The Construct Validity of a Brief Neurocognitive Screening Battery in a Paediatric Oncology Population

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Abstract

Introduction: Central nervous system (CNS) tumours and leukaemia in children are associated with detrimental neurocognitive outcomes across a wide range of cognitive domains. It is recommended these children receive regular neuropsychological assessment to screen for deficits that may affect their long term outcomes. Barriers to this include time constraints and practice effects associated with traditional neuropsychological assessment. CogState is a brief computerised neuropsychological battery which assesses the neurocognitive domains at risk in this population. This study aimed to evaluate the construct validity of the battery in this population through convergent validity with standardised neuropsychological measures. A secondary aim was to investigate the relationship between time since diagnosis and performance on the CogState battery.

Method: A cross-sectional within subject correlation design was used to assess the construct validity in a sample of 37 children aged 8-16 years treated for leukaemia or CNS tumours. Partial correlation was used to assess the relationship between overall performance on the battery and time since diagnosis controlling for IQ and emotional distress.

Results: One subtest of the CogState battery correlated significantly with the standard measure assessing the same cognitive domain, showing a large effect size. Four further subtests showed small to medium correlations, however these were not significant and confidence intervals were large. One subtest showed no clear correlation. No significant correlation was found between overall performance on the battery and time since diagnosis, however there was also no relationship between time since diagnosis and IQ in this sample.

Conclusion: This study provides some evidence for the construct validity of sections of the CogState battery in a paediatric oncology population. Sample characteristics and methodological limitations which may have affected the scope and reliability of results are discussed. Further research in larger samples is needed before it can be recommended as a standard follow up assessment.

Table of Contents

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List of Appendices

List of Tables

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1 Introduction

1.1 Overview

In this chapter an overview of cancer in children will be presented, focused on the two most common forms, leukaemia and brain tumours (BT). The evidence for the neuropsychological effects most commonly seen in the literature following treatment for these conditions will be discussed along with the literature on the progression of these effects over time. This is followed by a description of the current recommendations for clinical monitoring. A detailed review of the available literature on screening measures and batteries employed in a paediatric oncology population, used either clinically or to facilitate large scale research, will be presented with a critical evaluation of their strengths and weaknesses. Finally the CogState measure will be introduced and its potential as a screening and monitoring measure in this population discussed, highlighting the need for the current research to investigate its construct validity in this setting. The chapter ends with the research questions and hypotheses for this study based on this literature.

1.2 Cancer in Children

1.2.1 Prevalence and prognosis.

Although cancer in children is much less common than in adults (Howlader et al., 2011) around 20,000 children are diagnosed with some form of cancer each year (Steen & Mirro, 2000) with 1,600 each year in UK (Scottish Intercollegiate Guidelines Network [SIGN], 2013). The two most common forms are leukaemias and central nervous system (CNS) tumours, which make up approximately half of

diagnoses (Stiller, 2007). It is estimated that there are 33,000 adult cancer survivors in the UK (SIGN, 2013).

Acute Lymphoblastic Leukaemia (ALL) is the most common form of leukaemia in children in Western Europe, accounting for around 80% of cases. It is followed by Acute Myeloid Leukaemia (AML) which accounts for almost 20% (Stiller, 2009). In total the age-standardised incidence of all types of leukaemia in the United Kingdom is 46.7 cases per million person-years in children aged 0-14 years (Stiller, 2009). Overall survival rates for children diagnosed with ALL have improved considerably in recent decades and recent estimates of five year survival rates are around 90% (Hunger et al., 2012).

There are a wide variety of different tumours affecting the brain in children which vary in location, histology and response to treatment. One of the most common is Medulloblastoma (MB), which makes up approximately 20% of all cases and is typically sited in the posterior fossa region of the brain. These tumours vary in histology and aggressiveness and those with the highest degree of dissemination are typically associated with the poorest prognosis (Ris & Abbey, 2010). Also common are low grade gliomas including Low grade Astrocytomas (LGA) and Oligodendrogliomas, both of which are histologically benign tumours. However they still require mainly surgical treatment and are associated with some late effects (Beebe et al., 2005; Steinlin et al., 2003). Low grade gliomas constitute around 25% of paediatric brain tumour diagnoses (Ris & Abbey, 2010). Overall recent estimates of five year survival are around 65% for children diagnosed with CNS tumours (Butler & Haser, 2006). However there is a large degree of variability depending on the tumour location, histology and relative risk (based on factors including age and degree of dissemination). For example, for standard risk MB five year progression

free survival rates of 81-86% have been reported (Packer et al., 2006) whereas the corresponding rate for children with high risk MB is 40-57% (Zeltzer et al., 1999). Similarly for low grade gliomas survival rates are estimated at around 90% (Pollack, 1999) whereas for high grade gliomas overall survival rate between 36-38% have been reported (Batra et al., 2014).

These survival rates, although varied, represent a large improvement over recent decades, largely due to improvements in treatment regimens. Therefore, increasing focus is now being placed on quality of life post treatment and the influence on late effects of both the disease and its treatment (Butler & Haser, 2006).

1.2.2 Treatment.

Treatment for ALL almost always consists of three phases, remission-induction therapy, intensification (consolidation) therapy and continuation (maintenance) treatment. Therapy directed at the CNS is started very early in the course of treatment and given for varying lengths of time dependent on the level of risk. Corticosteroids, including dexamethasone, are very commonly used during the initial remission-induction phase. During the intensification phase chemotherapeutic agents including high dose methotrexate (MTX) amongst others are given (Pui & Evans, 2006). The most common form for treatment for ALL is intravenous chemotherapy combined with intrathecal chemotherapy (ITC), which is chemotherapy injected within the cerebrospinal fluid (Butler & Haser, 2006). ITC is mainly a prophylactic treatment aimed at preventing relapse. Cranial radiation therapy (CRT) is also used when the risk of CNS relapse is high. Periods of 12 to 18 months of continuation therapy consisting of moderately intensive chemotherapy, including weekly MTX, are generally required (Pui & Evans, 2006).

Treatment for CNS tumours is more variable due to the wide variation in location and type of tumour. Treatment for MB generally involves a combination of surgery and targeted or cranospinal radiation therapy (RT) and is risk-adapted so that more toxic treatment is only given if required by high-risk disease. Surgical treatments aim for gross total resection of the tumour and this is often achieved through incision in the cerebellar vermis (Ris & Abbey, 2010). In general RT needs to be given to the entire neuroaxis (cranospinal RT) with a boost to the tumour site. Recent protocols include the use of conformal RT which delivers the radiation in small doses through multiple planes to reduce the dose given to surrounding healthy tissue. The dose of RT is measured in grays (Gy) or centigrays (cGy). Standard therapy would be 5,400 cGy to the tumour site and 3,600 to the neuroaxis (Ris & Abbey, 2010) although more recently reduced doses have been trialled in an effort to reduce neurocognitive effects (Mulhern et al., 2005). Proton therapy is another recent advance in RT where a proton beam rather than photon beam, as in standard RT, is used. Protons have advantages over photons as they deposit most of their dose at the end of their range with almost no dose travelling further than this into healthy tissue meaning the treatment can be more accurately targeted (Schulz-Ertner & Tsujii, 2007). This has been shown to greatly reduce the radiation received by surrounding healthy tissue (Fossati, Ricardi, & Orecchia, 2009; Stokkevag et al., 2014). However, this treatment is not currently available in the UK or recommended by the NHS for MB treatment abroad (NHS National Specialist Commissioning Team, 2011). Chemotherapy is often given as an adjunctive therapy. For LGA surgery is the most common treatment to achieve gross total resection of the tumour. Focal RT is sometimes given following subtotal resection but chemotherapy is not used in these cases (Ris & Abbey, 2010).

Of these treatments cranospinal RT is considered the most toxic, targeted RT at intermediate toxicity and surgery and chemotherapy the least toxic with regard to long term neuro-behavioural effects (Ris & Abbey, 2010).

1.3 Neurocognitive Late Effects

It has been reported that between 40-100% of brain tumour survivors will experience some neurocognitive late effects (Glauser & Packer, 1991) with figures of between 40% and 70% reported for ALL survivors (Ashford et al., 2010; Kunin-Batson, Kadan-Lottick, & Neglia, 2014; Moleski, 2000). Neurocognitive late effects are defined as "problems with thinking, learning, and remembering among survivors of childhood cancer" (Mulhern and Palmer, 2003, p. 117) with late effects more generally meaning "long term or remote sequelae of cancer and its treatments" (Ris and Abbey, 2010, p. 92).

1.3.1 Demographic factors affecting neurocognitive outcome.

Younger age at diagnosis and treatment has been found to be associated with poorer outcome, with the risk being particularly high for those under three years old (Caron et al., 2009; Ribi et al., 2005) indicating that the degree of maturation of the brain may mediate the risk associated with treatment. A reduction in the volume of normal-appearing white matter (NAWM) both through loss and deficient development, potentially connected to increased oxidative stress, has been suggested as a mechanism for this (Caron et al., 2009; Mulhern et al., 2001).

Several studies have also shown a gender variation in responses to treatment with girls being most at risk (e.g. (Christie, Leiper, Chessells, & Vargha-Khadem, 1995; Peterson et al., 2008; Waber, Tarbell, Kahn, Gelber, & Sallan, 1992) although the

opposite pattern has also been observed (Kahalley et al., 2013). While the mechanism for this is unclear, recent animal studies have shown that irradiation in young mice effects the development of white matter significantly more in females than males (Roughton, Bostrom, Kalm, & Blomgren, 2013).

Research on the impact of socioeconomic status on neurocognitive outcome is mixed (e.g. (Butler et al., 2013; Kaleita, Reaman, MacLean, Sather, & Whitt, 1999; Rubenstein, Varni, & Katz, 1990)), however, it is generally accepted that sociodemographic factors can have a large impact on IQ and academic functioning (Vanderploeg, 1998). Mechanisms for this may include the value placed on academic achievement in the home and school environment and the resources available to support development (Nathan et al., 2007).

1.3.2 Treatment factors affecting neurocognitive outcome.

Of all the approaches used in treatment of paediatric brain tumours and leukaemia CRT has consistently been shown to have the strongest association with the poorest neurocognitive outcomes (Anderson, Godber, Smibert, & Ekert, 1997; Butler, Hill, Steinherz, Meyers, & Finlay, 1994; Copeland et al., 1988; Mulhern et al., 1999; Schatz, Kramer, Ablin, & Matthay, 2004). Whilst early whole brain irradiation protocols have largely been discontinued due to the evidence of their impact on cognitive functioning; reduced dose radiation, targeted radiation and conformal radiation have still been shown to have cognitive late effects (Kiehna, Mulhern, Li, Xiong, & Merchant, 2006; Rubenstein et al., 1990) although they appear to be reduced (Mulhern et al., 1998). There is no current published evidence on the neurocognitive outcome following proton therapy, however clinical trial data in this area is being collected (Tarbell, 2005) and it has been modelled that cognitive

late effects (as represented by IQ) should be reduced (Merchant, 2013) due to the reduced radiation received by surrounding tissue with this technique, particularly in children who are younger at time of treatment.

However it can be difficult to study the effects of CRT in isolation as patients will often also be receiving chemotherapy. For example a study into different strength CRT protocols found no significant differences between a 24 Gy, 18 Gy and no CRT group with around 22-30% of children in all groups showing a significant decline in IQ. One possible explanation for this was the increased dose of intrathecal and intravenous MTX that the children on the lower or no CRT groups were receiving to compensate (Mulhern, Fairclough, & Ochs, 1991). This study highlights both the methodological challenges in pinpointing the separate effects of treatments but also the potential neuro-toxicity of chemotherapy.

The literature on the effect of chemotherapy on the developing nervous system is more varied than for CRT however there are several studies of children treated with chemotherapy alone, particularly intrathecal MTX, where declines in aspects of neurocognitive functioning have been found (Brown et al., 1998; Espy et al., 2001). A recent meta-analysis of thirteen studies of children with ALL treated with chemotherapy found significant mean effect sizes for deficits in a wide range of cognitive abilities including attention, processing speed, executive functioning and verbal memory although there was a significant level of variability in the results reflecting the varied measures and results among the studies reviewed (Peterson et al., 2008). In addition several studies have found a synergistic detrimental effect of ITC when given in combination with CRT (Riva et al., 2002; Waber et al., 1995). Recent studies are also finding subtle deficits following systemic MTX, previously thought to be relatively benign, especially where certain genetic predispositions are

present (Reddick & Conklin, 2010). Corticosteroids have also been shown to be associated with both cognitive and neurobehavioral effects both during active treatment (Mrakotsky et al., 2011) and at five years post diagnosis (Waber et al., 2013), although the nature of these deficits appears to be more subtle than other forms of treatment.

Surgery alone, without further CNS directed therapy has been described as the least toxic treatment modality (Ris & Abbey, 2010) however a number of studies have shown it to be associated with deficits (e.g. Carpentieri et al., 2003). Two small studies of children with posterior fossa tumours treated with surgery alone still showed impairments in the patients on measures of motor speed, attention, executive functions, visuo-spatial function, and expressive language when compared to standard norms (Levisohn, Cronin-Golomb, & Schmahmann, 2000; Rønning, Sundet, Due-Tønnessen, Lundar, & Helseth, 2005).

In summary, whilst protocols of treatment for childhood brain tumours and leukaemia are often multimodal and it can be difficult to pick apart the impact of the individual treatment components and the disease itself, there is evidence within the literature of neurocognitive deficits following all forms of commonly used treatment. The nature of these deficits does appear to vary in type and severity but based on the current literature children treated with any of the currently used CNS directed protocols should be considered to be at risk of some neurocognitive late effects from their treatment.

1.4 Cognitive Domains Most Commonly Affected

Early studies into cognitive late effects focused exclusively on deficits in intelligence and academic attainment (e.g. (Fletcher & Copeland, 1988)) and these

areas, particularly IQ, continue to be reported on in most outcome research. Peterson and colleagues' (2008) meta-analysis of outcome studies on ALL finds a highly significant weighted mean effect size of 0.76 (95% CI: 0.42-1.12) for deficits in full scale IQ across seven studies. Similarly for brain tumour survivors a meta-analysis of 32 studies including 1096 participants reported a weighted Hedges g effect size of -0.83 (95% CI: -0.65—1.00) (Robinson et al., 2010). However, some studies which report on IQ and broader neurocognitive abilities have shown that in some cases total IQ can be within the normal range even though specific deficits in areas such as immediate memory and processing speed are present (Anderson et al., 1997).

Several more specific areas of neuropsychological functioning have now been investigated in addition to IQ and academic achievement. Recent studies have suggested that primary deficits in the core processes of attention and concentration, working memory and processing speed may underlie academic problems and more general intellectual deficits (Campbell et al., 2007; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Schatz et al., 2004). Aspects of these processes have been conceptualised as part of the executive functions (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Mulhern & Palmer, 2003) with additional difficulties such as cognitive flexibility, goal setting, planning and organisation of behaviour also included in this term. In addition to the above difficulties deficits have also frequently been reported in visual perceptual and psychomotor abilities (Butler & Haser, 2006; Nathan et al., 2007). All of these areas are most strongly associated with the non-dominant hemisphere, with language related deficits less common apart from in children treated at a very young age (Butler et al., 2013). This may be understood as a lateralized dysfunction, however, this pattern of discrepancy is a common finding in children and from a developmental perspective may actually be

better interpreted as the developing brain compensating to preserve verbal over non-verbal abilities (Baron, 2004). Such neuroplasticity has been reported in studies of unilateral lesions in children which indicate that if the area of the cortex traditionally responsible for language is damaged this function is reorganised and taken on by areas which would typically be responsible for visuo-spatial skills to the detriment of the later (Goodman & Yude, 1996; Vargha-Khadem, Isaacs, & Muter, 1994). A consequence of this plasticity in brain development in children can be "sleeper" effects where late emerging abilities such as executive functioning are subtly compromised by much earlier insult and subsequent reorganisation (Warner-Rogers, 2013), although these effects may also in part reflect deficits in later emerging abilities becoming more apparent as the brain develops. Such late emerging effects are consistent with the pattern of late effects seen in this population where greater deficits may be seen several years after treatment in areas such as executive functioning (e.g. Copeland, Moore, Francis, Jaffe, & Culbert, 1996).

Each of the cognitive constructs mentioned above will now be considered in turn beginning with Attention.

1.4.1 Attention.

Attention is not a unitary construct but rather a collection of inter-related functions. Several models of attention have been proposed, each subdividing attention into multiple component processes. Posner and Peterson (1990) propose three inter-related systems; orienting, mediated by posterior brain regions including the posterior parietal lobe and responsible for directing spatial attention; selection, related to the anterior cingulate and responsible for conscious target selection; and alerting or sustained attention which has been hypothesized to be linked to right

anterior prefrontal regions and represents being able to sustain continued responding over time in the absence of engaging stimuli. Preliminary support for this model has been reported (Swanson et al., 1998) however other authors report a different neuroanatomical division. Jain, Brouwers, Okcu, Cirino, and Krull (2009) describe three overlapping attentional systems with different neural substrates; an anterior attentional system which mediates the ability to shift attention along with other functions related to executive control; a posterior attention system particularly involved in filtering and focusing on incoming information and a subcortical information system involved in the maintenance of attention over time. They do also acknowledge the importance of executive functioning skills in the maintenance of attention highlighting that the three systems do not operate independently from each other. The importance of anterior brain regions, particularly in attentional control systems is supported by neuroimaging studies (D'Esposito et al., 1995). Clinically the subdomains of selective or focused attention, divided attention, sustained attention or vigilance and alternating attention or attentional control are most commonly referred to (Baron, 2004), although there is some overlap with models of executive functioning which would typically include the concept of attentional control. Attentional abilities develop gradually over childhood and into adolescence with visual selective attention developing earliest and being established around 5-6 years old, focused attention developed at around 7 years and sustained attention continuing to develop into adolescence (Baron, 2004).

Within the literature on paediatric oncology neurocognitive late effects there is strong evidence for deficits in attention. Robinson et al. (2010) performed a meta-analysis on studies of brain tumour survivors and from the nine studies which included at least one measure of attention (n=226) they found a large effect size of

g=-1.22 for attention deficits. In a similar review for ALL survivors {Campbell, 2007 #130} a medium effect size of g=-0.57 was calculated from 15 studies (n not reported). However, due to the varied methodologies of the studies included in these reviews it is not possible to ascertain the specific aspects of attention which are most at risk. In studies which do report more specific assessments, deficits in focused attention and sustained attention have been most consistently reported (Dennis, Hetherington, & Spiegler, 1998; Mulhern et al., 2001; Reddick et al., 2003).

Jain et al. (2009) studied the relative impact on the anterior (attention shifting), posterior (focused attention) and subcortical (sustained attention) attention systems in a large sample of 103 long term ALL survivors and found that deficits were mediated by both gender and intensity of treatment; with higher treatment intensity related to significantly poorer sustained attention and girls performing more poorly than boys in this area. Significant difficulties in attention shifting were also seen in the girls. This pattern of sustained attention and attention shifting being most at risk replicates a pattern seen in other studies of ALL survivors treated later in childhood (Lockwood, Bell, & Colegrove, 1999).

Several studies have suggested that the volume and integrity of white-matter in the brain is related to attentional performance (Reddick et al., 2006; Reddick et al., 2003). For example Reddick et al. (2006) investigated the relationship between attention and white-matter volume in children treated for ALL with either chemotherapy alone or chemotherapy and CRT. They found significant deficits in measures of attention on the Conners Continuous Performance Task (Conners, 1992) which were significantly correlated with reduced volumes of white-matter.

The area of memory and learning will be considered in the next section.

1.4.2 Memory and learning.

Memory is a highly faceted construct with numerous classifications and explanatory models. The basic processes of memory are the encoding, storage (consolidation) and retrieval (recall or recognition) of information. Learning describes the acquisition of knowledge via this system. Types of memory can be defined in a number of ways (Lezak, Howieson, & Loring, 2004). The basic distinction of explicit or declarative memory and implicit or nondeclarative memory is agreed on by most theorists (Wright & Limond, 2004). Explicit memories, i.e. memories of facts and events of which one is explicitly aware, are most often assessed clinically. They are held in the working memory system, for short term storage and manipulation of information, and may then be encoded into long term memory. The most influential model of working memory was put forward by Baddeley and Hitch (1974) and proposes that it is made up of specialised 'buffer' systems for visuospatial or phonological information (short term or immediate memory) which are controlled by a 'central executive'. These distinctions are well supported by a wide range of data from experimental studies on adults, neuropsychological studies and brain imaging studies (Gathercole, 1998). Working memory is often included as an aspect of executive function, although the immediate memory aspect of it is also heavily dependent on attention (Lezak et al., 2004). Long term memory describes the storage and retrieval of information over longer periods of time. It can be further divided into memory for events (episodic memory) and facts (sematic memory). Types of memory can also be defined by the modality of the information to be remembered i.e. visual or verbal. Clinically memory assessments typically distinguish immediate and delayed memory, working memory, visual and verbal memory, recognition and recall, and learning although there is inconsistency

across measures (Baron, 2004). Working memory abilities develop qualitatively in the first seven years of life with evidence that rehearsal does not form part of the phonological loop until this age (Gathercole, 1998). Quantitative improvement in memory continues into early adolescence, for example memory span (the number of unrelated items that can be held in short term memory) has been shown to increase from between 2-3 items at age four to around six items at age twelve (Gathercole, 1998).

Several areas of the brain are known to be vital for memory function including the hippocampus and the medial temporal lobe (Lezak et al., 2004). The role of connections between these areas and areas of the frontal lobes, including the orbitofrontal/ventromedial prefrontal cortex in the Papez circuit, in memory processes are also being increasingly understood (Simons & Spiers, 2003). This highlights that memory function involves several distributed processes and can be impacted on by diffuse axonal injury as well as localised lesions. The role of the cerebellum in working memory, through its interactions with the frontal cortex via the cerebello-thalamo-cerebral pathways (Salmi et al., 2009), is becoming increasingly apparent.

Within the paediatric oncology literature memory deficits are frequently reported for both BT and ALL survivors, although the aspect of memory studied is variable and results are not fully consistent. In their meta-analysis of studies looking at BT patients Robinson et al. (2010) compiled results on verbal memory, visual memory and working memory (although this was placed in the category of executive functioning in this review) however enough data to calculate a weighted effect size was only available for the verbal memory category. In this area a large mean effect of g=-1.14 was found indicating significant deficits although there was significant

heterogeneity in effect sizes across the nine studies indicating that moderating variables such as treatment dose may influence the amount of deficit seen. This amount of variability in the results between studies is not unexpected given the heterogeneity of samples included in the review. In the equivalent meta-analysis for ALL patients (Campbell et al., 2007) verbal memory was found to have a small mean effect size of g=-0.39 and visual memory a medium effect size of g=-0.62. Working memory was not considered in this analysis. After accounting for CRT which consistently leads to worse outcomes in this group, these results were not significantly heterogeneous suggesting that this is a robust and generalizable finding across the studies.

Individual studies which have looked specifically at working memory have demonstrated impairments in this area and have begun to investigate the biological basis for this. Conklin et al. (2013) have found that groups of brain tumour survivors perform significantly worse on two non-standardized computerised measures of working memory (verbal and visual) than sibling controls or solid tumour controls. Howarth et al. (2014) used the same tasks to investigate the role of genetic polymorphisms in the COMT gene, involved in dopamine levels in the prefrontal cortex, in performance. Their results suggest a potential role in verbal but not visual working memory however the direction of the result was inconsistent with the wider COMT literature and needs further investigation. Robinson et al. (2010) investigated the neural substrates of working memory in a small sample of ALL survivors using functional neuroimaging. They found a trend for ALL survivors to perform less accurately than controls on an n-back task as difficulty increased which was associated with greater activation of the dorsolateral prefontal cortex and anterior

cingulate cortex than controls, suggesting that greater levels of energy and effort is required in the survivor group to complete the same task.

The next cognitive construct to be reviewed will be executive functioning.

1.4.3 Executive function.

Executive function is an "umbrella term" for high-level cognitive functions required to identify, work towards and achieve personal goals and to modify actions in relation to those goals (Burgess & Simons, 2005). Processes associated with executive function by theorists include anticipation, goal selection, planning, initiation of activity, self-regulation, mental flexibility, deployment of attention, and utilization of feedback (Anderson et al., 2002). Several models of executive function have been proposed to account for how these processes interact including the Supervisory Attentional System (Norman & Shallice, 1986) and Anderson's developmental model (Anderson et al., 2002) derived empirically from factor analysis of outcome parameters of executive function test batteries. This model highlights the role of attentional control over information processing, cognitive flexibility and goal setting abilities.

Executive function development begins in early childhood with selective attention skills starting in the first year followed by information processing around the second, cognitive flexibility around the third and goal setting in the fourth year (Anderson et al., 2002; Garon, Bryson, & Smith, 2008). There is a critical period for development between 7 and 9 years with skills rapidly improving during this time period. In contrast between the ages of 11 to 17 years old the developmental trajectory is comparatively flat across all domains (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001) although some development continues into young

adulthood, (Anderson et al., 2002) making it one of the last cognitive skills to reach maturity. This development follows the pattern of progressive neuronal myelination in the brain (Barnea-Goraly et al., 2005) a process which is disrupted by CNS directed therapies.

Neuropsychological case studies (e.g. (Stuss & Benson, 1986)), imaging studies (Jurado & Rosselli, 2007) and examination of neural architecture and connectivity (Royall et al., 2007) support the role of the prefrontal cortex in executive function. The circuitry involves dispersed regions of cortex and sub-cortical structures meaning damage to these areas, or circuits in the form of diffuse white matter damage, can produce deficits in executive function without direct damage to the prefrontal cortex (Stuss & Levine, 2002; Vaquero, Gomez, Quintero, Gonzalez-Rosa, & Marquez, 2008).

The literature on executive function deficits as a late effect of treatment for childhood brain tumour or leukaemia is variable due to methodological differences and small sample sizes. However there is strong evidence that a substantial subset of children experience difficulties in this area following both brain tumours of all diagnoses and leukaemia. A meta-analysis of 15 studies including a measure of executive function (five different measures were reported measuring varied areas of executive function) in children treated for ALL found a small to moderate effect size of -0.46 for deficits in this area (Campbell et al., 2007). The most consistent evidence is for processes associated with cognitive flexibility (Riva et al., 2002; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004) although deficits in all theorised aspects of executive function have been observed (Wolfe, Madan-Swain, & Kana, 2012). Younger age at treatment appears to be a particular risk factor for later executive function deficits (Campbell et al., 2009; Riva et al., 2002) consistent with a

developmental model that suggests early CNS insult would interrupt the normal development of these processes.

In the next section the construct of processing speed will be reviewed.

1.4.4 Processing speed.

Processing speed is a core cognitive function which describes the ease and speed with which an individual completes cognitive operations (Kahalley et al., 2013), registering and integrating information across multiple distributed brain networks (Turken et al., 2008). Processing speed has been described as a key cognitive resource that underlies ability in a wide range of cognitive domains and measures of processing speed correlate strongly with other general measures of cognitive ability (Li et al., 2004). Within the literature on the effect of CRT on IQ there is evidence to support a mediating role for processing speed abilities in understanding the impact of CRT on working memory, which then subsequently mediates the relationship of CRT and IQ (Schatz, Kramer, Ablin, & Matthay, 2000). This supports the fundamental role of processing speed in higher order functions. Processing Speed develops throughout childhood and adolescence following an exponential function with large increases in ability during younger childhood becoming smaller with age (Kail, 1991).

Processing speed is a widely distributed function associated with the integrity of white matter tracts within the whole brain, particularly with superior longitudinal fasciculus which sub-serves fronto-parietal integration (Turken et al., 2008). Evidence from a neuroimaging study in children treated for brain tumours and ALL found decreased levels of axonal integrity and myelination in patients compared to controls in a number of areas including the body of the corpus callosum and the right

inferior fronto-occipital fasciliculus which was correlated with measures of speed of processing (Aukema et al., 2009) providing further evidence of the importance of white matter tracts in this area.

Processing speed deficits are commonly reported in the literature on neurocognitive late effects in a paediatric oncology population (Nathan et al., 2007) and are particularly highly correlated with CRT (Mabbott et al., 2008; Schatz et al., 2000). A meta-analysis of eleven studies of children treated for ALL found a medium effect size of g=-0.52 for deficits in information processing (Campbell et al., 2007). Deficits in this area have been found to be significant even when estimates of general ability are within the normal range (Kahalley et al., 2013) and other cognitive processes such as attention and working memory are largely intact (Mabbott et al., 2008). As such they are likely to be missed by more general batteries which do not investigate this area specifically.

The final area of neurocognitive processing commonly affected in this population, visual perceptual and psychomotor abilities, will be considered in the next section.

1.4.5 Visual perceptual and psychomotor abilities.

Visuospatial, visuoperceptual and visuomotor abilities relate the integration and interpretation of visual information and the translation of this into a motor response. These nonverbal abilities are an integral part of all commonly used general intelligence measures (Baron, 2004) and develop rapidly during the first two years of life but continue to be refined over the first decade (Johnson, 2005).

The role of the primary visual cortex, the posterior parietal cortex and inferior temporal cortex in the dorsal processing stream and ventral processing stream

respectively is well defined, as are connections to the primary motor cortex (Johnson, 2005). More recently the role of the cerebellum in visuomotor processing has been investigated (Van Braeckel & Taylor, 2013).

Within the paediatric oncology literature the relatively greater deficits commonly seen on measures of performance IQ relative to verbal IQ can be interpreted as being reflective of visual perceptual difficulties (Nathan et al., 2007). The strongest evidence of visuoperceptual, visuospatial and visuomotor deficits is in children treated for BT particularly those in the posterior fossa. A meta-analysis of children treated for all types of BT (Robinson et al., 2010) reported large effect sizes for deficits in both psychomotor (g=-1.43) and visual perceptual skill (g=-1.14). Levisohn and colleagues (2000) studied 19 children with posterior fossa tumours treated only with surgery and found deficits in visual spatial function in 7 of these, and marked impairment in fine motor functioning in 14. Although this is a small study, the fact that the participants were assessed following surgery only highlights the role of the cerebellum in these functions as any treatment related damage would have been specific to this area rather than the more defuse impacts of both RT and chemotherapy. However, damage to the cerebellum is not limited to those with tumours in this area. Horska et al. (2010) found impaired performance on visual-spatial and fine motor tasks in ten children with a variety of tumour locations and one with ALL treated with CRT, which was correlated with cerebellar vermis volume. A meta-analysis of studies of children treated for ALL found a small but significant effect size (g=-0.34) for psychomotor skills deficits (based on 14 studies) and a medium effect size (g=-0.57) for visuospatial skill deficit (Campbell et al., 2007). More broadly Dockstader et al. (2013) have shown that slowed activation of both visual and motor cortices, along with atypical neuronal patterns reflective of

increased top down control, is associated with poorer performance on a visual-motor reaction time task in children treated with CRT for posterior fossa tumours relative to controls. They relate their findings to slower information processing speed in general in these children which they report indicates these cognitive functions are interdependent.

1.5 Change in Neurocognitive Effects Over Time

Within the field of paediatric oncology it has been commented recently that there is a "striking dearth of longitudinal data which track and characterise the evolution of neurocognitive and behavioural functioning that may unfold during and after treatment" (Noll et al., 2013, p. 1049). However, the longitudinal studies that have been done suggest that there is a decline in abilities relative to peers over time. The largest studies have been done on children treated with radiotherapy and chemotherapy for MB and are limited to assessment of IQ and academic functioning. Ris and colleagues have studied two samples of this type (2001; 2013). In their first study 43 children completed between two and five assessments up to four years post RT (although due to large drop-out rates only data up to three years is considered here) and an average drop in Full Scale IQ of 4.3 points per year was found. More recently they reported on a larger sample of 110 children following a similar treatment protocol who were assessed up to six years after RT, although almost half of this sample completed only baseline assessment and therefore did not contribute to the full model. In this study there was an average drop in Full Scale IQ of 1.9 points per year. This sample were significantly older than the previous one at time of treatment which may account for some of the difference in the decrease found. Mulhern et al. (2005) found a similar magnitude of decline (-1.59 points per year) in

their sample of 111 MB patients with significantly greater rates of decline for those younger at diagnosis or treated with more aggressive therapy.

All of these studies had the methodological problems inherent in such longitudinal research including drop out and variety in the age appropriate measures needed to cover the time span. However, they have used robust statistical analysis to account for this where possible and the finding that IQ declines over time appears to be a robust one, in this specific group of patients at least. It has been neatly demonstrated in another longitudinal study in this population of children treated with RT for MB (Palmer et al., 2001) that these declines represent a failure to keep up with the rate of progression of their peers rather than a loss of function, as raw scores on the IQ measures were still found to significantly increase over time, even though there was a significant decline in scaled scores. This highlights the ongoing developmental impact of late effects of treatment, where the impact is to divert children from the standard developmental trajectory rather than statically impair performance.

These studies assume linearity in the rate of decline of IQ scores however this may not be the case. Spiegler et al. (2004) report that in their sample of 34 children the rate of decline was not linear, being most rapid in approximately the first five years post treatment and attenuating over time.

For children with ALL less longitudinal data is available. One study (Krull et al., 2013) reports on a sample of 102 survivors treated with CRT and chemotherapy and assessed between one and ten years after completing treatment (retrospective data gained from medical files) and then again at a median interval of 28.5 years post treatment. They found initial significant deficits in Full Scale IQ and Performance IQ and significant declines in Verbal IQ (-10.31 points) and Full Scale IQ (-4.75 points)

at follow up. They report that these deficits at follow up were significantly related to current measures of sustained attention and reading but not processing speed, exective function or memory although no details of how these constructs were measured is given. Interestingly only 48% of their sample showed a significant decline but they did not find any significant association between that decline and demographic variables such as CRT dose, age at diagnosis or gender suggesting that it is difficult to predict which children will significantly decline over time in advance.

Far fewer longitudinal studies have considered specific cognitive functions in addition to global measures of IQ. Decline in performance has been seen in visual-motor functioning, memory, executive functioning and fine motor functioning in one small study of posterior fossa tumour patients (Spiegler et al., 2004). Copeland et al. (1996) studied non-irradiated patients with leukaemia or non-CNS tumours at both three years post treatment and between five and 11 years post treatment. Their results are varied finding no significant declines at three years and a significant decline in the 5-11 year group only on executive function tests with perceptual IQ and tactile-spatial skills significantly improving. Some further support for declining performance over time in specific neurocognitive functions can be found in cross-sectional studies which have found significant correlations between time since diagnosis or treatment and assessment scores, although these data are also variable. Mulhern et al. (2001) report significant correlations between time since CRT and verbal memory in a study of 42 MB patients, but no such correlation for sustained attention. Edelstein et al. (2011) also found a significant association between time since diagnosis for working memory and global functioning in their sample of 20 MB patients who were assessed between 6.5 and 42.2 years since diagnosis, but no

such associations for processing speed, executive function, immediate or delayed memory or motor dexterity. Further research is needed looking specifically at defined neurocognitive functions to further understand how they change over time since treatment and how this relates the more global failure to acquire the skills measured in IQ tests at the same rate as peers.

1.6 Summary of Neurocognitive Deficit Literature

In summary, whilst the literature on neurocognitive late effects is variable, most likely due to small samples which are heterogeneous for disease, age of diagnosis, treatment and assessment method, there is evidence for deficits in attention, working memory, verbal memory, visual memory, executive functions, processing speed, visuomotor and visuoperceptual abilities in a significant proportion of children treated for BT and leukaemia. These deficits have been found, although not consistently, following all currently used treatment methods and in meta-analyses the effect sizes range from small to very large. There is good evidence that IQ declines over time, due to a failure to keep pace with peers, and some evidence of decline in more specific cognitive functions over time.

Several studies (Anderson et al., 1997; Horska et al., 2010; Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006; Mulhern et al., 2001; Riva et al., 2002) have suggested these deficits are mediated by damage to the existing white matter in the brain as well as significantly less development of NAWM. This developmental impact may help to explain why some deficits only become pronounced several years after the completion of treatment (Copeland et al., 1996). Given that the prefrontal and frontal lobes have a comparatively greater volume of

white matter than other areas of the brain, are among the last areas of the brain to mature, and immature oligodentrites are thought to be more vulnerable to injury that mature cells (Mulhern et al., 2004), it follows that areas of cognition hypothesised to be mediated by these areas, such as attention, working memory and executive function, and diffuse functions like processing speed, are particularly affected, and especially so in younger children (Caron et al., 2009; Mahone, Prahme, Ruble, Mostofsky, & Schwartz, 2007). Other markers of injury have also been observed including cortical atrophy, enlarged ventricles, breakdown of the blood brain barrier, microvascular occlusion and calcifications in cortical grey matter. Basal ganglia and cellular and subcellular damage is also believed to occur however a full understanding of the precise mechanisms of damage requires further research (Mulhern et al., 2004).

