Bridging Neurology and Psychology: Investigating Accelerated Forgetting in Temporal Lobe Epilepsy and the Impact of Psychological States on Awake Craniotomy Recovery

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THESIS PORTFOLIO: CANDIDATE DECLARATION

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Declaration and signature of candidate
I confirm that the thesis submitted is the outcome of work that I have undertaken during my programme of study, and except where explicitly stated, it is all my own work. I confirm that the decision to submit this thesis is my own. I confirm that except where explicitly stated, the work has not been submitted for another academic award. I confirm that the work has been conducted ethically and that I have maintained the anonymity of research participants at all times within the thesis. Signed:  Date: 30th May 2025

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Thesis Abstract

This thesis brings together three studies at the interface of neurology and psychology, with the overarching aim of improving the detection and understanding of how psychological dimensions are intertwined with specific neurological presentations. Implications relate to the patient-centred management of memory and mood-related challenges in neurological populations.

Paper One presents a literature review of Accelerated Long-Term Forgetting (ALF) in Temporal Lobe Epilepsy (TLE). Fourteen quasi-experimental studies (2014-2024) were critically appraised against Joanna Briggs Institute criteria and key ALF-specific methodological considerations. Despite heterogeneous methods, consistent evidence emerged that verbal word-list paradigms detect ALF within hours of learning, whereas narrative and visual based tasks yield more variable results. Few studies assessed both recall and recognition, or considered the impact of ceiling or floor effects, highlighting gaps in methodological standardisation. The review underscores the need for ecologically valid, multi-modal, and methodologically rigorous tools to bridge the disconnect between patients' experiences of forgetting and clinical test outcomes.

Paper Two reports a cohort study of adults undergoing awake craniotomy. Pre-operative anxiety and depression were measured through validated, self-report scales. Intra-operative and post-operative pain, quality of life, and patients' subjective assessments of their mood, cognition, speech, and motor function were tracked at one-month and six-month follow-up. Findings indicate that pre-operative depression significantly predicts higher intra-operative pain and poorer early quality of life. Pre-operative anxiety showed significant prediction of later quality of life. The study also considers demographic and clinical predictors of pre-operative anxiety, examining the potential mitigating role of pre-operative psychological preparation. The findings highlight the clinical value of pre-surgical

psychological screening and targeted interventions to optimise surgery tolerance and recovery.

The third paper provides an executive summary of the empirical research presented in Paper Two. The summary distils key findings, their relevance for recovery, and implications for key stakeholders. It translates the findings into accessible insights, tailored for patients, their loved ones, and healthcare professionals. The findings emphasise how pre-operative emotional states can influence recovery and underscore the importance of holistic, patient-focused care in the context of awake brain surgery.

Collectively, this thesis highlights the interplay between neurological status and psychological well-being. It calls for robust, methodologically sound research to better understand and assess cognitive and affective sequelae, and advocates for the integration of tailored psychological support within neurological and neurosurgical care pathways – ultimately aiming to enhance both clinician practice and patient experience.

Paper One

Accelerated Long-Term Forgetting in Temporal Lobe Epilepsy: A Review of Detection Methods and Materials

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(Aims and scope of the journal can be found in Appendix A)

Abstract

Accelerated Long-Term Forgetting (ALF) is a phenomenon where memories are retained normally in the short term but decay at an abnormally rapid rate over extended intervals (Blake, 2000; Kapur et al., 1997). This paper aims to review the methods used to detect ALF in Temporal Lobe Epilepsy (TLE), and the adherence of research to recommended guidelines. A systematic search identified 14 studies utilising verbal, visual, and autobiographical memory tasks with varying materials and time delays. Key findings reveal significant heterogeneity in methodologies, including differences in task design, control group matching, and delay intervals. Word lists emerged as sensitive tools for detecting ALF, revealing deficits within hours post-learning (Audrain & McAndrews, 2019; Hoefeijzers et al., 2015). Conversely, narrative-based tasks provided mixed results, requiring longer delays to observe ALF (Cassell et al., 2016; Contador et al., 2021; Laverick et al., 2021).

Visual memory assessments showed potential to be reliable measures, but studies were limited by methodological inconsistencies (Cassell et al., 2016; Puteikis et al., 2023). Few studies evaluated both recall and recognition processes, despite evidence suggesting distinct neural mechanisms for these memory types (Yonelinas et al., 2024). Furthermore, patient-reported difficulties highlight the need for ecologically valid assessments, particularly for episodic memory (Lemesle et al., 2022; Tramoni et al., 2011). This review underscores the importance of adhering to standardised protocols to improve comparability and utility of research. Developing reliable tools for ALF detection remains critical to addressing the disconnect between neuropsychological test results and patients' lived experiences, paving the way for targeted interventions.

Keywords: Temporal Lobe Epilepsy, Accelerated Long-Term Forgetting, Neurocognitive Testing, Verbal Memory, Visual Memory, Episodic Memory

Introduction

Fifty million people suffer from a form of epilepsy (World Health Organisation, 2024), making it the most common neurological disease globally, affecting people of all ages. It is a chronic condition, characterised by two (or more) recurrent unprovoked seizures, caused by excessive electrical discharge in a group of brain cells (International League Against Epilepsy; ILAE, 2014).

Temporal Lobe Epilepsy (TLE), i.e., seizures that arise from anywhere within the temporal lobe of the brain, is the most common form of adult epilepsy (Tatum, 2012). It can be associated with a range of causes, most commonly hippocampal sclerosis, infections, benign tumours, traumatic brain injury, or vascular abnormalities (McIntosh & Das., 2019). Studies have shown that recurrent seizures impact all areas of cognition, including intelligence, language, visuoperception, memory, executive function, and motor speed (Hermann et al., 2006). The specific symptoms of focal seizures reflect the brain network implicated, for example abnormal activation in motor areas would impair motor control resulting in jerks, twitches, or automations of particular muscle groups (Ghulaxe et al., 2023).

Most TLE seizures start in the Medial Temporal Lobe (MTL), which contains structures essential for declarative memory (Squire et al., 2004). TLE seizures are typically associated with atrophy of the hippocampus (i.e., hippocampal sclerosis) and anterior thalamus (Bercovici et al., 2012; Chauhan et al., 2022); areas associated with conscious long-term memory recall and recognition (Hotting et al., 2010). Several studies also outline working memory deficits in temporal lobe epilepsy including visuospatial (Abrahams et al., 1999) and verbal deficits (Wagner et al., 2013).

Remote/Long Term Memory

Remote or Long-Term Memory (LTM) refers to memories from the distant past. Explicit LTM can include episodic memories., i.e., memories of personal experiences from an individual's own life (autobiographical memory) and specific events in time. It also encompasses semantic knowledge i.e., memory for facts and concepts, general knowledge about the world such as the meaning of a word or the capital city of a country.

For patients with TLE, studies have explored the impact of seizures on LTM through assessing a range of materials, with some competing findings. Seizure frequency has been shown to worsen episodic memory, including autobiographical incidents and news-events, whilst sparing semantic memory (Voltzenlogel et al., 2014), with Lah et al., (2006) showing that people with TLE show impairments for public events disproportionate to the loss of autobiographical events. In contrast, a review of research published between 1990 and 2014 found evidence for the disturbance of semantic memory in patients with TLE (Jaimes-Bautista et al., 2015). However, the authors stress that it is important to consider that the majority of tests used to evaluate semantic memory involve other cognitive processes (e.g., attention, executive function, language), so it is possible that semantic dysfunction in TLE is secondary to deficits in other processes.

Accelerated Long-Term Forgetting

"Accelerated Long-Term Forgetting" (ALF) refers to the phenomenon whereby memories are retained normally in the short term, but then are forgotten at an abnormally rapid rate in the long term. The term was first coined by Blake (2000) and has since been commonly used, though prior to this the phenomenon has been described as "accelerated forgetting" "long term forgetting" "long-term amnesia" "transient amnesia" (Kapur et al., 1997; Hodges & Warlow, 1990; Geurts et al., 2015). However, these terms are not synonymous. For example, Liampas et al. (2021) state that transient amnesia episodes resolve

in 24 hours with full recovery, whilst Stilling et al. (2022) describe a case study of long-term amnesia where the patient's memory difficulties persisted for eight months. As such, for the purposes of this paper, only the term ALF will be used.

The phenomenon was first described by De Renzi and Lucchelli (1993) in a case study of a 26-year old man who had become cyanotic following a farming accident. Since then, many further case studies have been published with a range of aetiologies, though the majority experienced temporal lobe epilepsy. Consequently, ALF group studies have mainly focused on people with temporal lobe epilepsy. However, the evidence for ALF in TLE has been extremely mixed (Elliot et al., 2014), with some studies detecting ALF in TLE and others not. The inconsistency in literature reflects the complex interplay of memory and epilepsy, with differences in underlying pathology, cognitive reserve, duration of epilepsy, epilepsy treatment all contributing to varying results.

It is also worth noting that the term "accelerated" in ALF may be somewhat misleading. While it suggests a rapid rate of forgetting, the reality of the phenomenon is more nuanced. As discussed by Mameniškienė et al., (2020), ALF may emerge from an inability to consolidate memories over time, rather than an actual acceleration of memory decay. As such, the term "accelerated" may be a misnomer and not fully capture the underlying mechanisms involved. Nevertheless, regardless of the underlying mechanism of ALF, the clinical importance of effective and accurate detection remains. In the absence of rigorous research into appropriate detection methods, service users with long-term memory problems continue to suffer.

Why Is ALF So Difficult to Study/Detect?

A significant issue in clinical practice and research is the narrow window of time within which standardised memory tests (e.g., the Repeatable Battery for the Assessment of

Neurological Status; Randolph, 1998) are typically administered, often only assessing recall over a 20-30-minute interval. This limitation makes existing tests inappropriate for detecting ALF where memory declines more steeply over extended periods beyond 30 minutes. Clinicians may encounter patients who report memory difficulties, yet their performance on memory tests fall within normal ranges. Consequently, it remains difficult to ascertain the severity or nature of memory complaints based only on self-report (Reed, 2019).

Furthermore, research into forgetting rates can be fraught with methodological issues, particularly with control groups and the suitability of test materials. As standardised tests or normative data for ALF are limited, researchers typically use control groups to compare forgetting rates in healthy participants against those with TLE. However, the criteria for matching control groups to TLE patient groups are inconsistent across studies.

One well-established extraneous factor influencing memory is intelligence (Alexander & Smales, 1997; Chooi, 2012; Cohen & Sandberg., 1977); though the relationship between intelligence and forgetting is less clear. Despite this, not all studies match groups based on Intelligence Quotient (IQ), and when they do the methods of measurement can vary. For example, Mameniskiene et al. (2020) did not match IQ, whilst Holdstock et al. (2002) used the Wechsler Adult Intelligence Scale-Revised, and Hoefeijzers et al. (2015) matched participants based on years of education. The recruitment of control participants can also be criticised with studies such as Bell et al., (2005) recruiting friends and family as control participants, a method that risks bias.

In addition to issues surrounding controls and participant recruitment, test materials and procedures used in studies investigating ALF vary significantly, posing challenges for reliability and comparison. Some studies (e.g., Miller et al., 2015) use standardised tests but extend the delay period whilst others design their own materials (e.g., Cassell et al., 2016) specifically for measuring ALF and in an effort to increase the ecological validity of the

results. The type of materials used to assess memory also differs; some studies assess both verbal and visual memory across recall and recognition tasks, whilst others focus more narrowly. For instance, Blake (2000) only used verbal tasks, and Bell et al. (2005) examined recall but not recognition. This distinction is critical because recall and recognition engage different neural circuits, with recall depending more on the hippocampus and recognition involving broader cortical areas (Audrain & McAndrews, 2019). Thus, the results from studies in this area should be generalised with caution.

Even within a single domain of memory, ALF has been studied using a wide range of tasks, including simple memory lists (Polat et al., 2020), stories involving schemas and context-bound information (Tramoni et al., 2011), navigational tasks (Cassell et al., 2016) and autobiographical memory (Steimel et al., 2023). This variation in materials and tasks make it challenging to draw consistent conclusions across studies and to determine which assessments are most useful for clinicians trying to reliably detect and assess ALF.

Further complicating matters, group studies often suffer from floor effects. For example, Manes et al. (2005) reported that four patients scored zero on recall tasks after six weeks, making it difficult to discern meaningful differences. Moreover, delay intervals in ALF research vary widely, from 24 hours (Muhlert et al., 2010) to six weeks (Wilkinson et al., 2012). This variation introduces another layer of inconsistency, complicating the comparison of findings across studies.

The wide variability in study designs and materials hinders the development of clear, practical guidelines for clinical application. Without any assessment tools, it is difficult to effectively support patients suffering with long-term memory loss and target any cognitive rehabilitation interventions. Futhermore, the psychological impact of memory difficulties is well-documented (Giovagnoli & Avanzini, 2000; Langfitt et al., 2007; Cano-López et al.,

2022). Patients report experiencing loss of precious memories e.g., weddings, birth of their children etc, loss of identity, and frustration in their ability to function day to day. Although less well documented, patients with ALF experience the added load of a lack of validation and explanation for their difficulties when told their test results fall within normal ranges. As such, it is essential that studies focused on developing a reliable test for detecting ALF are methodologically sound and consistent.

A key review paper by Elliot et al., (2014) highlights the inconsistencies in ALF research methods, which have contributed to mixed findings. The authors propose seven key recommendations (outlined in Table 1) aimed at improving reliability and detection of ALF, whilst also evaluating the extent to which studies conducted between 1991 and 2013 have adhered to these guidelines. Ultimately, the authors highlight the need for appropriate tests, that can eventually be used clinically, to measure ALF and stress the clinical importance of investigating this phenomenon.

Table 1

Seven Methodological Considerations (and Definitions/Explanations) Outlined by Elliot et al., (2014) For Researchers Designing ALF Studies

Elliot et al., (2014) recommendations	Definitions/Explanations
1. Patient and control groups should be matched, at least for age and intellectual ability	Control groups are used to monitor healthy rates of forgetting. Control participants should be matched with the patient group to ensure the validity of the results.
2. Ideally, both verbal and non-verbal test material should be used	Verbal memory, a type of episodic memory, refers to memory for verbally presented information (Tatsumi & Watanabe, 2009). Non-verbal memory could include visual, episodic, and autobiographical memory. Visual memory refers to memory of information viewed by the eye and not available to other senses, or information that is stored in the brain as images (Magnussen, 2001). Episodic memory refers to the ability to recall specific events and experiences (e.g., a birthday party or a significant personal setback) – a kind of "mental time-travel" (Suddendorf et al., 2009). Autobiographical memory encompasses episodic memories but also includes general knowledge about one's own life and identity. It may involve broader life themes, such as the experience of being a teenager or growing up in a foreign country.
3. Ideally, forgetting should be measured using both recall and recognition tests	Recall tests measure the process of retrieving the information without a prompt/cue. Recognition tests measure the ability to identify familiar items previously encountered

4. Ceiling and floor effects should be avoided as far as possible	Ceiling effects occur when most participants score at the upper limit of the test. Floor effects occur when participants perform at the lower limit of the test.
5. The potential for rehearsal and repeated recall should be avoided as far as possible	Rehearsal is when participants internally repeat information to help remember it. Counter-measures could include not forewarning participants of later requests for recall, purposefully selecting stimuli which are difficult to rehearse, and asking participants who are related/close friends to not discuss material outside of the memory test. Repeated recall is when participants are asked to recall the same information on multiple occasions, leading to rehearsal. Counter-measures could include presenting different stimuli at each delay period or using large stimuli sets.
6. The immediate delay period should be long enough to ensure information is stored in LTM and retrieval is not reliant on STM processes	Best practice would be to test participants following a filled delay of at least 10 sec, giving a more accurate measure of learning and strengthening the validity of measuring forgetting from LTM later.
7. Effort should be made to equate initial learning (whilst avoiding overlearning)	There are several methods to match initial learning between groups to avoid bias. Researchers should be mindful of the potential implications in their interpretation of results.

Note: LTM=Long-Term Memory, STM=Short-Term Memory

Rationale/Aims

The last known review of research looking at the methodology used to detect ALF in TLE was conducted ten years ago, with specific recommendations made for researchers investigating ALF. Since 2014, further studies have explored new ways to detect ALF, providing insights into long-term memory processes. At the same time, the memory difficulties associated with ALF can cause significant distress to patients and clinically can go undetected (and unsupported) due to the lack of appropriate assessment methods.

As such, this review aims to explore whether research methodology has improved since 2014 and whether any strides have been made in terms of ALF detection methods. The paper will summarise and evaluate research conducted in the last ten years relating to detecting ALF in TLE populations, with a particular focus on the paradigm (i.e., recall and/or recognition) and testing materials (e.g., verbal, visuospatial, episodic) used to assess forgetting. The review also aims to critically appraise recent research against the methodological recommendations for research into accelerated forgetting, as outlined by Elliot et al., (2014).

Methodology

Search Strategy

An initial scoping search was carried out through Google Scholar and Cochrane Reviews to identify any existing systematic reviews and ascertain the feasibility and relevance of a review on ALF in TLE. A systematic search was conducted using search terms relating to ALF and TLE. Boolean operators were used to combine search terms ("AND") or add in variations of each search term ("OR"). The final search term was (Accelerated Long-Term Forgetting OR Accelerated Forgetting OR Long Term Forgetting) AND (Temporal Lobe Epilepsy OR Temporal Lobe Seizures). Search terms were developed based on those used by Elliot et al., (2014).

The databases used for the search were MEDLINE, PubMed Central, Science Direct, Elsevier, SCOPUS, and CINAHL Plus. To ensure the relevancy of the studies, only articles published from January 2014 to June 2024 were included. Additionally, reference lists of relevant papers and Google Scholar results were hand-searched for further suitable papers, though no further studies were added from this.

Inclusion Criteria

- Studies including a sample of adult (18+) participants with Temporal Lobe Epilepsy
- Studies that included participants with "Transient Epileptic Amnesia", only if neurological screening was used during recruitment and participants were identified as having seizures originating from the Temporal Lobe, or if the results were reported for a subgroup of participants with a Temporal Lobe Epilepsy diagnosis
- Studies published in a peer-reviewed journal
- Studies that compared rates of forgetting in TLE with healthy control participants, in a quasi-experimental design

Exclusion Criteria

- Studies on children (below the age of 18), as the memory of children qualitatively differs from adults
- Review papers, magazine articles, book chapters etc.
- Studies only involving healthy participants.
- Studies where evaluating rates of forgetting is not the primary aim of the paper e.g., papers looking at the impact of an intervention
- Studies looking at the experience of patients with memory difficulties/using qualitative data

Publication Bias

As discussed by Nair (2019), publication bias refers to the failure to publish the results of studies with statistically insignificant or negative results. To consider the impact of publication bias, grey literature was also searched. Due to a cyber-attack, the British Library Electronic Theses Online Service (EThOS) Database was inaccessible at the time of the search. Subsequently, the search for grey literature was conducted via STORE (Staffordshire University internal repository of theses) which yielded zero results.

A search of dissertations and theses on ProQuest was conducted which produced 14 results. Two of these were included in the final sample of papers.

Critical Appraisal

The papers in this review were assessed using the quasi-experimental version of the Joanna Briggs Institute's (JBI) critical appraisal tools for assessing the trustworthiness, relevance, and results of published papers (Barker, 2024). The JBI tool has been used in the development of this review as studies comparing the efficacy and validity of appraisal tools

have demonstrated the JBI to be the most coherent overall, due to its focus on congruity between research methods and research design (Hannes et al., 2010). In addition to the JBI tool, Elliot et al., (2014) discusses methodological issues when assessing ALF in research, making seven recommendations for researchers to consider (Table 1). These seven criteria were also use to assess the degree to which the studies consider key methodological issues in this area.

The results of the critical appraisal can be seen in Appendix B and C. For both appraisal tools, a number scoring system was used to help evaluate and compare studies – a score of 0 was given if the criteria were not met, 1 if the criteria were partially met, and 2 if the criteria were fully met. Percentages were calculated by dividing the sum of each study's ratings by the number of criteria, multiplied by 100.

Synthesis Method

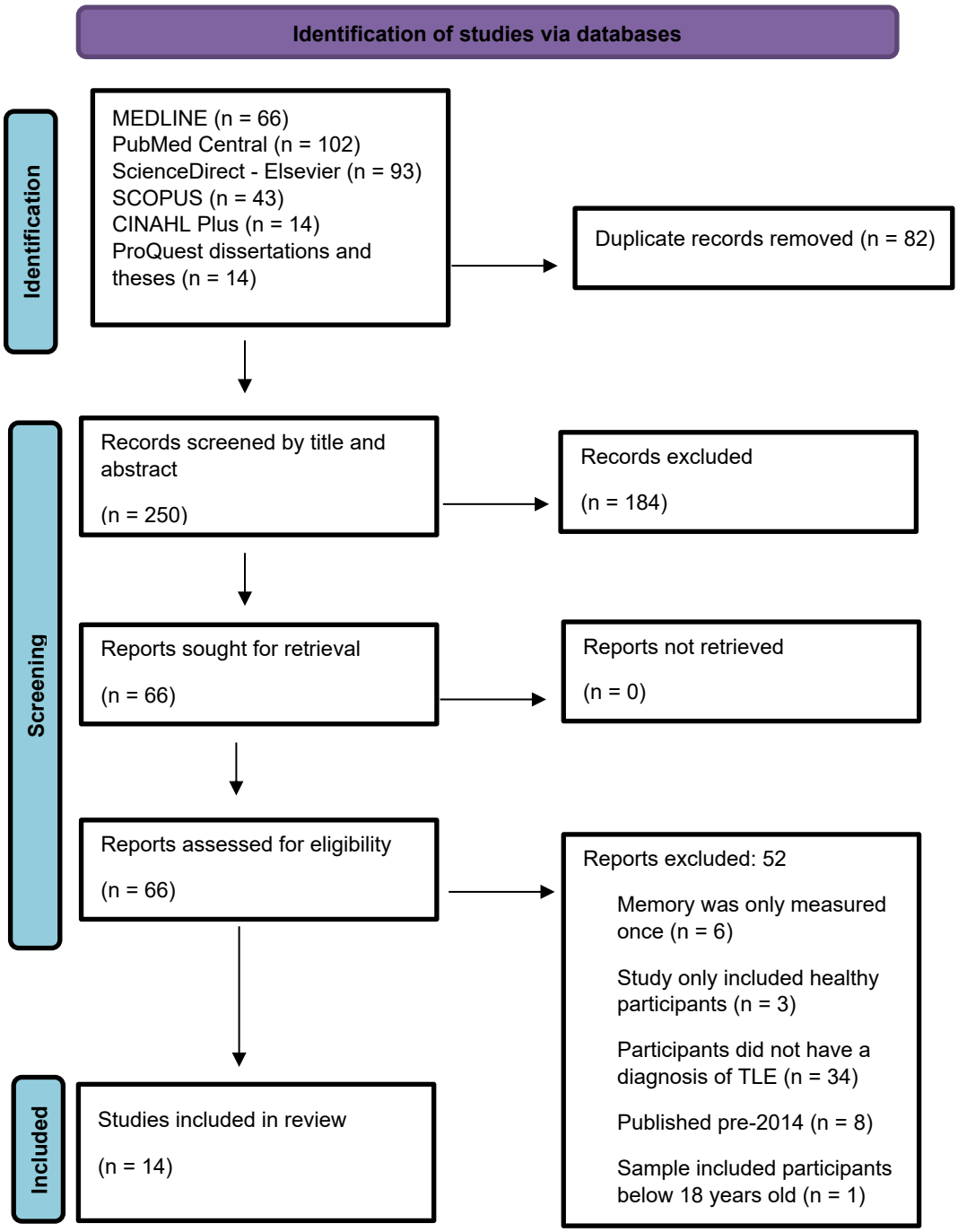
Due to the range of materials used across the papers, and the discrepancies in procedure and delay times, a narrative synthesis method was adopted. Given the heterogeneity seen in the literature, it was not considered appropriate to conduct a meta-analysis. Guidance from Popay et al (2006) on conducting a narrative synthesis in systemic reviews was used, and organisation of results was informed by Elliot et al., (2014).

