Neural correlates of verbal fluency and associations with demographic, mood, cognitive and tumour factors in brain tumour patients.

Charlene Louise Thwaites

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The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

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Abstract

Verbal fluency tests are one of the most commonly used measures of executive functioning in neuropsychological testing and play an important role in the assessment, diagnosis and care planning of patients with a variety of conditions, including brain tumour. There is little conclusive evidence about which factors may influence verbal fluency outcomes. No studies to date have investigated the interactions between a comprehensive range of demographic variables, mood scores, tumour factors and key cognitive skills with the focus of verbal fluency outcomes in brain tumour patients. Similarly, clarification is required across studies assessing the localisation effects of verbal fluency skills. To address these gaps in the evidence base this study used a retrospective cohort design of cross-sectional data from patients with brain tumours, to investigate their performance of both phonemic and semantic verbal fluency. More specifically this study used simple linear and multiple regression calculations to analyse the interactions between these variables and other potentially important factors such as localisation, depression and anxiety (using the HADS), age, gender, education, premorbid functioning (using the TOPF), semantic memory (using the GNT), and tumour type.

The results showed that an increase in phonemic fluency performance was significantly correlated with being educated, an increase in semantic memory, and an increase in premorbid functioning. Phonemic fluency was also significantly correlated with localisation. In general, a decrease in phonemic fluency was significantly associated with tumours in the left frontal lobe. An increase in semantic fluency was correlated with an increase in semantic memory. No other factors showed significant associations with phonemic or semantic fluency. The outcomes from the hierarchical multiple regressions indicated that localisation, gender, education, tumour type, depression, semantic memory, and premorbid functioning when combined can predict phonemic fluency variance. Combining localisation effects, semantic memory, depression and education together do not result in a model that predicts semantic fluency, as within this model the only significant relationship was between semantic memory and semantic fluency. These findings show that, for brain tumour patients, it

is important to take into consideration tumour localisation, education, semantic memory, and premorbid functioning when assessing and care planning for deteriorations in phonemic fluency. Similar patients with deteriorations in semantic fluency need to have their results considered in light of performance in semantic memory tests.

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3MS	The Modified Mini-Mental State Examination
ANT	Animal Naming Test
BNT	Boston Naming Test
CNS	Central Nervous System
COWA	Controlled Oral Word Association Test
CT	Computerised Tomography
DKEFS	Delis Kaplan Executive Functioning System
fMRI	Functional Magnetic Resonance Imaging
GAD	Generalised Anxiety Disorder
GHQ 12	General Health Questionnaire 12
GNT	Graded Naming Test
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety
HADS-D	Hospital Anxiety and Depression Scale – Depression
IQ	Intelligence Quotient
MAE	Multilingual Aphasia Examination
MDT	Multi-Disciplinary Team
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NART	National Adult Reading Test
NCCEA	Neurosensory Centre Comprehensive Examination for Aphasia
NICE	National Institute of Clinical Excellence
OCD	Obsessive Compulsive Disorder
ONS	Office of National Statistics
TOPF	Test of Premorbid Functioning

UK	United Kingdom
WHO	World Health Organisation
WIAT-II	Wechsler Individual Achievement Test – Third Edition
WTAR	Wechsler Test of Adult Reading

Introduction

Verbal fluency is a particularly specialised area of research within the larger field of cognitive functioning. This study aimed to build upon previous research in this area by investigating relationships between verbal fluency outcomes and tumour variables (localisation and tumour type), mood factors (depression and anxiety), cognitive factors (premorbid functioning and semantic memory), and demographic factors (education and gender).

The following introduction will begin by providing background information on brain tumours and their symptoms, with a particular focus on cognitive abilities, psychological wellbeing, and what it is about tumours that can lead to these outcomes. The literature review will initially focus on research within the broader area of cognitive functioning in the brain tumour population, with the aim of better understanding the gaps in the research base relating to verbal fluency. This review will then focus in on the evidence base behind the relationships between mood, localisation effects and verbal fluency skills, which will form the foundations of the research questions for this project. These questions are operationalised throughout the method section.

What is a brain tumour

A brain tumour is a collection of abnormal growths of tissue (neoplasm) that arise in the brain or structures closely related to the functioning of the brain, such as the meninges. Brain tumours account for the majority of central nervous system (CNS) tumours. If they start in the brain they are called primary brain tumours. If they spread into the brain from somewhere else in the body they are called secondary brain tumours. Due to a variety of tumours being classified as “brain tumour” but situated in areas other than the brain itself, it has been suggested that the term brain tumour can be misleading, and the terminology “intracranial neoplasm” is more fitting (DeAngelis, 2001). The World Health Organization makes more sense of this by grouping together these (and related other) tumours under the category of “Tumours of the Central Nervous System” (Louis et al., 2007, 2016). However, a vast majority of research in this area, and the majority of services, charities, and organisations within the community who support

these patients still separate brain tumours from other central nervous system tumours and therefore, use the terminology “brain tumour” (Cancer Research UK). In line with this, this study will continue to use the terminology brain tumour more generally, and will focus more specifically upon certain types of brain tumour relevant to this research.

Classifying brain tumours

The intricacies of tumour classification have been refined and updated in line with scientific developments over the years (Kleihues et al., 2002; Louis et al., 2007, 2016). The most commonly used classification systems are those developed by the World Health Organization, the most recent of which was published in 2016 (Louis et al., 2016). It is important to note that there are always exceptions to classifications of tumour, especially with brain tumours, as there are many grey areas in the classification criteria used, and variations in how the tumour behaves and develops within each classification (Yang et al., 2008).

Tumour grading and malignancy

Tumours are graded between 1 and 4 depending on how quickly they are likely to grow. These can be more largely separated into ‘high-grade’ and ‘low-grade’ tumours, relating respectively to whether the tumour grows rapidly and is aggressive, or develops more slowly (Louis et al., 2007; NICE, 2006). Low grade tumours (grades 1 and 2) are generally regarded as benign and high-grade tumours (grades 3 and 4) are commonly regarded as malignant. Benign tumours are relatively slow growing and unlikely to spread to other areas. As a result they may only require surgery as a treatment option (not radiotherapy or chemotherapy as well), and are less likely to return following resection. Malignant tumours are comparatively faster growing and more likely to spread to other parts of the brain or spinal cord. They tend to require treatments such as radiotherapy or chemotherapy as well as surgery, and even with these treatments they are more likely to re-occur post-treatment.

Tumour type and origin

There are about 130 different types of brain tumour (Louis et al., 2007). Most brain tumours are generally named after the type of cell they developed from and/or the area of the brain they are growing in, for example, tumours within the meninges (the membranes that surround and protect the brain) are referred to as a meningioma. The main types of tumour relevant to this study are glioma and meningioma.

Within the tumours that occur in the brain and CNS in adults, the cerebrum is the most common origin (Louis et al., 2016). Secondary to this, around a quarter (24%) of brain and CNS tumours start in the meninges, and around 10% start in the glands within the brain, such as the pituitary and pineal gland. In children the picture is significantly different, with about 60% of childhood brain tumours originating in the cerebellum or brain stem (Wefel, Vardy, Ahles, & Schagen, 2011).

Aetiology of brain tumour

The aetiology of brain tumours is largely unknown and there is little evidence that they can be prevented by lifestyle changes (NICE, 2006). The risks of developing a brain tumour are dependent on age and gender, with trends of diagnoses showing an inverse social gradient, being more common in more affluent groups and developed countries (Quinn & Babb, 2000). However, it could be argued that this perception is strongly biased by inaccurate report rates as opposed to being indicative of actual prevalence rates (NICE, 2006).This is largely due to the bias in reporting created by developed countries being more likely to provide healthcare systems able to fund expensive scanning technologies (e.g. CT head scanners) and a structured means to record and report said diagnoses. Similarly, people from affluent groups are likely to reside in countries with this access to services, as well as having greater access to healthcare education, further enhancing the likelihood that they would present to services when experiencing symptoms. These factors are more likely to increase reporting rates as opposed to increase the prevalence of the condition within the population.

Prognosis of patients with brain tumour

Tumours cause risk for a number of factors as they grow, firstly they can increase intracranial pressure which can cause severe (and sometimes fatal) symptoms (NICE, 2006). Additionally, they weave into adjacent normal brain tissue in a manner which can make surgical removal very difficult (NICE, 2006). A brain tumour can therefore rarely be completely removed because of its relation to critical functional structures within the brain and the infiltrating nature of the tumour. These difficulties generally lead to a poor prognosis for the condition (NICE, 2006).

It can take several years to collect data and compile statistical reports. Cancer Research UK have compiled the latest review (for 2014) from a range of sources reporting across the UK such as the Office for National Statistics, and the National Cancer Intelligence Unit (Cancer Research UK). From this data they believe that in 2014 alone 10,981 new cases of CNS and intracranial tumour were reported in the UK, which is 3% of the total cancer cases reported that year (Cancer Research UK). This consisted of 5,288 (48%) males and 5,693 (52%) females. These statistics also indicate a 30% increase in brain tumour incidence rates since the early 1990's, consisting of 2881 (55%) males and 2342 (45%) females (Cancer Research UK). This increase resulted in 5,223 deaths in 2014, nearly half of whom (47%) were in people aged 70+ (Cancer Research UK).

Of equal importance, changes in cognitive function can have prognostic significance in patients with brain tumours (Taphoorn & Klein, 2004), for example, tumour patients' performance on verbal memory tasks have been linked to survival rates (Meyers, Hess, Yung, & Levin, 2000). Therefore, having an awareness of changes in a patient's cognitive functioning can have implications for their ability to plan for and receive appropriate care.

Diagnosis and treatment plans

It has been shown that cognitive deterioration can indicate tumour progression before signs of tumour recurrence are evident on CT or MRI scans (Armstrong, Goldstein, Shera, Ledakis, & Tallent, 2003; Meyers & Hess, 2003). However, a wide range of symptoms have been associated

with a diagnosis of brain tumour, including headache, nausea, vomiting, seizure, memory loss, limb pain, loss of sensation, weakness, visual difficulty, and change in behaviour or personality (NICE, 2006). When symptoms of a possible brain tumour are raised as a concern, the patient is sent for a CT or MRI scan, and the diagnosis is confirmed through a biopsy (NICE, 2006). A confirmed diagnosis will often lead to care support through a specific neuroscience brain and other CNS tumour multidisciplinary team (MDT), with an important aspect of this support being a focus on maximizing their quality of life (NICE, 2006). Many patients (and/or their relatives/carers) will also access psychological support from specific members of the MDT.

There are a wide variety of tumour classifications and a variety of treatment approaches can be recommended in relation to these, such as resection (surgical removal of as much of the tumour as possible), radiotherapy, chemotherapy, or a combination of these. Intracranial pressure and related symptoms (such as one sided weakness) can often be reduced using steroids (NICE, 2006). Consultants will consider the grade of the tumour, whether it is malignant or benign, the tumour type and its origin/location to decide upon the best treatment pathway. Therefore, the diagnostic classification of the tumour is instrumental in attempting to predict treatment and prognosis for each individual.

The effects of brain tumour

There are a wide variety of physical, cognitive and psychological symptoms associated with the impact of a brain tumour, which can be influenced by its anatomical location (Jenkins, Drummond, & Andrewes, 2016; Lynam et al., 2007; Meyers, Berman, Scheibel, & Hayman, 1992; Meyers et al., 2000; Weitzner & Meyers, 1997). Patients may experience epilepsy, headache, social dysfunction, cognitive deficit, behavioural, emotional and personality changes (Gregor et al., 1996; Jenkins et al., 2016; Meyers et al., 1992; Taphoorn & Klein, 2004; van Breemen, Wilms, & Vecht, 2007). These symptoms tend to be biologically linked to progressive focal neurological deficits and/or raised intracranial pressure. Raised intracranial pressure typically causes headaches which are worse in the morning, nausea, vomiting or visual deterioration. Gradual-onset weakness or sensory

loss on one side of the body is common, as is difficulty with speech or understanding, and unilateral visual field loss (NICE, 2006).

The role of brain tumour patients in localisation studies

Cognitive neuroscience utilises a wide range of techniques to investigate the neural architecture of the brain. These types of investigation are historically rooted in theories based on the assumption that discrete anatomical modules deal with different cognitive functions, referred to as a 'modularity assumption' (Shallice, 1988). Some of the first cases demonstrating this method used single dissociation lesion-behaviour mapping in patients with neurological damage (e.g. the famous case described by Oliver Sacks of 'the man who mistook his wife for a hat'; Sacks, 2011). This traditional approach involved observing a specific behavioural deficit related to a subcomponent (function Y) of a complex cognitive task (despite intact functioning in another subcomponent of that skill; function X). The dissociation in functioning would either be observed following surgical removal of, or damage to a specific neural area. Otherwise the patient's brain would be dissected after they had died to figure out which neural region had been damaged. This information would be used to imply that damage to this specific region impacts the behavioural subcomponent of interest (function Y).

By advancing the approach of single dissociation lesion-behaviour mapping to include two experimental manipulations (which each have different effects on two dependent variables) the ability to make specific inferences about brain function and function localisation is increased. This is referred to as a double dissociation (Teuber, 1955). More explicitly, drawing from the example above, this would involve comparing two patients with brain lesions in different areas demonstrating opposing deficits from the subcomponents analysed (i.e. patient 1 having a deficit in function Y but not X, and patient 2 having a deficit in function X but not Y). The main advantage of the lesion-behaviour mapping method is that it allows us to see that a certain neural region is necessary for a specific cognitive function, which is why this approach has made huge contributions to our

understanding of neuroanatomical functioning both historically and in the present era (Rorden & Karnath, 2004).

However, there are methodological drawbacks to the above theoretical approaches, such as the restrictions imposed by making assumptions of modularity when it may often be the case that the cognitive functions of interest are carried out in a distributed manner, with larger regions of the brain working together in a more fluid/plastic state (Farah, 1994). Similarly there are inferences that neural areas not obviously damaged in the observed lesion are functioning adequately (Farah, 1994). This can be problematic particularly in studies with brain tumour patients as there are often effects from other sources such as neural pressure caused by oedema that can impact functioning more broadly around the tumour location. Advancements in technologies (such as fMRI scanning) have allowed investigations of neural-behavioural associations in neurologically healthy individuals which can complement results found in lesion-behaviour mapping studies as they don't suffer from the methodological issues of having to focus on a single, fixed neural-correlate location, or the additional complications created by illness and injury. However, there are significant limitations to interpreting brain activation studies (Sarter, Berntson, & Cacioppo, 1996). Primarily, while they provide evidence that a particular activation area correlates with the performance of a task they can't infer that the area is actually necessary to perform the task, or whether the activation of that area is a 'by-product' to the activation of another area (Sarter et al., 1996). Furthermore, the interpretation of regions where no change in activation is shown on the scans can be misleading because the fMRI scanner cannot detect the possible contributions of regions that are constantly active, regardless of the task (Rorden & Karnath, 2004). The fMRI approach (measuring activation) therefore has a poorer level of inference than the lesion method (measuring disruption) which allows us to infer that the neural correlate investigated is actually required for the task being measured (Rorden & Karnath, 2004; Sarter et al., 1996).

In addition there are practical restrictions often imposed on researchers as the use of technologies such as fMRI scanners is costly and often not part of standard healthcare protocol, meaning that there are fewer

opportunities for researchers to use this approach, particularly when a vast majority of research is derived from poorly funded or voluntary sources. For these reasons lesion-behaviour mapping studies are still a popular approach to investigating the neural correlates of cognitive function and patients with brain tumour are an invaluable source of information in continuing to advance the evidence base in this arena.

Anxiety and depression

Mixed anxiety and depression is the most common mental health condition in Britain, with 7.8% of people meeting criteria for clinical diagnosis (NICE, 2011; Pilling, Whittington, Taylor, Kendrick, & Guideline Development Group, 2011). Those from poorer or disadvantaged backgrounds are more likely to be affected by common mental health problems and their consequences (Patel, Lund, Hatherill, Plagerson, Corrigall, Funk, 2010). In the most recent survey (undertaken 2014 to 2015) by the Office for National Statistics (ONS), as measured using the General Health Questionnaire (GHQ 12), 17.3% of individuals in the UK reported scores that indicate mild-to-moderate levels of anxiety or depression (ONS, 2017). This is a positive reduction from the previous year's score of 19.7%, however, it still indicates that nearly one in five adults experience these symptoms (ONS, 2017). The survey highlights that individuals living in the north-east (18.7%), people aged 16 to 24 (19.4%) and women (20.1%) are most likely to report difficulties with symptoms of anxiety or depression (ONS, 2017). These difficulties have been estimated to cause one fifth of days lost from work in Britain and so are not only significantly disabling the individuals concerned, but are associated with significant financial costs to the workforce and the National Health Services (Das-Munshi et al., 2008).

Anxiety and depression in patients with brain tumour

The impact of a diagnosis of brain tumour has been shown to be devastating for both the patient and the family (Wideheim, Edvardsson, Påhlson, & Ahlström, 2002). Prevalence rates of patients with intracranial brain tumours who experience psychological distress, such as anxiety and depression, vary significantly among reports from 16% (Pringle, Taylor, & Whittle, 1999), to more than double this at 42.7% (Zabora, Brintzenhofeszoc,

Curbow, Hooker, & Piantadosi, 2001). In comparison to other types of cancer patient, the severity of psychological distress in patients with brain tumour has been found to be second only to patients with lung cancer (Zabora et al., 2001). Additionally, the likelihood of anxiety and depression has been shown to be greater prior to surgery for tumour resection (Pringle et al., 1999) in meningioma patients in comparison to patients with other types of brain tumour (Pringle et al., 1999), and has been positively correlated with levels of physical disability and cognitive dysfunction (Anderson, Taylor, & Whittle, 1999). Psychological distress is therefore a present and important factor to consider in this population.

Cognitive Functioning

Cognitive function can be defined as cerebral processing that we use to perceive, understand, navigate and behave within our surroundings (Lezak, 1995). More specifically, discrete cognitive functions have been defined within the areas of motor skills, perception, attention, memory, language, visual and spatial processing. Executive functioning is seen as a higher-order form of cognitive processing that integrates and coordinates these more discreet skills (Lezak, 1995).

Cognitive functioning in patients with brain tumour

A number of systematic reviews have been conducted on the topic of cognitive functioning in patients with brain tumour, often focusing on one specific histological type, such as meningioma (Meskal, Gehring, Rutten, & Sitskoorn, 2016), or a histological tumour type specified further by its grading, for example, low grade glioma (van Loon et al., 2015), or high grade glioma (Weitzner & Meyers, 1997). Systematic reviews in this area tend to draw similar conclusions, highlighting that patients with brain tumour, to some extent, appear to experience deficits in a range of cognitive functions, most obviously prior to tumour resection, but also following resection (Meskal et al., 2016; van Loon et al., 2015; Weitzner & Meyers, 1997). However, they also conclude that the evidence base in this area is difficult to integrate and make sense of in a clinically meaningful or reliable way. This has been discussed as being due to a number of key reasons:-

- very few studies in this area have provided severity data (e.g. effect sizes, incidences) to allow the comparison and integration of outcomes
- a majority of the studies have used relatively insensitive assessment measures, such as the MMSE and 3MS which are not sensitive enough to discriminate between mild cognitive impairment and normal cognitive functioning (Meyers & Hess, 2003)
- the assessment measures used have been too varied across the evidence base to allow for valid and reliable comparison of results
- the definitions of what constitutes cognitive dysfunction have been too varied across the evidence base to allow for valid and reliable comparison of results
- many studies have failed to consider important mitigating factors that impact the assessment of cognitive functioning, such as premorbid functioning, mood, location of the tumour, size of the tumour, types of treatment received prior to testing, and the time of measurement (Habets et al., 2014; Meskal et al., 2016; van Loon et al., 2015; Weitzner & Meyers, 1997).

These difficulties in making sense of the evidence base mean that the results found cannot be interpreted with confidence by either practitioners or academics. However, these results do provide a general view that patients with brain tumours are impaired to some extent in many areas of cognitive functioning (Meskal et al., 2016; van Loon et al., 2015; Weitzner & Meyers, 1997).

Executive functioning

Executive functioning has been hypothesised to represent an individual's ability to integrate a range of cognitive functions (such as memory and language) while promoting cognitive flexibility and problem solving skills (Della Sala, Gray, Spinnler, & Trivelli, 1998). The range of functions covered by this concept is vast, however, mental set shifting, information updating and monitoring, and inhibition of dominant responses have been commonly linked to some of the key tests used to assess

executive functioning (Fisk & Sharp, 2004; Miyake et al., 2000). These core executive functioning skills are moderately correlated with one another, but clearly separable functions in their contributions to common executive functioning assessments (Miyake et al., 2000).

Executive functioning in patients with brain tumour

Deficits in executive functioning are commonly found in patients with brain tumours, as measured directly (Davidson et al., 2008) and through observer ratings of functional difficulties associated with executive functioning, such as issues of impulsivity and inflexibility (Jenkins et al., 2016). Studies investigating executive functioning have similar methodological difficulties to studies investigating cognitive functioning (discussed above), in terms of there being too much variability in decisions about the definition of executive functioning and the best way of measuring it (Alvarez & Emory, 2006). In terms of measurement, there are many different tests of executive functioning, as well as complete batteries, which test a wide range of different executive functions such, as the Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001b).

Verbal fluency

Verbal fluency tests require the co-ordination of a range of cognitive skills and functions, meeting the criteria of commonly used definitions for executive functioning (Miyake et al., 2000; Stuss & Levine, 2002). These tests are one of the most commonly used measures of executive functioning in neuropsychological testing, as they are quick, easy to administer, and do not rely upon examinee motor skills which often impede test outcomes for many people with neurocognitive difficulties. Verbal fluency outcomes play an important role in the diagnosis of a number of conditions within the clinical population, such as attention deficit/hyperactivity disorder (Andreou & Trott, 2013), Alzheimer's disease (Mathuranath, Nestor, & Berrios, 2010; Monsch et al., 1992; Zhao, Guo, & Hong, 2013), and Parkinson's disease (Pettit, McCarthy, Davenport, & Abrahams, 2013). Verbal fluency tests therefore play a highly instrumental role in neuropsychological assessment and diagnosis. This means that advancing the knowledge base in this area

is important to ensure the provision of accurate and reliable neuropsychological assessment and care of patients.

Verbal fluency tests can be semantic (sometimes described as category fluency), which would involve generating names that belong to a certain category (e.g. animals or fruits), or phonemic, which would involve generating words that begin with a certain letter of the alphabet. Phonemic and semantic fluency tests are similar in the sense that they both require a number of information processing demands including retrieval fluency and figuring out strategies to search the lexicon. They also both involve language abilities, oral-motor processing, and selective attentional processes (such as self-monitoring answers already given), using effortful control perseveration, self-initiation and inhibition of responses where appropriate to prevent errors (McCloskey & Perkins, 2012). However, there are some key differences in the skills and processes required for each of these forms of verbal fluency test (McCloskey & Perkins, 2012).

Phonemic verbal fluency

In addition to the skills highlighted above, phonemic fluency requires the generation of non-habitual strategies based primarily on lexical representations, meaning the individual needs to have a level of phonemic awareness to be able to complete this task (McCloskey & Perkins, 2012). Utilising this kind of orthographic criteria is quite unusual in relation to everyday functions, making it a more valid test of organic executive functioning as opposed to a learned and practised skill. In line with this, it has been suggested that phonemic fluency is a more accurate measure of executive functioning than semantic fluency, due to the novelty of the strategies required to complete phonemic fluency tests and the reliance of semantic fluency on semantic memory, as opposed to executive dysfunction (Ardila, Ostrosky-Solís, & Bernal, 2006; Henry & Crawford, 2004).

One of the most common tests to measure phonemic verbal fluency is the FAS test, but some tests use other letters, such as C, F and L (Benton et al., 1994; Spreen & Strauss, 1998). Slight differences in letter difficulty and word fluency have been described in some studies for each letter (e.g. Barry, Bates, & Labouvie, 2008). This indicates that separate norms should

be used for each version of this test (Strauss, Sherman, Spreen, & Spreen, 2006). However, correlations between letter sets are generally quite high (e.g. .83 between FAS and BHR in the DKEFS) demonstrating that this test holds its validity between different forms (Delis, Kaplan, & Kramer, 2001a). The FAS test is formally included as a subtest in a variety of neuropsychological batteries, including the Neurosensory Centre Comprehensive Examination for Aphasia (NCCEA; Spreen & Benton, 1977), and the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001a). It can also be used on its own as various norms, and meta norms are readily available in a number of studies (Gladsjo et al., 1999; Loonstra, Tarlow, & Sellers, 2001; Rodriguez-Aranda & Martinussen, 2006; Strauss et al., 2006). The internal consistency has been found to be high in this test (r = .83), and test-retest reliability is moderately high .74 (Tombaugh, Kozak, & Rees, 1999).

Semantic verbal fluency

Semantic fluency tests are thought to rely heavily on processes involved in the concept of ‘clustering’ where the participant will be required to find groups of related words within a certain category. For example, under the category of ‘animals’ an individual might consider selecting clusters such as ‘pets’, ‘woodland creatures’, or ‘safari animals’. Semantic fluency tasks therefore rely heavily on the participant having an intact semantic memory organisation/network. The skill of switching between clusters when the participant has run out of ideas within a cluster also plays an important role in semantic fluency performance.

The most common semantic fluency test is the Animal Naming Test (ANT), used in larger neurocognitive batteries such as the D-KEFS (Delis et al., 2001b). The ANT can also be used on its own, with norms being readily available in a number of studies (Gladsjo et al., 1999; Tombaugh et al., 1999). The internal consistency of the ANT has been measured by age groups divided roughly into decades (Delis et al., 2001a). For the adult age groups (aged 16-89) the internal consistency ranges between 0.60 (group 16-19 years) and 0.76 (groups 30-39 and 80-89 years) (Delis et al., 2001a). The test-retest reliability coefficient measured for all ages was 0.79 (Delis et

al., 2001a). Using the category ‘animal’ has significant advantages to other categories because it is a clear enough semantic category to use with different languages and different cultures, and it is considered to be a relatively easy semantic category with only minor differences in performance across people of different educational systems or generations (Ardila et al., 2006).

