Optimising perioperative language assessment in awake craniotomy: picture naming with nouns and finite verbs in the past and present tense

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A thesis submitted in partial fulfilment of the requirements of Liverpool John Moores University for the degree of Doctor of Philosophy.

May 2024

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Glossary of abbreviated terms

ANFV	Action Naming with Finite Verbs
BNT	Boston Naming Test
BOLD	Blood Oxygen Level-Dependent
CAT	Comprehensive Aphasia Test
CT	Computerised Tomography
DES	Direct Electrical Stimulation
DuLiP	Dutch Linguistic Intraoperative Protocol
ELGGN	European Low-Grade Glioma Network
fMRI	Functional Magnetic Resonance Imaging
GD	Patient
Gy	Gray Unit of Ionising Radiation
Hz	Hertz
iMRI	Intraoperative Magnetic Resonance Imaging
JLR	Patient
mA	Milliamps
MRI	Magnetic Resonance Imaging
ms	Milliseconds
MW	Patient
NHS	National Health Service
nTMS	Navigated Transcranial Magnetic Stimulation
PADILIH	PAst DIscourse LInking Hypothesis
PET	Positron Emission Tomography
PPTT	Pyramid and Palm Trees Test
RS	Patient

rTMS	Repetitive Transcranial Magnetic Stimulation
s	Seconds
SLT	Speech and Language Therapist
TDCS	Transcranial Direct Cortical Stimulation
TMS	Transcranial Magnetic Stimulation
TMT	Trail Making Test
VAN-POP	Verb And Noun Testing for Perioperative Testing
WAB	Western Aphasia Battery
WHO	World Health Organization

Acknowledgements

I would like to dedicate this thesis to the memory of my grandfather, James Mackenzie, who sadly passed away in February 2020. I wish you were here to celebrate me becoming "the first Dr in the family", as you would proudly tell your friends (and anyone who would listen!).

To all who have played a part in my PhD journey, I would like to express to you my deepest gratitude for the help and support during what has been the greatest challenge of my life so far – it would not have been possible without you all.

Supervisors

First and foremost, my three supervisors, who have taught me so much and have each supported me in different ways throughout the PhD, especially during the trials and tribulations of completing a clinical project during a global pandemic. It was an honour to be supervised by you and I will forever be in your debt.

To Dr Daniel Roberts – for allowing me an incredible opportunity to undertake an innovative and ambitious project beyond my wildest dreams. Your expertise has been essential to the success of this project and thesis; you have taught me a great deal and challenged me develop my skills as a researcher.

To Professor Francis McGlone - for sparking my passion for cognitive neuroscience as an undergraduate over 12 years ago, which inspired me to pursue a PhD in the first place. Thank you for your ongoing support, guidance, and belief in me - especially through the difficult times.

To Dr Samantha Brooks – who has shown me a great deal of support and encouragement. You have inspired me, kept me motivated and guided me through the tough times.

Family and friends

To my Mum, Alison and my partner, Chris, for their unwavering support and encouragement in achieving my goals. Thank you for believing in me always and helping me through the tough times. To my Godmother, Jackie, Auntie Marg, my Dad, Graeme and all the family, of whom there are too many to mention, for their ongoing love, support, and interest in what I have been doing.

To my amazing friends, Joanne, Liam, Yasmine, Ciaran, Joss and Tarryn – for simply being there (and listening to my complaining) and supporting me over the years. To Michelle and George, my dear friends and fellow PhD students, who have been a great source of support both personally and academically; not forgetting my other fellow PhD students with whom I have made great friendships and have all helped me in one way or another along the way - Sarah, Jamie, Connor, Andrea, Kate, Ben, Deb, Ishi, Adarsh, Claire, Chris, Serena, Sophia, Sharon, Kelly-Ann, Alex, Kat, Ansofie, Elaine and Rachel).

The Walton Centre NHS Trust

To the Walton Centre staff for their cooperation in undertaking this project, in addition to their already demanding roles in the NHS. Neurosurgeons, Mr Michael Jenkinson, Mr Andrew Brodbelt, Mr David Lawson and Mr Emmanuel Chavridakis, for allowing me access to patients in theatre for data collection; Dr Jacqui Vinten (Clinical Neuropsychologist) and Ms Hannah Jones-Reynolds (Speech and Language Therapist), for assisting recruitment and supporting intra- and pre-/post-operative data collection; Mr Kumar Das (Neurologist) and Ms Sharon Gould (Radiographer) for providing patient MRI data; and finally, oncology nurses, Ms Jan Holding and Ms Anna Crofton, who supported with recruitment and data collection.