1.7 Impact of Neurocognitive Late Effects

Research into the impact of neurocognitive late effects on survivors of childhood cancers has indicated wide ranging detrimental effects. A recent study by Kunin-Batson et al. (2014) found that deficits in verbal cognitive abilities and visual-motor integration skills were significant predictors of poor quality of life in the areas of school and physical abilities in a large sample of children treated for ALL with chemotherapy (including corticosteroids) only. Deficits in executive functioning abilities have been found to significantly predict poor parent-reported social skills in childhood brain tumour survivors (Wolfe et al., 2013). Selective attention deficits have been shown to significantly predict health-related quality of life one year after diagnosis in a mixed sample of children treated for brain tumours (Penn et al., 2010). Qualitative research with young adult brain tumour survivors has shown that

concerns over cognitive decline and poor social skills, along with the impact on future education and vocational opportunities, are prevalent in this group (D'Agostino & Edelstein, 2013). More broadly, poor neuropsychological performance has been associated with lower educational level, earnings in later life, chance of being married and health related quality of life (Ness et al., 2008).

1.8 Recommendations for the Assessment of Neurocognitive Consequences

Given this literature, several bodies including the Children's Oncology Group (COG), the National Institute for Health and Clinical Excellence (NICE), and the Scottish Intercollegiate Guidelines Network (SIGN) recommend neuropsychological assessment as a routine part of long term follow up for survivors of childhood cancer at risk of neurocognitive late effects. COG recommends a baseline assessment at entry into long term follow up as a minimum, and additional assessments at times of transition or if any difficulties arise (Nathan et al., 2007). NICE recommend access to neuropsychological services for all patients, particularly those with CNS tumours, and highlight the importance of such assessments in guiding schooling and later career decisions (National Institute for Health and Clinical Excellence [NICE], 2005). It is recommended in the guideline that "all children and young people with CNS malignancies have access to a neuro-rehabilitation service, even years after treatment" (p. 69) and this recommendation now forms a quality standard for children and young people with cancer (National Institute for Health and Clinical Excellence, 2014). Neuro-rehabilitation is defined as "A care package including services that will take into account the effects of the cancer and its treatment on neurological, physical, psychological and academic function, recognising that these effects can become more evident over time." (NICE, 2014 p. 28) meaning that

accurate and repeatable neuropsychological evaluation will need to form an integral part of this care package.

The SIGN recommendations highlight that those children who have received CRT are especially at risk of neurocognitive late effects and should therefore be assessed prior to treatment and annually thereafter to monitor change over time (SIGN, 2013), with lifelong follow up currently recommended as best practice for brain tumour patients. However, these recommendations should be considered a minimum and given evidence that suggests early intervention has considerable benefits (Nathan et al., 2007) more frequent assessment may be clinically useful.

In addition to recommendations for cognitive assessments to form a routine part of clinical follow up, their importance in research and clinical trials has also been highlighted. The COG blueprint for research in the area of behavioural science (Noll et al., 2013) has stated that neurocognitive assessments should be included in all trials of contemporary paediatric cancer therapies with known or suspected adverse effects on the CNS, citing benefits of this including for the child as discussed above; gathering additional long term outcome data; and providing an additional outcome measure to help clinicians choose between treatments with similar medical outcomes.

1.8.1 Limitations in meeting recommendations.

It is acknowledged that these recommendations are currently not being fully implemented (Nathan et al., 2007; Noll et al., 2013). There are several barriers to this including the time and therefore cost involved in a full neuropsychological assessment combined with limited resources in the form of clinic space and appropriately qualified staff. Tonning Olsson, Perrin, Lundgren, Hjorth, and

Johanson (2013) report that in their study of 132 paediatric brain tumour patients in Sweden only 48% were referred for neuropsychological evaluation in spite of most of the non-referred group having significant risk factors for, or reports of, cognitive impairment. They suggest this low level of referral may have been due to the paucity of neuropsychological services available in Sweden at the time of the study although the reasons for referral or non-referral in each case were not stated. Whilst referring to a different health care system this study highlights that organisational factors and limited resources may have a significant impact on the assessment and rehabilitation of children at risk of cognitive impairment following treatment for cancer. In the UK NICE (2005) acknowledge that "Both professionals and parents/carers have identified a significant lack in formal psychological input … which represents a significant area of unmet need" (p. 75), indicating that similar resource issues are a factor in the ability of health services in the UK to meet current recommendations in this area. In multi-site research, data accrual levels of <30% for neurocognitive data are common (Noll et al., 2013).

1.8.2 Potential for screening instruments to increase assessment.

The utilization of brief cognitive screening instruments that can be more easily incorporated into the routine follow up of these patients has the potential to increase the numbers of children receiving assessment for potential cognitive late effects. Such a screen would need to be time efficient and sensitive to the areas of cognitive deficit most commonly highlighted in the literature to date (Noll et al., 2013) which are summarised above. Educational evaluations are not adequate for detecting these deficits (Nathan et al., 2007) and functional measures have been found to be insensitive to serious cognitive shortcomings (Rønning et al., 2005).

1.9 Current Literature on Screening Assessments

To determine the current literature on screening assessments or batteries in a paediatric oncology population a detailed review of the literature was conducted in February 2014. Inclusion criteria were original papers describing a screening assessment or battery of assessments designed for the routine evaluation of children treated for cancer in clinical practice or consistent use in research. Web of Knowledge (all databases incorporating Medline) was searched using the search terms: ("neuro-oncology" OR oncology OR cancer) AND (Child* OR Paediatric OR Pediatric) AND (neuropsycholo* OR "cognitive functioning" OR neurocognitive) AND (assessment OR screen*) all within the Topic field. No limits were placed on year of publication, language was limited to English. Lemmization was turned on. Meeting reports and abstracts were excluded. One hundred and fifty two results were returned and titles and abstracts were reviewed to determine the relevance to the search question. Twelve articles were found to meet the inclusion criteria reporting on eleven different screening measures or batteries. Information on the studies is presented in Table 1 together with a critical evaluation based on three main factors; comprehensiveness of the measure/battery with reference to the literature on the range of neurocognitive deficits seen in this population; generalizability of the sample and rigour of the evaluation (i.e. evidence of the validity, reliability, acceptability and feasibility in this population).

1.9.1 Informant report measures.

Six of the studies evaluated single informant report measures, five of which were parent report (Howarth et al., 2013; Lai, Butt, et al., 2011; Lai, Zelko, et al.,

Table 1

Studies Examining Cognitive Screening Measures or Batteries in a Paediatric Oncology Population

Reference	Sample size	Diagnosis	Age range	Mode of assessment	Screening measures	Cognitive domains covered	Time to complete	Critical Evaluation of Results
Corklin et al. 2013	24	BT treated with conformal RT	13-18 years	Computerized Battery "ImPACT" (age modified for adolescents)	Speed Click Word Memory Design Memory X's and O's Symbol match Colour Match Four Letters Word memory – delay Design memory-delay	Reaction time Visual and verbal learning and memory Spatial working memory PS Divided attention Delayed recognition memory	Approx 45 minutes	**Comprehensiveness:** High, but no measure of executive functioning other than working memory **Generalizability:** Narrow age band included, excluded IQ<70, did not include other at risk groups (eg ALL or other treatment types) **Rigour:** Comparison to Solid tumour and sibling control groups matched for age and gender but not IQ Provides some of evidence criterion validity for limited subtests. No correction for multiple comparisons. Some evidence for convergent validity from additional computerised measures of recognition memory and working memory only. Some evidence of clinical predictive validity but limited by small sample size.
Embry et al. 2010	159	MB	2-21 years	Battery of standard neurocognitive assessment measures	Age appropriate versions of Vocabulary, BD, SS, coding, DS, logical	Intelligence, Attention, PS, WM, EF, Verbal and Visual memory,	60 minutes	**Comprehensiveness:** High in general, but more limited for younger children (<4 years). **Generalizability:** Limited to MB but broad age range.

Reference	Sample size	Diagnosis	Age range	Mode of assessment	Screening measures	Cognitive domains covered	Time to complete	Critical Evaluation of Results
Embry et al. cont.				"ALTE07C1"	memory, Face and spatial memory, CVLT. Parents: BASC-II, BRIEF, ABAS-II and PedsQL 4.0	Behavioural/ Social emotional function, adaptive function		**Rigour:** Used measures with established reliability and predictive validity but not evaluated in this population. Evidence of acceptability and feasibility from high participation rate (96% time 1, 95% time 2).
Gross-King et al. 2008	12	Not fully reported: received "treatment involving CNS"	Not fully reported	Battery of Standard neuropsychological measures	WRAT-3 reading subtest, WISC-III DS, SS and Coding subtests	Estimated IQ, WM, PS	Not fully reported; WRAT-3 reading took 15-30 minutes	**Comprehensiveness:** Low; no measure of visual or verbal memory, sustained attention, selective attention or EF. **Generalizability:** Unclear due to poor reporting but very small sample size. **Rigour:** No evaluation of acceptability, reliability, practice effects for serial testing, construct validity or criterion validity in this sample. Qualitative descriptions of feasibility.
Howarth et al. 2013	50	BT treated with conformal RT	8-18 years	Parent report	BRIEF-WM scale	WM	Not reported	**Comprehensiveness:** Low as specific to working memory and low sensitivity and specificity. **Generalizability:** Excluded IQ<70, did not include other at risk groups (e.g. ALL or other treatment types) **Rigour:** Comparison to Solid tumour

Reference	Sample size	Diagnosis	Age range	Mode of assessment	Screening measures	Cognitive domains covered	Time to complete	Critical Evaluation of Results
Howarth et al. cont.								and sibling control groups matched for age and gender and controlled for IQ provides evidence criterion validity. Limited evidence of construct validity from correlation with digit span backwards and self-ordered search tasks but low sensitivity and specificity to detect difficulties (.4 and .56 respectively). Some evidence of feasibility and acceptability from high participation rate (82%).
Kieffer et al. 2012	29	Cerebellar BT (Astrocytoma and MB)	6-11 years	Teacher report	Deasy-Spinetta questionnaire	Learning difficulties, Socialization, Disturbing Behaviour	Not reported	**Comprehensiveness:** Limited due to general nature of constructs measured. **Generalizability:** Limited as only included cerebellar BT patients and excluded those in special education. Narrow age range. **Rigour:** Qualitative report of acceptability. Evaluation of factor structure of measure which reveals a lack of reliability. Some evidence of criterion validity for learning difficulties factor. Some evidence of construct validity for learning difficulties factor.

Reference	Sample size	Diagnosis	Age range	Mode of assessment	Screening measures	Cognitive domains covered	Time to complete	Critical Evaluation of Results
Krull et al. 2008	240	Varied – consecutive sample in Long term survivors clinic	6-18 years	Battery of standard neuro-psychological measures "DIVERGT"	DS, Grooved Peg Board Test Verbal Fluency Test TMT	WM Psychomotor speed and fine motor dexterity Attention switching EF	20-30 minutes	**Comprehensiveness:** Reasonable but no measure of visual or verbal memory or learning, PS, sustained or focused attention. **Generalizability:** Broad age range. All diagnoses included in consecutive clinic sample, so high generalizability to standard clinic **Rigour:** High. Evidence of test-retest reliability (average 1 year), discriminative and predictive validity. Evidence of feasibility and acceptability from high recruitment rate (estimated 82%)
Lai et al. (2011a, 2011b)	1409	General population sample (including 23 BT)	7-17 years	Parent report "pedsPCF"	Item bank of 43 items used as full questionnaire and in Computerized Adaptive Testing (CAT)	"Perceived Cognitive Functioning" Including Memory retrieval, attention/concentration and working memory	Less than 2 minutes (using CAT)	**Comprehensiveness:** Developed in the context of a BT population to cover difficulties most commonly seen. However final scale does not explicitly cover all areas. **Generalizability:** Assessed in a general population sample with a subset of BT (and other neurological) patients. Needs further assessment in paediatric oncology setting to determine generalizability. **Rigour:** Strong evidence for internal consistency of the scale and correlation of CAT to full scale. Some evidence for criterion validity.

Reference	Sample size	Diagnosis	Age range	Mode of assessment	Screening measures	Cognitive domains covered	Time to complete	Critical Evaluation of Results
Lai et al. cont.								Some evidence of construct validity from CBCL. No evaluation of relationship between 'perceived' cognitive functioning and 'measured' cognitive functioning.
Msall et al. (2010)	76	MB	<36 months	Parent report	ASQ, Pediatric Independence Measure (WEE FIM), Motor Quotient, CLAMS and additional questions on health, developmental and adaptive status	Gross motor, Fine Motor, Problem Solving, Personal -Social, Self-care, mobility, social-cognition, communication	30 minutes	**Comprehensiveness:** Functionally comprehensive for this age range **Generalizability:** Specific diagnosis and age range studied limits generalizability. **Rigour:** Some elements of the screen used well validated instruments but also unclear use of additional questions. Stated con-current neuropsychological evaluation but no data presented to support construct validity. Report of high feasibility and acceptability but unsupported.
Patel et al. (2007)	70	BT	6-16 years	Parent report	Child Behavioural Check List	Attention	15 minutes	**Comprehensiveness:** Limited to attentional difficulties only **Generalizability:** Wide age range but did not include other at risk groups (e.g. ALL) and based on retrospective data which may over represent survivors at risk of cognitive impairment. **Rigour:** Evaluated construct validity relative to objective measures of

Reference	Sample size	Diagnosis	Age range	Mode of assessment	Screening measures	Cognitive domains covered	Time to complete	Critical Evaluation of Results
Patel et al. cont.								attention providing some limited evidence of construct and criterion validity. However the attention scale was not a significant predictor of attention dysfunction and the social problems scale showed poor sensitivity and specificity (52% and 26% respectively).
Pejnovic et al. (2012)	59	Varied – consecutive sample of patient who would receive CNS-directed therapy	0-16 years	<3 years: Parent report >3 years: Battery of standard neuropsychological measures and standardised questionnaires (including parent report) "Trackwell"	<3 : Vineland adaptive behaviour scales >3: Coding, SS, Sentence Repetition, DS, Visual attention, sky search, telephone search, Beery-Buktenica Development Test of visual-motor integration, Statue, TMT, Category fluency, COWAT, Phonological Processing,	PS, WM, Selective attention Visuomotor integration and motor co-ordination Cognitive flexibility Verbal Fluency Reading Spelling Maths Behaviour EF	Mean 49.4 minutes SD 12.8 Range 30-75	**Comprehensiveness:** High but no measure of visual or verbal memory or learning or sustained attention. Less comprehensive for younger children **Generalizability:** Broad age range. Targeted recruitment to population most at risk. Assessed at diagnosis so unclear if the battery would be feasible with children post treatment where more difficulties likely to be evident. **Rigour:** Good evidence of feasibility within a defined model. Compared to a control group, but unmatched for age (smaller age range) or ability. Acceptability high assessed by both participant and researcher. Added value assessed compared to medical notes. No report of validity or reliability in this paper.

Reference	Sample size	Diagnosis	Age range	Mode of assessment	Screening measures	Cognitive domains covered	Time to complete	Critical Evaluation of Results
Pejnovic et al. cont.					subtests of WIAT >8: Self report BASC-2 Parents: PEDS, BASC-2 and BRIEF			
Quigg et al. 2013	30	Varied - All new oncology except benign haematology	4-48 months	Parent report	Ages and Stages questionnaire 3rd Edition	Communication Gross Motor Fine Motor Problem solving Personal-social	10-15 minutes (estimated)	**Comprehensiveness:** Functionally comprehensive for this age range Sensitivity of questionnaire only 72% so may miss subtle difficulties. No objective measurement included. **Generalizability:** Suitable for very young, but narrow age range. All oncology diagnoses included, consecutive sample, so high generalizability to standard clinic **Rigour:** Did not corroborate identified 'at risk' or 'delayed' children with objective assessment so no evidence of validity in this population. Some evidence of feasibility through high rates of completion and follow up to 12 months.

Note. BT = brain tumour; RT = radiotherapy; PS = Processing Speed; MB = Medullablastoma; WM = working memory; EF = Executive function; BD = block design task from Weschler tests; SS = Symbol search task from Weschler tests; DS = Digit Span task from Weschler tests; CVLT = Calafornia Verbal Learning Test; BRIEF = Behaviour Rating Inventory of Executive Function; BASC-II = Behaviour Assessment System for Children 2nd Edition; ABAS-II = Adaptive Behaviour Assessment System 2nd Edition ; CNS = Central Nervous System; WRAT-3 = Wide Ranging Achievement Test 3rd Edition; WISC-III =

Weschler Intelligence Scale for Children 3rd Edition; WIAT = Weschler Individual Achievement Test; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Task; CLAMS = Clinical Linguistic and Auditory Milestone Scale ; PEDS = Parent's Evaluation of Developmental Status; ASQ = Ages and Stages Questionnaire

2011; Msall, 2010; Patel, Lai-Yates, Anderson, & Katz, 2007; Quigg, Mahajerin, Sullivan, Pradhan, & Bauer, 2013) and one was teacher report (Kieffer et al., 2012). Quigg et al. (2013) and Msall et al. (2010) reported on measures designed for use with young children aged 48 months and under. Whilst these measures are functionally comprehensive for this age range they are inherently limited as screens for use in the general clinic population by being inappropriate for older children. In addition the Ages and Stages Questionnaire used by Quigg et al. showed low sensitivity for difficulties so may be of limited use even in this age range. Howarth et al. (2013) and Patel et al. (2007) report on well validated measures for use with a much wider, although older, age range; the Behaviour Rating Inventory of Executive Function (BRIEF) and Child Behaviour Check List (CBCL) respectively. However there are several limitations with using these measures as stand-alone screens. Firstly as informant report measures they can only provide information on difficulties "perceived" by the rater rather than objectively "observed" impairments. Whilst informant report measures can provide very useful additional information it is recommended they are included as part of a broader battery (Baron, 2004). Secondly both measures are limited in focus to single cognitive construct and therefore do not cover the broad range of relevant areas. In addition Patel et al. (2007) found the CBCL to be a poor predictor of attention dysfunction and to lack sensitivity and specificity for social problems limiting its usefulness further. Similarly the BRIEF working memory scale also showed very low sensitivity and specificity for impairments seen on objective tasks indicating that, whilst it may provide additional information to these tasks, it should not replace them. Kieffer et al. (2012) assessed the usefulness of the Deasy-Spinetta questionnaire, a teacher report measure, as a screening tool. However, as it is both very general in the constructs it covers and

lacks reliability in its factor structure it appears it is of limited value. The most promising of the standalone informant report measures is the 'pediatric perceived cognitive function item bank' (pedsPCF) reported on by Lai and colleagues (2011a, 2011b). This 43 item bank was developed to cover the full continuum of the constructs of cognitive functioning in a paediatric brain tumour population and shows promising statistical properties based in a very large general population sample. Using the bank with computerized adaptive testing (CAT) means that it can take as little as two minutes to get as reliable an estimate of cognitive functioning as from completing the full scale, which would make this approach highly feasible to fit into routine clinic follow up. However, whilst a broad range of cognitive areas were theoretically included in the item bank, factor analysis of the normative data most strongly supports a single factor (a requirement for CAT) and therefore subtle deficits in individual areas may not be adequately probed by the scale. In addition no data are yet available on the construct validity of the scale relative to standard objective measures and so the relationship between 'perceived' cognitive function and 'observed' cognitive function is unclear. With further evaluation this may be a useful tool to get a general assessment of cognitive functioning with very little input of professionals' time, which could then identify those in need of a more comprehensive assessment.

1.9.2 Batteries of standard neuropsychological measures.

Four studies report on the use of batteries of standard neuropsychological measures as screening tools (Embry et al., 2012; Gross-King, Booth-Jones, & Couluris, 2008; Krull et al., 2008; Pejnovic et al., 2012). Gross-King and colleagues (2008) used a very brief battery consisting of the Wide Ranging Achievement Test,

version 3 (WRAT-3) reading subtest to provide an estimate of IQ and three subtests of the Wechsler Intelligence Scale for Children, version 3 (WISC-III); Digit Span to measure verbal working memory, Symbol Search to measure processing speed and Coding to measure visual-motor speed in their very small study. It is hard to draw any conclusions from the lack of data presented however the battery itself is very limited in scope and therefore a poor candidate for a widespread screening tool.

Krull et al. (2008) evaluated a battery assessing executive function, attention and psychomotor speed using established neuropsychological measures which took 30 minutes to administer and was found to have good test-retest reliability (r=0.72) and predictive validity for IQ, reading ability and mathematical ability in a varied and generalizable sample. However it does not include measures of visual or verbal learning or memory, processing speed and sustained or focussed attention and therefore does not cover all the areas known to be affected in these patients.

Pejnovic et al. (2012) reported on a comprehensive battery which included standardised measures of processing speed, selective attention, working memory, psychomotor function, executive function, behaviour and reading, spelling and maths which took a mean of 49.4 minutes (SD 12.8) to administer. They also included a validated parent report measure for use when the patient was under three years old, however, limited data on this group is presented. The main battery was shown to be acceptable to families and feasible for use in this clinical population but reliability and validity data were not presented so it is not possible to evaluate these aspects or consider the screen rigorously tested at this stage.

Embry et al. (2010) evaluated a comprehensive battery of measures drawn from widely available and generally well validated assessments aiming to increase the collection of neurocognitive data in clinical trials. Their battery covers a very

wide age range of 2-21 years and therefore uses several different measures of the same construct for different age groups. Whilst this is a pragmatic approach it does increase the variability in the battery as a whole, potentially increasing the measurement error. They report that the battery took 60 minutes to complete and, within the context of a research study aimed at collecting complete data, they achieved very high participation rates indicating that this is acceptable to families.

All of these batteries reduce their administration time by using single subtests from larger standard measures. Whilst this has the advantage of enabling a broad range of constructs to be assessed in a brief battery it may reduce the reliability of the assessment. It also requires the availability of several measures to extract the subtests from, which may increase the cost of such a screening tool if they are not already available. Whilst several studies reported the administration time of the battery none reported on time taken to score the assessments which can also equate to a significant amount of the clinicians' time. Standard neuropsychological measures need to be administered by suitably qualified professionals and are often subject to practice effects which generally preclude retesting within a year. This limits the flexibility of using these batteries to track change over shorter time frames, or at times of transition if these fall between yearly assessments.

1.9.3 Computerized measures.

One study by Conklin et al. (2013) has evaluated a computerized screening tool. The ImPACT battery is a well validated adult measure previously used following mild brain injuries. It includes measures of divided attention, visual and verbal learning and memory, spatial working memory, processing speed and reaction time (a measure of psychomotor speed) but lacks any broad measures of executive

function. The version used in this study was modified to make it suitable for adolescents (13-18 years) by elaborating and simplifying the instructions, however, the age range covered is still narrow compared to other screens in this review and the age range of children seen in follow up clinics. Participants in the study were 24 children treated for BT with conformal CRT, along with solid tumour and sibling control groups. The results demonstrated criterion validity on some of the outcome measures reported (four of the eight accuracy measures and all speed measures) and convergent construct validity for verbal and visual memory tasks (with small to medium effect sizes r=.25-.30) but not working memory tasks. Construct validity was not assessed for divided attention, processing speed, and psychomotor speed. The small sample included in this study is fairly specific in both diagnosis and treatment and may therefore not be representative of the full population of children at risk of cognitive late effects. Advantages of computerized assessment over standard assessment measures noted by the authors include the accuracy with which processing speed can be measured and the reduced level of expertise and therefore cost needed to administer the battery. They claim that the battery has also been shown to have limited practice effects meaning it can flexibly be used to track change over time.

1.9.4 Conclusion of detailed literature review.

This detailed review of the literature shows that whilst several potential screening batteries have been evaluated in this population none could be considered fully comprehensive, or rigorously tested in a sample that is easily generalizable.

Informant report measures have the advantages of being inexpensive, quick and easy to administer but they are often limited in scope or very general in the

constructs they measure which limits their usefulness in a general clinic. The relationship between perceived and observed deficits is also unclear meaning that equivalence between these measures and standard neuropsychological assessments cannot be assumed. Therefore, whilst such measures can potentially add useful information to a screening battery, they should not replace other more specific assessments.

The batteries of standard measures which have been investigated are able to provide more specific and detailed information and are comparatively quick to administer compared to a full length neuropsychological assessment. An advantage of using measures which are familiar to practicing psychologists in the clinic setting may be that these batteries would be fairly easy to incorporate into practice. However they also retain the disadvantages of traditional assessment including high levels of expertise needed to administer and score them and lengthy gaps needed between assessments to prevent practice effects.

Computerised assessment can potentially limit the effects of many of these problems. The ImPACT battery could be administered by a wider range of professionals without expert knowledge or training, is less affected by practice effects and can assess a wide range of constructs in a single measure. However it has currently only been assessed in a narrow segment of the paediatric oncology population and still lacks some evidence of the criterion and construct validity which needs to be demonstrated before it could be used in general practice. It also lacks a broad measure of executive function, and may therefore miss more subtle cognitive deficits which may be increasingly evident as treatment approaches continue to improve.

Therefore, whilst recent progress has been made in this areas, there is still a need for further comprehensive, sensitive and repeatable screening batteries which could be used with a large proportion of the population seen in paediatric oncology late effects clinics or clinical trials.

1.10 CogState

CogState is a brief computerized neurocognitive battery designed to assess psychomotor function, processing speed, visual attention, vigilance (sustained attention), working memory, visual learning and memory and executive function (Collie, Maruff, McStephen, & Darby, 2003; Pietrzak et al., 2008). It is formed of simple experimental psychology paradigms such as n-back tasks; forced choice reaction time tasks etc. which have been shown to provide robust measures of cognitive constructs and have been widely used in neuroimaging and cognitive psychology research (e.g. (Cohen & Leckman, 1994; Salthouse & Davis, 2006; Squire & Kandel, 2000). These tasks have then been modified to make them applicable and acceptable in clinical use and sensitive to change over time (Pietrzak et al., 2009). The battery makes use of non-verbal and culturally neutral stimuli in order to make it familiar and acceptable to individuals from diverse cultural and social groups (Maruff et al., 2009). It has been shown to demonstrate virtually no practice effects in adults or children after the second administration (Falleti, Maruff, Collie, & Darby, 2006; Mollica, Maruff, Collie, & Vance, 2005) allowing for repeated administration to accurately assess any change over time. Its computerised administration allows for accurate collection of data and automated scoring which facilitates the collection of consistent data across different sites (Collie et al., 2007).

1.10.1 Psychometric properties in other populations.

CogState was originally developed specifically to assess cognitive change over repeated assessment (Collie et al., 2003) and has been assessed in a wide variety of settings. The largest studies investigating construct validity and criterion validity have been samples of healthy adults and adults with schizophrenia, mild traumatic brain injury (TBI) and AIDs dementia complex (Cysique, Maruff, Darby, & Brew, 2006; Maruff et al., 2009; Pietrzak et al., 2009; Yoshida et al., 2011). Strong correlations with standard measures of the same cognitive constructs were found in healthy adults and patients with chronic schizophrenia (*r*'s=.49-.83) supporting the construct validity of CogState in these groups (it was not investigated in the other groups). The effect sizes for the magnitude of the deficits when comparing controls to patient groups were large (*d*=-.60 to -1.80) and in the Pietrzak et al. study comparable to the battery of standard neuropsychological measures used indicating that CogState is sensitive to impairments in these groups and performs as well as standard measures in detecting them.

CogState has also been investigated for use with children. It has been used in healthy samples (Mollica et al., 2005; Thomas, Reeve, Fredrickson, & Maruff, 2011) and been shown to have good test-retest reliability and the same limited practice effects as in adults, making it potentially very useful for assessing change over time in the context of a developing CNS. Subtests from the CogState battery, particularly the Groton Maze Learning Task, have been used in a number of studies with children from paediatric populations including children with ADHD (Mollica, Maruff, & Vance, 2004; Snyder, Maruff, Pietrzak, Cromer, & Snyder, 2008) cerebral malaria (Bangirana et al., 2009); poor motor coordination (Rigoli et al., 2013); HIV (Boivin et al., 2010) and in-utero exposure to cocaine (Mayes, Snyder, Langlois, & Hunter,

2007) which provide some evidence of criterion validity in these populations. However specific studies of criterion validity have not been done and there is currently no published evidence of construct validity for the paediatric battery.

1.10.2 Potential for use in the paediatric oncology population.

To date there are no published studies using CogState in the paediatric oncology population. One study (Ichimura et al., 2010) has used four subtests of the Japanese version of the adult CogState battery with adult patients who have received surgery only for posterior fossa lesions including brain tumours. They found the battery to be more sensitive to subtle cognitive difficulties than standard measures (which exhibited practice effects).

COG have recently highlighted the potential of computerised assessments, specifically CogState, over traditional neuropsychological measures, as "a time-efficient approach to facilitate collection of psychometrically robust data" (Noll et al., 2013 p. 1051) both in order to follow children over time to investigate the time course of deficits and to screen children to identify those in need of further comprehensive assessment. Currently the paediatric CogState battery is embedded in one COG trial of high risk ALL patients. However they acknowledge that studies which link the CogState battery to traditional measures are still needed to "provide critical data related to the validity of brief computerized measures" (p. 1051).

1.11 Psychometric Theory of Validity

Psychometric theory states that assessments should be reliable, valid, standardised and free from bias (Rust, 2012). Within this, validity refers to the extent to which an assessment is fit for purpose i.e. does it measure what it claims to

measure in a sensitive and specific way? There are many different types of validity including face validity (the extent to which an assessment is acceptable as a measure of what it claims to measure); predictive validity (the extent to which performance on a measure is predictive of other measures of functioning) and criterion validity (the extent to which a measure differentiates between groups specified by a particular criterion). Construct validity relates to the extent to which a measure taps the construct it is claiming to assess. It can be determined in a number of ways. Convergent (or concurrent) validity is one way of assessing construct validity and relates to the correlation between the measure which is being evaluated and established measures of the same construct (Rust, 2012).

1.12 Summary and Rationale for Current Study

In summary, neurocognitive late effects are common in the paediatric oncology population where treatment is directed at the CNS. Although the use of CRT has been consistently connected to poor neurocognitive outcomes there is evidence of deficits following all commonly used treatment methods. Deficits have been found in the areas of attention (especially selective and sustained attention), memory (especially visual and verbal immediate memory and working memory), processing speed, executive functioning (especially cognitive flexibility) and visual-percetual and visuomotor processing. There is evidence that global deficits, measured by IQ, deteriorate over time due to a failure to keep pace with the cognitive development of peers. It is recommended that all children at risk of these deficits be screened at least annually and at times of transition to ensure that any difficulties are picked up early and can be addressed. Currently this recommendation is not being consistently followed likely due to the cost, expertise and time required to carry out

these assessments. In response to this, brief screening measures and batteries have been developed however none of the batteries in the current literature have been shown to be ideal for this task to date. CogState is a brief computerised neurocognitive screening battery which has been identified to show promise as a screening instrument in this population. However, currently there is no evidence of its validity in a paediatric oncology setting. Therefore, the current study primarily aims to begin to assess the construct validity of the paediatric CogState battery by determining its concurrent validity with standard neuropsychological measures. In addition a secondary aim is to add to the currently limited literature on change in specific neurocognitive functions over time by investigating the relationship between time since diagnosis and performance on the CogState battery.

1.13 Research Questions and Hypotheses

The primary research questions are:

1. Does CogState demonstrate adequate construct validity in a population of children who have survived a brain tumour or leukaemia when compared to a standard neuropsychological battery?

The standard battery used in this study is made up of neuropsychological tests and subtests chosen to assess the same neurocognitive constructs which the CogState battery reports that it covers. The battery is made up of the Grooved Peg Board (Klove, 1963), the Trail Making Test (TMT) A and B (Reitan, 1958, 1971), the Symbol Search and Digit Span subtests from the Weschler Intelligence Scale for Children version four (WISC-IV) (Wechsler, 2003), the Map Mission and Score! subtests from the Test of Everyday Attention for Children (TEA-Ch) (Manly,

Robertson, Anderson, & Nimmo-Smith, 1999) and the Dot Location subtest from the Children's Memory Scale (CMS) (Cohen, 1997) and the Behaviour Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy, & Kenworthy, 2000). The properties of these tests and the reasons they were selected are discussed further in the Method chapter.

Both batteries cover most of the areas of neurocognitive functioning shown by previous research to be often affected by childhood cancer and its treatment. If CogState is a valid assessment of these areas in this population several hypothesis can be made about which of its subtests will correlate with which standard neuropsychological tasks:

Hypothesis 1: The Detection task of the Cogstate battery measures psychomotor function and processing speed and will be positively correlated with performance on the Grooved Peg Board task and the WISC-IV Symbol Search subtest.

Hypothesis 2: The Identification task of the Cogstate battery measures visual attention and vigilance and will be positively correlated with performance on the Map Mission and Score! subtests of the TEA-Ch.

Hypothesis 3: The One-Card Learning Task of the CogState battery measures visual learning and memory and will be positively correlated with performance on the CMS Dot location subtest.

Hypothesis 4: The Continuous Paired Associate Learning Task of the CogState battery measures visual learning and memory and will be positively correlated with performance on the CMS Dot location subtest.

Hypothesis 5: The One-Back Task of the CogState battery measures working memory and will be positively correlated with performance on the WISC-IV Digit Span subtest.

Hypothesis 6: The Groton Maze Learning Task of the CogState battery measures executive function, including cognitive flexibility, and will be positively correlated with performance on TMT B and the BRIEF total score.

2. Given the research showing intellectual performance declines over time since treatment (e.g. (Spiegler et al., 2004)) is there a relationship between time since diagnosis and performance on the CogState battery?

Hypothesis 7: Time since diagnosis will be negatively correlated with overall performance on the CogState battery.

2 Method

2.1 Overview

In this chapter the methodology employed in the study will be described. This includes a description of the design of the study, the sample and recruitment, the measures used with a focus on their psychometric properties, the testing procedure, ethical considerations involved in the study and it will end with a description of the plan of analysis.

2.2 Design

The construct validity of the CogState battery was investigated using a within subject correlational design. Each participant completed both the CogState battery and a battery of standard neuropsychological subtests which have been shown in previous research to measure the same cognitive constructs as the CogState tasks are designed to measure. Subtests of standard measures were used rather than indices or composite scores in order to facilitate evaluating the full CogState battery within a time scale that could feasibly be completed in one research visit. Whilst this may have reduced the reliability in the measures this method was chosen in order to limit variation in results due to environmental factors that two visits would have entailed, reduce burden on participants and increase the feasibility of the study. Performance on each pair of corresponding subtests was correlated. The study was cross sectional as all measures were completed at a single time point.

The relationship between time since diagnosis and overall performance on the CogState battery was also investigated using a cross sectional correlation design. IQ and mood have been shown in the literature to affect performance on neuropsychological assessments (Baron, 2004) therefore data were collected on these

variables to facilitate a partial correlation analysis should they be shown to correlate significantly with performance in this study.

It could be argued that a longitudinal study following the same participants over time would be a more powerful and valid way to assess the relationship between time since diagnosis and performance on the CogState battery. However, the time constraints of the current study meant it was unfeasible to consider this design for this project.

2.3 Participants

2.3.1 Population of study.

Children who had received a diagnosis of a brain tumour or a leukaemia were chosen as the study participants. This is because these are the most common malignancies in children and have been shown most often in the literature to experience neurocognitive deficits following their cancer treatment (Butler & Haser, 2006). Whilst it is acknowledged that this variety in diagnoses resulted in a heterogeneous sample it was decided that limiting the sample to one specific diagnosis would be detrimental to the study for several reasons. Firstly the literature indicates that the most significant cognitive deficits are seen following certain types of brain tumour (Ris & Abbey, 2010) however these populations are so small that to recruit from this single diagnosis would significantly reduce the pool of potential participants and result in the study becoming unfeasible. Secondly, if only patients with leukaemia were included, brain tumour patients likely to have more severe cognitive impairments and who are therefore more likely to require neuropsychological assessment would be excluded and the clinical efficacy of the study would be reduced. In addition, the within subject correlational design used to

address the first research question mitigates to an extent the effect of having a heterogeneous sample on the power of the analysis. A strength of using a heterogeneous sample when considering the utility of the CogState battery as a screening instrument for use in general clinics was the increased generalizability of the results to clinical settings.

The participants had all completed the active part of their treatment prior to taking part in the study, defined as being off active therapies for brain tumour patients and at least in maintenance therapy for ALL patients This was to ensure that the results do not reflect the immediate cognitive effects of undergoing stressful hospital treatment and to avoid the additional stress of asking patients and their families to take part in research during an acutely difficult time for them.

2.3.2 Inclusion and exclusion criteria.

Participants were between 8 and 16 years of age inclusive. This age range was chosen to cover the widest age range seen in the paediatric oncology clinics as possible whilst maintaining a requirement for one battery of assessments. Participants were required to have received a diagnosis of a brain tumour or leukaemia, with stable disease as determined by the primary physician and checked by the Principle Investigator in each recruitment site. This included being off active therapies for brain tumour survivors and at least in maintenance therapy or off therapy for children with leukaemia. English was required to be the participant's primary language to ensure that all assessments could be understood.