Verbal fluency in patients with brain tumour

Only seven studies have been conducted that compare healthy controls to tumour patients pre-surgery in measures of semantic and phonemic fluency, with the few that meet this criteria focusing on a wider range of neurocognitive impairments, as opposed to focusing more specifically on verbal fluency outcomes (Hoffermann et al., 2017; Klein et al., 2001; Miotto et al., 2011; Påhlson, Ek, Ahlström, & Smits, 2003; Talacchi et al., 2011; Tucha, Smely, & Lange, 2001; Tucha et al., 2003). Miotto et al., (2011) conducted the only study found demonstrating deficits in both semantic and phonemic fluency (using the ANT and the FAS test respectively) in pre-surgery glioma patients (both low and high grade). Due to a low sample size (N: 27) they were unable to complete any statistical analyses, so these outcomes are based on counting the number of patient deficits, most likely compared to the norms of the test (although this method is not confirmed in the paper). When including studies using resected tumour patients, statistically significant differences have been found in both semantic and phonemic fluency (also using the ANT and the FAS test) with patients with mixed tumour types of grades 1-2 (Goldstein, Obrzut, John, Hunter, & Armstrong, 2004) and grades 2-4 (Davidson et al., 2008) compared to healthy controls.

Phonemic fluency differences (in comparison to healthy controls) have been reported in patients who have non-resected meningioma (Tucha, Smely, & Lange, 2001; Tucha et al., 2003), glioma (Påhlson et al., 2003; Talacchi et al., 2011) and mixed tumour type (Hoffermann et al., 2017). However, only two of these studies (Hoffermann et al., 2017; Oliver Tucha et al., 2003) were able conduct statistical analyses and report significant differences due to sample size limitations. Semantic fluency has been even

less frequently studied, with only one study reporting statistically significant differences between healthy controls and high and low grade glioma patients (Klein et al., 2001). A similar study looking at patients with resected tumours has also demonstrated significant differences in semantic fluency between healthy controls and low grade meningioma patients (van Nieuwenhuizen et al., 2007).

It is clear that there is a limited range of studies available in this area, with this range further reduced by a large percentage of the studies not having sample sizes large enough to complete statistical analyses. However, among these studies there is a consistent consensus of deficits in both phonemic and semantic fluency being present in the brain tumour population. It is therefore important that these deficits are comprehensively understood to ensure appropriate care and treatment for patients with brain tumour diagnoses.

Factors influencing verbal fluency

Age, gender, and education are the most commonly evaluated demographic variables within neurocognitive research, and studies in phonemic and semantic fluency are no exception. Of equal relevance to this study, education, premorbid functioning and semantic memory will also be reviewed in terms of their associations with verbal fluency outcomes.

Demographic factors: Age, gender and education

Phonemic and semantic fluency both tend to improve during childhood, however, this increase is accelerated more within phonemic fluency (Delis et al., 2001a). This increase has been shown to peak when an individual reaches their thirties and shows a mild decline in old age (Delis et al., 2001a; Tombaugh et al., 1999). However, when considering the influence of ‘age of onset of condition’ of patients and the diversity of population norms within the brain tumour population (from non-clinical population norms), accounting for time related effects such as age can become more complex and less clinically meaningful. It may therefore be a less reliable trait of influence in this study.

Many studies have individually found little evidence of gender differences between phonemic and semantic fluency (e.g. Riva, Nichelli, & Devoti, 2000; Tombaugh et al., 1999). However, when a meta-analysis was conducted by Loonstra et al., (2001) the outcomes highlighted that women (M equals 35.14, SD equals 12.59) perform slightly better than men (M equals 33.28, SD equals 12.96) in letter fluency. This difference has not been replicated in semantic fluency (Delis et al., 2001a).

Education has been consistently highly correlated with both phonemic and semantic fluency outcomes, with high levels of education being associated with better performance (Delis et al., 2001a; Gladsjo et al., 1999; Loonstra et al., 2001).

Cognitive factors: IQ, semantic memory and premorbid functioning

IQ shows an even stronger relationship to phonemic fluency than education and is often considered a more reliable and valid influencing variable to measure (Steinberg, Bieliauskas, Smith, & Ivnik, 2005). IQ is therefore an important factor to consider when evaluating specific cognitive functions. However, it is important to consider that current IQ is likely to vary as a result of neurological injury, and that this variability would need to be accounted for when considering the influence of various demographic variables with a specific cognitive function. Premorbid functioning refers to the cognitive and functional abilities of a person prior to the onset of injury or illness. Knowing an individual's premorbid functioning is important because it allows for a more accurate measurement of any change in functioning that the individual has experienced, as opposed to making assumptions based on population norms. Premorbid functioning is therefore an important variable to consider in looking at cognitive outcomes in populations with neurological deficits (Crawford, Moore, & Cameron, 1992; Strauss et al., 2006). In support of this, modest to high correlations (.27-.67) have been reported between premorbid functioning (as measured by the NART) and phonemic fluency (Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2004; Crawford et al., 1992; Ross, 2003) and between phonemic fluency and the 'word reading' subtest of the WIAT-II (Davis et al., 2017). This

suggests that there is a premorbid relationship between phonemic fluency and word reading as measured by these tests (Bird et al., 2004; Crawford et al., 1992; Davis et al., 2017;Ross, 2003; Strauss et al., 2006).

The Test of Premorbid Functioning (TOPF; Wechsler, 2011) is a similar reading test to the two tests used in the above studies (NART and WIAT-II). It has been shown to overcome criticisms of previous tests (such as the WTAR; Wechsler 2001) which revealed the estimates of functioning were lower than expected for people with neurodegenerative conditions such as dementia and brain injury. One of the design aims of the TOPF was to reduce the effect of brain injury and dementia on the predictive equations, to obtain a more accurate estimate of premorbid ability, particularly within populations who have neurodegenerative conditions (Wechsler, 2011). As a result of this increase in validity, the TOPF has become a primary part of common neurocognitive assessment batteries used in neuropsychology services today and therefore holds greater clinical utility within these services. As premorbid functioning has been highlighted as a more accurate predictor of phonemic fluency than the more commonly measured ‘education’, and the TOPF is the test of premorbid functioning with the greatest clinical utility at this moment in time, it is important for correlations between the TOPF and phonemic fluency to be investigated. Unfortunately, such investigations have not been conducted and so need to be analysed to support the effectiveness of the design of future research and clinical considerations using these measurement factors.

As described above verbal fluency tasks require a substantial verbal component, for example, phonemic fluency is highly correlated with general measures of verbal skills (see Henry & Crawford, 2004, for a review). Semantic memory is a more specific component of verbal language skills which focuses on an individual’s ability to process ideas and concepts from their long-term memory that are not drawn from personal experience. Semantic memory is often associated with ‘common knowledge’ and includes things such as names of colours, capital cities, and types of furniture. The Boston Naming Test (BNT; Goodglass, Kaplan, & Weintraub, 1983) and the Graded Naming Test (GNT; Mckenna & Warrington, 1980) are tools commonly used to measure semantic memory by assessing an

individual's ability to name common objects. Semantic memory (as assessed by the BNT) has been associated with both phonemic and semantic fluency in two studies, with semantic fluency showing stronger correlations (.57- .86) than phonemic fluency (.43 - .50) in both papers (Henry, Crawford, & Phillips, 2004; Riva et al., 2000). Due to a lack of studies in this area it is difficult to draw confident conclusions about relationships between semantic memory and verbal fluency outcomes, however, the papers discussed consistently highlight positive relationships between both semantic and phonemic fluency and semantic memory test outcomes.

Tumour factors: type, size, speed of growth, grading

As discussed above there are over 130 different types of tumour, which vary in histological factors such as type, grading and growth speed/size (Louis et al., 2007; NICE, 2006). The impact of these different factors on cognitive functioning in patients with brain tumour has been researched to some extent, the results of which will be described below.

Due to there being no studies focusing more specifically on verbal fluency and tumour histology effects, this topic will be discussed in relation to the effects of tumour factors more generally on cognitive functioning.

Type of tumour

Very few studies have investigated the effects of tumour type on cognitive functioning. In fact only one study has explicitly set out to look at this relationship. Kayl and Meyers (2003) investigated the relationship between tumour histology and cognitive functioning in patients with glioblastoma multiforme and anaplastic astrocytoma. They found that the mean test scores in patients with anaplastic astrocytoma were superior on nearly all measures administered, in comparison to patients with glioblastoma multiforme, however, these differences were not statistically significant. They concluded that tumour histology was not a significant predictor of cognitive functioning after controlling for tumour volume (Kayl & Meyers, 2003). However, it is worth noting that these patients were assessed post-surgery, meaning that the tumours had been removed and the patients had started their recovery (Kayl & Meyers, 2003). It makes sense that tumour effects are going to be most obvious when the tumour is

still present and impacting upon patient's performance, as opposed to measuring the effects of the remaining lesion. Additionally, this study did not appear to consider the effects of pre-morbid functioning or mood, which are important factors to consider when assessing any form of cognitive functioning.

A small number of studies have analysed these relationships as part of a more general focus looking into different aspects of cognitive functioning in patients with brain tumour, finding no significant relationships between these specific factors (Hoffermann et al., 2017; Hom & Reitan, 1984; Scheibel, Meyers, & Levin, 1996). A study by Hahn et al., (2003) did show mixed results, in that there was a significant difference in neuropsychological functioning between patients with glioblastoma multiforme and patients with other types of tumour. Unfortunately the paper does not discuss what tumour types were included in the 'other types of tumour' group. More specifically they highlight that, when the tests were separately analysed, patients with glioblastoma multiforme performed significantly poorer than patients with other types of tumour on a visual scanning task to measure components of executive functioning (Trails A). They also found similar differences in phonemic fluency (as measured by the COWA test) between the patient groups, with the differences approaching significance ($p = 0.056$). However, no other significant effects were found despite testing a range of cognitive functions (Hahn et al., 2003). Interestingly, the two test outcomes described above which did show some difference (Trails A and COWA) are both forms of executive functioning measure, indicating that perhaps this is an area of cognitive functioning especially sensitive to the impact of tumour type. Although it is worth noting that other tests of executive functioning were assessed (such as Trails B and the Stroop Colour-Word Test) which showed no difference between the groups (Hahn et al., 2003). It is not clear within the paper whether the patients had received chemotherapy or other treatment related to their condition. The paper does discuss that some patients may have been in the early stages of receiving radiotherapy, which has been linked with changes in cognitive functioning (Correa, 2010; Douw et al., 2009) and so could have influenced results. These very few studies do point towards trends in differences between the effects of different tumour

types, more specifically indicating that glioblastoma multiforme tumours are more likely to impact certain tests of executive functioning (including phonemic fluency), but they do not provide statistically significant evidence or information on a wider range of tumour types. This is an area where more research is required.

Tumour size/volume

Kayl and Meyers, (2003) concluded that the lack of significant effects found in the above study were most strongly linked to the influence of tumour volume (Kayl & Meyers, 2003). More direct correlations were found by Talacchi, Santini, Savazzi, and Gerosa, (2011) who assessed patients with various grades of glioma pre-operatively, finding that 79% of patients were impaired across a wide range of tests, and that these effects were related to larger tumour size (as well as higher tumour grade and the impact of oedema). This study has an impressively comprehensive methodology, ensuring that practice effects were controlled for in nearly all their assessments and assessing for both anxiety and depression. They limited their recruitment to glioma patients only, so these results are not representative of the brain tumour population more broadly, and they were only able to recruit 29 patients, which is likely to have limited the power and generalisability of their results.

Very few studies have further investigated and reported on the impact of tumour volume, despite the correlations found above. The exceptions include two studies which found no significant relationships (Noll, Sullaway, Ziu, Weinberg, & Wefel, 2014; Oliver Tucha et al., 2003). Unlike the study above (Talacchi et al., 2011), the studies that have not found effects appear to be slightly less rigorous in the measures taken to account for confounding variables, such as mood (Noll et al., 2014) and premorbid functioning (Oliver Tucha et al., 2003). Additionally, Tucha et al., (2003) chose to categorise the tumours into two tumour volume groups (small and large), but did this by ranking the patients in order of tumour size, dividing the ranking into three groups (smallest, medium and largest), then comparing the bottom third (smallest) with the top third (largest) and ignoring the middle third. Creating a dichotomous variable from a range of scores in this way results in the loss of

a significant amount of the data relevant to the analysis, and so the outcomes were not representative of the population studied. In conclusion, there is some evidence that tumour size impacts cognitive functioning but that these results have not been replicated in proceeding studies. These discrepancies may be due to methodological flaws. This is therefore another area where further research is required.

Tumour growth speed

Hom & Reitan (1984) conducted one of the earliest studies on the effects of tumour growth speed on cognitive functioning in patients with brain tumour. While they did not classify the brain tumours by distinct type in line with the more developed classification systems used clinically today, they did use various forms of biological and technological examination to classify their 92 patients into four different grades of rapid to slow growing types of tumour. Each patient was given an extensive battery of psychological tests, which comprised of measures related to verbal and performance abilities, attention, speech – sounds perception, executive functioning and primary motor functioning. Their results highlighted that rapidly growing tumours were associated with greater performance deficits (Hom & Reitan, 1984). However, it is worth noting that their inclusion criteria were relatively broad, not taking into account different pathological characteristics of the tumour, most importantly tumour size. Similarly they did not match the patients by age, with the comparable groups varying significantly in this demographic. Each of these factors are quite important to consider when investigating cognitive functioning and could have been having an underlying effect in place of the growth speed effects found.

Tumour grading

Tumour grading has been slightly more extensively considered, particularly within glioma focused studies (Hom & Reitan, 1984; Kayl & Meyers, 2003; Miotto et al., 2011; Noll et al., 2014; Talacchi et al., 2011). It is often the case that speed of growth and tumour grading are considered synonymously, for example, the study above by Hom & Reitan (1984) was primarily focused on speed of growth of the tumour, however, the way they grouped their participants was by the expected growth speed of specific

grades of tumour (with rapid growth being associated with grade three or four, and slow growth being associated with grades one and two). While their study lacked validity by not considering age or tumour volume effects (as discussed above) they did find significant differences in cognitive performance between the two groups, with the lower grade tumour patients showing less cognitive deficit (Hom & Reitan, 1984).

Kayl & Meyers, (2003) controlled for more variables by matching their participants on various demographics, including age and tumour volume, however, they focused on a narrow range of tumour types (grade four glioblastoma and grade three anaplastic astrocytoma). They did not find any significant results once controlling for tumour volume, but their sample only consisted of 48 participants. Considering that this small number of participants was used to account for a large number of variables, and the fact that they were unable to assess each patients tumour volume at the same time as their neurocognitive functioning, meaning their argument is relatively weak (Kayl & Meyers, 2003).

Miotto et al., (2011) also compared cognitive functioning in a range of low grade and high grade glioma patients (including astrocytoma, oligodendroglioma, and multiforme glioblastomas), finding that patients with high grade glioma experienced significant impairment on a range of cognitive functions, particularly executive functioning and memory tests. It is worth considering that their sample size was quite small with only 19 low-grade glioma patients and eight high grade glioma patients. Additionally, while they excluded patients if they had a history of psychosis or depression, there were no attempts to measure current mood in the sample, which has been shown in similar studies to influence the correlations found between tumour grading and cognitive functioning (Talacchi, Santini, Savazzi, and Gerosa, 2011). Nor were tumour volume or location considered.

The study by Noll, Sullaway, Ziu, Weinberg, and Wefel, (2014) was designed with the aim of overcoming some of these methodological flaws, preoperatively assessing the impact of tumour grade in 72 left temporal lobe (grade two to four) tumour patients (including oligodendroglioma, astrocytoma, and mixed glioma). They found that processing speed, verbal

learning, executive functioning, and language abilities were more impaired in patients with grade four tumours compared to patients with lower grade tumours. They were able to improve upon a number of the methodological weaknesses discussed above by controlling for tumour volume, seizure status, and anti-epileptic or steroid use, with their results remaining significant (grade four tumour patients performing significantly lower than grades two and three) following this.

While conclusions were drawn only based upon generic neurocognitive functioning, Noll et al., (2014) helpfully reported their outcomes for each individual test which included a measure of phonemic fluency (the MAE COWA test). This outcome highlighted that there was a significant difference between phonemic fluency scores in patients with grade four tumours in comparison to patients with grade two and three tumours (Noll et al., 2014). This outcome, supported by the wider evidence base indicating links between tumour grades and cognitive performance more generally, indicates that there may be a relationship between tumour grade and phonemic fluency performance in patients with brain tumour (Hom & Reitan, 1984; Miotto et al., 2011; Noll et al., 2014).

Summary of the effects of tumour factors on cognitive functioning and verbal fluency

It would be fair to conclude that there is a significant lack of research in this area, with the few studies available showing mixed results and being unable to rule out a number of methodological flaws which may have influenced the conclusions. Trends have been found indicating that tumour type (Hahn et al., 2003; Kayl & Meyers, 2003) and tumour size may be associated with some aspects of cognitive functioning more generally. However, only one study included a test of phonemic fluency and no studies looked into semantic fluency. Additionally the results supporting these trends were either not significant or have not been replicated in later studies factors (Hoffermann et al., 2017; Hom & Reitan, 1984; Scheibel et al., 1996). There were also methodological issues which may have impacted the validity of the results, most significantly in relation to the patients being assessed post-surgery (Kayl & Meyers, 2003). Tumour growth speed has been shown to

impact cognitive functioning, however, this has only been investigated in one study (Hom & Reitan, 1984). These areas therefore require further investigation.

The effects of tumour grading have been more readily reported and these results are slightly more consistent, indicating that higher graded tumours will have a greater impact on cognitive performance, with one study showing significant differences whilst confounding factors were controlled for (Noll et al., 2014). This study was also the only study to highlight a relationship between tumour factors and a test of verbal fluency more specifically, indicating that patients with grade four tumours are likely to score lower in phonemic fluency in comparison to patients with grade two and three tumours (Noll et al., 2014).

Mood factors: depression and anxiety

Depression

The influence of depression on cognitive functioning has been historically reported (Blaney, 1986; Brown, Scott, Bench, & Dolan, 1994; Johnson & Magaro, 1987; Miller, 1975), and reviewed in a meta-analysis highlighting that not only does depression create deficits in the vast majority of cognitive functions, but it does so increasingly as the severity of depression increases (Christensen, Griffiths, MacKinnon, & Jacomb, 1997). Patients with depression present with poorer outcomes in a wide range of tests designed to capture executive dysfunction (Nathan, Wilkinson, Stammers, & Low, 2001). In comparing the deficits of executive functioning skills (such as verbal fluency), to differential cognitive deficits (such as psychomotor speed) it has been suggested that perhaps depression creates a generalised cognitive impairment, as opposed to a specific deficit in executive functioning (Henry & Crawford, 2005).

In contrast to this, while some patients demonstrate deficits in a wide range of cognitive functions when depressed, it has been found that deficits in executive functioning are more strongly associated with depression than other cognitive functions (Kaiser et al., 2003; Veiel, 1997). More specifically, in some studies, tests of verbal fluency have been shown to be the most sensitive to changes in levels of depression, in comparison to other

executive or cognitive functioning tests (Brown et al., 1994; Talacchi et al., 2011; Trichard et al., 1995).

Further discrepancies about the effects of depression on each of the verbal fluency tests have arisen between study outcomes, with some studies showing that both semantic and phonemic fluency are equally affected by depression (Brown et al., 1994; Christensen et al., 1997; Trichard et al., 1995; Yochim, Mueller, & Segal, 2013), others showing that semantic fluency is more impaired than phonemic fluency (Fossati, Amar, Raoux, Ergis, & Allilaire, 1999), and others showing that phonemic fluency is more impaired than semantic fluency in depressed patients (Beatty, Wonderlich, Staton, & Ternes, 1990). A thorough meta-analysis has attempted to resolve these discrepancies, showing that when the standard methodology adopted by other meta-analytic reviews was used to assess the performance of semantic and phonemic fluency in depressed patients, the outcome indicated that semantic fluency was most sensitive to the effects of depression (Henry & Crawford, 2005). However, when they applied a more rigorous method of meta-analysis the results showed that both phonemic and semantic fluency were similarly impaired by the presence of depression symptoms (Henry & Crawford, 2005). While there is not a large evidence base behind this topic area, the results from this meta-analysis appear relatively reliable and noteworthy (Henry & Crawford, 2005) and the majority of evidence suggests that depression negatively impacts executive functioning, including both phonemic and semantic verbal fluency performance (Beatty et al., 1990; Brown et al., 1994; Christensen et al., 1997; Fossati et al., 1999; Kaiser et al., 2003; Nathan et al., 2001; Talacchi et al., 2011; Trichard et al., 1995; Veiel, 1997; Yochim et al., 2013).

Anxiety

The area of verbal fluency and anxiety has received comparatively little attention in previous research, with few studies in the area of executive functioning and anxiety in the adult population, fewer on the more specific area of anxiety and verbal fluency, and still fewer studies including semantic fluency alongside phonemic fluency in their outcomes (O'Shea et al., 2016). In the study described above by Talacchi et al. (2011), relationships were

found between depression and verbal fluency, however similar relationships between anxiety and cognitive functioning, executive functioning, or phonemic fluency were not. This suggests that these two types of psychological distress may have very different effects on functioning (Talacchi et al., 2011) and so it is important to consider them separately. In support of a lack of interactions between anxiety and verbal fluency, Smitherman, Huerkamp, Miller, Houle, and O'Jile (2007) found little association between phonemic fluency and anxiety in a mixed psychiatric sample of adults.

Airaksinen, Larsson, & Forsell, (2005) further differentiated the impact of psychological distress by hypothesising that differences would be found in the effects of anxiety on executive functioning between different anxiety related conditions. They studied patients with a range of different anxiety disorders (panic disorder, social phobia, generalised anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and specific phobia) on a range of executive functioning tests including phonemic fluency (FAS). Interestingly, they did find differences among the different anxiety conditions, some of which contrasted the results found by Talacchi et al., (2011). More specifically, Airaksinen et al., (2005) concluded that executive functioning (as measured by components of the Trail making test from the DKEFS) was impaired in patients who experience panic disorder and OCD, but not in patients who suffered from specific phobias or GAD. However, similar to the above studies they also found that phonemic fluency was not affected by anxiety in any of the groups (Airaksinen et al., 2005). These results support the idea that there are different mechanisms at play between different types of anxiety, and different types of executive functioning. It's important to note however, that while the participants were selected based on their diagnostic category, their levels of anxiety at the time of testing were not measured (Airaksinen et al., 2005). As clinical diagnostic categories acknowledge fluctuations in presenting symptoms across time (American Psychiatric Association, 2013), this makes it significantly harder to imply any causal relationship between levels of anxiety and performance by using this approach.

Yochim et al. (2013) sought to uncover this more specific relationship between levels of anxiety and performance in executive functioning skills. They assessed older adult patients on a wider range of executive functioning assessments, looking at levels of anxiety at the time of testing (using the geriatric anxiety scale). Similarly to Airaksinen et al., (2005), they did find that higher levels of anxiety were associated with poorer performance on some executive functioning tests (the Trail making test and the 20 questions test from the DKEFS), but that anxiety did not predict performance in phonemic fluency (Yochim et al., 2013). They also investigated semantic fluency which, similar to phonemic fluency, was found to have no associations with anxiety (Yochim et al., 2013).

O'Shea et al. (2016) conducted one of the only studies which has investigated both semantic and phonemic fluency in adults with varying levels of anxiety, looking more specifically at the interactions between fluency, anxiety and fatigue. They found that high anxiety increases performance in adults who were also fatigued (O'Shea et al., 2016). However, they were unable to rule out any underlying effects of depression, which is often present in people who are anxious, meaning these results could have been confounded by the effects of depression. Additionally, the same relationships with anxiety and verbal fluency performance were not apparent in individuals without high levels of fatigue, meaning that the relationships found were contextually contingent on the presence of fatigue and could not be extrapolated more generally to the adult population.

It is very difficult to draw conclusions about how levels of anxiety may affect verbal fluency in adult patients with brain tumour, as these studies are not representative of this population. The above results provide some support for the idea that anxiety is likely to have a negative effect on a small range of executive functioning skills (Airaksinen et al., 2005; Yochim et al., 2013) but that phonemic fluency (Airaksinen et al., 2005; Talacchi et al., 2011; Yochim et al., 2013), and possibly semantic fluency (Yochim et al., 2013) appear to be unaffected by anxiety in the same way. However, due to such a sparsity of results, particularly in the area of adult verbal fluency performance considered alongside anxiety during neurocognitive testing, this conclusion is weak and requires further exploratory investigation.

Summary of factors influencing verbal fluency

Few studies have investigated the relationships between verbal fluency skills and the demographic, cognitive, tumour and mood factors discussed above. Those that have investigated these factors more consistently show significant relationships between phonemic fluency and age (Delis et al., 2001a; Tombaugh et al., 1999), gender (Loonstra et al., 2001), education (Delis et al., 2001a; Gladsjo et al., 1999; Loonstra et al., 2001), premorbid functioning (Bird et al., 2004; Crawford et al., 1992; Davis et al., 2017; Ross, 2003), semantic memory (Bird et al., 2004; Henry et al., 2004; Riva et al., 2000) and depression (Brown et al., 1994; Henry & Crawford, 2005; Talacchi et al., 2011; Trichard et al., 1995). Age (Delis et al., 2001a; Tombaugh et al., 1999), education (Delis et al., 2001a; Gladsjo et al., 1999; Loonstra et al., 2001), depression (Henry & Crawford, 2005) and semantic memory (Henry, Crawford, & Phillips, 2004; Riva et al., 2000) appear to be related to semantic fluency. However, the relationships between both types of fluency, anxiety and tumour grading are not clearly evidenced and therefore would benefit from further exploratory investigation.

Localisation of verbal fluency

Historically executive functions have been correlated with processes that involve the frontal cortex (Alvarez & Emory, 2006; Roca et al., 2010). Verbal fluency tasks are often considered to involve executive functioning skills, with research in this area often focused on the localisation of verbal fluency within different areas of the frontal lobes (see Henry & Crawford, 2004 for a review). However, there is a significant lack of consistency between findings in studies looking into the localisation (or ‘localisations’) of verbal fluency, with a number of studies finding no correlation between certain outcomes of either semantic or phonemic fluency and lesion location or laterality (Babulal, 2016; Davidson et al., 2008; Vilkki & Holst, 1994). As discussed above, there are clear distinction between the cognitive processes of different types of verbal fluency, and so the research into the corresponding neural correlates should be reviewed separately (Szatkowska, Grabowska, & Szymańska, 2000).