Study Selection

The initial search yielded 332 studies in total (see Figure 1 for a flowchart). All citations were imported into RefWorks; a web-based reference manager tool. After duplicates were removed, 250 studies remained. Studies were screened for relevancy based on their title and abstract, and 184 studies were excluded. The full-texts of the remaining 66 studies were evaluated and 52 were excluded on the basis of the inclusion/exclusion criteria. In total, 14 studies met the criteria.

Figure 1

PRISMA Flow Diagram Showing the Study Identification Process



Results

All 14 studies were quasi-experimental designs, comparing patient(/s) with Temporal Lobe Epilepsy to control groups, on a range of memory tests at multiple time points. A summary of the studies characteristics is shown in Table 2.

With regards to overall quality, differences were observed between the two tools. Casell et al., (2016), Contador et al., (2021), Laverick et al., (2021) and Lah et al., (2014) scored 100% on the JBI tool whilst only Evans et al., (2014) scored 100% against the recommendations outlined by Elliot et al., (2014). Interestingly, Lah et al., (2014) ranked 12th when assessed against the Elliot et al., (2014) recommendations, meeting only 14.3% of the criteria. Thus, demonstrating that, despite being a high scoring quasi-experimental design, it is important to consider criteria specific to ALF when appraising studies in this area. Using guidance from the two tools, areas where the studies were most problematic are discussed in further detail.

Table 2

Study Characteristics and Results

Author(s)/Year	Participants	Matched	Tests	Delay intervals	Summary of results
Audrain & McAndrews (2019)	TLE = 23 Controls = 24 recruited via online data platform	Age Gender	Object-Scene pairs (Item Memory)	15 minutes 90 minutes 6 hours 16 hours 72 hours	ALF reliably present by 72 hours. Effect sizes indicated that increased forgetting was present at 90 minutes and marginally significant by 6 hours
Carlesimo et al., (2017)	TLE = 1 (case study) Controls = 18, recruitment unknown	Age Gender Level of education	Word list Faces	30 minutes 1 hour 7 days	No evidence of ALF
Cassell et al., (2016)	TLE = 18 Controls = 18 via volunteers	Age Gender Level of education IQ	Stories and Routes	30 seconds 10 minutes 1 day 1 week	ALF was demonstrated on the verbal task. On the visuospatial task, TLE participants forgot material at an accelerated rate between 30 seconds and 10 minutes, but comparable forgetting thereafter.
Contador et al., (2017)	TLE = 5 Controls = 10, recruitment unknown	Age Gender Years of education IQ	Stories and Routes (Spanish version)	30 seconds 10 minutes 1 day 1 week	No evidence of ALF

Contador et al., (2021)	TLE = 14 Controls = 14, recruitment unknown	Age Gender Years of education IQ	Stories and Routes (Spanish version)	30 seconds 10 minutes 1 day 1 week	No evidence of ALF
Evans et al., (2014)	TLE = 6 Controls = 25 volunteers	Age Gender Years of education IQ Hand laterality Mood	Visual Scenes Test Stories (from Isaac & Mayes, 1999)	Immediate 30 minutes 1 week	ALF demonstrated for spatial and descriptive free recall, visual recognition, story recall and story recognition
Hoefeijzers et al., (2015)	TLE = 11 Controls = 16 volunteers	Age Years of education	Word list	30 minutes 3 hours 8 hours 24 hours	ALF at 3, 8, and 24 hours delay. Retention dropped significantly more between 30 minutes and 8 hours.
Lah et al., (2014)	TLE = 23 (12 with hippocampal abnormalities, 11 without) Controls = 27 friends & family of TLE participants	Age Gender Level of education IQ	Hopikins Verbal Learning Test - Revised (HVLT-R)	Immediate 30 minutes 1 day 1 week	TLE participants (with abnormalities) recalled significantly less words by 1-day delay. By day 7, both TLE groups recalled significantly less words than controls. No significant difference between TLE groups.

Laverick et al., (2021)	TLE = 14 Controls = 28 friends & family of researchers	Age	Crimes and Doors test	Immediate 30 minutes 24 hours 1 week	ALF demonstrated on both tasks. On Crimes test, significant main effect of group, delay, and interaction. On Doors test, significant differences between short vs long delay. ALF did not differ across task.
Lemesle et al., (2022)	TLE = 47 Controls = 35, recruitment unknown	Age Gender Years of education Hand laterality	Epireal Test Free and Cued Selective Reminding Test (FCSRT)	20 minutes 3 weeks	ALF was demonstrated on both the Epireal and FCSRT. No significant correlation between the Epireal and FCSRT
McArdle (2021)	TLE = 32 Controls = 11 outpatient cognitive neurology unit	None	Logical Memory Test Face-Name Associative Memory Exam (FNAME)	20 minutes	No evidence of ALF
Puteikis et al., (2023)	TLE = 33 Controls = 57 health workers from same hospital and health workers' friends/family	Age Gender	Rey Auditory Verbal Learning Test (RAVLT) Rey-Osterrieth Complex Figure Test (ROCFT) Short verbal story recall	30 minutes 4 weeks	ALF was demonstrated for left TLE. Participants with right TLE performed worse than controls at 30 minutes and 4 weeks. Verbal story recall was non-significant.

Ricci et al., (2015)	TLE = 21 Controls = 29, recruitment unknown	Age Level of education	Autobiographical experiences	30 minutes 24 hours 4 days	ALF was demonstrated for both recall and recognition
Talis (2021)	TLE = 15 Controls = 60 friends & family of TLE participants and primary researchers	Age Years of education	Logical Memory Test	Immediate 30 minutes	ALF was demonstrated - No significant difference in immediate memory and significant difference at 30 minutes recall.

Selection of Participants

A significant area of complexity when researching ALF and other memory deficits is the selection of participants. Since standardised tests with normative data are very limited for accelerated forgetting, studies compare with a healthy, matched control group to evaluate "normal" rates of forgetting. To maintain internal validity, control groups should be as similar to the patient group as possible, so that any differences seen in rates of forgetting can be attributed to TLE rather than any other difference in participant characteristics. However, there has been debate around which factors are important to consider when matching groups for accelerated forgetting, and in their review, Elliot et al., (2014) advise to match groups for at least age and general function by IQ or educational background.

Only one paper out of the 14 did not match controls with participants. McArdle (2021), a doctoral thesis, utilised archival data and compared TLE patients with other neurology outpatients seen at a cognitive neurology clinic for non-epileptic concerns. McArdle (2021) did not find any significant difference between their participants and controls on verbal or visual memory; however, it is plausible that their control group included participants with other neurological conditions impacting memory. Although studies have focused on TLE, ALF has been seen in neurodegenerative disorders and, according to a recent systematic review, could also be an early marker for Alzheimer's disease (Rodini et al., 2022). Furthermore, the TLE sample for McArdle (2021) was comprised of people with generalised, complex-partial and simple-partial seizures, with different seizure foci (left, right, or bilateral). In addition, the age at which the participant experienced their first seizure ranged from 1 years old to 62 years old, and frequency of seizures per year had a standard deviation of 268 (1.d.p). This introduces several confounding factors (Voltzenlogel et al. 2014; Karunanayaka et al., 2011; Rice et al., 2018). Due to the heterogeneity of the TLE

participant sample and the absence of matching, the validity of findings from McArdle (2021) is unclear at best.

Of the remaining 13 studies, 11 matched for both age and IQ or years of education, with both Puteikis et al., (2023) and Talis (2021) only matching for age. With many different types of memory (episodic, working memory, procedural etc) and "intelligence" being a multifaceted construct, the relationship between the two is a complex one. However, research generally agrees that people with high IQ's have a greater capacity to leverage their knowledge – supported by semantic and episodic long-term memory – to aid problem solving and pattern recognition (i.e., crystallised intelligence) (Neuro Launch, 2024). Although the relationship between "intelligence" and forgetting is less well-established, it remains important that differences in IQ are considered when comparing two groups on memory. This is especially meaningful when considering that duration of epilepsy is associated with ongoing cognitive deterioration and a widening discrepancy between pre-morbid functioning estimates and current IQ (Jokeit & Ebner, 2002). Moreover, several papers (Carlesimo et al., 2017; Hoefeijzers et al., 2015; Lemesle et al., 2022; Ricci et al., 2015; Talis, 2021) used years of education as an estimate of cognitive ability and, for patients with TLE, this is unlikely to be representative of current aptitude.

In terms of recruitment, three papers (Lah et al., 2014; Laverick et al., 2021; Puteikis et al., 2023) recruited their control group from family and/or friends of the patients or researchers. This can be problematic because of the risk of discussion among the participants and repeated rehearsal outside of testing sessions, weakening the validity and replicability of the results. It was noted however that Laverick et al., (2021) do try and control for this by limiting their recruitment of controls to only one per household.

Ceiling/Floor Effects

An area which was noticeably neglected by the papers relates to ceiling/floor effects. Both result in reduced variability in the data, potentially masking differences between participants, leading to inaccurate conclusions. Elliot et al., (2014) highlight the importance of considering ceiling/floor effects in ALF, as patients with TLE are at risk of reaching floor levels of memory tests whilst control participants are at risk of performing at ceiling levels. Consequently, variation in forgetting may be occurring beyond the test limits, but cannot be seen.

Notably, only 28.6% of the papers reviewed managed the impact of ceiling/floor effects, through post-hoc analysis or piloting materials before administering them. This illustrates the need to consider the sensitivity and range of materials used to assess both groups to ensure optimal difficulty.

Recall vs Recognition

A key recommendation by Elliot et al. (2014) was to examine both recall and recognition in memory assessments. However, most studies reviewed did not follow this guidance, with only four studies (Evans et al., 2014; Hoefeijzers et al., 2015; McArdle, 2021; Ricci et al., 2015) including both types of task. In these studies, differences between recall and recognition were either not observed or not analysed.

Notably, Contador et al. (2017; 2021) separately explored recognition and recall processes using similar materials but tested different patient groups. The 2017 paper focused on a case study of a 38-year old woman, while the 2021 study examined a mixed-sex cohort with a mean age of 24 years. These methodological differences complicate direct comparisons.

Nevertheless, research has shown that recall and recollection involve distinct processes, supported by different neural mechanisms, with recollection dependent upon the hippocampus whilst recognition/familiarity relies on the perirhinal cortex (Yonelinas et al., 2024). Overall, the limited exploration of the distinctions between recall and recognition in the reviewed papers underscores the need for further research to clarity their interaction in TLE patients and to better understand the underlying neural mechanisms.

Reliability of Measures

Using a well-established measure of memory recall/recognition ensures the availability of normative data and allows for confidence in its reliability and validity, as these measures have already been rigorously tested and analysed in prior research. Majority of the papers included utilised some kind of bespoke or novel material to measure ALF. The reliability (or lack thereof) of these measures used is one factor which can threaten the validity of the conclusions drawn (Barker et al., 2024). As such, best practice would be for authors to pilot any newly designed material to ensure they produce reliable and replicable results, before applying novel tests in full-scale studies. Cassell et al., (2016) demonstrate this in their study, where Story and Route task materials were piloted to ensure feasibility and equivalence of difficulty at each trial.

In contrast, Audrain and McAndrews (2019) developed Object-Scene pairs for their study. The topics for the materials chosen were Tools, Animals, and Food, and the materials were "not considered emotionally salient" (*p*.103), however the authors fail to explain why these particular themes were selected and how they determined a lack of emotional salience. Furthermore, the "organization of the timing of the encoding sessions, test sessions, and delays were decided verbally between patients and the experimenter" (*p*.103), introducing further variability and weakening the reliability of their results.

Appropriate Statistical Analysis

As highlighted by Barker et al., (2024), low statistical power is an important threat which can weaken the validity of inferences made about the statistical relationship between ALF and TLE. As seen when appraising the papers using the JBI tool (Appendix B), six papers failed to include a power analysis and/or effect sizes in their analysis.

Summary of Findings

The results have been organised into verbal memory tests, visual memory tests, and other tests, informed by existing reviews (Elliot et al., 2014; Hansen & Lautenbacher, 2017). Sections have been further divided into discussing the use of existing memory measures and the use of bespoke measures designed specifically for ALF research. Table 3 below lists all the measures used by studies reviewed in this paper.

Table 3

Measures Used in The Included Studies, By Type of Memory Measured Cross-Tabulated with Whether the Measure Is A Pre-Existing or Novel Test.

Type of measure	Existing measures	Novel measures
Verbal memory	Logical Memory subtests from the Wechsler Memory Scale (WMS; Wechsler, 2010) Hopkins Verbal Learning Test – Revised (HVLT-R; Benedict et al., 1998) Rey Auditory Verbal Learning Test (RAVLT; Lezak, 2012)	Word Lists (Carlesimo et al., 2017; Hoefeijzers et al., 2015) Stories (Contador et al., 2021; Cassell et al., 2016; Contador et al., 2017) Crimes subtest from the Crimes and Doors test (Baddeley et al., 2019)
Visual memory	Rey-Osterrieth Complex Figure test (ROCF) Face-Name Associative Memory Exam (FNAMES)	Routes (Cassell et al., 2017) Faces (Carlesimo et al., 2017) Doors subtest from the Crimes and Doors test (Baddeley et al., 2019) Visual Scenes (Evans et al., 2014)
Episodic/Autobiographical memory	None included	Epireal Test (Lemesle et al., 2022) Experiences from assessment appointment (Ricci et al., 2015)

Verbal Memory Tests

Out of the 14 studies reviewed, 11 assessed ALF using verbal memory tests. Among these 11, four papers utilised existing measures, namely the Logical Memory Test (LMT), the Hopkins Verbal Learning Test – Revised (HVLT-R; Benedict et al., 1998), and the Rey Auditory Verbal Learning Test (RAVLT; Lezak, 2012). The HVLT-R and the RAVLT use lists of words to measure verbal memory, whilst the LMT, a subtest of the Wechsler Memory Scale (WMS, Wechsler, 2010) assesses verbal memory for stories. The LMT is the most frequently administered WMS subtest (Ahn et al., 2020) and has been translated into over 20 languages, highlighting its' widespread applicability. The remaining seven studies tested materials/procedures designed specifically for detecting ALF.

Existing Memory Measures

Of the four studies examining verbal memory with pre-existing measures, two employed the LMT. Both were unpublished doctoral dissertations utilising existing data from patients' medical records and neurology outpatient databases. Clinically, the WMS (which includes the LMT) is widely used in neuropsychology and often forms part of a routine battery of tests administered to patients with potential memory deficits. A significant advantage of using known tools is not only having established psychometric properties and good reliability metrics, but also that patients suspected of ALF may have already undergone a WMS, providing baseline data for longitudinal comparisons.

The LMT has a greater likelihood of reflecting functional impairment (i.e., ecological validity) compared to HVLT-R and RAVLT as it involves recalling aspects of stories rather than lists of words. Story-based tasks more closely mirror everyday memory challenges faced by patients, such as remembering events or conversations (Higginson et al., 2000; Butler & Zeman, 2008). Interestingly, Puteikis et al., (2023) found contrasting results between using a short verbal story recall task (VLS) and RAVLT in patients with TLE. Evidence for ALF was

detected with the RAVLT tool, but not with the VLS which was more reflective of patients' subjective self-reports. However, in this study patterns of ALF on the RAVLT were not prominent at the individual level, and the significant results were likely driven by subtle trends that emerged once the data was averaged.

In both the Talis (2021) and McArdle (2021) papers, the Logical Memory II task was administered only 20-30 minutes after Logical Memory I, with no subsequent recall tasks. This may be down to pressure to conform to the standardised instructions of the WSM or concerns that they only had one opportunity to administer the test in order to maintain its' validity, since the normative sample had only completed the test once. This may have also been done because consideration of ALF only emerged after memory was seen to be preserved on the short delay. Nevertheless, as stated by Elliot et al., (2014), a delay period of at least 30 minutes is "critical for claiming reliable evidence of ALF" (p. 28). Accordingly, other studies have found non-significant results at 30 minutes, with ALF only becoming evident at much longer delays of 24 hours and 1 week (e.g., Lah et al., 2014), with Hoefeijzers et al., (2015) showing detection of ALF after a three-hour delay at the earliest. Whilst Talis (2021) did find significantly increased forgetting in the TLE group compared to the control group after a 30-minute delay, re-testing at longer delays is advisable to substantiate these findings, particularly in a clinical setting on individual patients.

Lastly, a further limitation of many existing (verbal) memory tasks, including the LMT and HVLT-R, is their omission of a distractor task before testing immediate recall. This omission increases the risk of rehearsal effects, potentially confounding results by participants relying on short-term memory rather than long-term memory processes, as in the later conditions. The RAVLT addresses this issue by introducing a distractor word list for the participant to recall before being asked to recall the original list. As such, this ensures that the

participant does not rehearse the words and recall of the original list depends on long-term memory processes.

Novel Measures

Seven studies utilised novel measures to assess verbal memory, often employing lists of words (Carlesimo et al., 2017; Hoefeijzers et al., 2015) or stories (Contador et al., 2021; Cassell et al., 2016; Contador et al., 2017). Cassell et al., (2016) developed four stories, allowing assessment across four delay intervals without repeated recall and re-encoding. The stories were matched for difficulty at 30-second recall intervals, thus avoiding ceiling or floor effects for both participant groups. The stories were later translated and used by Contador et al., (2017; 2021) to assess recognition and recall, respectively. Distractor tasks were also included between learning and initial recall, with participants instructed not to rehearse the material.

Results from story-based studies were mixed. Cassell et al., (2016) observed increasingly faster forgetting in the TLE group compared to controls, but this difference only became statistically significant at the one-week interval. In contrast, the Spanish versions by Contador et al., (2017; 2021) found no evidence of ALF, even at one week. Methodological differences may account for these discrepancies, as ceiling and floor effects were noted in the latter studies, but were controlled for in Cassell et al., (2016)'s work. Additionally, Cassell et al., (2016) reported that 28% of their TLE participants experienced seizures during the study week, whilst Contador et al., (2021) recruited TLE participants who reported that their seizures were well controlled, with 79% having experienced two or less seizures in the last year. It is possible that participants in the Cassell et al., (2016) study who were experiencing recurrent seizures during the study, encountered neural processes impacting memory consolidation and/or retrieval. Finally, although their results were non-significant, effect sizes

were moderate for Contador et al., (2021), implying low reliability of the stories test or possibly small sample sizes.

Novel tests like the Crimes and Doors test (Baddeley et al., 2019) have also been employed. Laverick et al., (2021) used this test to assess verbal memory through passages of texts describing specific crimes. ALF was detected, with recall significantly decreasing between 24 hours and one week.

While word lists can be criticised for lacking ecological validity, these studies remain valuable as it is important for research to explore verbal memory using a variety of materials to confidently draw conclusions. In addition, lists of words, to some extent, can reflect everyday memory tasks for patients e.g., recalling grocery lists or tasks to do. They also carry the advantage of being time efficient to administer. Furthermore, neutral word lists also minimise the impact of emotional salience on recall compared to stories or crimes (Yonelinas & Ritchey., 2015).

Lists of words have been used by both Carlesimo et al., (2017) and Hoefeijzers et al., (2015). In the case study of EF, Carlesimo et al., (2017) found that she demonstrated verbal memory recollection levels comparable to healthy controls at the 10- and 30-minute delay tests. However, her scores significantly declined by 1 hour, reaching floor levels by 1 week. Similarly, in a group study, Hoefeijzers et al., (2015) found that patients with TLE retained significantly fewer words than controls at 3, 8, and 24 hours. Looking at word/scene associations, Audrain and McAndrews (2019) also found that ALF was reliably present for item memory by 72 hours, though the effect sizes indicate that accelerated forgetting was present by as early as 90 minutes and “marginally significant” (p.103) by 6 hours delay.

Overall, the materials used to assess verbal memory consist of lists and narrative passages, each with their benefits and weaknesses. Ideally, for a comprehensive assessment,

both types of materials would be utilised to assess the nuances of patients' memory deficits, however this may not always be realistic or ethical. Although stories may be more functionally reflective, studies produced varying results whilst recent studies show that word lists have reliably detected ALF in TLE. In a clinical setting, consideration must be given to time restraints, the possibility of floor/ceiling effects, and patient-reported difficulties.

Visual Memory

From the 14 studies reviewed here, seven assessed ALF using visual memory (alongside verbal memory). Most of the papers developed original material for their research, with only one (Puteikis et al., 2023) using the Rey-Osterrieth Complex Figure test (ROCF); a well-established, commonly used tool for neuropsychological assessment (Zhang et al., 2021). This test requires participants to copy complex geometric shapes and then reproduce them from memory. Puteikis et al., (2023) observed a pattern consistent with ALF in participants with left TLE, with normal performance at 30 minutes but increased forgetting at four weeks. In contrast, participants with right TLE performed worse than controls at both time intervals. However, due to limited testing intervals and the absence of equated learning, it is unclear if these results are due to an earlier or greater acceleration of forgetting for those with right TLE. As suggested by Laverick et al., (2021), failing to perform at "normal" levels on initial tests does not necessarily eliminate the possibility of forgetting at an accelerated rate, but they suggest that a different term could be used to describe these cases, proposing the term "Speeded Long-term Forgetting" or SLF. Overall, the ROCF holds promise for assessing ALF in visual memory, but could be modified to include additional intervals to improve reliability and allow for detection at the earliest possible delay.

Aiming to better reflect patients' real-life experience of visual ALF, Cassell et al., (2017) designed a visuospatial task based on a driving route with landmarks and decision points. Interestingly, participants with TLE showed accelerated forgetting of routes only

between 30 seconds and 10 minutes after learning. At subsequent testing intervals (24 hours and 1 week), the forgetting rates between controls and participants were comparable. Using similar materials, Contador et al., (2017; 2021) found non-significant differences in rates of forgetting between TLE and control participants. As previously discussed, several methodological differences were highlighted between these studies. Furthermore, the TLE participant group tested in the Cassell et al., (2017) included patients with bilateral seizures, whereas Contador et al., (2021) did not. This is significant as spatial navigational processes have been suggested to involve bilateral medial temporal lobe interactions (Canovas et al., 2011). Furthermore, Cassell et al., (2017) note that their TLE participants complained of poor spatial navigation specifically, making the task more demanding for them.

Looking at the remaining studies, Evans et al., (2014) used visual scenes of various common locations (e.g., kitchen, park, bakery etc). Consideration was given to prevent ceiling and floor effects, and guessing from the participants was avoided by adding in items that were not natural to the scene. Distractor tasks were also used to prevent recall in between testing. ALF was observed in spatial free-recall and visual recognition tasks. Evans et al., (2014) also compared TLE participants pre and post epilepsy surgery and found that participants did not display ALF post-surgery, supporting the idea that ALF may be linked with seizure activity disrupting the consolidation process and that retention of visual memory can be improved by stabilising or eliminating seizures.