Patients were excluded if they had a pre-existing neurodevelopmental or genetic disorder or history of head injury to ensure as far as possible that any

cognitive deficits found in the study were as a result of the cancer and its treatment alone.

Patients with sensory or motor impairment severe enough to prevent testing were excluded to ensure that all participants were able to complete the full battery. Examples of impairments which led to exclusion from recruitment included not having the use of one hand or visual impairment severe enough to require large print written material at school.

Patients who had been assessed within the last year using any of the neuropsychological tests in the standard battery were also excluded to prevent practice effects.

2.3.3 Sample size.

Sample size calculations were performed using G. Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009). For the first research question the expected effect size was determined by taking the average correlation between the CogState subtests used in this study and the standard neuropsychological comparator tests in two large studies validating CogState in adult clinical populations (Maruff et al., 2009; Pietrzak et al., 2009). The correlation coefficients in these studies range from 0.49-0.83 with a mean of 0.52. Using this value with a power of 0.8 and an alpha level of 0.05 for a two-tailed test gives a sample size of 26 for a correlation analysis.

For the second research question the estimated effect size was taken from Mulhern et al. (2001) who found a Pearson's product moment correlation of -0.46 for time since CRT and estimated full scale IQ in sample of patients with a medulloblastoma. Using this effect size with a power of 0.8 and an alpha level of 0.05 for a two-tailed test gives a sample size of 32 for a correlation analysis.

Given these power calculations the study aimed to recruit a minimum of 32 patients.

2.4 Recruitment Procedure

Paediatric oncology care in the region is organised by the East of England Children and Young People's Cancer network. In this model Addenbrooke's Hospital (part of Cambridge University Hospitals NHS Foundation Trust) co-ordinates the cancer treatment of all paediatric (0-16 years) cancer patients in the region and is the Principle Treatment Centre (PTC). All diagnostic and treatment decisions are made at this hospital and it also co-ordinates late effects and psychosocial care. There are ten other hospitals in the region which are designated Paediatric Oncology Shared Care Units (POSCUs) and which provide some aspects of the patient's care closer to their home.

The Clinical Psychologists providing input to the paediatric oncology multidisciplinary teams at Addenbrooke's Hospital and two local POSCU's; The Norfolk and Norwich University Hospital (NNUH) and The Queen Elizabeth Hospital King's Lynn (QEHKL), were approached with initial information about the project and asked if their department would be interested in taking part. These centres were chosen due to their geographical proximity and to facilitate a wide range of time since diagnosis in the potential participants approached during the recruitment period, since patients who are in long term follow up are only seen approximately annually at the PTC. All three centres responded positively and following gaining ethical approval, local research governance approval was sought to recruit participants from each centre. As all patients in the region are known to the

PTC care was taken when recruiting from all sites to ensure that the family had not been previously approached by another team.

Potential participants meeting the inclusion and exclusion criteria were identified by the paediatric oncology team in each hospital. They were then approached by a member of the clinical team to provide them with initial information about the study and obtain consent to be contacted by the researcher (see Appendices A-E). This occurred either during a routine clinic visit or by posting the invitation letter and consent form to potential participants and following up with a telephone call to ensure they have received the information and obtain verbal consent to be contacted by the researcher.

Once consent to contact was received, the researcher contacted the family to arrange a convenient and suitably quiet time and location to meet to answer any further questions they had and obtain appropriate consent/assent for the study (see Appendices F-I). Provided consent/assent was obtained the study measures were also completed at this visit.

In total 37 participants were recruited to the study; 9 through QEHKL, 16 through NNUH and 13 through Addenbrooke's hospital.

2.5 Assessment Measures

The assessment battery completed by each participant was made up of the CogState battery and a Standard battery including a range of standardised tests and subtests and one informant report questionnaire measure. These standard measures were chosen to match the relevant CogState task based on a combination of factors. These included established psychometric properties in the relevant area of cognition which the CogState task is described as measuring, described in the test manual or

wider literature and summarised below; prior use in adult validity studies of CogState (Cysique et al., 2006; Maruff et al., 2009; Pietrzak et al., 2009; Yoshida et al., 2011); general use in clinical settings and availability to the researcher. Not all factors were satisfied for each measure with some, such as availability to the researcher needing to be prioritised. Table 2 lists the neurocognitive domain and related tests for both batteries. In addition a brief IQ measure, the Wechsler Abbreviated Scale of Intelligence (WASI) and a brief self-report questionnaire measure of mood, the Paediatric Inventory of Emotional Distress (PI-ED) were administered to account for potential confounding variables. Two unstandardized questionnaires regarding demographic information and the acceptability of the CogState battery were also completed.

Table 2

Neurocognitive Domains Measured by Subtests in the CogState and Standard Batteries

Neurocognitive Domain	CogState Tasks	Standard Neuropsychological Tasks
Psychomotor function Processing speed	Detection Task	Grooved peg board WISC-IV Symbol Search Subtest
Visual attention Vigilance	Identification Task	TEA-Ch Map Mission Subtest TEA-Ch Score! Subtest
Visual learning and memory	One Card Learning Task Continuous Paired Associate Learning Task	CMS Dot Location Subtest
Working memory	One Back Task	WISC-IV Digit Span Subtest
Executive function	Groton Maze Learning Task	Trail Making Test-B BRIEF Global Executive Composite

Note. BRIEF = Behaviour Rating Inventory of Executive Function, CMS = Children's Memory Scale, TEA-Ch = Test of Everyday Attention for Children. WISC-IV=Wechsler Intelligence Scale for Children Fourth Edition

Each element of the battery will now be outlined further in detail including its psychometric properties and administration.

2.5.1 CogState Battery (Pietrzak et al., 2009).

2.5.1.1 Description.

CogState is a brief computerized neurocognitive battery formed of simple standardised experimental psychology paradigms such as n-back tasks and forced choice reaction time tasks etc. which have been shown to provide robust measures of cognitive constructs in experimental settings. These tasks have then been modified to make them applicable and acceptable in clinical use and sensitive to change over time (Pietrzak et al., 2009). The battery makes use of non-verbal and culturally neutral playing card stimuli, abstract shapes and mazes and has been shown to demonstrate virtually no practice effects in adults or children (Falleti et al., 2006; Mollica et al., 2005) allowing for repeated administration to assess any change over time. Its computerised administration allows for accurate collection of data and automated scoring.

For this study six tasks were used covering the neurocognitive functions most commonly found to be affected by childhood cancer and its treatment as described in the Introduction. A description of the tasks, the constructs that the test publisher describes them as measuring, and their primary outcome measures can be found in Table 3.

The measure was provided without charge under license for research purposes by CogState Inc.

Table 3

CogState Subtest Descriptions

Subtest (primary cognitive constructs measured)	Abbreviation	Description	Primary Outcome Variable
Detection Task (Psychomotor function, processing speed)	DET	The participant must press the "yes" key as soon as the single card in the centre of the screen flips over. In the 10-16 years battery a joker is used. In the 8-9 years battery a smiling face is used.	Speed of performance (Log_{10} transformation of mean reaction time)
Identification Task (Attention/Vigilance)	IDN	The participant must respond "yes" if the card presented is red and "no" if it is black as soon as it flips over. In the 10-16 years battery a joker is used. In the 8-9 years battery a smiling face is used.	Speed of performance (Log_{10} transformation of mean reaction time)
One Card Learning Task (Visual recognition memory)	OCL	The participant must respond "yes" if they have seen the card presented before in this subtest and "no" if they have not. There are four target cards which repeat nine times during task. In the 10-16 years battery standard playing cards are used. In the 8-9 years battery coloured numbers and symbols are used.	Accuracy of performance (Arcsine transformation of proportion of correct responses)
One Back Memory Task (Working memory)	OBK	The participant must respond "yes" if the current card is the same as the previous card and "no" if it not. In the 10-16 years battery standard playing cards are used. In the 8-9 years battery	Speed of performance (Log_{10} transformation of mean reaction time)

		coloured numbers and symbols are used.	
Continuous Paired Associate Learning Task (Visual associate learning and memory)	CPAL	After a learning phase during which all the shapes are visible the participant must chose the matching shape from a choice of eight hidden locations (six hiding shapes and two decoy). They continue choosing on each trial until the correct shape is found.	Total Errors
Groton Maze Learning Task (Executive functioning including problem solving, reasoning and error monitoring)	GMLT	The participant must find the correct path through a 10x10 grid from a starting point to a target following three rules. For the 10-16 years battery the previous steps taken are hidden, for the 8-9 years battery they remain visible. Five trials are presented with the same 29 step path on each occasion.	Total Errors (Summed across the five trials; Total Rule Break Errors is an alternative variable)

2.5.1.2 Psychometric properties.

Test-retest reliability of the CogState subtests used in this study has been reported as between .84 and .91 in a sample of 300 healthy young adults (Collie et al., 2003). The construct and criterion validity of the subtests has been well established in adult samples. An early version of the battery including the DET, IDN and OBK tasks was studied in 62 adults with HIV and 21 control subjects (Cysique et al., 2006) providing good evidence of criterion validity in this sample and some evidence of construct validity although the results were at times contradictory. Maruff et al. (2009) report on a sample of 215 healthy adults who were administered the DET task, IDN task, OBK task and OCL task and comparator

neuropsychological tasks including the Grooved Peg Board task and the Trail making task amongst others. Pearson's Product-Moment correlations ranged from .79 to .81 for tasks measuring similar constructs providing evidence for convergent validity. Divergent validity was also shown with unrelated tasks not showing significant correlations. The above tasks and the GMLT were also administered to 120 healthy control subjects in a study reported by Pietrzak et al. (2009) with correlations between .45 and.75 found with comparator tasks measuring the same cognitive construct. Both studies investigated the criterion validity of the CogState battery by comparing the performance of healthy controls to patient groups (adults with schizophrenia, mild TBI and AIDs dementia) on both the Cogstate and standard comparator batteries. In both studies the patient groups showed comparable significantly worse performance on both batteries. Yoshida and colleagues (2011) investigated the Japanese version of the CogState battery including the DET, OBK, CPAL and GMLT in a sample of 40 patients diagnosed with schizophrenia and 40 controls finding at least partial evidence for the construct validity of all of these tasks except the CPAL (p=.25-.34).

In children sections of the battery have been used in both healthy samples (Thomas et al., 2011), and a variety of samples of children from paediatric populations (Bangirana et al., 2009; Boivin et al., 2010; Mayes et al., 2007; Mollica et al., 2005) and have been shown to provide comparable information to standard neuropsychological tests although construct validity has not been specifically assessed. There are no published data on the CogState battery in paediatric oncology populations.

2.5.1.3 Administration.

This six task CogState battery was administered in approximately 20 minutes using a Toshiba Satelite Pro C850 1K4 laptop computer. The participant was guided through the tasks by on screen instructions with further verbal instructions from the researcher supervising the testing. Practice periods were presented prior to the CPAL and GMLT to ensure the participant understood the instructions before beginning the scored portion of the test. On the other tasks particular attention was given to the participant's first few responses and the instructions of the test were repeated if necessary. Responses to the DEC, IDN, OCL and OBK tasks were made using simple keyboard strokes. An external mouse was used for the CPAL and GMLT. Participants were encouraged to be as quick and accurate as possible in their responses. An error sound was heard each time the participant made a mistake. The scores generated by the CogState subtests include measures of reaction time and errors made as described in Table 3. Age standardised scores are provided for the four card based tasks (DEC, IDN, OCL and OBK) however as the CPAL and GMLT are at an earlier stage of development in the paediatric battery robust standardised scores are not available for these subtests and raw data was be used in the analysis. In addition a summary score of performance on the four standardised subtests can be calculated.

2.5.2 Standard battery.

The subtests used to form the standard battery are described below, grouped by the measures they are taken from. A summary of the subtests which make up the battery, in the order they were completed, can be found in Table 4.

Table 4

Standard Battery Subtest Descriptions

Subtest (primary cognitive constructs measured)	Abbreviation	Description	Primary Outcome Variable
Grooved Peg Board (psychomotor speed, and dexterity)	GPB	Participants place 25 grooved pegs into matching holes using first their dominant hand and then their non-dominant hand. Eight year olds only place 10 pegs.	Time to completion (dominant hand only)
Symbol Search (processing speed)	SS	Participants scan search groups of five symbols for either of two target symbols marking "yes" if there is a match and "no" if there is not. As many items as possible are completed in 120 seconds.	Total correct minus total incorrect converted to Scaled Score
Map Mission (selective/focused visual attention)	MM	Participants must circle as many target symbols on the map as they can in 60 seconds ignoring distractor symbols.	Total identified converted to Scaled Score
Score! (auditory sustained attention)	-	Participants listen to 10 sequences of sounds presented on a tape between nine and 15 sounds in length. They must count the length of each string.	Total correct converted to Scaled Score
Dot Location (visual/spatial short term memory and learning)	DL	Participants must place chips on a response grid from memory to replicate the stimulus pattern shown. Three learning trials and an immediate memory trial are completed.	Total correct across all four trials converted to Scaled Score
Digit Span (auditory short term memory including working memory)	DS	Participants must repeat strings of numbers of increasing length presented verbally. Forwards and Backwards conditions	Total correct across all trials converted to Scaled Score. (Longest Digit Span Backwards

		are included. Two trials are completed per string length. If the participant fails both trials the test is stopped.	is an alternative outcome variable specific to the Backwards condition)
Trail Making Test (Executive function including attentional control, inhibitory control and cognitive flexibility)	TMT	In the A condition participants must join numbers scattered across a page by a single line in ascending order. In the B condition they must alternate between connecting numbers in ascending order and letters in alphabetical order.	Time to competition (TMT-B only)

2.5.2.1 Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV; Wechsler, 2003).

2.5.2.1.1 Description.

This standard test of intellectual function for children aged 6-16 years is widely used and well validated. The full test is made of up four indices; Verbal Comprehension, Perceptual Reasoning; Processing Speed and Working Memory. Two subtests, taken from the last two of these indices, the Symbol Search subtest and the Digit span subtest, were used to provide a standardised measure of processing speed and working memory respectively.

Symbol search is a pencil and paper task which required the child to follow a simple set of instructions to visually scan a group of symbols looking for the presence of a target symbol. It does not become progressively more difficult as the task progresses but does require quick accurate responses to score highly and therefore is strongly reliant on processing speed. In addition it has been described as requiring short-term visual memory, visual-motor co-ordination, cognitive flexibility,

visual discrimination and concentration to complete successfully(Flanagan & Kaufman, 2009; Sattler, 2001). The Symbol Search subtest was chosen to match the DET task in preference to the Coding subtest, the other component of the Processing Speed Index as it is less dependent on fine motor control, although use of a pencil is still required, and therefore is more similar to the limited motor responses required by the DET task.

Digit span is a widely used measure of working memory designed to measure auditory short-term memory, sequencing skills, attention and concentration, in addition to the strong working memory component in the backwards condition especially (Flanagan & Kaufman, 2009; Groth-Marnat, 2009; Sattler, 2001). It was chosen as the measure of working memory as performance on this subtest on its own has been found to correlate well with the full WISC-IV working memory index (*r*=.86) and it has been included in a short form of the WISC-IV as the most psychometrically sound representative of the working memory subtest (Crawford, Anderson, Rankin, & MacDonald, 2010). Whilst it is auditory in modality, rather than visual like the OBK task, it was chosen to match this task due to its ease of administration, and sound psychometric properties covering the age range of the study sample.

2.5.2.1.2 Psychometric properties.

The WISC-IV battery as a whole was standardized on a large American sample of 2,200 children aged between 6-16 years, with the UK edition subsequently standardized on a sample of 780 children (Wechsler, 2003). In these samples the subtests used in this study showed good evidence of reliability. Average split-half reliability for Digit span across all age bands was .87 which is good. As split-half

reliability is not appropriate for processing speed measures test-retest reliability is given as the main measure of reliability for Symbol Search and was found to be .79 which is acceptable. Evidence for validity is presented from a number of sources. The internal structure of the test supports the underlying construct validity of each subtest, with Digit Span correlating most highly with the other measure of working memory in the battery (e.g. *r*=.49 with Letter-Number sequencing) and Symbol search correlating most highly with the other measures of processing speed (e.g. *r*=.53 with Coding). Criterion validity has been established in a number of special group studies also described in the technical manual. Performance on Digit span and Symbol Search were significantly poorer in a group of 89 children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) consistent with the literature suggesting children with ADHD perform worse on measures of processing speed and working memory in spite of overall IQ scores within the normal range (Doyle, Biederman, Seidman, Weber, & Faraone, 2000). The Symbol Search subtest was shown to significantly distinguish between children with both open and closed TBI giving evidence that it is sensitive to the difficulties in processing speed often seen in this group (Williams, Weiss, & Rolfhus, 2003).

2.5.2.1.3 Administration.

Symbol Search is a pencil and paper subtest. Participants were required to determine whether one of two target symbols were present in a group of five search symbols for each item. The participant completed as many items as they could in 120 seconds. Instructions were given verbally by the examiner as well as being demonstrated and the participant completed two practice items before starting the test. The Digit span subtest required participants to verbally repeat back strings of

numbers of increasing length spoken to them by the examiner. In the forwards condition the numbers were repeated exactly as heard. In the backwards condition the numbers must first be mentally reversed by the participant before being given. Two trials were completed at each number string length. If the participant gets a least one trial correct they progress to the next length of number string. The participant's raw score was calculated by totalling the number of correct strings given on all trials across both the forwards and backwards conditions and converted into an age standardised scaled score. Approximately 10 minutes was required to complete both subtests.

2.5.2.2 Children's Memory Scale (CMS; Cohen, 1997).

2.5.2.2.1 Description.

The CMS is a test of memory standardised for use in individuals 5-16 years of age. It assesses memory in three domains; auditory/verbal, visual/nonverbal and attention/concentration. For this study the Dot location subtest from the visual/nonverbal index was used to provide a measure of visual learning and memory as it comprises three learning trials and an immediate recall trial. Dehn (2008) describes it as a measure of visual-spatial short term memory and learning. The Dot location subtest was chosen to measure this domain due to these features of combining a spatial memory task with learning processes thereby covering the both cognitive domains reported to be measured by the OCL and CPAL tasks in the CogState battery. Alternative measures which could have been used include the Visual Learning subtest of the Wide Range Assessment of Memory and Learning (Sheslow & Adams, 1990) which has a similar format of presentation of visual information over several learning trials, or the Continuous Recognition Memory Test

(Hannay & Levin, 1989; Hannay, Levin, & Grossman, 1979) which has a very similar format to the OCL task of CogState however normative data is not available for this measure for the full age range covered in this study.

2.5.2.2.2 Psychometric properties.

The Children's Memory Scale was standardised on a representative sample of 1000 children from the US. Using this sample split-half and test-retest reliability data was calculated. The Dot Location subtest has a split-half reliability of .76 and a test re-test reliability of .81 which are both good. Practice effects on the battery were shown to be up to one standard deviation indicating that it is not suitable for retesting within a short period of time.

Validity of the scale is supported by internal factor analysis supporting the presence of three factors; auditory/verbal, visual/non-verbal and attention/concentration. The Dot location subtest is within the visual/non-verbal factor and correlates more strongly with other sub-tests in this factor aiming to assess similar visual memory constructs than those in other factors. The scale also shows moderate to high correlations with the Wechsler Memory Scale –III (Wechsler, 1997) and moderate correlations with the Wide Range Assessment of Learning and Memory –II (Sheslow & Adams, 2003). Clinical validity studies presented in the manual indicate that the scale is sensitive to memory impairments in children with TBI and brain tumours compared to normal controls. It is criticized for having strong floor effects in the youngest children as average scaled scores can be achieved for chance responding (Baron, 2004), however for the age range used in this study this is less of a problem.

2.5.2.2.3 Administration.

The Dot location subtest is administered by the examiner using a stimulus book and response grid and chips. Participants are shown a stimulus of eight dots (six for eight year olds) randomly located on a page for five seconds. The stimulus is then removed and the participant is required to replicate the locations of the dots on their response grid (4 squares by 4 squares for 9-16 year olds, 4 squares by 3 squares for 8 year olds) using the chips. This is repeated three times. A distractor stimulus is then shown and replicated before the participant is asked to replicate the first stimulus from memory. The score on all four trials is totalled and an age based standard score is calculated. This subtest was completed in approximately 7 minutes.

2.5.2.3 Trail Making Test A & B (TMT; Reitan, 1958, 1971).

2.5.2.3.1 Description.

The Trail Making Test Parts A & B, is a well-established and widely used measure of executive functioning particularly attention shifting, inhibitory control and cognitive flexibility (Kelly, 2000; Lezak et al., 2004). It was originally developed as part of the Army Individual Test Battery (Army Individual Test Battery, 1944) before being incorporated into the Halstead-Reitan Neuropsychological Test Battery (Halstead, 1947; Reitan, 1958), and later adapted for children (Reitan, 1971). It has been shown to be sensitive to general frontal lobe dysfunction (Pontius & Yudowitz, 1980; Stuss et al., 2001) although it has limitations in localizing the dysfunction (Lezak et al., 2004). This test was chosen as it assesses aspects of executive functioning similar to those reported to be captured by Total Errors and Rule Break Errors variables of the GMLT, and it has been used in previous adult construct validity studies (Cysique et al., 2006; Maruff et al., 2009).

The test is quick to administer with minimal equipment required making it suitable for assessment in participants homes and it is freely available. The Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) includes a version of the Trail Making Test with more robust normative data covering the age range included in this study however unfortunately it was unavailable for use. An alternative measure with more face validity in terms of comparison with GMLT could have been a maze task such as Porteus Maze Task (Porteus, 1959) however normative data covering whole sample age range is not available for this measure.

2.5.2.3.2 Psychometric properties.

Normative data for the TMT is available for children aged 7-13 from a sample of 392 children separated into one year brackets (Anderson et al., 1997). For adolescents normative data is available from a sample of 100 (mean age = 15.9 years, SD = 0.98) separated by gender (Barr, 2003). Older normative data is available for this age range from (Knights, 1966) and (Fromm-Auch & Yeudall, 1983) separated into age bands. For consistency with the normative data for the younger age range this data was used.

Test re-test reliability data for the TMT is variable but has been shown to be acceptable in an adolescent sample for Part B (r=.65), and to be good in some adult samples (Dikmen, Heaton, Grant, & Temkin, 1999; Levine, Miller, Becker, Selnes, & Cohen, 2004).

Evidence for the validity of the TMT as a measure of attentional abilities and more specifically executive functions including cognitive flexibility and attentional control is given by its moderate correlation with other measures of these areas including the Wisconsin Card Sorting Test (WSCT) and the Paced Serial Attention

Test (PASAT) seen in a number of studies (Kortte, Horner, & Windham, 2002; O'Donnell, Macgregor, Dabrowski, Oestreicher, & Romero, 1994) although this has not been replicated by all studies (Ardila et al., 2000). There is evidence that the TMT is sensitive to neurocognitive deficits including close-head injury with diffuse axonal damage (Felmingham, Baguley, & Green, 2004).

2.5.2.3.3 Administration.

The TMT is a timed pen and paper test completed in two parts. Part A requires the participant to draw a line connecting numbered circles scattered across the page in ascending numerical order. Part B requires them to alternate between numbers in ascending numerical order and letters in alphabetical order in the sequence they connect. Instructions for both parts of the test were given following those provided by (Strauss, Sherman, & Spreen, 2006). Both parts were completed as all published test instructions include both sections and Part A familiarises the child with the general concept of the task before moving on to the more complicated instructions of Part B. A short practice of each test to illustrate the instructions was given before the full test. Children under 15 completed an intermediate version with 15 circles in each part whilst children over 15 completed the adult version which has 25 circles in each part. If the child makes a mistake this is immediately pointed out by the examiner and they must correct the mistake before proceeding. The outcome variable which was used for further analysis was the time taken to completion on Part B with longer times indicating worse performance. On average 5 minutes was needed to complete both parts of the test.

2.5.2.4 Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson, & Nimmo-Smith, 1999).

2.5.2.4.1 Description.

The TEA-Ch is a test of attention standardised for use with individuals aged 6-15 years 11 months. The Map Mission subtest was used to provide a standardised measure of visual selective attention. This subtest was conceptually derived from selective attention measures in the adult measure, the Test of Everyday Attention (TEA) (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994). The Score! subtest was used to provide a standardised measure of vigilance (sustained attention). It is a children's version of a well validated approach to assessing sustained attention in adults, also found in the TEA (Robertson et al., 1994; Wilkins, Shallice, & McCarthy, 1987). These two subtests were chosen out of the full TEA-Ch battery because they are brief to administer, simple to understand, have adequate psychometric properties and cover visual attention and vigilance, the two aspects of attention measured by the IDN task of the CogState battery. Alternative measures of vigilance are relatively limited, but one of the most often used in research is the Connor's Continuous Performance Test (Conners, 1992) which is a computer based task that requires participants to press a button in response to any letter apart from X. It has a wide range of outcome variables and has normative data for ages 4 to adulthood, however, it requires around 14 minutes to administer, significantly longer than the Score! subtest, is not commonly used in clinical practice and was unavailable at the time of testing.

2.5.2.4.2 Psychometric properties.

The TEA-Ch was standardized on a large sample of Australian children aged between 6 and 15 years 11 months. Reliability was assessed using test-retest correlations where a suitable range in the data was available and percentage agreement in scores (within one standard deviation for first and second testing) where there was a ceiling effect. The Map mission subtest has a reliability coefficient of .65 which is acceptable. The Score! subtest has a percentage agreement of 76.2%.

Structural equation modelling of the full TEA-Ch battery supports a good fit for a three factor model; selective attention, attention control/switching and sustained attention. This measure of internal consistency within the battery supports the construct validity of the two subtests used in this study as measures of selective attention (Map Mission) and sustained attention (Score!). In addition when compared to other measures of attention the Map Mission subtest correlates significantly with the Stroop task (Trenerry, Crosson, DeBoe, & Leber, 1989), a measure of selective attention and the Score! subtest correlates significantly with the Matching Familiar Figures Test (Arizmendi, Paulsen, & Domino, 1981), a task which assesses impulsivity.

The TEA-Ch has also been assessed in a sample of 18 children with TBI (Manly et al., 1999) and significant difference in performance, compared to the control sample, was found on the Map Mission subtest at the α=0.001 level indicating it is sensitive to impairment. Performance on the Score! subtest was not significantly different between the groups in this small sample.

2.5.2.4.3 Administration.

The Map Mission subtest required the child to search a map and find as many target symbols as they could in one minute. The Score! subtest required the child to listen to a tape recording and keep track of how many 'scoring' sounds they hear. It is a task that has little intrinsic interest and is therefore a good measure of how well the child is able to sustain attention for a period of time. Approximately 10 minutes was required to administer both subtests. Both subtests are scored on the basis of the number of targets correctly identified and these raw scores are then converted into age scaled scores on the basis of gender specific normative data. As there is no equivalent measure of attention for children aged 16 years (the adult version of this measure having 18 years as its lower cut off) the normative data for the age group 15 years -15 years 11 months was used to standardise the data of 16 year old participants.

2.5.2.5 Grooved Pegboard (Klove, 1963).

2.5.2.5.1 Description.

The grooved pegboard is a test of manual dexterity which assesses speed and accuracy of hand eye co-ordination. Participants are required to rapidly place small pegs into holes under time constraints. It has been widely used in research and industrial settings and is included in several neuropsychological test batteries (Yancosek & Howell, 2009). It was used in this study to provide a measure of psychomotor function and was chosen as it has been used in previous adult validation studies of the CogState battery (Cysique et al., 2006; Maruff et al., 2009) and found to correlate significantly with the DET task.

2.5.2.5.2 Psychometric properties.

Normative data are available for the grooved peg board for ages eight to 14 years in age bands of one year divided by hand and statistically "smoothed" to provide consistent standard scores from age level to age level ((Knights, 1970) cited in (Baron, 2004)). Normative data for 15 and 16 year olds divided by hand are available in the test manual as part of a group of 172 15 to 19 year olds (Lafayette Instruments, 2002). Reliability data are reported from a large adult study (Ruff & Parker, 1993) which show test-retest reliability to be good (dominant hand $r=.72$, non-dominant hand $r=.74$, $p<.01$).

A recent MRI study in adults with brain tumours (Otten et al., 2012) provides construct validity evidence for the Grooved Peg Board test showing that performance on the task is correlated to connectivity between different motor areas of the brain and in those participants showing reduced connectivity performance was significantly different from controls. The test has also been used with children with learning disabilities showing a similar pattern or performance to adults with brain injury (Rourke, Yanni, MacDonald, & Young, 1973).

2.5.2.5.3 Administration.

The grooved peg board is a practical test which requires the participant to place 25 small metal pegs, with a rounded side and a grooved side into 25 similarly shaped but randomly orientated holes on a response board. This means the participant must rotate the peg before placing it in the hole. The task is completed twice, once using only the dominant hand and once only the non-dominant hand. The time taken to complete each trial is recorded. Age and gender based means and standard deviations are available allowing the calculation of z-scores. Only the

dominant hand score was used in the primary analyses. This test took approximately five minutes to complete.

2.5.2.6 Behaviour Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000)).

2.5.2.6.1 Description.

The BRIEF, an 86-item informant rated questionnaire, was used to provide a measure of executive function. It comprises eight clinical subscales which form two index scores and can be combined to give a global score (Global Executive Composite). The Inhibit, Shift and Emotional control subscales form the Behavioural Regulation index. The Initiate, Working Memory, Plan/Organise, Organisation of Materials and Monitor subscales form the Metacognition Index. Given the broad range of areas of executive function covered by the BRIEF, and the fact that it is tapping into behaviour by the child in their normal environment over a long time period, it provides information of high ecological validity of a type that is very difficult to obtain from direct psychometric testing in a structured environment. The measure was included in this battery for this reason, in order to assess the relationship between the GMLT and a more ecologically valid assessment of executive function than that provided by the TMT-B.

There are two versions of the BRIEF, one for parents and one for teachers. Whilst inter-rater reliability between the two versions has been found to only be moderate it is consistent with the different environmental settings observed. Equivalence was found between mother's and father's ratings. In this study only the parent form was completed by either the mother or father of the child depending on who was present at the testing session.

2.5.2.6.2 Psychometric properties.

The BRIEF was standardised on a large representative American sample of 1419 parent respondents (and 720 teacher respondents) of children aged between 5 and 18 years old. The internal consistency of the scale is reported as between 0.80-0.98 in the different parent, teacher and clinical or non-clinical samples. Test-retest reliability for the parent normative sample was r=.81 over an average interval of two weeks and for the clinical sample was r=.79 over an average interval of three weeks indicating that the test is stable.

Evidence to support this scales validity comes from correlations with the ADHD-Rating Scale-IV (DuPaul, Power, Anastopoulos, & Reid, 1998), Child Behaviour Checklist (Auchenbach, 1991) and Behaviour Assessment for Children (Connors, 1989; Reynolds & Kamphaus, 1992) which indicate that whilst the BRIEF is measuring similar constructs (i.e. subscales looking at the same construct were highly correlated) it also adds significantly different information. The Inhibit and Working Memory scales were able to distinguish children diagnosed with ADHD from controls and preliminary studies in the manual suggest it is sensitive to executive difficulties in children with TBI and frontal lobe lesions among a range of other conditions.

2.5.2.6.3 Administration.

The BRIEF is a parent completed rating scale in which the parent is asked to respond to 86 statements about children's behaviour by rating on a three point scale how often their child has had problems with the behaviour in the last six months. Printed instructions were given on the record form as well as verbally by the

examiner before the parent completed the scale to encourage the importance of accurate reporting. Parents were encouraged to ask for help if they had problems completing the questionnaire and all questionnaires were checked for completion. One parent completed the scale whilst the child was completing the CogState battery. On average parents took between 10 and 15 minutes to complete the measure. Age-standardise T-scores can be calculated for each index and the overall score. Only the Global Executive Composite score was used in the main correlation analysis. As there are several subscales of interest (including Inhibit, Shift, Working Memory and Monitor) which fall into both of the index scores (BRI and MI) the GEC score was chosen in preference to the subscale scores and index scores to limit the number of correlations conducted whilst including the widest possible information on executive function provided by the measure.

2.5.3 Confounding variable measures.

2.5.3.1 Wechsler Abbreviated Scale of Intelligence (WASI;Wechsler, 1999).

2.5.3.1.1 Description.

The two subtest version of this abbreviated test of intellectual function was used to provide a brief measure of IQ. The two subtests included are Vocabulary and Matrix reasoning. The Vocabulary subtest provides a good measure of crystallized intelligence and general intelligence. The Matrix Reasoning subtest is a measure of non-verbal fluid reasoning and general intellectual ability. A second edition of the WASI has recently been published and given the Flynn effect (Flynn, 1987b) of the inflation of IQ scores over time it would have been preferable to use this measure, however it was unavailable at the time of testing.

Brief measures of intelligence have been criticized for failing to provide a broad range of clinically useful information that can be obtained from a broader battery (Baron, 2004). However, in this instance the aim of using the measure is simply to obtain a brief indication of overall ability level to allow for consideration of it as a potential confounding factor, given the correlation between IQ and performance on other neuropsychological measures (e.g. (Duncan, 1995). Brief measures have been shown to do this well (see psychometric properties) in a way which is time efficient, which is of primary importance in the present case in order to keep the battery as a whole feasible for the child to complete in one session.

2.5.3.1.2 Psychometric properties

The WASI has been standardised for ages 6-89 years on a large representative American sample (n=2245) including 1100 children. Reliability of the two-subtest version calculated using the split half method is reported as ranging between .92 and .95 in the child sample with an average of .93 which is very good. Test-retest reliability at a mean re-test interval of 31 days was an average of .87 in the child sample indicating the test is stable. Inter-rater reliability of the scoring of the Vocabulary subtest, which requires some judgement on the part of the examiner was .98 indicating it can be scored very reliably.

Validity of the WASI two-subtest short form is supported by a strong correlation (.81) with the WISC-III, a more comprehensive assessment of intelligence in a sample of 176 children aged 6-16 years. It has been shown to be sensitive to deficits in clinical groups including children with learning disabilities and TBI when compared to matched controls.

2.5.3.1.3 Administration.

The two subtests were administered to the participant by the examiner in the order Vocabulary followed by Matrix Reasoning. The Vocabulary subtest required participants to orally define a series of words which become progressively more difficult. The words are presented in written form as well as being said to the participant by the examiner. The Matrix Reasoning subtest involved the participant choosing the most appropriate pattern to complete a grid or series from five options presented visually in a stimulus book. On average 20 minutes was needed to complete both subtests.

2.5.3.2 Paediatric Inventory of Emotional Distress (PI-ED; O'Connor, Carney, House, Ferguson, & O'Connor, 2010).

2.5.3.2.1 Description.

This 14-item self report measure is validated for use with children aged 7-17 and provides a measure of emotional distress (cothymia) over the previous week. It was developed as a paediatric version of the Hospital Anxiety and Depression scale (Zigmond & Snaith, 1983) and therefore retains the aim of that scale to avoid items about symptoms which may be due to either depression and anxiety or physical disease e.g. dizziness or tiredness, often included in other measures of depression and anxiety. This makes it particularly suitable for use in this study with a paediatric oncology population. It was included in the battery to provide a measure of emotional distress in order to investigate whether this is a confounding variable in performance on the neuropsychological tests in this study as evidence from the literature suggests low mood and anxiety can impair performance (Douglas, Porter,

Knight, & Maruff, 2011; Elderkin-Thompson et al., 2003; Emerson, Harrison, Everhart, & Williamson, 2001).

2.5.3.2.2 Psychometric properties.

The PI-ED was standardised in large school based sample of 1108 children aged between 7 and 17 years old, and a sample of 117 paediatric outpatients. Split-half reliability was found to be .83 in this sample for the overall cothymia factor, with test-retest reliability as .81 indicating that the measure is internally consistent and stable. Validity was investigated by analysing the correlation with the Beck Anxiety Inventory – Youth (BAI-Y) and Beck Depression Inventory – Youth (BDI-Y) scales with a correlation coefficient of .69 indicating that the measures are all tapping into strongly related constructs.

2.5.3.2.3 Administration.

The PI-ED was completed by the participant with supervision from the examiner to ensure they understood the instructions. One sample question was completed prior to moving on to the main portion of the measure to give the child the chance to practice using the four point response scale of 'Always', 'A lot of the time', 'Sometimes' and 'Not at all'. The measure took approximately 5 minutes to complete.

2.5.4 Un-standardised questionnaire measures.

2.5.4.1 Demographic questionnaire (Appendix J).

Participants and their parents were asked their age, gender and parental level of education, diagnosis, treatment received, time since diagnosis and time since

treatment finishing. For those participants still on maintenance treatment details of this were collected.