Localisation of semantic fluency

Broader lateralisation studies (as opposed to more specific localisation studies narrowing their focus down to more precise brain regions) appear to be quite contradictory when looking at semantic fluency deficits, with patients with right hemisphere lesions being more likely to show deficits over patients with left hemisphere lesions (Schweizer, Alexander, Susan Gillingham, Cusimano, & Stuss, 2010); other studies highlighted that semantic fluency deficits are more likely to be correlated with patients who have lesions in the left hemisphere (Goldstein et al., 2004; Vilkki & Holst, 1994) while other studies have found no lateralisation effects at all (Klein et al., 2001; Robinson, Shallice, Bozzali, & Cipolotti, 2012).

When looking at more specific localisation effects, semantic fluency has been correlated with a variety of areas within the cortex, including both the left and the right dorsolateral frontal lobes, both the superior and inferior medial frontal lobes, and the left temporal lobe (Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998). A different study has correlated semantic fluency performance with a similarly broad range of areas including the prefrontal cortex more generally, the right ventromedial areas and, similarly to the findings above, both the left and right dorsolateral frontal lobes (Szatkowska et al., 2000). One study focusing solely on the frontal and temporal lobes found similar deficits in semantic fluency outcomes between patients with lesions in these areas, implying that both areas are equally involved in the task, however, as they did not investigate any other cortical areas they were unable to justify the specificity of these results (Metternich, Buschmann, Wagner, Schulze-Bonhage, & Kriston, 2014). A similarly focused study using fMRI scanners has also highlighted specific correlations between semantic fluency performance and the left inferior frontal gyrus, the anterior cingulate, and the bilateral superior parietal gyri (Hirshorn & Thompson-Schill, 2006).

Localisation of phonemic fluency

Outcomes of phonemic fluency have been slightly more refined in terms of the range of areas implicated as important, with a number of studies associating phonemic fluency performance with left frontal functioning (Metternich et al., 2014; Robinson et al., 2012; Szatkowska et al., 2000; Troyer, Moscovitch, & Winocur, 1997), in particular the left dorsolateral prefrontal cortex (Szatkowska et al., 2000; Troyer et al., 1997). Additionally the medial frontal lobe has been shown to play a role in phonemic performance (Crowe, 1992), more specifically the superior medial frontal lobe (Troyer et al., 1997). Again, there are a number of studies that contradict these outcomes, having found little or no correlational effects between localisation, or lateralisation and phonemic fluency performance (Babulal, 2016; Goldstein et al., 2004; Hoffermann et al., 2017; Vilkki & Holst, 1994).

Summary of localisation effects of verbal fluency

Outcomes of phonemic fluency studies more commonly associate phonemic fluency with left dorsolateral prefrontal cortex (Metternich et al., 2014; Robinson et al., 2012; Szatkowska et al., 2000; Troyer et al., 1997). Other studies show that the superior medial frontal lobe also plays a role in phonemic fluency performance (Crowe, 1992; Troyer et al., 1997). A considerably broader array of cortical areas have been associated with semantic fluency performance, including the prefrontal cortex more generally, both the left and the right dorsolateral frontal lobes, both the superior and inferior medial frontal lobes, the right venture medial areas and the left temporal lobe (Szatkowska et al., 2000; Troyer et al., 1998). Other studies support the idea that even for patients who have cognitive deficits related to tumour localisation, they will still exhibit more global difficulties due to the requirement of cooperation of the brain as a whole neural network, as opposed to distinct areas of functioning (Hoffermann et al., 2017; Klein, 2012).

Despite this succinct summary, research in this area is often quite restricted, due to the difficulty of recruiting the high number of patients required to create an adequately powerful analysis because of the rarity of

the neurological conditions of interest. This has resulted in studies in this area being unable to statistically and reliably compare each of the cortical areas of interest once the sample has been collected and filtered appropriately (Goldstein et al., 2004). This is a common outcome in quantitative research attempting to focus on a number of variables whilst specialising in studying patients with relatively rare conditions, such as brain tumours or stroke (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Crawford, 2003; Crowe, 1992; Maxwell, 2004; Schweizer et al., 2010). This presents a problem, because there are such a wide range of factors that can influence the patient's performance in any area of cognitive functioning.

More specifically in relation to verbal fluency, as discussed above, depression (Henry & Crawford, 2005), age (Delis et al., 2001a; Tombaugh et al., 1999), gender (Loonstra et al., 2001), education (Delis et al., 2001a; Gladsjo et al., 1999; Loonstra et al., 2001), premorbid functioning (Bird et al., 2004; Crawford et al., 1992; Davis et al., 2017; Ross, 2003) and semantic memory (Bird et al., 2004; Henry et al., 2004; Riva et al., 2000) have been shown to influence phonemic fluency outcomes. Similarly, depression, age and education appear to be related to semantic fluency (Delis et al., 2001a; Gladsjo et al., 1999; Henry & Crawford, 2005; Loonstra et al., 2001; Tombaugh et al., 1999). Depression in particular is a significant factor to consider given the strong evidence behind its influence (Henry & Crawford, 2005) and potentially high levels of psychological distress in this population of individuals (Pringle et al., 1999; Zabora et al., 2001). Yet none of the localisation studies discussed above have considered the influence of this, or a number of the variables listed, let alone measured their interactions (Babulal, 2016; Goldstein et al., 2004; Hoffermann et al., 2017; Klein et al., 2001; Metternich et al., 2014; Robinson et al., 2012; Schweizer et al., 2010; Szatkowska et al., 2000; Troyer et al., 1997, 1998; Vilkki & Holst, 1994). It is therefore possible that the contradictory/weak effects found within these localisation studies are present due to their lack of consideration for a comprehensive range of influential factors within their patient samples.

Research aims

Verbal fluency tests are one of the most commonly used measures of executive functioning in neuropsychological testing and play an important role in the diagnosis of a number of conditions within the clinical population (Andreou & Trott, 2013; Pettit et al., 2013; Zhao et al., 2013). There is a notable lack of research in performance of patients with brain tumour pre-surgery in measures of semantic and phonemic fluency, with the few that are in this area focusing on a wider range of neurocognitive impairments, as opposed to focusing more specifically on verbal fluency outcomes (Hoffermann et al., 2017; Klein et al., 2001; Miotto et al., 2011; Påhlson, Ek, Ahlström, & Smits, 2003; Talacchi et al., 2011; Tucha, Smely, & Lange, 2001; Tucha et al., 2003). As a result there is little conclusive evidence about which factors may influence verbal fluency outcomes, more specifically in relation to semantic fluency (Bird et al., 2004; Davis et al., 2017; Noll et al., 2014). There are no studies to date which have investigated the interactions between a comprehensive range of demographic variables, mood scores, and verbal fluency outcomes in patients with brain tumour. By facilitating a greater insight into these associations clinicians will have more evidence behind clinical decision making when considering the outcomes of this tool in patients with comorbid mood difficulties and other mitigating factors (in line with the variables this research considers). In addition, the ability to use lesion-behaviour mapping across two subcomponents of verbal fluency could allow for the application of a double dissociation model to increase the ability to draw inferences about the localisation of the different subcomponents of verbal fluency (Teuber, 1955). It is our belief that having a greater understanding of these relationships could enhance the clinical utility of this widely used cognitive assessment tool more generally, and within the brain tumour population specifically.

This gap in the research base alone is noteworthy, however, answering the above questions would also be of great value to adding to and strengthening the evidence base surrounding the localisation effects of verbal fluency skills (Babulal, 2016; Goldstein et al., 2004; Hoffermann et al., 2017; Klein et al., 2001; Metternich et al., 2014; Robinson et al., 2012;

Schweizer et al., 2010; Szatkowska et al., 2000; Troyer et al., 1997, 1998; Vilkki & Holst, 1994). By applying appropriate statistics to a large database, with a comprehensive range of variables that have been acquired by experienced clinicians, I aim to provide clinically meaningful results which clarify some of the contradictions in the research base to date. It is also hoped that the results will broaden clinicians' understanding of the impact of these factors on verbal fluency, which will support them in making predictions about expected performance and tailor interventions accordingly.

Study aims

The aim of this study was to better understand the relationships between phonemic and semantic verbal fluency performance, tumour localisation, tumour type, tumour size, depression, anxiety, semantic memory, premorbid functioning, education and gender. More specifically the research questions were as follows:-

Research questions

1) Which tumour lesion localisations are most highly correlated with phonemic and semantic verbal fluency performance in patients with brain tumour?

2) Which demographic, cognitive, mood, and tumour related factors best predict phonemic and semantic verbal fluency performance in patients with brain tumour?

Hypotheses

1) Scores on the FAS will be negatively associated with tumours located in the left dorsolateral prefrontal cortex and the medial frontal lobe, depressed mood (HADS-D), tumour size and patients with grade four tumour (in comparison to patients with lower grade tumours).

2) Scores on the ANT will be negatively associated with tumours located in both the left and the right dorsolateral frontal lobe, the medial frontal lobes, the left temporal lobe, and depressed mood (HADS-D).

3) Scores on the FAS will be positively associated with the following: Semantic memory (GNT), premorbid functioning (TOPF), women (in comparison to men), and higher levels of education.

4) Scores on the ANT will be positively associated with higher levels of education and semantic memory (GNT).

5) Anxiety and tumour type will be investigated to explore any relationships with the FAS and the ANT.

Method

Study design

This was a quantitative study with a retrospective cohort design of cross-sectional data routinely collected in the Neuropsychology Department at James Cook Hospital as part of their service into the neuro-oncology multi-disciplinary team (MDT). The analysis looked at the associations between verbal fluency performance, brain tumour location and the role of other potential mediator variables. More specifically the variables of interest were as follows:-

Criterion/dependent variables of interest

Phonemic fluency

Semantic fluency

Main predictor independent variable of interest

Tumour Localisation

Mediator predictor independent variables of interest

Depression

Anxiety

Semantic memory

Premorbid functioning

Tumour Type

Tumour Size

Gender

Education

Data collection

Data was provided by the Neuropsychology department within the Medical Psychology Team at James Cook University Hospital (under South Tees Hospitals NHS Foundation Trust). The data came from a database they held consisting of information routinely collected as part of their service into the neuro-oncology multi-disciplinary team (MDT). Due to the data being provided by the service consisting of information routinely collected as part of their service evaluation data, patient consent specific to this study was not required. The research proposal was reviewed and approved by the Research and Development Service in South Tees Hospitals NHS Foundation Trust and The School of Medicine Ethics Committee who granted ethical approval for the study. This department received referrals from County Durham, Teesside, Darlington, and North Yorkshire for patients that were being considered for tumour resection and/or for assessment and support with managing cognitive/emotional difficulties. Participant data was selected to be included in the study if they met the following criteria at the time they attended for assessment:-

- They had received a formal diagnosis of brain tumour. For patients proceeding to tumour resection this diagnosis will have been confirmed by a neuropathologist. For those who were not referred for surgery their diagnosis will have been made by a neuroradiologist
- They were referred for neuropsychological assessment at the neuropsychology department, within the Medical Psychology Team at James Cook University Hospital (under South Tees Hospitals NHS Foundation Trust) following a diagnosis of brain tumour
- They had attended for assessment between January 2011 and July 2017 prior to receiving surgery, chemotherapy or radiotherapy
- They were aged 18 or over
- Their first language was English

- They had completed the all the tests of interest to this study (listed below) as part of the service's standard battery of assessments.

A staff member affiliated with both the neuropsychology service and the research team extracted the data from the database based on the eligibility criteria (above). This staff member anonymised all of the data before it was securely transferred to the researcher. This data include some patient demographics (education and gender) as well as scores for each of the relevant assessment tools and information about the tumour type, size and localisation. Localisation was initially coded prior to the dataset being obtained by the researcher by the neurosurgery team using CT head scans.

Operationalisation and coding of variables

Criterion/dependent variables

FAS Test (Phonemic fluency)

One of the first verbal fluency tests was developed by Thurstone in 1938 as a means for assessing letter fluency in a written format (Thurstone, 1938, as cited in Delis, Kaplan, & Kramer, 2001). This test has since been developed into a test of phonemic fluency made readily accessible for clinician with normative data published in a range of papers (Gladsjo et al., 1999; Loonstra et al., 2001; Rodriguez-Aranda & Martinussen, 2006; Strauss et al., 2006; Tombaugh et al., 1999). The FAS test requires participants to produce words starting with the letters F, A or S (within the set time period of 60 seconds). The participant is restricted from providing words that were names (e.g. Andy), places (e.g. Antarctica), or the same words with different endings (e.g. aim, aims, and aiming). The participant is also restricted from repeating the same words or producing words that do not start with the allocated letter. Any violations of these restrictions result in an error score and the word not being counted as part of the outcome score. The number of correct words produced for each category were tallied, and an average score is produced from the three categories as the overall outcome. This was then converted to a scaled score using information summarised in Strauss et al., (2006). The use of scaled scores provide a robust method to

attenuate the effects of outliers and normalise distributions of multiple neuropsychological tests using a common metric (Tabachnick & Fidell, 2013). The data for this test was included as a single continuous variable using the scaled scores.

Animal Naming Test (Semantic fluency)

One of the first researchers to introduce category fluency procedures in experimental studies of patients with brain damage was Rosen (Rosen, 1980). The most commonly used category to measure category fluency is under the subject “animal” (often referred to as the ANT). This has been made readily accessible for clinician use as a standalone assessment using normative data stratified by age and education published by Tombaugh et al., (1999). The total score is calculated based on the number of animals that have been listed within the set time period (60 seconds). The participant is also restricted from repeating the same words or producing words that do not start with the allocated category. Any violations of these restrictions result in an error score and the word not being counted as part of the outcome score. This was then converted to a scaled score using information summarised in Strauss et al., (2006). The use of scaled scores provide a robust method to attenuate the effects of outliers and normalise distributions of multiple neuropsychological tests using a common metric (Tabachnick & Fidell, 2013). The data for this test was included as a single continuous variable using the scaled scores.

Predictor/independent variables

Tumour Localisation

Due to the database involving input from a variety of clinicians over a long period of time, and the vast nomenclature used among tumour localisations, the initial dataset included a wide range of different tumour localisations. To prepare this data for analysis the researcher created a number of higher-order codes which were then verified independently by two clinicians from the neuropsychology department, with the aim of increasing interrater reliability of the codes created (see Appendix A).

Further revisions of the statistical model were required when it became apparent that fewer variables were needed to increase the power of the analysis (see Appendix B). Due to this category 2 was condensed down into two new data coding sets to consider. Initially category 4 was created which included seven main localisation areas including the localisation category of ‘other’ which included an amalgamation of the data points which did not fit the main six selected localisations. These main six locations were selected based on the lobes of the brain most likely to be involved in cognitive tasks (frontal, parietal and temporal). This was with the aim of retaining as many data points as possible. However, as the data points that did not meet the main six localisations came from dispersed locations throughout the brain, coding them as ‘other’ and including them in the analysis would not be meaningful to the hypothesis. Category 5 was then created with the ‘other’ group data points coded as ‘missing data’. It was considered that the increase in power gained by the reduction of four variables was likely to outweigh the power lost in the reduction of data points included, based on the rough principles of needing 10 participants per variable. Coding reliability for localisation was assessed using the Kappa statistic. The outcome for each of the five categories described above was a score of 1. As this demonstrated perfect agreement no further analyses were required. The analyses were completed using the coding for category 5. This variable is categorical and was therefore transformed into a range of ‘dummy variables’, in line with the chosen higher order groupings, in preparation for use in the analysis.

Tumour Type

Data for tumour type was also provided in a range of specialised classifications. These classifications were similarly grouped into higher order codes, as described in more detail below (see Appendix C).

In reviewing the tumour types across the database it became apparent that patients with ‘cysts’ had been included in the data. While a cyst is still likely to create cognitive difficulties through increase in oedema/pressure, the nature of a cyst differs from tumours in terms of not being likely to infiltrate tissue, meaning the effects are likely to be more

variable in nature. Due to this the impact is slightly different and it was felt that this data should be excluded from the study to maintain the homogeneity of the population group being studied. The remaining tumour types were initially grouped into four categories with a focus on specificity. However, further revisions of the statistical model highlighted that fewer variables were required to increase the power of the analysis. Due to this category 1 was condensed down into a dichotomous variable consisting of the main two tumour types, glioma and meningioma. The other data points were coded as 'missing data' using the same process as for localisation. It was considered that the increase in power gained by the reduction of three variables was likely to outweigh the power lost in the reduction of data points included, based on the rough principles of needing 10 participants per variable. Coding reliability for tumour type was assessed using the Kappa statistic. The outcome for both category one and the dichotomous variable coding described above were scores of 1. As this demonstrated perfect agreement no further analyses were required. The analyses were completed using the dichotomous variable for glioma and meningioma.

Tumour Size

Data for tumour size was provided in two dimensions (two separate width values). These values were combined to create a single variable providing a surface area estimate by multiplying the two width scores together. This surface area value was recorded for each data point and used in the analysis as a single continuous variable.

Hospital Anxiety and Depression Scale (Anxiety and Depression)

The Hospital Anxiety and Depression Scale (HADS) is a self-report, 14 item screening tool, with two subscales (seven items each) which assess for levels of anxiety and depression. The scores can be separated for anxiety (HADS-A) and depression (HADS-D). It was developed by Zigmond & Snaith, (1983) specifically to avoid reliance on common somatic symptoms of illness, for example insomnia and fatigue, with the aim of being a more valid and reliable measure to use to assess anxiety and depression in people with physical health problems. The internal consistency of this scale has been demonstrated to be high, with Cronbach's α ranging between 0.67

and 0.90 for the HADS-D, and 0.68 and 0.93 for the HADS-A (Bjelland, Dahl, Haug, & Neckelmann, 2002; Smarr & Keefer, 2011). The HADS has been correlated against the Beck Depression Inventory and the General Health Questionnaire to show adequate levels of validity, with coefficients ranging between 0.60 and 0.80 (Bjelland et al., 2002; Julian, 2011; Smarr & Keefer, 2011).

The HADS is quick to administer (about five minutes) and the responses are focused on the relative frequency of symptoms experienced by the participant over the last week. Items are scored on a Likert scale ranging from 0 to 3 (0 = not at all; 3 = very often). Therefore the scores derived for each subscale (anxiety or depression) can range between 0 – 21, with higher scores indicating greater likelihood of depression or anxiety. The test authors suggest that raw scores of between 8 and 10 identify mild cases, 11 – 15 identify moderate cases and 16 or above indicate serve levels of anxiety or depression (Zigmond & Snaith, 1983). The cut-off point of 8/21 for caseness in both anxiety and depression has been suggested, which gives a specificity of 0.78 and 0.79 and a sensitivity of 0.9 and 0.83 for anxiety and depression respectively (Bjelland et al., 2002). This cut off point was used to create dichotomous categorical variables for anxiety and depression separately, where scores of 0-7 were coded as ‘not depressed’/‘not anxious’ and scores of 8-21 were coded as ‘depressed’/‘anxious’ for HADS-D and HADS-A respectively.

Graded Naming Test (Semantic memory)

Deficits in a person’s ability to retrieve the name of an object is often the first indication of impaired language functioning. The Graded Naming Test (GNT) is a commonly used language assessment more specifically focused on semantic memory, which was developed by McKenna and Warrington (1980). They demonstrated good validity for this test by correlating it (.69 and .73) with two separate tests of reading (Mckenna & Warrington, 1980). Bird et al., (2004) tested reliability in the normal population using a one month follow up period, showing a reliability coefficient of .92 ($p < .001$). Within clinical populations (patients with neurodegenerative disorders) high test-retest reliability was also found at .93

(Bird & Cipolotti, 2007), however, low intra-subject variability was also apparent in this study, resulting in the authors suggesting new reliable change indices for neurological patients (+/-4.6). Its approach of grading the levels of difficulty throughout the test helps to avoid the problem of ceiling effects, meaning that the GNT is often chosen above other types of naming test. Participants are shown 30 black and white line drawings/pictures (graded and ordered by difficulty) and asked to say what the picture is. The total score is calculated via the total correct answers given. This score was recorded for each data point and used in the analysis as a single continuous variable.

Test of Premorbid Functioning (Premorbid functioning)

Reading tests have historically been used to predict premorbid IQ based on the concept that reading skills have been shown to be less susceptible to brain injury or decline than other cognitive skills (Crawford, 2003; Johnstone, Hogg, Schopp, Kapila, & Edwards, 2002). The Test of Premorbid Functioning (TOPF) is a reading test which can be used to enable clinicians to estimate an individual's level of intellectual functioning before the onset of injury or illness (D Wechsler, 2011b). It requires the participant to read aloud words with irregular spellings that have an atypical grapheme to phoneme translation. As these words cannot be decoded phonologically the correct pronunciation is thought to come from the participant's knowledge of the word acquired prior to their cognitive deterioration. The outcome can provide estimates, based on population norms, of a range of areas of premorbid intellectual functioning, as well as a general premorbid intelligence score. This type of test score can be calculated in conjunction with demographic variables to provide a more powerful prediction of premorbid functioning than other methods/tests available (Crawford, Stewart, Parker, Besson, & Cochrane, 1989; Reynolds, 1997). Test-retest reliability was calculated from a sample of 293 examinees from the US who completed the test twice, with about a 3 week interval (Wechsler, 2008). This was then analysed by age group with the correlation scores ranging between .89 and .95 (Wechsler, 2011). The internal consistency of the test was calculated on a standardisation sample from the UK, using total scores of the two half-tests, corrected for length of the test using the Spearman-Brown

formula. The outcomes indicated a high level of internal consistency, with a Chronbach's α of 0.95 (95% CI = 0.94 to 0.96) and a split-half reliability coefficient of 0.95 (Wechsler, 2011).

The participant is asked to read aloud from a list of 70 words (graded and ordered by difficulty). The test is terminated at the point where the individual scores 0 for five answers in a row and the score is calculated by the number of correct responses prior to this point. This total score was recorded for each data point and used in the analysis as a single continuous variable.

Gender

Data for gender was provided as either 'male' or 'female' and therefore coded as a dichotomous categorical variable with these same codes.

Education

Data for education was provided as either 'no exams' or as a range of qualifications beginning with CSE and ending with degree. This range was initially coded as a categorical variable with a separate level for each type of qualification. However, due to further revisions of the statistical model due to the decision to increase the power of the analysis through decreasing the number of variables, it was decided to code this variable as a dichotomous categorical variable with two levels, 'no exams' and 'exams'.

Power analyses and sample size estimation

In this study there were two criterion/dependent variables for the verbal fluency outcome (FAS Score and ANT Score), each of which were analysed against the main predictor variable (tumour localisation) and seven mediator predictor variables (HADS Depression, GNT score, TOPF score, tumour type, tumour size, education and gender).

The initial statistical model was based on the localisation category having 18 levels, therefore counting as 17 predictor 'dummy' variables (see table X, Category 1), tumour type having five levels, therefore counting as 4 predictor 'dummy' variables (see table X, Category 1) and education having six levels, therefore counting as 5 predictor 'dummy' variables. Combined

with the above listed variables of interest that totalled the number of predictor variables to consider in the power analysis to 31.

In planning the study two power analyses were considered:-

1) It is recommended that the data set should contain at least 10 times the number of participants as you have predictor variables to ensure stability and reliability when completing multiple regression (Harrell, 2001). If this analysis were to retain the 31 variables, an expected sample size of 123 would not be considered adequate.

2) To take a more specific approach we considered effect sizes. Cohen (1988, 1992) advises an order of magnitude for the effect size with 0.02 being appropriate for a small effect, 0.15 for a moderate effect and 0.35 for a strong effect. This has been defined using the following equation for multiple regression calculations:-

$$f^2 = \frac{R^2}{1 - R^2}$$

It is expected that the larger the effect size, the smaller the sample size required. In line with this G*Power (Faul, Erdfelder, Buchner, & Lang, 2009) was used to calculate a priori power analysis for a multiple regression with 31 predictors, an alpha value of .05 and an aim to achieve a power of .8 (80%). This calculation indicated that a sample size of 96-190 would be required to detect a medium to large effect size as outlined by Cohen above. Therefore, the expected number of participant data sets were unlikely to be sufficient to meet the aims of the project.

As described above the model was revisited and refined resulting in a number of the categorical variables being reduced. Some were reduced to dichotomous variables, e.g. tumour type, education and gender) and localisation was reduced to six levels. As tumour localisation has six levels it requires five ‘dummy variables’ for the analysis, meaning that localisation will count as five variables. This means that each analysis had twelve predictor variables to account for. When G*Power (Faul et al., 2009) was used to calculate a priori power analysis for a multiple regression with twelve predictors, an alpha value of .05 and an aim to achieve a power of .8 (80%).

This calculation indicated that a sample size of 61-127 would be required to detect a medium to large effect size as outlined by Cohen above. Therefore, the expected number of participant data sets were sufficient to meet the aims of the project.

