV, RAVLT and RCFT) are copyrighted and therefore 50 score sheets will have to be purchased for the study; printing and mail costs are also required, all funded by the University of Glasgow. Travel expenses will be claimed back from NES through NHS Lanarkshire.

Health and Safety Issues

Researcher and Participant Safety Issues

If the researcher has to travel to different health centres independently, lone working policies for NHS Lothian will be followed and a mobile telephone and personal alarm will be carried at all times. The assessments are brief, standardised on large populations, regularly used with clinically impaired populations and generally well accepted by children and adults. If a participant is becomes fatigued or anxious, a break will be given and the participant will be provided with any appropriate support by the researcher (a Trainee Clinical Psychologist with significant experience in emotional distress and administering neuropsychological assessments). Participants will be reminded of their right to withdraw at any stage if it is felt appropriate.

Ethical Issues

Due to the vulnerable nature of the sample, written informed consent from young people and also their parents if they are below 16. If a participant is becomes fatigued or distressed, a break will be given and the participant will be provided with any appropriate support by the Principle Investigator (a Trainee Clinical Psychologist in the final year of training with significant clinical experience in administering neuropsychological assessments and in treating emotional disorders). If participants show elevated levels of anxiety or depression in their questionnaires, they will discussed with the Field Supervisor, Dr Ruth Sumpter, Clinical Psychologist in the Paediatric Psychology and Liaison Service at the Royal Hospital for Sick Children. Any appropriate onward referrals will be made to support or mental health services and a letter sent to their General Practitioner. All feedback about memory impairments will be given to participants in a sensitive way, to avoid them becoming upset.

Assessment sessions will be arranged on the same days as clinical reviews as far as possible, and second appointments will be offered locally to families who live far from the hospital, in order to minimise the family's travelling time and costs. Actiwatches must be worn every day and night within the week between the assessment sessions. They are well tolerated by children for week-long use and are similar to wearing a wrist watch. Participants will be given a report regarding their memory, sleep, anxiety and depression, and appropriate referrals will be discussed with Dr. Ruth Sumpter (Clinical Psychologist in Paediatric Psychology and Liaison Service). Participants will be given information about their right to withdraw at any stage without it affecting the care they receive. Ethical approval will be sought from NHS Lothian Ethics committee. Participants' General Practitioners will be sent a letter notifying them of their participation in the study.

Timetable

October 2014: Ethical approval

November 2014: Begin recruiting and data collection

May 2015: Finish data collection

Practical Applications

If the results suggest children who have survived a brain tumour have impaired retention of long-term memory, it would suggest that this population is vulnerable to academic and possibly social difficulties and would support the use of memory-based interventions and additional support in school within this population. It will also build on existing knowledge of the psychological factors associated with neurocognitive functioning in this population.

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Appendix 2.2 Letter of approval from West of Scotland Research Ethics Service

Letter Amended 27 October 2014

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 5
Ground Floor - Tennent Building
Western Infirmary
38 Church Street
Glasgow
G11 6NT

Date 10 October 2014

Direct line 0141 211 2102
E-mail WoSREC5@ggc.scot.nhs.uk

Mrs Frances Brown
c/o Rachel McAndrew, Oncology Research Nurse
Oncology/Haematology Department
Royal Hospital for Sick Children
Edinburgh
EH9 1LF

Dear Mrs Brown

Study title: **Memory After Tumours of the CNS in Childhood (MATCCh): Long-Term Memory Retention in Paediatric Brain Tumour Survivors**
REC reference: **14/WS/1091**
IRAS project ID: **159076**

Thank you for your email of 6 October 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 23 September 2014.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Participant consent form [Controls over 12]	1	02 October 2014
Participant consent form [Assent for controls under 12]	1	02 October 2014
Participant information sheet (PIS) [Parent]	7	02 October 2014
Participant information sheet (PIS) [Siblings]	4	02 October 2014
Participant information sheet (PIS) [Young Adult]	6	02 October 2014
Participant information sheet (PIS) [Young person]	6	02 October 2014
Research protocol or project proposal	2	02 October 2014