To the four patients, RS, GD, MW and JLR, and their families, for dedicating their time to this research, despite the life-changing health issues they were facing. I am forever grateful for your invaluable contribution to this research.

Funders

To Liverpool John Moores University for seeing the value of this research project and providing a full scholarship; the Doctoral Training Alliance for the research training and support; Guarantors of Brain and the NIH for awarding additional travel bursaries to disseminate this research at international conferences.

Abstract

Direct electrical stimulation to map neural language functions during awake craniotomy for low-grade gliomas (brain tumours) is the gold-standard neurosurgical approach. This technique, known as cortical mapping, involves delivering inhibitory electrical currents to brain regions while language functions are assessed through simultaneous neuropsychological testing. Current intraoperative language assessment protocols, however, lack standardisation and rigour. Basic tasks such as counting, object naming, and reading offer limited scope to assess more intricate linguistic components such as grammatical processing (e.g., verbs vs. nouns). This presents significant limitations to intraoperative language mapping that may compromise preserving patients' language functions postoperatively. Moreover, insensitivity in testing also extends to pre- and post-operative clinical assessment. Standard aphasia assessment is designed predominantly for stroke patients and recent studies demonstrate its limited capacity to capture subtle impairments in the preoperative glioma language profile (e.g., accuracy vs. reaction time). The aim of the present thesis was to address this issue and improve postoperative language outcomes for low-grade glioma patients undergoing awake craniotomy.

Through a systematic review of the neurosurgical literature, Study 1 (Chapter 3) aimed to synthesise data from brain stimulation mapping studies of different cognitive and linguistic tasks used during awake craniotomy. This provided an improved understanding of the brain areas successfully mapped with different tasks to support the development and implementation of comprehensive protocols for optimising cognition and language mapping; both among the clinical and research community.

For the first time within the UK NHS, a standardised English version of a new linguistic protocol already in practice around Europe, was adopted and trialled for pre-, intra and post-operative language assessment (Study 2, Chapter 4). The Verb and Noun Test for perioperative

testing (VAN-POP) consists of object naming and action naming with finite verbs (ANFV) which come together to assess the complex linguistic components (semantic, phonological and grammatical processes) involved in sentence production. However, unlike versions developed in other languages which only assess present tense finite verb production, the English version includes an additional subset assessing finite verb production in the past tense. Therefore, this study novelly implements a three-task approach of object naming and ANFV in the past and present tense. The VAN-POP successfully mapped and monitored language in four patients with suspected low-grade gliomas (frontal, parietal, temporal, and fronto-temporal). Additionally, these tasks enabled the detection of some novel grammatical interferences relating to tense and inflection that have not yet been reported in the awake neurosurgical literature.

Study 3 (Chapter 5) adapted the VAN-POP into speeded naming tasks to assess preoperative baseline and short and longer-term postoperative changes in language function. Accuracy and reaction time data were collected in three patients recruited for Study 2 (Chapter 4) at preoperative, postoperative (1-month) and follow-up timepoints (3-month) and compared with healthy controls. Variable performance (improvements and declines) was observed for different tasks in patients over the postoperative course compared to baseline and control performance. Crucially, reaction times, which often go unmeasured clinically, captured the patients' language impairment better than accuracy at all testing stages. At follow-up, all patients were found to have impaired lexical retrieval speed on at least two tasks either in relation to controls or their preoperative baseline. However, none of the patients were significantly impaired with regards to accuracy. This finding suggests that both accuracy and reaction time measures are important in obtaining a comprehensive understanding of impairment within the glioma language profile. Moreover, the finding which was most consistent across all patients was a greater impairment in retrieval for past tense ANFV

compared to present tense ANFV. This novel finding may be further understood within the context of time-reference theories and suggests that more specific testing of verb morphology in glioma patients is warranted.