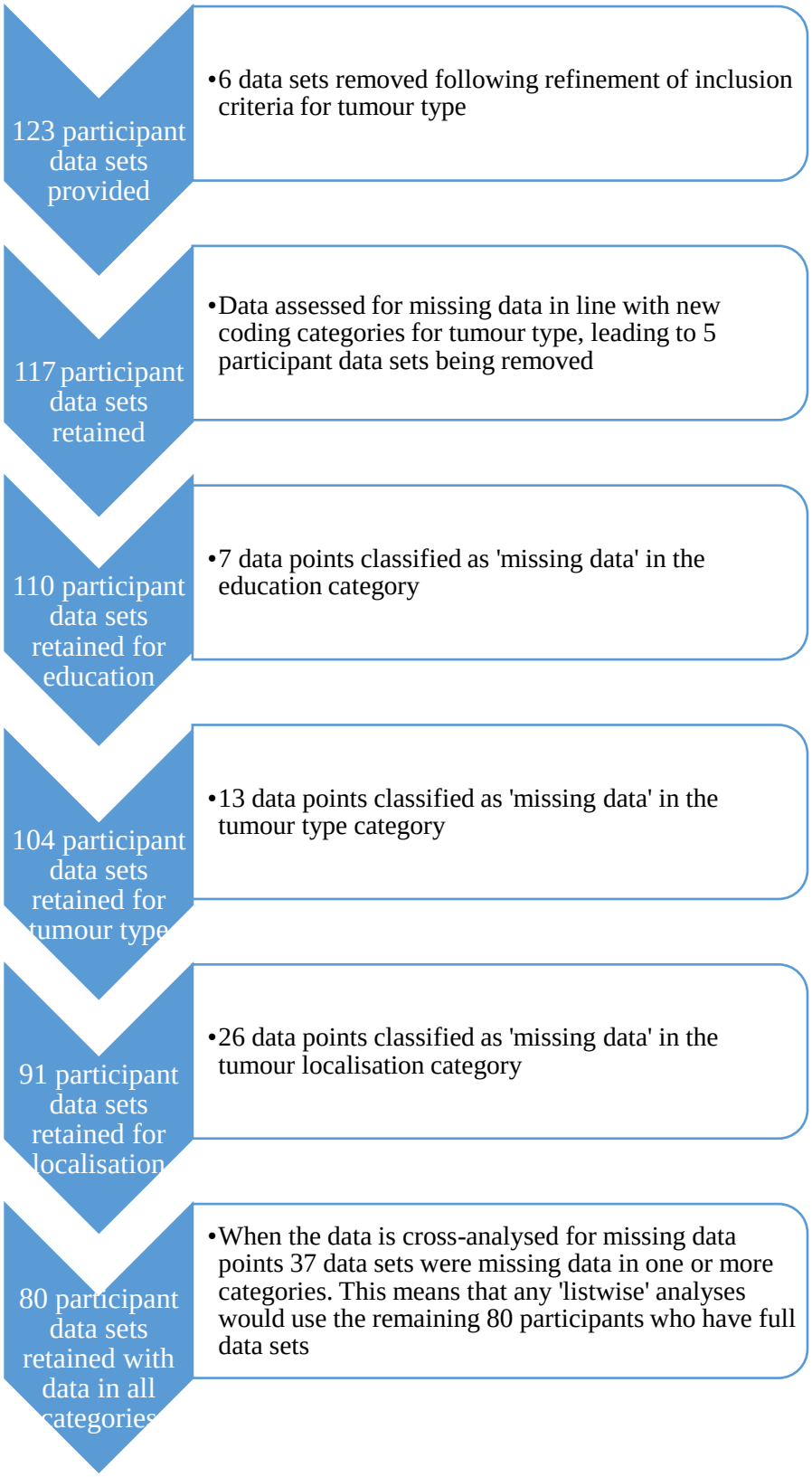
Data analysis

Demographic characteristics of the data set were evaluated and reported. The criterion/dependent variable was the verbal fluency outcomes as measured by the scaled scores corresponding to the average of the three phonemic fluency trials (F, A, S) and the total number of responses obtained from the ANT. The main predictor variable was tumour localisation (as coded by the neurosurgery team, using CT head scans). The control/predictor variables were mood (as measured by the anxiety and depression scores from the HADS), semantic memory (as measured by the GNT), premorbid functioning (as measured by the TOPF), tumour histology (size of tumour and tumour type), education and gender. All analyses were conducted using IBM SPSS Statistics software version 24. An alpha level of .05 was used to define statistical significance.

Data inclusion

Data was available for 123 participants who were included in this study. Six cases were removed following the discovery that these cases were cysts instead of tumours during the coding of tumour type, leaving a data set of 117 participants. Within this data 117 participant cases included data on gender, TOPF score, FAS score, ANT score, GNT score, and both versions of the HADS. Some data was missing for the other categories of interest, either due to the data being missing on acquisition from the service, or due to the points being excluded through the coding process (explained above). Therefore, despite 117 cases being used in the analysis, there was a reduction in the total available to analyse for education (110), tumour type (113), tumour localisation (91) and tumour size (41). This is explained in more detail in the flow chart below:-

Figure 1. Flow chart of data retention



Results

Demographics

As described in the method, the inclusion criteria for participant data selection were:-

- They had received a formal diagnosis of brain tumour. For patients proceeding to tumour resection this diagnosis will have been confirmed by a neuropathologist. For those who were not referred for surgery their diagnosis will have been made by a neuroradiologist
- They were referred for neuropsychological assessment at the neuropsychology department, within the Medical Psychology Team at James Cook University Hospital (under South Tees Hospitals NHS Foundation Trust) following a diagnosis of brain tumour
- They had attended for assessment between January 2011 and July 2017 prior to receiving surgery, chemotherapy or radiotherapy
- They were aged 18 or over
- Their first language was English
- They had completed the all the tests of interest to this study (listed below) as part of the services standard battery of assessments.

Data for 123 participants met this criteria and so were initially included in the study. The age range was 22 to 90 years old, with a mean age of 54.56 and a standard deviation of 15.5. The categorical demographic variables are displayed in table 1. There were 52 males (42.3%) and 71 females (57.7%) in the sample. The majority identified themselves as predominantly right-handed (109, 88.6%) with 14 left-handed (11.4%) and no one identifying themselves as ambidextrous. In terms of education, 10 participants had been educated to degree level (8.1%), 16 had completed further education (13%), three had achieved A levels (2.4%), 27 had CSE level qualifications (22%), 28 had GCSEs (22.8%), which when amalgamated into the category ‘educated’ meant that 64 (74%) of participants were educated and 32 (26%) had no academic qualifications.

Table 1. Frequency data for demographic categorical variables

	Category	Frequency (n, %)	Valid	Missing (n, %)
Handedness	Left Handed	14, 11.4	123	0, 0
	Right Handed	109, 88.6		
Gender	Male	52, 42.3	123	0, 0
	Female	71, 57.7		
Education	No exams	32, 27.6	116	7, 5.7
	GCSE	28, 24.1		
	CSE	27, 23.3		
	A level	3, 2.6		
	Further education	16, 13.8		
	Degree	10, 8.6		

Tumour characteristics

Tumour size was the only continuous tumour data variable and data was available for 41 participants. The mean size was 966.63, range 256 - 3888mm^2, with a standard deviation of 744.28.

Data from six participants were removed due to the tumour type being a cyst as opposed to a tumour, five were other types of tumour, and two participant's tumour types had not been recorded. The remaining data on tumour type included 21 (17.9%) gliomas, 83 (70.9%) meningiomas and 13 (9.1%) classified as 'other' and then 'missing' in the higher order categorisation process.

Coding for localisation as described in the method section resulted in six categories, with the smallest frequency being for tumours situated in the left parietal lobe (4, 4.4%) and the largest in the left frontal lobe (44, 37.6%). There was missing localisation data for 26 participants (22.2%). Table 2 illustrates this data.

Table 2. Frequency data for categorical variables related to tumour factors

	Category	Frequency (n, %)	Valid	Missing (n, %)
Tumour type	Glioma	21, 18.3	115	2, 1.7
	Meningioma	83, 72.2		
	Missing/Other	11, 9.6		
Tumour localisation	Frontal	6, 5.1	117	26, 22.2
	Left Frontal	44, 37.6		
	Left Parietal	4, 4.4		
	Left Temporal	7, 7.7		
	Right Frontal	24, 26.4		
	Right Parietal	6, 6.6		

Neurocognitive and mood assessment

In terms of the neuropsychological assessments included in the data set, each assessment had a valid data point for each participant case, meaning there was no missing data among these variables. The FAS scores ranged between 2 and 17 with a mean of 8.28. The ANT had a very similar range to the FAS (1 – 18) with a mean of 8.52 and the GNT scores ranged between 2 and 28, with a mean of 19.47. The scores for the TOPF ranged from 13 to 67, with a mean of 39.98. The mood measures both had the same range (0-20), with HADS-A having a mean of 8.68 (with 56.9% of participants meeting the criteria for caseness/anxiety) and HADS-D being 6.12 (with 35% of participants meeting the criteria for caseness/depression). This data is illustrated in table 3 and a more detailed breakdown of the frequency distribution of the scores for depression can be viewed in Appendix D, and for anxiety can be viewed in Appendix E.

Table 3. Frequency data for neurocognitive and mood factors

	Valid	Missing (n, %)	Frequency (n, %)	Mean	Min	Max
FAS	123	0, 0	123, 100	8.27	2.0	17.0
ANT	123	0, 0	123, 100	8.52	1.0	18.0
TOPF	123	0, 0	123, 100	39.98	13.0	67.0
GNT	123	0, 0	123, 100	19.47	2.0	28.0
HADS A	123	0, 0	123, 100	8.68	.0	20.0
HADS D	123	0, 0	123, 100	6.12	.0	20.0

Data cleaning

The dataset contained a number of variables with missing data. Of most significance, usable data for tumour size was found only to be present in 41 cases (66.7% missing) and each of these cases fell into the tumour type category of meningioma. Due to the limited data available for this variable and the fact that it is not randomly dispersed among the other variables, it was removed from further analysis.

Each variable was analysed to assess the rates of missing data. There were no missing data for any of the continuous variables, but missing data was found among three of the categorical variables (tumour type at 1.7%; education with 5.7%, and tumour localisation at 22.2%). Little's 'Missing Completely at Random' (MCAR) chi square statistic was calculated for all variables to test whether there was any systematic pattern to the missing data (Little 1988; Graham, 2009). The Little chi-square test shows little evidence that data is missing other than MCAR (Chi-Square = 13.183, DF = 7, Sig. = .068), and so MCAR is assumed. Consequently complete case analysis is assumed to be unbiased by missing data.

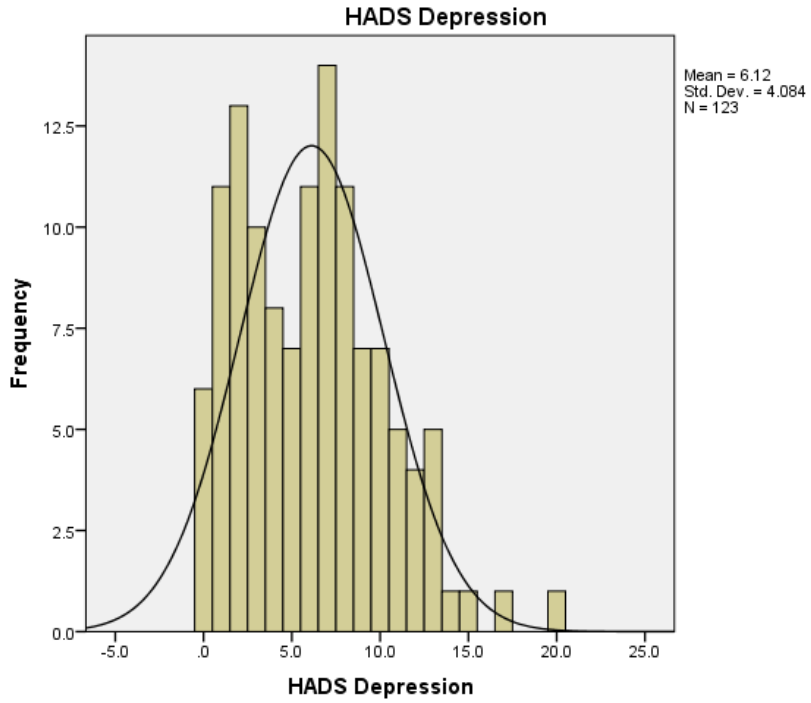
Missing data can result in a reduction of statistical power. This is often accounted for by using imputation methods such as 'mean imputation' which replaces the missing values with a mean score for that data set (van der Heijdena, Donders, Stijnene, & Moons, 2006; Little & Rubin, 2014). However, due to the missing data in this set being exclusively from dummy categorical variables relating specifically to clinically meaningful binary outcomes (e.g. tumour type), imputation methods would risk diluting the clinical meaning behind the results discovered. Therefore, the missing data were labelled to be recognised by the statistical analysis software and accounted for through listwise deletion within the relevant analyses.

Assessing normality of the continuous variables

The continuous variables were assessed for the normality assumptions of a regression analysis initially through exploration of the distribution of the data using histograms and Q-Q plots. It was felt that a relatively normal bell curve was visible in most of the variables histograms.

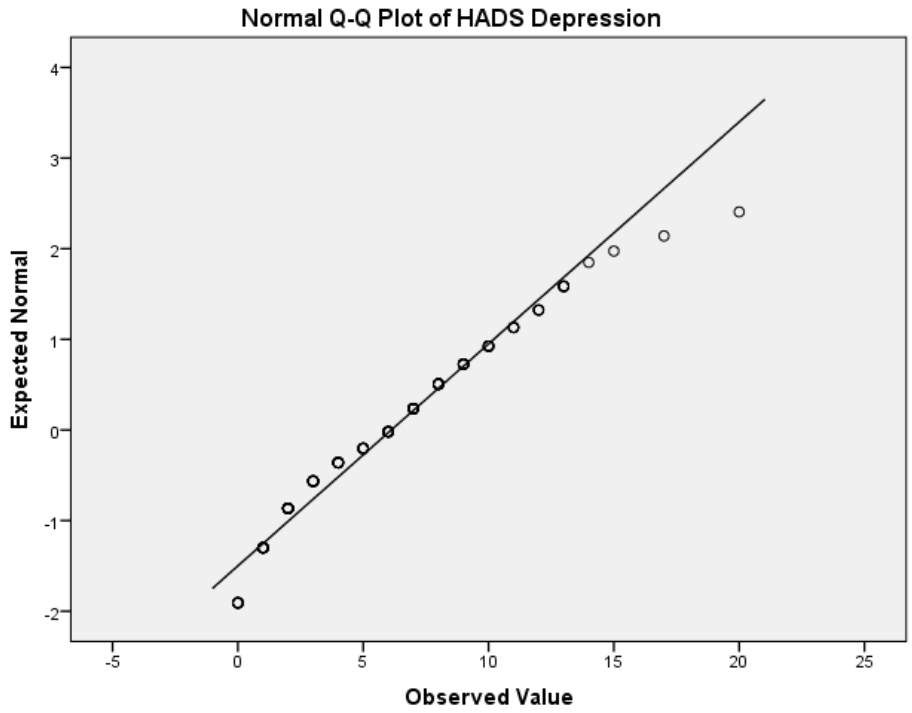
Two exceptions to this were the graphs for HADS-D and the GNT, which will be described in more detail below in figures 2-5.

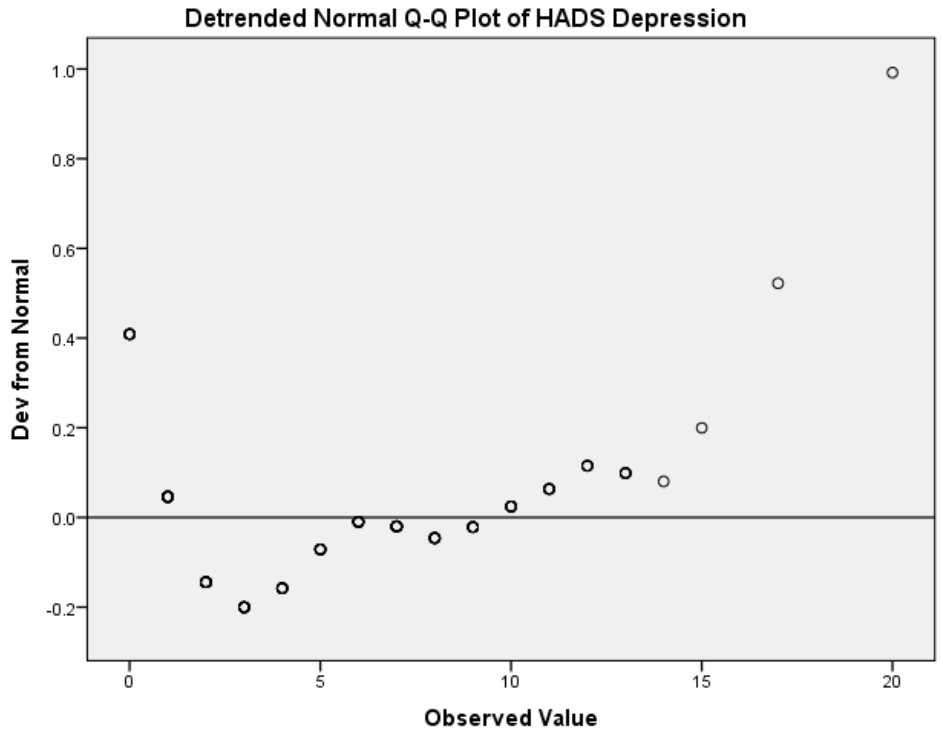
Figure 2. Histogram showing distribution of data for the HADS-D



As might be expected the HADS Depression histogram (see figure 2) appears to be slightly positively skewed with two distribution peaks and it does look like a somewhat leptokurtic tail, particularly to the left of the distribution.

Figure 3. Normal and Detrended Q-Q Plots for the HADS-D data

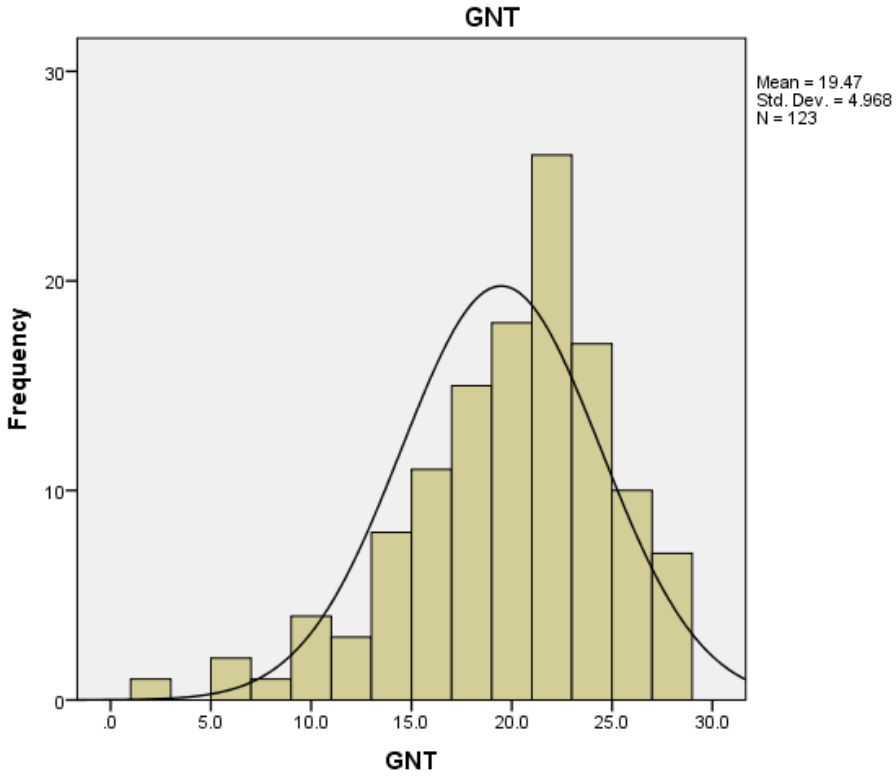




This normal Q-Q plot (see figure 3) has a slight positive skew (a slight shift in the data away from the bisection line, at the tail ends, with the tail ends below the bisection line and the middle data above the line). Additionally the tail ends are slightly heavy (more spaced out). The de-

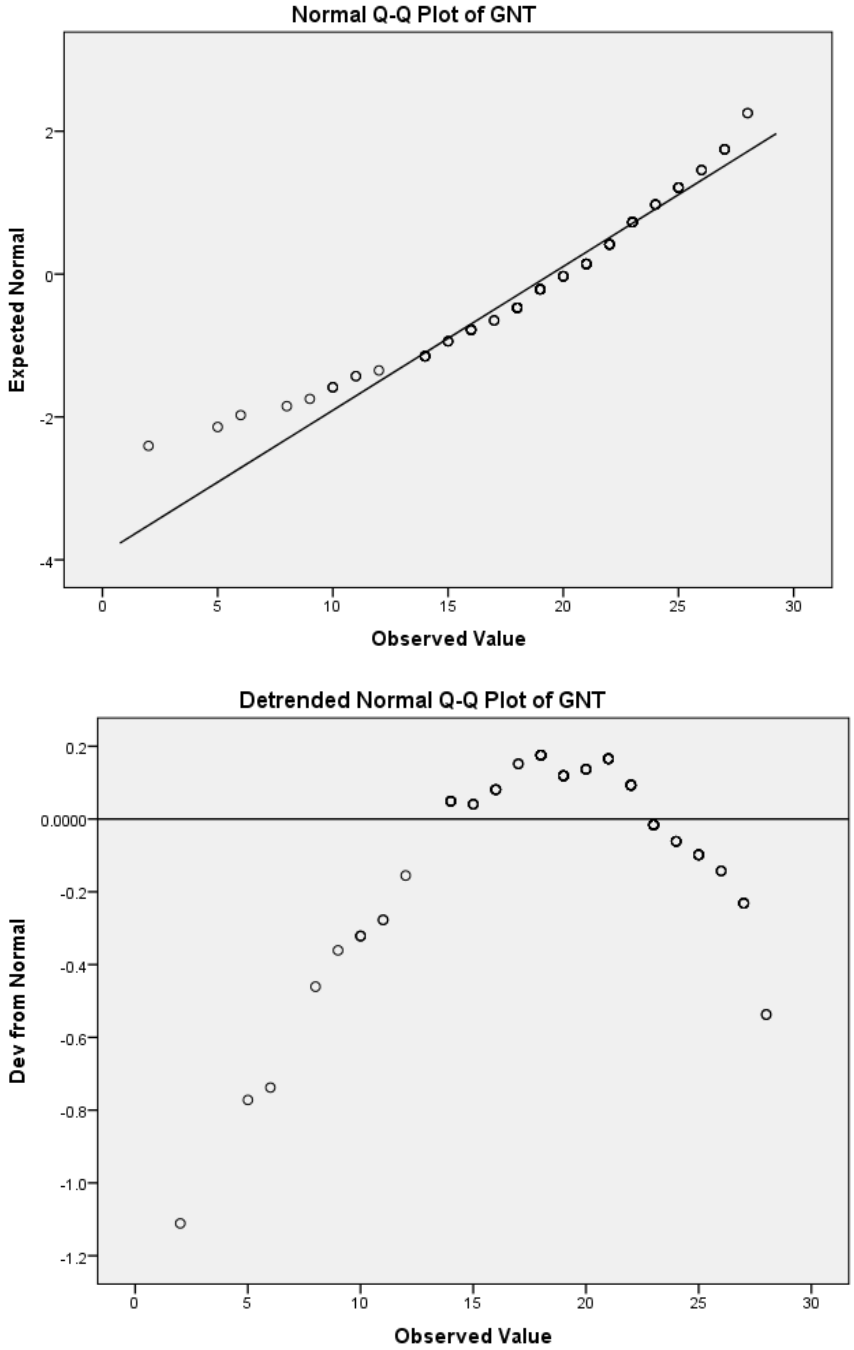
trended Q-Q plot also supports the view of a positive skew due to the ‘v’ shape scatter.

Figure 4. Histogram showing distribution of data for the GNT



The GNT histogram (see figure 4) appears to be somewhat negatively skewed with a leptokurtic tail, particularly to the right of the distribution where there is a relative lack of a graded ending.

Figure 5. Normal and Detrended Q-Q Plots for the GNT data



This normal Q-Q plot (see figure 5) has a slight negative skew (a slight shift of the data away from the bisection line at the tail ends, with the tail ends above the bisection line and the middle data below the line). Additionally the tail ends are slightly heavy (more spaced out) than the data across the middle of the pattern. The de-trended Q-Q plot also supports the view of a negative skew.

To more rigorously assess the continuous variables in this data set for normal distribution SPSS provides two statistical tests, the Kolmogorov-

Smirnov and the Shapiro-Wilk. The results from the Kolmogorov-Smirnov test highlighted that age was the only variable that did not have a significant outcome (and hence did meet the assumptions of normality). However, the Kolmogorov-Smirnov test is commonly considered to be overly conservative, with a high sensitivity to extreme values and a low power. This means it is likely to lead to systematic errors and is now traditionally ignored by researchers (Ghasemi & Zahediasl, 2012; Steinskog, Tjøstheim, & Kvamstø, 2007). The significant results from the Shapiro-Wilk outcomes for each variable indicate that none of the variables meet the assumptions of normality. However, these outcomes need to be interpreted with caution, as it is commonly accepted that due to the increase of power in large sample sizes, and the unrealistic likelihood that perfectly normally distributed data will exist in real population data, even very small deviations from normality will result in a significant outcome on the Shapiro-Wilk test (Öztuna, Elhan, & Tüccar, 2006). Due to this SPSS recommends that data sets containing more than 50 cases do not rely on this statistic to guide the treatment of their data, but instead act as an indicator to assess the variables in more depth via other means (Elliott & Woodward, 2007).

Following this guidance the researcher calculated Z-scores for the skewness and kurtosis statistical outcomes for each variable (see table 4) using the following calculations:

$$Z_{Skewness} = \frac{Skewness\text{-}0}{SE_{Skewness}} \quad \text{and} \quad Z_{Kurtosis} = \frac{Kurtosis\text{-}0}{SE_{Kurtosis}}$$

Table 4. Skewness and Kurtosis Z value calculations for continuous variables

		TOPF	FAS	ANT	GNT	HADS A	HADS D
N	**Valid**	123	123	123	123	123	123
	Missing	0	0	0	0	0	0
Mean		39.984	8.276	8.520	19.472	8.675	6.122
Skewness		.211	-.013	-.310	-.882	.374	.571
Std. Error of Skewness		.218	.218	.218	.218	.218	.218
Skewness Z Score		0.97	-0.06	-0.60	-4.05	1.72	2.62
Kurtosis		-.587	-.249	.052	1.030	-.438	.113
Std. Error of Kurtosis		.433	.433	.433	.433	.433	.433
Kurtosis Z Score		-1.36	-0.58	0.12	2.38	-1.01	0.26

The Z-Score is considered significant at $P < 0.05$ if it is greater than 1.96 or lesser than -1.96, however, it is advised that for larger samples the criterion should be changed to + or – 2.58, and very large samples should not be assessed for normality at all (Field, 2009; Ghasemi & Zahediasl, 2012). So within these guidelines there are two variables that exhibit a level of skewness which are considered to violate the normality assumptions (HADS-D, which is only just past the significance cut-off, and GNT which is slightly more skewed at -4.05).

The outliers for these two variables were viewed through boxplot graphs (HADS-D had one outlier at participant 2, GNT had three outliers at participants 1, 70 and 110). Removal of these outliers was considered, however it was felt that due to the naturally variable nature of clinical population data it would risk reducing the validity of the research outcomes by removing data in this way. Therefore, it was decided that the outliers would continue to be included in the analyses.

Transformations of these two variables were attempted (using a LOG10 transformation), however, the transformations created greater deviations from normality than was originally present within those variables.