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster]	2	17 July 2014
GP/consultant information sheets or letters [Letter to GP]	2	17 July 2014
Instructions for use of medical device [Actiwatch Information Sheet]	2	11 August 2014
IRAS Checklist XML [Checklist_26082014]		26 August 2014
Letter from sponsor [Confirmation Letter from Sponsor]	1	12 August 2014
Letters of invitation to participant [Letter of Invitation to Parents]	5	17 July 2014
Letters of invitation to participant [Letter of Invitation to Participants who are over 16]	5	17 July 2014
Letters of invitation to participant [Reminder to Participants who are over 16]	2	17 July 2014
Letters of invitation to participant [Reminder to Parents]	2	17 July 2014
Other [Sleep Diary]	1	10 August 2014
Other [CV Rachel McAndrew]	1	09 July 2014
Participant consent form [Consent to be Contacted for Parents]	3	17 July 2014
Participant consent form [Consent to be Contacted Young Adult Participants]	3	17 July 2014
Participant consent form [Consent form for participants over 12]	5	17 July 2014
Participant consent form [Assent for controls under 12]	1	02 October 2014
Participant consent form [Parent Consent Form]	5	17 July 2014
Participant consent form [Controls over 12]	1	02 October 2014
Participant consent form [Assent form for participants under 12]	3	17 July 2014
Participant information sheet (PIS) [Young Adult]	6	02 October 2014
Participant information sheet (PIS) [Young person]	6	02 October 2014
Participant information sheet (PIS) [Siblings]	4	02 October 2014
Participant information sheet (PIS) [Parent]	7	02 October 2014
REC Application Form [REC_Form_26082014]		26 August 2014
Research protocol or project proposal	2	02 October 2014
Summary CV for Chief Investigator (CI) [CV Thomas McMillan]	1	08 August 2014
Summary CV for student [CV Frances Brown]	1	14 July 2014
Summary CV for supervisor (student research) [CV Thomas McMillan]	1	08 August 2014
Validated questionnaire [Sleep Self Report]		
Validated questionnaire [Fatigue Scale Adolescent]		
Validated questionnaire [Hospital Anxiety and Depression Scale]		

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

14/WS/1091	Please quote this number on all correspondence

Yours sincerely

[redacted]

Mrs Sharon Macgregor
REC Manager

Copy to: Professor Thomas McMillan, University of Glasgow
Mr Raymond Hamill, NHS Lanarkshire

Appendix 2.3 Letter of approval from NHS Lanarkshire Research and Development

Professor Thomas McMillan
Professor of Clinical Neuropsychology
University of Glasgow
Institute of Health and Wellbeing
Gartnavel Royal Hospital
1055 Great Western Road
GLASGOW
G12 0XH

R&D Department
Corporate Services Building
Monklands Hospital
Monkscourt Avenue
AIRDRIE
ML6 0JS

Date 6 November 2014
Enquiries to Elizabeth McGonigal,
R&D Facilitator
Direct Line 01236 712459
Email Elizabeth.mcgonigal@lanarkshire.scot.nhs.uk

Dear Professor McMillan,

Project title: Memory After Tumour of the CNS in Childhood (MATCCh): LongTerm Memory Retention in Paediatric Brain Tumour Survivors

R&D ID: L14060_EXT

I am writing to you as Chief Investigator of the above study, which received a favourable ethical opinionon 10 October 2014 and also received local R&D Management Approval from NHS Lothian

As you are aware, NHS Lanarkshire has agreed tobe the Sponsor for your study. On its behalf, the R&D Department has a number of responsibilities; these include ensuring that you understand your own role as Chief Investigator of this study. To help with this we have outlined the responsibilities of theChief Investigator in the attached document for you information.

I trust these conditions are acceptable to you.

Yours sincerely,

[redacted]

Raymond Hamill– Corporate R&DManager

c.c.: Thomas.mcmillan@glasgow.ac.uk

NAME	TITLE	CONTACT ADDRESS	ROLE
Frances Brown		Frances.brown4@nhs.net	Student

Enc 1 x Site File
1 x Responsibilities as Sponsor Notes

Responsibilities of Chief Investigator

Site File

As an aid to the conduct of your study we have provided a Site File that you may wish to use. As Sponsor of the study we are required to carry out audit of all project, and to conduct detailed monitoring visits for a proportion (approximately 10%) - The study Site File should help you ensure that you have the relevant documentation to assist in this process. If your project is selected for monitoring, we will contact you well in advance to arrange a suitable time.

Our responsibilities as Sponsor are defined within the Research Governance Framework for Health and Community Care. A summary of these, along with those of the Chief Investigator, is provided in the following table for your information.