This research has expanded on previous studies that have established the application of object and action naming to optimise intraoperative and perioperative assessment in frontal, temporal, and parietal glioma. Importantly, in line with other recent research, slower processing speed appears to be a more central characteristic of the glioma language profile; with these subtler, yet salient, impairments shown to extend and further decline postoperatively. Collectively, the findings of this thesis question the status quo of neurosurgical practice and neuropsychological testing in terms of the sensitivity and scope of intraoperative and perioperative tasks. As demonstrated, incorporating rigorous and comprehensive linguistic testing such as VAN-POP, in the pre-, intra, and post-operative period is crucial for assessing the intricacies of the glioma language profile and in turn, maximising postoperative neuropsychological outcomes.

Chapter 1: Introduction to awake craniotomy for brain tumours

1.1. Chapter overview

The treatment of brain tumours depends on several factors such as their size, type, grade, location, metastasis, and any risk of side effects. Treatment options include surgery, radiotherapy, chemotherapy, and targeted therapy. Surgery is the focus of this thesis. The first section of this chapter will provide a brief introduction to neurosurgery, synthesising historical and current perspectives on the practice of awake craniotomy and language mapping. Secondly, the patient population of interest – brain tumour patients (low-grade glioma) – will be discussed. The final section will provide a critical overview of language testing throughout the surgical process (pre-, intra-, and post-operatively).

1.2. Awake craniotomy with language mapping: A brief history and current perspectives

Awake craniotomy with direct electrical stimulation (DES) language mapping is regarded as the gold-standard neurosurgical intervention for the resection of brain tumours or epileptogenic tissue in cases of intractable epilepsy (Bu, Zhang, Lu, & Wu, 2021; De Witt Hamer, Robles, Zwinderman, Duffau, & Berger, 2012). The main procedure is performed while the patient is conscious to allow the assessment of neuropsychological, sensory, and motor functions of brain regions in the vicinity of the surgical target site (De Witte & Marien, 2013). Since its introduction for epilepsy treatment in the 1950s by Wilder Penfield and colleagues (Penfield & Rasmussen, 1950), the key procedural techniques have been refined by George Ojemann in the 1970s (Ojemann & Mateer, 1979; Ojemann, 1979). Subsequently, the procedure was adopted by neuro-oncologists, owing to the seminal work of Mitchell Berger in the 1990s – namely, for the surgical treatment of low-grade glioma (Berger & Ojemann, 1992; Hervey-Jumper et al., 2015).

Spoken language is the principle means by which humans communicate, but the ability to reliably capture disturbances to an array of linguistic functions in awake neurosurgery is challenging, both theoretically and practically (De Witte & Marien, 2013; Rofes & Miceli, 2014; Rofes, Spena, Miozzo, Fontanella, & Miceli, 2015c). Traditionally, language has been assessed in neuro-theatre using only basic tasks, such as counting (e.g., 1-20), repetition, object naming (pictures) and reading of single words or short sentences. Such tasks have been used since Penfield began to map regions that were considered the main speech and language centres in the brain (Broca and Wernicke's areas), during which time there was only a limited understanding of the neural underpinnings of language. Advancements in the research of language systems have created a shift from the localisationist perspectives of clinico-anatomical correlation on which these tasks were built, towards more connectionist thinking (Catani et al., 2012). Yet, these basic language tasks have remained widely popular among neurosurgical clinicians around the world (Alimohamadi et al., 2016; Chan, Loh, Yeo, & Teo, 2019; Duffau et al., 2003; Duffau et al., 2005; Duffau, Peggy Gatignol, Mandonnet, Capelle, & Taillandier, 2008; Li et al., 2015; Mandonnet, Gatignol, & Duffau, 2009; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007; Robles, Gatignol, Lehéricy, & Duffau, 2008; Tomasino et al., 2014), likely owing to their ease of administration and importantly, for their tolerability in patients. Moreover, these tasks appear to be successful in practice, in that they are often capable of mapping perisylvian language sites of the language dominant hemisphere, at least for detecting low level speech functions and to an extent, semantic retrieval (object naming). Problematically, however, there exists a clear lack of standardisation and rationale in the development of these materials, which have a very limited scope to assess the wider and more intricate linguistic components according to new theoretical perspectives in language research. Connectionist or Parallel Distributed Processing (PDP) models have sought to better represent language as part of the wider neural network of motor, sensory and cognitive systems