When regression calculations are conducted with a large enough sample size (some have placed a numerical value on this of about 35+),

small violations in normality assumptions shouldn't cause significant difficulties with the outcomes of the analysis (e.g. Pallant, 2007). Furthermore, it has been stated that if a sample consists of hundreds of observations, it is acceptable to ignore the distribution of the data entirely (Altman & Bland, 1995; Field, 2009; Ghasemi & Zahediasl, 2012). This database contains over 100 cases, the visual assessment of the histograms and Q-Q plots were relatively normal for all variables, and the two variables that demonstrated slight deviations from normality were independent variables (which are of less concern than the dependent variables). It would therefore be fair to assume that slight statistical deviations in normality distribution can be considered ignorable and the use of parametric procedures is acceptable with this dataset.

Assessing for linearity, independent errors and homoscedasticity

To test whether the outcome variable is related linearly to each of the predictor variables the standardised residuals were plotted against the standardised predicted values for each of the dependent variables. The points are relatively well scattered across negative and positive values (largely between the ideal range of -3 and +3) with no obvious pattern. This is more the case for the FAS (see figure 6), however, both variables produce an acceptable amount of scatter in the plotted residuals so there is no reason to doubt the linearity assumption. Similarly this pattern shows that the residuals don't indicate autocorrelation and so the errors are normally distributed and the independent errors assumption is met. The scatter and the residual statistics also indicate that the variance of the residuals are constant and so the assumptions of homoscedasticity are also met (see figure 7 and table 5).

Figure 6. P-P Plot for FAS data

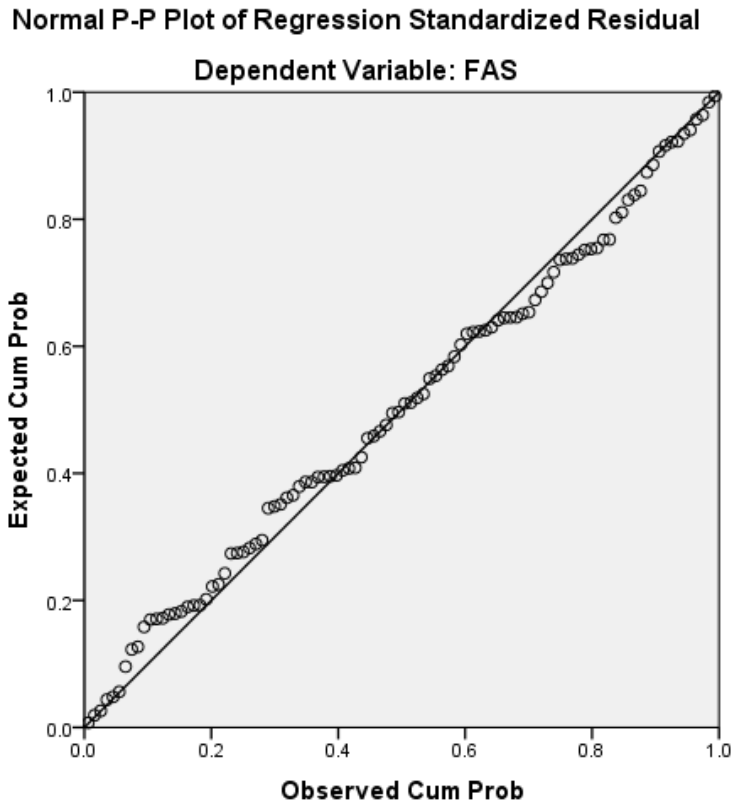


Figure 7. Scatterplot for FAS data

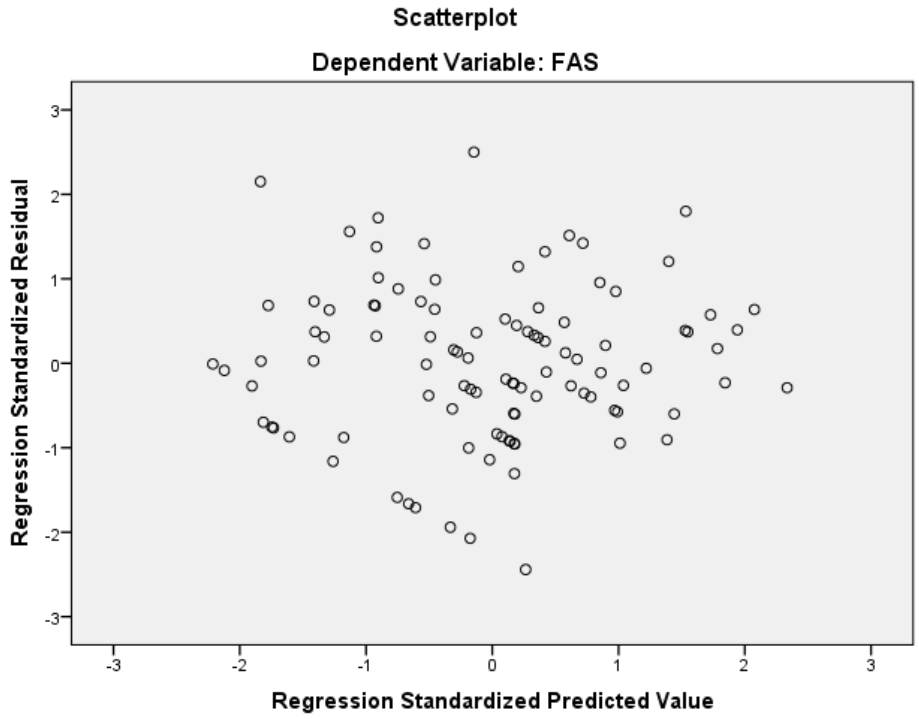


Table 5. Residual statistics for FAS data

	Minimum	Maximum	Mean	SD	N
Residual	-6.9041	7.0687	.0314	2.5831	102
Std. Residual	-2.442	2.500	.011	.914	102
Cook's Distance	.000	.160	.012	.024	101
Centered Leverage	.064	1.060	.231	.132	102

Assessing for multicollinearity

The correlation matrix was viewed (see appendix F^{i} and F^{ii}) to assess the correlation coefficients for each pair of explanatory variables. The correlation coefficient is considered appropriate if it is less than -0.8 or greater than 0.8 (Petrie & Sabin, 2009). Each correlation coefficient in this data set met these requirements and so there were no concerns relating to multicollinearity. In line with this the tolerance collinearity statistic for each variable was relatively high (lowest value being 0.437 for age) and higher than the 0.2 error indicator. Similarly, the variance inflation factor collinearity statistics are all lower than the cut off of 10 (highest value 2.289, again for age). These outputs indicate that the multicollinearity assumptions have been met.

Statistical analyses

To test the study hypotheses analytic statistics were conducted using IBM SPSS Statistics 24, in the form of multiple linear regression. The assumptions for this model were met within the data set as described above. This particular statistical method was chosen because there were multiple predictor variables, and multiple linear regression allows for the determination of which predictors are significantly associated with the independent (criterion) variable, while taking into account that the predictors may be related to each other (Howitt & Cramer, 2005). Within this approach the method of hierarchical linear regression was employed due to there being specific hypotheses developed based on theories derived from previous research in relation to the role of tumour localisation in phonemic fluency performance (Field, 2009). In line with this the localisation variable was added to the model in the first stage of the regression, with the predictor variables whose assumed influence was more clearly supported by prior

research entered second (gender and education); additional predictor variables added in the second stage. Significance was assessed at an α level of 0.05.

Due to the unexpected loss of usable data through the data cleaning and categorising process, particularly when considering the hierarchical multiple regression analyses (reducing from 123 to 80 cases) with a relatively high number of variables, a post hoc power analysis is recommended to determine the chance of the results being due to a type 2 error. G*Power (Faul et al., 2009) was used to calculate a post hoc analysis for each of the regression analyses based on their number of predictors, their sample size, an alpha value of .05, and an f^2 effect size calculated using the R_2 value provided in the analysis results.

To control for the false discovery rate associated with multiple comparisons the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) was used to adjust the *P* values, using a false discovery rate of .1. This rate was chosen to balance the high rate advised in the use of hypotheses that are quite explorative in development (due to a limited evidence base), whilst attempting to ensure potential false positive results are controlled for as stringently as possible.

Associations between verbal fluency and demographic factors

Single linear regressions were calculated to predict phonemic fluency (FAS scores) based on education and gender. Phonemic fluency and education were significantly correlated (F(1,115) 7.639 p=.007), with an R^2 of .066 for the effects of education, an f^2 effect size of 0.071 and a power (1-β) of 0.782. Participants' predicted FAS score was equal to 6.906 + 1.966 (education) where education is coded as 0 = no exams, 1 = educated. Participants' mean FAS score increased by .091 for participants who were educated. Phonemic fluency and gender were not significantly correlated (F(1,115) 1.664 p=.200), with an R^2 of .014 for the effects of gender, an f^2 effect size of 0.014 and a power (1-β) of 0.248. Participants' predicted FAS score was equal to 7.880 + .821 (gender) where gender is coded as 0 =

males, 1 = females. Participants' mean FAS score increased by .821 for participants who were female.

A single linear regression was calculated to predict semantic fluency (ANT scores) based on education. The regression approached significance (F(1,108) 3.422 p=.067), with an R^2 of .031 for the effects of education, an f^2 effect size of 0.032 and a power (1-β) of 0.453. Participants' predicted ANT score was equal to 7.500 + 1.410 (education) where education is coded as 0 = no exams, 1 = educated. Participants' mean ANT score increased by 1.410 for participants who were educated.

Associations between verbal fluency and cognitive factors

Single linear regressions were calculated to predict phonemic fluency (FAS scores) and semantic fluency (ANT) based on semantic memory (GNT scores). A significant regression equation was found for phonemic fluency and semantic memory (F(1,115)13.702, p=.000), with an R^2 of .106, an f^2 effect size of 0.119 and a power (1-β) of 0.956. Participants' predicted FAS score was equal to 3.996 + 0.223 (GNT) points. Participants' FAS score increased by .223 for each point of increase on the GNT. A significant regression equation was also found for semantic fluency and semantic memory (F(1,115) 20.523, p=.000), with an R^2 of .151, an f^2 effect size of 0.178 and a power (1-β) of 0.994. Participants' predicted ANT score was equal to 3.001 + .282 (GNT) points. Participants' ANT score increased by .282 for each point of increase on the GNT.

A single linear regression was calculated to predict phonemic fluency (FAS scores) based on premorbid functioning (TOPF scores). Phonemic fluency and premorbid functioning were significantly correlated (F(1,108)14.106, p=.000), with an R^2 of .109 for the effects of premorbid functioning, an f^2 effect size of 0.122 and a power (1-β) of 0.961. Participants' predicted FAS score was equal to 4.717 + 0.091 (TOPF) points. Participants' FAS score increased by .091 for each point of increase on the TOPF.

Associations between verbal fluency and tumour factors

A single linear regression was calculated to predict phonemic fluency (FAS scores) based on tumour type. Phonemic fluency and tumour type were not significantly correlated (F(1,102) .428, p=.514), with an R^2 of .004 for the effects of tumour type, an f^2 effect size of 0.004 and a power (1-β) of 0.097. Participants' predicted FAS score was equal to 7.880 + .821 (tumour type) where tumour type was coded as 1 = meningioma, 2 = glioma. Participants' mean FAS score increased by .545 for participants with meningioma in comparison to those with glioma. There were no hypotheses based on tumour factors and semantic fluency.

Associations between verbal fluency and mood factors

Single linear regressions were calculated to predict phonemic fluency (FAS scores) and semantic fluency (ANT scores) based on depression (HADS-D) and anxiety (HADS-A). The regression outcomes for phonemic fluency and depression approached significance (F(1,115) 3.857, p=.052), with an R^2 of .032 for the effects of depression, an f^2 effect size of 0.033 and a power (1-β) of 0.489. Participants' predicted FAS score was equal to 8.792 - 1.292 (depression) where depression was coded as 0 = not depressed, 1 = depressed. Participants' mean FAS score decreased by 1.292 for participants who were coded as depressed in comparison to those who were not. Phonemic fluency and anxiety were not significantly correlated (F(1,115) .019, p=.890), with an R^2 of .000 for the effects of anxiety, an f^2 effect size of 0.033 and a power (1-β) of 0.489. Participants' predicted FAS score was equal to 8.302 + .089 (anxiety) where anxiety was coded as 0 = 'not anxious', 1 = 'anxious'. Participants' mean FAS score increased by .089 for participants who were anxious in comparison to those who were not.

The single linear regression calculated to predict semantic fluency (ANT) based on depression (HADS-D) approached significance (F(1,115) 3.249, p=.074), with an R^2 of .027 for the effects of depression, an f^2 effect size of 0.370 and a power (1-β) of 0.999. Participants' predicted ANT score was equal to 8.935 - 1.260 (depression) where depression was coded as 0 = not depressed, 1 = depressed. Participants' mean ANT score decreased by 1.260 for participants who were coded as depressed in comparison to those

who were not. Semantic fluency and anxiety were not significantly correlated (F(1,115) .461, p=.498), with an R^2 of .004 for the effects of anxiety, an f^2 effect size of 0.004 and a power (1-β) of 0.103. Participants' predicted ANT score was equal to 8.755 - .458 (anxiety) where anxiety was coded as 0 = 'not anxious', 1 = 'anxious'. Participants' mean ANT score increased by -.458 for participants who were anxious in comparison to those who were not.

Associations between verbal fluency and localisation

A multiple regression was calculated to predict phonemic fluency based on localisation, with Left Frontal being the reference condition. A significant regression equation was found (F(5,85)3.552, p=.006), with an R^2 of .173, an f^2 effect size of 0.209 and a power (1-β) of 0.924 for the effects of localisation. The predicted FAS score for participants with tumours situated in the left frontal lobe was equal to 7.568 (CI 6.575-8.526) given that the other localisation areas take the value of zero. Predicted FAS score increased by an additional 2.307 points, on average, if the tumour was in the right frontal lobe, or 3.098 points if the tumour was in the right parietal lobe compared with the results for the left frontal lobe. These relationships were shown to be significant (p = .007 and p = .035 respectively). A similar relationship was seen in participants who have tumours in the frontal area, showing an increase of 1.932, but this was not significantly different to the results for left frontal lobe (p = .184). Predicted FAS score decreased by an additional 2.318 points if the tumour was in the left parietal lobe, and 1.425 points if the tumour was in the left temporal lobe. These relationships were not significant (p = .184 and p = .294 respectively).

Table 6. Predictor coefficients for linear regression analyses predicting FAS scores for participants with tumours in different localisations

	Unstandardized Coefficients		Standardized Coefficients		
	B	**Std. Error**	**β**	**t**	**Sig.**
(Constant)	7.568	.500		15.146	.000
Frontal	1.932	1.442	.136	1.339	.184
Left Parietal	-2.318	1.731	-.135	-1.339	.184
Left temporal	-1.425	1.349	-.108	-1.057	.294
Right Frontal	2.307	.841	.289	2.743	.007
Right Parietal	3.098	1.442	.218	2.148	.035

A multiple regression was calculated to predict semantic fluency based on localisation, with Left Frontal being the reference condition. The results highlight that the regression equation was not significant (F(5,79) .932, p=.465), with an R^2 of .056, an f^2 effect size of 0.059 and a power (1-β) of 0.342 for the effects of localisation. The coefficients are summarised in table 7.

Table 7. Predictor coefficients for linear regression analyses predicting ANT scores for participants with tumours in different localisations

	Unstandardized Coefficients		Standardized Coefficients		
	B	**Std. Error**	**β**	**t**	**Sig.**
(Constant)	8.167	.582		14.040	.000
Frontal	1.833	1.783	.115	1.028	.307
Left Parietal	.083	1.973	.005	.042	.966
Left Temporal	-.738	1.539	-.054	-.480	.633
Right Frontal	1.786	1.007	.206	1.772	.080
Right Parietal	.167	1.645	.011	.101	.920

False discovery rate control

Due to the multiple comparisons conducted throughout the individual variable linear regression analyses a correction was required to account for the potential false discovery rate. The Benjamini-Hochberg Procedure (Benjamini & Hochberg, 1995) was applied to the *P* values calculated for the analyses conducted with the FAS (see table 8) and ANT (see table 9).

Table 8. Benjamini-Hochberg outcomes for FAS analyses

Variable correlated with FAS	Original *P*-values	Benjamini-Hochberg *P*-values	Benjamini-Hochberg significance (0.1 error rate)
TOPF	0	0	significant
GNT	0	0	significant
Left Frontal	0	0	significant
Education	0.007	0.018	significant
Right Frontal	0.007	0.018	significant
Right Parietal	0.035	0.076	significant
HADS-D	0.052	0.097	significant
Frontal	0.184	0.26	not significant
Left Parietal	0.184	0.26	not significant
Gender	0.2	0.26	not significant
Left Temporal	0.294	0.347	not significant
Tumour type	0.514	0.557	not significant
HADS-A	0.89	0.89	not significant

After controlling for the error rate using the Benjamini-Hochberg Procedure (Benjamini & Hochberg, 1995) on the analyses conducted for the FAS the significance of the HADS-D correlation changed from not significant (at an α level of .05) to significant (at an error rate of 0.1). While most of the other variables had altered values, they all remained significant or non-significant in line with the significance outcome of the original value.

Table 9. Benjamini-Hochberg outcomes for ANT analyses

Variable correlated with ANT	Original *P*-values	Benjamini-Hochberg *P*-values	Benjamini-Hochberg significance (0.1 error rate)
GNT	0	0	significant
Left Frontal	0	0	significant
Education	0.067	0.16	not significant
HADS-D	0.074	0.16	not significant
Right Fontal	0.08	0.16	not significant
Frontal	0.307	0.512	not significant
HADS-A	0.498	0.711	not significant
Left Temporal	0.633	0.791	not significant
Right Parietal	0.92	0.966	not significant
Left Parietal	0.966	0.966	not significant

After controlling for the error rate using the Benjamini-Hochberg Procedure (Benjamini & Hochberg, 1995) on the analyses conducted for the ANT all variables remained significant or non-significant in line with the significance outcome of the original value.

Further analyses with phonemic fluency

Hierarchical regression analyses were performed to assess the value of associations between the predictor variables gender, education, tumour type, depression, semantic memory, and premorbid functioning on the relationship between localisation and phonemic fluency. Localisation (with Left Fontal as the reference category) was entered into the first stage of the analysis (block one) to allow for comparison of the effects of the other variables during each stage of the model. Localisation predicted 17.2% of the variance in phonemic fluency scores. The predictor variables (gender, education, tumour type, depression, semantic memory, and premorbid functioning) were added to the second stage of the analysis (block 2). Following the additions in block 2 the total variance explained by the model was 47%, F (6, 68) 6.394, p = 0.000. This means that the predictor variables (gender, education, tumour type, depression, semantic memory, and

premorbid functioning) explained an additional 29.9% of the variance in phonemic fluency scores after localisation had been accounted for. In model 2 there were statistically significant relationships between FAS and a number of the predictors added after localisation. Gender (β = .228, p = .030) and education (β =.192, p = .047) were statistically significant demographic predictors. Depression (β = -.200, p = .034) and GNT (β = .274, p = .012) were statistically significant psychometric/neuropsychological assessment predictors. The TOPF score variable approached significance (β = .197, p = .077). Table 10 summarises the predictor coefficients for this analysis.

Table 10. Predictor coefficients for hierarchical multiple regression analyses predicting FAS scores

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	7.718	.543		14.216	.000
	Frontal	1.082	1.610	.073	.672	.504
	Left Parietal	-2.468	1.780	-.150	-1.387	.170
	Left Temporal	-1.575	1.392	-.124	-1.132	.261
	Right Frontal	2.335	.949	.277	2.461	.016
	Right Parietal	2.949	1.487	.217	1.983	.051
2	(Constant)	-.845	1.917		-.441	.661
	Frontal	.817	1.381	.055	.592	.556
	Left Parietal	-1.067	1.559	-.065	-.684	.496
	Left Temporal	.267	1.308	.021	.204	.839
	Right Frontal	2.123	.803	.252	2.642	.010
	Right Parietal	3.721	1.294	.274	2.877	.005
	TOPF	.055	.031	.197	1.796	.077
	GNT	.192	.074	.274	2.576	.012
	Depressed	-1.473	.679	-.200	-2.169	.034
	Gender	1.636	.740	.228	2.210	.030
	Education	1.518	.749	.192	2.027	.047
	Tumour type	.870	.909	.099	.957	.342

Post hoc power analysis of phonemic fluency hierarchical regression

G*Power (Faul et al., 2009) was used to calculate a post hoc analysis for a multiple regression with eleven predictors, an alpha value of .05, a sample size of 80 and an f^2effect size of 0.887 as calculated using the R_2 value provided in the analysis results (0.47). This calculation indicated that

the power achieved in this analysis was 0.99, which is a very high power score, indicating that the likelihood of the results being due to a type 2 error are very low.

Further analyses with semantic fluency

Hierarchical regression analyses were performed to assess the value of associations between the predictor variables education, depression, and semantic memory on the relationship between localisation (with Left Frontal as the reference condition) and semantic fluency. Localisation was entered into the first stage of the analysis (block one) to allow for comparison of the effects of the other variables during each stage of the model. Localisation did not predict variance in semantic fluency scores (F(5,79) .932, p=.465), with an R^2 of .056. The predictor variables (education, depression, and semantic memory) were added to the second stage of the analysis (block 2). Following the additions in block 2 the total variance explained by the model was 24%, F (3, 76) 6.158, p = 0.001. This means that the predictor variables (education, depression, and semantic memory) explained an additional 18.5% of the variance in semantic fluency scores after localisation had been accounted for. In model 2 there was a statistically significant relationship between ANT and GNT (β = .360, p = .001). The association between ANT and depression approached significance (β = -.176, p = .086). Table 11 summarises the predictor coefficients for this analysis.

Table 11. Predictor coefficients for hierarchical multiple regression analyses predicting ANT scores

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	8.167	.582		14.040	.000
	Frontal	1.833	1.783	.115	1.028	.307
	Left Parietal	.083	1.973	.005	.042	.966
	Left Temporal	-.738	1.539	-.054	-.480	.633
	Right Frontal	1.786	1.007	.206	1.772	.080
	Right Parietal	.167	1.645	.011	.101	.920
2	(Constant)	2.414	1.767		1.366	.176
	Frontal	.912	1.649	.057	.553	.582
	Left Parietal	1.059	1.836	.060	.577	.566
	Left Temporal	.828	1.465	.061	.565	.574
	Right Frontal	1.475	.928	.170	1.589	.116
	Right Parietal	.312	1.513	.021	.207	.837
	GNT	.269	.079	.360	3.397	.001
	Depressed	-1.366	.784	-.176	-1.742	.086
	Education	1.349	.873	.160	1.545	.126

Post hoc power analysis of semantic fluency hierarchical regression

G*Power (Faul et al., 2009) was used to calculate a post hoc analysis for a multiple regression with eleven predictors, an alpha value of .05, a sample size of 85 and an f^2effect size of 0.316 as calculated using the R_2 value provided in the analysis results (0.240). This calculation indicated that the power achieved in this analysis was 0.994, which is a very high power score, indicating that the likelihood of the results being due to a type 2 error is very low.

Summary of results

An increase in phonemic fluency was significantly correlated with being educated (F(1,115) 7.639 p=.007; R^2 = .066), an increase in semantic memory (F(1,115)13.702, p=.000; R^2 = .106), and an increase in premorbid functioning (F(1,108)14.106, p=.000; R^2 = .109). Phonemic fluency was significantly correlated with localisation (F(5,85)3.552, p=.006; R^2 = .173). More specifically, an increase in phonemic fluency was significantly associated with tumours in the right frontal and right parietal lobes (p = .007 and p = .035 respectively) in comparison to the left frontal lobe. Phonemic fluency was not significantly correlated with depression (F(1,115) 3.857, p=.052; R^2 = .032) in the original regression analysis, however when the Benjamini-Hochberg Procedure was applied to account for the false discovery rate phonemic fluency was significantly correlated with depression (0.097; using an error rate of 0.1).

An increase in semantic fluency was correlated with an increase in semantic memory (F(1,115) 20.523, p=.000; R^2 = .151).

Phonemic fluency was not significantly correlated with gender (F(1,115) 1.664 p=.200; R^2 = .014), tumour type (F(1,102) .428, p=.514; R^2 = .004), or anxiety (F(1,115) .019, p=.890; R^2 = .000). Neither was phonemic fluency significantly correlated with tumours situated in the frontal lobe (p = .184), left parietal lobe (p = .184), or the left temporal lobe (p = .294) in comparison to the left frontal lobe.

Semantic fluency was not correlated with education (F(1,108) 3.422 p=.067; R^2 = .031), or depression (F(1,115) 3.249, p=.074; R^2 = .027), however, there were trends indicating that an increase in semantic fluency was associated with being educated and a decrease in depression scores. Semantic fluency was not correlated with anxiety (F(1,115) .461, p=.498; R^2 = .004) or localisation (F(5,79) .932, p=.465; R^2 = .056).

Discussion

This chapter summarises the above results and discusses the hypotheses tested, evaluating the strengths and limitations of the study in relation to the current literature. The clinical utility of the results will be

considered and suggestions for future studies provided. This section will begin with a summary of the findings and then discuss the findings for each area of interest (demographic factors, cognitive factors, tumour factors, mood factors and localisation) in more detail. Following the discussion about the outcomes this section will go on to consider the strengths and weaknesses of this study, concluding with reflections on the clinical implications of these outcomes and suggestions for future research.

Summary of findings

Poorer performance in phonemic fluency was significantly correlated with not completing educational exams, higher levels of depression and poorer performance in semantic memory and premorbid functioning. Phonemic fluency was also significantly correlated with localisation. More specifically, a decrease in phonemic fluency was significantly associated with tumours in the left frontal lobe in comparison to right frontal and right parietal lobes which were associated with an increase in performance in this function. Poorer performance in semantic fluency was correlated with poorer performance in semantic memory.

Phonemic fluency was not significantly correlated with gender, tumour type, or anxiety. Neither was phonemic fluency significantly correlated with tumours situated in the frontal lobe, left parietal lobe, or the left temporal lobe, in comparison to the left frontal lobe. Semantic fluency was not correlated with anxiety or localisation. Neither was semantic fluency correlated with education or depression, although, there were trends indicating that an increase in semantic fluency performance was associated with completing educational exams.

The outcomes from the hierarchical multiple regressions indicated that localisation, gender, education, tumour type, depression, semantic memory, and premorbid functioning, when combined, can predict phonemic fluency variance. Localisation, semantic memory, depression and education do not predict semantic fluency, as within this model the only significant relationship was between semantic memory and semantic fluency (which mimics the outcomes of the simple linear analyses conducted for semantic fluency).