A further two papers used face recall tasks (Carlesimo et al., 2017; McArdle, 2021) to assess visual memory, but found no significant difference between TLE participants and controls. This is in contrast with previous literature which has shown accelerated forgetting for faces in patients with TLE (e.g., Hötting et al., 2010) Although using faces may have high ecological validity, face processing and recognition implicates neural networks outside of the medial temporal lobe, such as the prefrontal cortex, that are not involved in memory for non-

social objects (Lopatina et al., 2018), which may confound results and lead to unreliable findings.

Alternatively, Laverick et al. (2021) employed the "Doors" subtest of the Crimes and Doors Test (Baddeley et al., 2019). While no significant differences were detected between individual time intervals, combining short (e.g., immediate and 30-minute) and long delays (e.g., one day and one week) revealed ALF, indicating low sensitivity.

Overall, the mixed conflicting nature of the evidence supports the recommendations made by Elliot et al., (2014) that both verbal and visual memory should be assessed within the same group. Recent research further underscores the need to explore the interplay of verbal and visual memory, with distinct tests.

Autobiographical/Episodic memory

A small number of papers looked at autobiographical/episodic memory in the context of ALF in TLE.

Interested in naturalistic, multi-sensory episodic memory, Lemesle et al., (2022) designed the Epireal Test where during verbal list learning (the distractor task), researchers staged eight mini-events (e.g., asking participant to pass them a green binder) for participants to recall three weeks later. Results showed significant memory impairments in TLE participants compared to controls, with 76.6% performing below the 5th percentile of controls. Importantly, these impairments did not correlate with a standard verbal memory test, suggesting that the Epireal test captures a distinct memory domain. Furthermore, Lemesle et al., (2022) highlight that the Epireal had a higher effect size than the Free and Cued Selective Reminding Test (FCSRT). Ricci et al., (2015) also examined autobiographical recall, asking participants to recollect events from their assessment, such as

the researcher pausing the assessment to answer a phone-call. ALF was observed for both recall and recognition tasks in the TLE group.

These findings suggest that ALF extends beyond verbal and visual domains to encompass multisensory episodic experiences. Incorporating tools such as the Epireal Test into clinical settings could considerably improve the detection of ALF, as these tests align closely with patient-reported difficulties. While such tasks may appear time-consuming, they could be integrated into standard neuropsychological assessments. These studies also support Tramoni et al., (2011) who hypothesised that context-rich information and context-free information is processed uniquely.

Discussion

The present review aimed to explore the methods and procedures used over the last decade to detect ALF in people with TLE. The paper draws attention to the lack of standardised measures for assessing ALF, which creates challenges for clinicians. Whilst patients with TLE may perform within normal ranges on standard memory tests, they report severe memory difficulties in everyday life. This disconnect between neuropsychological testing and lived experience complicates the formulation of targeted care plans or interventions. The development of reliable, ecologically valid tools is essential for addressing these challenges.

Research into ALF has yielded mixed results, partly due to methodological inconsistences. A previous review by Elliot et al., (2014) outlined how these issues have hindered consensus in the field and provided key considerations for future research. Building on this, the current review focused on studies from the last ten years, focusing on methodological concerns and outlining the range of materials that can be used to detect ALF in TLE. Consistent with earlier recommendations, this review stresses the importance of assessing both verbal and visual given the mixed nature of results. This is further emphasised when considering evidence that seizure laterality can be related to the type of memory deficits seen (Willment & Golby, 2013). However, only six of the reviewed studies assessed both verbal and visual memory in the same TLE sample (Carlesimo et al., 2017; Cassell et al., 2016; Contador et al., 2017; 2021; Evans et al., 2014; Laverick et al., 2021; Puteikis et al., 2023), with just one study examining both recall and recognition processes (Evans et al., 2014). Notably, only one paper in the last decade adhered to all of Elliot et al.'s (2014) recommendations (Evans et al., 2014). This review indicates that a much greater focus on methodology considerations in ALF research is needed in order to achieve reliable, valid results.

For verbal memory, word lists emerged as a reliable tool providing consistent results, however when introducing stories or passages to make the test more reflective of everyday experiences, the results can be more mixed. Overall, word lists appear to be more sensitive for detecting ALF as early as 1 hour – 1.5 hours post-learning (Audrain & McAndrews, 2019; Carlesimo et al., 2017). In contrast, for narratives ALF may be more difficult to detect, only becoming evident after longer delays or in groups (e.g., one week in Cassell et al., 2016). This may be further explained by forgetting being related to emotional salience or arousal (LaBar & Phelps, 1998) or individual familiarity with the material (Tse et al., 2007). Clinically, testing intervals may need to be adjusted for individual patients depending on their baseline immediate memory, as some floor effects were noted by the last testing interval (e.g., Lah et al., 2014). Whilst word lists may be more efficient to administer, especially if the goal is to simply indicate the presence or absence of ALF, using a narrative may better capture more functional impairments.

For visual memory, this review suggested that ALF is more reliably detected when using visual materials rather than verbal. From a practical perspective, visual materials are also very accessible across IQ, disability, and education levels of patients in clinical settings. Tests involving faces, though ecologically valid, may confound results due to emotional salience and the involvement of other neural networks specific for face recognition. Tests such as the ROCF and route memory tasks (e.g., Cassell et al., 2016) are methodologically robust tests, demonstrated by their high scores on both the JBI and Elliot et al., (2014) criteria, though floor effects and additional delay intervals remain important considerations for the ROCF.

The use of tests looking at autobiographical memory, particularly episodic memory, remains underrepresented in ALF research. Both studies in this review assessing autobiographical memory detected ALF using easily replicable methods. These findings

suggest that incorporating episodic memory assessments into clinical practice, to complement existing tests, could better capture patients' everyday experiences, as memory in real-world contexts is inherently multisensory and context-rich. Tramoni et al., (2011) supported this notion, arguing that ALF demonstrates a disruption in the long-term consolidation process of episodic memory. Their study assessing both contextually-bound and context-free memory, after a six-week delay, participants showed significant impairments in the context-rich information but preserved context-free information. This pattern aligns with the theory that context-rich episodic memory and context-free semantic memory may follow different consolidation pathways.

This review, and the included papers, has several limitations. Firstly, the lack of additional raters to independently appraise the papers may introduce bias, although quality scores are provided as an indication of the papers' quality. The inclusion of grey literature partially mitigates publication bias, but the inability to fully search the EThOS system limits the breadth of grey literature considered. Consequently, some relevant research providing a different perspective on detecting ALF may have been omitted. In addition to this, ALF was detected largely due to trends that could only be detected once group data was pooled together. In order to create clinically useful tools, researchers must consider the sensitivity of tests at the individual level. On the other hand, some papers did show evidence for ALF at quite early time intervals (e.g., Audrain & McAndrews, 2019) or yielded non-significant results but with moderate effect sizes (e.g., Contador et al., 2021), but were limited by small samples/low statistical power. However, it is important to highlight that sample sizes are often small in TLE studies due to a limited pool of eligible participants, and Contator et al., (2021) point out that their sample size of 14 falls within the 50% central distribution of sample sizes in this area.

Despite some advances in exploring new ALF tests, progress in understanding and assessing ALF in TLE remained limited, with very few papers fully meeting the established appraisal criteria in the last decade. The review gives rise to several areas that could be explored in future research. A crucial focus should be refining procedures to address the methodological gaps highlighted in this – and previous – reviews. Once more consistent methodology can be seen in literature, more advanced reviews using meta-analyses could be used. Direct comparison of verbal and visual memory recall and recognition tasks could clarify the relative sensitivity and reliability of these measures, and establish the psychometric properties of tests. Of particular importance is establishing normative data for forgetting rates with longer delays for both healthy controls and TLE patients, as this would enable the development of clinical guidelines for ALF assessment. This has been illustrated by Miller et al., (2015) who provide normative data on three recall tests, based on a sample of 60 healthy participants, and suggest cut-offs for detecting ALF. However, these results should be substantiated with further studies. Finally, exploring neurological, social, and physical correlates of ALF in TLE populations may provide insights into underlying mechanisms and interventions.

Conclusions

This review highlights the complexities and challenges of assessing ALF in TLE. Despite the methodological issues discussed in this review, the presence of ALF in the majority of the studies included in this review demonstrates the robustness of the phenomenon. While the majority of studies indicate the presence of ALF, the lack of standardised testing procedures hinders the field's ability to draw robust conclusions. The disconnect between standard memory assessments and patients' reported memory difficulties further emphasises the need for reliable, ecologically valid tools that can better capture functional impairments.

Verbal and visual memory assessments have both demonstrated promise in detecting ALF, whilst the underrepresentation of autobiographical memory assessments points to an important avenue for future research. Additionally, the failure to consider differences in recall verses recognition processes further highlights the need for more research to tease apart the nuances of ALF. Moreover, greater attention to individual-level sensitivity, as well as the incorporation of contextual and emotionally salient factors into testing, could significantly enhance the area.

Future research should prioritise bridging the gap between experimental findings and clinical application. By addressing methodological limitations and expanding the scope of ALF studies to include broader neuropsychological, social, and physical factors, researchers can pave the way for targeted, evidence-based interventions. Such advancements are essential to equip clinicians with the tools needed to deliver more effective support to patients with TLE, ultimately improving their experience of healthcare.

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Appendices

Appendix A: The Clinical Neuropsychologist journal aims and scope

The Clinical Neuropsychologist (TCN) serves as the premier forum for (1) state-of-the-art clinically-relevant scientific research, (2) in-depth professional discussions of matters germane to evidence-based practice, and (3) clinical case studies in neuropsychology. Of particular interest are papers that can make *definitive statements* about a given topic (thereby having implications for the standards of clinical practice) and those with the potential to *expand today's clinical frontiers* (e.g., introduction of a disorder that is typically not under the purview of clinical neuropsychology, yet presents with neurocognitive sequelae; introduction of new assessment or intervention tools). Research on all age groups, and on both clinical and normal populations, is considered.

1. Scientific research. *TCN* publishes research that is of interest to practicing clinicians, with the over-arching goal of contributing to advances in evidence-based practice. Original empirical research, meta-analyses/systematic reviews, and critical integrative reviews of clinically-relevant topics are considered. Of particular interest are studies pertaining to the following:

- neuropsychological, behavioral, and psychiatric manifestations of neurodevelopmental, neurodegenerative, and neuropsychiatric conditions, and acquired brain disorders
- brain-behavior relationships, especially if pertaining to performance on clinical neuropsychological measures, or if pertaining to a specific disorder
- psychometrics and/or norms of clinical instruments
- forensic applications
- professional issues (e.g., credentialing, education and training, and ethics) and practice-related surveys

2. Professional discussions. TCN publishes both invited and unsolicited papers that contribute to the journal's over-arching goal of establishing (and raising) standards of practice. These include the following:

- practice guidelines, consensus statements, and position papers that guide clinicians and clinical educators
- invited opinions, commentaries, or discussions
- book reviews (solicited by the Book Review section editor)

3. Case studies. The *Grand Rounds in Clinical Neuropsychology* section of the journal is devoted to single case study presentations of interesting, timely, important, or unusual cases. Cases should be instructive and focus on the contributions that competent neuropsychological assessment make in terms of (a) elucidating brain-behavior relationships, (b) determining the functional status of patients, and (c) instructing intervention, treatment, rehabilitation, education, etc. Essential elements of a case study submission include the following:

- a well-documented history of the patient
- medical/neurologic/psychiatric findings, and neuroimaging (preferred, but not required)
- detailed results of neuropsychological evaluation
- discussion of differential diagnosis and relevent treatment/management considerations

An additional online forum, in the form of an annual online supplement, aims to provide an outlet for narrow interest sound practice research that may only be of benefit to clinicians whose services are provided in the context of other languages or cultures. For more information on the online supplement and the types of articles considered, please read

the TCN:OS Aims & Scope document here (PDF).

As a service to readers, select articles in each issue are available for CE credits, which are provided under the auspices of AACN via its website.

TCN and the AACN jointly sponsor a yearly competition for the best scholarly manuscript based on a student project. The winner will be announced at the AACN annual meeting (starting in 2016). The first-prize winner will receive a $1000 monetary award, and two runner-ups will receive $500 each.

Peer Review: All submitted manuscripts are subject to initial appraisal by the Editor-in-Chief, and, if found suitable for further consideration, are then peer reviewed by independent, anonymous expert referees. All peer review is single anonymized and submission is online via ScholarOne Manuscripts

Appendix B: JBI Critical Appraisal table

JBI Quasi-Experimental Design Critical Appraisal Tool/Authors (Year)	Cassell et al., (2016)	Contador et al., (2021)	Contador et al., (2017)	Lah et al., (2014)	Carlesimo et al., 2017	Evans et al., (2014)	Hoefeijzers et al., (2015)	Laverick et al., (2021)	Lemesle et al., (2022)	Puteikis et al., (2023)	Ricci et al., (2015)	Talis (2021)	Audrain & McAndrews (2019)	McArdle (2021)
Is it clear in the study what is the "cause" and what is the "effect" (i.e., there is no confusion about which variable comes first)?	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Was there a control group?	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Were participants included in any comparisons similar?	2	2	2	2	1	2	1	2	1	1	1	1	2	0
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	2	2	2	2	2	2	2	2	2	2	2	1	0	0

Were there multiple measurements of the outcome, both pre and post the intervention/exposure ?	2	2	2	2	2	1	2	2	2	1	2	0	2	0
Were the outcomes of participants included in any comparisons measured in the same way?	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Were outcomes measured in a reliable way?	2	2	2	2	1	2	1	2	1	2	1	2	0	2
Was appropriate statistical analysis used?	2	2	1	2	2	1	2	2	2	1	2	1	1	1
Total %	100	100	93.75	100	87.5	87.5	87.5	100	87.5	81.25	87.5	68.75	68.75	56.25

Appendix C: Elliot et al., (2014) Critical Appraisal Table

Recommendations /Author	Evans et al., (2014)	Cassell et al., (2016)	Contador et al., (2021)	Contador et al., (2017)	Hoefeijzers et al., (2015)	Laverick et al., (2021)	Carlesimo et al., 2017	Audrain & McAndrews (2019)	Ricci et al., (2015)	Lemesle et al., (2022)	Puteikis et al., (2023)	Lah et al., (2014)	McArdle (2021)	Talis (2021)
Patients and controls should be matched on age and general cognitive functioning/educational background	2	2	2	2	2	2	2	2	2	2	1	2	0	1
Verbal and non-verbal tests should be used	2	2	2	2	2	2	2	0	0	0	2	0	0	0
Ideally, recall and cued recall/recognition procedures should be used	2	0	0	0	2	0	0	0	2	0	0	0	2	0
Ceiling and floor effects should be avoided	2	2	2	2	0	0	0	0	0	0	0	0	0	0
The potential for rehearsal and repeated recall should be avoided	2	2	2	2	2	2	2	2	1	1	1	0	0	Unclear
To prevent that immediate recall can rely on short term memory it must be ensured	2	2	2	2	0	2	2	2	2	0	0	0	0	Unclear

that information is stored in long-term memory. A filled delay of at least10 s before immediate testing is recommended, to ensure that information is retrieved from long-term memory on both time points														
Efforts should be made to equate initial learning	2	2	2	0	2	2	0	2	0	2	0	0	0	0
Total %	100	85.7	85.7	71.4	71.4	71.4	57.1	57.1	50.0	35.7	28.6	14.3	14.3	7.1

Paper Two

Awake Craniotomies: The Impact of Pre-Operative Anxiety and Depression

The impact of anxiety and depression on post-operative pain, quality of life, and patients' subjective assessment of outcomes following an Awake Craniotomy

Iram Munir

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Word Count: 8111

Target journal: The British Journal of Clinical Psychology (Journal aims and scope can be found in Appendix H)

Abstract

Background: Awake craniotomies facilitate maximum safe brain tumour resection but can cause significant pre-operative anxiety and depression for patients. While psychological factors are known to influence post-operative outcomes more broadly, their specific impact following an awake craniotomy, particularly on longer-term outcomes, requires further investigation.

Aims: This study investigates the impact of pre-operative anxiety and depression on intra-operative and post-operative pain, quality of life, and patients' subjective assessments of their cognition, mood, speech, and motor function changes following an awake craniotomy. A secondary aim explored potential demographic and clinical predictors (age, sex, tumour grade, location and hemisphere of surgery) of pre-operative anxiety.

Method: Data were drawn from routine clinical outcome measures within an NHS neuropsychology service for 205 adults undergoing awake craniotomies (2018-2025). Measures included the Hospital Anxiety and Depression Scale (HADS), Functional Assessment of Cancer Therapy – Brain (FACT-Br), an internal pain questionnaire, and subjective outcome ratings. Analyses focused on one-month and six-month time points using separate samples, with multiple imputation employed. Ordinal and linear regression analyses were conducted, controlling for relevant covariates.

Results: Pre-operative depression significantly predicted higher levels of intra-operative pain (β=0.228, p=.024) and lower quality of life at one-month follow-up (β=-.102, p=.034). Pre-operative anxiety was not significantly associated with pain but showed a trend towards predicting lower quality of life at six months (β=-.087, p=.045, prior to covariate adjustment). Neither pre-operative anxiety nor depression consistently predicted subjective changes in

mood, speech, or motor function. No significant differences in pre-operative anxiety were found based on patient age, sex, tumour location, hemisphere, or grade.

Conclusions: Pre-operative depression appears to significantly impact early outcomes following awake craniotomy, specifically intra-operative pain experiences and quality of life within the first month. Pre-operative anxiety may have subtle, later influences on quality of life and subjective cognitive appraisals. The lack of association between demographic/clinical factors and pre-operative anxiety could reflect the impact of pre-operative neuropsychological input (i.e., psychology-led surgery preparation sessions). Routine screening, especially for depression, and tailored psychological support post operatively may be valuable in optimising "at-risk" patient's recovery trajectories after awake craniotomies.

Keywords: awake craniotomy, pre-operative anxiety, pre-operative depression, quality of life, longitudinal data

Introduction

Brain tumours, defined as the growth of abnormal cells in brain tissue, can originate primarily within the brain or metastasize from elsewhere. They are classified as benign (non-cancerous) or malignant (cancerous), though even benign tumours can cause significant harm depending on their location. The World Health Organisation (WHO) provides standardised classification (currently WHO CNS5), grading tumours based on biological behaviour. Low-grade tumours (Grades 1-2) are typically slower growing, though Grade 2 can invade tissue and turn malignant. High-grade tumours (Grades 3-4) are malignant and aggressive, particularly Grade 4, which grows and spreads rapidly (Torp et al., 2022)

These tumours present a significant epidemiological burden, with around 12,700 new cases annually in the U.K. (the 9th most common cancer), a figure projected to rise to 13,600 cases per year by 2038-2040 (Cancer Research UK., 2020). While survival rates vary, overall U.K. brain cancer survival has doubled over the last 50 years, highlighting treatment advancements but also the growing survivor population. This necessitates a research focus that extends beyond survival metrics to encompass the crucial aspects of long-term quality of life, functional recovery, and the overall wellbeing of patients after treatment.

Surgical resection is a cornerstone in the management of both primary brain tumours and accessible brain metastases in adults (NICE, 2021). The fundamental goal of neurosurgical intervention is maximal safe resection – removing as much of the tumour volume as possible while meticulously preserving surrounding healthy brain tissue responsible for critical neurological functions, such as movement, sensation, and language. Damage to healthy areas during surgery can lead to permanent neurological deficits, severely impacting a patient's functional independence and quality of life.

In this context, awake craniotomies (AC) are a highly valuable technique. AC allows the surgical team to perform real-time functional brain mapping during resection. In this procedure, the patient is deliberately kept awake and responsive for either the entirety or, more commonly, specific portions of the surgery. While the patient is awake, the neurosurgeon uses a small electrical probe to stimulate the brain in the vicinity of the tumour or lesion. Simultaneously, the patient is asked to perform specific tasks relevant to the function of the nearby brain tissue – for instance, naming objects, moving limbs, or describing sensations. If stimulation of a particular area disrupts the patient's ability to perform the corresponding task, that area is identified as functionally critical and is carefully avoided during tumour removal. This intraoperative mapping provides the surgeon with a personalized functional map of the patient's brain, guiding the resection margins to maximise removal while minimising the risk of postoperative neurological injury. Consequently, AC is associated with a low incidence of new permanent neurological deficits (approximately 1.7%) and often facilitates shorter postoperative hospital stays compared to traditional craniotomy under general anaesthesia for similarly located tumours (Hall et al., 2021).

Despite the benefits, AC procedures can understandably evoke significant anxiety and fear for patients. In neurosurgical patients, Perks et al., (2009) reports an incidence rate of approximately 89% for high pre-operative anxiety, highlighting the substantial psychological stress associated with impending brain surgery. The impact of pre-operative distress, particularly pre-operative anxiety and depression has been investigated in several studies.

Bunevicius et al. (2014) studied patients undergoing various types of brain surgery and found that higher levels of pre-surgical anxiety were significantly associated with lower health-related quality of life. Notably, anxiety measured before surgery predicted worse quality of life both pre-operatively and at three-months post-surgery, suggesting a lasting influence on recovery.

Pre-operative anxiety may also interact with cognitive function. Goebel et al. (2012) examined the relationship between affective state and cognitive performance in patients prior to surgery for intracranial tumours. While anxiety did not significantly contribute to cognitive performance in the overall sample, patients experiencing extreme levels of anxiety performed significantly worse on cognitive tests assessing working memory compared to those with low anxiety levels. This suggests that, while baseline neurocognitive measures may be generally valid for most, very high levels of anxiety can impair specific cognitive domains. In addition, Pranckeviciene et al. (2017) observed a significant correlation between higher distress levels and a greater number of subjective cognitive complaints reported by the patients themselves, particularly concerning memory, attention, and executive functions. This study raises the important point that a patient's perception of their cognitive abilities can be strongly influenced by their emotional state, even if objective testing does not show a deficit, though the persistence of these subjective complaints post-surgery was not examined.

Furthermore, preoperative anxiety can influence mood during the recovery period. D'Angelo et al. (2008) investigated psychological outcomes in 114 patients following brain tumour surgery. They found that the presence of higher anxiety before surgery was significantly correlated with the presence of depression at both one month and three months post-surgery. Logistic regression analysis confirmed that pre-operative anxiety was the primary determinant of depression at one-month follow-up.

The affective condition of a patient before surgery has been increasingly recognised as a significant factor that can influence post-operative recovery, including the experience of pain. Several systemic reviews and meta-analyses have synthesised evidence supporting the link between pre-operative depression and pain. Lee et al., (2023) completed a meta-analysis of 18 studies, and found that pre-operative depression was significantly associated with higher post-operative pain, greater than six months after major surgery. Similarly, Yang et

al., (2019) reviewed 33 studies and reported several significant pre-operative predictors of higher acute post-operative pain, including anxiety and depressive symptoms which had pooled odds ratios of 1.71 and 1.22 respectively.

However, a systemic review assessing the association between pre-operative depression and post-operative pain across a range of surgeries — including bariatric, breast, and orthopaedic procedures — reported substantial heterogeneity in results (Dadgostar et al., 2017). Of the 18 studies included, only 8 found a significant effect, while 10 did not. Importantly, none of the included studies focused on brain surgery, let alone awake brain surgery. This limitation highlights the need for more targeted research into whether similar relationships exist within neurosurgical and AC populations, where the psychological demands and physiological context differ markedly from other surgical types.