2.5.4.2 Acceptability questionnaire (Appendix K).

This questionnaire covered the acceptability of the testing procedure using the CogState battery by asking participants to rate the battery as a whole on 3 point Likert scales regarding difficulty, fatigue, distress, length, enjoyment and interest based on the protocol used by Pejnovic et al. (2012). A summary question asking participants if they would be happy to complete the tasks again was also included as was a question asking if they have any further comments they would like to make about the tasks. This questionnaire was analysed as part of an integrated service based research project (see Appendix L).

2.6 Assessment Procedure

The CogState battery, standard neuropsychological battery and paper questionnaire measures were completed by the child, and their parent where applicable, during a single study visit. Visits took place in the child's home at a table in at least a relatively undisturbed environment. The CogState battery was administered first followed by the acceptability questionnaire to allow for the acceptability of the battery to be assessed without interference from the other tasks. Following this the questionnaire measures and WASI were completed and then the standard neuropsychological battery. This order was the same for every participant. This is due to the fact that it is not recommended that the CogState subtests be counterbalanced to address order effects due to the risk of proactive interference between tasks which use similar stimuli (OCL and OBK). As such, to maintain

consistency in the presentation of both batteries the standard battery was also presented in a fixed order as described in Table 2. A break was offered to the child following completion of the WASI and additional breaks could be requested as required by the child or were suggested by the researcher if needed to maintain the arousal level of the child.

2.7 Ethical Considerations

2.7.1 Ethical approval.

Appropriate NHS Ethical approval and local Research and Development approval was sought prior to the study commencing (see Appendices M-P).

2.7.2 Use of children in research and potential burden to participants.

As this study involves participants under 16 years old the Medical Research Council Ethics Guide on involving children in research (Medical Research Council, 2004) were considered. This guidance states that "research involving children should only be carried out if it cannot feasibly be carried out on adults" (p.13). This study aimed to validate a measure already validated in adult populations for use with a particular child population. It was therefore not possible to carry out the study without the use of child participants. The MRC Ethics guide also emphasises the importance of assessing the risk to the child participants and the potential benefits and harm resulting from participation. This study involved only procedures such as questioning and observing the child's performance on cognitive assessments. It was considered unlikely that this would result in any harm to the child beyond potential boredom and tiredness however if psychological distress was seen to be caused by the testing procedure it was stopped immediately, the cause of the distress discussed

and appropriate support identified. This occurred on one occasion resulting in the testing session being terminated, further support identified in the form of an upcoming clinic visit the next week, feedback being sent to the clinical team with the consent of the family and the participant being excluded from the analysis. The potential benefits for the children participating included a brief assessment of their neuropsychological functioning which may have informed further assessment based on the clinical judgement of their clinical team. More prominently it was hoped that by validating a brief and easily administered neurocognitive assessment tool in this population it may become part of standard clinical practice and therefore contribute to meeting the recommendation of the Children's Oncology Group (Nathan et al., 2007) that all at risk children receive some neuropsychological evaluation.

2.7.3 Informed Consent.

Informed consent was sought for all study participants. For participants aged 8-15 years consent was sought from a person with parental responsibility and assent was sought from the child. For participants aged 16 years consent was sought from them with consent also being sought from their parent regarding the questionnaire measures they completed. If a child and their parent did not agree on taking part in the study the child was not recruited as the cooperation of both parties was required to complete the study measures, however this situation did not occur.

2.7.4 Coercion.

Potential participants were initially approached by members of the clinical team with whom they were familiar. It was made clear that it was their choice if they would like to be contacted by the researcher or not and that there were no adverse

consequences if they decided they would not like to take part. There was an opportunity to ask questions to the researcher at the visit prior to the consent/assent forms being signed. It was also made clear that participants could withdraw their consent/assent at any time without giving a reason.

2.7.5 Access to appropriate follow up.

With the family's consent a brief report of the child's performance on the standard neuropsychological measures and the measure of emotional distress was sent to the child's clinical team via the principal investigator for each of the three paediatric oncology services taking part in the study. It was the responsibility of the clinical team to determine if further testing or follow up was required based on the child's scores on the research measures. The three paediatric oncology services approached to take part in the study indicated that they were able to provide appropriate follow up as required. Families were informed that they may be approached by their clinical team regarding follow up if the team thought this was required.

2.7.6 Confidentiality.

Participant's details were passed to the researcher only once they had given their consent for this to happen. Each participant was given a unique participant number and all assessment information was coded with this number and stored separately to identifiable information and consent forms to ensure anonymity of assessment results.

2.7.7 Protection of information.

All paper information generated during the study was stored securely in locked filing cabinets at the University of East Anglia (UEA). A locked briefcase was used to transport data. All electronic information was stored on password protected UEA computer systems and an encrypted memory stick for use on other computers. Data were not saved to any other computer. Data will be stored for a minimum of 5 years as per UEA and NHS protocols and will then be securely disposed of.

2.8 Plan for Data Analysis

Data will be entered into SPSS for analysis. Assumptions of parametric tests will be checked. All data will be transformed into z-scores for ease of comparison across the different subtests as suggested by Crawford (2013) where suitable normative data is available. Where higher scores indicate poorer performance z-scores will be multiplied by -1 to aid interpretation so that across all tests higher values indicate better performance. Raw data will be used for the Continuous Paired Associate task and the Groton Maze Learning task as no suitable normative data is available.

For the first research question regarding construct validity the six a priori hypotheses will be investigated using Pearson's product moment correlations to determine the size and significance of each relationship (if assumptions for parametric tests are met, Spearman's rho if the data is non parametric). This will involve nine separate comparisons and significance tests will be adjusted for multiple comparisons using the Holm method (Wright, 1992) to reduce the risk of type 1 errors. The Holm method is a modification of the Bonferroni correction which

maintains the experimentwise error rate of α but is considered less conservative and was selected for this reason. It follows a sequential procedure in which the uncorrected *p* values are ordered by size and tested, beginning with the smallest value, with each *p* value compared to α/(n-*i* +1) where *i* is the position in the sequence, rather than α/n as in a standard Bonferroni correction. Once a non-significant result is obtained all larger *p* values are deemed non-significant. Additional exploratory analysis of components of the standard tests will conducted if indicated.

The second research question will also be investigated using Pearson's product moment correlations to determine the size and significance of the relationship between months since diagnosis and a summary score of overall performance on the CogState battery (if assumptions for parametric tests are met, Spearman's rho if the data is non parametric). IQ and total score on the PI-ED will also be correlated with the CogState summary score and if this relationship is significant then a subsequent partial correlation analysis will be carried out to remove the effect of the co-variant.

Acceptability of the testing procedure will be descriptively reported giving proportions of respondents rating the tasks positively, neutrally and negatively. Feasibility will be reported as the percentage of eligible patients completing the CogState assessment and the mean length of time to complete and score the battery. This data forms part of a separate but integrated service based research project the results of which are presented in Appendix L.

3 Results

3.1 Overview

In this chapter the results of the study are presented in five parts. First an overview of the clinical and demographic characteristics of the sample is given. This is followed by a description of the preliminary analysis of the data including accounting for issues in the data and investigating the distribution of each variable. The third and fourth sections address the two main research questions and associated hypotheses in turn. The final section provides a summary of the results.

3.2 Demographic and Clinical Characteristics of the Sample

Thirty-seven participants were included in the study aged between 8 years 6 months and 16 years 11 months. The demographic and clinical details of the sample are presented in Table 5.

Table 5
Demographic and Clinical Characteristics of the Sample

Participant Characteristic	Whole Sample (n=37)
Gender n (%)	
Male	16 (43)
Female	21 (57)
Age at testing (years)	
Mean	12.7
SD	2.4
Range	8.5-16.9
Age at diagnosis (years)	
Mean	5.5
SD	3.6
Range	0.5-15.6
Time since diagnosis (years)	
Mean	7.1
SD	3.6
Range	0.25-13.25
Diagnosis n (%)	
Acute Lymphoblastic Leukaemia	27 (73)
Other Leukaemia	2 (5)
CNS Tumour	8 (22)
Treatment n (%)[a]	

Participant Characteristic	Whole Sample (n=37)
Surgery	7 (19)
Chemotherapy (inc. ITC)	30 (81)
Radiotherapy	2 (5)
Corticosteroids	26 (70)
Other	3 (8)
Maintenance treatment at time of testing n (%)	
Yes	4 (11)
No	33 (89)
Parental Level of Education n (%)	
None	1 (3)
GCSE/O Level	12 (32)
A-level or equivalent	11 (30)
Undergraduate	11 (30)
Post Graduate	2 (5)
WASI Two-subtest IQ (standard score)[b]	
Mean	101.50
SD	14.86
Range	78-135
PI-ED total score[c]	
Mean	12.05
SD	5.89
Range	3-28

Note. CNS=Central Nervous System, IT=intrathecal chemotherapy
[a] Up to three treatments were recorded for each participant.
[b] WASI = Wechsler Abbreviated Scale of Intelligence; Standard scores have a mean 100 and a standard deviation of 15
[c]PI-ED = Paediatric Inventory of Emotional Distress; Clinical cut off is 10 for males and 11 for females

A significant majority (75%) of the sample had a diagnosis of leukaemia with only 22% having been treated for a variety of brain tumours. Whilst leukaemias are more prevalent in the population of children and young people treated for cancer accounting for around 31% of 0-19 year olds diagnosed with any form of cancer in America as of January 2011 verses 18% for CNS tumours (Howlader et al., 2011), the proportions in this study do not fully reflect this clinical picture (if the recruitment had been fully representative 63% of the sample would have a diagnosis of leukaemia and 37% would have a diagnosis of a CNS tumour). A number of factors, including survival rates, severity of motor and sensory late effects, and

current service provision of neuropsychological assessment may account for this discrepancy and will be discussed further in the next chapter.

General intellectual ability in the sample as measured by the WASI two-subtest short form does not differ significantly from the normative mean suggesting that on this brief global measure there is no significant impairment in functioning compared to typically developing peers. This contrasts with some other studies using similar mixed diagnosis samples (e.g. Krull et al., 2008) where the mean Full Scale IQ was 91.9 (SD 16.09)) and may reflect the low use of radiation treatment in the sample. Of note, performance on the more specific neuropsychological measures in the standard battery, described below, does indicate some significant levels of impairment in the sample, especially on measures of executive function, which are not reflected in the brief global IQ assessment. Table 6 presents the performance on these standard measures, and the CogState tasks, expressed as standard scores with a mean of 100 and standard deviation of 15 for ease of interpretation. In addition the number of children scoring ≥1SD below the mean on each task is indicated.

Overall scores on the PI-ED exceed the clinical cut off indicating the presence of clinically significant levels of emotional distress within the sample. Specifically 8 of the male participants (50%) and 15 (71%) of the female participants met or exceeded the clinical cut off score.

Table 6

Clinical performance on the Standard Battery and CogState battery

Task	Mean	SD	Median	Number ≥1SD below the mean (%)
Standard Battery				
Grooved Peg Board	79.15	31.95	86.05††	18 (49)
Symbol Search	99.10	15.15	100.00	10 (27)
Map Mission	90.85*	19.20	89.95	14 (38)
Score!	89.95**	15.15	89.85	17 (46)
Dot Location	100.45	14.25	100.00	10 (27)
Digit Span	90.40	11.55	85.00††	19 (51)
TMT-B	81.85	30.45	94.15†	16 (43)
BRIEF GEC	83.65**	20.70	82.00	22 (59)
CogState				
Detection	103.90	14.70	103.30	3 (8)
Identification	103.30	17.25	103.75	6 (16)
One Card Learning (outlier removed)	100.60	19.95	107.05	9 (25)
One Back	98.20	18.60	101.95	7 (19)
Composite	100.9	15.00	99.55	3 (8)

Note. BRIEF GEC=Behaviour Rating Inventory of Executive Function General Executive Composite, TMT-B = Trail Making Test –B
* p≤.05 **p≤.001 both One-sample t-test
†p≤.05 †† p≤.001 both One-sample Wilcoxin Signed Rank test

3.3 Preliminary Analysis

3.3.1 Missing data.

Data were missing in two variables in the standard battery. Two participants were unable to complete the Score! subtest due to technical difficulties with the audio equipment needed for this test. One participant did not complete the TMT-B subtest due to the materials being unavailable at the time of testing. Participants with missing data points were excluded pairwise from the relevant analysis so as to ensure maximum use of the available data.

3.3.2 CogState auditory feedback.

Due to a technical difficulty with the hardware running the CogState programme, which was subsequently resolved, the first six participants completed the CogState battery with no auditory feedback. Visual feedback was still present

within each task which were otherwise completed in the same way as the other 31 participants who had auditory feedback. To determine if this difference in administration significantly affected the results obtained on the primary outcome variables the group means for each group (sound and no sound) were compared with an independent t-test. Homogeneity of variance assumptions were not violated. No significant differences in mean were found for any of the six variables (p= 0.19-0.96) indicating that the distribution of results was not affected by the presence or absence of auditory feedback. Unequal group sizes can impact on the robustness of the independent t-test, however the impact is to increase the likelihood of Type 1 errors therefore this would not affect the conclusion from this test. Therefore the entire sample has been retained for the remaining analysis and no further distinction will be made between those participants who received auditory feedback and those who did not.

3.3.3 Descriptive statistics and tests for normality.

Prior to analysis the distribution of each variable was assessed using descriptive statistics for central tendency (mean and median), variance (range and standard deviation) and for adherence to a normal distribution (skew and kurtosis). In addition normality was assessed by visual inspection of histograms and box plots and by calculating the Kolmogrov-Smirnov statistic (D). As the CogState primary outcome variables are provided as transformed distributions further transformations of the data to meet the assumptions of parametric analysis were not considered. Outliers were examined individually as described below to determine if they should be excluded from the analysis due to extraneous factors affecting the score. This should only be done if there is good reason to believe the score is not representative of the sample under test (Field, 2009).

For clarity, the signs of the z-scores have been reflected where necessary so that lower scores indicate poorer performance on all variables. Where raw scores were used in the analysis this was not possible and the impact of this on the direction of the relationship is discussed below where applicable.

3.3.3.1 CogState.

The descriptive data for the primary outcome variable for each of the four CogState subtests with sufficient normative data to allow z-scores to be calculated are displayed in Table 7, along with a composite score derived from the mean of these four subtests z-score for each participant.

Table 7
Descriptive Statistics for the CogState Subtests with z-score Distributions

		Range					Skew		Kurtosis	
Variable	n	Min	Max	Median	M	SD		SE		SE
DET (log_{10} reaction time)	37	-1.65	2.11	0.22	0.26	0.98	-0.05	0.39	-0.64	0.76
IDN (log_{10} reaction time)	37	-2.09	2.87	0.25	0.22	1.15	0.14	0.38	-0.22	0.76
OCL (arcsine square root accuracy)	37	-10.21	2.83	-0.03	-0.24	2.13	-2.87	0.39	12.97	0.76
OCL (outlier removed)	36	-3.35	2.82	0.47	0.04	1.33	-0.10	0.39	0.37	0.77
OBK (log_{10} reaction time)	37	-3.64	3.19	0.13	-0.12	1.24	-0.29	0.39	1.85	0.76
Composite	37	-2.95	2.03	-0.03	0.06	1.00	-0.64	0.39	1.06	0.76

Note. DET=Detection, IDN=Identification, OCL=One Card Learning, OBK=One Back

The DET (D(37)=0.08), IDN (D(37)=0.07) and OBK (D(37)=0.10) subtest z-score distributions are not significantly different from the normal distribution (all $p>0.05$) and therefore suitable for parametric analysis. The Composite score distribution was also not significantly different from normal (D(37)=0.09). The OCL z-score distribution is significantly different from normal, (D(37)=0.184, $p<0.01$) with significant negative skew and leptokurtosis meaning the assumptions of

normality have been violated. Inspection of the boxplot revealed one extreme outlier in the data (z=-10.21). Examining this case in more detail showed there was no error in data recording but that this participant's testing session had taken place amid unavoidable moderate levels of distraction. Given this and the fact that the score on this subtest was inconsistent with the participants performance on the CPAL task (also measuring visual learning and memory) it was decided that this data point should be excluded from the analysis. Following the removal of this outlier the distribution of the One Card Learning task was no longer significantly different from normal ($D(36)=0.09$, $p>0.05$) and suitable for parametric analysis.

Suitable normative data are not currently available for the Continuous Paired Associate Task or the Groton Maze Learning Task due to low numbers. Therefore the raw data was used in the main analyses. As different versions of the GMLT are presented in the 8-9 year old battery and the 10-16 year old battery this data is presented separately. Descriptive data for these two subtests are presented in Table 8.

Table 8
Descriptive Statistics for the CogState Subtests Using Raw Data in the Primary Outcome Variable

		Range					Skew		Kurtosis	
Variable	n	Min	Max	Median	M	SD		SE		SE
CPAL (errors)	37	1	71	8	14.27	15.31	2.54	0.39	7.36	0.76
GMLT 8-9 years (total errors)	8	34	76	50	51.13	13.92	0.69	0.75	0.41	1.48
GMLT 10-16 years (total errors)	29	45	82	63.5	61.37	11.84	0.30	0.75	0.03	1.48

Note. CPAL=Continuous Paired Associate Learning, GMLT=Groton Maze Learning Task

The Groton Maze Learning Task total errors variable distribution is not significantly different from the normal distribution for either age range (8-9 years $D(8)=0.14$; 10-16years $D(29)=0.11$). However the Continuous Paired Associate

Learning task accuracy variable distribution is significantly positively skewed and leptokurtic with analysis indicating it is significantly different from the normal distribution ($D(37)=0.193$, $p<0.05$). Inspection of the histogram and stem and leaf plot reveal two significant outliers. Examining these cases in more detail did not reveal any data errors or particular difficulties in the testing session. Of note the two outliers were obtained by the two youngest children in the sample (8 years 6 months and 8 years 8 months). However there was deemed to be no justifiable reason to remove these data points therefore they were retained and non-parametric analysis was used for this variable.

3.3.3.2 Standard battery.

Descriptive statistics for the z-score distribution of each variable from the standard battery are presented in Table 9.

Table 9
Descriptive Statistics for the Primary Outcome Variables in the Standard Battery

		Range					Skew		Kurtosis	
Variable	n	Min	Max	Median	M	SD		SE		SE
GPB (D-hand)	37	-8.8	1.54	-0.93	-1.39	2.13	-1.87	0.39	4.34	0.76
SS	37	-2.0	2.0	0.00	-0.06	1.01	-0.02	0.39	-1.02	0.76
MM	37	-3.0	1.67	-0.67	-0.61	1.28	-0.22	0.39	-0.52	0.76
Score!	35	-2.67	1.33	-0.67	-0.67	1.01	0.14	0.40	-0.63	0.78
DL	37	-2.0	1.67	0.00	0.03	0.95	-0.18	0.40	-0.82	0.76
DS	37	-1.67	1.33	-1.00	-0.64	0.77	0.62	0.39	-0.36	0.76
TMT-B	36	-7.44	1.36	-0.39	-1.21	2.03	-1.41	0.39	1.86	0.77
BRIEF GEC	37	-4.40	0.80	-1.20	-1.09	1.38	-0.52	0.39	-0.38	0.76

Note. BRIEF GEC = Behaviour Rating Inventory of Executive Function General Executive Composite, D = Dominant, DL=Dot Location, DS = Digit Span, GPB = Grooved Peg Board, SS = Symbol Search, TMT-B = Trail Making Test-B

Of these variables five (WISC Symbol Search, $D(37)=0.14$; TEA-Ch Map Mission, $D(37)=0.08$, TEA-Ch Score!, $D(35)=0.13$; CMS Dot location, $D(37)=0.13$; and BRIEF GEC, $D(37)=0.12$) were not significantly different from the normal distribution (all $p>0.05$) and suitable for parametric analysis. The distributions of three variables were found to be significantly different from the normal distribution.

The Grooved Peg Board dominant hand distribution (D(37)=0.16, p=0.02) was significantly negatively skewed and leptokurtic. Inspection of the boxplot revealed one extreme outlier (>3xIQR) and two further outliers in the data. Examination of these individual cases did not reveal any data errors or difficulties in the testing session therefore there was considered to be no justifiable reason to remove them. The WISC Digit Span distribution (D(37)=0.19, p<0.01) was significantly positively skewed however no outliers were identified on the boxplot. The TMT-B distribution (D(36)=0.19, p<0.01) was significantly negatively skewed and leptokurtic. Inspection of the boxplot revealed two outliers in this variable. Examination of these cases revealed no data errors and no particular difficulties in the testing sessions, with these scores being consistent with the impairment shown in the BRIEF GEC (both >2SD below the mean). Therefore it was decided that there was no justification to remove these data points. As a result non-parametric analysis was used for correlations involving these variables.

3.3.3.3 Confounding variables.

Descriptive statistics for the two potentially confounding variables relevant to research question two; IQ as measured by the WASI two sub-test version and emotional distress as measured by the PI-ED, are presented in Table 10.

Table 10
Descriptive Statistics for IQ and the PI-ED

		Range					Skew		Kurtosis	
Variable	n	Min	Max	Median	M	SD		SE		SE
IQ z-score	37	-1.47	2.33	-.067	.10	.99	.38	.39	-.87	.76
PI-ED total score	37	3	28	11.88	12.05	5.89	.33	.39	-.12	.76

Note. PI-ED = Paediatric Inventory of Emotional Distress

Both variables were found to be normally distributed (IQ, D(37)=.13, p>.05; PI-ED, D(37)=.10, p>.05), and therefore suitable for parametric analysis.

3.4 Primary Research Question 1: Does CogState demonstrate adequate construct validity in a population of children who have survived a brain tumour or leukaemia when compared to a standard neuropsychological battery?

Both batteries cover the main areas of neurocognitive functioning shown by previous research to be most often affected by childhood cancer and its treatment. If CogState is a valid assessment of these areas in this population several hypotheses can be made about which of its subtests will correlate with which standard neuropsychological tasks. Each of these hypotheses will now be considered in turn. Where both variables met the assumptions of parametric analysis Pearson product-moment correlation (r) was used to investigate the relationship between them. Where either of the variables violated the assumptions of parametric analysis Spearman's Rho (r_s) was used. In addition 95% bootstrap confidence intervals (1000 samples, simple sampling and percentile method) are reported for each correlation. Scatterplots of all of the correlations below are presented in Appendix Q.

In the data analysis plan nine correlations were planned to address these hypotheses with the significance level adjusted using the Holm correction to reduce the risk of Type 1 errors. Given the need to analyse the data from the Groton maze learning task in two separate age bands due to the lack of appropriate normative data, two further comparisons are required reducing the significance level further. Further unplanned correlations between components of the standard tests and the CogState subtests are considered exploratory and are not included in this correction. Given the relatively conservative nature of this adjustment specific p values are reported to allow consideration of relationships which may be significant at the standard $\alpha = .05$

level. All probabilities are two-tailed. Correlation coefficients constitute an effect size, describing the strength of the relationship between the variables (Field, 2013). They are reported in full and described following the convention of Cohen (Cohen, 1992) as 0.1 being small, 0.3 medium and 0.5 large.

3.4.1 Hypothesis 1: The Detection task of the Cogstate battery measures psychomotor function and processing speed and will be positively correlated with performance on the Grooved Peg Board task and the WISC-IV Symbol Search subtest.

Performance on the Detection task as measured by the primary outcome variable of reaction time (Log_{10} tranformation) was found to be not significantly positively related to performance on the Grooved peg board dominant hand, r_s = .33, p = .05, 95% CI [-.01, .58] or the Symbol Search subtest, r = .28, p = .10, 95% CL [-.03, .59] at the corrected α-level. Both relationships represent a moderate effect size and for the GPB the relationship is significant at α=0.05, however the 95% confidence intervals for both correlations include zero indicating that this result is not robust. Therefore the hypothesis that it is a valid measure of psychomotor function and processing speed in a paediatric oncology population based on its correlation with the GPB and SS tasks does not appear to be supported based on this data. This is in contrast to the available literature on the construct validity of the adult battery and possible reasons for this disparity will be discussed in the next chapter.

3.4.2 Hypothesis 2: The Identification task of the Cogstate battery measures visual attention and vigilance and will be positively correlated with performance on the Map Mission and Score! subtests of the TEA-Ch.

Performance on the Identification task as measured by the primary outcome variable of reaction time (Log_{10} tranformation) was found to be significantly positively correlated with performance on the Map mission subtest, r = .47, p 0.003, 95% CI [.33, .75]. This relationship has a large effect size. The relationship with the Score! Subtest (n = 35) was not significant but still represents a moderate effect size, r = .32, p = .06, 95% CI [.01, .58]. Therefore the hypothesis that the Identification task is a valid measure of visual attention in a paediatric oncology population is supported based on its correlation with the Map Mission task and the hypothesis that it is a valid measure of vigilance is partially supported based on its correlation with the Score! task.

3.4.3 Hypothesis 3: The One-Card Learning Task of the CogState battery measures visual learning and memory and will be positively correlated with performance on the CMS Dot location subtest.

Performance on the One Card Learning task as measured by the primary outcome measure of accuracy (arcsine square root transformation) was not significantly correlated with overall performance on the Dot location subtest, r = .19, p = .26, 95% CI [-0.13, 0.43]. This result indicates that evidence for the construct validity of the One-Card Learning task as a measure of visual learning and memory in a paediatric oncology population is not provided based on its convergent validity with the Dot location subtest in this sample. This is in contrast to the available

literature on the One-Card Learning task in adult populations and potential contributing factors will be considered in the next chapter.

3.4.4 Hypothesis 4: The Continuous Paired Associate Learning Task of the CogState battery measures visual learning and memory and will be positively correlated with performance on the CMS Dot location subtest.

Performance on the Continuous Paired Associate Learning task as measured by the primary outcome variable of total errors was not significantly related to performance on the Dot location subtest, r_s = -.33, p = .04, 95% CI [-0.57, -.02] however this analysis does reveal a medium effect size for the relationship which is significant at the uncorrected level and the confidence intervals do not include zero indicating that some level of negative correlation is a robust finding, although the range in size is very large. The correlation is negative rather than positive but this is due to the fact that higher scores on the CPAL task reflect poorer performance therefore the underlying relationship is in the expected positive direction. Based on this analysis there is some evidence in support of hypothesis that the CPAL task is a valid measure of visual learning and memory in a paediatric oncology population through convergent validity with the Dot location test.

3.4.5 Hypothesis 5: The One-Back Task of the CogState battery measures working memory and will be positively correlated with performance on the WISC-IV Digit Span subtest.

Performance on the One-back task as measured by the primary outcome variable of reaction time (Log_{10} transformation) was not significantly positively

correlated with performance on the Digit Span subtest although a small to medium positive relationship was found, r_s = .23, p = .17, 95% CI [-.12, .53].

The WISC-IV Digit Span subtest is made up of both forwards and backwards conditions which tap more specifically into efficiency of attention and working memory respectively (Baron, 2004). Given the hypothesis specifically relates to working memory it was decided to further investigate this hypothesis by using Longest Digit Span Backwards (LDSB) as the outcome variable for the Digit Span Subtest. Means and standard deviations for this measure separated into one year age groups are given in the WISC-IV manual (Wechsler, 2003) allowing the calculation of age corrected z-scores. The distribution of these scores was found to be not significantly different from normal, *M* =-.28, SD =.66, D(37) = .10, p>.05, therefore Pearson's product-moment correlation analysis was used. The relationship between LDSB and the One-Back task is significant and has a medium effect size, *r* = .37, p = .042, 95% CI [-.07, .60]. However the 95% confidence intervals for this correlation are wide and include zero meaning that this finding is not robust.

Based on this analysis there is some evidence in support of the hypothesis that the One-Back task is a valid measure of working memory in a paediatric oncology population based in its convergent validity with the Digit Span subtest but with limited confidence.

3.4.6 Hypothesis 6: The Groton Maze Learning Task of the CogState battery measures executive function, including cognitive flexibility and will be positively correlated with performance on TMT-B and the BRIEF total score.

Performance on the Groton Maze Learning Task (GMLT) was measured by the primary outcome total errors, using the raw data as suitable normative data was not available in order to calculate age corrected z-scores. High scores on this variable indicate poorer performance, therefore negative correlations indicate a positive relationship. As the task had alternate forms in the battery presented to the 8-9 year olds and the 10-16 year olds these scores cannot be considered to come from the same distribution and therefore were considered separately.

For participants aged 10-16 years (n = 28), although a small to medium relationship was found between GMLT and TMT-B it was in the opposite direction to expected and non-significant, r_s = .19, p = .33, 95% CI [-.12, .60]. For participants aged 8-9 years (n = 8) a significant relationship with a large effect size was found between performance on the GMLT and Trails B in the expected direction, r_s = -.86, p = 0.007. 95% CI [-1.00, -.29]. However, as this sample size is very small this result should be treated with caution.

The relationship between performance on the GMLT and the BRIEF Global Executive Composite (GEC) score for participants aged 10-16 years (n=29) was not significant, r_s = .14, p = .47, 95% CI [-.18, .46]. However for participants aged 8-9 years (n=8) a relationship with a large effect size was found in the expected direction, although not significant in this small sample and of questionable reliability given this and the wide confidence intervals r_s = -.60, p = 0.12, 95% CI [-.92, .15].

Given that the BRIEF GEC is a generalised measure of many aspects of executive functioning it was decided to investigate if significant relationships were present between the GMLT total errors variable and selected subtests from the BRIEF measuring aspect of executive function which are more specifically targeted in the GMLT including monitoring, working memory, cognitive flexibility and inhibition (Pietrzak et al., 2008). Given the small numbers, these analyses were not performed in the 8-9 age group. In the 10-16 year age group correlations were calculated between GMLT total errors variable and the more specific measure GMLT rule break errors variable and the Inhibit, Shift, Working Memory and Monitor subtests of the BRIEF. No significant relationships were found at α-level 0.05.

Therefore, these specific analyses do not appear to provide support for the validity of the version of the GMLT in the 10-16 year old battery as a measure of executive function based on its convergent validity with either Trails-B or the BRIEF. However, the converse it true for the 8-9 year old age group, where this analysis provides some evidence of a strong relationship between the measures indicating that this version of the task may be a valid measure of executive function in this population, although this conclusion is based on a very small sample size and should be treated with caution. This unexpected pattern of results will be considered further in the discussion.

3.5 Primary research question 2: Given the research showing intellectual performance declines over time since diagnosis (e.g. Spielger et al., 2004) is there a relationship between time since diagnosis and performance on the CogState battery?

Based on this research question one hypothesis was made which is considered below.

3.5.1 Hypothesis 7: Time since diagnosis will be negatively correlated with overall performance on the CogState battery.

This hypothesis was investigated by analysing the correlation between time since diagnosis (months) and the CogState composite score derived from four of the six tasks included in the CogState battery; DET, IDN, OCL and OBK. Two tasks, CPAL and GMLT, were not able to be included in the composite score due to the current lack of robust normative data for these subtests meaning that valid z-scores could not be calculated. As a result of this the composite score does not include any measures that claim to assess executive functioning. The composite score was calculated by taking the mean of the participant's z-scores across the four tasks included following the procedure detailed by the test publisher (A. Schembri, personal communication, May 20th, 2014).

As IQ and mood have been shown in the literature to correlate with performance on neuropsychological tasks (Baron, 2004) these variables were investigated as potential confounding factors in the relationship between time since diagnosis and performance on the CogState battery. The two-subtest short form of the WASI was used to provide an estimate of IQ. The PI-ED self-report questionnaire was used to provide a measure of emotional distress in the week preceding testing. To determine if these variables were significantly related to the

CogState composite score, or time since diagnosis, Pearson's product-moment correlations were calculated and are presented in Table 11.

Table 11

Correlations between IQ, Emotional Distress, CogState Overall Performance and Time Since Diagnosis

	Time since diagnosis (months)	CogState composite z-score	IQ z-score	PI-ED total score
Time since diagnosis	1	.32	-.06	.28
CogState composite z-score	-	1	.43**	.12
IQ z-score	-	-	1	-.26
PI-ED total score	-	-	-	1

Note. PI-ED = Paediatric Inventory of Emotional Distress
**p<.01 (two-tailed)

This analysis shows that there is a medium but non-significant relationship between time since diagnosis and the CogState composite score although it is in the opposite direction to expected i.e. as time since diagnosis becomes longer overall performance on the battery improves. However, there is also a significant medium to large relationship between estimated IQ and the CogState composite score and a medium but non-significant relationship between time since diagnosis and PI-ED total score. Therefore a partial correlation controlling for the effect of IQ and emotional distress was conducted. Controlling for these relationships the relationship between time since diagnosis and performance on the CogState composite score did not reach significance at the α=.05 level r =.32, p = .06, 95% CI [.01, .57] although the confidence interval is wide indicating this is not a robust finding. Based on this analysis the hypothesis that time since diagnosis will be negatively correlated with overall performance on the CogState battery is not supported.

In addition to considering overall performance on the CogState battery this analysis also shows that in this sample there is no significant relationship between

time since diagnosis and IQ, r=-.06, p=.71, 95% CI [-.34, .21] in contrast to the current literature. This result remains the same when controlling for the effect of emotional distress at the time of testing, r=.01, p=.96, 95% CI [-.27, .33]. This will be discussed further in the next chapter.

3.6 Summary of the results

In summary, in relation to the first research question regarding the construct validity of the CogState battery, based on convergent validity with the standard measures used in this study only the Identification task is robustly supported as a measure of visual attention. There is partial support for it as a measure of vigilance. Partial support is given to the CPAL task as a measure of visual learning, and the One-Back task as a measure of working memory. The GMLT in the under 10 year old battery is partially supported as a measure of executive functioning although with caution given the very small sample size. The results of this study do not provide evidence in support of the validity of the Detection task as a measure of psychomotor functioning or processing speed, the One Card Learning task as a measure of visual learning and memory or the GMLT in the 10-16 year old battery as a measure of executive function based on convergent validity with the specific measures used to provide a standard measure of each construct. These results are in contrast to the current adult construct validity literature on CogState and possible contributing factors will be considered further in the next chapter

In relation to the second research question regarding overall performance on the Cogstate battery decreasing as time since diagnosis increases the results of this study do not support this hypothesis. In addition no relationship was found between IQ and time since diagnosis.

The possible reasons for these results and their clinical and theoretical implications are discussed in the next chapter.

4 Discussion

4.1 Chapter Overview

This chapter provides an overview of the results of the study and places them in the context both of the previous literature on the CogState battery but also wider clinical factors. The strengths and weakness of the methodology used are described and the potential impact of this on the outcomes of the study are considered. Following this the implications of this study both in clinical and theoretical contexts are discussed and recommendations for future research given. The chapter ends with a brief conclusion.

4.2 Evaluation of Research Hypotheses

In this section each research hypothesis will be considered in turn and the results of this study discussed in relation to the existing literature.

4.2.1 Research question 1: Does CogState demonstrate adequate construct validity in a population of children who have survived a brain tumour or leukaemia when compared to a standard neuropsychological battery?

4.2.1.1 Factors affecting the interpretation of all hypotheses.

Before considering the hypothesis in turn the factors which impact in general on the interpretation of the results will be discussed.

4.2.1.1.1 Computerised verses standard assessment measures

Firstly the impact of computerised assessment verses standard measures should be considered. Whilst the tasks chosen in each cognitive domain aim to measure the same cognitive construct it may be that the way children approach these tasks when administered on a computer or by a person could be different, meaning that it is the methodology, or form of delivery of the tests, rather than the cognitive skill per se

that is contributing more to the variance in scores. There is limited literature on this topic to inform what these differences might be as most validation studies of computerised tests do not discuss the effects of the mode of presentation specifically. Early reviews of the use of computerised measures commented that the extraneous factors associated with computerised assessment when compared to "pen and paper" assessment should be identified and studied to determine if they have disruptive effects on outcome (Schatz & Browndyke, 2002) however few studies have explicitly done this. Luciana and Nelson (Luciana & Nelson, 2002) looked at the CANTAB computerised assessment battery in young children aged 4-12 years. They found that for the four year old group in their sample the computerised administration of particularly complex strategy based tasks appeared to impair the children's performance, which improved when a 3D model of the task was presented in addition to the computer based stimuli. However no difficulties were noted in the rest of the sample indicating that this may only affect very young children. In adults, whilst several standard neuropsychological measures have been adapted into computerised versions with comparable psychometric properties there are some notable exceptions including the Wisconsin Card Sort Task where equivalence between the computer and standard versions has not been shown (Fortuny & Heaton, 1996). Lalonde and colleagues (Lalonde, Henry, Drouin-Germain, Nolin, & Beauchamp, 2013) studied a virtual reality version of the Stroop test in adolescents and compared their performance to the version of the Stroop Test in the D-KEFS battery and to the BRIEF finding medium to large correlations for both but larger for the BRIEF. Given the equivalence of the test stimuli the fact that this correlation was lower than that of the BRIEF measure with the virtual reality Stroop task suggests the mode of task delivery did have a significant effect on the outcome.