(McClelland & Rogers, 2003; McClelland, St. John, & Taraban, 1989). According to such models, the perisylvian language regions (e.g., Broca and Wernicke's areas) are not domain-specific centres for expressive and receptive language, but rather, are part of a constellation of cortico-subcortical networks of regions underpinning (but not limited to) different language functions (Campbell & Tyler, 2018; Catani et al., 2012). Critical nodes within these networks (e.g., the temporal lobe or "semantic hub" ; Patterson & Ralph, 2016) serve as epicentres for the integration of multimodal information from various participating centres in the network. Connectionist models propose that damage to a participating region within the network would result in an impairment to specialised language functions of that area (e.g., syntax) and cause partial disruption to neighbouring connections, while functions supported by connections that are downstream may remain intact (Catani et al., 2012). However, lesions to critical nodal hubs or convergence zones such as the inferior frontal or anterior temporal lobes, or visual and sensorimotor cortices where such functions are highly localised, may cause a more global impairment to language (e.g., Broca and Wernicke's aphasia). Furthermore, it is not only through focal cortical damage that the relay of information within the network can be inhibited; crucially, the disconnection of cortical regions via damage to the subcortical white matter tracts (Catani & Mesulam, 2008), can affect network traffic or connectivity and thus subcortical DES mapping is becoming more prominent in the literature (De Witte et al., 2015b; Duffau et al., 2005; Rofes et al., 2019; Rofes et al., 2017b; Rolland, Herbet, & Duffau, 2018; Sarubbo et al., 2020).

Many linguistic protocols used for awake craniotomy are theoretically insensitive with respect to connectionist models, increasing the potential for type II errors (i.e., false negative mapping; Pallud et al., 2017). This ultimately depends upon the location of stimulation and whether the tasks used capture the specific linguistic role of a given cortico-subcortical site (Sarubbo et al., 2020). This is a significant limitation to intraoperative language mapping that

may compromise the overarching goal of awake craniotomy in preserving patients' language functions postoperatively. While aphasia arising from craniotomy is thought to affect up to 50% of cases, the level of impairment has previously been regarded as mild to moderate in nature (Davie, Hutcheson, Barringer, Weinberg, & Lewin, 2009), and transient in duration, with permanent deficits estimated to occur in less than 5% of patients (De Witte & Marien, 2013). However, a recent study comparing the language profiles of stroke and post-surgical low-grade glioma patients suggests that awake craniotomy can cause a generalised decline of language processing abilities or a moderate global aphasia, as opposed to impairments to specific processes (e.g., Broca or Wernicke's aphasia) arising from stroke lesions (Zyryanov et al., 2022).

Over the last decade, clinicians and researchers have begun to recognise the limitations of basic linguistic testing intraoperatively, and more recently pre- and post-operatively (De Witte & Marien, 2013), and how this may contribute to the severity of postoperative impairments. The research in this thesis has embedded neurosurgical teams (e.g., neurosurgeons, neuropsychologists, speech and language therapists, neurologists, radiographers) from the outset, with the aim to optimise assessments and improve clinical outcomes for patients. Recent advancements in intraoperative testing include the introduction of comprehensive linguistic test batteries such as the Dutch Linguistic Intraoperative Protocol (DuLIP) and tasks targeting additional morphosyntactic (grammatical) components that are relevant to real-world language functioning (De Witte et al., 2015b; Rofes et al., 2019; Rofes et al., 2015c; Rofes et al., 2017b). The DuLIP offers a comprehensive and tailored approach to testing by prescribing a variety of sophisticated tasks (e.g., semantic, phonological, grammatical etc.) according to the neuroanatomical basis of each patient's tumour location.

The use of different tasks and approaches to cognitive-linguistic testing each have their own merits and limitations, both theoretically and in practice, which will be discussed in

Chapter 3. The focus of this thesis will be the optimisation of intraoperative, as well as pre- and post-operative linguistic assessment according to the latter approach - specifically, using a newly developed trio of tasks - object naming and action naming with finite verbs in the past and present tense (Ohlerth, Valentin, Vergani, Ashkan, & Bastiaanse, 2020). The remainder of the current chapter will offer a general introduction to the clinical cohort of interest - brain tumour patients (specifically those with low-grade gliomas) - as well as an overview of pre- and post-operative language assessment in awake craniotomy. The latter will discuss the key principles and methodology, in terms of both intraoperative techniques, and as part of a wider multidisciplinary patient care pathway lending expertise from a variety of clinical perspectives.