Looking at the link between pre-operative anxiety and post-operative pain, Valencia et al., (2022) investigated patients following craniotomy under general anaesthesia. They demonstrated that higher levels of pre-operative anxiety significantly predicted greater post-operative pain intensity at 1, 8, 24, and 48 hours after craniotomy. Specifically, the authors identified that patients scoring >24.5 on the Stat-Trait Anxiety Inventory (STAI) were significantly more likely to experience at least moderate pain 24 hours post-surgery. Furthermore, they found that males, younger age, and depression were also predictors of increased post-operative pain. This research demonstrates how early identification of at-risk patients before surgery could allow clinical teams (e.g., surgeons, anaesthesiologists, nurses, psychologists etc.,) to implement targeted strategies proactively for these individuals. Such early identifications could also allow healthcare professionals to potentially tailor adjuvant analgesic plans for those identified as “high-risk”. As such, by identifying significant risk factors, such as pre-operative anxiety, this offers a pathway to potentially improving post-craniotomy pain management.

However, the study by Valencia et al., (2022) has several key limitations. Firstly, the follow-up period was limited to only 48-hours post-operatively. Given other research demonstrating that patients can endure pain beyond the initial post-operative period (De Gray & Matta, 2005), further research is needed with longer follow-up periods to fully explore the links between pre-operative anxiety and post-operative pain. Additionally, although a useful tool, the STAI takes 20-minutes to administer which (as suggested by the authors) may be too long for routine clinical practice and unsuitable for some patients shortly after surgery. Therefore, studies should be repeated with other, shorter, quicker, post-operative anxiety screening tools that are more appropriate for routine clinical use.

While the above studies provide valuable insights into the detrimental effects of preoperative anxiety and depression in the broader neurosurgical population, they do not specifically focus on the unique cohort undergoing AC. The AC procedure, with its requirement for patient consciousness and active participation during surgery, likely imposes unique psychological challenges. The existing literature suggests that higher pre-operative anxiety and depression are associated with poorer quality of life, lower cognitive performance, increased risk of post-operative depression, and a more negative self-perception of cognitive function. These states may negatively influence not only the patient's immediate experience but could also shape their longer-term recovery trajectory and physical wellbeing.

More recently, in a systemic review of 24 papers, Mofatteh et al., (2022) concluded that the majority of studies showed that AC's performed by experienced teams does not cause an increase in anxiety, stress, or depression in patients. However, the review lays out several gaps in the literature, making strong recommendations for future research. Namely, the authors urge researchers to conduct studies which evaluate all phases of AC consistently – the majority of papers they reviewed did not assess outcomes at both pre and post-operative phases, with no study looking at pre-operative, intra-operative, and post-operative stages.

Additionally, the authors stress the importance of future research looking into influencing factors, such as operational details (e.g., lesion size/location) or duration of hospitalisation. Finally, echoing the limitations in pain research, the authors highlight the need for studies evaluating longer-term follow-up to better understand the sustained impact of the AC procedure.

As demonstrated, the relationship between pre-operative anxiety and post-operative outcomes is complex and likely mediated by various factors. As noted, patients' sex may play a role with studies often reporting higher pre-operative anxiety in women (Perks et al., 2009), although Valencia et al., (2022) paradoxically found that male sex predicted higher post-operative pain. Tumour characteristics themselves might also be influential. Mainio et al., (2003) found a significant difference in in pre-operative anxiety between patients with tumours located in the right versus left hemisphere. Similarly, tumour histology may also be an important factor, with Pringle et al., (1999) reporting that patients with a malignant tumour obtained significantly higher pre-operative anxiety scores compared with patients with other types of brain tumour, likely reflecting the prognostic implications associated with malignancy. These factors warrant consideration when evaluating the interplay between anxiety and outcomes after AC.

Research Aims and Hypotheses

While AC procedures are considered generally safe, significant gaps remain in our understanding of factors which influence post-operative recovery. Specifically, there is a need for research which consistently evaluates the impact of anxiety and depression across all phases of AC, explores mediating clinical and demographic factors, and utilises long-term follow-up to assess chronic outcomes.

As such, the current study aims to explore the impact of pre-operative anxiety and depression on post-operative pain, quality of life, and patients' own perception of their cognition, mood, motor functioning and speech. Importantly, the current study will include data from one month and six-month follow-up sessions to consider long-term outcomes. Furthermore, the study aims to explore the impact of mediating clinical and demographic factors. Based on previous literature, the following is hypothesised:

1. Patients with higher pre-operative anxiety or depression will report higher intra-operative pain and higher post-operative pain at one-month follow-up.
2. Patients with higher pre-operative anxiety or depression will report a lower quality of life at one-month and six-month follow-up.
3. Patients with higher pre-operative anxiety or depression will be more likely to rate their post-operative memory, cognition, mood, and language as worse compared to pre-operatively.
4. There will be a significant difference in pre-operative anxiety and depression (HADS) depending on patients' sex, age, tumour location, and tumour grade.

Method

Design

The study uses a retrospective cohort study design, using data routinely collected at a local neuropsychology NHS service. As part of their pre-operative and follow-up sessions with the service, patients undergoing an AC were asked to complete a series of questionnaires administered by an Assistant Psychologist or Clinical Neuropsychologist. Patients are all adults, aged 18 or above. The results were then stored in an internal database.

Data from 2018 to March 2025 were anonymised by clinicians providing direct care, removing any personal indefinable information (e.g., patient names, NHS numbers, etc.) before being shared with the research team.

Measures

Hospital Anxiety and Depression Scale (HADS): The HADS is a screening tool used to assess a patient's mood. The results are scored on a scale of 0 to 21 for both anxiety and depression. Scores indicate whether an individual is within the non-clinical range (0-7), mild range (8-10), moderate range (11-14), or severe range (15-21). The HADS is a widely used tool, with good validity and Cronbach's alpha of 0.83 (Bjelland et al., 2002).

Functional Assessment of Cancer Therapy – Brain (FACT-Br): The FACT-Br is a quality-of-life instrument that has been widely used with patients who have brain metastases and has undergone psychometric validation with such populations (Thavarajah et al., 2013). It assesses five domains across 51 questions, including physical, social, emotional, and functional well-being, and additional wellbeing concerns. Patients are asked to rate statements from "not at all (0)" to "very much (4)" as it applies to the past seven days (e.g., I have difficulty expressing my thoughts). Thavarajah et al., (2013) found that the FACT-Br has good "clinical validity", with a Cronbach's alpha of 0.79 for the total score.

Pain and Nausea Questionnaire: This questionnaire was designed internally by the Midlands Neuropsychology team. As such, this questionnaire has not been validated and no reliability and validity statistics are currently available. It is an 11-item questionnaire, with items 1 to 7 covering the patients' experience during surgery and items 8-11 covering post-surgery. Patients' intra-operative pain scores were derived from items 5 and 6 while post-operative pain scores were derived from items 8 and 9.

The questionnaire asks how much the patient remembers of the surgery, and any pain or discomfort they remember experiencing. Two items ask the patient to describe their experience in their own words, thus producing qualitative data, whilst the remainder of the questionnaire is multiple-choice. Since this questionnaire was designed internally, there exists no specific scoring system and frequency count data will be derived, e.g., number of responses per category.

The HADS, FACT-Br and the Pain and Nausea questionnaire can all be seen in Appendix B.

Patients' subjective assessment of outcomes: During follow-up assessments, patients are asked if they feel their speech, memory, cognition, and mood are ‘'better', 'worse', or the 'same' since having surgery. As such, data collected for this measure will be frequency count (i.e., total number of 'better' responses etc).

Demographics: Patients' age, sex, tumour location and hemisphere, and grade of the tumour were collected as part of routine clinical interviews and included in the data.

Procedure

Once the AC procedure has been agreed as the intervention for a patient, pre-operative preparations begin including blood tests, scans, anaesthetic review etc. This also includes meeting with the Neuropsychology team for baseline neurocognitive testing and

psychological preparation for the surgery. During these sessions, the pre-operative questionnaires (i.e., HADS and FACT-Br) are also administered. The time period between confirmation of the AC to having the surgery can vary depending on urgency, however most patients complete the psychology preparation session (and pre-operative questionnaires) approximately one week prior to surgery.

On the day of the surgery, a Neuropsychologist is present to support and monitor the patient before and during the surgery. Afterwards, the patient is taken to recovery and then to an inpatient ward once they have woken up for monitoring for around 24 to 48 hours. The next day after the surgery, an Assistant Psychologist visits the patient on the ward and administers the post-operative questionnaires, including the Pain and Nausea questionnaire from which patients' recollection of intraoperative pain is derived (items 5 and 6 on the questionnaire). If there are no post-operative complications, the patient is then discharged and invited back for post-operative follow-up appointments at one-month, three-month, six-month, and 12 months after their surgery. Questionnaires are re-administered at these time points, with the exception of the Pain and Nausea Questionnaire which is only administered one day and one-month post-op. Majority of patients are discharged after 12 months follow-up, though some may be referred onto community rehabilitation services.

Ethics

The study was reviewed and approved by the Staffordshire University Ethics Committee, the local NHS Trust R&D, and HRA and HCRW (Appendix A).

Since clinically collected, anonymised data can be used for research without consent (ICO, 2023), and to mitigate any further patient distress, consent from patients was not sought.

Data Analysis

Data were imported from Microsoft Excel to SPSS (v29) for analysis. A total of 205 participants were included in the raw database. The participants had a mean age of 50.1 years (SD=14.8), ranging from 18 years old to 85 years old. Out of the 205, 45.4% were of female sex (n=93) whilst 54.6% were male sex (n=112). The mean pre-operative anxiety score was 6.86 (SD=4.492) while the mean pre-operative depression score was 4.36 (SD=4.048), both ranging from 0 to 21.

Missing Value Analysis and Multiple Imputation

On visual examination, there were considerable types of missing data in the dataset. Participants did not complete questionnaires for a range of possible reasons, including not surviving surgery or having passed away at follow-up, being too physically unwell or cognitively impaired to complete questionnaires, the emergency nature of the surgery, or the questionnaires being inappropriate to administer given their prognosis etc. Table 1 below shows the percentage of missing data for all variables across all follow-up time points.

Table 1

Percentages of missing data

Variable	Pre-operative	One day	One month	Three months	Six months	12 months
Pre-operative anxiety	18 %	90%	52%	93%	65%	77%
Pre-operative depression	18%	90%	52%	93%	65%	77%
Post-operative pain	-	68%	64%	-	-	-
FACT-Br z-scores	24%	-	47%	-	66%	77%
SR of mood	-	69%	54%	92%	67%	81%
SR of cognition	-	68%	54%	92%	67%	81%
SR of speech	-	68%	54%	92%	66%	80%
SR of motor functioning	-	68%	54%	92%	67%	81%

Note: SR=subjective rating

Sample sizes were sufficient to analyse one-month and six-month data. It should be noted that these are two separate samples of participants, which impose constraints on between group comparisons (see discussion section). Each sample may contain patients who attended both follow-up appointments at one-month and six-months post-surgery, however the groups may also contain patients who only completed one set of follow-up questionnaires (i.e., either at one-month follow-up only or at six-month follow-up only). Failed data collection might be due to the patient passing away, non-attendance, inability to complete the questionnaire due to changes in their cognition and/or physical ability, staff shortages, etc. Nevertheless, each sample should be treated as distinct.

Missing value analysis was conducted for both one-month and six-month data. For one-month data, 33 out of 205 participants had complete data with no missing variables. Participants missing data for more than two sets of outcomes (i.e., FACT-Br z-scores, intra-operative or post-operative pain, and subjective ratings of outcomes) or missing both pre-operative anxiety and pre-operative depression were removed from the sample. The remaining sample consisted of 79 participants. For six-month data, 35 out of 205 participants were missing no variables and had complete data. Participants missing data from both pre-operative variables and both post-operative sets of outcomes (i.e., FACT-Br and subjective ratings of outcomes) were removed, leaving 77 participants. Table 2 below displays the number of participants with missing data for each variable, in both samples.

Table 2

Number of Participants Left with Missing Data

Variables	One-month (*n*)	Six-month (*n*)
Pre-operative anxiety	0	1
Pre-operative depression	0	1
Post-operative FACT-Br z-scores	3	20
Intra-operative pain	22	-
Post-operative pain	25	-
SR of mood	11	19
SR of speech	10	18
SR of cognition	10	19
SR of motor functioning	10	18

Note: SR=subjective rating

To manage the remaining missing data and reduce potential bias, multiple value imputation was used for both one-month and six-month data, using five imputed datasets for each sample. The imputation model for each follow-up dataset included all variables mentioned in Hypotheses 1 to 3 which had missing data. This approach assumes that the data were missing at random.

Results

Following missing value imputation, the analyses for Hypothesis 1 to 3 were conducted on each of the five imputed datasets. SPSS (v29) only generates pooled statistics for parameter estimates/coefficients, therefore model fit statistics were interpreted across the five sets of data for each sample.

Table 3 and Table 4 below display the distribution of the data for one-month follow-up and six-month follow-up samples across the demographic and clinical factors. For the one-month sample, the mean age was 47.48 years (SD=14.40) ranging from 23 to 76 years old. For the six-month sample, the mean age was 47.12 years (SD=13.43) ranging from 23 to 76 years old.

Table 3

Frequencies and Percentages for One-Month Follow-Up Sample

Variable		Frequency	Percentage
Sex	Male	39	49.4
	Female	40	50.6
Grade of tumour	No tumour	2	2.5
	Grade 1	2	2.5
	Grade 2	13	16.5
	Grade 3	33	41.8
	Grade 4	29	36.7
Hemisphere of surgery	Left	69	87.3
	Right	10	12.7
Location of surgery	Frontal	38	48.1
	Parietal	5	6.3
	Insula	26	32.9
	Temporal	6	7.6
	Multiple	4	5.1

Table 4

Frequencies and Percentages for Six-Month Follow-Up Sample

Variable		Frequency	Percentage
Sex	Male	41	46.8
	Female	36	53.2
Grade of tumour	No tumour	2	2.6
	Grade 1	2	2.6
	Grade 2	13	16.9
	Grade 3	36	46.8
	Grade 4	24	31.2
Hemisphere of surgery	Left	62	80.5
	Right	15	19.5
Location of surgery	Frontal	39	50.6
	Parietal	4	5.2
	Insula	22	28.6
	Temporal	8	10.4
	Multiple	4	5.2

For both groups, most participants had surgery to the frontal lobe, with 48% in the one-month group and 50.6% in the six-month group. Similarly, most surgeries were in the left hemisphere in both the one-month sample at 87.3% and the six-month sample at 80.5%. In both samples, most participants had a high-grade tumour (i.e., Grade 3 or Grade 4), with Grade 1 tumours and No Tumour being the smallest group. This is reflective of detection, with lower grade tumours being harder to detect until a later stage. The “No Tumour” group contained patients who were still undergoing an awake craniotomy but for a different histology such as a haematoma or necrosis due to radiation.

Hypothesis 1

Patients with higher pre-operative anxiety or depression will report higher intra-operative and post-operative pain at one-month follow-up.

To test this hypothesis, two ordinal logistic regressions were run to determine if pre-operative anxiety and pre-operative depression predict the level of reported post-operative pain at one-month follow-up. The analysis controlled for patient age, sex, surgery location, surgery hemisphere, and grade of the tumour.

Intra-Operative Pain:

Model fit statistics (Pearson) indicated adequate fit across all five imputed data sets, $\chi^2 \leq 228.6$, $p \geq .206$. The proportional odds assumption was assessed with the test of parallel lines, which showed inconsistent results across the sets of data, indicating that results should be interpreted with caution. Table 5 summarises the pooled parameter estimates.

Table 5

Pooled Parameter Statistics for Intra-Operative Pain at One-Month Follow-Up

		Parameter estimate (β)	SE	*p*
Pre-operative anxiety		-0.0107	0.083	0.198
Pre-operative depression		0.228	0.101	0.024
Age		-0.008	0.022	0.730
Sex	Female	0.873	0.522	0.095
	Male	.000	.000	-
Grade of tumour	None	.000	.000	-
	Grade 1	0.141	1.44	0.0922
	Grade 2	-0.746	1.48	0.615
	Grade 3	-0.706	1.53	0.644
	Grade 4	-0.872	1.38	0.938
Location of surgery	Frontal	-0.791	1.27	0.534
	Parietal	0.873	1.47	0.555
	Insula	-0.557	1.22	0.649
	Temporal	-0.082	1.47	0.956
	Multiple	.000	.000	-
Hemisphere of surgery	Left	-0.356	0.735	0.628
	Right	.000	.000	-

Note: SE=standard error

The pooled parameter estimates showed that pre-operative depression was a statistically significant predictor of intra-operative pain (β = 0.228, SE=.101, *p* = .024). The OR indicated that for each one-unit increase in HADS Depression score, the odds of reporting a higher pain level increased by a factor of 1.26 (95% CI [1.03, 1.53]). Pre-operative anxiety was not found to be a statistically significant predictor of intra-operative pain (*p* = .198).

Furthermore, no significant associations were found between reported intra-operative pain and age (p=.73), grade of tumour (all $p \geq .61$), surgery hemisphere (p = .628) or surgery location (all $p > .53$). Patient's sex (p=.09) also did not reach statistical significance.

Post-Operative Pain:

Goodness of fit tests (Pearson) indicated adequate model fit across all imputed datasets ($\chi^2 \leq 232.7$, $p \geq .157$). However, the test of parallel lines was statistically significant for four datasets, with only one p=.110, indicating that the proportional odds assumption did not hold for majority of the data.

Table 6

Pooled Parameter Statistics for Post-Operative Pain at One-Month Follow-Up

		Parameter estimate (β)	SE	*p*
Pre-operative anxiety		-0.114	0.077	0.138
Pre-operative depression		0.087	0.095	0.357
Age		-0.005	0.023	0.821
Sex	Female	-0.008	0.529	0.987
	Male	.000	.000	-
Grade of tumour	None	.000	.000	-
	Grade 1	0.700	1.679	0.678
	Grade 2	-0.028	1.590	0.986
	Grade 3	-0.130	1.812	0.943
	Grade 4	-0.531	1.596	0.356
Location of surgery	Frontal	-0.702	1.230	0.571
	Parietal	-0.486	1.501	0.748
	Insula	-1.047	1.528	0.504
	Temporal	-0.260	1.467	0.860
	Multiple	.000	.000	-
Hemisphere of surgery	Left	-0.64	0.669	0.924
	Right	.000	.000	-

Note: SE=standard error

The pooled parameter statistics (Table 6 above) indicated that neither pre-operative anxiety nor pre-operative depression were statistically significant predictors of post-operative pain levels. Specifically, pre-operative anxiety scores were not significantly associated with post-operative pain (β = -0.114, *p*=.138, OR=0.89, 95% CI [0.77, 1.04]), and pre-operative depression scores were also not significantly associated with post-operative pain levels (β = 0.087, *p* = .357, OR = 1.09, 95% CI [0.91, 1.32]).

Furthermore, none of the additional variables included in the model were significantly associated with post-operative pain: age (p = .821), sex (p = .987), surgery hemisphere (p = .924), surgery location (all comparisons $p \geq .504$), and tumour grade (all comparisons $p \geq .356$).

Hypothesis 2:

Patients with higher pre-operative anxiety or depression will report a lower quality of life at one-month and six-month follow-up.

One-month follow-up:

To test whether patients with higher pre-operative anxiety and depression report a lower quality of life, a multiple linear regression was carried out (Model 1). A second model to see if the addition of clinical and demographic variables (age, sex, tumour grade, surgery location, and surgery hemisphere) significantly improved FACT-Br z-score prediction (Model 2) was also run.

There was independence of residuals across the five datasets, as assessed by Durbin-Watson statistics which ranged from 2.057 to 2.245. Visual inspections of scatterplots of for all five data sets showed homoscedasticity (Appendix C). There was no evidence of multicollinearity with tolerance values for all datasets above 0.1. Participant 172 was highlighted in all five datasets as having a standardised residual greater than -3, so was removed from the regression. Values for Cook's distance for the remaining data were all below 1. The assumption of normality was met, visually assessed with P-P plots (Appendix D).

The overall model (Model 1) of pre-operative anxiety and depression to predict FACT-Br z-scores was statistically significant for all five datasets (Table 7 below). The pooled coefficients showed that only pre-operative depression significantly contributed to the

model, β = - .102, SE=.048, *p*=.034. Pre-operative anxiety was non-significant (β = - .036, SE=.039, *p*=.352).

Table 7

ANOVA Statistics for All Imputed Data Sets, at One-Month Follow-Up.

Imputation Number	Model	Sum of Squares	df	Mean Square	F	Sig.
1	Regression	14.43	2	7.26	5.22	.007
	Residual	105.71	76	1.39		
	Total	120.24	78			
2	Regression	17.10	2	8.55	7.38	.001
	Residual	88.03	76	1.16		
	Total	105.13	78			
3	Regression	18.70	2	9.25	7.71	<.001
	Residual	92.14	76	1.21		
	Total	110.84	78			
4	Regression	18.53	2	9.26	8.03	<.001
	Residual	87.65	76	1.15		
	Total	106.18	78			
5	Regression	15.96	2	7.98	6.77	.002
	Residual	89.56	76	1.18		
	Total	105.51	78			

Note: df=degrees of freedom, F=test statistic, Sig.=significance (*p* value).

The addition of the clinical and demographic variables (Model 2) did not lead to a statistically significant increase in R^2 in any of the five datasets. Furthermore, none of the additional variables significantly contributed to the overall model, with only pre-operative depression reaching significance, β = - .128, SE=.051, *p*=.012.

Six-month follow-up:

A multiple regression at six-month follow-up explored the impact of pre-operative anxiety and pre-operative depression on post-operative quality of life (Model 1) with the

addition of clinical and demographic factors (age, sex, tumour grade, surgery location, surgery hemisphere) to see if this improved the prediction of quality of life (Model 2).

There was independence of residuals across the five datasets, as assessed by Durbin-Watson statistics which ranged from 1.749 to 2.023. Visual inspections of scatterplots of studentized residuals versus unstandardized predicted values for all five data sets showed homoscedasticity (Appendix E). There was no evidence of multicollinearity with tolerance values for all datasets above 0.1. Participant 71 was highlighted in all five datasets as having a standardised residual greater than -3, so was removed from the regression. Values for Cook's distance for the remaining data were all below 1. The assumption of normality was met, visually assessed with P-P plots (Appendix F).

Model 1 showed that pre-operative variables significantly predicted post-operative quality of life at 6-months follow-up for all five data sets (Table 8).

Table 8

ANOVA Statistics for All Imputed Data Sets, at Six-Month Follow-Up.

Imputation Number	Model	Sum of Squares	df	Mean Square	F	Sig.
1	Regression	29.17	7	4.17	3.18	.006
	Residual	89.12	68	1.31		
	Total	118.29	75			
2	Regression	30.49	7	4.36	3.85	.001
	Residual	76.82	68	1.13		
	Total	107.30	75			
3	Regression	37.63	7	5.38	5.38	< .001
	Residual	67.98	68	1.00		
	Total	105.61	75			
4	Regression	31.94	7	4.56	4.65	< .001
	Residual	66.67	68	0.98		
	Total	98.61	75			
5	Regression	34,87	7	4.98	4.00	.001
	Residual	84.75	68	1.25		
	Total	119.62	75			

Note: df=degrees of freedom, F=test statistic, Sig.=significance (*p* value).

The addition of demographic and clinical variables (age, sex, surgery location, surgery hemisphere, and tumour grade) in Model 2 resulted in a statistically significant increase in the variance accounted for in post-operative FACT-Br z-scores for four out of five data sets (Table 9).

Table 9

Model summary statistics for all imputed datasets.