Demographic factors and verbal fluency

It was hypothesised that higher levels of education would have a positive association with both phonemic and semantic fluency. The findings indicate that there was a significantly positive association between education and phonemic fluency, but not for education and semantic fluency. There was a trend towards having an education being positively associated with semantic fluency, but unfortunately the analysis lacked both power and effect, meaning that more research would be warranted in this area. While there was a lack of significant results for semantic fluency and education, the trends in these results did point towards a positive relationship between being educated and an increase in semantic fluency. This combined with the significant results for phonemic fluency support a number of other papers who were able to conduct analyses with higher levels of power to find positive relationships between levels of education and an increase in performance of semantic and phonemic fluency, (e.g. Gladsjo et al., 1999 and Loonstra et al., 2001). More specifically, the study by Gladsjo et al., (1991) found these significant results with a non-clinical population of 768 adults, using number of years in education as the measurement for this variable, and the same measures for phonemic and semantic fluency used in this study (FAS and ANT). The analysis they conducted was therefore likely to have considerably more power to detect an effect and the use of a continuous variable for education would have likely yielded richer results. It could be assumed that if this study were able to be replicated with an increased number of participants (and perhaps measuring education in a more meaningful way) it may be possible to detect significant results for associations between semantic fluency and education.

It was also hypothesised that being female would have a positive association with phonemic fluency based on the meta-analysis conducted by Loonstra et al., (2001). Conversely, the results for the analysis of phonemic fluency and gender in this study were not significant, in line with the outcomes of a number of earlier studies looking at this association, such as Riva, Nichelli, & Devoti, (2000) and Tombaugh et al., (1999). However, the reason the hypothesis for this study was focused on the results found by Loonstra et al., (2001) was because they used these initial studies within

their meta-analysis to find significant correlations when combining the papers (to increase the power of the analysis). Despite our hope of having an increased power in this study's analysis, for this association there was actually low power in the outcome (0.453). It is therefore possible that further research in this area utilising a higher powered analysis may bring to light detectable significant correlations. This idea is further supported by the outcomes from the hierarchical multiple linear regression which demonstrated a significant relationship between gender and phonemic fluency when localisation effects had been accounted for and the other variables had been entered alongside gender to heighten the power of the analysis and absorb some of the residual variance of the phonemic fluency scores.

Cognitive factors and verbal fluency

It was hypothesised that higher scores in semantic memory would be positively associated with both phonemic and semantic fluency. The results significantly support both of these hypotheses and the findings previously documented by Henry, Crawford, & Phillips, (2004) and Riva et al., (2000). This is a useful addition to the evidence base as it is the first study to look more specifically at correlations with both types of verbal fluency and semantic memory using the GNT as opposed to the BNT, which allows some generalisation of the relationship between semantic memory as a concept as opposed to a relationship with one specific test.

It was also hypothesised that higher scores in premorbid functioning would be positively associated with phonemic fluency. This hypothesis was supported by significant results. Previous studies showing correlations of these skills have used more dated tests of premorbid functioning, such as the NART (Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2004; Crawford et al., 1992; Ross, 2003) and the WIAT-II (Davis et al., 2017). The results from this study are therefore particularly important, as the TOPF is currently considered a core component in most neurocognitive batteries, whereas the NART and WIAT-II are comparatively outdated.

Tumour factors and verbal fluency

It was hypothesised that there would be a difference in association between phonemic fluency and tumour type. The results of this study do not support this hypothesis. It is difficult to compare this outcome to the results from the only related study available that included the effects of tumour type and a measure of phonemic fluency functioning (Hahn et al., 2003). This is because the study by Hahn et al., (2003) did not discuss the specific types of tumour assessed against the main tumour group (glioblastoma multiforme). Additionally, glioblastoma multiforme was not a tumour type this study was able to focus on (as this study did not have enough data to breakdown the variables into groups outside of glioma and meningioma). The results of this study are therefore more in line with the results found in the few studies looking more generally at cognitive functioning and tumour type, where no significant associations were found (Hoffermann et al., 2017; Hom & Reitan, 1984; Kayl & Meyers, 2003; Scheibel et al., 1996). It is also worth noting that the power within this analysis of tumour types and fluency was very low, meaning that the chances for a type 2 error was quite high and so further research in this area would be warranted. There were no hypotheses for tumour type related to semantic fluency.

It is important to note that, due to a lack of data on tumour size this study was unable to account for this variable in this analysis. As it has been highlighted that increased tumour size is likely to have a greater association with performance deficits than the type of tumour (Kayl & Meyers, 2003), it is possible that this unmeasured variable could have moderated the effects found for type of tumour in this study.

Mood factors and verbal fluency

It was hypothesised that increased levels of depression would be associated with poorer performances in both phonemic and semantic fluency, but that anxiety would not affect either form of verbal fluency. Phonemic fluency showed a significant negative association with depression (once the false discovery rate was controlled for), which was further supported by the significant association found between these variables when they were entered into the hierarchical multiple regression.

There was not a significant relationship between semantic fluency and depression. The discrepancy in this result is surprising, as the outcome of this relationship is in opposition to the majority of outcomes found to date between these two variables (Brown et al., 1994; Christensen et al., 1997; Fossati et al., 1999; Henry & Crawford, 2005; Trichard et al., 1995; Yochim et al., 2013). This is particularly surprising in light of the result being accompanied by a strong effect size and a high level of power, indicating that the lack of significance was less likely to be due to a type 2 error. It is therefore important to consider the wider influences to this outcome. One factor to reflect on would be that some assessment tools are significantly more sensitive when used with brain tumour patients than others, meaning that variability below a certain baseline within some tests may not be detected (Hom & Reitan, 1984; Archibald, Lunn & Ruttan et al., 1994). This difficulty is partly in relation to the population norms used to detect clinical difficulties and is most likely to create issues if used in relation to a 'cut-off' of clinical caseness/neurological deficit. Similarly, it is advisable to use population specific norms to measure outcomes in clinical populations. A specific cut-off was not used for the ANT data, but while the test was not specifically normed to the brain tumour population it was designed in the first instance as a means of measuring neurological deficit for a range of neurological difficulties which may impact verbal communication skills.

The HADS was used to measure depression and the norms for this test were not derived from a population of individuals with brain tumour. However, this test was designed specifically for populations of individuals with health conditions (including cancer) with the aim of accounting for physical/somatosensory symptoms which can be confused/overlap with symptoms attributed to mood effects. This measure had therefore been chosen as the best option for capturing mood effects in this population. A similar consideration is that converting a continuous variable into a dichotomous variable in this way (caseness versus no caseness) can make the results more clinically meaningful. However, it is also worth noting that this approach to manipulating the data will have reduced the richness of the data available on depression, possibly reducing the effect size. It would be worth following these contradictory results up with a study using a richer

array of mood data designed more specifically for the brain tumour population.

Other factors that may have had an influence on these controversial outcomes could include effects specific to this sample of individuals with brain tumour. One key factor to consider is the distribution of scores for the measures used (ANT and the HADS-D). During the assessment of normality the HADS-D stood out as a variable that required further consideration. The frequency division between the caseness criteria (depressed v not depressed) included only 43 (35%) participants having scores meeting the criteria for depression. As can be seen in Figure 2, when assessing the distribution of the HADS-D it stood out from the other variables in that it was slightly positively skewed, with a leptokurtic tail particularly to the left of the graph. While a normal distribution would still expect to see fewer data points in the extremities of the bell curve, this sample had considerably fewer than would be expected in an ideal distribution and there was a heavier weighting of participants with lower depression scores. More specifically, when the frequency distribution of the raw scores are considered in more detail (see Appendix D) it becomes apparent that, from the 43 (35%) participants in the depressed group, the sample is heavily weighted in the lower scores (between 8 and 11) with only 13 people (7.3%) scoring between 12 and 20 (indicating higher levels of depression). It is suggested by the author of the HADS that moderate cases of depression (or anxiety) should fall between 11 and 15, and that severe cases should fall above this range (Zigmond & Snaith, 1983). While our cut-off criteria were chosen to be more inclusive to a range of levels of depression, it makes sense that stronger effects of depression would be found in a sample of individuals with higher levels of depression (e.g. in the ‘severe’ range/16+). There were only 2 individuals (1.6%) in this current sample who met this ‘severe’ criteria, and as described above, not many participants fell in the moderate range either. It is therefore possible that the lower levels of depression among this study’s population sample reduced the effects available to detect in this analysis. A similar design using a sample including a more balanced frequency of participants with higher levels of depression could possibly bring to light significant relationships between semantic fluency and depression.

Anxiety was investigated as an exploratory variable. The results indicate that it is not associated with either form of verbal fluency. This is in line with the limited range of previous studies looking into associations with anxiety and verbal fluency (Airaksinen et al., 2005; Talacchi et al., 2011; Yochim et al., 2013) and so could be assumed to be an accurate representation of the relationship. However, as has been discussed above, some variables have shown non-significant associations in individual studies, but then highlighted significant associations when combined in a meta-analysis, producing greater power. As the results for anxiety and both types of fluency in this study lacked power, the presence of a type 2 error is possible, meaning these findings may be similarly worth following up with a meta-analysis and/or a study with higher levels of power.

Localisation of phonemic fluency

Based on a relatively conclusive range of evidence (Metternich et al., 2014; Robinson et al., 2012; Szatkowska et al., 2000; Troyer et al., 1997), it was hypothesised that poorer performance in phonemic fluency would be more strongly associated with participants who had tumours in the left frontal lobe than in other areas. More specifically it was hypothesised that tumours in the left dorsolateral prefrontal cortex would correlate with poorer phonemic fluency performance (Szatkowska et al., 2000; Troyer et al., 1997). Unfortunately, at the phase of data coding it became apparent that the information in the data set did not allow us to focus on this specific area and so inferences could only be drawn at the wider regional area of the left frontal lobe, reducing the specificity of the localisation effects in this study.

The results indicated that tumour location was a significant predictor for variance in phonemic fluency scores and that the left frontal localisation was strongly associated with variance in phonemic fluency. This result is supported by a medium effect size and a high power value, indicating that the results are unlikely to be due to a type 2 error. The results also indicate a trend in higher scores in phonemic fluency being associated with the frontal, right frontal and right parietal areas, indicating that these areas are not involved in phonemic fluency performance in comparison to the left frontal area. These results are supportive of a general lateralisation effect where

phonemic fluency functioning is related to the left side of the brain as opposed to the right. These findings are also in line with this study's hypothesis. The association between phonemic fluency and frontal lobe tumours was not significant. The association between phonemic fluency and right parietal tumours only approached significance (although very closely at .051), however, once the effects of the additional predictor variables were accounted for in model 2, the effects for the right parietal tumour effects became significant ($p = .005$). People with right frontal tumours were significantly associated with higher phonemic fluency scores in comparison to people with left frontal tumours in both model 1 and model 2. People with tumours in the left parietal and left temporal areas were not significantly associated with variance in the FAS scores in comparison to the left frontal lobe in either model. They both followed a trend of participants scoring lower on phonemic fluency if they had tumours in this area in comparison to those that had tumours in the left frontal area.

When taking into account the localisations which were unable to demonstrate significant associations, this analysis provides results that indicate that participants with tumours in the left frontal lobe will on average score significantly lower in phonemic fluency than participants who have tumours in the localisation areas investigated in this study on the right cerebral hemisphere (right frontal and right parietal). This is therefore supportive of both a left sided lateralisation effect and, in line with the assumptions made by modularity models of cognition (Shallice, 1988) infers that the left frontal lobe is involved in phonemic fluency functioning. There is a trend indicating lower phonemic fluency scores in comparison to the left frontal lobe for other areas on the left cerebral hemisphere (left parietal and left temporal), however, these results were not significant.

It is important when interpreting these results to consider the impact of sample size in each of the localisation categories. While the regression calculation held a high level of power as a whole, this power isn't directly applicable to each individual localisation level due to there being a very uneven distribution of participants across each category. The areas where significant results were not found all had seven or less participant data sets assigned to them. In the areas where there were more data (e.g. left frontal

and right frontal) significant associations were more likely to be found. The results from areas where there were a very small number of participants are therefore less replicable and representative of the population. This naturally brings to question the reliability of these results when interpreted as a whole 'localisation effect', because there are clearly differences among the localisation groups.

Localisation of semantic fluency

It was hypothesised that poorer performance in semantic fluency would be associated with patients who have brain tumours in both the left frontal lobe, the right frontal lobe or the left temporal lobe. The results show that there were no significant effects of localisation on the variance of semantic fluency scores. This therefore means that the results found for phonemic fluency cannot be further validated with a dissociation model (Teuber, 1955) due to the comparison to another subcomponent of verbal fluency localisation not being available (however, the more generic lateralisation effects and modularity based lesion-behaviour mapping reasoning focusing on the left frontal lobe are still valid).

This result for semantic fluency was surprising, particularly in light of the significant results found for phonemic fluency from the same data set. However, when power is low (e.g. approximately .50) an inconsistent pattern of results may be seen among research in that area, where some results are significant and others not (Kazdin & Bass, 1989; Rossi, 1982, 1986, 1990). The power for this calculation was small (0.342), indicating that differences that may have been present in this sample were unlikely to be detected.

It could also be hypothesised that due to semantic fluency requiring less input from higher order executive functions (McCloskey & Perkins, 2012), and therefore drawing from a less diverse range of functions, the neural correlates of this skill are more precise and so the broad localisation categories used within this study were not able to accurately detect the more precise areas relevant to that skill. However, this finding is inconsistent with previous studies in this area which point to semantic fluency being correlated with quite a broad range of localisations (Crowe, 1992; Metternich et al., 2014; Robinson et al., 2012; Szatkowska et al., 2000; Troyer et al., 1998).

Along the same lines it is worth noting that these studies were able to focus their neural correlate search on more specific regions within the broader range of areas investigated, such as the ‘left dorsolateral and/or lenticular striate frontal regions’ (Loonstra et al., 2001) in comparison to the broader ‘left frontal lobe’ category used in the present study. It would make sense that this specificity would reduce the likelihood of dilution of results in patients who have lesions in the left frontal lobe (to use this current example) but not more specifically in the left dorsolateral and/or lenticular striate frontal regions.

There are also a range of limitations to the design and analysis used in this study which may have influenced this study’s ability to find significant results in some areas, discussed in more detail below.

Predicting phonemic fluency

The hierarchical multiple regression used to analyse the associations between gender, education, tumour type, depression, semantic memory, and premorbid functioning on the relationship between localisation and phonemic fluency demonstrated a good model fit (explaining 47% of the variance in total), with localisation predicting 17.2% of the variance in phonemic fluency scores; and gender, education, tumour type, depression, semantic memory, and premorbid functioning explaining an additional 29.9% of the variance in phonemic fluency scores after localisation had been accounted for. However, within this model tumour type was not a significant predictor. It would have been helpful to have completed a further analysis of the strength of this model without the non-significant predictor (tumour type) included, so this would be a good point to revisit in future research.

Predicting semantic fluency

The inclusion of localisation, semantic memory, depression and education as predictor variables for semantic fluency in the hierarchical multiple regression highlighted that this model predicted only 18.5% of the variance in semantic fluency scores. The only significant relationship within this model was between semantic memory and semantic fluency. This unsurprisingly mimics the outcomes of the simple linear analyses conducted for semantic fluency.

Strengths and weaknesses of the study

Alongside the factors discussed above critiquing more specific elements of the study in relation to the outcomes, this study will be evaluated in light of four criteria, test administration and standardisation, recruitment and participation, study design and statistical analysis. The study discussion will then be summarised and concluded with a focus on the clinical utility of the results and recommendations for future research.

Test administration and standardisation

Standardisation (in relation to the administration of the assessment) refers to the likelihood of variations in how the test is administered to each participant. Changes in administration such as frequency of prompting, accuracy in timing, and more subtle aspects such as intonation in the delivery of instructions can have an effect on the patient's performance. All the tests used in this study were administered by highly trained clinicians which reduces the chance of variation in test delivery and supports the likelihood that administration was conducted appropriately. Along with the skills of the administrator, the guidance provided by the test developer can also influence the likelihood of standardisation of administration. The assessment tools used varied in the level of instruction provided with the test equipment to guide both administration and scoring of the assessment. The TOPF for example is a test with a clear instruction manual, clear instructions on how to respond to participants seeking further guidance, and significant support in scoring and interpreting the outcomes (such as a cd with an audio recording of the accepted phonemic expressions to guide scoring). This leaves limited room for the influence of subjective bias in delivery and interpretation. The HADS on the other hand is a measure which is naturally subjective in interpretation by the respondent (relying on a Likert scale of experiences), which can often lead to the participant feeling unsure about how to answer and seeking further guidance from the administrator. Further guidance instructions are minimal, leaving a wider range of decisions on how to respond to the participant and deliver the assessment up to the assessor. Therefore, it is important to consider that while the administrators were highly trained, some of the tests used (particularly the mood measure)

require a level of caution in interpretation of the outcomes due to the subjective nature of the responses. This is not unusual in tests of mood, as the construct of mood in itself is a subjective state.

Along similar lines, one of the key difficulties in the evidence base to date is the vast range of tests available claiming to measure the same symptoms/skills, which are inconsistently used among researchers (van Loon et al., 2015), and to some degree clinicians. This lack of consensus created some difficulty in selecting variables in the first place, based on previous research. The clearest example of this was when considering the test of semantic memory, as the data in this study was based on the use of the GNT, however, the (very few) studies used in previous research looking at the relationships between semantic memory and verbal fluency used the BNT. While these tests are very similar, it is difficult to draw reliable and valid conclusions on the effects found across two different tests in this fashion. Equally, these results require similar caution when being used within the clinical population to consider the predictions of verbal fluency in patients who have competed tests of semantic memory other than the GNT. This understandably limits the clinical utility of this work and further research comparing semantic fluency (or any of the other cognitive skills reported in this study) among different test outcomes would enhance this deficit.

Recruitment and participation

The participant data was provided solely from the neuro-oncology department within the Medical Psychology Team at James Cook University Hospital (under South Tees Hospitals NHS Foundation Trust). Due to the data being provided by the service consisting of information routinely collected as part of their service evaluation data, patient consent specific to this study was not required. This means that there was no bias created by participant interest in the topic area, increasing the representativeness of the study sample. However, due to the data coming from one service, the representativeness of the population only expands to neuro-oncology patients within the areas of County Durham, Teesside, Darlington, and North Yorkshire, between the ages of 22 and 90, and more specifically with gliomas or meningiomas. It would be fair to assume the geographic location

of the participants was generalisable to rest of the UK population, however, as more precise population factors were not measured (such as ethnicity, religion, sexuality or occupation) this cannot be explicitly stated.

Study design

This research project is novel in the literature focusing on neural correlates of verbal fluency due to its design being inclusive of a wider range of factors (i.e. mood effects, tumour effects, cognitive measures, and demographics) than similar studies preceding it. This means that it has been able to more reliably and inclusively explore the associations between verbal fluency performance and localisation in patients with brain tumour. This study has also played a role in developing a very sparse evidence base around factors which may affect this important and clinically instrumental skill. More specifically the novelty and utility of this study was further enhanced by the inclusion of a test of premorbid functioning (TOPF), semantic memory (GNT) and a measure of depression which was designed specifically to be more reliable and valid for populations with health conditions.

This study used a cross-sectional design meaning all the data was collected in one respective time point. Similarly this study is limited to the use of ‘attribute variables’ which limits the types of conclusion and inferences which can be drawn from this study (Tupper & Rosenblood, 1984). Due to these design factors causality cannot be determined and fluctuations in results over time could not be investigated. A study with a longitudinal design and ‘active’ variables would enhance our understanding of the findings in this project (Tupper & Rosenblood, 1984).

The variables list was chosen based on indications of effect (or a lack of consistency in effect) from the evidence base on and around the topics of interest. This is a standard scientific approach to take when designing studies, particularly those focused on a wide range of potential influential variables. However, it does limit the investigations to an already narrowed range, excluding investigation into a wider range of potentially influential effects which could have improved the predictive power of the proposed model. Of similar relevance, due to the population of interest being ‘self-

selected' based on a commonality of certain attributes (having a brain tumour), random assignment of variables within the study is not an option. Due to this any differences seen between variables of interest cannot be solely attributed to that variable as the differences could have occurred due to a different extraneous variable confounded with the variable of interest.

Another design difficulty related to the lack of assignment control in this approach is the occurrence of unequal numbers of participants in different categories/cells, for example, within localisation, 37.6% of participants had tumours in the left frontal area and 4.4% of participants had tumours in the left parietal area. This means that it is harder to detect the effects within the categories with lower numbers of participants (e.g. left parietal), and that the power results measured from the equation as a whole (e.g. the effects of localisation and fluency) becomes less applicable. This has been discussed in more detail in the results section.

One specific weakness of the study is that it did not account for age effects. The evidence base has highlighted that there are clear links between age and verbal fluency performance, with phonemic and semantic fluency both tending to improve during childhood, peaking when an individual reaches their thirties, and declining in old age (Delis et al., 2001a; Tombaugh et al., 1999). It was decided when designing the study that including the age of the participants would be less clinically meaningful as it doesn't take into account the fact that age effects would become nullified at the point verbal fluency is impacted by the presence of the tumour. This study did not have information on the date of diagnosis, which may have given a closer insight into these effects. However, even if this study had been able to acquire this information, it still would not necessarily be representing the date the tumour itself was formed, or the date the tumour started to impact on functioning. This study therefore was designed in the most clinically relevant way to measure the effects most likely to be relevant to verbal fluency performance, meaning that age effects were not part of the factors measured.

During the design phase it was felt important to include the data for tumours labelled as 'frontal' in the data set (meaning they could be

positioned in either frontal lobe, but data wasn't available to specify which). This decision was made due to the influence these tumours may have had if both left and right frontal tumours were associated with one of the forms of fluency, and for the purpose of retaining as much data as possible. However, retrospectively this can be considered as a design flaw. It makes sense in this analysis that the results for 'frontal' were weak in effect due to the fact that the frontal tumours spanned both the left and the right lobes, and may well have impacted either area, or both areas simultaneously. It was not possible to define these regions from the data provided by the service. Due to this, in the event where only the left frontal lobe, or only the right frontal lobe were implicated in fluency function any effects created by tumours impacting the left frontal area (within the 'frontal' group) were possibly diluted by data included that impacted only the right frontal area (again, within the 'frontal' group), leading to a lack of significance, and meaning, behind the outcomes for this area. Given the results from this study and results from previous studies, this was more likely to be the case with phonemic fluency as it was not associated with the right frontal lobe, but strongly associated with the left frontal lobe.

There are methodological drawbacks to using lesion-behaviour mapping approaches. Some of these common drawbacks were overcome by the design of this study, for example many studies only focus on participants with deficits in the function of interest, not including participants who perform well in the function (Rorden & Karnath, 2004). Despite this inferences are still often made about the neural areas which are not impaired functioning adequately, which is not a reliable inference to make (Farah, 1994). This study sought to include participants with a range of performance levels in the cognitions measured and included localisations covering large regions of the cortex, including areas which were not of primary focus. This study therefore demonstrate methodological strength in this remit.

However, there are still some limitations to this study that were unavoidable in relation to the underlying theories used in lesion-behaviour mapping. Of particular relevance is the assumption of modularity (Shallice, 1988) in what is a form of executive function. Executive functions are commonly considered higher order due to their nature of integrating a range

of skills (such as memory and language) while promoting cognitive flexibility and problem solving (Della Sala et al., 1998). It would make sense that skills of this nature are ever more likely to involve functions carried out in a distributed manner, with larger regions of the brain working together in a more fluid/plastic state (Farah, 1994). With this reasoning in mind, incorporating methods that allow the monitoring of processes over time (including aspects of feedback between neural areas) would be highly beneficial. An example of this would be to use scanning methods such as fMRI to further support the outcomes found in this study. Unfortunately this approach was beyond the remit of this piece of research.

Using patients with brain tumour also has implications for the outcomes as there are often effects of neural pressure caused by oedema that can impact functioning more broadly around the tumour location. Again using method relying on technologies such as fMRI scanning would have allowed investigations of neural-behavioural associations in neurologically healthy individuals which would complement the results found in this lesion-behaviour mapping study.

Statistical analysis

Data from 123 participants were initially included in the study, with 80 participants being included within the final hierarchical analyses looking more inclusively at all the relevant variables. This is a sample size which was considered to provide excellent power (up to 0.99) for the multiple regression analyses conducted. As discussed in the literature review, due to the rarity of the neurological conditions of interest (in localisation studies more generally, and studies with patients with brain tumour more specifically), very few studies have been conducted which match or exceed this level of power, with many not even being able to conduct statistical analyses on the range of variables intended due to their small sample size (Goldstein et al., 2004). This ensures that the results found are more reliable and less likely to be indicative of a type 2 error, further increasing the utility of this study both in terms of clinical application and in terms of enhancing a sparse evidence base that has been difficult to draw reliable conclusions from in the past.

Statistical errors are highly common within research studies, with reviews suggesting that around 50% of published articles have at least one error (Curran-Everett, 2004). The analytical work within this study has been thoroughly and competently approached with significant support from qualified statisticians. Additionally, statistical software was used to run the statistical calculations, further reducing the risk of human error. It is therefore hoped that the results discovered are reliable and accurate, however, as stated above, there is always a risk of human error in complex work with a large database.

It is advised within neuropsychological research to convert all raw score outcomes to standardised scores, such as scaled scores or z scores, so that they can be more meaningfully compared within the analysis (Crawford, 2003). Where possible scaled scored were used. This meant that the FAS and ANT test scores were converted into scaled scores before the analysis. Unfortunately, scaled scores were not available for the GNT or the HADS. However, scaled scores will hold the same distribution shape (as would a z score) as the set of raw scores, as long as the variable is normally distributed. As all the variables used in this study were all relatively normally distributed this can be considered as less of an issue.

Clinical implications

Verbal fluency tests are very useful in measuring, monitoring and highlighting deficits in verbal communication difficulties and components of executive functioning following brain injury/degeneration (Strauss et al., 2006). More specifically, verbal fluency outcomes play an important role in the diagnosis of a number of conditions within the clinical population, such as attention deficit/hyperactivity disorder (Andreou & Trott, 2013), Alzheimer's disease (Mathuranath et al., 2010; Monsch et al., 1992; Zhao et al., 2013), and Parkinson's disease (Pettit et al., 2013). Verbal fluency tests therefore play a highly instrumental role in neuropsychological assessment and diagnosis. This means that advancing the knowledge base in this area is important to ensure the provision of accurate and reliable neuropsychological assessment and care of patients.