RESPONSIBILITIES OF CHIEF INVESTIGATOR	NHSL RESPONSIBILITIES AS SPONSOR
Obtain relevant / appropriate Research Ethics opinion.	Assess adequateness of the independent, expert review.
Obtain NHSL Research Management Approval.	Ensure that the Chief/Principle Investigator has the necessary expertise, experience and education to conduct the study.
Ensure that the members of the research team have the necessary expertise, experience and education to perform their roles.	Provide a formal written agreement of sponsorship conditions, and notification of confirmation of the sponsorship role.
Ensure the necessary resources are available for the study.	Provide NHS indemnity to the Chief Investigator and research team.
Act in accordance with regulations set out by your professional body(s) and the conditions of your employment contract.	Provide mechanisms and processes to exploit any potential Intellectual Property.
Identify archiving arrangements at the study outset.	Project monitoring commensurate with risk.
Record and review significant developments that may affect the study, particularly those which put the safety of the individuals at risk or affect the scientific direction and report to the sponsor as appropriate.	Make available local, national and international guidelines, regulations and legislation governing research in the UK.
Record, report and review all untoward medical occurrence (adverse events or reactions) including classification of causality, seriousness and expectedness.	Provide ongoing advice and guidance to promote quality study management and conduct.
Notify R&D and appropriate REC of significant news, changes, amendments and modifications to the study.	Determine the acceptability of the archive arrangements proposed by the Chief Investigator and, if the archive facility becomes unsuitable, provide alternative arrangements.
Maintain a record of all incidents, providing an annual report to the sponsor.	
Inform REC and R&D of the study end.	

 Cont...

RESPONSIBILITIES OF CHIEF INVESTIGATOR	NHS L RESPONSIBILITIES AS SPONSOR
Maintain a log of archived documents and their location. Inform R&D of any publications arising from the study or dissemination of findings. Inform R&D of any potential Intellectual Property.	Determine length of archive/retention period for essential study documents and subsequent destruction date

Appendix 2.4 Letter of approval from NHS Lothian Research and Development

University Hospitals Division

NHS Lothian

Queen's Medical Research Institute
47 Little France Crescent, Edinburgh, EH16 4TJ

FM/LM/approval

04 November 2014

Research & Development
Room E1.12
Tel: 0131 242 3330

Email:
R&DOffice@nhslothian.scot.nhs.uk

Director: Professor David E Newby

Miss Frances Brown
c/o Rachel McAndrew
Oncology Research Nurse
Oncology Dept,
Royal Hospital for Sick Children
EDINBURGH
EH9 1LF

Dear Miss Brown

Lothian R&D Project No: 2014/0349

Title of Research: Memory After Tumours of the CNS in Childhood (MATCCh): LongTerm Memory Retention in Paediatric Brain Tumour Survivors

REC No: 14/WS/1091

Participant Information Sheet: Parent: Version 7 dated 2 October 2014; Siblings: Version 4 dated 2 October 2014; Young Adult (Over 16), Young Person (11-16): Version 6 dated 2 October 2014

Consent Form: Controls over 12: Version 1 dated 2 October 2014; Consent to be contacted (Parents), Consent to be contacted (Young person over 16),: Version 3 dated 17 July 2014; Consent form (Young person over 12), Parent Consent Form: Version 5, 17 July 2014
Assent Form: Assent for controls under 12: Version 1 dated 2 October 2014; Assent form (Young person under 12): Version 3 dated 17 July 2014

Protocol: Version 2 dated 2 October 2014

I am pleased to inform you that this study has been approved for NHS Lothian and you may proceed with your research, subject to the conditions below. This letter provides Site Specific approval for NHS Lothian.

We note that this project includes a researcher(s) who will require a Clinical Research Access letter from NHS Lothian. The individual(s) concerned <Frances Brown> should contact our offices with a view to applying for the necessary documentation. Please note all final paperwork will have to be signed and returned to our R&D offices before the researcher(s) can commence work on the project.

Please note that the NHS Lothian R&D Office must be informed if there are any changes to the study such as amendments to the protocol, recruitment, funding, personnel or resource input required of NHS Lothian.

Substantial amendments to the protocol will require approval from the ethics committee which approved your study and the MHRA where applicable.

Please inform this office when recruitment has closed and when the study has been completed.

I wish you every success with your study.

STA034

Yours sincerely

[redacted]

Ms Fiona McArdle
Deputy R&D Director

CC: Professor Thomas McMillan, Professor of Clinical Neuropsychology, University of Glasgow

Appendix 2.5 Sleep Diary

Sleep Diary

Name:

	Time you got in bed	Time you turned out the lights	Time when you fell asleep	Times you were awake during the night		Time your alarm went off	Time you got out of bed	Times you were asleep during the day (naps)	Notes (did you take the actiwatch off?)
Friday night					Saturday Morning				
Saturday Night					Sunday Morning				
Sunday Night					Monday Morning				
Monday Night					Tuesday Morning				
Tuesday Night					Wednesday Morning				
Wednesday Night					Thursday Morning				
Thursday Night					Friday Morning				

Appendix 2.6 Correspondence with Authors of Assessments

RE: Fatigue Scale-Adolescent

Hinds, Pamela [PSHinds@childrensnational.org]

You replied on 23/07/2015 10:31.