Imputation Number	R^2	R^2 Change	F Change	df1	df2	Sig.
1	.247	.101	1.821	5	68	.120
2	.284	.164	3.110	5	68	.014
3	.356	.179	3.781	5	68	.004
4	.324	.117	2.362	5	68	.049
5	.292	.163	3.129	5	68	.013

Note: df=degrees of freedom, Sig.=significance (*p* value).

Looking at the individual contribution of the pre-operative variables, for Model 1, only pre-operative anxiety significantly added to the prediction of FACT-Br z-scores, β = -.087, SE=.043, p=.045. Pre-operative depression was non-significant, β =- .032, SE=.062, p=.613.

Despite the significant overall improvement in model fit, none of the individual predictors in Model 2 (including pre-operative anxiety) reached statistical significance. While severe multicollinearity was not indicated by tolerance/VIF statistics, the predictive power may be distributed across the additional inter-related variables.

Hypothesis 3

Patients with higher pre-operative anxiety or depression will be more likely to rate their post-operative memory, cognition, mood, and language as worse compared to pre-operatively.

To test this hypothesis, four ordinal logistic regressions were run to determine the impact of pre-operative anxiety and depression on patient's subjective perceptions of their mood, speech, motor functioning, and cognition, respectively. The tests were repeated for the

one-month and the six-month follow-up data. Clinical and demographic factors were also included to control for age, sex, tumour grade, surgery hemisphere, and surgery location.

Mood

At one-month follow-up, goodness of fit tests (Pearson) indicated adequate model fit across all imputed datasets ($\chi^2 \leq 150.6$, $p \geq .316$). However, the test for the proportional odds assumption yielded inconsistent results, holding for the original data and four imputed datasets, but failing for one imputation (p=0.043), suggesting some caution is warranted. Based on the pooled parameter estimates, neither pre-operative anxiety ($\beta = 0.058$, SE = 0.072 p = .420) nor pre-operative depression ($\beta = -0.101$, SE = 0.090, p = .261) were significant predictors of self-reported changes in mood. None of the covariates significantly predicted change in mood: age (p = .447), sex (p = .313), surgery hemisphere (p = .341), surgery location (all $p \geq .091$), and tumour grade (all $p \geq .153$).

At six-month follow-up, adequate model fit was indicated for all datasets, $\chi^2 \leq 155.0$, $p \geq .167$. The test of parallel lines was significant for two datasets ($\chi^2 \leq 32.2$, p=.002 and $\chi^2 \leq 22.9$, p=.043) but non-significant for the remaining three ($\chi^2 \leq 21.6$, $p \geq .063$). Looking at the pooled parameter estimates, none of the variables, including pre-operative anxiety (p= .134) and pre-operative depression (p= .172), significantly predicted change in mood: age (p = .482), sex (p = .317), surgery hemisphere (p = .320), surgery location (all $p \geq .301$), and tumour grade (all $p \geq .512$).

Speech

Goodness of fit tests suggested the model adequately fit the data across all datasets ($\chi^2 \leq 162.0$, $p \geq 0.132$). However, the test of parallel lines was significant for three out of five datasets ($p \leq .015$) suggesting the proportional odds assumption did not hold and results should be interpreted with caution. None of the variables in the model were significant in the

pooled parameter estimates: pre-operative anxiety (p=.095), pre-operative depression (p=.948), age (p = .669), sex (p = .656), surgery hemisphere (p = .547), surgery location (all $p \geq .212$), and tumour grade (all $p \geq .831$).

For six-month follow-up, adequate model fit was indicated $\chi^2 \leq 151.8$, $p \geq .216$. Similar to the one-month data, the parallel lines test showed some inconsistency with four non-significant data sets ($\chi^2 \leq 22.0$, $p \geq .055$), and one significant dataset ($\chi^2 \leq 23.6$, p =.035). From the pooled parameter estimates, neither pre-operative anxiety (β = - 0.063, SE = 0.115, p=. 594) nor pre-operative depression (β = 0.113, SE=0.115, p= .336) significantly predicted self-reported changes in speech. For surgery hemisphere, patients who had a left sided hemisphere surgery showed 5.76 times the odds of reporting a worse post-speech outcome (β=1.751, OR 95% CI [0.92, 35.98], p=.060); but did not reach statistical significance. None of the other variables significantly predicted change in speech ratings: age (p=.261), sex (p=.529), surgery location (all $p \geq .668$), and tumour grade (all $p \geq .657$).

Motor Functioning

At one-month follow-up, goodness of fit tests suggested the model adequately fit the data across all datasets ($\chi^2 \leq 170.7$, $p \geq .057$), and the proportional odds assumption also held for most datasets ($\chi^2 \leq 20.8$, $p \geq .655$) with one violation (χ^2 = 22.6, p=.046). Overall, there were no statistically significant predictors of patients' subjective ratings of motor functioning at one month: pre-operative anxiety (p=.116), pre-operative depression (p=.670), age (p = .265), sex (p =.785), surgery hemisphere (p = .164), surgery location (all $p \geq .282$), and tumour grade (all $p \geq .167$).

For six-month follow-up data, the model for all datasets showed adequate goodness-of-fit ($\chi^2 \leq 163.7$, $p \geq .075$), and the proportional odds assumption held for all datasets with $\chi^2 \leq 19.1$, $p \geq .120$ on the test of parallel lines. On the pooled parameter estimates, female sex

was significantly associated with increased odds of a worse motor-functioning self-rating compared to male sex, β = 1.724, SE=0.700, OR=5.61, 95% CI [1.34, 23.5], *p*=.020. Conversely, surgery being on the left hemisphere (compared to the right) was significantly associated with decreased odds of a worse motor-functioning self-rating, β = -1.809, SE=.790, OR=0.164, 95% CI [.034, .787], *p*=.024, indicating that those with surgery in the left hemisphere are significantly more likely to rate their motor-functioning better or same. No other predictors reached statistical significance (all $p \geq .128$).

Cognition

At one-month follow-up, the goodness of fit indicated that the model fit was acceptable, $\chi^2 \leq 153.6$, $p \geq .257$. The test of parallel lines was non-significant for one imputation only ($\chi^2 \leq 12.0$, *p*=.524). For two data sets, the test could not be performed (due to the log-likelihood being larger for the null model than the general model).

From the pooled parameter estimates, pre-operative anxiety was not statistically significant, β =.145, SE=.076, p=.058. None of the remaining variables reached statistical significance, including pre-operative depression (*p*=.365): age (*p* = .481), sex (*p* =.236), surgery hemisphere (*p* = .656), surgery location (all $p \geq .400$), and tumour grade (all $p \geq .138$).

For six-month follow-up, the goodness of fit was acceptable for all the datasets, $\chi^2 \leq 162.1$, $p \geq .087$ and the proportional odds assumption also held with $\chi^2 \leq 9.07$, $p \geq .768$. The pooled parameter estimates showed that none of the variables reached statistical significance: pre-operative anxiety (*p*=.343), pre-operative depression (*p*=.382), age (*p* = .744), sex (*p* =.169), surgery hemisphere (*p* = .169), surgery location (all $p \geq .302$), and tumour grade (all $p \geq .855$)

Hypothesis 4

There will be a significant difference in pre-operative anxiety and depression depending on patients' sex, age, surgery hemisphere, surgery location, and tumour grade.

Missing value analysis was completed on the original dataset with 205 participants, with pre-operative anxiety and depression, sex, age, surgery hemisphere, surgery location, and tumour grade. The analysis showed that 37 participants were missing data for pre-operative anxiety whilst 6 participants did not have data for grade of tumour. These participants were removed from the sample, leaving n=162 with no missing data for the above variables.

Participant age ranged from 18 years old to 85 years old, with a mean of 51.2 years (SD=14.5). The sample consisted of 77 males and 85 females. Participants had a mean pre-operative anxiety score of *M*=6.91 (SD=4.48). Figures 1 to 3 below illustrate the distribution of data across clinical variables (grade of tumour, hemisphere of surgery, and location of surgery).

Figure 1

Bar Graph Showing Number of Participants by Grade of Tumour

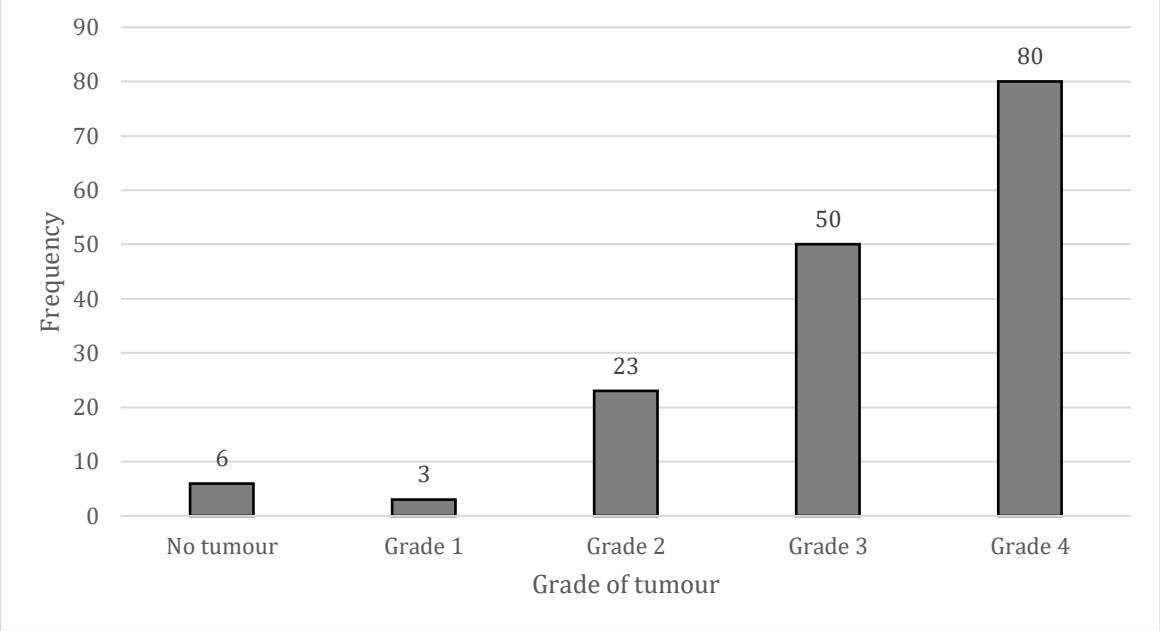


Figure 2

Bar Graph Showing Number of Participants with Left Hemisphere vs Right Hemisphere Surgery

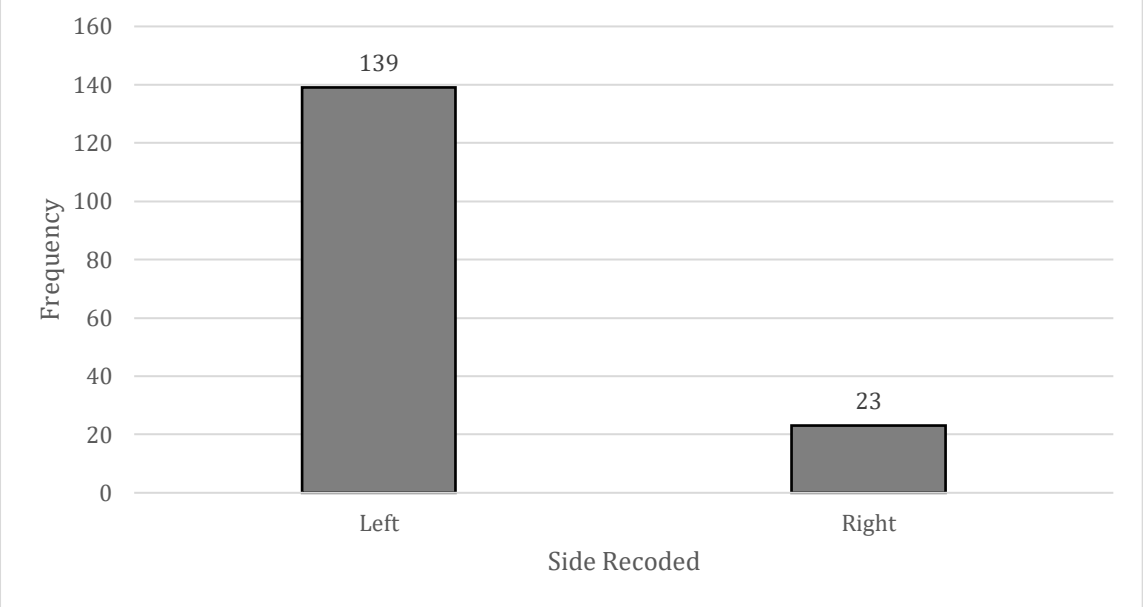
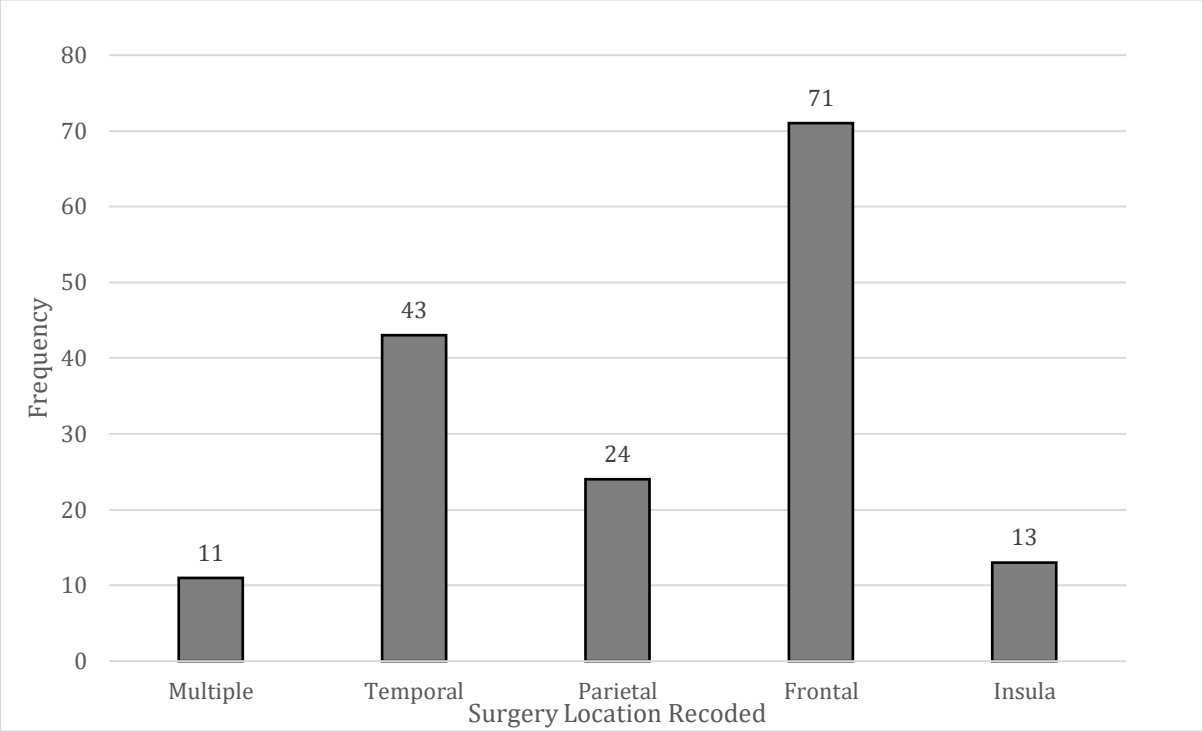


Figure 3

Bar Chart Showing Number of Participants by Location of Surgery



A multiple regression was run with total HADS scores (i.e., the sum of pre-operative anxiety and pre-operative depression). The Shapiro-Wilk test on the residuals was significant (p=.006). However, the assumption of normality was met by the Kolmogorov-Smirnov test, p=.200 and visual inspection of the Q-Q plot (Appendix G). Cook's Distance values were all below 1, and the assumption of multicollinearity was met with all tolerance values close to 1. The Durbin-Watson statistic of 1.968 suggests independence of errors.

The overall model was significant (Table 10). However, examination of the individual variables (Table 11) indicated that there was not a significant difference in pre-operative HADS scores for all demographic and clinical variables.

Table 10

ANOVA Statistics for Multiple Regression on Pre-Operative HADS

Model	Sum of Squares	df	Mean Square	F	Sig.	R^2
Regression	456.34	5	91.27	1.516	.188	.046
Residual	9391.23	156	60.20			
Total	9847.57	161				

Note: Sig.=significance (*p* value), df=degrees of freedom.

Table 11

Model Coefficients for Hypothesis 4

	B	SE	*t*	Sig.
(Constant)	13.766	3.104	4.43	<.001
Sex	-2.252	1.234	-1.83	.070
Grade of tumour	-0.246	0.717	-0.34	.732
Hemisphere of surgery	3.368	1.771	1.90	.059
Location of surgery	-0.209	0.566	-0.37	.713
Age	-0.011	0.049	-0.22	.827

Note: SE= standard error

Discussion

This study aimed to explore the impact of pre-operative anxiety and depression on post-operative outcomes following an awake craniotomy as well as the influence of demographic and clinical factors on pre-operative anxiety. The study focused on three primary outcomes: (1) intra-operative and post-operative pain at one-month follow-up, (2) quality of life at one and six-month follow-up, and (3) patients' subjective assessments of their cognition, mood, speech, and motor functioning at one and six-month follow-up.

Summary and Interpretation of Results

The results showed that pre-operative depression significantly predicted higher levels of intra-operative pain, even after controlling for a range of demographic and clinical factors, including age, sex, tumour grade, and the specific site of the craniotomy. This finding aligns with a growing body of literature underscoring the influence of psychological distress on pain experiences across various surgical contexts. Depression has been found to modulate the central processing of pain, increase pain sensitivity, and reduce the efficacy of analgesic interventions (Ghoneim & O'Hara, 2016). This study reinforces this association in the specific context of awake craniotomies, perhaps because this procedure may amplify the psychological components of the pain experience due to the patient's conscious state during surgery.

In contrast, pre-operative anxiety did not emerge as a statistically significant predictor of post-operative pain, a finding which diverges from some previous reviews and meta-analyses (e.g., Yang et al., 2019; Valencia et al., 2022) which have reported anxiety as a significant risk factor for heighted post-operative pain. Several factors may account for this discrepancy. The present study assessed pain only once at one-month, whereas other studies have typically used a range of follow-up periods, potentially capturing transient post-operative effects that might diminish or accumulate over time. It is also important to note the

limitations posed by the violation of the proportional odds assumption in some of the models, which may have attenuated the ability to detect significant effects.

Results also revealed distinctions between the effects of anxiety and depression over time. At one-month follow-up, pre-operative depression was a significant predictor of lower quality of life, independent of pre-operative anxiety. This reinforces existing evidence that depressive symptoms can differentially affect post-operative recovery trajectories (Lee at al., 2023). Notably, the current study strengthens this association by accounting for pre-operative anxiety, isolating the unique contribution of depression to early quality of life outcomes.

At six months, the predictive pattern showed that pre-operative anxiety, rather than depression, was a predictor of lower quality of life. However, this effect did not show when demographic and clinical covariates were added to the model. One possible interpretation could be that anxiety may exert a delayed but sustained influence on recovery, becoming entangled with clinical variables such as surgery success and prognosis. Another possibility is that the study lacked sufficient power to detect more subtle effects once the model's complexity increased. The transition from statistical significance to non-significant in the full model may reflect a Type II error.

The third hypothesis proposed that higher levels of pre-operative anxiety would be associated with more negative subjective perceptions of post-operative outcomes, including mood, speech, cognition, and motor functioning. Contrary to predictions, neither pre-operative anxiety nor depression significantly predicted patients' self-reported changes in mood or speech at either follow-up point. A trend was observed for left-sided surgeries to be associated with worse perceived speech outcomes at six months, which aligns with well-established neuroanatomical knowledge—namely, the dominance of the left hemisphere for language processing in most individuals (Broca, 1861; Wernicke, 1874). However, this did

not reach statistical significance. For perceived motor functions, both patient sex (p=.02) and hemisphere of surgery (p=.024) were statistically significant, with those of female sex showing increased odds (OR=5.61) of worse motor functioning self-rating and those with left hemisphere surgery showing decreased odds (OR=0.164) of worse motor functioning self-rating. Association of the right hemisphere of the brain with emotion processing and spatial awareness (Bernard et al., 2018) could explain why patients with right hemisphere surgery rated their physical ability as worse due to changes in their self-perception, though this requires further exploration.

Interestingly, pre-operative anxiety approached significance in predicting worse subjective cognitive ratings at one month, suggesting that anxiety may heighten patients' perceptions of cognitive deficits during the early stages of recovery. This aligns with prior findings that psychological distress correlates more closely with subjective cognitive complaints than with objective neuropsychological test performance (Goebel et al., 2012; Pranckeviciene et al., 2017). Taken together, these results suggest that while pre-operative anxiety may influence patients perceived cognitive functioning, its impact on other outcomes may be less direct.

The overall lack of support for the third hypothesis could be partly attributed to methodological challenges. Specifically, the assumption of proportional odds was not met in several models, limiting the interpretability of the ordinal regression outputs. Furthermore, asking patients to evaluate changes in their own mood, speech, or cognition presumes a high level of metacognitive insight—an assumption that may not hold uniformly, especially in the context of recent neurosurgical intervention. Future studies may benefit from a mixed-methods design, incorporating qualitative interviews to triangulate subjective ratings and deepen our understanding of how patients interpret their recovery experiences.

Contrary to some existing literature (e.g., Mofatteh et al., 2022), this study found no statistically significant differences in pre-operative anxiety and depression based on age, sex, tumour location, hemisphere of surgery, or tumour grade. This could be indicative of the unique psychological environment surrounding awake craniotomies at the participating service. All patients are considered by a multi-disciplinary surgical team, including two clinical neuropsychologists and an assistant psychologist and, if needed, are offered preparatory sessions prior to surgery. These sessions likely functioned as both psychoeducational and emotional support interventions for those patients who were particularly anxious, possibly mitigating the influence of demographic or tumour-related variables on pre-operative anxiety and depression.

Indeed, prior to multiple imputation, 48% of participants scored within the "normal" range (i.e., a score of 0-7) on pre-operative anxiety (Beekman & Verhagen, 2018) on the day of surgery, a finding that may reflect the effectiveness of this psychological preparation. This contrasts with studies examining more traditional surgical contexts, where patients often report heightened anxiety pre-operatively due to uncertainty, perceived loss of control, and fear of complications (Perks et al., 2009). The tailored neuropsychological preparation afforded to AC patients may buffer against these stressors, thus weakening commonly observed demographic and clinical influences

In summary, the findings provide a nuanced picture. Pre-operative depression emerged as a more consistent predictor of negative early outcomes (i.e., intra-operative pain and quality of life at one month), while pre-operative anxiety showed some indication of impacting longer-term quality of life (though not holding statistical significance in the full model when demographic and clinical factors are included). The general lack of association between pre-operative psychological states and most subjective neurological outcomes, and the lack of influence of demographic/clinical factors on pre-operative anxiety levels, were

notable. That is because previous research has demonstrated the impact of pre-operative anxiety on cognition (Gobel et al., 2012; Pranckeviciene et al., 2017) and differences in pre-operative anxiety based on sex and tumour location/hemisphere (Perks et al., 2009; Valencia et al., 2022; Pringle et al., 1999; Mainio et al., 2003). However, the current study does address the concerns highlighted by Mofatteh et al., (2022) by examining all stages of the AC procedure (i.e., pre-operative, intra-operative, and post-operative), controlling for influencing factors, and exploring long-term outcomes.