In summary the specific impact of the computerised modality of testing on performance is surprisingly not well understood. It seems likely, however, based on the current limited literature that this difference in the surface characteristics of the tests could have an impact on the strength of the relationship between performance on the tests that may or may not be related to the cognitive construct they are designed to assess.

4.2.1.1.2 Child verses adult assessment

Secondly when considering comparisons between this study and previous CogState construct validity studies (Cysique et al., 2006; Maruff et al., 2009; Pietrzak et al., 2009; Yoshida et al., 2011) the most striking difference is that these studies were conducted with adults rather than children. The changes to the tasks in the CogState paediatric battery compared to the adult battery are fairly minimal, consisting mainly of more user friendly card stimuli for the youngest age group, two fewer target cards in the OCL task for all age groups and the maze being visible once found in the GMLT for the youngest age group. There were also other subtle changes in the appearance of the tasks (e.g. a grey background instead of a green background, size of the cards slightly enlarged) due to an updated version of the battery being used in this study compared to that used in previous publications. However, beyond these cosmetic changes in the appearance of the battery it is possible that developmental changes in the acquisition of cognitive skills will differentially affect performance on computer based tasks verses standard neuropsychological measures, and the specific cognitive skills that the children use when performing the tasks compared to adults. As discussed above there is some evidence that very young children find computerised 2D representations of complex strategy formation tasks more difficult than the 3D standard version, although this did not seem to affect the

children in the age range covered by this study and no such stimuli are used in the CogState tasks. However the literature in this area is very limited. It could be hypothesised based on the ubiquity of computers in everyday life that has developed over the last 20 years that children may be more familiar with using computers and engaging with digital stimuli than many adults are, however there is no research within the cognitive assessment literature to support this claim and consider its implications for computerised testing.

When considering children's approach to neuropsychological measures in general when compared to adults it is important to remember that children are not just very young adults and that brain-behaviour relationships seen on a given test in adult sample may not apply in the same way to children (Baron, 2004). For example the Trail Making Test is described as measuring attentional control, inhibitory control and cognitive flexibility (Baron, 2004; Lezak et al., 2004) however in children aged 7-8 years where speed of response is still at an early developmental stage this ability may have a larger influence on performance than in older children or adults (Kelly, 2000). These factors may be further complicated by the developmental impact of early brain insults and subsequent potential for reorganisation of functioning (Warner-Rogers, 2013) meaning that the primary cognitive abilities affecting a child's performance on a given task are not always necessarily clear.

4.2.1.1.3 Effect of the clinical presentation in children treated for cancer

Thirdly no previous studies have assessed the CogState battery in children who have been treated for CNS tumours or leukaemia, therefore the potential for factors associated with this clinical population to differentially affect performance on computerised verses standard measures should be considered. Previous adult

construct validity research has used control, schizophrenia, AIDS dementia complex, and mild TBI samples. Two studies (Pietrzak et al., 2009; Yoshida et al., 2011) have reported correlations for both their control sample and sample of patients diagnosed with schizophrenia separately to allow comparison of construct validity in the two groups. These studies show generally comparable patterns of relationship strength with the correlations mostly higher in the patient groups suggesting that for these clinical populations other effects of their clinical presentation did not differentially influence the computerised or standard assessment. For children treated for cancer the potential extraneous clinical characteristics which could differentially affect their performance on the different assessments include sensory difficulties and motor impairments (Armstrong et al., 2009). Although difficulties severe enough to prevent testing were an exclusion criterion for the study more subtle difficulties could have been present which could have influenced the study findings. Examples of this which are specific to particular tests are discussed below with the relevant hypothesis.

4.2.1.1.4 Use of single measures in each cognitive area

Fourthly this study has used single tests or subtests in each cognitive area, except executive function, to measure performance. The reasons for this are discussed in section 2.1 and 4.4.4.1 however the broad impact of this on the interpretation of the results will be considered here. Best practice in clinical and research settings would be to include multiple measures of each construct being tested (Baron, 2004; Kelly, 2000). This increases the reliability of the results by reducing the impact of extraneous variables such as a lapse in concentration on one test. It also allows for further consideration of method variance (i.e. the method or form of measurement) compared to trait or construct variance by allowing for comparison between different standard measures as well as between the standard measures and the computer

measures. Use of a composite score based on more than one measure would also have allowed different facets of each cognitive domain to be included providing a more comprehensive measure of the construct. Both reliability factors and method variance may have contributed to the wide confidence intervals seen for each correlation co-efficient through increasing the standard error of measurement. Given these wide confidence intervals the presence or lack of correlation seen between specific measures in this study should be interpreted with a degree of caution.

Factors specific to each hypothesis will now be discussed including reference to previous research on that task.

4.2.1.2 Hypothesis 1: The Detection task of the Cogstate battery measures psychomotor function and processing speed and will be positively correlated with performance on the Grooved Peg Board task and the WISC-IV Symbol Search subtest.

This hypothesis was not firmly supported based on the data in this study with moderate correlations found between these subtests in the expected direction which were non-significant when correction for multiple comparisons was applied and had broad confidence intervals containing zero.

The GPB task was chosen as a measure of psychomotor function and has been used to assess this construct in previous larger studies of the CogState battery in an adult population (Cysique et al., 2006; Maruff et al., 2009). In these studies a stronger relationship was found between the GPB dominant hand variable and DET (r=.57-.81) which has not been replicated by these results (r_s=.33). However another adult study using an alternative measure of psychomotor processing, the Token Motor task, with similar dexterity requirements to the GPB (Yoshida et al., 2011),

failed to find any significant correlation with the DET task. They suggest this may be due to the increased fine motor control and dexterity requirements of the Token Motor task when compared to the response required in the DET task. This may also have played a role in this study as the GPB requires participants to pick up and manipulate small pegs in contrast to the simple button presses which form the response modality of the DET task. There is some evidence that around a quarter of children treated for ALL display impaired motor and dexterity performance (De Luca et al., 2013) which may have differentially affected their performance on the GPB compared to the DET task. This hypothesis is supported by the fact that the mean performance of the whole sample on the GPB task was greater than 1 SD below the normative mean (z=-1.39) with 18 participants (49%) scoring in this impaired range whereas on the DET task mean performance was z=0.26 and only three participants (8%) scored lower than 1 SD below the normative mean. Therefore the lower correlation between the two tasks in this study may reflect an increased impact of the dexterity aspects of the GPB relative to the psychomotor processing aspects than in previous adult samples.

The Symbol Search task was used as a measure of processing speed to assess this aspect of the DET task, as it has much lower psychomotor requirements than the GPB, although it does still require fine motor skills in order to manipulate the pencil. This specific task has not been used before in studies of the construct validity of CogState however the small to medium correlation found in this study (r=.28) is lower than would be predicted based on previous analyses of the DET task as a measure of processing speed. In their large study of adults diagnosed with schizophrenia Pietrzak et al. (2009) used the TMT-A, a coding task and a category fluency task as measures of processing speed to compare to the DET task finding

large correlations for all three (r=.56-.79). Although these three tasks place more demand on different cognitive constructs in addition to processing speed when compared to Symbol Search (e.g. TMT-A requires visuo-spatial attention, coding requires increased working memory and fine motor control and category fluency requires cognitive flexibility) it is unclear why these differences should increase rather than decrease the relationship to the DET task, which is a simple reaction time task. However, given the impairments seen on the GPB in this sample it could be that even the reduced psychomotor requirements of the SS test were still significantly impacting on the ability of this test to provide a relatively pure measure processing speed in this population, when compared to the simple reaction time results on the CogState DET task.

4.2.1.3 Hypothesis 2: The Identification task of the Cogstate battery measures visual attention and vigilance and will be positively correlated with performance on the Map Mission and Score! subtests of the TEA-Ch.

This hypothesis was supported for the visual attention aspect of the IDN with a large relationship to the Map Mission subtest found (*r*=.52) and partially supported for the vigilance aspect with a moderate but non-significant correlation (*r*=.32) found.

Previous studies of the construct validity of the IDN task have focused either on its visual attention aspect (Cysique et al., 2006; Maruff et al., 2009) or on its vigilance or sustained attention aspect (Pietrzak et al., 2009) but none have considered both aspects simultaneously. Those studies which have looked at visual attention have found large positive correlations (.60 -.78) with tasks such as TMT-A and the Symbol Digit Modalities Test (SDMT; (Smith, 1982)) which assess complex

visual attention and scanning, and are affected by processing speed given the timed nature of the tasks. These skills are similar to those required by the Map Mission subtest which also requires selective attention in order to focus on the target symbol amid the detailed distracting background and is a timed test. The present result fits well with this previous research further supporting the importance of visual attention to performance on the IDN task.

The vigilance aspect of the IDN task has only be considered in one study (Pietrzak et al., 2009) which correlated it with a visual continuous performance task (CPT) finding a large relationship (r=.57). The Score! subtest used in this study does not show such a strong relationship which may, in part, reflect the different modality of the test with the IDN and CPT requiring visual sustained attention and Score! requiring auditory sustained attention. Recent research suggests that poor performance on attention tests in the auditory modality may be due to the effects of boredom whereas for tests in the visual modality distractibility may have a bigger effect (Berry, Li, Lin, & Lustig, 2014) indicating that different processes underpin successful performance in the different modalities. In addition speed of presentation has been shown to affect performance (Thompson, Opton, & Cohen, 1963) and this varied across the two tasks, with the Score! task being presented at a predetermined rate and the items in the IDN task presented as fast as the participant responded (indeed speed of response is the primary outcome variable so it encourages quick responding). Given these differences it may have been preferable to use a vigilance and sustained attention task in the visual modality such as Connor's Continuous Performance task (Conners, 1992) as the comparator task in this study to minimise the effect of modality and outcome variable on the result, however this task was unavailable to the researcher.

4.2.1.4 Hypothesis 3: The One-Card Learning Task of the CogState battery measures visual learning and memory and will be positively correlated with performance on the CMS Dot location subtest.

This hypothesis was not supported by the data as only a small to medium non-significant correlation (r_s=.19) was found between the two tasks. Whilst the Dot location subtest has not been studied before in relation to the OCL task this result is contrary to the current literature on the version of this task included in the adult battery which has been shown to have a large correlation with tasks of visual memory. Pietrzak and colleagues (2009) compared performance on the OCL task to the Brief Visuospatial Memory Test –Revised (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996) a task which requires participants to learn geometric designs and their location on the page over three learning trials making it similar in content to the Dot Location subtest. They found large correlations in both controls (r=.63) and people diagnosed with schizophrenia (r=.76). Using the same test Maruff et al. (2009) also found a large correlation in their sample of adult controls (r=.83), with significant correlations also being shown in their sample with the TMT-B, Symbol-Digit Modalities Test, Spatial Span and Rey Complex Figure Test-Delayed Recall.

One possible explanation for the lack of correlation in this study could be a lack of sensitivity in the Dot Location task. It has been criticised for floor effects in young children as an average scale score can be achieved by chance (Baron, 2004) and if such effects had occurred in the data it would lead to range restriction and reduce the ability to find a significant correlation (Goodwin & Leech, 2006). Inspection of the data shows that whilst mean performance on the test was close to

the normative mean (z=0.03) a wide range of scores were achieved (min: z=-2.0, max: z=1.67) and there is an acceptable standard deviation (SD=0.77) meaning the distribution of the scores was not significantly different from the normal distribution. This is not consistent with significant floor effects. It is unclear therefore why the relationship between these variables is so much smaller than analogous tasks in the previous adult literature.

4.2.1.5 Hypothesis 4: The Continuous Paired Associate Learning Task of the CogState battery measures visual learning and memory and will be positively correlated with performance on the CMS Dot location subtest.

This hypothesis was partially supported with a medium correlation (r=.33) found in the expected direction, although non-significant when the correction for multiple comparisons was applied.

The CPAL task of the CogState battery is a newer subtest which has been studied relatively less. One study has compared the Japanese version of this task to a digit sequencing task (Yoshida et al., 2011) classifying it as a measure of working memory. In this study no significant correlation was found for controls (n=40, r=.19) or for adults diagnosed with schizophrenia (n=40, r=.28) however for the total sample including both groups the correlation did reach significance (n=80, r=.32). This correlation is comparable to that observed in this study (r_s=-.33) although in this study it was investigated as a measure of visual memory and learning. This highlights the overlap between cognitive constructs and the skills required by any assessment measure, which are very unlikely to tap into only one narrowly defined aspect of cognitive functioning. Whilst a digit sequencing task does not include an element of learning over time as new number sequences are presented on each trial,

the Dot Location subtest does include an element of working memory in addition to learning as the participant must hold the locations of the dots in mind whilst manipulating the response chips into the correct positions on each trial. Therefore the current evidence tentatively suggests that the CPAL task involves visual working memory (perhaps to enable the participant to hold in mind where they have previously searched whilst looking for the correct location) in addition to the more overt construct of learning over time, both of which will be captured in the "accuracy" outcome variable.

4.2.1.6 Hypothesis 5: The One-Back Task of the CogState battery measures working memory and will be positively correlated with performance on the WISC-IV Digit Span subtest.

This hypothesis was partially supported. A non-significant small to medium correlation (r=.23) was found for the total Digit Span scaled score. When considering the more specific LDSB measure of working memory a medium (but still non-significant) correlation (r=.37) was found although the confidence intervals around this value were wide.

The construct validity of the OBK task has been studied in previous adult research relative to a variety of working memory tasks, although Digit Span has not been used before. Maruff et al. (2009) found the strongest associations were between the OBK tasks and a spatial span test (taken from the WMS-III; Wechsler) and the SDMT (r=.80-.81) although the visual and auditory versions of the test are not distinguished in this report. Cysique et al. (2006) also used the SDMT with the results separated by modality finding significant medium to large correlations between both the visual modality (r=.43) and auditory modality (r=.40) in their adult

sample of patients with HIV. Pietrzak et al. (2009) also used the spatial span test and a letter-number span test in their study. They found large correlations for the letter-number span test in both controls (r=.61) and people diagnosed with schizophrenia (r=.74) and medium to large correlations for the spatial span test (r=.43 for controls and r=.56 for patients). In contrast Yoshida et al. (2011) did not find a significant correlation in their study using a digit sequencing task as the standard measure of working memory (total sample r=.18). They claim the difference in modalities of the tests (OBK is visual and the digit sequencing is auditory) could be the reason for this lack of relationship however is not consistent with the other studies quoted above where both visual and auditory tasks have been used and comparable or even larger correlations found between OBK and the auditory tasks. Therefore whilst the different modality of the OBK and Digit Span tests might have had some impact on the strength of the relationship between performances on these tests it is unlikely to be the only reason for the weaker relationship found in this study.

4.2.1.7 Hypothesis 6: The Groton Maze Learning Task of the CogState battery measures executive function, including cognitive flexibility and will be positively correlated with performance on TMT-B and the BRIEF GEC.

The analysis of this hypothesis was limited by the lack of current acceptable normative data for this task in children covering the full age range used in this study and the different versions of the task used for different age groups. However when the data was analysed separated by age group the results suggested that for the 8-9 year old group (n=8), for whom the path through the maze remained visible as they completed the task, a strong relationship was present with both TMT-B (r_s=-.86) and BRIEF GEC (r=-.61) although the second of these is a less reliable relationship as

the 95% confidence intervals included zero. For the older group (n=29), for whom the task was the same except the path did not remain visible during the task, no significant relationships were found for either the TMT-B (r_s=.24) or the BRIEF GEC (r=.12).

The reasons for this differential finding for the two versions of the task are not clear. Firstly it must be considered that the younger age group is very small, increasing the chances of finding a significant correlation by chance. However this is taken into account with the significance testing of the correlation and the relationship between the GMLT and TMT-B remains highly significant (p=.007). Therefore whilst this result should be treated with caution given the sample size, it does tentatively indicate that the different task requirements of the two versions of the GMLT may influence the constructs which the task primarily measures.

The 10-16 year old version of the task appears to have a much higher working memory load than the version for younger children, as they must remember each step in the pathway individually without ever seeing the shape of the path as a whole. However, this is not supported by previous analysis of the constructs measured by the various outcome variables of the GMLT in adults, which did not find a significant correlation between GMLT-Total Errors and the OBK task (r=.04) thought to measure working memory (Pietrzak et al., 2008). However, in this study whilst the correlation between the GMLT and OBK was non-significant and very small, r=.004, p=.49, the relationship with LDSB, the standard measure of working memory, was significant, r=-.47, p=0.008 indicating a relationship with a large effect size between the two variables. This result suggests that working memory (as measured by LDSB) does have an effect on performance on the version of the GMLT administered to 10-16 year olds, accounting for 22% of the variance in

performance on this task. It is of note that the OBK task does not display the same relationship, suggesting that the aspect of cognitive functioning tapped into by the GMLT and LDSB is not shared by the OBK task, as might have been expected if all three tasks are measuring an aspect of working memory. Relationships between GMLT Total Errors and measures of working memory in the younger age group are not significant however this is hard to interpret given the very small sample size. These results tentatively suggest that the different task requirements in the versions of the GMLT given to 8-9 year olds and 10-16 year olds may mean that the task relies less or more strongly on working memory dependent on presentation. Previously published studies of this discrepancy in administration are not available, however, previous studies of the GMLT in children (aged between 7-9 years, but completing the version of the GMLT given to 10-16 year olds in this study) has suggested that by using the more specific outcome measure of Rule Break Errors, the effects of spatial memory and executive functioning can be distinguished (Thomas et al., 2011). When using this more specific variable the relationships with LDSB did reduce in strength (r=-.29) suggesting it may be less impacted by working memory however, the correlations with TMT-B and BRIEF GEC remained small and non-significant (r=.19 and .14 respectively). In summary the discrepancy between the strong large correlations seen for the 8-9 year old and the small to medium seen for the 10-16 year olds is difficult to explain. It may relate to a lack of reliability in the 8-9 year old data given the small sample size or the differential impact of working memory on performance. However the impact of working memory ability alone does not explain the small relationships seen in the older age group as when its impact is reduced the correlation does not increase.

In comparison to the more reliable 10-16 year old data, previous validity studies in adults have found medium to large relationships between the GMLT and other measures of executive function. Peitrzak et al. (2009) studied the relationship between the Total Errors variable of the GMLT and the Neuropsychological Assessment Battery Mazes task (Stern & White, 2003) finding a large correlation in both their control and patient samples (both r=.56). They report this as evidence for the GMLT Total Error variable as a measure of reasoning and problem solving, which are both aspects of executive function. These tasks are, at a face validity level, more similar to each other in form which may account in part for larger relationship found than in the older age group in this study. Yoshida et al. (2011) also included the GMLT in their adult validation study of the Japanese version of CogState comparing it to the Tower of London Task, again describing both as measures of reasoning and problem solving. They found a significant but small to medium relationship between these variables for their total sample only (r=.25).

The findings of this study are more in line with this later research, and may similarly be impacted by the different surface characteristics of the comparator task and measure used. There is no research on the relationship between the GMLT and informant report measures such as the BRIEF. Previous research looking at the relationship between the BRIEF and observed performance based measure of executive function have found small to medium effect sizes for the relationship (Mahone et al., 2002; Mangeot, Armstrong, Colvin, Yeates, & Taylor, 2002) indicating that these measures do assess different aspects of executive function. In this study the relationship between the TMT-B and the BRIEF GEC was large (r=.51) which exceeds that found in other similar studies but supports these two very different modalities of measurement as tapping into related constructs. However, the

increased variation in the data due to the mode of measurement, not just of computer to non-computer tasks, but also of performance to informant report measures may account for the lower correlations seen in this study when considering the more reliable 10-16 year old group.

4.2.1.8 Comparison with other screening measures previously evaluated in a paediatric oncology population.

Of the screening measures discussed in section 1.9 three addressed issues of construct validity through convergent validity with other measures, all of which found correlations of the order found in this study. Conklin et al. (2013) studying the Impact, computerized battery assessed only the concurrent validity of the verbal, visual and working memory tasks in their battery (the processing speed, psychomotor speed and divided attention tasks were not addressed) with other computerised experimental tasks of the same constructs. They found only small to medium correlations (r=.25-.30) for the verbal and visual tasks only with no relationship found for the working memory tasks. Given that both their experimental and comparator tasks were in a computerised format with much more similar surface characteristics than the tasks used in this study it is notable that they did not find stronger relationships. The other two papers were reporting on informant report measures of single constructs only. Howarth et al. (2013) found small to medium correlations between the BRIEF working memory scale and digit span forwards and backwards and self-ordered search tasks (r=.21-.24). Patel et al. (2007) found small to medium correlations between the social problems subscale (r=.31) and the attention problems subscale (r=.22) of the CBCL and their classification of children as have attention impairment based on six standard measures of attention. Therefore, whilst the correlations found in this study are not as high as previous adult construct

validity studies of the CogState battery they are comparable to those found in studies of other measures in this paediatric oncology population. This may suggest that factors associated with this clinical population, not least the smaller sample sizes achieved in each of these studies when compared to the adult literature, may impact upon the correlations achieved.

4.2.2 Research Question 2: Given the research showing intellectual performance declines over time since diagnosis (e.g. (Spiegler et al., 2004)) is there a relationship between time since diagnosis and performance on the CogState battery?

This research question gave rise to one hypothesis, considered below. In addition to the hypothesis itself the result regarding the relationship between time since diagnosis and IQ will also be considered in this section.

4.2.2.1 Hypothesis 7: Time since diagnosis will be negatively correlated with overall performance on the CogState battery.

This hypothesis was not supported with the data showing a trend towards a medium relationship in the opposite direction to that predicted, although considerable variability in the data means that the confidence intervals are wide and cross zero indicating there may be no relationship at all. In spite of this potential lack of reliability in the data it is interesting that there is a trend towards participants who are further from their diagnosis and therefore treatment performing better on the battery, in contrast to the current literature. This could suggest that the CogState battery is not sensitive to a decrement in performance over time, or that within this mixed diagnosis and treatment sample a decrement over time in performance in the specific areas measured by the DET, IDN, OCL and OBK tasks, is not present, and instead

performance actually improves. In support of the second of these alternatives is the fact that there is also no significant relationship between time since diagnosis and IQ as measured by the WASI in this sample. However, mean performance in the sample on both the CogState composite variable and the IQ variable is not significantly different from the normative mean in spite of significant impairments in several of the standard tests (Grooved Peg Board, Map Mission, Score!, Digit Span, TMT-B, BRIEF GEC) suggesting that these variables are not capturing the clinical deficits seen in the sample, which may be the aspect of performance that decreases over time. The clinical characteristics of the sample in this study should also be considered when comparing these results to the current literature. Spielger et al. (2004), Ris et al. (2001, 2013), Mulhern et al. (2001) and Krull et al. (2013) all of whom found significant decreased in IQ over time all studied samples of children who had received cranial radiation therapy. In this sample only two children had received radiotherapy with the majority of the sample being treated with one or more of chemotherapy (including intrathecal chemotherapy), corticosteroids and surgery. A more similar clinical sample was studied by Copeland et al. (1996) whose longitudinal study sample did not include any children who had received CRT, instead being treated with chemotherapy that was either intrathecal (ITC) or intravenous. In this study in the first three years post treatment mean scores on IQ measures, academic achievement, language, memory, executive function and "freedom from distractibility" were all within the normal range with no significant declines over time and significant improvements in performance IQ, "freedom from distractibility" and fine motor skills. Perceptual motor skills declined in the group who had received ITC chemotherapy but not those who hadn't. In the subset of children who were followed up between 5 and 11 years after their diagnosis, most

similar in the course of their recovery to this sample, significant decline in performance was only seen for executive function skills with performance IQ and tactile spatial skills improving and all other areas remaining constant. The results of this study fit well with this pattern suggesting that in the absence of CRT significant declines in cognitive functioning are not found to be widespread. However further longitudinal research following children who have received less aggressive treatments such as ITC over time would be needed to provide a clearer picture of how deficits in cognitive functioning develop or remit.

4.3 Additional Discussion of Cognitive Impairment in the Sample

As mentioned above, in characterising the clinical performance of the sample it was noted that the sample as a whole did not show significant deficits in performance on the WASI measure of estimated IQ, or any of the CogState tasks, however significant deficits were found on the Grooved Peg Board, Map Mission, Score!, Digit Span, TMT-B and BRIEF GEC tasks indicating difficulty in the areas of psychomotor processing, visual attention, sustained attention, working memory and executive functioning respectively. Whilst an analysis of the criterion validity of the CogState battery is beyond the scope of this project these results do tentatively suggest that it may not be sensitive to the areas of impairment indicated by the standard measures. However other possibilities should be considered, including the current normative data available for the CogState battery overestimating the performance of the children in this sample, or the standard assessment measures being differentially affected by other clinical variables in the sample including fine motor ability and fatigue. Further research using a matched control sample to examine the relative performance of children treated for cancer and typically

developing children on both batteries is needed to form more reliable conclusions in this area, which could also include consideration of the CPAL and GMLT tasks of the CogState battery excluded from this analysis.

Apart from the sensitivity or not of the CogState battery it is of note that the mean IQ in the sample was not significantly different from normal, even in the face of more specific neuropsychological impairments (effect sizes for the impairments were all medium to large). There are two factors to consider here, the representativeness of the estimated IQ scores compared to more comprehensive assessments of IQ and the WASI in particular, and the frequency of this pattern of results in the literature. Firstly the measure of IQ used in this study is a short form which can provide an estimate of total IQ which correlates strongly with full scale IQ scores based on comprehensive IQ batteries (r=.81 with WISC-III) but which does not include assessment of all of the areas of cognitive functioning that go into such measures, such as a measure of working memory or processing speed. Therefore although the WASI can provide a reasonably reliable estimate of full scale IQ it will not necessarily reflect broader areas of deficit. It should also be noted that the WASI was published 15 years ago and the normative data is therefore somewhat out of date. As a result of this scores may have become inflated due to the Flynn effect (Flynn, 1984, 1987a) which may be masking deficits in overall intellectual functioning that would be detected on more up to date measures.

However given these limitations, the pattern of overall IQ scores being within the normal range but more specific deficits being present is not that uncommon in the literature, especially in children who have not been treated with CRT. For example Anderson et al. (1997) reported on their sample of children treated with or without CRT in addition to chemotherapy finding that subtle deficits in neurocognitive

functioning in areas such as executive function were still present in groups where no overall intellectual deficit was found. Vaquero et al. (2008) found no significant difference in overall IQ in their Astrocytoma patient group treated with surgery alone compared to controls, however, there were significant deficits on tasks of working memory and executive functioning. Waber at al. (2013) report on children treated only with corticosteroids finding significant impairments on tasks of visuospatial construction and memory when the overall IQ measure was in the normal range. Within this context the results of this study fit well given the very low levels of radiotherapy received in the sample and further highlight the need for any screening measure to be broad enough to cover all areas of neurocognitive functioning which may have been affected by treatment, even when overall intellectual functioning appears to be normal.

4.4 Critique of Methodology

This section provides a critique of the methodology used in the current study and considers methodological strengths and weaknesses of the research and possible impacts on the findings of the study.

4.4.1 Design and analysis.

The study used a cross sectional correlation design to investigate the convergent construct validity between the CogState tasks and selected standard neuropsychological measures. This is a widely used design for research of this type which facilitates examination of both the significance of the relationships between variables and also the effect size of the relationship in the form of the correlation coefficient, providing more information about its clinical significance. Specific a priori hypotheses were developed about which assessment measures would be

significantly correlated based on previous research into the cognitive construct they were designed to test. This was done in order to focus the analyses and reduce the risk of type 1 errors associated with the large numbers of correlations conducted in a full correlation matrix. This method has been employed in several previous studies of the CogState battery (Cysique et al., 2006; Pietrzak et al., 2009; Yoshida et al., 2011) and other neuropsychological measures (e.g. (Conklin et al., 2013). However a weakness of this approach was that only convergent and not discriminant validity was explored. Using both of these methods is described as best practice in this area (Campbell & Fiske, 1959) and would provide a more robust understanding of the specificity of the constructs measured by the CogState tasks and a more accurate reflection of the fact that no neuropsychological measure measures only one precise cognitive construct (Maruff et al., 2009). This method was not chosen as the sample size which would be needed to conduct this analysis including appropriate adjustments for multiple comparisons exceeded that which was feasible to collect during the period of the study.

Whilst the focused analysis and correction for multiple comparison mean that the chance of type 1 error in the results has been minimised, the correction applied to the α level in this study, using the Holm method, although less conservative than the Bonferonni method, is still quite conservative and may have led to the disregarding of theoretically important correlations between the variables (type 2 error). To counteract this correlation coefficients and p-values have been reported in full in the results section to illustrate the strength of relationships which did not meet the strict criterion set for significance and confidence intervals were calculated to provide further information on how reliable these estimates of relationship are. In addition to the already relatively strict correction in the plan of analysis this was further reduced

due to the unanticipated need to split the GMLT data into two age groups. This may have reduced the power of the study to detect the anticipated effects, however a sensitivity analysis with the obtained sample size of 37 and α=.05 indicates the study was able to detect effect sizes at the predicted level based on previous research (.50) with a power of .90, higher than the .80 aimed for. This was due to the study recruiting 37 participants rather than the 32 required by the sample size calculation.

For the second research question concerning the relationship between time since diagnosis and performance on the CogState battery a correlation design was also used. The advantages of this approach included the ability to collect this data within the same research design as utilised for the first research question and the ability to control for the effects of potentially confounding variables using partial correlation. Weaknesses of this design are that it does not provide information about the time-course of the development of difficulties in an individual, only providing a cross sectional snapshot across individuals in the study group. Given the heterogeneity in diagnosis and treatment within this group (due to both pragmatic recruitment reasons and to improve the ability to generalise the results to research question 1) significant relationships between time since diagnosis and overall cognitive ability in particular individuals who received particular treatments may have been masked. A longitudinal research design which followed a more well defined and homogenous group of patients would be a more powerful way to approach this research question, however, such designs are pragmatically challenging and beyond the scope of this study and therefore were not possible. In the absence of being able to use a longitudinal design the partial correlation used was appropriate. A further weakness in the data when addressing this question was that at the time of analysis suitable normative data were not available for the CPAL or GMLT from the

CogState battery meaning that z-scores could not be calculated and they could not contribute to the composite z-score of performance on the battery as a whole. This meant that this composite score did not include a measure of executive functioning, one of the aspects of cognitive functions which may be more likely to show deterioration over time compared to peers due to the later developmental trajectory for the development in this area. This may have contributed to the finding for this hypothesis as discussed above in section 4.2.2.1.

4.4.2 Procedure.

Assessment sessions took place in participant's homes. This was a strength of the procedure in that it limited the burden on families who already have numerous hospital visits to attend, and also meant that the children were in a familiar setting which may have lessened their test taking anxiety. However testing in this setting did limit the control which the researcher could exert over the environment leading to some distractions being present (such as dogs barking, people walking through the room) during some testing sessions. These distractions may have affected the participant's performance on particular subtests thereby increasing the error variance in the data and one data point on the OCL task was excluded for this reason. Research in adults with mild TBI has shown that distraction can have a significant negative effect on task performance relative to controls (Schnabel & Kydd, 2012) suggesting it may have impacted this sample given their similar neuropsychological weaknesses. However no major difficulties were noted during the sessions (with the exception mentioned above) with most taking place in quiet rooms, so it is therefore unlikely the effect on the data was large or systematic.

The CogState battery was completed once by participants in this study. It is recommended by the Test publishers that ideally when children complete the battery for the first time they complete a practice session prior to the testing session. This is to familiarise them to the controls and negate the practice effects which are seen from the first to second completion but not thereafter. However given that this study was not interested in change in performance on the battery over time it was advised that this practice session could be omitted without significant detriment to the validity of the assessment (A. Schembri, personal communication, October 6, 2013). To maintain the ability for the entire research battery to be completed in one testing session that did not place an undue burden of fatigue on the participant this approach was adopted. The administration of the battery in this study involved the researcher sitting with the child and going through the instructions with them prior to each subtest to support their understanding of the task, with additional support provided in the first few trials if there appeared to be any misunderstanding. Practice trials were included in the CPAL and GMLT tasks where the task rules were more complex. If difficulties in understanding the battery had been a factor in this study it would be expected that overall scores would show lower performance relative to the normative data. As there were no significant differences on any of the scales this was unlikely to have been a factor.

All participants completed the tests in a standard order with the CogState battery first and the standard battery second. This format was chosen to facilitate assessment of the acceptability of the CogState battery (see Appendix L) without interference from the other tests. Within the batteries the tasks and subtests were also presented in a standard order as described in the Method chapter. This was due to the fact that the CogState task order should not be counterbalanced as there may be

proactive interference between similar stimuli in the OCL and OBK tasks (B. Harel, personal communication, March 6, 2013). In order to standardise presentation across the two batteries the standard battery of tasks was also presented in a fixed order. Set order of subtest presentation is standard practice in most neuropsychological assessment measures (e,g (Wechsler, 2003)), however, the potential order effects which may have resulted from this should be considered. It is commonly understood that fatigue towards the end of long testing sessions can impair the child's motivation affecting performance (Baron, 2004) although the literature on the effects of fatigue is mixed, with some studies finding it leads to significant decrease in performance (Krupp & Elkins, 2000) and others finding no significant effect, even in clinical groups more susceptible to the effects of fatigue (Johnson, Lange, DeLuca, Korn, & Natelson, 1997). If fatigue did effect performance in this study it may have differentially affected those tasks completed at the end of the session which included the Digit Span subtest and the Trail Making Test. These two tests showed some of the greatest levels of deficit in performance relative to normative samples and it cannot be discounted that fatigue may have contributed to this. However, the strong correlation between the BRIEF scores, completed by the parent, and TMT performance does indicate that the levels of deficit seen in this area on both assessments are in large part due to executive function difficulties. To lessen the chances of a significant effect of fatigue a rest break was offered to all participants prior to starting the standard battery of tests (and accepted by the majority) with additional breaks available on request or if felt necessary by the researcher to maintain motivation and arousal levels.

4.4.3 Sample.

The sample achieved is a strength of the study. Although this size of sample is relatively small in comparison to those reported in the adult validity studies of CogState it is comparable to others in this difficult to recruit clinical group. The sample size exceeded that required by the power calculation meaning that the study was not underpowered for the analyses planned. There was minimal missing data meaning the majority of analyses were conducted with full power. The recruitment rate was very high in the two clinical services where the entire eligible clinical population was approached (75% at NNUH and 75% at QEHKL). Recruitment rate is harder to interpret in the third service (Addenbrooke's, 19%) as recruitment was limited to those who had responded by the time the sample size was achieved.

The sample was well balanced by gender with wide age at testing and age at diagnosis ranges. The wide range of times since diagnosis meant that range restriction in this variable was not an issue in relation to the second research question. This variability in the sample also increases the generalisability of the results to a clinical outpatient setting. Recruitment was not stratified by diagnosis. This was done for pragmatic reasons of facilitating the largest possible sample in the time available for the study. The mix of diagnoses in the sample is weighted towards leukaemia, with fewer brain tumour patients than might be expected. Several factors could have influenced this. Firstly patients with motor or sensory impairments severe enough to prevent testing were excluded from the study. This will have differentially excluded patients treated for brain tumours where these difficulties are more common (Armstrong, 2010; Ward, DeSantis, Robbins, Kohler, & Jemal, 2014). Secondly recruitment was conducted first at the two POSCUs in the region due to the order in which regulatory approvals were achieved. These centres see relatively

fewer brain tumour patients than the PTC where recruitment was limited partly by the remaining space in the sample. Thirdly, at the PTC a newly commissioned service specifically aimed at brain tumour survivors opened just prior to the recruitment period. This meant that several potentially eligible participants had either recently received a neuropsychological evaluation or where due to do so soon making it clinically inappropriate to include them in the study.

It is also interesting that the mix of treatments received by the study sample included very limited amounts of radiotherapy. This may reflect the clinical picture in the UK where radiotherapy is largely a treatment of last resort for the treatment of ALL, replaced by ITC (Pui & Evans, 2006). In the case of BT, radiotherapy is a more integral part of many treatment regimens. Dose related effects of radiotherapy on cognitive outcomes have been frequently shown (e.g. Armstrong, 2010; Spiegler et al., 2004) leading to protocols which aim to postpone radiotherapy for the youngest patients (e.g. Batra et al., 2014) however, some evidence relating to newer conformal radiotherapy protocols suggests no detrimental effects. Merchant et al. (2004) report no effect on IQ, academic performance, memory or learning up to four years after treatment influencing other treatment protocols to include radiotherapy. However it remains the case that in this sample only 2 participants, one treated for ALL and one for BT, received this treatment.

However, given the study questions and methodology the mix of diagnoses and treatments achieved is not of great detriment to the conclusions which can be drawn. There was no range restriction in performance on any of the measures suggesting that a suitable range in presentations in order to be able to detect the relevant correlations was present. Each participant served as their own control in respect to the first research question meaning that the variability in the sample would

not have affected the results here. It may have been more detrimental to the analysis of the second research question as discussed above.