1.3. Brain tumours

1.3.1. Type, incidence, mortality, and survival

Primary brain tumours are defined as either malignant (cancerous) or benign (non-cancerous) masses that form through DNA mutations in healthy brain cells, causing them to rapidly grow and divide (Lapointe, Perry, & Butowski, 2018). Brain tumours can also be secondary or *metastases*, which have spread to the brain from another part of the body (Patchell, 2003). In the UK there are over 12000 new brain tumour cases each year, representing 3% of all new cancer diagnoses (UK, 2017). Brain tumours are the 9th most common cause of cancer deaths (~5400 each year), with greater mortality (34%) amongst the older (aged 75+) population, peaking in those aged over 90. Despite this, mortality figures for both males and females have remained stable over the past 10 years and is predicted to drop 2% by 2035. Following diagnosis, one-year and five-year survival rates are approximately 40% and 12%, respectively. The outlook is better for those under 40 with a 60% survival rate, compared to approximately 1% for people aged over 80 years.

1.3.2 Histopathology

Brain tumours consist of a collection of abnormal cells derived from different types of brain tissue and are classified according to those in which they originate. In 2007 the World Health Organization (WHO) classified central nervous system tumours into two overarching categories – those of neuroepithelial tissue and those of non-neuroepithelial tissue. Most brain tumours fall into the neuroepithelial category, of which there are several further subgroups (Louis et al., 2007). One of the most common types are gliomas, accounting for more than 50% of tumours. Gliomas develop from the cells that support neuronal functioning, known as glial cells, and further subtypes can be defined based on the specific glial cell type in which they have formed from (e.g., astrocytoma, oligodendroglioma, ependymoma). The histopathology of the tumour can often be speculated based on structural neuroimaging, however, a biopsy taken either prior to, or during the debulking surgery itself, must be cytogenically analysed to confirm the specific diagnosis and grade.

1.3.3. WHO tumour grades

The rate at which tumorous cells grow and spread is expressed in four grades, with I and II being low-grade, and III and IV being high-grade (Kleihues, Burger, & Scheithauer, 1993). Tumours can often be mixed in terms of the high and low-grade cells they contain and are not always distinct; for example, tumours may constitute predominantly low-grade cells, but may also contain higher-grade cells. However, the tumour is always classified according to the highest grade of cells it contains, irrespective of the quantity of each cell type.

Grade I and II tumours (e.g., low-grade gliomas) are slow growing, typically benign, and are often curable through surgical intervention without recurrence (Pignatti et al., 2002; Schiff, Brown, & Giannini, 2007). Grade II tumours are more likely to return at a higher-grade following resection (Murphy et al., 2018), thus adjuvant chemotherapy and radiotherapy are often administered (van den Bent, 2015; Wang & Mehta, 2019). Grade III and IV (e.g.,

glioblastoma multiforme) are rapidly growing malignant tumours that are highly likely to reoccur and metastasise, despite aggressive treatment with both surgical resection and adjuvant chemoradiotherapies. The prognosis is poor for such patients, although interventions strive to reduce tumour size as much as possible to extend survival, ease symptoms, and improve quality of life (Clavreul et al., 2021).

1.4. Preoperative, intraoperative, and postoperative language assessment

The aim of awake craniotomy as a neuro-oncology treatment is to remove as much of the tumour as possible whilst minimising damage to surrounding neural structures that may cause sensory, motor, or cognitive impairment postoperatively. Preserving function and optimising the oncological outcomes for patients relies on a collaborative team of specialist clinicians using state-of-the-art equipment, methods, and techniques, from diagnosis to discharge, and follow up. The next section will provide a contextual overview of the awake craniotomy surgical procedure, before discussing perioperative linguistic testing and mapping.