Clinical Implications

There are several clinical applications of these findings. First, the association between pre-operative depression and higher post-operative pain and reduced early quality of life underscores the importance of routine screening for depressive symptoms in patients undergoing surgery. Early identification of "at-risk" patients could inform tailored psychological interventions prior to surgery and during follow-up. Furthermore, the findings suggest a potential role for interdisciplinary collaboration in analgesic and anaesthetic planning, whereby psychological risk factors are incorporated into peri-operative care protocols. As Vacas and Van de Wiele (2017) propose, integrating psychological risk assessments into routine surgical planning could allow clinicians to optimise pain management strategies, initiate early psychological support, and improve overall outcomes. The current study provides preliminary evidence to support this model of care in the context of awake craniotomies.

Finally, although not a primary focus of the study, evidence suggesting that female patients reported worse motor functioning at six months warrants further investigation. These findings resonate with a broader literature on sex differences in post-surgical recovery and pain perception (Osborne & Davis, 2022). They highlight the need for sex- and gender-sensitive approaches to rehabilitation planning, including consideration of how societal

gender roles may shape patients' self-reporting of symptoms and engagement with recovery processes.

Study Limitations and Directions for Future Research

Missing data represented the most substantive limitation of this study. To address this problem, multiple imputation – a robust statistical method – was employed, which indicated that analyses could proceed. Although there is no obvious reason that missing data are due to a confound (i.e., an unexpected source of error such as non-randomness), it is possible that patients who were too unwell, deceased, or undergoing emergency surgery may systematically differ from those included in the analyses, introducing bias that imputation cannot fully correct. Furthermore, the use of separate samples at the one-month and six-month follow-ups limits the ability to draw firm conclusions about longitudinal trajectories of recovery. Moreover, the sample size, though drawn from an initial database of over 200 patients, was ultimately reduced to smaller subsamples due to attrition and data availability. This limited statistical power overall.

Measurement limitations also warrant consideration. The pain and nausea questionnaire used in the study was developed internally for clinical monitoring and lacks published psychometric validation. This restricts the confidence that can be placed in pain-related findings and highlights the need for future studies to employ validated instruments and/or to assess the psychometric properties of internally developed tools. Similarly, the HADS is a screening tool for general anxiety and depression, rather than surgery-specific distress. This distinction is important, as patients' responses may reflect broader life circumstances unrelated to the surgical context. Future studies may benefit from using instruments that specifically target pre-surgical anxiety (e.g., the Amsterdam Preoperative Anxiety and Information Scale). Furthermore, the reliance on ordinal data poses interpretive challenges and constrains the analytical techniques available. While the brevity of the

questionnaires was likely necessary given the cognitive and emotional burden placed on patients pre-operatively, future work should seek to balance psychometric rigour with feasibility. In particular, co-designing research tools with patients and clinical staff may yield measures that are both psychometrically sound and sensitive to the lived realities of brain tumour patients.

Another question is the binary approach to sex in our analysis. Research does highlight various physiological mechanisms underlying pain which could differ in males and females, such as neuroimaging studies which suggest that sex specific neural circuitry influences the transmission of pain signals (Osborne & Davis, 2022). Whilst this evidence-base exists, Keogh (2025) highlights that a more dimensional gender-based approach to pain, which includes the consideration of wider gender constructs, is required for us to fully understand differences in pain experiences. For example, gender self-identity and roles, shaped by societal constructs of masculinity and femininity, influence individuals' pain experiences and reporting, often linking “masculine” personality traits such as stoicism and assertiveness to lower pain and “feminine” personality traits like being emotionally expressive to higher pain (Alabas et al., 2012). Moreover, broader gender-related beliefs, expectations, and interpersonal social contexts significantly affect pain behaviours and communication of these (Vigil and Alcock, 2014; Edwards et al., 2017). As such it may be too simplistic to examine differences in subjective experiences based on sex, and studies should consider the more complex and mediational relationship between sex and gender for a more comprehensive understanding of individual differences in post-operative experiences.

Finally, the study did not differentiate between patients with primary verses secondary brain tumours. According to Ostgathe et al. (2009), patients with primary brain tumours and those with secondary (metastatic) brain tumours present with distinct palliative care needs and symptom burdens. For example, patients with secondary brain tumours

frequently suffer from symptoms related to their primary cancer elsewhere in the body in addition to their neurological symptoms, while those with primary brain tumours have often experienced a longer disease trajectory with progressive symptoms and specific symptoms such as seizures. As such, Ostgathe et al., (2009) recommend that researchers make this important distinction when studying experiences of patients with brain tumours.

Conclusions

In summary, this study contributes to a growing understanding of the psychological determinants of post-operative outcomes in patients undergoing AC. Pre-operative depression emerged as a significant predictor of heightened post-operative pain and reduced quality of life, while pre-operative anxiety showed potential longer-term effects on quality of life and subjective perceptions of cognition, albeit not reaching statistical significance. Among other intervention implications, findings underscore the need for routine psychological screening, the value of patient psychoeducation and preparation, and tailored multidisciplinary care for patients undergoing complex neurosurgical procedures. Despite methodological limitations, this study lays important groundwork for future prospective and mixed-method research that can deepen our understanding and enhance care for very vulnerable patients in a highly specialised context.

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Appendices

Appendix A: HRA and HCRW, and local NHS Trust approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

14 March 2024

Dear Miss Munir

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**The impact of pre-operative anxiety and depression on post-operative pain, quality of life, and PTSD symptoms following an Awake Craniotomy**
IRAS project ID:	**336907**
REC reference:	**23/LO/1013**
Sponsor	**Staffordshire University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **336907**. Please quote this on all correspondence.

Yours sincerely,
Hayleigh Keating
Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Professor Nachiappan Chockalingam*

Research & Development Department
Harplands Hospital
Hilton Road
Stoke-on-Trent
ST4 6TH
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NHS
North Staffordshire
Combined Healthcare
NHS Trust

11 June 2024

Researcher:
Iram Munir
Trainee Clinical Psychologist
Midlands Partnership NHS Foundation Trust

Dear Iram

Letter of Access for Research

Research Reference Numbers	**R&D:** CHC0258/RS	**IRAS:** 336907
Research Title	The impact of anxiety and depression on post-operative pain, quality of life, and PTSD symptoms following an awake craniotomy	
Research Dates	**Start:** 11/06/2024	**End:** 30/04/2025
Letter of Access Dates	**Start:** 11/06/2024	**End:** 01/04/2025
Local Research Manager	Kerri Mason	
Research Activity	Access to anonymised patient data in NHS premises	

This letter has been issued by North Staffordshire Combined Healthcare NHS Trust, Research and Development Department, and is confirmation that the relevant pre-engagement checks in accordance with the *National Institute for Health Research (NIHR) "Research in the NHS - HR Good Practice Resource Pack" (April 2019)*[1] have been undertaken, enabling you to undertake research activity at this organisation. It should be presented, to this organisation, before you commence your research at this site.

In accepting this letter, North Staffordshire Combined Healthcare NHS Trust confirms your right of access to conduct research through its organisation, for the purpose and on the terms and conditions set out below. This right of access commences on **11/06/2024** and ends on **01/04/2025** unless terminated earlier in accordance with the clauses below:

1. You have a right of access to conduct such research as confirmed in writing in the *Letter of Trust Authorisation for Research* from this organisation. *Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from this organisation, giving authorisation to conduct the project at its organisation.*

2. As an existing NHS employee you do not require an additional honorary research contract with this organisation. This organisation is satisfied that the research activities you will undertake at its organisation are commensurate with the activities you undertake for your employer. Your employer is fully responsible for ensuring such checks as are necessary have been carried out. Your employer has confirmed in writing to this organisation that the necessary pre-engagement checks are in place in accordance with the role you plan to carry out in this organisation. *Please*

Research & Development Department
Harplands Hospital
Hilton Road
Stoke-on-Trent
ST4 6TH
Email research@combined.nhs.uk
Follow us on twitter @nschtresearch

note that evidence of these checks is available on request to North Staffordshire Combined Healthcare NHS Trust.

3. You are considered to be a legal visitor to North Staffordshire Combined Healthcare NHS Trust premises. You are not entitled to any form of payment nor access to other benefits provided by North Staffordshire Combined Healthcare NHS Trust, nor to its employees, and this letter does not give rise to any other relationship between you and North Staffordshire Combined Healthcare NHS Trust, in particular that of an employee.

4. While undertaking research through North Staffordshire Combined Healthcare NHS Trust, you will remain accountable to your employer, but you are required to follow the reasonable instructions of your nominated manager at this organisation or those instructions given on their behalf in relation to the terms of this right of access.

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

6. You must act in accordance with North Staffordshire Combined Healthcare NHS Trust policies and procedures, which are available upon request, and the UK Policy Framework for Health and Social Care Research[2].

7. You are required to co-operate with North Staffordshire Combined Healthcare NHS Trust in discharging its duties under the Health and Safety at Work Act 1974, and other health and safety legislation, and to take reasonable care for the health and safety of yourself and others while on North Staffordshire Combined Healthcare NHS Trust premises. Although you are not a contract holder, you must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder, and you must act appropriately, responsibly and professionally at all times.

8. If you have a physical or mental health condition or disability which may affect your research role, and which might require special adjustments to your role, if you have not already done so, you must notify your employer and North Staffordshire Combined Healthcare NHS Trust prior to commencing your research role at this site.

9. You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 2018. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution. North Staffordshire Combined Healthcare NHS Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality nor breach of the Data Protection Act 2018. Any breach of the Data Protection Act 2018, may result in legal action against you and/or your employer.

Research & Development Department
Harplands Hospital
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Email research@combined.nhs.uk
Follow us on twitter @nschtresearch

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NHS Trust

10. You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on North Staffordshire Combined Healthcare NHS Trust premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this organisation does not accept responsibility for damage to nor loss of personal property.

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

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

13. If your circumstances change in relation to your health, criminal record, professional registration or suitability to work with adults or children, or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform your employer through their normal procedures. You must also inform the nominated manager in this organisation.

Yours sincerely

Kerri Mason
R&D Lead

cc: **Louise Alston, R&D Office, NSCHT [louise.alston@combined.nhs.uk]**
Ben Rogers, Director of Psychological Services, MPFT [ben.rogers@mpft.nhs.uk]

[1] Research in the NHS – HR Good Practice Resource Pack (2019) National Institute for Health Research (NIHR)
[2] UK Policy Framework for Health and Social Care Research (2018) Health Research Authority (HRA)

Appendix B: Questionnaires

Hospital Anxiety and Depression Scale (HADS)

NFER NELSON

Name: _____ Date: _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

FOLD HERE

A	D			A	D
		I feel tense or 'wound up'	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		3
2		A lot of the time	Very often		2
1		From time to time, occasionally	Sometimes		1
0		Not at all	Not at all		0
		I still enjoy the things I used to enjoy	**I get a sort of frightened feeling like 'butterflies' in the stomach**		
	0	Definitely as much	Not at all	0	
	1	Not quite so much	Occasionally	1	
	2	Only a little	Quite often	2	
	3	Hardly at all	Very often	3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
3		Very definitely and quite badly	Definitely		3
2		Yes, but not too badly	I don't take as much care as I **should**		2
1		A little, but it doesn't worry me	I may not take quite as much care		1
0		Not at all	I take just as much care as ever		0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Very much indeed	3	
	1	Not quite so much now	Quite a lot	2	
	2	Definitely not so much now	Not very much	1	
	3	Not at all	Not at all	0	
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**		
3		A great deal of the time	As much as I ever did		0
2		A lot of the time	Rather less than I used to		1
1		Not too often	Definitely less than I used to		2
0		Very little	Hardly at all		3
		I feel cheerful	**I get sudden feelings of panic**		
	3	Never	Very often indeed	3	
	2	Not often	Quite often	2	
	1	Sometimes	Not very often	1	
	0	Most of the time	Not at all	0	
		I can sit at ease and feel relaxed	**I can enjoy a good book or radio or television programme**		
0		Definitely	Often		0
1		Usually	Sometimes		1
2		Not often	Not often		2
3		Not at all	Very seldom		3

Now check that you have answered all the questions

A D

TOTAL ☐☐

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Br (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An16	I get headaches	0	1	2	3	4

During the operation

1. *How much of the time that you were in the operating room do you remember?*

□ I remember most of my time in the operating room

□ I remember a little of the time I was in the operating room

□ I remember nothing about the time I was in the operating roo

2. *Which of the following do you remember? (Please tick any of the options that apply):*

□ I remember waking up and seeing the anaesthetist and/or psychologist in front of me

□ I remember naming various objects on a computer screen with the psychologist

□ I remember being told that I was going off to sleep for the last part of the operation

□ I remember being awake on my bed in the operating theatre, after the operation

□ I remember being in the recovery room after the operation

3. *How did you feel during the operation?*

□ I remember that I felt at ease during the procedure

□ I remember that I felt uneasy during the procedure

□ I don't remember

4. *If you felt uneasy during your time in the operating room, please could you describe what particularly contributed to this?*

5. *Did you experience any pain during the operation?*

□ Yes, I remember being in pain during the operation

□ No, I remember being comfortable during the operation

□ I don't remember

6. *If you experienced pain or discomfort during the operation, how severe was it at its worst?*

□ Mild

□ Moderate

□ Severe

7. *If you experienced pain or discomfort during the procedure, can you describe when it happened or how long it lasted?*

After the operation

8. *Do you remember being in pain after the operation, in the recovery room or back on the ward?*

□ Yes

□ No

□ I don't remember

9. *If you experienced pain after the operation, how severe was it at its worst?*

□ Mild

□ Moderate

□ Severe

10. Did you feel sick or nauseous after the operation?

□ I remember feeling sick or nauseous after the operation

□ I remember that I did not feel nauseous after the operation

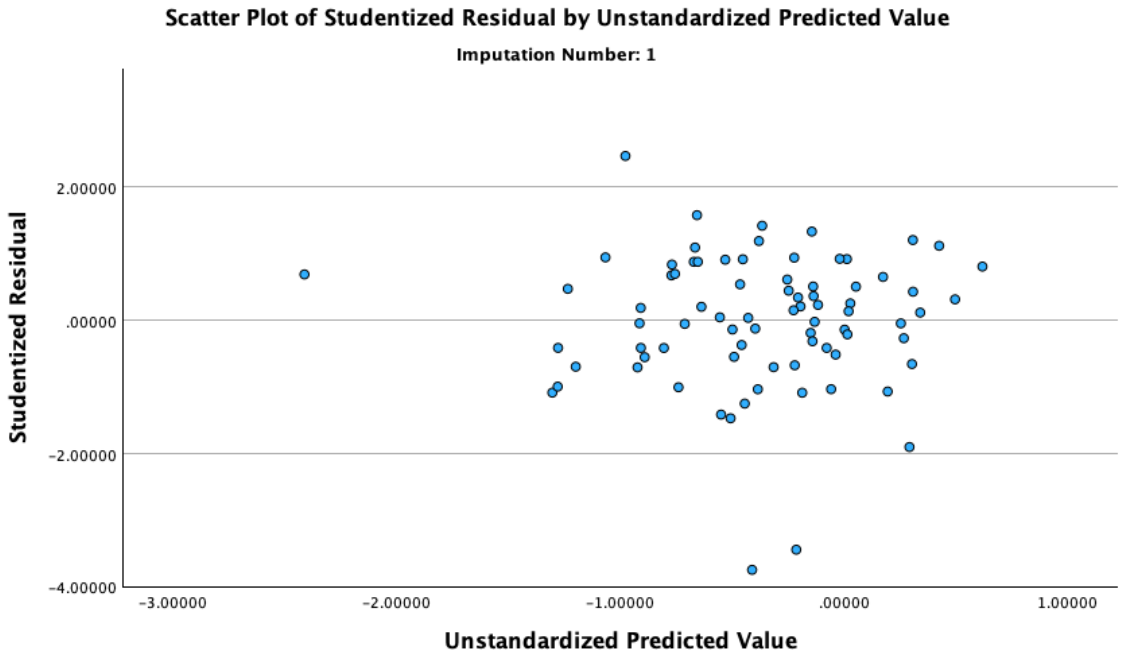
□ I don't remember

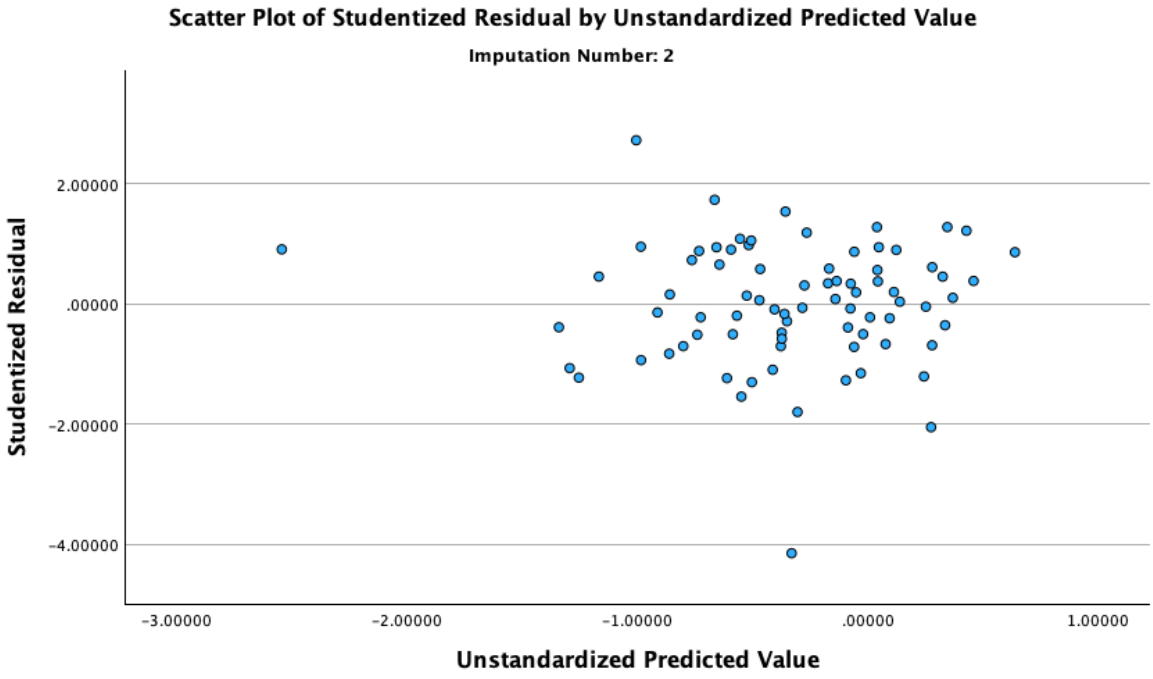
11. How soon after the operation were you discharged home?

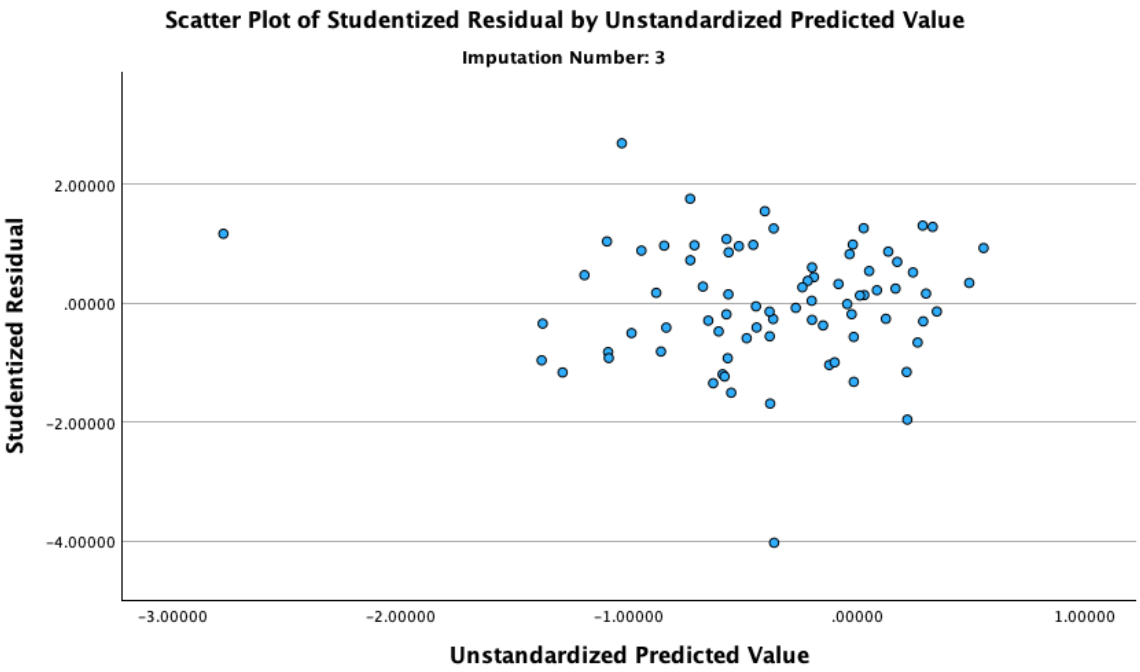
□ the day after the operation

□ two or more days after the operation [Please write the number of days . . ..]