Prior to this study there was a notable lack of research in the performance of patients with brain tumour (particularly pre-surgery) in measures of phonemic and semantic fluency, with the few that were available focusing on a wider range of neurocognitive impairments, as opposed to focusing more specifically on verbal fluency outcomes (Hoffermann et al., 2017; Klein et al., 2001; Miotto et al., 2011; Påhlson, Ek, Ahlström, & Smits, 2003; Talacchi et al., 2011; Tucha, Smely, & Lange, 2001; Tucha et al., 2003). As a result there was little conclusive evidence about which factors may influence verbal fluency outcomes, most considerably in relation to semantic fluency (Bird et al., 2004; Davis et al., 2017; Noll et al., 2014). This is the first study to date which has investigated the interactions between a comprehensive range of demographic, cognitive, tumour and mood factors with verbal fluency outcomes in patients with brain tumour.

These clinically meaningful results have increased some clarification of the contradictions in the research base to date. It is also hoped that the results will broaden clinicians' understanding of the impact of these factors on verbal fluency, which will support them in making predictions about expected performance and tailor interventions accordingly. This study strengthens the concept that phonemic fluency is correlated with being educated, an increase in semantic memory, and an increase in premorbid functioning. Phonemic fluency was also significantly correlated with localisation. More specifically, an increase in phonemic fluency is associated with tumours in the right frontal and right parietal lobes in comparison to the left frontal lobe. This study also supports an association between semantic fluency with semantic memory. Knowing the influences created by these important factors allows clinicians to be more considerate of variations in performance of patients with brain tumour who also align with these associative factors. This further enhances the accurate interpretation of neurocognitive assessment and diagnostic work and hence the planning of appropriate care in patients with brain tumour. Further research in this area, particularly with a focus on longitudinal data collection and more precise localisation mapping may further enhance the findings in this study. More specifically the variables which were unable to show significance possibly

due to low power and effect size, as opposed to a clear non-significant results with an adequate power outcome should be further investigated using studies with more rigorous methodological approaches and enhanced power through increased sample size and inclusion of factors this study was unable to include as planned (such as tumour size).

Summary of further research

Phonemic fluency and gender showed a non-significant correlation, however, other papers finding non-significant correlations have been combined in a meta-analysis to show significant positive associations between these variables. This indicates that greater power could still yield significant associations if there is enough power to detect an effect.

There was also a lack of significant results for semantic fluency and depression, which were interestingly supported by a reasonably high level of power, inferring the likelihood of a type 2 error was low and therefore the results reliable. These results have opposing outcomes to other studies in this area and it is hard to explain this result, given the information this study holds. It would be interesting to complete a similar study using continuous data for depression instead of taking a caseness v non-caseness approach and see how these results compare to those found in the studies showing relationships between these variables.

There was a lack of significant results for analyses looking at anxiety and each form of fluency. These results support the limited number of previous studies analysing similar variables (Airaksinen et al., 2005; Talacchi et al., 2011; Yochim et al., 2013) and so could be assumed to be an accurate representation of the relationship. However, as has been discussed above, some variables have shown non-significant associations in individual studies, but then highlighted significant associations when combined in a meta-analysis. As the results for both types of fluency in this study lacked power, indicating the possible presence of a type 2 error, these results may be similarly worth following up with a meta-analysis and/or a study with higher levels of power.

This study had aimed to look in more detail at tumour factors, including size and a greater range of tumour types than was achieved. Due

to the need to reduce the number of variables in the analysis to attempt to maintain some power this study was only able to look for results between glioma and meningioma, which were insignificant, but which also lacked power. This is unfortunate as there is such a sparsity of research in the area of tumour type and verbal fluency that being able to fill this gap in the evidence base could have been very valuable. Additionally there was an unexpected lack of data for tumour size which did not pass the MCAR test of distribution of missing data and so needed to be dropped from the analysis. Previous research has indicated that an increase in tumour size is likely to have a greater association with performance deficits (Kayl & Meyers, 2003). Further research utilising similar methods to this study with a greater number of participants in both these areas would be beneficial to filling these gaps in the evidence base and further informing clinical practice.

While there were some significant results for localisation effects in phonemic fluency they needed to be interpreted with caution due to the very variable distribution of data among the localisation categories (meaning a number of the localisations had very low participant numbers). The areas where significant results were not found all had seven or less participant data sets assigned to them in the analysis of localisation of phonemic fluency. This naturally brings to question the reliability of these results when interpreted as a whole ‘localisation effect’ as there is clearly differences among the localisation groups in how replicable and representative the outcomes in the groups with a small sample size are. Further research in this area where it is possible to collect a more even distribution of data among the localisation areas of interest would help clarify the outcomes found in this study. More importantly, this study was unable to analyse the more specific localisations of interest (e.g. left dorsolateral frontal lobe) due to this data not being available from the service. Being able to focus an analysis to this level of specificity would be likely to yield more reliable and clinically meaningful results because the broader the area considered, the greater the likelihood of inclusion of data that is not related to the neural areas relevant to the skills being assessed. Similarly, the more specific the associations found in studies like these, the more helpful the results will be for clinicians supporting patients with brain tumour as they can consider with

more certainty the influence of the patient's tumour localisation on the skill of interest.

A number of methodological design flaws related to the assumptions of modularity theory and the use of lesion-behaviour mapping have been discussed above. The results of this study could be further validated by collaborating with studies in this area using neurologically healthy participants and forms of activation monitoring (such as fMRI scanning), most specifically to allow monitoring of timing information on the stages of process and the roles of feedback within verbal fluency performance (Rorden & Karnath, 2004).

Summary and conclusion

Verbal fluency tests are very useful in measuring, monitoring and highlighting deficits in verbal communication difficulties and components of executive functioning following brain injury/degeneration (Strauss et al., 2006). More specifically they play a highly instrumental role in neuropsychological assessment and diagnosis of patients with a range of neurological conditions (Andreou & Trott, 2013; Mathuranath et al., 2010; Monsch et al., 1992; Pettit et al., 2013; Zhao et al., 2013).

This study correctly hypothesised that having a tumour in the left frontal lobe, being male, not having acquired exams during education, being depressed, having poor semantic memory, and having poor premorbid functioning are good predictors of phonemic fluency outcomes in patients with brain tumours. Knowing the influences created by these important factors will allow clinicians to be more considerate of variations in performance of patients with brain tumour who also align with these associative factors. This further enhances the accurate interpretation of neurocognitive assessment and diagnostic work and hence the planning of appropriate care in patients with brain tumour. Further research in this area, particularly with a focus on longitudinal data collection using methods that add to the lesion-behaviour mapping models applied here, such as using neurologically healthy participants with scanning techniques (such as fMRI) and more precise localisation mapping, may enhance the findings in this study.

Our hypotheses around the factors that influence semantic fluency were not supported. More specifically, localisation, semantic memory, depression and education did not predict semantic fluency. Semantic memory is a good predictor for semantic fluency, and was the only significant predictor found in this study for semantic fluency. Suggestions have been discussed that may support an increased likelihood of detecting significant effects in future analyses of factors influencing semantic fluency, such as the importance of ensuring an adequate sample of participants with higher levels of depression, accounting for age effects, tumour size effects, being able to focus on more precise localisations, and ensuring more adequate distribution of participants across these localisations.

These results have increased some clarification of the contradictions in the research base to date, but there are still areas where further information is required to better make sense of the outcomes. It is hoped that these results will broaden and strengthen clinicians' understanding of the impact of some of the factors highlighted here to play a role in verbal fluency performance. This should hopefully support them in making predictions about expected performance and tailor interventions accordingly, particularly for patients with tumours in the left frontal lobe. This study has also served to further highlight some of the requirements for more research in this complex topic area which is clearly lacking clarity and support from the current evidence base.

List of references

Airaksinen, E., Larsson, M., & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: Evidence of episodic memory dysfunction. *Journal of Psychiatric Research*, *39*(2), 207–214. http://doi.org/10.1016/j.jpsychires.2004.06.001

Altman, D. G., & Bland, J. M. (1995). Statistics notes: the normal distribution. *BMJ (Clinical Research Ed.)*. http://doi.org/10.1136/bmj.310.6975.298

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review*, *16*(1), 17–42. http://doi.org/10.1007/s11065-006-9002-x

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (Fifth ed). Arlington, VA: American Psychiatric Publishing. http://doi.org/10.1176/appi.books.9780890425596.744053

Anderson, S. I., Taylor, R., & Whittle, I. R. (1999). Mood disorders in patients after treatment for primary intracranial tumours. *British Journal of Neurosurgery*, *13*(5), 480–485. http://doi.org/10.1080/02688699908540622

Andreou, G., & Trott, K. (2013). Verbal fluency in adults diagnosed with attention-deficit hyperactivity disorder (ADHD) in childhood. *ADHD Attention Deficit and Hyperactivity Disorders*, *5*(4), 343–351. http://doi.org/10.1007/s12402-013-0112-z

Ardila, A., Ostrosky-Solís, F., & Bernal, B. (2006). Cognitive testing toward the future: The example of Semantic Verbal Fluency (ANIMALS). *International Journal of Psychology*, *41*(5), 324–332. http://doi.org/10.1080/00207590500345542

Armstrong, C. L., Goldstein, B., Shera, D., Ledakis, G. E., & Tallent, E. M. (2003). The predictive value of longitudinal neuropsychologic assessment in the early detection of brain tumor recurrence. *Cancer*, *97*(3), 649–656. http://doi.org/10.1002/cncr.11099

Babulal, G. M. (2016). Associations between stroke lesion location and

verbal fluency tests in a sub-acute stroke population. *Neurological Disorders and Therapies*, *1*(August), 1–5. http://doi.org/10.15761/NDT.1000101

Baldo, J. V, Schwartz, S., Wilkins, D., & Dronkers, N. F. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of the International Neuropsychological Society : JINS*, *12*(6), 896–900. http://doi.org/10.1017/S1355617706061078

Barry, D., Bates, M. E., & Labouvie, E. (2008). FAS and CFL Forms of Verbal Fluency Differ in Difficulty: A Meta-analytic Study. *Applied Neuropsychology*, *15*(2), 97–106. http://doi.org/10.1080/09084280802083863

Beatty, W. W., Wonderlich, S. A., Staton, R. D., & Ternes, L. A. (1990). Cognitive functioning in bulimia: comparison with depression. *Bulletin of the Psychonomic Society*, *28*(July 1990), 289–292. http://doi.org/10.3758/BF03334024

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate：a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society*, *57*(1), 289–300.

Benton, A. L. (1976). *Multilingual aphasia examination* (First). IOWA City: University of Iowa.

Bird, C. M., & Cipolotti, L. (2007). The utility of the recognition memory test and the graded naming test for monitoring neurological patients. *British Journal of Clinical Psychology*, *46*(2), 223–234. http://doi.org/10.1348/014466506X150282

Bird, C. M., Papadopoulou, K., Ricciardelli, P., Rossor, M. N., & Cipolotti, L. (2004). Monitoring cognitive changes: Psychometric properties of six cognitive tests. *British Journal of Clinical Psychology*, *43*, 197–210. http://doi.org/10.1348/014466504323088051

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale. *Journal of Psychosomatic Research*, *52*, 69–77. http://doi.org/10.1016/S0022-3999(01)00296-3

Blaney, P. H. (1986). Affect and memory: a review. *Psychological Bulletin*, *99*(2), 229–246. http://doi.org/10.1037/0033-2909.99.2.229

Brown, R. G., Scott, L. C., Bench, C. J., & Dolan, R. J. (1994). Cognitive function in depression: its relationship to the presence and severity of intellectual decline. *Psychol Med*, *24*(May), 829–847. http://doi.org/10.1017/S0033291700028932

Cancer Research UK. (n.d.-a). Brain, other CNS and intracranial tumours incidence statistics. Retrieved 24 July 2017, from http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours/incidence#ref-0

Cancer Research UK. (n.d.-b). Brain tumours. Retrieved 24 July 2017, from http://www.cancerresearchuk.org/about-cancer/brain-tumours/about

Christensen, H., Griffiths, K., MacKinnon, a, & Jacomb, P. (1997). A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *J Int Neuropsychol Soc*, *3*(1997), 631–651.

Cohen, J. (1988). Statistical power analysis for the behavioral sciences Lawrence Earlbaum Associates. *Hillsdale, NJ*.

Cohen, J. (1992). Quantitative Methods in Psychology. *Psychological Bulletin*, *112*(1), 155–159. http://doi.org/10.1037/0033-2909.112.1.155

Correa, D. D. (2010). Neurocognitive function in brain tumors. *Current Neurology and Neuroscience Reports*, *10*(3), 232–239. http://doi.org/10.1007/s11910-010-0108-4

Crawford, J. R. (2003). Psychometric foundations of neuropsychological assessment. *Clinical Neuropsychology: A Practical Guide to Assessment and Management for Clinicians*, 121–140.

Crawford, J. R., Moore, J. W., & Cameron, I. M. (1992). Verbal Fluency: A NART-based equation for the estimation of premorbid performance. *British Journal of Clinical Psychology*, *31*(3), 327–329. http://doi.org/10.1111/j.2044-8260.1992.tb00999.x

Crawford, J. R., Stewart, L. E., Parker, D. M., Besson, J. A. O., & Cochrane,

R. H. B. (1989). Estimation of premorbid intelligence: combining psychometric and demographic approaches improves predictive accuracy. *Personality and Individual Differences*, *10*(7), 793–796. http://doi.org/10.1016/0191-8869(89)90126-8

Crowe, S. F. (1992). Dissociation of two frontal lobe syndromes by a test of verbal fluency. *Journal of Clinical and Experimental Neuropsychology*, *14*(2), 327–39. http://doi.org/10.1080/01688639208402832

Curran-Everett, D. (2004). Guidelines for reporting statistics in journals published by the American Physiological Society. *Journal of Applied Physiology*, *97*(2), 457–459. http://doi.org/10.1152/japplphysiol.00513.2004

Das-Munshi, J., Goldberg, D., Bebbington, P. E., Bhugra, D. K., Brugha, T. S., Dewey, M. E., … Prince, M. (2008). Public health significance of mixed anxiety and depression: Beyond current classification. *British Journal of Psychiatry*, *192*(3), 171–177. http://doi.org/10.1192/bjp.bp.107.036707

Davidson, P. S. R., Gao, F. Q., Mason, W. P., Winocur, G., Anderson, N. D., Davidson, P. S. R., … Anderson, N. D. (2008). Verbal fluency, trail making, and Wisconsin Card Sorting Test performance following right frontal lobe tumor resection. *Journal of Clinical and Experimental Neuropsychology*, *30*(1), 18–32. http://doi.org/10.1080/13803390601161166

Davis, A. S., Finch, W. H., Drapeau, C., Nogin, M., Moss, L. E., & Moore, B. (2017). Predicting verbal fluency using Word Reading: Implications for premorbid functioning. *Applied Neuropsychology: Adult 2016*, *23*(6), 403–410. http://doi.org/10.1080/23279095.2016.1163262

DeAngelis, L. M. (2001). Brain tumors. *The New England Journal of Medicine*, *114*(2), 114–123. http://doi.org/10.1056/NEJM200101113440207

Delis, D., Kaplan, E., & Kramer, J. (2001a). D-KEFS technical manual. San Antonio TX: Psychological Corporation.

Delis, D., Kaplan, E., & Kramer, J. (2001b). Delis-Kaplan executive function

system (D-KEFS).

Della Sala, S., Gray, C., Spinnler, H., & Trivelli, C. (1998). Frontal lobe functioning in man: The riddle revisited. *Archives of Clinical Neuropsychology*, *13*(8), 663–682. http://doi.org/10.1016/S0887-6177(97)00093-0

Douw, L., Klein, M., Fagel, S. S., van den Heuvel, J., Taphoorn, M. J., Aaronson, N. K., … Heimans, J. J. (2009). Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *The Lancet Neurology*, *8*(9), 810–818. http://doi.org/10.1016/S1474-4422(09)70204-2

Elliott, A. C., & Woodward, W. a. (2007). *Statistical Analysis Quick Reference Guidebook: With SPSS Examples* (1st ed.). London: Sage Publications Ltd. http://doi.org/10.4135/9781412985949

Farah, M. J. (1994). *Neuropsychological inference with an interactive brain: A critique of the "locality" assumption*. *BEHAVIORAL AND BRAIN SCIENCES* (Vol. 17).

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149–1160. http://doi.org/10.3758/BRM.41.4.1149

Field, A. P. (2009). *Discovering statistics using SPSS* (3rd ed.). London: SAGE Publications.

Fisk, J. E., & Sharp, C. a. (2004). Age-related impairment in executive functioning: updating, inhibition, shifting, and access. *Journal of Clinical and Experimental Neuropsychology*, *26*(7), 874–90. http://doi.org/10.1080/13803390490510680

Fossati, P., Amar, G., Raoux, N., Ergis, A. M., & Allilaire, J. F. (1999). Executive functioning and verbal memory in young patients with unipolar depression and schizophrenia. *Psychiatry Research*, *89*(3), 171–187. http://doi.org/10.1016/S0165-1781(99)00110-9

Ghasemi, A., & Zahediasl, S. (2012). Normality tests for statistical analysis: A guide for non-statisticians. *International Journal of Endocrinology and*

Metabolism, *10*(2), 486–489. http://doi.org/10.5812/ijem.3505

Gladsjo, J., Schuman, C., Evans, J., Peavy, G., Miller, S., & Heaton, R. (1999). Norms for letter and category fluency: Demographic corrections for age, education, and ethnicity. *Assessment*, *6*(2), 147–178.

Goldstein, B., Obrzut, J. E., John, C., Hunter, J. V, & Armstrong, C. L. (2004). The impact of low-grade brain tumors on verbal fluency performance. *Journal of Clinical and Experimental Neuropsychology*, *26*(6), 750–8. http://doi.org/10.1080/13803390490509376

Gregor, A., Cull, A., Traynor, E., Stewart, M., Lander, F., & Love, S. (1996). Neuropsychometric evaluation of long-term survivors of adult brain tumours: Relationship with tumour and treatment parameters. *Radiotherapy and Oncology*, *41*(1), 55–59. http://doi.org/10.1016/S0167-8140(96)91782-X

Habets, E. J. J., Kloet, A., Walchenbach, R., Vecht, C. J., Klein, M., & Taphoorn, M. J. B. (2014). Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochirurgica*, *156*(8), 1451–1459. http://doi.org/10.1007/s00701-014-2115-8

Hahn, C. A., Dunn, R. H., Logue, P. E., King, J. H., Edwards, C. L., & Halperin, E. C. (2003). Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumors. *International Journal of Radiation Oncology Biology Physics*, *55*(4), 992–999. http://doi.org/10.1016/S0360-3016(02)04205-0

Harrell, F. E. (2001). *Regression modeling strategies : with applications to linear models, logistic and ordinal regression, and survival analysis*. New York: Springer-Verlag.

Henry, J. D., & Crawford, J. R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology*, *18*(2), 284–295. http://doi.org/10.1037/0894-4105.18.2.284

Henry, J. D., & Crawford, J. R. (2005). A Meta-Analytic Review of Verbal Fluency Deficits in Depression. *Journal of Clinical and Experimental Neuropsychology*, *27*(1), 78–101.

Henry, J. D., Crawford, J. R., & Phillips, L. H. (2004). Verbal fluency

performance in dementia of the Alzheimer's type: A meta-analysis. *Neuropsychologia*, *42*(9), 1212–1222. http://doi.org/10.1016/j.neuropsychologia.2004.02.001

Hirshorn, E. A., & Thompson-Schill, S. L. (2006). Role of the left inferior frontal gyrus in covert word retrieval: Neural correlates of switching during verbal fluency. *Neuropsychologia*, *44*(12), 2547–2557. http://doi.org/10.1016/j.neuropsychologia.2006.03.035

Hoffermann, M., Bruckmann, L., Mahdy Ali, K., Zaar, K., Avian, A., & von Campe, G. (2017). Pre- and postoperative neurocognitive deficits in brain tumor patients assessed by a computer based screening test. *Journal of Clinical Neuroscience*, *36*, 31–36. http://doi.org/10.1016/j.jocn.2016.10.030

Hom, J., & Reitan, R. M. (1984). Neuropsychological correlates of rapidly Vs . slowly growing intrinsic cerebral neoplasms Growing Intrinsic Cerebral Neoplasms. *Journal of Clinical Neuropsychology*, *6*(3), 309–324. http://doi.org/10.1080/01688638408401221

Howitt, D., & Cramer, D. (2005). *An introduction to statistics in psychology*. PearsonPrentice Hall.

Jenkins, L. M., Drummond, K. J., & Andrewes, D. G. (2016). Emotional and personality changes following brain tumour resection. *Journal of Clinical Neuroscience*, *29*, 128–132. http://doi.org/10.1016/j.jocn.2015.12.007

Johnson, M. H., & Magaro, P. a. (1987). Effects of mood and severity on memory processes in depression and mania. *Psychological Bulletin*, *101*(1), 28–40. http://doi.org/10.1037/0033-2909.101.1.28

Johnstone, B., Hogg, J. R., Schopp, L. H., Kapila, C., & Edwards, S. (2002). Neuropsychological deficit profiles in senile dementia of the Alzheimer's type. *Archives of Clinical Neuropsychology*, *17*(3), 273–281. http://doi.org/10.1016/S0887-6177(01)00112-3

Julian, L. J. (2011). Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care & Research*, *63*(S11), S467–S472. http://doi.org/10.1002/acr.20561

Kaiser, S., Unger, J., Kiefer, M., Markela, J., Mundt, C., & Weisbrod, M. (2003). Executive control deficit in depression: Event-related potentials in a Go/Nogo task. *Psychiatry Research - Neuroimaging*, *122*(3), 169–184. http://doi.org/10.1016/S0925-4927(03)00004-0

Kaplan, E., Googglass, H., & Weintraub, S. (1983). *Boston Naming Test*.

Kayl, A. E., & Meyers, C. A. (2003). Does brain tumor histology influence cognitive function? *Neurooncology*, *5*(4), 255–260. http://doi.org/10.1215/S1152

Kleihues, P., Louis, D. N., Scheithauer, B. W., Rorke, L. B., Reifenberger, G., Burger, P. C., & Cavenee, W. K. (2002). The WHO Classification of Tumors of the Nervous System, *61*(3), 215–225.

Klein, M. (2012). Neurocognitive functioning in adult WHO grade II gliomas: Impact of old and new treatment modalities. *Neuro-Oncology*, *14*(SUPPL.4), 17–24. http://doi.org/10.1093/neuonc/nos161

Klein, M., . Taphoorn, M. J. B., Heimans, J. J., van der Ploeg, H. M., Vandertop, W. P., Smit, E. F., … Aaronson, N. K. (2001). Neurobehavioral Status and Health-Related Quality of Life in Newly Diagnosed High-Grade Glioma Patients. *Journal of Clinical Oncology*, *19*(20), 4037–4047.

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). New York, Oxford: Oxford University Press.

Loonstra, A. S., Tarlow, A. R., & Sellers, A. H. (2001). COWAT Metanorms Across Age, Education, and Gender. *Applied Neuropsychology*, *8*(3), 161–166. http://doi.org/10.1207/S15324826AN0803_5

Louis, D. N., Ohgaki, H., Wiestler, O. D., Cavenee, W. K., Burger, P. C., Jouvet, A., … Kleihues, P. (2007). The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathologica*, *114*(2), 97–109. http://doi.org/10.1007/s00401-007-0243-4

Louis, D. N., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W. K., … Ellison, D. W. (2016). The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathologica*.

http://doi.org/10.1007/s00401-016-1545-1

Lynam, L. M., Lyons, M. K., Drazkowski, J. F., Sirven, J. I., Noe, K. H., Zimmerman, R. S., & Wilkens, J. A. (2007). Frequency of seizures in patients with newly diagnosed brain tumors: A retrospective review. *Clinical Neurology and Neurosurgery*, *109*(7), 634–638. http://doi.org/10.1016/j.clineuro.2007.05.017

Mathuranath, P. S., Nestor, P. J., & Berrios, G. E. (2010). A brief cognitive test battery to differentiate Alzheimer ' s disease and frontotemporal dementia. *Neurology*, *55*(9), 1613–1620. http://doi.org/10.1212/WNL.55.11.1613

Maxwell, S. E. (2004). The persistence of underpowered studies in psychological research: causes, consequences, and remedies. *Psychological Methods*, *9*(2), 147–63. http://doi.org/10.1037/1082-989X.9.2.147

McCloskey, G., & Perkins, L. A. (2012). *Essentials of executive function assessment*. John Wiley & Sons.

Mckenna, P., & Warrington, E. K. (1980). Testing for nominal dysphasia. *Journal of Neurology Neurosurgery, and Psychiatry*, *43*(March), 781–788. http://doi.org/10.1136/jnnp.43.9.781

Meskal, I., Gehring, K., Rutten, G. J. M., & Sitskoorn, M. M. (2016). Cognitive functioning in meningioma patients: a systematic review. *Journal of Neuro-Oncology*, *128*(2), 195–205. http://doi.org/10.1007/s11060-016-2115-z

Metternich, B., Buschmann, F., Wagner, K., Schulze-Bonhage, A., & Kriston, L. (2014). Verbal fluency in focal epilepsy: A systematic review and meta-analysis. *Neuropsychology Review*, *24*(4), 200–218. http://doi.org/10.1007/s11065-014-9255-8

Meyers, C. A., Berman, S. A., Scheibel, R. S., & Hayman, A. (1992). Case report: acquired antisocial personality disorder associated with unilateral left orbital frontal lobe damage. *Journal of Psychiatry & Neuroscience : JPN*, *17*(3), 121–125.