4.4.4 Measures.

The choice of measures used in this study is central to the findings of the study. The matching of the CogState and standard tasks, factors affecting the use of subtests more generally and particular issues will be discussed below.

4.4.4.1 Matching of CogState and standard tasks

Given the decision to focus the analyses in the current study on to the relationships between the CogState tasks and specific standard measures covering the same cognitive construct the matching of those measures is an important element of the methodology which could have had a large impact on the results found. Standard measures were chosen based on several factors described in the Method chapter including established psychometric properties in the relevant cognitive area, prior use in adult construct validity research of the CogState tasks, clinical usage and availability to the researcher. Of these, established psychometric properties in the area of construct validity is most important from a theoretical standpoint, given these measures were being used as an established measure of the construct against which the CogState tasks were evaluated. All of the tasks used do report evidence of validity in the given area as described in the Method chapter, however the applicability of this evidence to this particular sample of children is perhaps questionable given that none of these measures (except the Dot Location subtests of the CMS which has been studied in children with brain tumours) have been evaluated for construct validity in children treated for cancer, and several of the normative data samples (e.g. for the Trail Making Test, the Dot Location subtest and the Grooved

Peg Board) used were collected in different countries. However this is a recognised limitation of the psychometric and normative data available for the majority of neuropsychological measures available for children (Baron, 2004) and is unavoidable given how widespread a problem it is. Several of the measures (e.g. Symbol Search, Digit Span, Trail Making Test, Map Mission and Grooved Peg Board) have been used in samples of children with traumatic brain injuries and other neurodevelopmental disorders such as ADHD providing some construct validity in similar populations.

The specificity of the tasks is considered in further detail below. It should be acknowledged that given the fact that no neuropsychological assessment measure can provide a pure measure of one neurocognitive construct, had different standard tasks been chosen to match the CogState tasks different correlations might have been found. Using more than one task in each area and creating a composite score for that construct might have helped to counteract these difficulties and may have improved the reliability of the results.

4.4.4.2 Use of subtests.

In the standard battery subtests from larger assessment measures were used to address five of the hypotheses. These were the Symbol Search measure from the Processing Speed index of the WISC-IV; the Digit Span subtest from the Working Memory index of the WISC-IV; the Map Mission subtest from the Selective/Focused attention factor of the TEA-Ch; the Score! subtest from the Sustained Attention factor of the TEA-Ch and the Dot Location subtest from the Visual Immediate index of the Children's Memory Scale. It was decided to use subtests rather than full index scores in these areas for the pragmatic reason of reducing the length of the testing session, thereby reducing the burden on participants and limiting the effects of

fatigue on the results. Using full index scores would have necessitated two research visits which would have resulted in the CogState battery and the standard battery being completed on different days. This would have led to an increase in error variance in the data by increasing the variability in the environmental variables affecting test performance.

The use of subtests as stand alone measures of cognitive constructs is not ideal and may reduce the reliability of the results. Subtests alone should only be used if they display adequate reliability properties (Campbell, Brown, Cavanagh, Vess, & Segall, 2008), which most of these tests do, however the reliability of Map Mission subtest and Score! subtests and the TMT is lower than the other measures being in the 'adequate' range. The decreased reliability associated with using subtest measures alone may account for the large confidence intervals seen in the data and therefore may have decreased the robustness of the results. However, for the reasons described above it was thought to be the best compromise in terms of breadth and brevity of the standard battery.

4.4.4.3 Normative data.

There were difficulties relating to the available normative data for several of the measures included in this study.

In the CogState battery the normative data available for the CPAL and GMLT tasks contained very low numbers in several of the age bands covered by this study therefore it was deemed unsuitable to use this data to calculate age standardised z-scores. This meant that raw data were used for these two subtests. For the CPAL task, where the same task was completed by all ages, this did not pose significant problems. However it is of note that the two lowest scores, which constituted outliers to the data set, were achieved by the two youngest participants in the study. This

highlights the importance of normative data, where these performances could have been put into the context of their peers. For the GMLT the lack of suitable normative data was more problematic as different versions of the task were completed by different age ranges meaning that the data had to be analysed separately. The implications of this have been discussed above but overall served to reduce the sample size in each age group and therefore reduce the reliability of the results.

The normative data for the TEA-Ch covers the age range 6-15:11 years despite several reviews of the test and the manual itself in parts describing the age range as 6-16 years. This restriction in the age range meant that the four 16 year old participants had their data on the Map Mission and Score! subtests standardized using the data from the 15-15:11 age group. No other suitable, widely clinically used attention measure which includes a measure of sustained attention is available for this age range. Using data from a younger comparison sample may have resulted in these participants receiving inflated standard scores, however the impact of this is likely to have been minimal given the developmental trajectory of these attention skills having stabilised by this age range. Within this data set two of the four affected participants scored ≥1SD below the mean on the Map Mission subtest and one on the Score! subtest (there was missing data for the other participant) suggesting that inflation of abilities did not significantly affect the data.

For the two measures included in the standard battery which were not part of larger assessments, the Grooved Peg Board and the TMT-B, the normative data is more fragmented as it was collected from a variety of different studies in different age groups. This may have increased error variation in the results due to different administration practices. Both measures are scored based on time to completion and include the need for the researcher to correct mistakes during this time meaning that

they may be vulnerable to different administration practices. However, both were administered in this study according to established administration guidelines to minimise the effect of this.

4.4.4.4 Specificity of measures and impact of surface variables.

No neuropsychological measure exclusively taps into one cognitive construct (Lezak et al., 2004), both because cognitive constructs do not exist in isolation and because assessment tasks are complex. At a baseline all measures require enough concentration to be able to attend to and complete the task. In addition, timed tasks will be affected by processing speed and any task requiring a motor response will be affected by psychomotor processing. Relative differences in the additional requirements of the CogState tasks and the standard battery tests may account for some of the variability in the relationships between them, separate from the construct of interest. For instance the Grooved Peg Board task was used as a measure of psychomotor processing, however it involves a much higher level of dexterity than that required by the Detection task. The Digit Span task was used as a measure of working memory however the total score is made up of both the forwards and backwards conditions meaning it is actually a measure of both immediate memory and working memory. To try to separate these processes out the Longest Digit Span Backwards variable was also used in the analysis but this measure also requires sequencing skills, auditory processing and attention to complete successfully (Wechsler, 2003). Of these skills, perhaps only attention is also required by the OBK task of the CogState battery.

Whilst these factors need to be taken into account when interpreting the strength of the relationships seen in this study the same would have been true regardless of the standard measures chosen given the different nature of completing

computerised and standard measures. Given this the size of the relationship seen between several of the variables is consistent with them tapping in to similar cognitive constructs. What the analysis in this study does not address is which other constructs they are also measuring, which could be addressed using discriminant validity methods.

4.5 Implications of the Study

4.5.1 Clinical implications.

The results of this study would not seem to fully support the use of the CogState battery clinically with a paediatric oncology population without further research (see below, section 4.6). However there are several clinical implications of the potential for this in the future and clinical implications arising from the characterising of this clinical sample more generally and the analysis of change in cognitive ability over time since diagnosis.

Computerised cognitive testing, once well validated, has many implications that need to be considered prior to use in clinical settings. There are considerable benefits to the speed with which children can complete the screening battery with little intervention required by the examiner opening the possibility for several children to be screened simultaneously. As the scoring system is automated both the time taken to score and the potential for errors in the scoring are reduced. However there are limitations. With the limited interaction between examiner and child there is less opportunity for observation of behavioural information often critical to the interpretation of results. Whilst the computer allows for a very standardised presentation of stimuli, the inflexibility of this means that the examiner is not able to "test the limits" of the child's ability in the same way that they might to obtain extra

qualitative information in a standard assessment (Schatz & Browndyke, 2002). As a result of these limitations, in the context of neuropsychological evaluation of children who have been treated for cancer, it is most clinically appropriate that computerised assessments such as the CogState battery, if further construct and criterion validity and appropriate sensitivity and specificity are established, are used for screening purposes only followed by full conventional assessment for those found to be impaired in any areas. However this screening function, if established, would still have significant positive impacts on the ability of services to meet the NICE and SIGN guidance that all at risk children should be assessed.

A relationship between time since diagnosis and performance on either the CogState battery or the IQ summary score was not established in this study. This is largely consistent with studies where children had not received CRT and inconsistent with studies where they had. This provides further support to the already established principle that CRT is particularly damaging to young children and has long term developmental consequences, and supports the more hopeful position that limiting the use of this treatment mitigates these effects to a large extent. However caution should be exercised in drawing any firm conclusions from this cross sectional analysis and further longitudinal research is required.

The pattern of impairment seen in this study on the standard measures has clinical implications for the breath of the assessments needed to detect areas of difficulty. Whilst overall IQ may be in the normal range, significant impairments can be present in specific cognitive areas. Any screening measure for use clinically should therefore cover all of these areas if it is to be useful in this population.

The level of impairment seen in the sample also has clinical implications. By definition all of the children in the sample had not received a neuropsychological

evaluation in the last year and the vast majority of the sample had never been assessed, up to several years after their treatment. This suggests that there may be significant levels of neurocognitive and psychomotor impairment which go unrecognised and therefore unaddressed in this population of children which, although relatively subtle, could have implications for their education, quality of life, social functioning and future prospects (Ness et al., 2008). This reinforces the level of need for all children at risk to have some form of assessment so that those experiencing difficulties can be identified and followed up.

4.5.2 Theoretical implications.

The areas of impairment seen in this study, in psychomotor skills, visual attention, sustained attention, working memory and executive functioning, fit in well with the previous literature on areas of cognition most often affected. Given the majority of the sample were not treated with radiotherapy and yet significant impairment was found compared to test normative data, these results also support the growing literature on the detrimental effects of chemotherapy treatment alone, without concurrent radiotherapy. The effects of chemotherapy treatment in the absence of radiotherapy are becoming more prominent, both clinically and in the literature, given the reduction in the use of radiotherapy as a first line treatment. Given that the impact of intrathecal chemotherapy is not limited to specific areas of the brain and rather is thought to negatively impact on the development of NAWM and the integrity of existing white matter (Reddick et al., 2006) the negative impact of chemotherapy on the cognitive areas seen in this study provides some support to theories that they are underpinned, at least in part, by diffuse neural networks reliant on the integrity of white matter.

The study also has theoretical implications regarding the importance of assessing construct validity of measures in specific populations and age groups. The adult version of the CogState battery has very good evidence of its construct validity in a wide range of populations. However, given the much reduced correlations found in this study, taking into account the limitations of the study, it is clear that it should not be assumed that construct validity remains stable across age ranges or clinical populations. Performance on measures of cognitive functions is only ever a proxy measure of the cognitive construct itself and may be affected by developmental and extraneous test factors. For example in this study significant levels of psychomotor impairment were seen, including fine motor skills and dexterity, on the GPB task. Fine motor skills are an integral part of any test requiring responses using a pen or pencil such as the SS and MM tasks, therefore ability in this area might account for a larger portion of the variance in performance on these tasks in this particular population than in other groups of children, diluting their ability to measure processing speed and visual attention respectively. These factors should be taken into account when evaluating new tests, and those with more established psychometric properties, in specific populations.

4.6 Future Research

The initial results of this study warrant further investigation in future research on the CogState paediatric battery, as although they are less conclusive than in the adult studies they are on the whole comparable with other batteries evaluated for use in this population. As the normative data for the battery improves through increasing use it will become easier to investigate the battery as a whole. A larger study with the power to address both concurrent and discriminant validity would increase

understanding of the cognitive constructs that the tasks are actually tapping in to in this population. Criterion validity and predictive validity also need to be addressed given the questions raised by the tentative analysis in this study over the sensitivity of the battery in this population. It has been shown to be sensitive to deficits in other adult and child populations therefore further research should be able to determine if this results of this study are truly representative of outcomes in this clinical group or not.

Following establishment of criterion and construct validity, inclusion of the battery in longitudinal studies alongside more traditional measures would be useful in establishing its sensitivity to change over time. This is particularly relevant due to the psychometric properties of the CogState battery meaning that it is suited to tracking change over much more flexible time courses than traditional measures.

More broadly, future research in this area needs to focus on translating the large body of literature describing the neurocognitive deficits seen in specific groups into practical and clinical outcomes for children attending paediatric oncology clinics. Of primary importance in achieving this outcome will be the further development and use of psychometrically sound neurocognitive screening tools, such as the CogState battery investigated in this study, in order to facilitate the assessment of *every* child at risk of neurocognitive impairment. Given the level of previously unknown cognitive impairment seen in the participants in this study, such screening protocols, if adopted clinically, would be likely to identify large numbers of children who have cognitive difficulties following their treatment and would benefit from support and treatment. Further research focused on what this support and treatment should be is also needed to clarify the effectiveness of both pharmacological and

cognitive rehabilitation based approaches, and to continue developing new interventions which may be of benefit to these children as they develop.

Such large scale screening approaches would also facilitate further progress in understanding the risk factors for poor neurocognitive outcome, including more recent research into genetic risk factors, and the characteristics of children who respond or fail to respond to various interventions. Furthermore, it would make the further longitudinal research needed to understand in more detail the time course of neurocognitive outcomes following particular treatment regimens increasingly feasible to complete.

To accomplish these aims the artificial boundary between research and clinical work will need to be removed so that all clinical work in the area of neurocognitive follow up is able to contribute to the research literature and all research includes neurocognitive measures which are embedded into clinical practice. Only by working in this way can sufficient children be studied to gather generalizable and robust data, and can that data be clinically useful, both as it is collected and beyond. Collaborations working towards this aim do exist around the world, but continued efforts towards increasing their coverage, especially in the UK, are always needed.

4.7 Conclusion

Whilst the CogState paediatric battery remains a promising tool as a screening measure in a paediatric oncology population, particularly relative to the other screening tools described in the current literature, the results of this study would not appear to provide strong and robust support for its construct validity. This may in part be due to methodological limitations of the current study and further

studies are needed in larger samples, using a wider variety of standard measures, to more firmly establish its construct validity, both concurrent and divergent. There is also a need to investigate the criterion validity of the battery further to establish that it is sensitive enough to detect the cognitive deficits seen in this clinical population. Once these factors have been established it may prove to be a useful screening tool in clinical practice and a quick and reliable measure for use in multisite research.

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Appendices

Appendix A

Invitation Letter and Consent to Contact Form

University of East Anglia

Faculty of Medicine and Health Sciences
School of Medicine
Department of Psychological Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom
Email:e.prince@uea.ac.uk
Web: www.uea.ac.uk

Dear Parent

We would like to invite you and your child to take part in a research study. This study is investigating a new way of assessing thinking and memory in children who have been treated for brain tumours or leukaemia. Previous research has found that children can often experience difficulties with parts of their thinking and memory after being treated for cancer. It is recommended that their thinking and memory is assessed as part of their long term follow up so that any problems can be identified early. This research aims to assess how good a short computerized measure is at doing this and to see if it can be easily used by patients and the service.

Enclosed with this letter is an information sheet giving further details about the study and the contact details of the researchers if you would like to ask any questions.

If you would like to find out more about the study and the possibility of you and your child taking part please complete the form at the bottom of this letter giving you consent to be contacted by the research team and return it to the person who gave you the letter.

Best wishes

Liz Prince

Trainee Clinical Psychologist

.....

I am interested in finding out more about the study: **Evaluation of a new cognitive assessment measure in children who have had cancer**
Please contact me on the following details:

Name of child: _____

Name of parent: _____

Address: _____

Telephone number: _____

Email address: _____

Please put a tick next to your preferred method of communication

Appendix B

Parent Participant Information Sheet

University of East Anglia
Faculty of Medicine and Health Sciences
School of Medicine
Department of Psychological Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom

Email:e.prince@uea.ac.uk

Web: www.uea.ac.uk

Information about the Research

Study Title: Evaluation of a new cognitive assessment measure in children who have had cancer

We would like to invite you and your child to take part in our research study. Before you decide if you and your child should take part we would like you to understand why the research is being done and what it would involve for you and your child. You will have the opportunity to go through the information sheet with one of the researchers and they will answer any questions you have. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you and your child if they take part.

Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear.

Part 1

What is the purpose of the study?
Children who have received treatment for cancer, particularly brain tumours or leukaemia, can experience difficulties in their thinking and memory in the months and years after their treatment. This can affect their performance at school as well as other areas of their lives. It is recommended that all children who are at risk of experiencing these problems receive an assessment of their thinking and memory as part of their long term follow up following cancer treatment. However not all children are currently receiving these assessments. Part of the reason for this may be that the assessments currently used take a very long time and are expensive to complete.

This study is investigating if a new, brief computerised assessment called CogState could be used with children with cancer. To do this we need to find out if CogState

measures the same things as the tests which are currently used and if it is as sensitive as the old tests in picking up and problems the child may have in their thinking and memory. We also want to know if children with cancer are happy to complete CogState and if it can be used easily within the oncology service.

This study is being conducted in part fulfilment of a Doctorate in Clinical Psychology at the University of East Anglia (UEA). The data will also be used in a separate project by another trainee clinical psychologist in part fulfilment of a Doctorate in Clinical Psychology at the University of East Anglia (UEA)

Why have my child and I been invited to take part?
Your child has been invited to take part because they have been treated for a brain tumour or leukaemia and are currently being followed up by the paediatric oncology team. You have been invited as your child's parent to complete some questionnaires about your child. We are aiming to recruit 35 children and their parents to the study in total. This means that not everyone who shows an interest in taking part in the study may be able to take part.

Do my child and I have to take part?
It is up to you to decide if you and your child should join the study. We will describe the study and go through this information sheet. If you agree to you both taking part, we will then ask you to sign a consent form. We will also ask your child to sign a form saying they are happy to take part in the study. You are free to withdraw your child at any time, without giving a reason. This would not affect the standard of care your child receives.

What will happen to me and my child if we take part?
If your child takes part in the study there will be no changes in their medical care.

A researcher will arrange to meet with you and your child for one visit that will last approximately 1 ½ hours with a break half way through. This visit can take place at a time and location which is convenient for you. This may be at your home, the hospital or a different location. During this visit the researcher will answer any questions you may have about the study and confirm that both you and your child are still happy to take part. The researcher will then complete a number of different cognitive assessments with your child. Some of these will be on a laptop computer and some will be pencil and paper tests. Your child will also be asked to complete two short questionnaires. Whilst these assessments are taking place you will be asked to complete three short questionnaires about your child.

Following this visit, with your consent, we will send a brief report of your child's results on the standard tests to the clinical team looking after your child's cancer treatment and follow up. You may be contacted by the team following this if they think the assessments indicate that your child may benefit from further testing or follow up.

We may wish to clarify information about your child's diagnosis and medical treatment by looking at their medical notes or speaking to their doctor.

What are the possible disadvantages/risks of taking part?
It is unlikely that there are any risks to child as a result of taking part in this study as no changes are being made to their medical care. Some children may find

completing the assessment measures tiring or distressing. If this should happen the assessment will be stopped and appropriate support for you and your child provided. You may be encouraged to contact your child's clinical team for further support if necessary. Your child will be able to take breaks during the assessment if they need to. The assessment can be stopped at any time if your child does not want to continue.

What are the possible benefits of taking part?

Your child may be helping to make assessments of thinking and memory more easily available to other children who have been treated for brain tumours or leukaemia.

What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my child's taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

What will happen if I don't want my child to carry on with the study?
If you don't want your child to continue with the study at any point you can withdraw your consent and the assessment will be stopped. Any information that identifies you or your child will be destroyed. Anonymous data collected up to that point may be retained.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. They can be contacted by email at e.prince@uea.ac.uk. If you remain unhappy and wish to complain formally, you can do this via the NHS Complaints Procedure. Details can be obtained from PALS (01603289036)

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of East Anglia but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will our taking part in the study be kept confidential?
All information which is collected about your child during the course of the research will be kept strictly confidential and stored in line with Caldicott principles, the Data Protection Act and the regulations of the UEA.

Data collected electronically will be kept on a password protected laptop and encrypted memory stick only. Information held on paper will be kept in a locked filing cabinet. The assessment results will be coded with a participant identification number and stored separately from any identifiable information. Data will only be accessible to members of the research team. Data will be kept for at least 5 years as per UEA regulations and then securely disposed of.

The data collected from your child will be collated with the data from other participants and written up in a way that means no individual participant is identifiable.

Will anyone be told that my child and I are taking part in the study?
We will inform the paediatric oncology service currently responsible for your child's cancer treatment and follow up that you and your child are taking part in this study.

If you consent we will also send them a brief report on your child's results on the standard assessment measures at the end of the study.

What will happen to the results of the research study?
The results of the study will be written up and submitted as two thesis assignments and two service research projects to the UEA in part fulfilment of the Doctorate in Clinical Psychology.
We will also seek to publish the results in relevant scientific journals.
You may request a brief report of the results of the study.

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Yorkshire & The Humber – Sheffield Research Ethics Committee.

Further information and contact details

For further information please contact:

Liz Prince
Trainee Clinical Psychologist
Norwich Medical School
University of East Anglia
Norwich Research Park
Norwich
Norfolk
NR4 7JT
Email: e.prince@uea.ac.uk.

Appendix C

16 Year Old Participant Information Sheet

University of East Anglia

Faculty of Medicine and Health Sciences
School of Medicine
Department of Psychological Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom

Email:e.prince@uea.ac.uk

Web: www.uea.ac.uk

Information about the Research

Study Title: Evaluation of a new cognitive assessment measure in children who have had cancer

We are asking if you would join in a research project to find the answer to the question of whether a new assessment is good at measuring the thinking and memory of children who have had cancer.

Before you decide if you want to join in, it's important to understand why the research is being done and what it will involve for you. So please consider this leaflet carefully. Talk to your family, friends, doctor or nurse if you want to. We will also ask you parent if they are happy to take part in the parts of the study which involve them.

Part 1 tells you the purpose of this study and what will happen if you take part.

Part 2 gives you more detailed information about how the study is being run.

Part 1

Why are we doing this research?
Children who have had certain types of cancer can sometimes have some problems with their thinking or memory after their treatment. There are ways to find out what these problems are by a clinical psychologist asking the child to complete a lot of different tests and puzzles. This takes a long time and is not currently done with everyone. We want to find out if a new short assessment on a computer is able to find this information in a quicker and easier way. To do this we need to compare it to the tests and puzzles used at the moment to see if it is as good as them.

The person doing this research and another trainee will also use the results to write two reports for a course they are doing in Clinical Psychology.

What is the assessment that is being tested?
The assessment is called CogState and is a group of games and puzzles on a computer often using playing cards. It has been used before with lots of other adults and children but not yet with children with cancer.

Why have I been invited to take part?
You have been invited to take part because you have been treated for a brain tumour or leukaemia and are currently being followed up by the paediatric oncology team. We are aiming to recruit 35 children to the study in total. This means that if more than 35 children reply saying they would like to take part not everyone will be able to be involved in this study.

Do I have to take part?
No. It is up to you. We will ask you for your consent and then ask if you would sign a form. We will also ask your parents to give their agreement to you taking part and their consent to complete the parts of the project which involve them. We will give you a copy of this information sheet and your signed form to keep. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect the care you receive.

What will happen to me if I take part?
If you take part in the study there will be no changes in your medical care.

The person doing the research will arrange to come and see you and your parents at a place and time you are happy with. This visit will take about 1 ½ hours with a break in the middle. During this visit the person doing the research will answer any questions you or your parents may have about the study and will ask you to sign a form to say you are happy to take part. Then you will complete a number of different tasks, puzzles and questionnaires with the person doing the research. Some will be on a computer and some will be on paper. While you are doing this you parent will fill in a few questionnaires about you.

After this visit, with your permission, we will send a brief report of how you did on the standard tests and puzzles used in the research to the team at the hospital who look after your cancer treatment. After seeing the report the team may think it would be helpful to find out some more information on how you are doing and they may contact you and your parents to discuss this.
As part of the research we might also want to check with your doctor or your medical notes some details about your illness and the treatment you have had.

Is there anything to be worried about if I take part?
It is very unlikely taking part in the study will harm you in any way. Some children might find completing the tests and puzzles a bit boring, tiring or upsetting. If you feel upset you can talk about this with the person doing the tests with you and they will tell you where you can get further help if you need it. You will be able to take a break at any point and you can ask for the session to stop completely if you want to.

What are the possible benefits of taking part?

You may be helping us to make these assessments of thinking and memory more easily available to other children like you who have been treated for cancer.

Contact details
If you would like more information about the study you can contact the research team by emailing e.prince@uea.ac.uk.

Thank you for reading so far – if you are still interested, please go to Part 2:

Part 2

What will happen if I don't want to carry on with the study?
If you don't want to continue with the study at any point you can withdraw your consent and the assessment will be stopped. Any information that identifies you will be destroyed. Anonymous data collected up to that point may be retained.

What if there is a problem or something goes wrong?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. They can be contacted by email at e.prince@uea.ac.uk If you remain unhappy and wish to complain formally, you can do this via the NHS Complaints Procedure. Details can be obtained from PALS (01603289036)

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of East Anglia but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will anyone else know I am doing this?
We will keep your information in confidence. This means we will only tell those who have a need or right to know. With your consent we will tell the team at the hospital who look after your cancer care that you are taking part. We will store your test results separately from your name so that people not involved in the research cannot tell who you are. All the information we collect will be kept in locked cupboards or on computers with passwords. It will be kept for at least 5 years as this is the rules of the university and the NHS, and then securely disposed of.

What will happen to the results of the research study?
The results of the study will be written up and submitted as two thesis assignments and two service research projects to the UEA in part fulfilment of the Doctorate in Clinical Psychology.

We will also seek to publish the results in relevant scientific journals. We will do this in a way that means it is not possible to tell who you are or results of you individual assessment.

You may request a brief report of the results of the study.

Who has reviewed the study?
Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is fair. Your project has been checked by the Yorkshire & The Humber - Sheffield Research Ethics Committee.

Thank you for reading this – please ask any questions if you need to

Appendix D

11-15 Year Old Participant Information Sheet

Faculty of Medicine and Health Sciences
School of Medicine
Department of Psychological Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom

Email:e.prince @uea.ac.uk

Web: www.uea.ac.uk

Information about the Research

Study Title: Evaluation of a new cognitive assessment measure in children who have had cancer

We are asking if you would join in a research project to find the answer to the question of whether a new assessment is good at measuring the thinking and memory of children who have had cancer.

We will ask your parent to give permission for you to take part. We will also like you if you want to take part. Before you decide if you want to join in, it's important to understand why the research is being done and what it will involve for you. So please consider this leaflet carefully. Talk to your family, friends, doctor or nurse if you want to.

Part 1 tells you the purpose of this study and what will happen if you take part.

Part 2 gives you more detailed information about how the study is being run.

Part 1

Why are we doing this research?
Children who have had certain types of cancer can sometimes have some problems with their thinking or memory after their treatment. There are ways to find out what these problems are by a clinical psychologist asking the child to complete a lot of different tests and puzzles. This takes a long time and is not currently done with everyone. We want to find out if a new short assessment on a computer is able to find this information in a quicker and easier way. To do this we need to compare it to the tests and puzzles used at the moment to see if it is as good as them.

The person doing this research and another trainee will also use the results to write a report for a course they are doing in Clinical Psychology.

What is the assessment that is being tested?
The assessment is called CogState and is a group of games and puzzles on a computer often using playing cards. It has been used before with lots of other adults and children but not yet with children with cancer.

Why have I been invited to take part?
You have been invited to take part because you have been treated for a brain tumour or leukaemia and are currently being followed up by the paediatric oncology team. We are aiming to recruit 35 children to the study in total. This means that if more than 35 children reply saying they would like to take part not everyone will be able to be involved in this study. However you might be able to be involved in other research in the future if you want to.

Do I have to take part?
No. It is up to you. We will ask you for your agreement and then ask if you would sign a form. We will also ask your parents to give their permission for you to take part. We will give you a copy of this information sheet and your signed form to keep. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect the care you receive.

What will happen to me if I take part?
If you take part in the study there will be no changes in your medical care.

The person doing the research will arrange to come and see you and your parents at a place and time you are happy with. This visit will take about 1 ½ hours with a break in the middle. During this visit the person doing the research will answer any questions you or your parents may have about the study and will ask you to sign a form to say you are happy to take part. Then you will complete a number of different tasks, puzzles and questionnaires with the person doing the research. Some will be on a computer and some will be on paper. While you are doing this you parent will fill in a few questionnaires about you. .

After this visit, if your parents agree, we will send your team at the hospital a brief report on how you did on the standard tasks and puzzles. If they think they might need some more information they may talk to your parents about this. As part of the research we might also want to check with your doctor or your medical notes some details about your illness and the treatment you have had.

Is there anything to be worried about if I take part?
It is very unlikely taking part in the study will harm you in any way. Some children might find completing the tests and puzzles a bit boring, tiring or upsetting. If you feel upset you can talk about this with the person doing the tests with you and they will tell you where you can get further help if you need it. You will be able to take a break at any point and you can ask for the session to stop completely if you want to.

What are the possible benefits of taking part?
You may be helping us to make these assessments of thinking and memory more easily available to other children like you who have been treated for cancer.

Contact details
If you would like more information about the study you can contact the research team by emailing e.prince@uea.ac.uk.

Thank you for reading so far – if you are still interested, please go to Part 2:

Part 2

What if there is a problem or something goes wrong?
If you are worried about any part of the study you should talk to your parents and the people doing the research first as they may be able to answer your question. If you are still worried and you would like to complain you can do so using the NHS complaints procedure. PALS will be able to help you and your parents to do this (01603289036).

If something does go wrong and you are harmed in away because of the research team doing something wrong you may be able to claim for compensation from the University of East Anglia. Your parents will help you to do this.

Will anyone else know I am doing this?
We will keep your information in confidence. This means we will only tell those who have a need or right to know. With your parent's permission we will tell the team at the hospital who look after your cancer care that you are taking part. We will store your test results separately from your name so that people not involved in the research cannot tell who you are. All the information we collect will be kept in locked cupboards or on computers with passwords.

Who has reviewed the study?
Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is fair. Your project has been checked by the Yorkshire & The Humber - Sheffield Research Ethics Committee.

Thank you for reading this – please ask any questions if you need to.

Appendix E

8-10 Year Old Participant Information Sheet

Faculty of Medicine and Health Sciences
School of Medicine
Department of Psychological Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom

Email:e.prince@uea.ac.uk

Web: www.uea.ac.uk

Study Title: Testing a new test of thinking and memory in children who have had cancer

We are asking if you would like to take part in a research project. We will ask your parents to give permission for you to take part. We will also ask you if you want to take part so this leaflet is to tell you what the research is about.

What is research? Why is this project being done?
Research is a way we try to find out the answers to questions.

We want to see if we can test the thinking and memory of children who have been treated for cancer in a quick and easy way.

Why have I been asked to take part?
You have been asked because you have been treated for a brain tumour or a blood cancer at the hospital.

Did anyone else check the study is ok to do?
Before any research is allowed to happen, it has to be checked by a group of people called a Research Ethics Committee. They make sure that the research is fair. Your project has been checked by the Yorkshire & The Humber- Sheffield Research Ethics Committee

Do I have to take part?
No. You can say no to the study if you want to. Nothing bad will happen if you decide to say no.

What will happen to me if I take part?
Nothing that the doctors are doing to look after you will change.

One person who is doing the research will come and visit you and your family. They will do some different games and puzzles with you. Your parents will need to answer

a few questions about you. This visit will take about 1 ½ hours with a break halfway through. You can ask for other breaks if you want them.

If your parents say yes, we will share some information about the tests and puzzles you did with your doctors. They might want to talk to your parents a bit more about this.

We might also ask your doctors for a bit more information about your illness and the treatment you have had.

Might anything in the research upset me?
It is very unlikely that anything will upset you. If you do get upset just talk to the person doing the research and they will stop the task.

Will joining help me?
You may be helping other children like you by making it easier to look at their thinking and memory in the future.

What if something goes wrong during the project?
If something goes wrong or you want to make a complaint you should talk to your parents and they will help you decide what to do next.

Will anyone else know I am doing this?
We will keep all your information private. We won't tell anyone you are taking part if they do not need to know.

What if I don't want to do the research anymore?
If at any time you don't want to do the research anymore, just tell your parents or the person doing the research. They will not be cross with you and will be able to stop you taking part.

Appendix F

Parent Consent Form (8-15 Year Old Participants)

Faculty of Medicine and Health Sciences
School of Medicine
Department of Psychological Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom

Email:e.prince@uea.ac.uk

Web: www.uea.ac.uk

Patient Identification Number for this trial:

CONSENT FORM

Study Title: Evaluation of a new cognitive assessment measure in children who have had cancer

Name of Researcher: Liz Prince

Please initial the box:

1. I confirm that I have read and understand the information sheet dated 10/6/2013 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my child's participation is voluntary and that they are free to withdraw at any time without giving any reason, without their medical care or legal rights being affected.

3. I understand that relevant sections of their medical notes and data collected during the study, may be looked at by individuals from the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to their records.

4. I agree to complete some questionnaires about my child as part of the study.

5. I agree to my child's paediatric oncology team being informed that my child is taking part in the above study.

6. I agree to my child's paediatric oncology team being sent a brief report of the results of the standard measures used in the study.

7. I agree for my child to take part in the above study.

_____	_____	_____
Name of Parent/Guardian	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix G

Parent Consent Form (16 Year Old Participants)

Faculty of Medicine and Health Sciences
School of Medicine
Department of Psychological Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom

Email:e.prince@uea.ac.uk

Web: www.uea.ac.uk

Patient Identification Number for this trial:

CONSENT FORM

Study Title: Evaluation of a new cognitive assessment measure in children who have had cancer

Name of Researcher: Liz Prince

Please initial the box:

1. I confirm that I have read and understand the information sheet dated 10/6/2013 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I agree to complete some questionnaires about my child as part of the study.

3. I agree for my child to take part in the above study.

_____	_____	_____
Name of Parent/Guardian	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix H

16 Year Old Participant Consent Form

Faculty of Medicine and Health Sciences
School of Medicine
Department of Psychological Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom

Email:e.prince@uea.ac.uk

Web: www.uea.ac.uk

Patient Identification Number for this trial:

CONSENT FORM

Study Title: Evaluation of a new cognitive assessment measure in children who have had cancer

Name of Researcher: Liz Prince

Please initial the box:

1. I confirm that I have read and understand the information sheet dated 10/6/2013 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. I agree to my parent completing some questionnaires about me as part of the study.

5. I agree to my paediatric oncology team being informed that I am taking part in the above study.

6. I agree to my paediatric oncology team being sent a brief report of the standard measures used in the study.

7. I agree to take part in the above study.

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix I

8-15 Year Old Participant Assent Form

Faculty of Medicine and Health Sciences
School of Medicine
Department of Psychological Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom

Email:e.prince@uea.ac.uk

Web: www.uea.ac.uk

Project title: Testing a new test of thinking and memory in children who have had cancer

Child (or if unable, parent on their behalf) /young person to circle all they agree with:

Has somebody else explained this project to you?	Yes/No
Do you understand what this project is about?	Yes/No
Have you asked all the questions you want?	Yes/No
Have you had your questions answered in a way you understand?	Yes/No
Do you understand it's OK to stop taking part at any time?	Yes/No
Are you happy to take part?	Yes/No

If **any** answers are 'no' or you don't want to take part, don't sign your name!

If you do want to take part, you can write your name below

Your name _____

Date _____

The person who explained this project to you needs to sign too:

Print Name _____

Sign _____

Date _____

Thank you for your help

Appendix J

Demographics Questionnaire

Patient Identification Number: _____ Date: _____

Age: _____years _____ months

Gender: MALE / FEMALE

Parental Level of Education: (Circle as appropriate)

GCSE / A Levels or equivalent / Undergraduate Degree / Post Graduate Degree

Diagnosis:

_____

Time since diagnosis: _____ years _____ months

Treatment: 1_____

2 _____

3 _____

Time since treatment 1: _____years _____ months

Time since treatment 2: _____years _____ months

Time since treatment 3: _____years _____ months

Current maintenance treatment? Yes⌈ No⌈

Details of maintenance treatment:

_____

_____

_____

Appendix K

Acceptability Questionnaire

Please can you answer these questions about the computer puzzles you have just done? Circle the answer you most agree with for each question.

1. How hard were the puzzles?

Easy A bit hard Very hard

2. Did you enjoy the puzzles?

Didn't enjoy it all Enjoyed it a little bit Enjoyed it a lot

3. Were the puzzles interesting?

Not interesting at all A little bit interesting Very interesting

4. Did the puzzles take a long time?

Not a very long time Quite a long time A very long time

5. Did you feel tired after doing the puzzles?

Not tired at all A little bit tired Very tired

6. Did you feel upset after doing the puzzles?

Not upset at all A little bit upset Very upset

7. Would you be happy to do the puzzles again?

No Yes

8. Is there anything else you would like to say about the puzzles? For example, was there a puzzle you liked the best? Or a puzzle you really didn't like?