Sent: 12 August 2014 13:24

To: Frances Brown

Attachments: Adoles FATIGUE SCALE FOR 1~1.doc (57 KB) [Open as Web Page]; Adolescent Fatigue Scale--~1.doc (39 KB) [Open as Web Page]

Good morning, Frances!

I am so pleased for you to have full access for this use. I am attaching both the 24 hour and 7 day versions

My very best,
Pam

-----Original Message-----
From: Frances Brown [mailto:f.brown.1@research.gla.ac.uk]
Sent: Tuesday, August 12, 2014 3:56 AM
To: Hinds, Pamela
Subject: Fatigue Scale-Adolescent

Dear Dr. Hinds,

I am a Trainee Clinical Psychologist in Glasgow and am doing my thesis in memory and sleep in paediatric bra
much like to use your Fatigue Scale-Adolescent, but am unable to get access to it.
I wonder if you would be able to let me know how I can access this scale and whether I get permission to use

Best wishes, Frances Brown

Re: FW: Research using sleep self-report

Judith Owens [owensleep@gmail.com]

You replied on 23/07/2015 10:21.

Sent: 26 January 2015 20:08

To: Frances Brown

Attachments: SleepSelfReport(Child'sFor~1.doc (44 KB) [Open as Web Page]

Hi; the SSR is attached. There are no established norms for the instrument, but there have been a number of published studie

On Mon, Jan 26, 2015 at 6:15 AM, Frances Brown <f.brown.1@research.gla.ac.uk> wrote:

> Dear Dr. Owens,
>
> I am doing a piece of research for my Psychology doctoral thesis and I would like to use the Sleep Self-Report.
> I wanted to confirm I had permission to use this, however. Can I please check that the version I should use is that from your artice titled
> Is there an 18 question alternative?
> I also wondered if you also had any norms for the tool?
>
> Any help would be much appreciated.
>
> Best wishes, Frances Brown

--
Judith Owens MD MPH
Professor of Pediatrics
George Washington University School of Medicine and Health Sciences

Appendix 2.7 Further Analyses on Sleep and Psychological Factors

Table 1. Results for Sleep and Psychological Factors

Measure		**Tumour Group *Mean (SD) Median (IQR)**	**n**	**Control Group Mean (SD) Median (IQR)**	**n**	**n in analysis**
HADS	Depression	4 (1.25)	10	1 (3)	10	20
	Anxiety	8 (4.76)*	10	4 (2.26)*	10	20
AFS	Total Fatigue Score	27 (5.31)*	10	18.44 (2.83)*	9	18
SSR	Total Sleep Problems Score	33 (5)	10	30 (4.5)	9	18
Actigraphy	Sleep Efficiency (Percentage)	78.59 (7.57)	10	77.44 (6.84)	9	18
	Sleep Latency (Minutes)	15.85 (35.66)	10	21.0 (19.03)	9	18
	Percentage of Immobile Minutes	86.74 (5.71)	10	84.60 (8.00)	9	18
	Fragmentation Index	24.12 (17.81)	10	33.70 (20.05)	9	18

Key
AFS= Adolescent Fatigue Scale
HADS= Hospital Anxiety and Depression Scale
SD= Standard Deviation
SSR= Sleep Self-Report

There were no significant group differences in sleep efficiency (Wilcoxon Signed Rank Test (WSRT); W=16, Z= -0.770, p=0.441, effect size 0.18). Sleep latency (WSRT; W=23, Z=0.059, p=0.953, effect size

-0.01), percentage of immobile sleep (WSRT; W= 18.0, Z= -0.533, p= 0.594, effect size 0.13) and the Fragmentation Index (an indication of greater restlessness in sleep; WSRT; W=31, Z=1.007, p=0.314, effect size -0.24) did not differ significantly between groups. There was a trend for higher self-reported sleep problems in the tumour compared to the control group (WSRT; W=3.5, Z= -1.781, p=0.075; effect size 0.42). The tumour group reported total sleep disturbance scores that were more than four, and the control group reported mean scores more than three standard deviations above reported normative data in

healthy children (Owens, Maxim, Nobile, McGuinn & Msall, 2000). The tumour group reported significantly higher fatigue than the control group (paired samples t-test; t=4.272, df= 8, p=0.003, d=2.01). The mean score in the tumour group was below the cut-off of 31 suggested by Mandrell et al. (2011) to identify high fatigue in adolescents receiving treatment for cancer. As all participants in the current sample had completed treatment at least six months before assessment, lower scores would be expected.