Meyers, C. A., & Hess, K. (2003). Multifaceted end points in brain tumor

clinical trials: cognitive deterioration precedes MRI progression. *Neuro-Oncology*, *5*(April), 89–95. http://doi.org/10.1215/S1522-8517-02-00026-1

Meyers, C. A., Hess, K. R., Yung, W. K., & Levin, V. A. (2000). Cognitive function as a predictor of survival in patients with recurrent malignant glioma. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *18*(3), 646–50. http://doi.org/10.1200/jco.2000.18.3.646

Miller, W. R. (1975). Psychological Deficit in Depression. *Psychological Bulletin*, *82*(2), 238–260. http://doi.org/10.1037/h0076367

Miotto, E. C., Junior, A. S., Silva, C. C., Cabrera, H. N., Machado, M. A. R., Benute, G. R. G., & Lucia, M. C. S. (2011). Cognitive impairments in patients with low grade gliomas and high grade gliomas. *Arq Neuropsiquiatr*, *69*(July 2010), 596–601.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49–100. http://doi.org/10.1006/cogp.1999.0734

Monsch, A. U., Bondi, M. W., Butters, N., Thal, L. J., Salmon, D. P., & Katzman, R. (1992). Comparisons of Verbal Fluency Tasks in the Detection of Dementia of the Alzheimer Type. *Archives of Neurology*, *49*(12), 1253–1258. http://doi.org/10.1001/archneur.1992.00530360051017

Nathan, J., Wilkinson, D., Stammers, S., & Low, J. L. (2001). The role of tests of frontal executive function in the detection of mild dementia. *International Journal of Geriatric Psychiatry*, *16*(1), 18–26. http://doi.org/10.1002/1099-1166(200101)16:1<18::AID-GPS265>3.0.CO;2-W

NICE. (2006). *Improving Outcomes for People with Brain and Other CNS Tumours*. London: National Institute for Health and Clinical Excellence.

NICE. (2011). *Common mental health problems: identification and pathways*

to care.

Noll, K. R., Sullaway, C., Ziu, M., Weinberg, J. S., & Wefel, J. S. (2014). Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro-Oncology*, *17*(4), 580–587. http://doi.org/10.1093/neuonc/nou233

O'Shea, D. M., De Wit, L., Szymkowicz, S. M., McLaren, M. E., Talty, F., & Dotson, V. M. (2016). Anxiety Modifies the Association between Fatigue and Verbal Fluency in Cognitively Normal Adults. *Archives of Clinical Neuropsychology*, *31*(September), 1043–1049. http://doi.org/10.1093/arclin/acw045

Office for National Statistics. (2017). Measuring National Well-being: Domains and Measures. Retrieved 28 August 2017, from https://www.ons.gov.uk/peoplepopulationandcommunity/wellbeing/datasets/measuringnationalwellbeingdomainsandmeasures

Öztuna, D., Elhan, A. H., & Tüccar, E. (2006). Investigation of four different normality tests in terms of type 1 error rate and power under different distributions. *Turkish Journal of Medical Sciences*, *36*(3), 171–176.

Påhlson, A., Ek, L., Ahlström, G., & Smits, A. (2003). Pitfalls in the assessment of disability in individuals with low-grade gliomas. *Journal of Neuro-Oncology*, *65*(2), 149–158. http://doi.org/10.1023/B:NEON.0000003727.09448.dd

Pallant, J. (2007). *SPSS survival manual, a step by step guide to data analysis using SPSS for windows* (3rd ed.). Sydney: McGraw Hill.

Patel, V., Lund, C., Hatherill, S., Plagerson, S., Corrigall, J., Funk, M., & Flisher, A. (2010). Equity, social determinants and public health programmes. Closing the gap in a generation: Health equity through action on the social determinants of health. *World Health Organization*.

Petrie, A., & Sabin, C. (2009). *Medical statistics at a glance*. Wiley-Blackwell.

Pettit, L., McCarthy, M., Davenport, R., & Abrahams, S. (2013). Heterogeneity of letter fluency impairment and executive dysfunction in Parkinson's disease. *Journal of the International Neuropsychological Society : JINS*, *19*(9), 986–94.

http://doi.org/10.1017/S1355617713000829

Pilling, S., Whittington, C., Taylor, C., Kendrick, T., & Guideline Development Group. (2011). Identification and care pathways for common mental health disorders: summary of NICE guidance. *BMJ (Clinical Research Ed.)*, *342*(5), d2868. http://doi.org/10.1136/bmj.d2868

Pringle, a M., Taylor, R., & Whittle, I. R. (1999). Anxiety and depression in patients with an intracranial neoplasm before and after tumour surgery. *British Journal of Neurosurgery*, *13*(1), 46–51. http://doi.org/10.1080/02688699944177

Quinn, M., P, B., & Babb, P. (2000). Cancer trends in England and Wales 1950–1999: studies on medical and population subjects. *Health Statistics Quarterly*, *8*, 324–334.

Reynolds, C. R. (1997). Postscripts on premorbid ability estimation: Conceptual addenda and a few words on alternative and conditional approaches. *Archives of Clinical Neuropsychology*, *12*(8), 769–778. http://doi.org/10.1016/S0887-6177(97)00051-6

Riva, D., Nichelli, F., & Devoti, M. (2000). Developmental aspects of verbal fluency and confrontation naming in children. *Brain and Language*, *71*(2), 267–84. http://doi.org/10.1006/brln.1999.2166

Robinson, G., Shallice, T., Bozzali, M., & Cipolotti, L. (2012). The differing roles of the frontal cortex in fluency tests. *Brain*, *135*(7), 2202–2214. http://doi.org/10.1093/brain/aws142

Roca, M., Parr, A., Thompson, R., Woolgar, A., Torralva, T., Antoun, N., … Duncan, J. (2010). Executive function and fluid intelligence after frontal lobe lesions. *Brain*, *133*(1), 234–247. http://doi.org/10.1093/brain/awp269

Rodriguez-Aranda, C., & Martinussen, M. (2006). Age-Related Differences in Performance of Phonemic Verbal Fluency Measured by Controlled Oral Word Association Task (COWAT): A Meta-Analytic Study. *Developmental Neuropsychology*, *30*(2), 697–717. http://doi.org/10.1207/s15326942dn3002_3

Rorden, C., & Karnath, H.-O. (2004). Using human brain lesions to infer

function: a relic from a past era in the fMRI age? *Nature Reviews Neuroscience*, *5*(10), 812–819. http://doi.org/10.1038/nrn1521

Rosen, W. G. (1980). Verbal fluency in aging and dementia. *Journal of Clinical Neuropsychology*, *2*(December 2013), 135–146. http://doi.org/10.1080/01688638008403788

Ross, T. P. (2003). The reliability of cluster and switch scores for the controlled oral word association test. *Archives of Clinical Neuropsychology*, *18*(2), 153–164. http://doi.org/10.1093/arclin/18.2.153

Ross, T. P. (2003). The reliability of cluster and switch scores for the Controlled Oral Word Association Test. *Archives of Clinical Neuropsychology*, *18*(2), 153–164. http://doi.org/10.1016/S0887-6177(01)00192-5

Sacks, O. (2011). *The man who mistook his wife for a hat*. New York: Pan Macmillan.

Sarter, M., Berntson, G. G., & Cacioppo, J. T. (1996). Brain Imaging and Cognitive Neuroscience Toward Strong Inference in Attributing Function to Structure. *American Psychologist*, *51*(1), 13–21.

Scheibel, R. S., Meyers, C. A., & Levin, V. A. (1996). Cognitive dysfunction following surgery for intracerebral glioma: influence of histopathology, lesion location, and treatment. *Journal of Neuro-Oncology*, *30*, 61–69.

Schweizer, T. A., Alexander, M. P., Susan Gillingham, B. A., Cusimano, M., & Stuss, D. T. (2010). Lateralized cerebellar contributions to word generation: A phonemic and semantic fluency study. *Behavioural Neurology*, *23*(1–2), 31–37. http://doi.org/10.3233/BEN-2010-0269

Shallice, T. (1988). *From neuropsychology to mental structure*. New York: Cambridge University Press.

Smarr, K. L., & Keefer, A. L. (2011). Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionna. *Arthritis Care & Research*, *63*(S11), S454–S466. http://doi.org/10.1002/acr.20556

Smitherman, T. A., Huerkamp, J. K., Miller, B. I., Houle, T. T., & O'Jile, J. R. (2007). The relation of depression and anxiety to measures of executive functioning in a mixed psychiatric sample. *Archives of Clinical Neuropsychology*, *22*(5), 647–654. http://doi.org/10.1016/j.acn.2007.04.007

Spreen, O., & Benton, A. L. (1977). *Neurosensory center comprehensive examination for aphasia (NCCEA), 1977 revision: manual of instructions*. Victoria, BC, Canada.

Steinberg, B. a, Bieliauskas, L. a, Smith, G. E., & Ivnik, R. J. (2005). Mayo's older Americans normative studies: Age- and IQ-adjusted norms for the Trail-Making Test, the Stroop Test, and MAE Controlled Oral Word Association Test. *The Clinical Neuropsychologist*, *19*(3–4), 329–377. http://doi.org/10.1080/13854040590945210

Steinskog, D. J., Tjøstheim, D. B., & Kvamstø, N. G. (2007). A Cautionary Note on the Use of the Kolmogorov–Smirnov Test for Normality. *Monthly Weather Review*, *135*(3), 1151–1157. http://doi.org/10.1175/MWR3326.1

Strauss, E., Sherman, E. M. S., Spreen, O., & Spreen, O. (2006). *A compendium of neuropsychological tests : administration, norms, and commentary* (Third). New York, Oxford: Oxford University Press.

Stuss, D. T., & Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annual Review of Psychology*, *53*, 401–33. http://doi.org/10.1146/annurev.psych.53.100901.135220

Szatkowska, I., Grabowska, A., & Szymańska, O. (2000). Phonological and semantic fluencies are mediated by different regions of the prefrontal cortex. *Acta Neurobiologiae Experimentalis*, *60*(4), 503–508.

Tabachnick, B. G., & Fidell, L. S. (2013). *Using multivariate statistics*. Pearson Education.

Talacchi, A., Santini, B., Savazzi, S., & Gerosa, M. (2011). Cognitive effects of tumour and surgical treatment in glioma patients. *Journal of Neuro-Oncology*, *103*(3), 541–549. http://doi.org/10.1007/s11060-010-0417-0

Taphoorn, M. J., & Klein, M. (2004). Cognitive deficits in adult patients with

brain tumours. *The Lancet Neurology*, *3*(3), 159–168. http://doi.org/10.1016/S1474-4422(04)00680-5

Teuber, H.-L. (1955). Physiological psychology. *Annual Review of Psychology*, *6*, 267–296. http://doi.org/10.1146/annurev.ps.06.020155.001411

Tombaugh, T. N., Kozak, J., & Rees, L. (1999). Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of Clinical Neuropsychology*, *14*(2), 167–177. http://doi.org/10.1016/S0887-6177(97)00095-4

Trichard, C., Martinot, J. L., Alagille, M., Masure, M. C., Hardy, P., Ginestet, D., & Féline, A. (1995). Time course of prefrontal lobe dysfunction in severely depressed in-patients: a longitudinal neuropsychological study. *Psychological Medicine*, *25*(May), 79–85. http://doi.org/10.1017/S0033291700028105

Troyer, A. K., Moscovitch, M., & Winocur, G. (1997). Clustering and switching as two components of verbal fluency: Evidence from younger and older healthy adults. *Neuropsychology*, *11*(1), 138–146. http://doi.org/10.1037/0894-4105.11.1.138

Troyer, A. K., Moscovitch, M., Winocur, G., Alexander, M. P., & Stuss, D. (1998). Clustering and switching on verbal fluency: The effects of focal frontal- and temporal-lobe lesions. *Neuropsychologia*, *36*(6), 499–504. http://doi.org/10.1016/S0028-3932(97)00152-8

Tucha, O., Smely, C., & Lange, K. W. (2001). Effects of surgery on cognitive functioning of elderly patients with intracranial meningioma. *British Journal of Neurosurgery*, *15*(2), 184–8. http://doi.org/10.1080/02688690151127608

Tucha, O., Smely, C., Preier, M., Becker, G., Paul, G. M., & Lange, K. W. (2003). Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. *Journal of Neurosurgery*, *98*(1), 21–31. http://doi.org/10.3171/jns.2003.98.1.0021

Tupper, D. E., & Rosenblood, L. K. (1984). Methodological considerations in the use of attribute variables in neuropsychological research. *Journal of*

Clinical Neuropsychology, *6*(4), 441–53. http://doi.org/10.1080/01688638408401234

van Breemen, M. S. M., Wilms, E. B., & Vecht, C. J. (2007). Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurology*, *6*(5), 421–430. http://doi.org/10.1016/S1474-4422(07)70103-5

van Loon, E. M. P., Heijenbrok-Kal, M. H., van Loon, W. S., van den Bent, M. J., Vincent, A. J. P. E., de Koning, I., & Ribbers, G. M. (2015). Assessment methods and prevalence of cognitive dysfunction in patients with low-grade glioma: A systematic review. *Journal of Rehabilitation Medicine*, *47*(6), 481–8. http://doi.org/10.2340/16501977-1975

van Nieuwenhuizen, D., Klein, M., Stalpers, L. J., Leenstra, S., Heimans, J. J., & Reijneveld, J. C. (2007). Differential effect of surgery and radiotherapy on neurocognitive functioning and health-related quality of life in WHO grade I meningioma patients. *Journal of Neuro-Oncology*, *84*(3), 271–278. http://doi.org/10.1007/s11060-007-9366-7

Veiel, H. O. F. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology*, *19*(4), 587–603. http://doi.org/10.1080/01688639708403745

Vilkki, J., & Holst, P. (1994). Speed and Flexibility on Word Fluency Focal Brain Lesions Tasks After Focal Brain Lesions. *Neuropsychologica*, *32*(10), 1257–1262.

Wechsler, D. (2008). *Wechsler adult intelligence scale WAIS-IV ; technical and interpretive manual*. San Antonio, TX: The Psychological Corporation, Pearson Inc.

Wechsler, D. (2011a). Test of premorbid functioning. UK version (TOPF UK). *UK: Pearson Corporation*.

Wechsler, D. (2011b). *Test of Premorbid Functioning*. *San Antonio, TX: The Psychological Corporation*.

Wefel, J. S., Vardy, J., Ahles, T., & Schagen, S. B. (2011). International

Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *The Lancet Oncology*, *12*(7), 703–708. http://doi.org/10.1016/S1470-2045(10)70294-1

Weitzner, M. a, & Meyers, C. A. (1997). Cognitive functioning and quality of life in malignant glioma patients: a review of the literature. *Psycho-Oncology*, *6*(3), 169–77. http://doi.org/10.1002/(SICI)1099-1611(199709)6:3<169::AID-PON269>3.0.CO;2-#

Wideheim, A.-K., Edvardsson, T., Påhlson, A., & Ahlström, G. (2002). A family's perspective on living with a highly malignant brain tumor. *Cancer Nursing*, *25*(3), 236–244.

Yang, S., Park, C., Park, S., Kim, D., Chung, Y., & Jung, H. (2008). Atypical and anaplastic meningiomas: prognostic implications of clinicopathological features. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*(5), 574–580. http://doi.org/10.1136/jnnp.2007.121582

Yochim, B. P., Mueller, A. E., & Segal, D. L. (2013). Late life anxiety is associated with decreased memory and executive functioning in community dwelling older adults. *Journal of Anxiety Disorders*, *27*(6), 567–575. http://doi.org/10.1016/j.janxdis.2012.10.010

Zabora, J., Brintzenhofeszoc, K., Curbow, B., Hooker, C., & Piantadosi, S. (2001). The prevalence of psychological distress by cancer site. *Psycho-Oncology*, *10*(1), 19–28. http://doi.org/10.1002/1099-1611(200101/02)10:1<19::AID-PON501>3.0.CO;2-6

Zhao, Q., Guo, Q., & Hong, Z. (2013). Clustering and switching during a semantic verbal fluency test contribute to differential diagnosis of cognitive impairment. *Neuroscience Bulletin*, *29*(1), 75–82. http://doi.org/10.1007/s12264-013-1301-7

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. http://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Appendix A: Table illustrating the initial higher order categories for localisation

Original label	Category 1 (18 categories)	Category 2 (10 categories)	Category 3 (2 categories)
Anterior Fossa	x	Frontal	x
Anterior third ventricle	Intraventricular	Intraventricular	x
Diffuse	Other	Other	x
Fourth ventricle	Intraventricular	Intraventricular	x
Frontal lobe	x	Frontal	x
Intraventricular	Intraventricular	Intraventricular	x
Left and right frontal	x	Frontal	x
Left anterior cranial fossa	Left anterior	Left anterior	Left
Left anterior fossa	Left anterior	Left anterior	Left
Left basal frontal	Left frontal	Left frontal	Left
Left cerebellar	Subcortical	Subcortical	Left
Left cerebellopontine angle Cistern	Subcortical	Subcortical	Left
Left frontal	Left frontal	Left frontal	Left
Left frontal	Left frontal	Left frontal	Left
Left frontal convexity	Left frontal	Left frontal	Left
Left frontal lobe	Left frontal	Left frontal	Left
Left frontal medial	Left frontal medial	Left frontal	Left
Left frontoparietal	Left fronto parietal	Left frontal	Left
Left frontoparietal lobe	Left fronto parietal	Left frontal	Left
Left fronto-temporal	Left fronto temporal	Left frontal	Left
Left lateral ventricle	Intraventricular	Intraventricular	Left
Left occipital, parafalcine	Left occipital	Left occipital	Left
Left parafalcine, Faulx	x	x	Left
Left parietal	Left parietal	Left parietal	Left
Left parieto-occipital	Left parieto occipital	Left parietal	Left
Left parieto-temporal	Left parieto temporal	Left parietal	Left
Left posterior frontal	Left frontal	Left frontal	Left
Left posterior frontal	Left frontal	Left frontal	Left
Left posterior parietal parafalcine	Left parietal	Left parietal	Left
Left posterior temporal	Left temporal	Left temporal	Left

Left spenoid wing	x	x	Left
Left sphenoid wing	x	x	Left
Left temporal	Left temporal	Left temporal	Left
Left temporal	Left temporal	Left temporal	Left
Left temporal lobe	Left temporal	Left temporal	Left
Medial anterior right frontal lobe	Right frontal medial	Right frontal	Right
Parasaggital frontal	x	Frontal	x
Parieto-occipital	x	x	x
Pituitary	Subcortical	Subcortical	x
Posterior fossa	Subcortical	Subcortical	x
Posterior left petrous temporal bone	x	x	Left
Right	x	x	Right
Right frontal	Right frontal	Right frontal	Right
Right frontal parafalcine region	Right frontal	Right frontal	Right
Right fronto-parietal	Right frontoparietal	Right frontal	Right
Right fronto-temporal	Right frontotemporal	Right frontal	Right
Right hemisphere	x	x	Right
Right parietal	Right parietal	Right parietal	Right
Right parietal	Right parietal	Right parietal	Right
Right posterior fossa	Right posterior	x	Right
Right posterior Temporal/parietal	Right posterior	x	Right
Sphenoid wing	x	x	x
Sub frontal	x	Frontal	x
Subcortical	Subcortical	Subcortical	x
Tentorial hiatus	Subcortical	Subcortical	x
Third ventricle	Intraventricular	Intraventricular	x

Appendix B: Table illustrating secondary higher order categories for localisation

Original label	Category 4 (7 categories)	Category 5 (6 categories)
Anterior Fossa	Frontal	Frontal
Anterior third ventricle	Other	X
Diffuse	Other	X
Fourth ventricle	Other	X
Frontal lobe	Frontal	Frontal
Intraventricular	Other	X
Left and right frontal	Frontal	Frontal
Left anterior cranial fossa	Other	X
Left anterior fossa	Other	X
Left basal frontal	Left frontal	Left frontal
Left cerebellar	Other	X
Left cerebellopontine angle Cistern	Other	X
Left frontal	Left frontal	Left frontal
Left frontal	Left frontal	Left frontal
Left frontal convexity	Left frontal	Left frontal
Left frontal lobe	Left frontal	Left frontal
Left frontal medial	Left frontal	Left frontal
Left frontoparietal	Left frontal	Left frontal
Left frontoparietal lobe	Left frontal	Left frontal
Left fronto-temporal	Left frontal	Left frontal
Left lateral ventricle	Other	X
Left occipital, parafalcine	Other	X
Left parafalcine, Faulx	Other	X
Left parietal	Left parietal	Left parietal
Left parieto-occipital	Left parietal	Left parietal
Left parieto-temporal	Left parietal	Left parietal
Left posterior frontal	Left frontal	Left frontal
Left posterior frontal	Left frontal	Left frontal
Left posterior parietal parafalcine	Left parietal	Left parietal
Left posterior temporal	Left temporal	Left temporal
Left spenoid wing	Other	X
Left sphenoid wing	Other	X
Left temporal	Left temporal	Left temporal
Left temporal	Left temporal	Left temporal
Left temporal lobe	Left temporal	Left temporal

Medial anterior right frontal lobe	Right frontal	Right frontal
Parasaggital frontal	Frontal	Frontal
Parieto-occipital	Other	X
	Other	X
Pituitary		
Posterior fossa	Other	X
Posterior left petrous temporal bone	Other	X
Right	Other	X
Right frontal	Right frontal	Right frontal
Right frontal parafalcine region	Right frontal	Right frontal
Right fronto-parietal	Right frontal	Right frontal
Right fronto-temporal	Right frontal	Right frontal
Right hemisphere	Other	X
Right parietal	Right parietal	Right parietal
Right parietal	Right parietal	Right parietal
Right posterior fossa	Other	X
Right posterior Temporal/parietal	Other	X
Sphenoid wing	Other	X
Sub frontal	Frontal	Frontal
Subcortical	Other	X
Tentorial hiatus	Other	X
Third ventricle	Other	X

Appendix C: Table illustrating higher order categories for tumour type

Original label	Category 1 (5 categories)	Category 2 (2 categories)
Astrocytoma	Glioma	Glioma
Colloid cyst	Cystic	Removed
Cystic	Cystic	Removed
Ependymoma	Glioma	Glioma
Glioblastoma	Glioma	Glioma
Glioma	Glioma	Glioma
Glioma/meningioma	Mixed	X
Meningioma	Meningioma	Meningioma
Mesenchymal chondrosarcoma	Other	X
Metastatic	Other	X
Neurocytoma	Other	X
Neuroma	Other	X
Non-specific	Other	X
Oligodendroglioma	Glioma	Glioma
Other/unknown	Other	X
Pituitary	Other	X
Porencepahlic cyst	Cystic	Removed
Subependymoma	Glioma	Glioma
Vestibular schwannoma	Other	X

Appendix D: Table illustrating breakdown of frequency data for HADS-D

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	.0	6	4.9	4.9	4.9
	1.0	11	8.9	8.9	13.8
	2.0	13	10.6	10.6	24.4
	3.0	10	8.1	8.1	32.5
	4.0	8	6.5	6.5	39.0
	5.0	7	5.7	5.7	44.7
	6.0	11	8.9	8.9	53.7
	7.0	14	11.4	11.4	65.0
	8.0	11	8.9	8.9	74.0
	9.0	7	5.7	5.7	79.7
	10.0	7	5.7	5.7	85.4
	11.0	5	4.1	4.1	89.4
	12.0	4	3.3	3.3	92.7
	13.0	5	4.1	4.1	96.7
	14.0	1	.8	.8	97.6
	15.0	1	.8	.8	98.4
	17.0	1	.8	.8	99.2
	20.0	1	.8	.8	100.0
	Total	**123**	**100.0**	**100.0**	

Appendix E: Table illustrating breakdown of frequency data for HADS-A

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	.0	1	.8	.8	.8
	1.0	2	1.6	1.6	2.4
	2.0	5	4.1	4.1	6.5
	3.0	6	4.9	4.9	11.4
	4.0	8	6.5	6.5	17.9
	5.0	9	7.3	7.3	25.2
	6.0	12	9.8	9.8	35.0
	7.0	10	8.1	8.1	43.1
	8.0	14	11.4	11.4	54.5
	9.0	7	5.7	5.7	60.2
	10.0	9	7.3	7.3	67.5
	11.0	7	5.7	5.7	73.2
	12.0	8	6.5	6.5	79.7
	13.0	6	4.9	4.9	84.6
	14.0	5	4.1	4.1	88.6
	15.0	4	3.3	3.3	91.9
	16.0	5	4.1	4.1	95.9
	17.0	2	1.6	1.6	97.6
	19.0	2	1.6	1.6	99.2
	20.0	1	.8	.8	100.0
	Total	**123**	**100.0**	**100.0**	

Appendix F[i]: Correlations matrix for FAS data

	FAS	Frontal	Left Frontal	Left Parietal	Left Temporal	Right Frontal	Right Parietal
FAS	1.00	.036	-.158	-.195*	-.186*	.273**	.188*
Frontal	.036	1.000	-.252*	-.059	-.080	-.144	-.074
Left Frontal	-.158	-.252*	1.000	-.224*	-.302**	-.544**	-.278**
Left Parietal	-.195*	-.059	-.224*	1.000	-.071	-.128	-.065
Left Temporal	-.186*	-.080	-.302**	-.071	1.000	-.173	-.088
Right Frontal	.273**	-.144	-.544**	-.128	-.173	1.000	-.159
Right Parietal	.188*	-.074	-.278**	-.065	-.088	-.159	1.000
TOPF	.436**	.042	.191*	-.221*	-.238*	.053	-.049
GNT	.377**	.175	.070	-.127	-.227*	.068	-.055
HADS-D	-.246*	.007	.097	-.065	.026	-.082	-.032
Gender	.085	-.071	.152	.098	-.068	-.013	-.212*
Education	.338**	.050	.012	-.108	-.194*	.095	.076
Tumour Type	.170	-.134	-.140	-.119	.272**	.069	.084

* $p < .05$; **$p < .01$

Appendix F[ii]: Correlations matrix for FAS data

	TOPF	GNT	HADS-D	Gender	Education	Tumour Type
FAS	.436**	.377**	-.246*	.085	.338**	.170
Frontal	.042	.175	.007	-.071	.050	-.134
Left Frontal	.191*	.070	.097	.152	.012	-.140
Left Parietal	-.221*	-.127	-.065	.098	-.108	-.119
Left Temporal	-.238*	-.227*	.026	-.068	-.194*	.272**
Right Frontal	.053	.068	-.082	-.013	.095	.069
Right Parietal	-.049	-.055	-.032	-.212*	.076	.084
TOPF	1.00	.450**	-.145	.117	.198*	.109
GNT	.450**	1.00	-.051	-.191*	.138	.063
HADS-D	-.145	-.051	1.000	.120	.052	-.162
Gender	.117	-.191*	.120	1.000	.075	-.315**
Education	.198*	.138	.052	.075	1.000	.127
Tumour Type	.109	.063	-.162	-.315**	.127	1.000

* $p < .05$; **$p < .01$