_____
_____
_____
_____
_____

Thank you for completing these questions!

Appendix L

Service Based Research Project: The Acceptability and Feasibility of a Brief Neurocognitive Screening Battery in a Paediatric Oncology Population

(Appendix Identifiers have been changed to reflect the location of the Appendix in the Thesis)

Abstract

Background. Children treated for CNS tumours and leukaemia are at risk of neurocognitive late effects. It is recommended that they receive regular neuropsychological assessment to facilitate appropriate follow up. Brief screening batteries, such as CogState, could help services meet this recommendation. This study aimed to assess the acceptability and feasibility of the CogState battery in a paediatric oncology population.

Method. Thirty-seven children completed the CogState battery and an acceptability questionnaire as part of a larger study into the construct validity of the battery. Time taken to complete and score the battery was recorded for comparison with a standard battery. Recruitment rate was recorded.

Results. Mean completion and scoring time of the Cogstate battery was significantly shorter than the standard battery. Recruitment rates were high and comparable to previous studies. Results indicated the battery was acceptable to the vast majority of participants in the areas assessed, and 89% reported they would be happy to complete the assessment again.

Conclusion. The CogState battery is acceptable to this population and can be completed and scored significantly faster than brief batteries of standard measures suggesting it is feasible for use by busy clinicians once the psychometric properties of the battery have been established.

Introduction

Around 20,000 children are diagnosed with some form of cancer each year (Steen & Mirro, 2000) of which around half are leukaemias and central nervous system (CNS) tumours. Five year survival rates for these types of cancer have increased dramatically in recent years meaning that the late effects of the disease and treatment regimens are becoming more prominent. Around 50%- 60% of survivors of childhood cancer will experience neurocognitive late effects (Hewitt, Weiner, & Simone, 2003) with survivors of leukaemia and CNS tumours most at risk (Costa, 2010). The primary areas of deficit identified are attention and concentration, processing speed, visual perceptual abilities, memory and executive function (Butler & Haser, 2006; Nathan et al., 2007; Peterson et al., 2008; Robinson et al., 2010). Several bodies including the Children's Oncology Group (Nathan et al., 2007), the National Institute for Health and Clinical Excellence (NICE, 2005) recommend neuropsychological assessment as a routine part of long term follow up for children at risk of neurocognitive late effects. It is acknowledged that these recommendations are currently not being fully implemented (Nathan et al., 2007). There are several barriers to this including the time and therefore cost involved in a full neuropsychological assessment combined with limited resources in the form of clinic space and appropriately qualified staff. NICE acknowledges that "Both professionals and parents/carers have identified a significant lack in formal psychological input … which represents a significant area of unmet need" (NICE, 2005 p. 75).

To address this problem, brief, easily administered valid and sensitive screening instruments are needed which cover the areas of neurocognitive function repeatedly demonstrated to be at risk in the literature. These instruments must be

acceptable to patients and their families and feasible for use within paediatric oncology services. It is reported that neuropsychological assessment can induce feelings of failure and frustration in some children (Baron, 2004) making it unpleasant for the child and influencing compliance and test performance. There is limited research literature on this topic however one study into the Paced Auditory Serial Addition Task (PASAT) in young adults has shown that it can induce negative mood in participants previously in positive or neutral mood states (Holdwick & Wingenfeld, 1999). It is therefore important to further understand the experience of completing a measure through acceptability analyses to fully understand any potential impact on both test performance and the child more widely.

Several screening batteries or measures have been assessed in the literature for use with this population, including informant report measures (e.g. Lai et al., 2011), batteries of standard neuropsychological measures (e.g. Krull et al., 2008) and computerized measures (Conklin et al., 2013). However, only one study (Pejnovic et al., 2012) specifically consider the acceptability and feasibility of their battery beyond stating their recruitment rate. Using a structured approach to feasibility assessment they focused on the brevity, simplicity, relevance, acceptability and value of their assessment battery made up of tests and subtests from standard neuropsychological measures. They assessed the battery in children newly diagnosed with cancer who would receive CNS-directed therapy as part of their treatment and in controls finding it to be brief (M= 49.4 minutes, SD =12.8), acceptable to patients and controls and to add significant information.

CogState is a brief computerized neurocognitive battery which takes approximately 20 minutes to complete. It consists of a selection of simple standardised experimental psychology paradigms such as n-back tasks and forced

choice reaction time tasks modified to make them applicable and acceptable in clinical use (Pietrzak et al., 2009). The battery makes use of non-verbal and culturally neutral stimuli and has been shown to demonstrate virtually no practice effects in adults or children (Falleti, Maruff, Collie, & Darby, 2006; Mollica, Maruff, Collie, & Vance, 2005) allowing for repeated administration over shorter time periods than traditional neuropsychological assessments. Subtests are available which are described as assessing psychomotor function, processing speed, visual attention, vigilance and sustained attention, visual memory and learning, working memory and executive functioning. Its computerised administration allows for accurate collection of data and automated scoring. Construct validity and criterion validity have been established in large samples of healthy adults, adults with schizophrenia, mild traumatic brain injury and AIDs dementia (Maruff et al., 2009; Pietrzak et al., 2009). It has been used with children and in both samples of typically developing children (Thomas, Reeve, Fredrickson, & Maruff, 2011) and a variety of samples from paediatric populations (Bangirana et al., 2009; Boivin et al., 2010; Mayes, Snyder, Langlois, & Hunter, 2007; Mollica, Maruff, & Vance, 2004). Construct and criterion validity in children is still being established. Given these properties the CogState paediatric battery has the potential to be a useful screening tool in paediatric oncology population at risk of neurocognitive late effects. In order for it to successfully incorporated into clinical services its construct and criterion validity, acceptability to services users and feasibility within the service context need to be assessed. This project aims to address the last two of these questions.

Research Questions

1. To determine if assessment with the CogState brief neurocognitive battery is acceptable to children receiving Paediatric Oncology follow up following treatment for CNS tumours or leukaemia.
2. To determine if assessment with the CogState brief neurocognitive battery is feasible for use in a Paediatric Oncology Outpatient setting.

Method

Design

The research questions were addressed as part of a larger cross-sectional correlation study focused on assessing the construct validity of the CogState battery in a paediatric oncology population. A questionnaire based design was used to address research question one with the participants of the larger study completing an acceptability questionnaire following completion of the CogState battery. Research question two was addressed in two ways. Firstly by recording the number of eligible patients approached to take part in the study who completed the battery. Secondly by recording the time taken to complete both the CogState battery and the standard battery to ascertain the brevity of the assessment compared to a brief battery of standard measures. The time taken to score both batteries for a sub-sample of five participants was also recorded. This was not recorded for the entire sample due feasibility difficulties in the larger study.

Participants

Participants in the study were children aged between 8-16 years who had been treated for a CNS tumour or leukaemia at one of three hospitals in the region (n=37). All participants had stable disease as determined by their primary physician

which required being off active therapies for those treated for CNS tumours and at least in maintenance therapy for those treated for leukaemia. All participants had English as their primary language to ensure they understood all of the assessments. Exclusion criteria were pre-existing neurodevelopmental or genetic disorder; history of head injury; sensory or motor impairment severe enough to prevent testing or a neuropsychological evaluation including any of the study measures in the last year. Further details of the study sample are presented in Table 1.

Table 1

Demographic and clinical details of the sample

Participant Characteristic	Whole Sample (n=37)
Gender n(%)	
Male	16 (43)
Female	21 (57)
Age at testing (years)	
Mean	12.7
SD	2.4
Range	8.5-16.9
Age at diagnosis (years)	
Mean	5.5
SD	3.6
Range	0.5-15.6
Time since diagnosis (years)	
Mean	7.1
SD	3.6
Range	0.25-13.25
Diagnosis n(%)	
Acute Lymphoblastic Leukaemia	27 (73)
Other Leukaemia	2 (5)
CNS Tumour	8 (22)
Treatment n(%)[a]	
Surgery	7 (19)
Chemotherapy	30 (81)
Radiotherapy	2 (5)
Corticosteroids	26 (70)
Other	3 (8)
Maintenance treatment at time of testing n(%)	4 (11)
Yes	33 (89)
No	

Parental Level of Education n(%)	
None	1 (3)
GCSE/O Level	12 (32)
A-level or equivalent	11 (30)
Undergraduate	11 (30)
Post Graduate	2 (5)
WASI Two-subtest IQ (standard score)[b]	
Mean	101.50
SD	14.86
Range	78-135
PI-ED total score[c]	
Mean	12.05
SD	5.89
Range	3-28

[a] Up to three treatments were recorded for each participant.
[b] WASI = Weschler Abbreviated Scale of Intelligence; Standard scores have a mean 100 and a standard deviation of 15
[c]PI-ED = Pediatric Inventory of Emotional Distress; Clinical cut off is 10 for males and 11 for females

Procedure

Ethical approval for the larger study was obtained from the Yorkshire & The Humber - Sheffield Research Ethics Committee (Appendix M). Local R&D approval was obtained from each clinical service (Appendices N-P) prior to recruitment beginning.

Participants were recruited through three local paediatric oncology teams. Clinicians screened potential participants against the inclusion and exclusion criteria of the study. Those who were eligible were initially approached by a member of the clinical team either during a routine clinic visit or by post with a follow up phone call, to provide initial information about the study (see Appendices A-E) and obtain consent to be contacted by the researcher. Following this the researcher contacted the family and arranged the study visit. Details of the recruitment rate at the three clinical services are presented in Table 2. Service A and B were smaller local teams where the entire eligible clinical population was approached. Service C was a larger regional centre covering a wide geographical region. Recruitment from this centre

was limited by the sample size requirements of the study (set by the power calculation for the larger study and the resources available) and was stopped when this sample size was reached and therefore it is likely it is not representative of true interest levels in the study.

Table 2

Recruitment rates by clinical service

	Service A	Service B	Service C	Total
Number of eligible patients identified and approached by the team	20	12	66	99
Number of patients expressing interest	17	10	19	46
Percentage of total approached	*85%*	*83%*	*30%*	*47%*
Number of patients recruited	15	9	13	37
Percentage of total approached	*75%*	*75%*	*19%*	*38%*

Prior to completing the study measures consent was obtained from the parents of children aged 8-15 years, with assent obtained from the child. For participants aged 16 years consent was obtained from both the child and the parent (see Appendices F-I). All study measures were completed in a single research visit to the home of the participant (lasting around 90 minutes) in order to minimise the burden of taking part in the project. All research visits followed a set order: the child completed the CogState battery followed by the acceptability questionnaire and then the remainder of the measures required by the construct validity study (listed below) were completed.

Measures

CogState

The CogState paediatric battery used in this study was made up of six tasks; Detection (DET), Identification (IDN), One Card Learning (OCL), One Back (OBK), Continuous Paired Associate Learning (CPAL) and Groton Maze Learning Task (GMLT). A description of these tasks and their primary outcome variables is presented in Table 3. All tasks were presented on a Toshiba Satelite Pro C850 1K4 laptop computer. The participant was guided through the tasks by on screen instructions with further verbal instructions from the researcher supervising the testing. Practice periods were presented prior to the CPAL and GMLT to ensure the participant understood the instructions before beginning the scored portion of the test. On the other tasks particular attention was given to the participant's first few responses and the instructions of the test were repeated if necessary. Responses to the DEC, IDN, OCL and OBK tasks were made using simple keyboard strokes. An external mouse was used for the CPAL and GMLT. Participants were encouraged to be as quick and accurate as possible in their responses. Auditory and visual feedback was given each time the participant gave an incorrect response.

Table 3

CogState Task Descriptions

Subtest	Abbreviation	Description	Primary Outcome Variable
Detection Task	DET	The participant must press the "yes" key as soon as the single card in the centre of the screen flips over. In the 10-16years battery a joker is used. In the 8-9years battery a smiling face is used.	Speed of performance (Log_{10} transformation of mean reaction time)
Identification Task	IDN	The participant must respond "yes" if the card presented is red and "no" if it is black as soon as it	Speed of performance (Log_{10} transformation of

		flips over. In the 10-16years battery a joker is used. In the 8-9years battery a smiling face is used.	mean reaction time)
One Card Learning Task	OCL	The participant must respond "yes" if they have seen the card presented before in this subtest and "no" if they have not. There are four target cards which repeat nine times during task. In the 10-16years battery standard playing cards are used. In the 8-9years battery coloured numbers and symbols are used.	Accuracy of performance (Arcsine transformation of proportion of correct responses)
One Back Memory Task	OBK	The participant must respond "yes" if the current card is the same as the previous card and "no" if it not. In the 10-16years battery standard playing cards are used. In the 8-9years battery coloured numbers and symbols are used.	Speed of performance (Log_{10} transformation of mean reaction time)
Continuous Paired Associate Learning Task	CPAL	After a learning phase during which all the shapes visible the participant must chose the matching shape from a choice of eight hidden locations (six hiding shapes and two decoy). They continue choosing on each trial until the correct shape is found.	Total Errors
Groton Maze Learning Task	GMLT	The participant must find the correct path through a 10x10 grid from a starting point to a target following three rules. For the 10-16years battery the previous steps taken are hidden, for the 8-9years battery they remain visible. Five trials are presented which the same	Total Errors (Summed across the five trials; Total Rule Break Errors is an alternative variable)

	29 step path on each occasion.

Acceptability Questionnaire

The acceptability questionnaire (Appendix K) was designed for the study based on the dimensions assessed by Pejnovic et al. (2012) in their participant survey. Participants were asked to rate the CogState battery on a three point Likert scale in the areas of difficulty, enjoyment, interest, length, fatigue and distress. A three point scale was used rather than a five point scale (as in Pejnovic et al., 2012) to ensure the questionnaire could be understood by participants across the entire age range and with potential intellectual impairment. Pejnovic et al. (2012) collapsed their five point scale to a three point scale for data analysis so comparison with previous research was still possible. Answer wording was specific to each question but with the same three levels across all questions (e.g. "Did the puzzles take a long time? Not a very long time; quite a long time; a very long time" and "Did you feel tired after doing the puzzles? Not tired at all; A little bit tired; Very tired") to aid comprehension but retain comparativeness across domains. Participants were also asked if they would be happy to complete the puzzles again. The questionnaire included a final question inviting the child to give any further comments they wished to.

Other measures

The other measures completed during the study visit related to the larger construct validity study. Participants completed the Wechsler Abbreviated Intelligence Scale two-subtest short form (Wechsler, 1999), and the Paediatric Inventory of Emotional Distress (O'Connor, Carney, House, Ferguson, & O'Connor,

2010) which analysed as covariates in the construct validity study. The standard battery of tests used for the main analyses were the Grooved Peg Board (Klove, 1963), the Symbol Search and Digit Span subtests of the Wechsler Intelligence Scale for Children version IV (Wechsler, 2003), the Map Mission and Score! subtests of the Test of Everyday Attention for Children (Manly, Robertson, Anderson, & Nimmo-Smith, 1999); the Dot Location subtest of the Children's Memory Scale (Cohen, 1997), the Trail Making Test A and B (Reitan, 1958) and the Behaviour Rating Inventory of Executive Functioning (Gioia, Isquith, Guy, & Kenworthy, 2000). The time taken to complete and score this battery was recorded for comparison with the CogState battery with reference to the feasibility of the CogState battery.

Statistical analysis

Statistical analyses were conducted using Excel 2013 and SPSS version 19. Descriptive statistics were used to describe the results of the acceptability questionnaire. Qualitative comments were arranged into themes. Brevity was analysed by taking the mean length of time to complete the CogState battery and compared to the standard battery using a paired sample *t*-test. Mean time to score a sub-sample of five data sets is reported and was analysed compared to the standard battery using an independent samples *t*-test. Percentage completion of the battery is reported.

Results

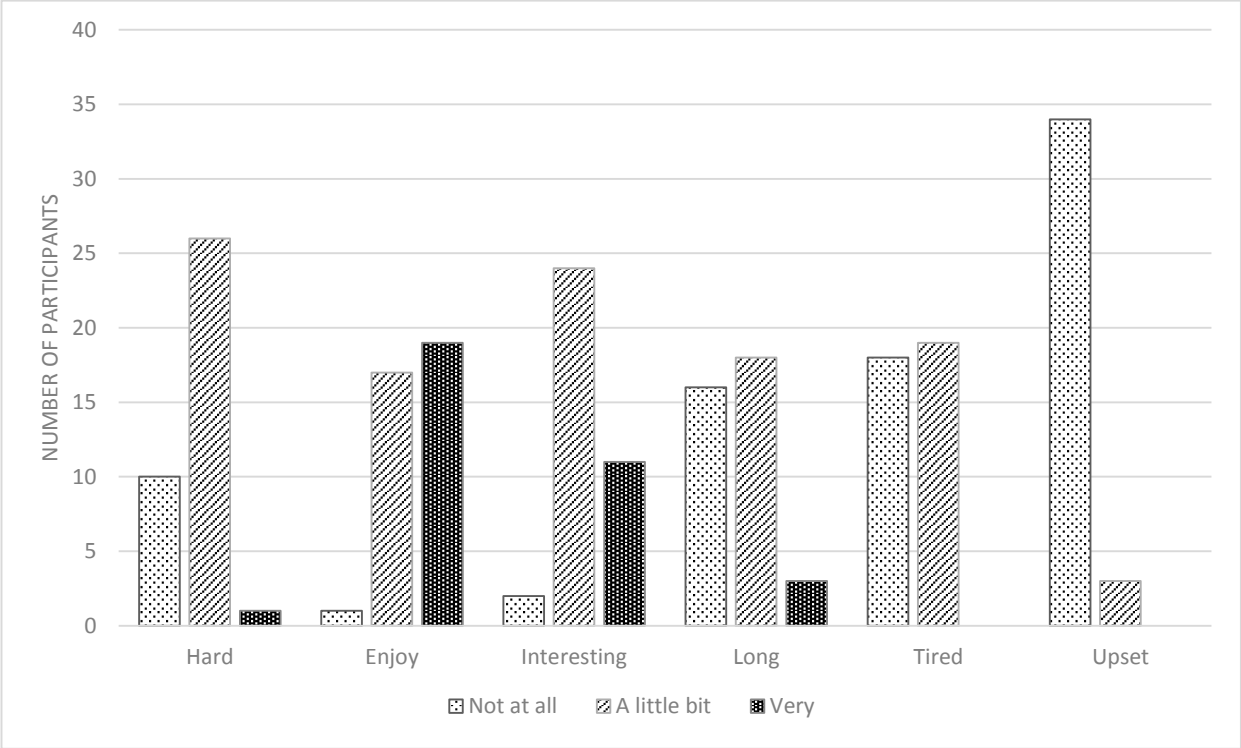
Acceptability Questionnaire

The results of the Acceptability questionnaire are presented in Figure 1. Only 3% of participants rated the battery as very hard. Similarly only 3% said they had not

enjoyed it at all. In total 95% of participants reported finding the tasks ‘a little bit’ or ‘very’ interesting. Only 8% of participants thought the battery took a ‘very’ long time to complete with 43% reporting it took “not a very long time at all”. No participants reported that they felt ‘very’ tired or upset after completing the tasks with the vast majority of participants (92%) saying the felt “not upset at all”.

Figure 1

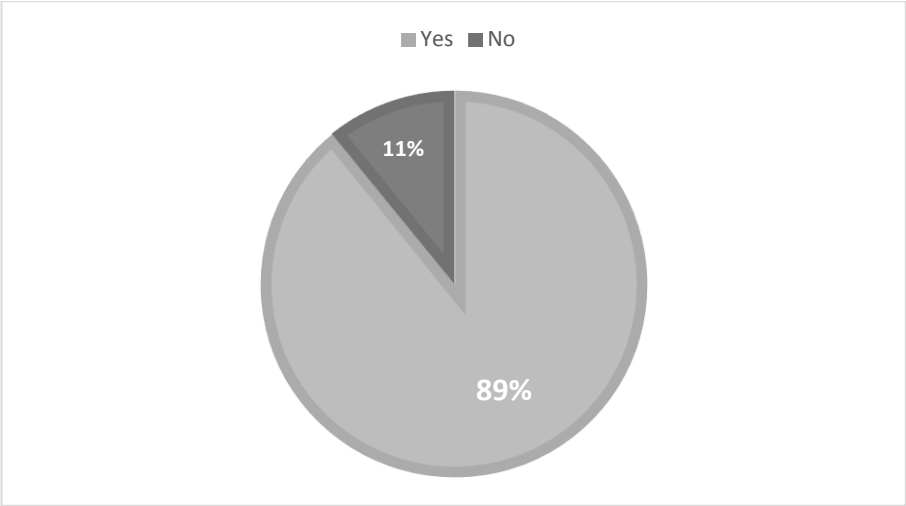
Acceptability Questionnaire Responses



The responses to the question asking participants if they would be happy to do the puzzles again are represented in Figure 2. The vast majority of participants responded positively.

Figure 2.

Pie chart of answers to the question “Would you be happy to do the puzzles again?”



Of the four participants (11%) who said they would not be happy to complete the battery again one child later reported to the researcher that they had actually enjoyed the CogState tasks the best of any of the tasks in the testing session as a whole. Two of the other children were among the most cognitively impaired children in the sample as a whole performing ≥1Standard Deviation below the mean on 8/9 tasks and 7/9 tasks in the standard battery and 1/4 and 2/4 CogState tasks (of the four tasks where this can be assessed) respectively.

Qualitative comments

The last question on the acceptability questionnaire invited participants to give any additional comments on their experience of completing the measure prompting them with the phrase "Is there anything else you would like to say about the puzzles? For example, was there a puzzle you liked the best? Or a puzzle you really didn't like?" Of the 37 participants 24 chose to leave a comment in this section, with 10 participants commenting on two separate aspects of the measure resulting in 34 comments in total.

Overall 22 positive comments were made (65%), either about the measure as a whole (three comments; e.g. "I enjoyed it a lot, I feel I would like to do this again")

or about specific tasks. Of the specific tasks eight participants said they enjoyed the GMLT, seven participants said that they enjoyed the CPAL task, and four mentioned enjoying the card based tasks (one singling out the OCL task and one the IDN and OBK tasks).

There were 10 comments made regarding aspects of the battery the participants did not like. Six participants reported they did not like specific tasks (GMLT (2), card tasks (4) including OCL (1)). Within this three participants gave reasons for their dislike. The two participants who referred to the GMLT stated it was too hard. The child who referred to the card based takes stated they "went on for quite a while". One participant commented that the keyboard controls for the tasks were "a bit annoying to use" and another than the feedback when they answered incorrectly on some items left them feeling "a bit demoralised". Lastly one participant commented that in general the tasks need to be made "a bit harder because they are too easy".

Lastly one neutral comment was made which stated "some of the tasks took longer than others".

Feasibility

Recruitment and Completion rates

The recruitment rates from each of the clinical services were presented in Table 2. The expression of interest rate at the two smaller services (A and B) was 85% and 83% respectively. In Service A three people declined to find out more about research. Of these, one family wished their child to have a full neuropsychological evaluation; one child had just finished their treatment and did not wish to have any further contact with services at that time and one family declined as they could not

see the benefit of the project to their child. In Service B two families declined to find out more about the research without providing a reason. In service C the expression of interest rate was much lower (46%) however this is likely due to the follow up phone calls from the service stopping once the sample size had been achieved.

In all three services the recruitment and completion rates of those who an expressed an interest were high. In Service A only two families who showed an interest in the study did not go on to complete the battery. One child was excluded prior to consent due to previous neuropsychological assessment in the past year. The other child was consented into the study, however during completion of the CogState battery asked to stop taking part and was subsequently excluded from the study with appropriate clinical support identified. In retrospect this child should have been excluded from recruitment due to motor impairment severe enough to prevent testing due to only being able to use one of their hands. This highlights the motor requirements of the battery, which may appear minimal but do require the use of both hands. In Service B one family expressed an interest but were not consented into the study due to difficulty arranging a suitable place to hold the testing visit. If the battery were a standard part of clinical practice this issue would not be relevant. In Service C six families who expressed an interest were not consented into the study. Of these one family had moved out of area, three were not possible to contact due to incorrect details, one was excluded due to the severity of their sensory impairment and one due to English not being their first language.

In summary the recruitment rate overall was high when taking into account the limitations of the sample size. Families were keen to take part and regularly expressed to the researcher their belief that cognitive screening is necessary and should be more widely available. Reasons for non-participation, where known, were

generally due to the practical aspects of the research rather than the content or topic of the study. All but one child (97%) completed the CogState battery without incident.

Brevity

Data on the time taken to complete and score both the CogState battery and the standard battery are presented in Table 4.

Table 4.

Completion and scoring times for the two test batteries

	CogState Battery	Standard Subtest Battery	
Completion time (n=34)			
Mean	22.1	32.6	p≤.001
SD	3.1	2.8	
Range	17-31	28-38	
Scoring time (n=5)			
Mean	3.8	31.4	p≤.001
SD	0.8	2.7	
Range	3-5	28-35	

Three participants did not complete the full standard battery therefore their data for both batteries was excluded. Scoring times are taken from a sub sample of five participants at the end of the recruitment phase when the researcher was familiar with the scoring process for both batteries. For CogState, which is automatically scored, this process involved taking the data off the testing computer on a secure memory stick, uploading it to the central DataPoint secure server and downloading a score profile. For the standard battery this process involved scoring each test and compiling the results into a spreadsheet. The time taken to write a report based on the scores is not included. The results shown that the CogState battery was significantly shorter to complete $t(33) = -22.18$, $p \leq .001$, with the difference representing a very

large effect size r=.96. It was also significantly shorter to score, $t(8) = -21.82$, $p \leq .001$ with the difference again representing a very large effect size r=.99.

Discussion

In summary the results of this study support the CogState battery as an acceptable and feasible measure for use with a paediatric oncology population in the areas assessed. Results of the acceptability questionnaire indicate that although around three quarters of the sample found the battery at least a little hard the vast majority of the participants did not find completing it at all upsetting or tiring and almost all found it at least a little interesting and enjoyable. Only three children felt the battery took a very long time to complete but around half felt it took quite a long time. In comparison with Pejnovic et al. (2012) more children reported finding the CogState battery at least a little hard, and quite long to complete but the results for fatigue, distress interest and enjoyment are comparably positive.

The difference in the children's impression of the difficulty of the battery may be related to the immediate feedback they received during the tasks. This feedback is not a common aspect of standard neuropsychological tests and would not have occurred on the battery of measures used by Pejnovic et al. (2012). Anecdotally the researcher observed several of the participants to show dismay or frustration when they received repeated feedback that they were getting items wrong, however the converse was also observed with children appearing pleased and motivated by positive feedback. One child made an explicit comment about the feedback as contributing to them feeling "demoralised" however this was not a common theme in the qualitative feedback. Given this and the positive results on the acceptability

questionnaire it does not appear that in general the feedback was upsetting to the participants even if it did impact their view of the difficulty of the assessment.

The difference in the children's perception of how long the battery took to complete is interesting given that the CogState battery was actually significantly quicker than the battery reported by Pejnovic et al. (2012), $t(81)=12.17$, $p\leq.001$, and significantly quicker than the battery of standard subtests used in this study. It could be hypothesised that this relates to the repetitiveness of the tasks, with up to 80 trials being completed in some tasks, or to the fact that all tasks were completed in one continuous session on the computer in contrast to the changes of equipment and response format when using standard measures. Two children commented specifically on this aspect of the battery with one saying the card based tasks in particular went on for a long time and another saying that the tasks felt a bit repetitive. However it should be remembered that 43% of the children reported finding the battery "not long at all" to complete and 89% said they would be happy to do the puzzles again indicating that for most of the children the length of the battery was not a significant issue.

The further analysis of the four children who reported not wanting to do the battery again revealed this group included the most impaired children in the sample on the standard neuropsychological measures, raising the possibility that for children with more significant difficulties the process of assessment is more aversive. This possibility is reported as common to all testing environments (Baron, 2004) however given the immediate feedback provided within the CogState battery it may be something that the examiner needs to be particularly aware of with this assessment. However, all but one of the sample successfully completed the entire battery in one

sitting without asking for breaks, indicating that the tasks are feasible for most children who do not have gross motor impairment.

The recruitment rate in this study was high in the two services where it was not limited and comparable to similar studies (Pejnovic et al. 2012; 75%; Krull et al. 2008; 82%). This gives broad support to the acceptability of the assessment to families, particularly given that in this study the CogState battery formed part of a longer assessment visit. It also suggests that the battery would be feasible to incorporate into standard clinical follow up as the reasons for non-participation were generally due to the practicalities of the research and would not apply in clinical practice.

Results regarding the brevity of the battery were strongly in the favour of CogState compared to both the brief standard battery used in this study and other brief screening measures in the literature. This study also considered scoring time, in contrast to other reports, highlighting the large advantage of computerised measures in this area for busy clinicians.

Limitations

This study used an appropriate and relevant approach to assessing the reported acceptability of the battery to a large and representative sample of children at risk of neurocognitive impairment. However there are limitations which should be considered. Other areas of feasibility such as the added value of the battery were not explicitly considered. Assessment of acceptability relied on self-report by the child and did not include structured observations by the examiner. The analysis of the time take to score the battery was conducted on a small sub-sample which may have limited its reliability, however given the size of the effect observed this is unlikely to

have significantly altered the conclusion. Recruitment rates may have been affected by the larger requirements of the full research visit and so may be an under representation of true interest in and uptake of the CogState assessment. The battery was completed in participants' homes so an evaluation of feasibility specifically in the clinic setting is beyond the scope of this project.

Clinical Implications and Conclusion

In conclusion, this study indicates that the CogState battery is acceptable to the vast majority of children at risk of neurocognitive impairment followed up through paediatric oncology outpatient clinics. In terms of feasibility, the battery was quick to complete and especially quick to score. Both of these things mean that it is highly suitable as a screening instrument in clinical settings once further research has been conducted to ascertain that it shows acceptable construct and criterion validity and sensitivity and specificity in this population.

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Appendix M

Ethical Approval Letter

Health Research Authority

National Research Ethics Service

NRES Committee Yorkshire & The Humber - Sheffield
HRA NRES Centre Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Tel
ephone: 0161 625 7832 Facsimile: 0161 625 7299 04 July 2013

Mrs Elizabeth Prince Trainee Clinical Psychologist Cambridgeshire and Peterborough NHS Foundation Trust Medical School University of East Anglia Norwich Research Park Norwich Norfolk NR4 7TJ

Dear Mrs Prince

Study title:	**An investigation into the construct validity of a brief neurocognitive screening battery in a paediatric oncology population**
REC reference:	**13/YH/0228**
IRAS project ID:	**121882**

The Proportionate Review Sub-committee of the NRES Committee Yorkshire & The Humber - Sheffield reviewed the above application on 01 July 2013.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Miss Helen Penistone, nrescommittee.yorkandhumber-sheffield@nhs.net.

Ethical opinion

The Committee queried if only 10 minutes would be allowed for consent. You advised that you are happy to allow as much time as is necessary to

answering parents and children's questions regarding the study before taking consent. 10minutes was an estimate of the average amount of time needed.

The Committee asked whether the participant's GP would be informed. You advised that you are not planning to inform the participants' GP. All the participants' will be open to a Paediatric Oncology Team for follow up and they will be informed of their patients' participation in the study as it is they who have identified the potential participants and they who may need to provide further assessment or follow up after the study subject to their clinical judgement. In the light of this it was felt unnecessary to inform the GP as well given no changes to treatment are being made in the study. This was referred to in the answer to QA49-1 on the REC form.

The Committee queried how long the data would be kept for after the end of the study. You explained that you will be keeping anonymised study data for 5 years and personal information of participants for 12 months.

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see
"Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Covering Letter from Liz Prince		25 June 2013
REC application	121882/468 523/1/641	25 June 2013
Protocol	4	10 June 2013
Investigator CV	Mrs Elizabeth Prince	01 March 2013
Investigator CV	Siân Coker	03 June 2013
Investigator CV	Judith Young	
Investigator CV	Dr Anna Adlam	
Investigator CV	Kiki Mastroyann opoulou	07 June 2013
Investigator CV	Suni Sthanakiya	12 June 2013
Letter of invitation to participant	2	10 June 2013
Participant Information Sheet: Parent Information Sheet	2	10 June 2013
Participant Information Sheet: 16 year old Information Sheet	2	10 June 2013
Participant Information Sheet: 11-15 year old Information Sheet	2	10 June 2013
Participant Information Sheet: 8-10 year old Information Sheet	2	10 June 2013
Participant Consent Form: Parent Consent Form	2	10 June 2013
Participant Consent Form: 16 year old Consent Form	2	10 June 2013

Participant Consent Form: Parent of 16 year old Consent Form	2	10 June 2013
Participant Consent Form: 8-15 year old Assent Form	2	10 June 2013
GP/Consultant Information Sheets	2	10 June 2013
Questionnaire: Paediatric Inventory of Emotional Distress (PIED)	1	31 May 2013
Questionnaire: Acceptability Questionnaire	1	31 May 2013
Questionnaire: Demographic Questionnaire		
Evidence of insurance or indemnity		18 June 2014

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
information is available at National Research Ethics Service website > After Review

13/YH/0228	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

On behalf of Professor Basil Sharrack Chair

Email: nrescommittee.yorkandhumber-sheffield@nhs.net

Enclosures: List of names and professions of members who took part in the review

"After ethical review – guidance for researchers"

Copy to: Susan Steel
University of East Anglia
Research & Enterprise Services
Environmental 0.28
University of East Anglia
Norwich
NR4 7TJ

Mr Stephen Kelleher
Cambridge University Hospitals NHS Foundation Trust
R&D Department
Addenbrookes Hospital
Hills Road
Cambridge
CB2 0QQ

NRES Committee Yorkshire & The Humber - Sheffield

Attendance at PRS Sub-Committee of the REC meeting on 01 July 2013

Committee Members:

Name	*Profession*	*Present*	*Notes*
Professor Basil Sharrack	Chair of REC and Consultant Neurologist	Yes	

Mrs Yvonne Stephenson	Lead Technician in the Department of Infection and Immunity	Yes	
Mr Neil Sykes	Retired Engineer/ Scientist	Yes	

Appendix N

Research and Development Approval from Cambridge University Hospitals NHS Foundation Trust

Cambridge University Hospitals NHS
NHS Foundation Trust

Research and Development Department
Box 277
Addenbrooke's Hospital
Hills Road
Cambridge
CB2 0QQ

Direct Dial: 01223 348492 Ext: 58492
Switchboard: 01223 245151
E-mail: katrina.gatley@addenbrookes.nhs.uk
r&denquiries@addenbrookes.nhs.uk
www.addenbrookes.org.uk

R&D ref: A092997

04/11/2013

Dr Angela Kirby
Addenbrookes Hospital
Box 267

Dear Dr Kirby

Re: 13/YH/0228 An investigation into the construct validity of a brief neurocognitive screening battery in a paediatric oncology population

In accordance with the Department of Health's Research Governance Framework for Health and Social Care, all research projects taking place within the Trust must receive a favourable opinion from an ethics committee and approval from the Department of Research and Development (R&D) prior to commencement.

R&D have reviewed the documentation submitted for this project, and has undertaken a **site specific assessment** based on the information provided in the SSI form, and I am pleased to inform you that we have no objection to the research proceeding within Cambridge University Hospitals NHS Foundation Trust.

Sponsor: University of East Anglia

Funder: University of East Anglia

End date: 01/09/2014

Protocol: Version 4, dated 10/06/2013
Conditions of Trust Approval:

- The project must follow the agreed protocol and be conducted in accordance with all Trust Policies and Procedures especially those relating to research and data management. Any mobile devices used must also comply with Trust policies and procedures for encryption to AES 256.
- You and your research team must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998 and are aware of your responsibilities in relation to the Human Tissue Act 2004, Good Clinical Practice, the NHS Research Governance Framework for Health and Social Care, Second Edition April 2005 and any further legislation released during the time of this study.

- Members of the research team must have appropriate substantive or honorary contracts with the Trust prior to the study commencing. Any additional researchers who join the study at a later stage must also hold a suitable contract.

- You and your research team must provide to R&D, as soon as available, the date of first patient first visit.

If the project is a clinical trial under the European Union Clinical Trials Directive the following must also be complied with:

- the EU Directive on Clinical Trials (Directive 2001/20/EC) and UK's implementation of the Directive: The Medicines for Human Use (Clinical Trials) Regulations 2004;

- the EU Directive on Principles and Guidelines for Good Clinical Practice (EU Commission Directive 2005/28/EC); and UK's implementation of the Directive: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006;

Amendments

Please ensure that you submit a copy of any amendments made to this study to the R&D Department.

Annual Report

It is obligatory that an annual report is submitted by the Chief Investigator to the research ethics committee, and we ask that a copy is sent to the R&D Department. The yearly period commences from the date of receiving a favourable opinion from the ethics committee.

Please refer to our website www.cuh.org.uk/research for all information relating to R&D including honorary contract forms, policies and procedures and data protection.

Should you require any further information please do not hesitate to contact us.