Objective sleep quality did not differ significantly between groups and there was a non-significant trend for higher self-reported sleep disturbance in the tumour group. Both groups had mean sleep efficiency scores indicative of poor sleep quality (based on the 85 percent level used in the literature; Astill et al., 2013). Half of the control sample were not in full-time employment/education or were on leave during the week of assessment, which may have affected their lifestyle and daily routine, and as a result their sleep quality. The groups are comparable in terms of psychosocial background, socioeconomic status and numbers not in full-time employment or study, but other lifestyle factors that may affect sleep were not controlled for and may have influenced results. Actigraphy data must also be interpreted with caution as adherence to the wearing the Actiwatches and filling in the sleep diaries was generally poor within the sample, questioning the validity of the data.

Self-report of fatigue was significantly higher in survivors, suggesting they experience greater daytime fatigue and physical tiredness, and require more rest than matched controls. Survivors reported significantly higher depression and anxiety than controls, although mean scores were within the normal range, suggesting that overall, the sample did not have significant psychological difficulties associated with having a brain tumour. The sample comprised survivors who had completed treatment at least two years before, which

may have been sufficient time to process some of the emotional impact of cancer diagnosis and treatment.

There is evidence of greater self-reported fatigue and disorders of excessive somnolence and of initiating and maintaining sleep in paediatric brain tumour survivors relative to normed data (Verberne, Maurice-Stan, Grootenhuis, Van Santen & Schouten-Van Meeteren, 2012). Current findings were consistent with this. Both tumour and control groups reported greater sleep disturbance (on Sleep Self-Report) than data from previous research with healthy children (Owens, Maxim, Nobile, McGuinn & Msall, 2000; Hinds et al., 2007). Recent research using the Sleep Self-Report to assess sleep in adolescents with Inflammatory Bowel Disease (IBD) reported a mean total score of 36.4 (standard deviation 4.3) for the mild IBD group, and although values were not reported for healthy controls, mean scores did not differ significantly (Pirinen, Kolho, Simola, Ashorn &Aronen, 2010). This suggests that adolescents may report more disturbed sleep than younger children. Melatonin is a hormone that regulates sleep; during puberty there is a decrease in the amount produced by the body (Carskadon, Vieira & Acebo, 1993), which affects sleep cycles in adolescence. As the current sample comprised adolescents, the described changes during puberty may have contributed to the poor sleep quality reported by both the tumour and the control groups.

Previous studies assessing sleep with Actigraphy found no differences between paediatric brain tumour survivors and age-matched healthy controls (Greenefield, Constantini, Tauman & Sivan, 2011), consistent with current findings. Both groups had mean sleep efficiency values that indicate poor sleep if using the 85 percent cut-off. This may reflect general sleep difficulties in adolescence and suggests no further treatment or tumour

factors affect sleep quality. Recent research assessing sleep in healthy adolescents reported mean sleep efficiency values of 81 percent (Astill et al., 2013), suggesting previous cut-offs suggested for adults may not be valid with this age group, although further research is warranted.

The tumour group reported significantly higher anxiety (paired-samples t-test; t=2.362, df=9, p=0.042 d=1.07) and depression (WSRT; W=1, Z= -2.205, p=0.027, effect size 0.49) than the control group, although mean scores fell within the normal range for both scales.

Higher Digit Span scores were associated with better recall after 30 minutes on the RAVLT (rho=0.693, p=0.026), suggesting that verbal working memory and long-term memory encoding and/or recall are related. In terms of sleep and psychological factors, higher self-reports of depression were associated with higher self-reports of anxiety (rho= 0.656, p=0.039) and a higher percentage of time in 'immobile sleep' (rho= 0.646, p=0.044). Better sleep efficiency was related to a higher percentage of time in 'immobile sleep' (rho= 0.661, p=0.038), and lower values for the Fragmentation Index (lower values indicating less restlessness in sleep) were associated with both better sleep efficiency (rho= -0.736, p=0.015) and a higher percentage of time in 'immobile sleep' (rho= -0.839, p=0.002). The associations between psychological and sleep variables were expected; there is high co-morbidity between anxiety and depression in the paediatric population (Garber and Weersing, 2010) and depression is related to increased deep, immobile sleep in adolescents (Rao & Poland, 2008).