Appendix C: Scatterplots of studentised residuals versus un-standardised predicted values for one-month follow-up data






Scatter Plot of Studentized Residual by Unstandardized Predicted Value
Imputation Number: 3
Studentized Residual
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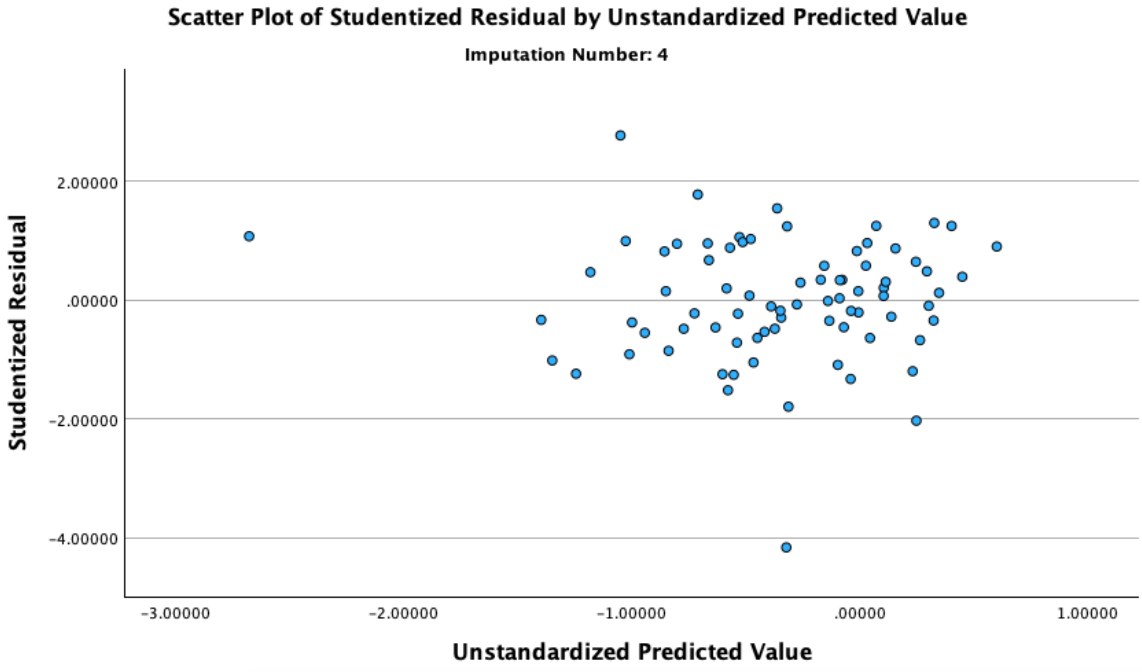
.00000
-2.00000
-4.00000
-3.00000
-2.00000
-1.00000
.00000
1.00000
Unstandardized Predicted Value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Imputation Number: 4
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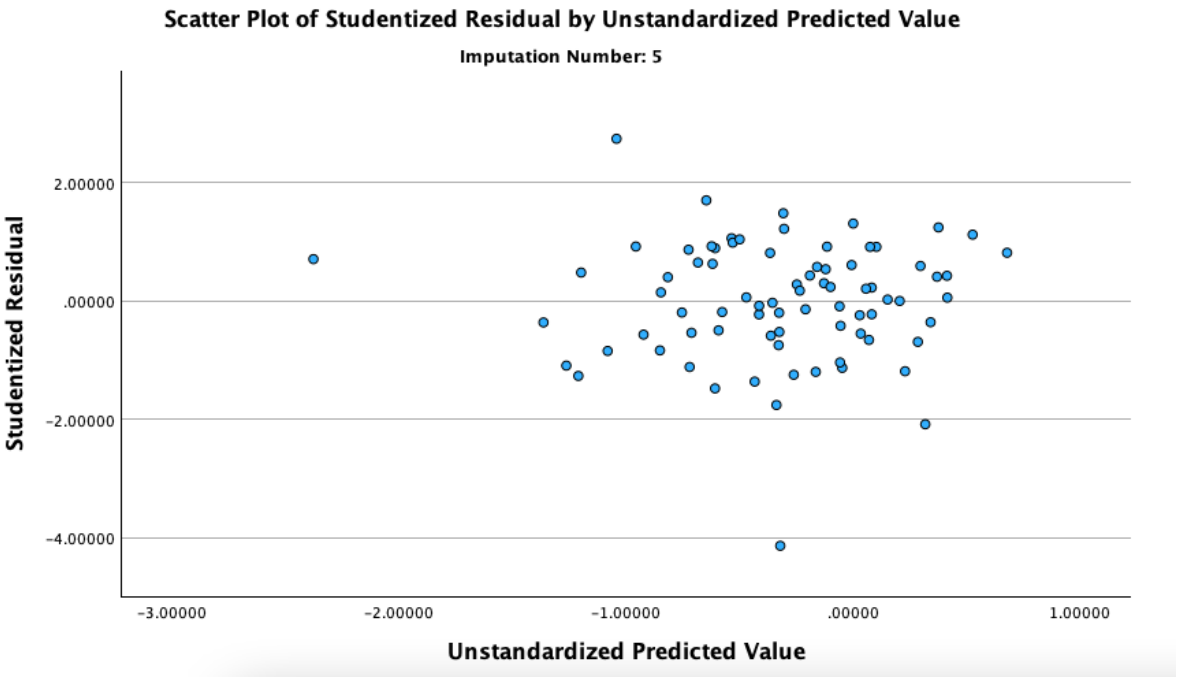
-2.00000
-1.00000
.00000
1.00000
Unstandardized Predicted Value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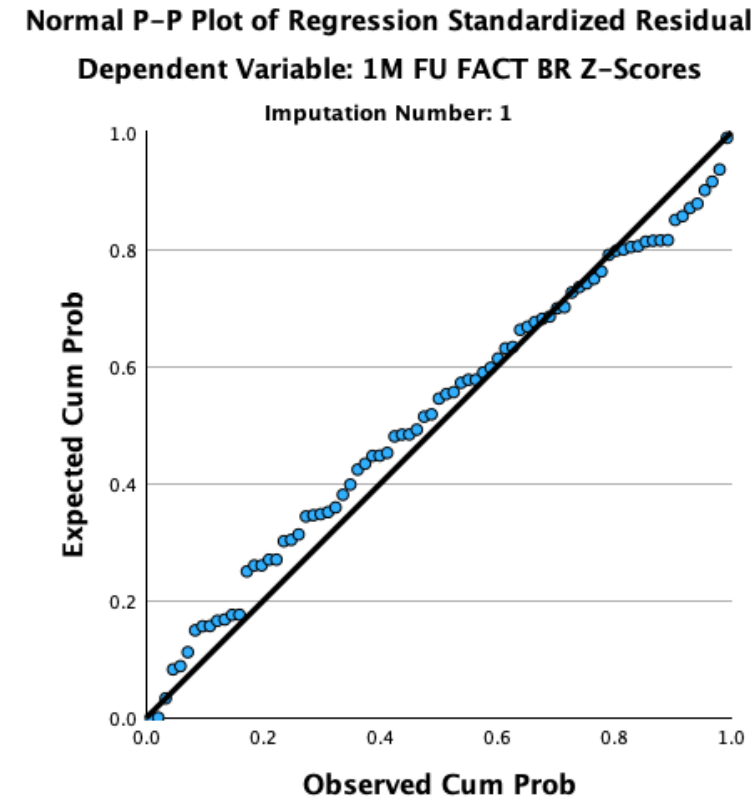
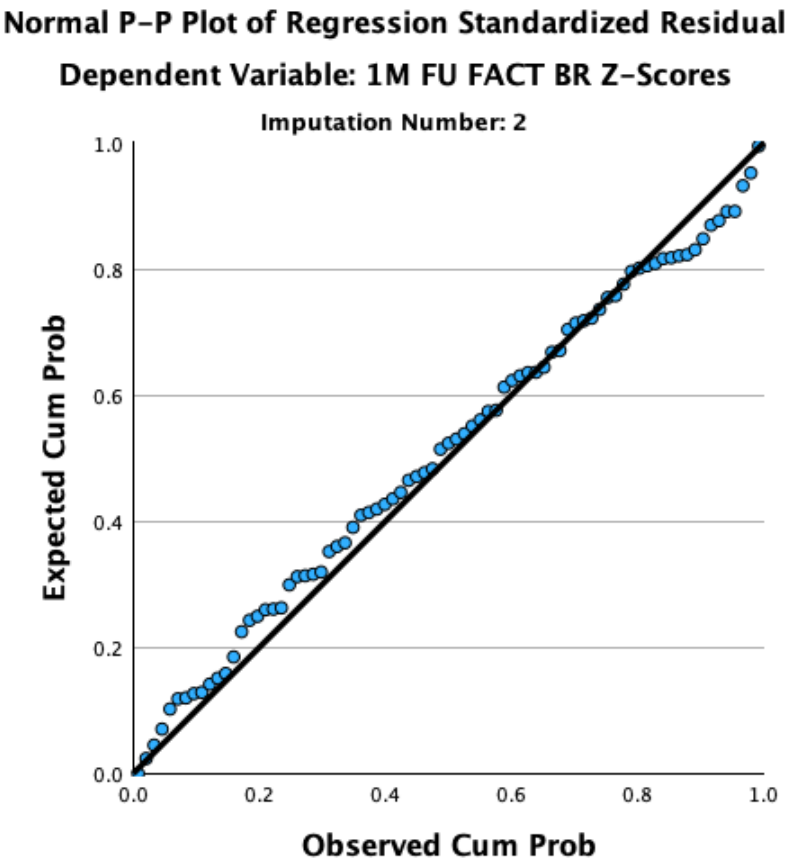
Imputation Number: 5
Studentized Residual
2.00000
.00000
-2.00000
-4.00000
-3.00000
-2.00000
-1.00000
.00000
1.00000
Unstandardized Predicted Value

Appendix D: P-P plots for one-month FACT-Br data




Normal P-P Plot of Regression Standardized Residual
Dependent Variable: 1M FU FACT BR Z-Scores
Imputation Number: 2
Expected Cum Prob
Observed Cum Prob
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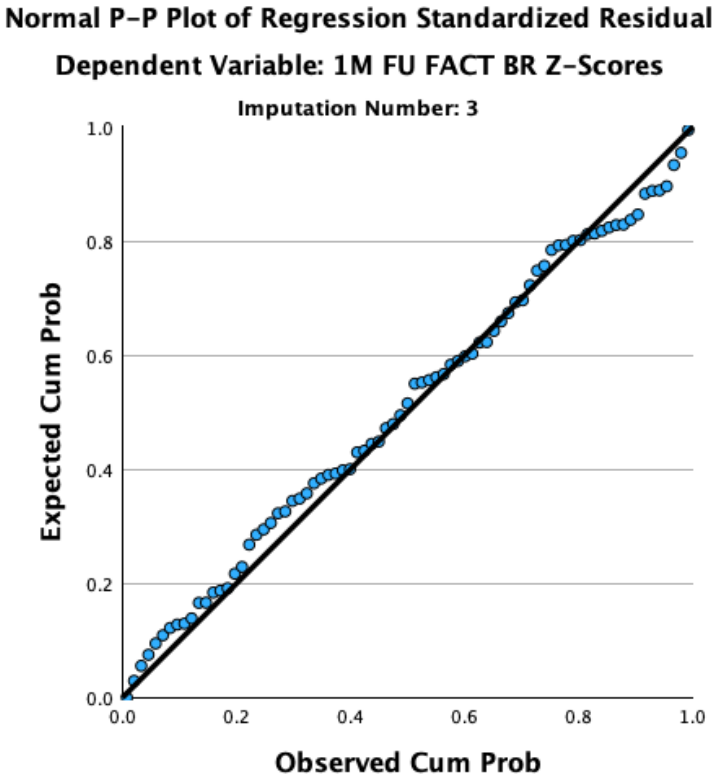
0.2
0.4
0.6
0.8
1.0


Normal P-P Plot of Regression Standardized Residual
Dependent Variable: 1M FU FACT BR Z-Scores
Imputation Number: 3
Expected Cum Prob
Observed Cum Prob
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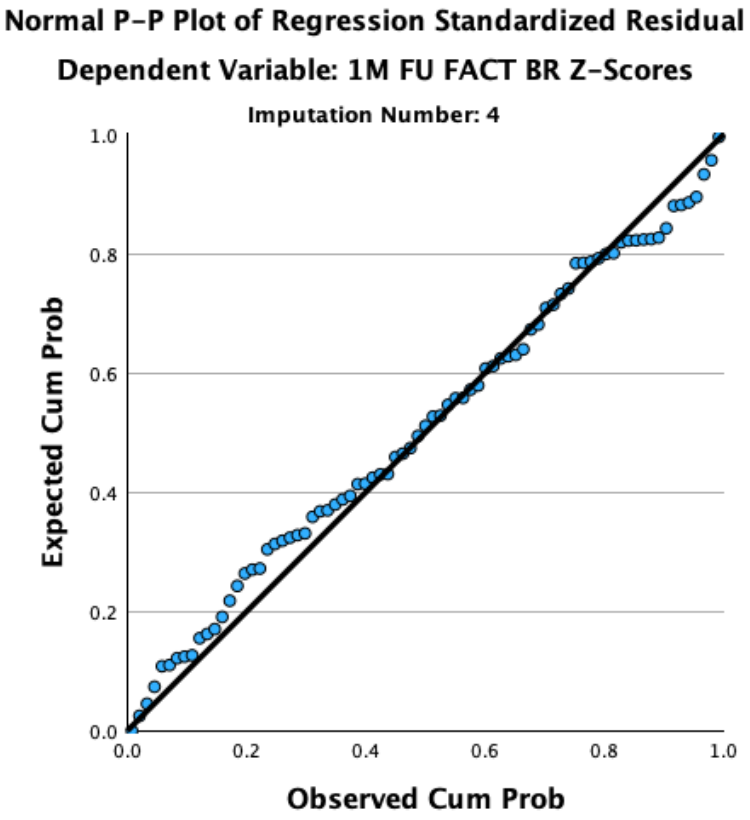
0.2
0.4
0.6
0.8
1.0


Normal P-P Plot of Regression Standardized Residual
Dependent Variable: 1M FU FACT BR Z-Scores
Imputation Number: 4
Expected Cum Prob
Observed Cum Prob
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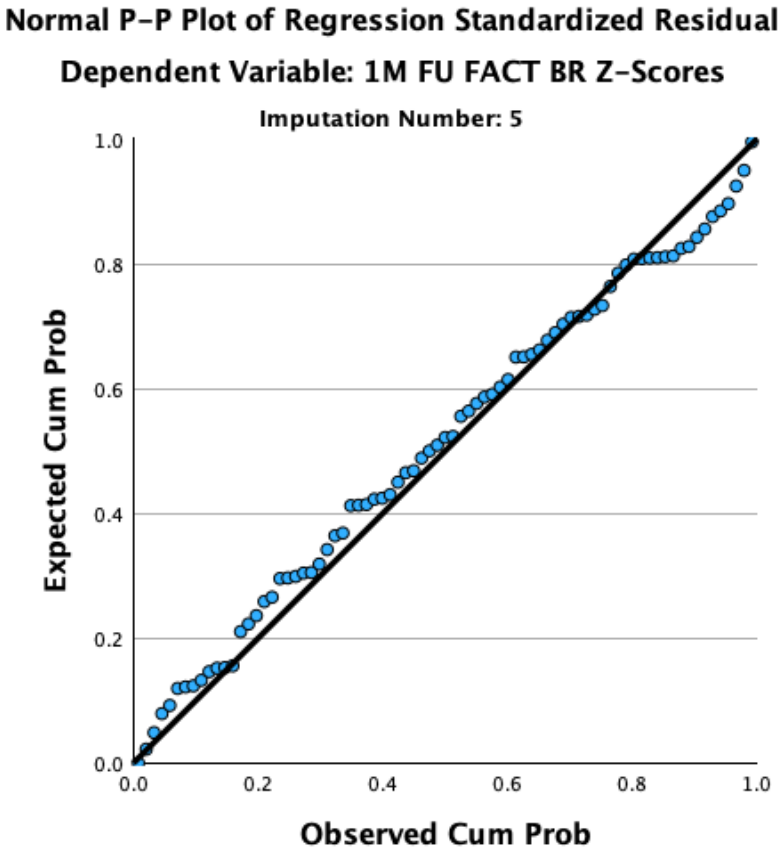
0.2
0.4
0.6
0.8
1.0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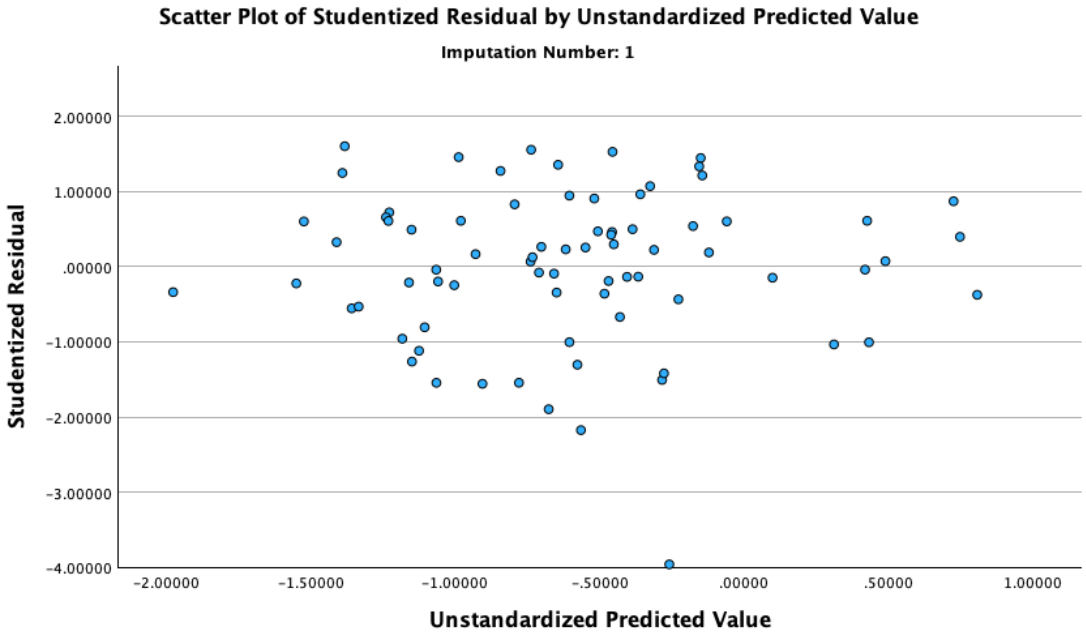
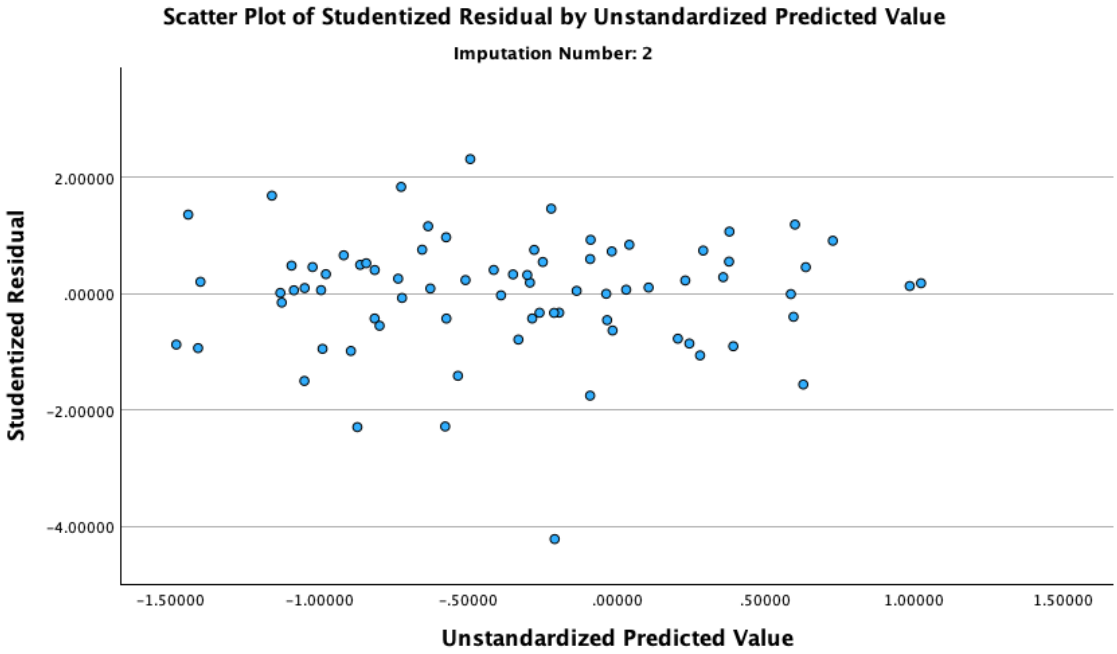
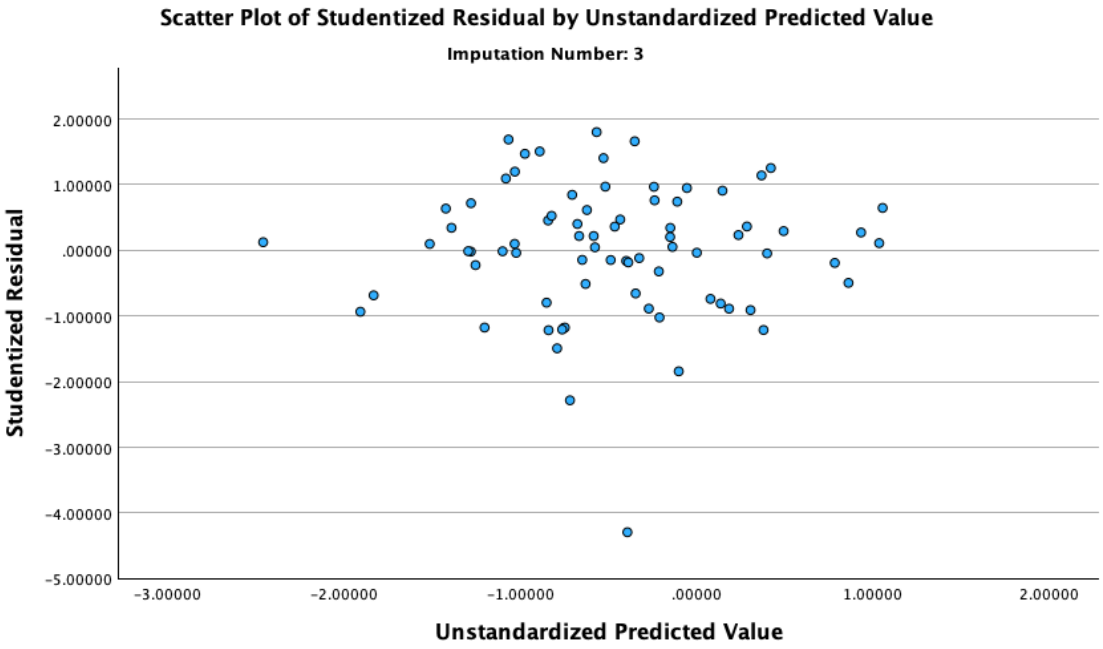
0.4
0.6
0.8
1.0

Appendix E: Scatterplots of studentised residuals versus un-standardised predicted values for six-month follow-up data



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Studentized Residual
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1.00000
.00000
-1.00000
-2.00000
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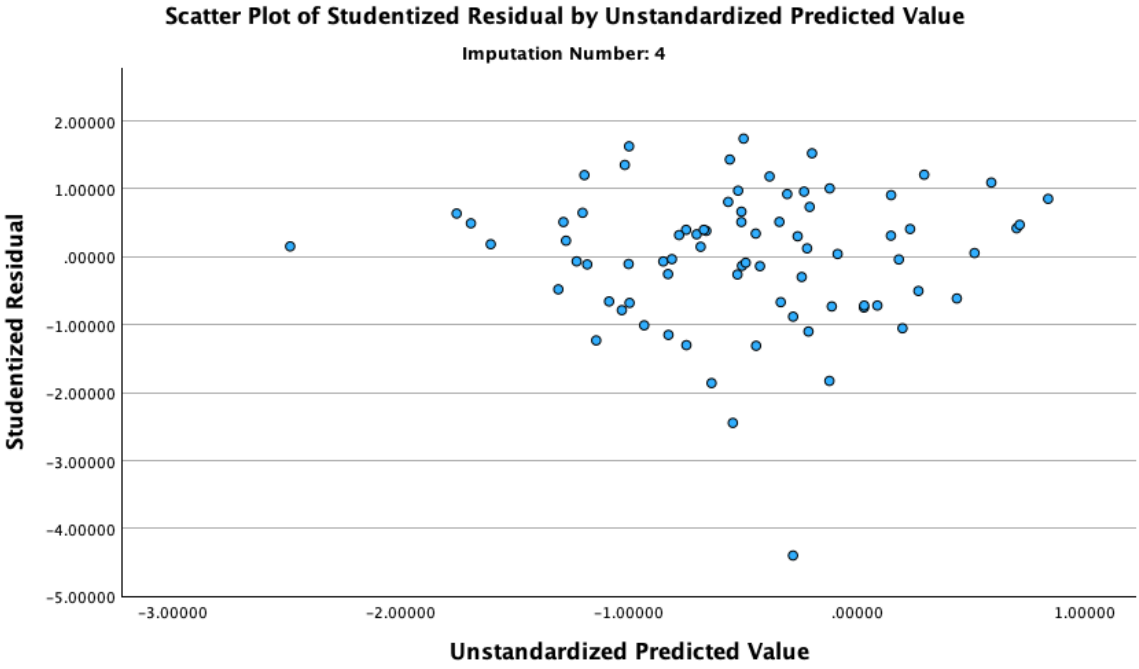
.00000
1.00000
2.00000
Unstandardized Predicted Value