Yours sincerely

Louise Stockley
Research Governance Manager

Cc Mrs Elizabeth Prince

Appendix O

Research and Development Approval from Norfolk and Norwich University Hospitals NHS Foundation Trust

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Mrs Elizabeth Prince
Norwich Medical School
University of East Anglia
Norwich Research Park
Norwich
NR4 7JY

Research & Development Office
Level 3 East
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

direct dial: 01603 287806
direct fax: 01603 289800
e-mail: rdoffice@nnuh.nhs.uk
website: www.nnuh.nhs.uk

14 October 2013

Dear Mrs Prince

Re: **IRAS Reference Number:** 121882
R&D Reference Number: 2013PAED10S (107-07-13)
Project Title: An investigation into the construct validity of a brief neurocognitive screening battery in a paediatric oncology population

I am pleased to inform you that the above project has been given full NHS permission for research at Norfolk & Norwich University Hospitals NHS Foundation Trust.

This NHS permission for research has been granted on the basis described in the application form, protocol and supporting documentation as listed below:

Document	Version	Date
Letter of invitation to participant	2	10/06/2013
Participant information sheet: Parent information sheet	2	10/06/2013
Participant information sheet: 16 year old information sheet	2	10/06/2013
Participant information sheet: 11-15 year old information sheet	2	10/06/2013
Participant information sheet: 8-10 year old information sheet	2	10/06/2013
Parent consent form: parent consent form	2	10/06/2013
Participant consent form: 16 year old consent form	2	10/06/2013
Participant consent form: Parent of 16 year old consent form	2	10/06/2013
Assent form: 8-15 year olds assent form	2	10/06/2013
GP letter	2	10/06/2013
Questionnaire: Acceptability questionnaire	1	31/05/2013
Questionnaire: Demographics questionnaire		
Questionnaire: Paediatric inventory of emotional distress		
Protocol	4	10/06/2013
NHS REC form	121882/468523/1/641	
NHS SSI form	121882/511481/6/494/199144/282923	10/10/2013

The agreed total local recruitment target for your study is 10 participants.

To support requirements of the National Institute of Health Research (NIHR) we will be monitoring and publishing outcomes of recruitment into your study. This includes benchmarking against a 70 day period from the time of receipt of a valid research application to this time of recruitment of the first patient for your study.

The date of receipt of a valid application for this study is 10/10/2013 and the benchmark of 70 days to recruit the first patient is 19/12/2013.

The R&D Office will contact you in due course to monitor progress against this benchmark.

I have enclosed two copies of the Standard Terms and Conditions of Approval. Please sign both copies and return one copy to the Research & Development Department at the above address and keep the other in your study file. Failure to return the standard terms and conditions may affect the conditions of approval.

Please note, under the agreed Standard Terms and Conditions of Approval you must inform the R&D department of any proposed changes to this study and submit annual progress reports to the R&D department.

If you have any queries regarding this or any other project please contact Seema Gopinath, Research Facilitator, at the above address. Please note, the reference number for this study is **2013PAED10S (107-07-13)** and this should be quoted on all correspondence.

Yours sincerely

Professor Marcus Flather
R&D Director

Appendix P

Research and Development Approval and Letter of Access from The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust

The Queen Elizabeth Hospital NHS
King's Lynn
NHS Foundation Trust

The Queen Elizabeth Hospital
Gayton Road
Kings Lynn
Norfolk
PE30 4ET
www.qehkl.nhs.uk

Research and Development

Mrs Elizabeth Prince
Trainee Clinical Psychologist
Medical School, University of East Anglia

Dr Parvez Moondi
Chair of the Research Governance Committee

R&D Co-ordinator – Karen Lupton
E-mail: karen.lupton@qehkl.nhs.uk

Tel: 01553 214571

2nd September 2013

Dear Mrs Prince

R&D ID: 36/13
An investigation into the construct validity of a brief neurocognitive screening battery in a paediatric oncology population

Thank you for sending the following documentation relating to the above study:

Protocol version 4 dated 10 June 2013
REC - 121882/468523/1/641

This study has been reviewed by the Trust's Research Governance Committee and we can confirm that the Trust is willing for this work to take place.

Please note that if an external member of the research team is required to visit our Trust in order to conduct research activities they must apply to the R&D department for a letter of access before this can commence.

I would like to take this opportunity to remind you that the Trust manages all research in accordance with the requirements of the Research Governance Framework.

In order to comply with the above, if the study is not completed within one year from the date of this letter, a report summarising the progress of the study should be submitted to the R&D Office. In the case of multi-centre studies this is usually provided by the Chief Investigator/Clinical Trials Unit. Alternatively, we can supply a blank form for you to complete: please contact us for a copy.

DATA

In relation to a discussion you held with our Caldicott Guardian, the following was agreed:
If there are practical reasons why the information should be carried with you intermittently then I you should go ahead and do that, but please be sure that the data is conveyed securely and only conveyed if necessary.

YOU ARE REQUIRED TO NOTIFY OUR R&D OFFICE THE DATE OF THE FIRST PARTICIPANT YOU RECRUIT TO THE STUDY – IF APPLICABLE

On completion of the project, please forward to the R&D Office any "final report" relating to the project – e.g. report from Chief Investigator/Clinical Trials Unit, copy of any published article, etc. Any reports resulting from the study, which may be produced at a later date, should also be forwarded, to ensure a complete record is held here.

If our department can be of any further assistance please do not hesitate to contact me.

Yours sincerely

Dr Parvez Moondi Chair of the Research Governance Committee

CC Dr Barbara Piel, Consultant Paediatrician
Judith Young, Clinical & Health Psychology

The Queen Elizabeth Hospital NHS
King's Lynn
NHS Foundation Trust

The Queen Elizabeth Hospital
Gayton Road
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www.qehkl.nhs.uk

Research and Development

Dr Parvez Moondi
Chair of the Research Governance Committee

R&D Co-ordinator – Karen Lupton
E-mail: karen.lupton@qehkl.nhs.uk

Tel: 01553 214571

Mrs Elizabeth Prince
Trainee Clinical Psychologist
Medical School, University of East Anglia

3rd October 2013

Dear Mrs Prince

Letter of access for research –
R&D ID: 36/13
An investigation into the construct validity of a brief neurocognitive screening battery in a paediatric oncology population

This letter confirms your right of access to conduct research through **The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust** for the purpose and on the terms and conditions set out below. This right of access commences on 7th October 2013 and ends on 7th October 2014 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at **The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust** has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to **The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust** premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust**, you will remain accountable to your employer **Cambridgeshire and Peterborough NHS Foundation Trust** but you are required to follow the reasonable instructions of **Val Newton, Deputy Director of Patient Experience** in this NHS organisation or those given on her behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on **The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust** premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and the Trust R&D department 01553 214571, karen.lupton@qehkl.nhs.uk and Occupational Health Department 01553 613757 prior to commencing your research role at the Trust.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

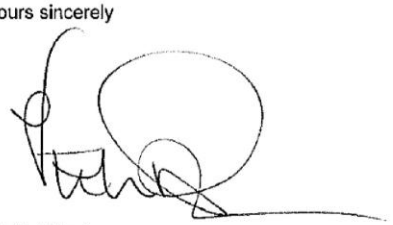
You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

Yours sincerely



Ms Val Newton
Deputy Director of Patient Experience

Cc Judith Young, Clinical and Health Psychology
Dr Barbara Piel, Consultant Paediatrician
Beth Meldrew, R&D CPET

Appendix Q

Scatter Plots of Correlations for Research Questions 1 and 2

Figure Q.1

Scatterplot of the relationship between Detection and Grooved Peg Board (Dominant)

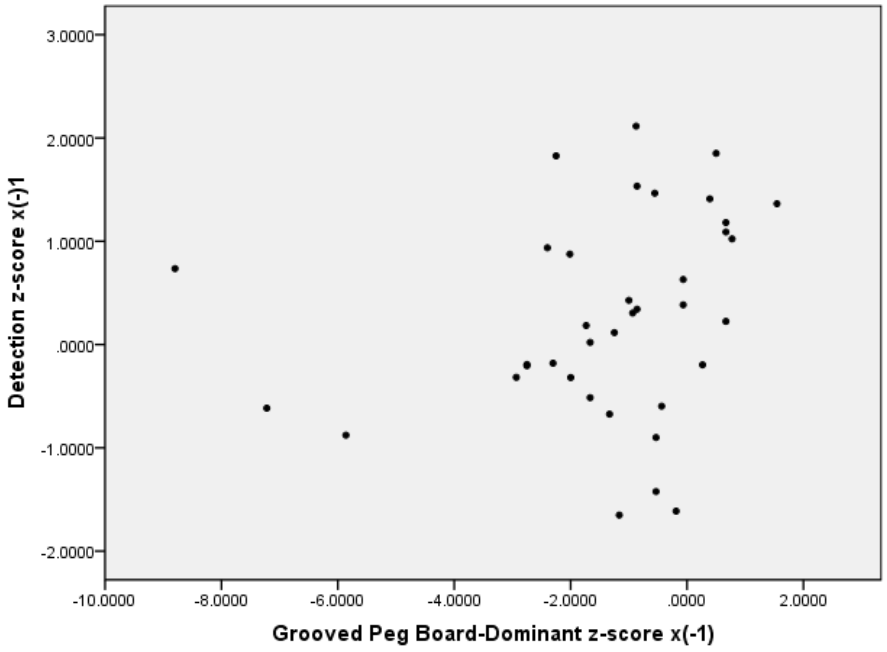


Figure Q.2

Scatterplot of the relationship between Detection and Symbol Search

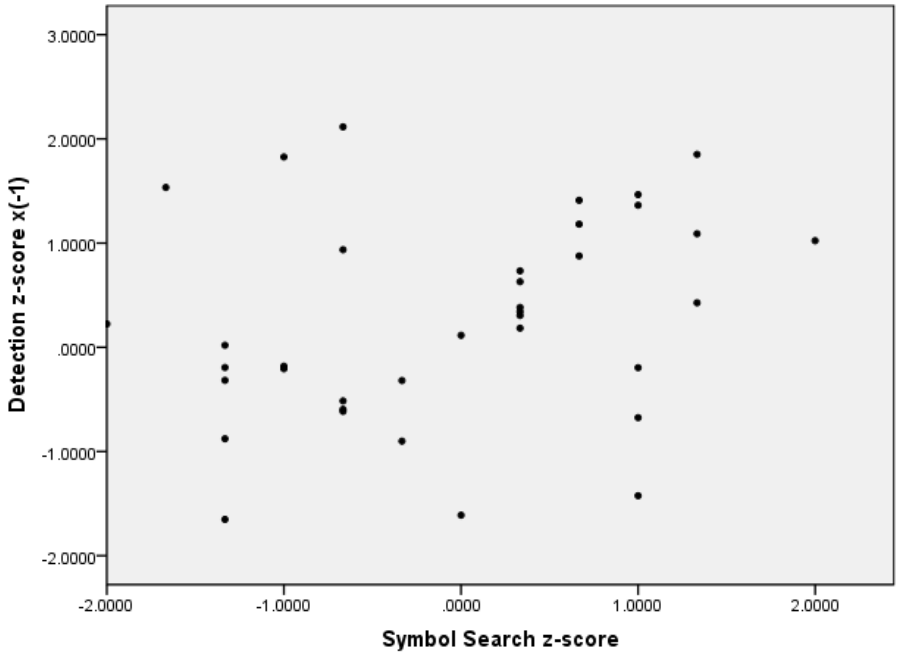


Figure Q.3

Scatterplot of the relationship between Identification and Map Mission

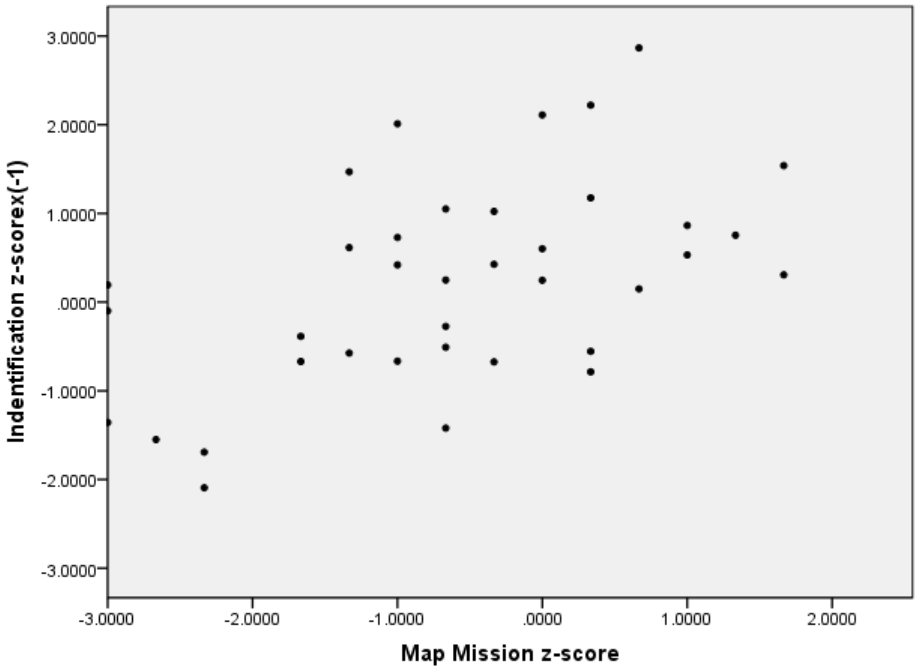


Figure Q.4

Scatterplot of the relationship between Identification and Score!

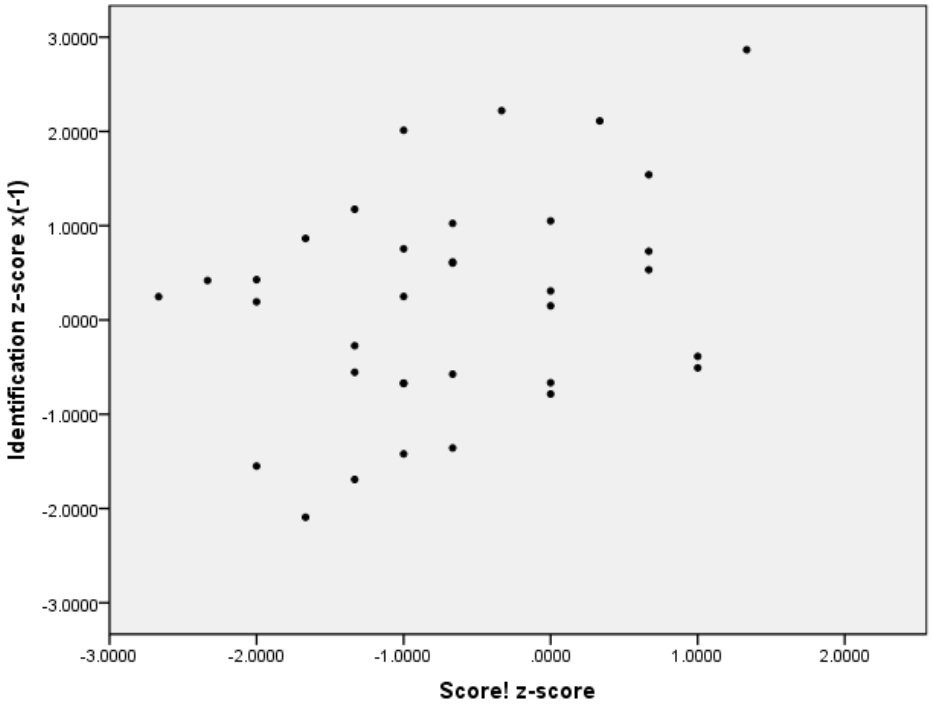


Figure Q.5

Scatterplot of the relationship between Once Card Learning and Dot Location

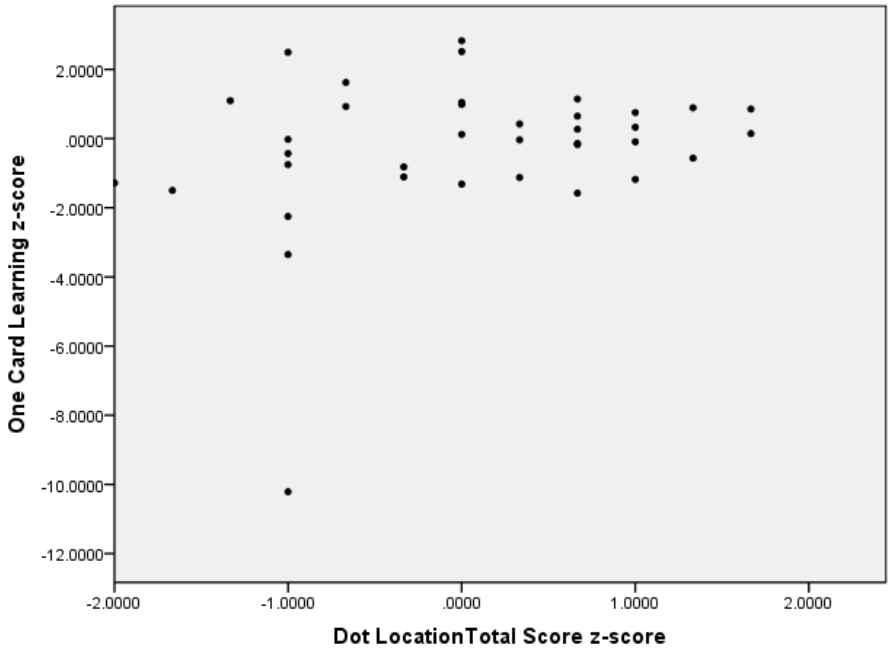


Figure Q.6

Scatterplot of the relationship between One Card Learning (outlier removed) and Dot Location

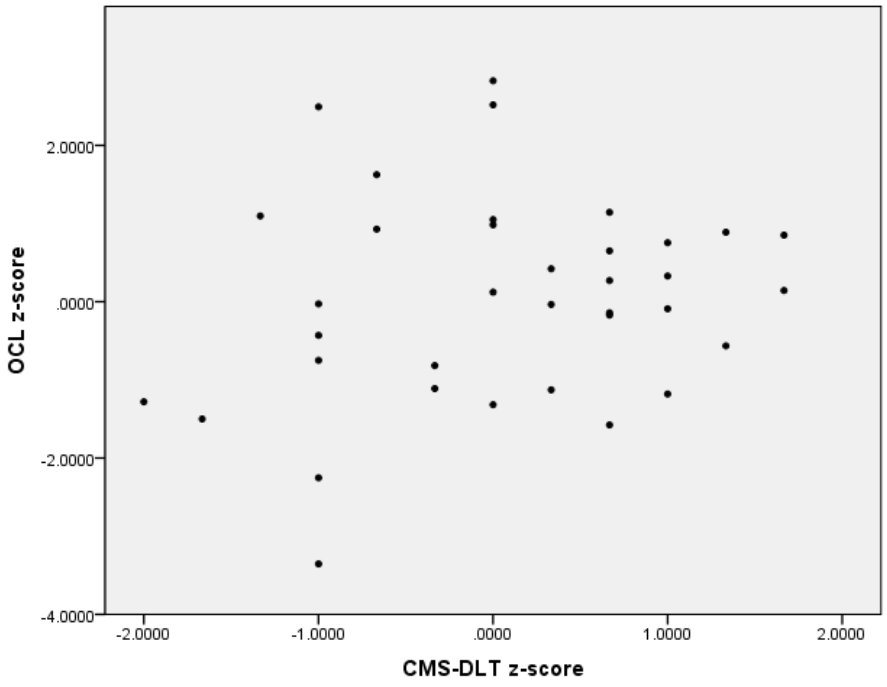


Figure Q.7

Scatterplot of the relationship between CPAL and Dot Location

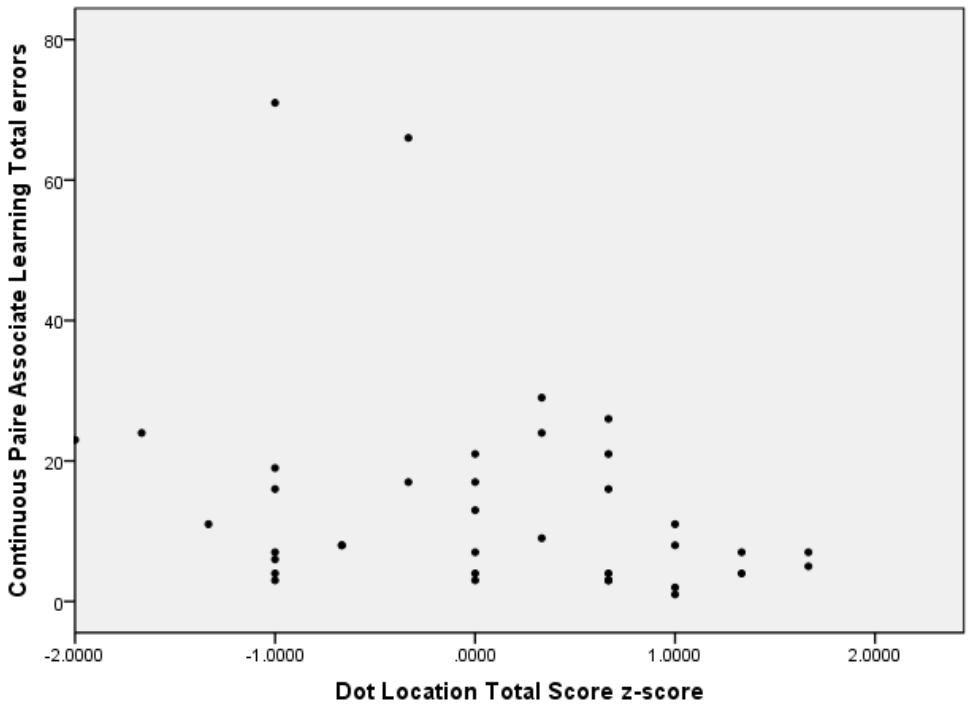


Figure Q.8

Scatterplot of the relationship between One Back and Digit Span

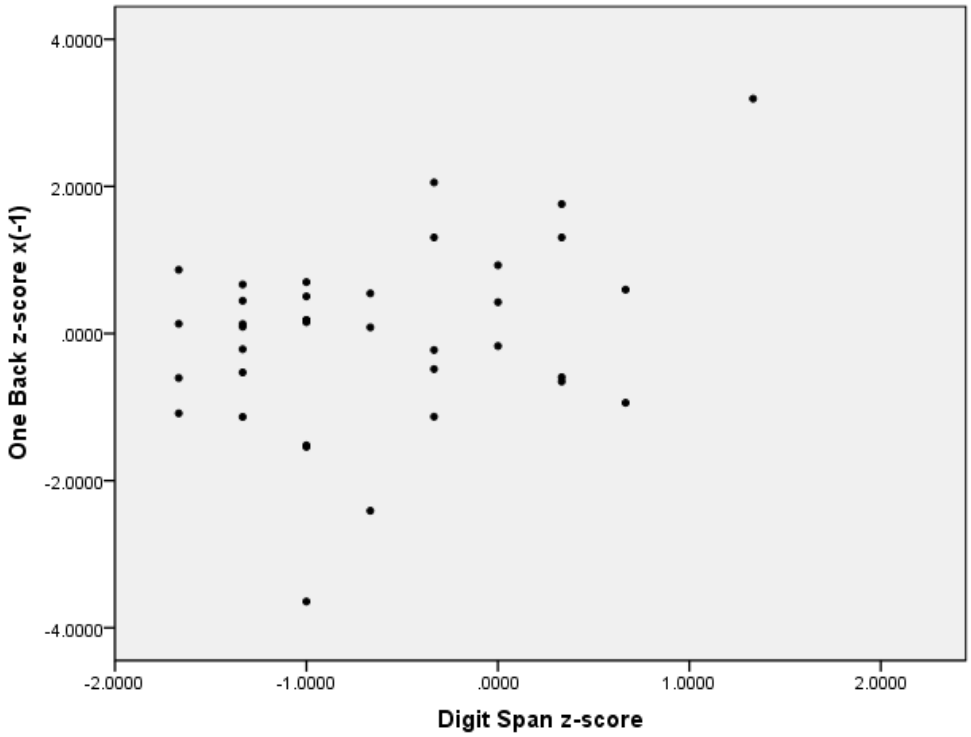


Figure Q.9

Scatterplot of the relationship between One Back and Longest Digit Span Backwards

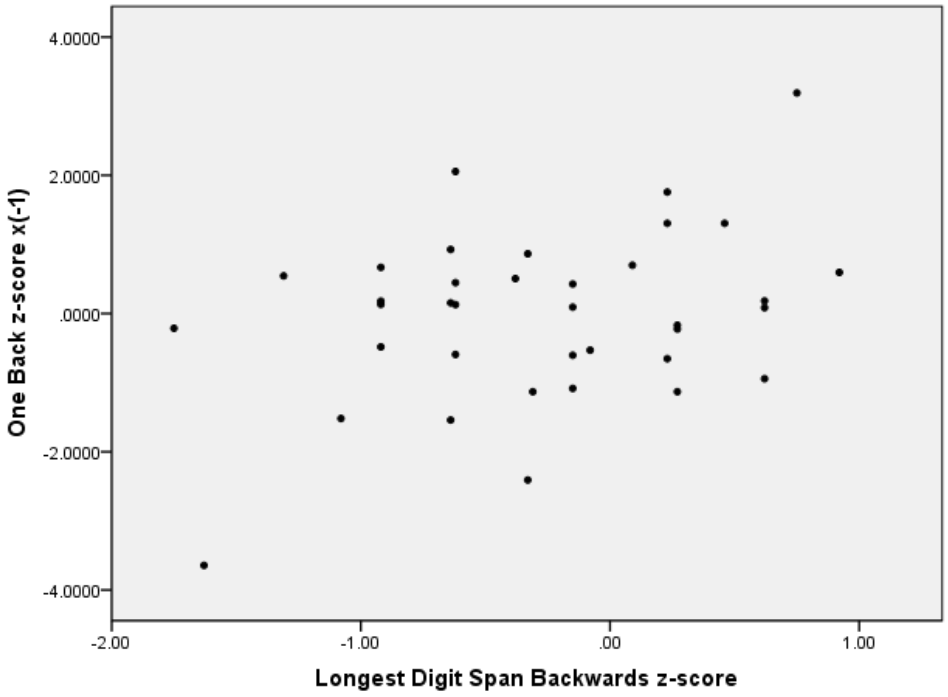


Figure Q.10

Scatterplot of the relationship between the GMLT and the BRIEF GEC in participants aged 10-16 years

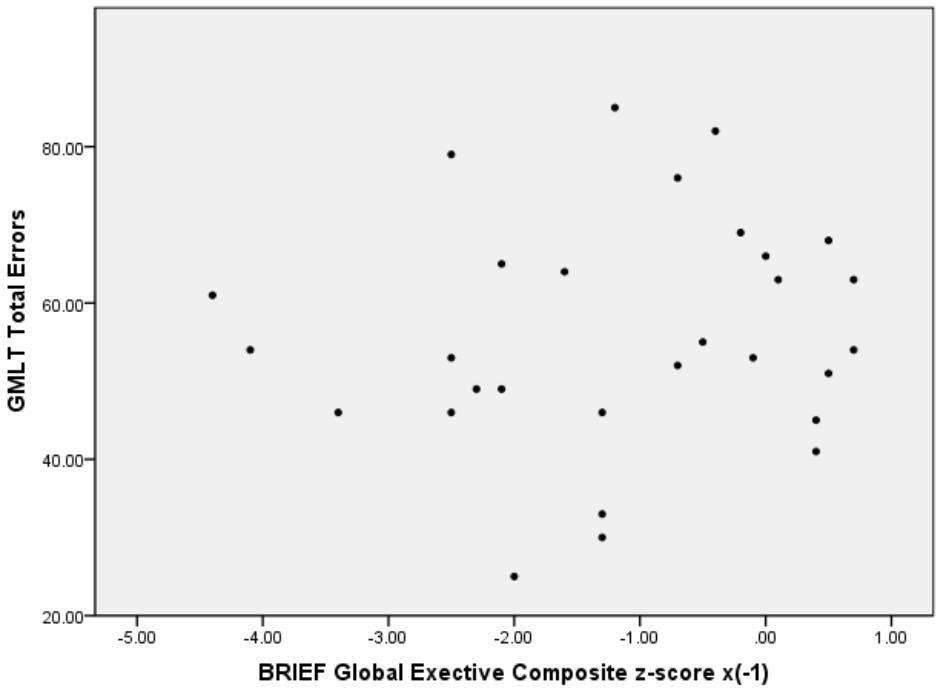


Figure Q.11

Scatterplot of the relationship between the GMLT and TMT-B in participants aged 10-16 years

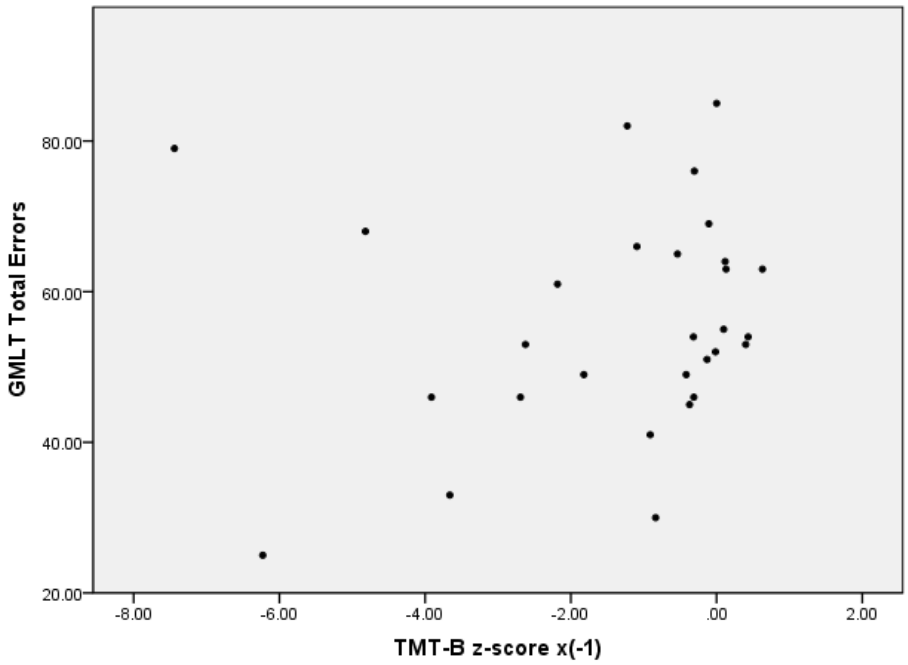


Figure Q.12

Scatterplot of the relationship between the GMLT and TMT-B in participants aged 8-9 years

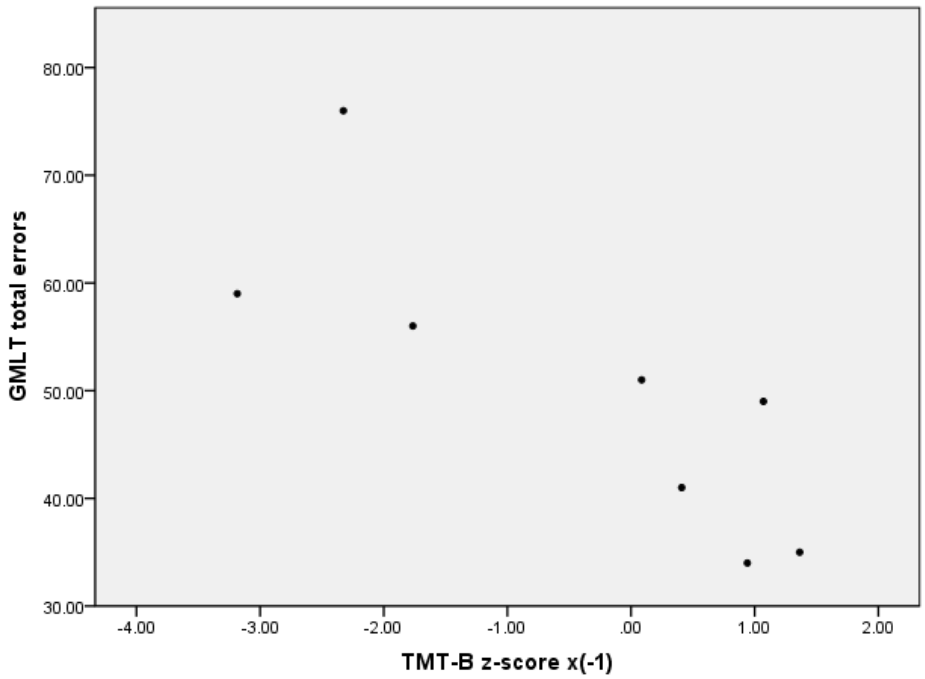


Figure Q.13

Scatterplot of the relationship between GMLT and the BRIEF GEC in participants aged 8-9years

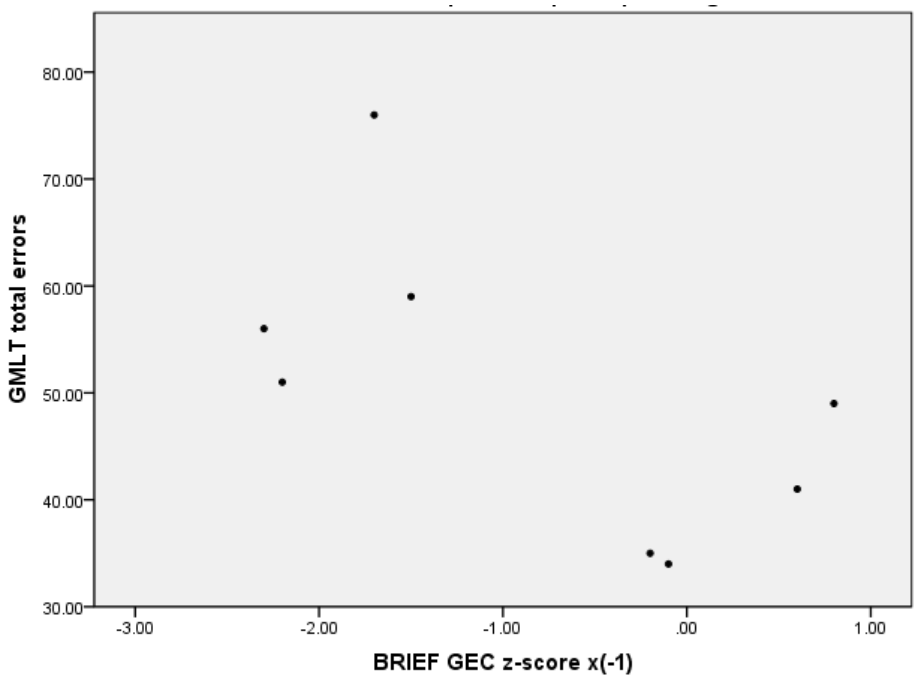


Figure Q.14

Scatterplot of the relationship between time since diagnosis (months) and CogState composite score

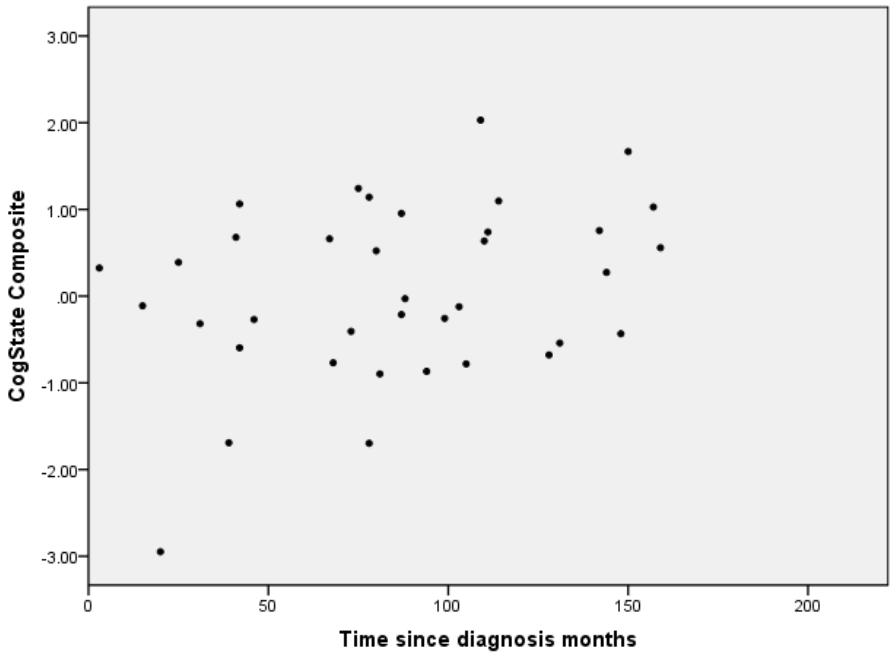


Figure Q.15

Scatterplot of the relationship between time since diagnosis (months) and IQ