Scatter Plot of Studentized Residual by Unstandardized Predicted Value
Imputation Number: 4
Studentized Residual
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1.00000
.00000
-1.00000
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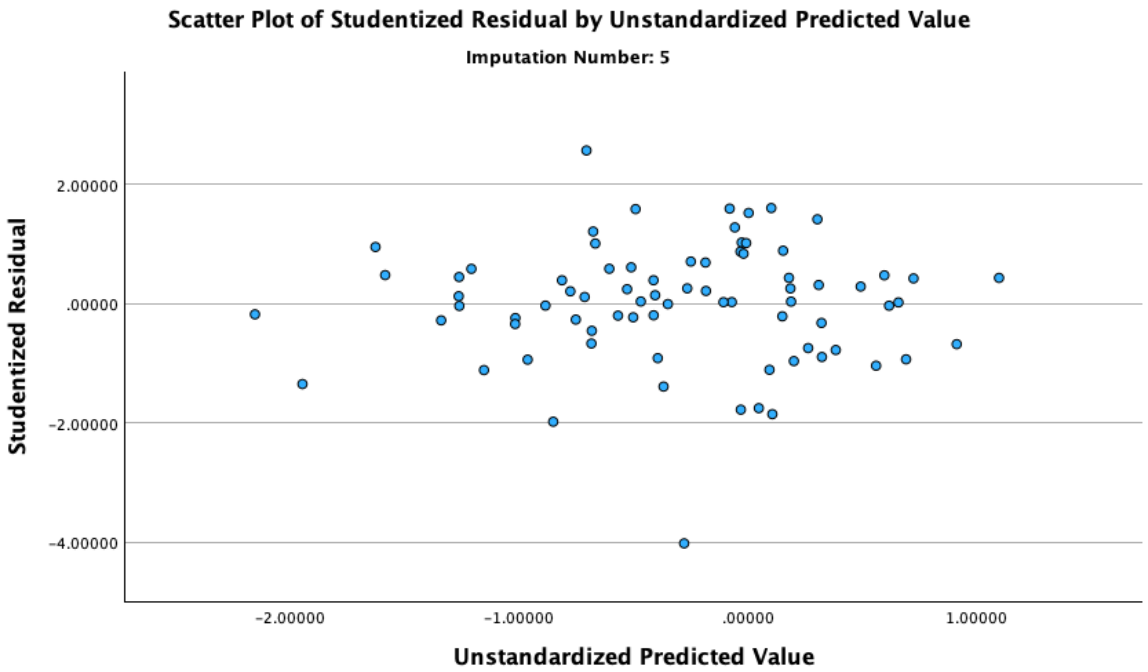
-2.00000
-1.00000
.00000
1.00000
Unstandardized Predicted Value


Scatter Plot of Studentized Residual by Unstandardized Predicted Value
Imputation Number: 5
Studentized Residual
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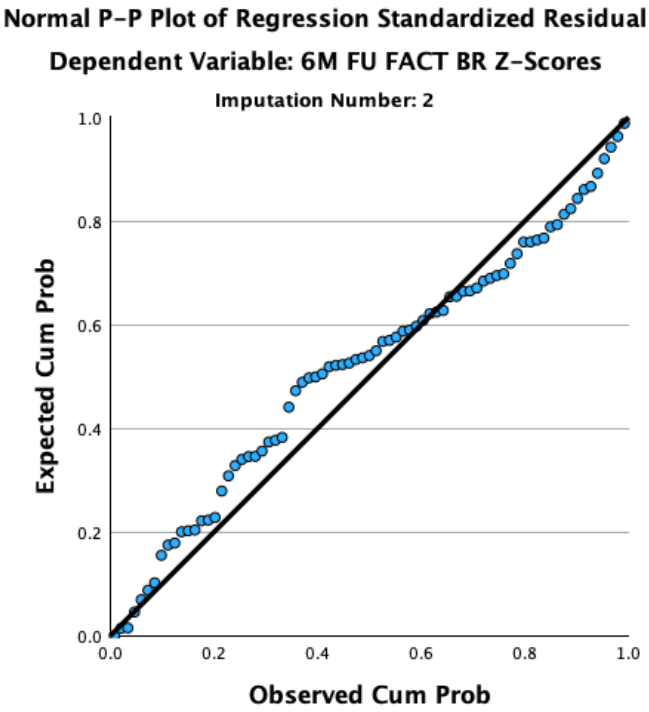
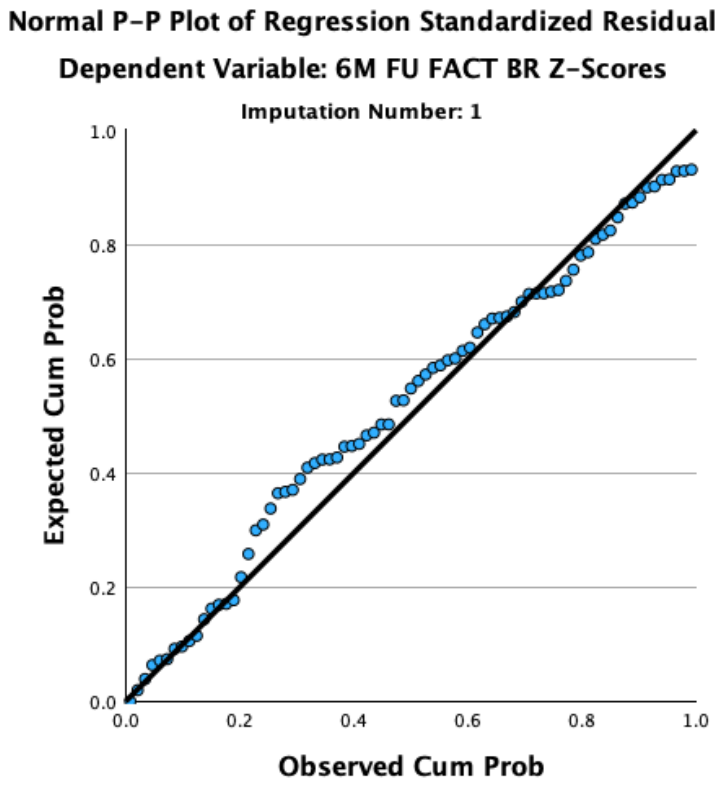
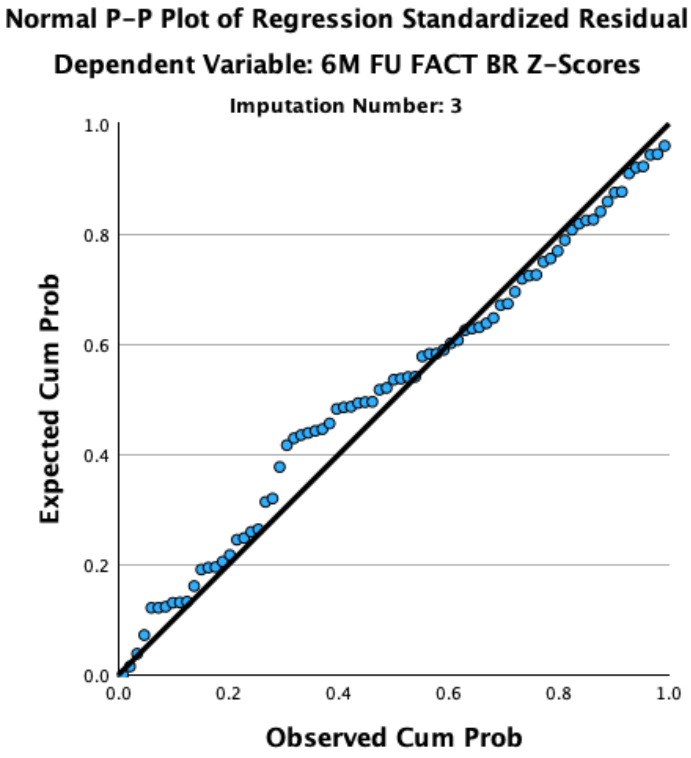
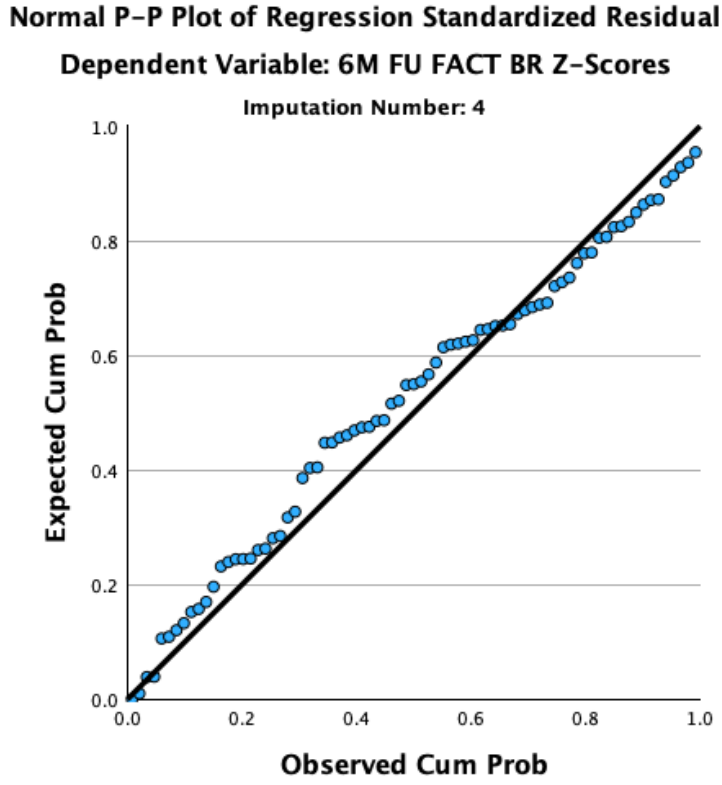
-2.00000
-1.00000
.00000
1.00000
Unstandardized Predicted Value

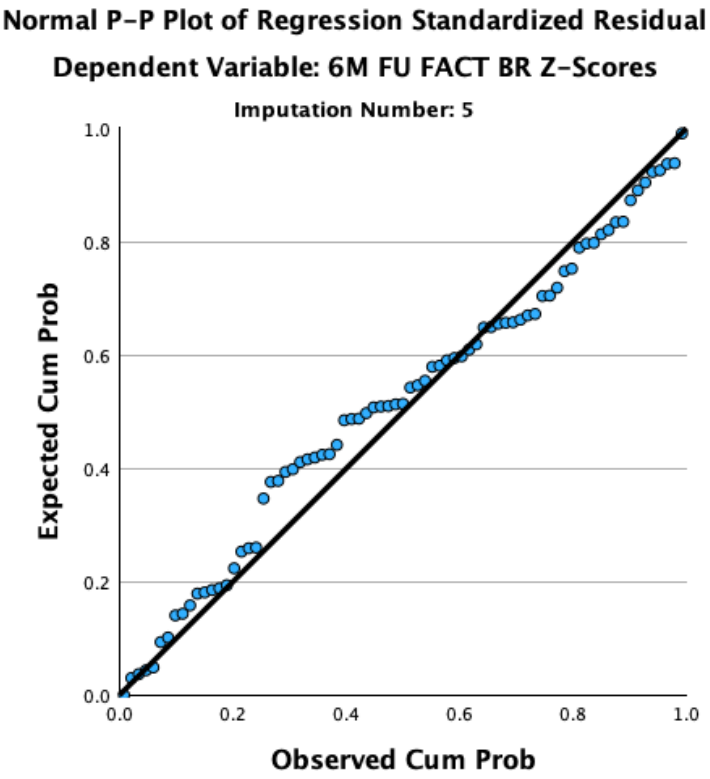
Appendix F: P-P plots for six-month FACT-Br data



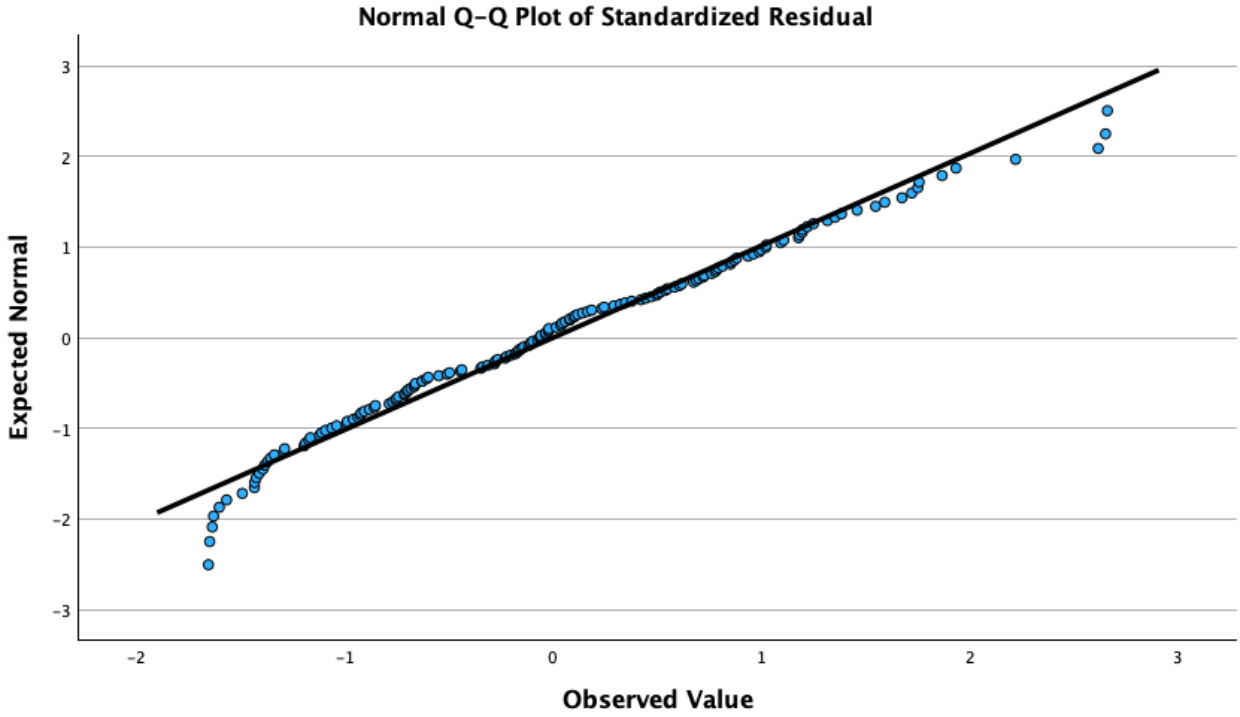



Normal P-P Plot of Regression Standardized Residual
Dependent Variable: 6M FU FACT BR Z-Scores
Imputation Number: 3
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0


Normal P-P Plot of Regression Standardized Residual
Dependent Variable: 6M FU FACT BR Z-Scores
Imputation Number: 4
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0


Normal P-P Plot of Regression Standardized Residual
Dependent Variable: 6M FU FACT BR Z-Scores
Imputation Number: 5
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0

Appendix G: Q-Q plot of standardised residuals



Appendix H: Journal aims and scope

The *British Journal of Clinical Psychology* publishes original research, both empirical and theoretical, on all aspects of clinical psychology:

- clinical and abnormal psychology featuring descriptive or experimental studies
- aetiology, assessment and treatment of the whole range of psychological disorders irrespective of age group and setting
- biological influences on individual behaviour
- studies of psychological interventions and treatment on individuals, dyads, families and groups

For specific submission requirements, read the Author Guidelines.

The Journal is catholic with respect to the range of theories and methods used to answer substantive scientific problems. Studies of samples with no current psychological disorder will only be considered if they have a direct bearing on clinical theory or practice.

The following types of paper are invited:

- papers reporting original empirical investigations;
- theoretical papers, provided that these are sufficiently related to empirical data;
- review articles, which need not be exhaustive, but which should give an interpretation of the state of research in a given field and, where appropriate, identify its clinical implications;
- Brief Reports and Comments.

Paper Three: Executive Summary

How Does Anxiety and Depression Before Awake Brain Surgery Impact Patient Outcomes?

Iram Munir

University of Staffordshire

Word count: 1,689

Table of Contents

Who Is This Summary For?

This summary is written for people who have had, or are preparing to have, an awake brain surgery (awake craniotomy), and for their families, carers, and loved ones. It is also intended for other users of neurosurgical and psychological services who might be interested in how mental health can affect recovery from surgery. Lastly, healthcare professionals, researchers, and NHS stakeholders who work closely with patients undergoing brain surgery may find this summary helpful as a clear, patient-focused explanation of this research and why it matters.

How Participants Helped Shape This Work

Although the participants included in this study were not actively involved in the design of the study, their experiences were central to identifying what matters most in their recovery journey. This research was inspired by the endless dedication of healthcare professionals, who strive to make every patient's experience as smooth and compassionate as possible, even within the reality of an overstretched and often under-resourced healthcare system. Through working closely with neuropsychology teams, it is clear how much unseen effort goes into preparing and supporting patients and their loved ones – not only to ensure treatment success - but to provide dignity, understanding, and emotional support throughout their care. This research reflects and honours that commitment and provides evidence to supports the continued development of holistic and patient-centred services.

At a later stage of the project, the executive summary will be shared among patients and their loved ones, as well as the neuro-oncology team for their feedback.

What Was This Research About?

Awake craniotomy is a specialist type of brain surgery performed while the patient is awake (at least for part of the procedure). It is used to remove brain tumours that are located near areas of the brain that control important functions, like speech, movement, or memory. By keeping the patient awake and able to respond during surgery, doctors can monitor how the brain is working in real time and avoid any areas of the brain that are really important.

This research focused on not only what happens during the surgery, but on how people feel before and after the operation. It sought to understand:

* Do people who feel more anxious or depressed before surgery have different experiences during and after surgery?
* Does the way someone feels before surgery impact how they feel about their own recovery outcomes?
* What are some of the factors which impact how anxious someone feels before their surgery?
* Ultimately, can understanding someone's mental state before surgery help healthcare teams support them better during recovery?

By answering these questions, the study hoped to learn about how to improve psychological support for people undergoing awake brain surgery, and to highlight the importance of considering emotional wellbeing alongside medical and functional outcomes.

Why Is This Important?

Awake craniotomy is a major medical procedure, often carried out in people diagnosed with a brain tumour. While the operation itself is designed to safely remove as much of the tumour as possible, the journey doesn't end in the operating theatre or even in the hospital. People recovering from brain surgery often face a long period of adjustment, which can include physical symptoms (like fatigue or pain), cognitive challenges (like memory or attention difficulties), and emotional changes (like low mood or anxiety).

In clinical settings, a lot of attention is given to how well the surgery goes, how much of a tumour is removed, and whether important brain functions are preserved. While these are all very important markers of success, less focus is often placed on the patient's mental health and emotional recovery. But for many patients, the emotional impact can be just as significant—and sometimes more so—than the physical outcomes.

By exploring how mental health before surgery relates to outcomes after surgery, this research aimed to shift the focus toward more holistic care, where services look at treating not just the brain, but the whole person.

What Did We Already Know from Previous Research?

Previous studies in other types of surgery have shown that people who feel more anxious or depressed before an operation often report more pain and a more difficult recovery afterwards. In brain surgery, especially during surgery where you are awake during it, the psychological experience may be even more intense. Patients are often very aware of the risks and are required to actively participate in the surgery. While this method does drastically improve surgical safety, it can understandably increase fear and anxiety before the surgery.

Several studies have found links between pre-operative anxiety (anxiety before the surgery) and how patients feel their mood and thinking skills have changed after surgery. Other research papers suggest that anxious and depressive symptoms before surgery might be linked to patients reporting higher pain levels and a lower quality of life afterwards.

However, there is a lot of inconsistency in the research. Also, most of the research looks at general brain surgery and other medical procedures. There are still relatively few studies focusing specifically on awake craniotomy patients, who have a unique experience and set of challenges.

How Was This Study Carried Out?

This study looked at a group of patients who underwent awake craniotomies at an NHS neuro-oncology service in the UK. All patients completed psychological questionnaires before (and after surgery), which measured:

* Anxiety
* Depression
* Quality of Life
* Pain
* Whether they thought their outcomes (like mood, thinking skills, speech, and physical movement abilities) were better, worse, or the same after surgery.

The study originally aimed to look at data one day, one month, three months, six months, and 12 months after the operation. However, due to data limitations, the study used evidence from the one-month and six-month follow-ups instead.

Statistical analysis was used to examine whether pre-operative anxiety and depression scores could predict (1) pain during and after the operation, (2) quality of life after the operation and, (3) patient's ratings of their outcomes. In essence, the study was asked "Does how someone feels emotionally before surgery relate to how they feel afterwards?" The study also looked at whether we could see any differences in how anxious someone is before their surgery based on age, sex, where their surgery is in the brain, and by how much their tumour has progressed.

What Did the Study Find?

Here are the key results:

1) Patients who felt more depressed before the operation tended to report feeling more pain during the operation. They also reported a lower quality of life one month after the operation.
2) Feeling more anxious before the operation wasn't strongly linked to pain levels.
3) How anxious or depressed patients were before the surgery didn't seem to predict how they personally rated changes in their mood, speech, or thinking skills later on. Patients of female sex were more significantly more likely to report worse motor skills, and patients with surgery to the left side of their brain were significantly less likely to report worse motor skills. However, this finding needs more exploration.
4) Things like patients' age or sex or details about their tumour didn't seem to relate to how anxious they were before the surgery. This was a surprising finding, and it might be because the hospital team included clinical psychologists who provided special psychological preparation sessions for very anxious patients beforehand, which might have helped level things out.

What Does This Mean for Patients and Services?

The findings suggest that it is important for services to think carefully about patients' mental wellbeing before their surgery – not just for their comfort, but also because it might influence how people recover afterwards.

Here are some things that services could do based on the research:

* Introduce routine psychological screening before surgery to help identify people who may be at higher risk for difficulties after surgery. These individuals could then be proactively offered extra support before and after the operation.
* Offer sessions with a psychologist before the operation to build on resilience strategies and help them feel more prepared, less anxious, and better able to manage any difficulties in their recovery.
* Integrate psychological factors and assessments with pain management planning.
* Enhance pre-operative psychoeducation by explicitly discussing how anxiety might influence a patient's perception of their outcomes, helping to manage expectations and distress.
* When assessing outcomes like pain or perception, use standardised, validated questionnaires wherever possible so that results can be interpreted and compared more effectively.

What Still Needs to Be Explored?

While this study offers some useful insights, it also highlights areas for future research:

* We need larger studies to confirm these findings. In other words, we need to have more confidence that results like these can be replicated.
* More diverse patient groups also need to be studied. In this paper, we didn't consider different gender identities, social backgrounds, culture etc, and we need to understand such factors to determine if findings like these apply across a range of diverse groups.
* We need longer follow-up periods. Some of the effects of surgery might not appear until months or years later. Following patients for a longer period would provide a more complete picture of recovery.
* We could also explore what kind of support works best. Now that we know that pre-operative mental wellbeing matters, the next step could be to test out different types of support (e.g., providing lots of information, group therapy, mindfulness techniques, etc.) and see what actually helps patients during and after surgery.

Some Final Thoughts

Awake craniotomy is a remarkable medical procedure that has changed the lives of many people with brain tumours. But recovery is not just physical – it's also emotional and psychological. This study shows that how people feel before surgery can shape how they feel afterwards, which has implications for the services and interventions that are offered.

By listening to patients, involving them in their care, and supporting their emotional wellbeing through every stage of their journey, we can improve not just survival, but the quality of life that follows. Such proactive processes and generative outcomes matter not only for patients, but also to the significant others in their lives.

[end]