1.4.1. Preoperative testing

Comprehensive preoperative language assessment is undertaken, usually a week before surgery, to understand the language status of the patient and determine the appropriateness of awake surgery (O'neill, Henderson, Duffy, & Kernohan, 2020; Rofes et al., 2017a). If preoperative language function is severely impaired, then performing the craniotomy awake would typically not be feasible due to the challenge of distinguishing between existing deficits and stimulation-induced interferences (De Witte & Marien, 2013). In low-grade tumour cases, however, where the mass is relatively slow-growing, existing language impairments are often mild, or appear to be absent (Anderson, Damasio, & Tranel, 1990; Davie et al., 2009; Duffau et al., 2008). Although preoperative neuropsychological assessments aim to provide a thorough overview of various linguistic and cognitive subdomains, standard speech and language assessments that are used (e.g., the Comprehensive Aphasia Test, CAT; Swinburn, Porter, &

Howard, 2005), have been primarily developed for use with post-stroke aphasic patients. While slow-growing tumours have the advantage of preoperative plasticity - the gradual functional reorganisation of language (Duffau, 2005; Ho, Khan, Fischberg, & Mahato, 2021; Piai, 2019) - the acute nature of stroke lesions, often leads to more discernible language impairments. Therefore, preoperative assessment may only consider clinically significant expressive and receptive language errors (e.g., semantic, phonological, or verbal paraphasias) typical of Broca and Wernicke aphasias, as indicators of language impairment. While low-grade glioma patients may perform assessments within normal accuracy, their slow processing speed (Mooijman et al., 2021), and delayed responses (Noll, Ziu, Weinberg, & Wefel, 2016) may be masked if only accuracy is measured. While current perspectives on neuronal damage to language systems suggests other distributed brain regions may compensate for the functional loss of perilesional language cortex in low-grade glioma patients (Catani et al., 2012), this may result in an inefficient network, with impairments better captured by reaction time (Mooijman et al., 2021; Moritz-Gasser, Herbet, Maldonado, & Duffau, 2012; Ras, Satoer, Rutten, Vincent, & Visch-Brink, 2020). These subtler delays are unlikely to be realised by clinicians or indeed, the patients themselves. However, processing speed is nonetheless important to consider in addition to accuracy-based language errors, not only to improve patient quality of life (Ammanuel et al., 2022; Gabel et al., 2019), but crucially, to improve patient survival rates which have shown to be associated with cognitive impairment in glioma patients (van Kessel et al., 2021).

1.4.2. Language mapping with functional imaging

Structural magnetic resonance imaging (MRI) or Computerised Tomography (CT) is conducted preoperatively to gather important neurological information including tumour size, location, and morphology, allowing the surgeon to determine the rate of resection according to the structural borders of the tumour. Additionally, patients usually undergo functional MRI

(fMRI) or to a lesser extent due to its invasive nature, Positron Emission Tomography (PET), to preoperatively map the locations of motor, sensory, and language/cognitive functions within the locality of the tumour borders. When engaged in these functional tasks the brain areas recruited to perform them pose a higher demand for oxygenated blood – known as the haemodynamic response function. fMRI utilises the subsequent deoxygenation of these areas (i.e., the blood oxygen level-dependent (BOLD) signal) as an indirect measure of neuronal activity. Similarly, PET indirectly measures neuronal activity via regional cerebral blood flow, with the difference of visualisation using a radioactive tracer injected intravenously. fMRI and PET can be useful to provide a more general overview of the potential locations of language-positive regions before surgery, allowing the surgeon to better predict the functional boundaries of the resection (i.e., the maximum amount of tumour that can be removed without impairing function). fMRI is widely performed for presurgical planning in glioma patients (Agarwal, Sair, Gujar, & Pillai, 2019; Pechenkova, Panikratova, Mershina, & Vlasova, 2022); indeed, a recent meta-analysis demonstrated that undergoing preoperative fMRI can reduce postoperative morbidity in brain tumour patients (Luna et al., 2021). Like intraoperative mapping, the tasks used for preoperative mapping in the scanner are variable, and often different than tasks used for DES mapping; thus, language activations visualised in neuroimaging may not be directly comparable to language sites localised with DES (Roux et al., 2003b), or indeed may depend on the language tasks used (Brennan et al., 2007). Furthermore, the choice of language tasks for use in the scanner can often be limited to those using button-press responses or silent responses (e.g., silent verb generation), owing to the motion artifacts created by overt verbal responses.

Compared to sensory and motor mapping, localising linguistic functions via fMRI and PET can be challenging due to the elusive nature of primary and secondary language organisation, the structural heterogeneity of key language regions, and the variability of

thresholds used for language activation (Brennan, Peck, & Holodny, 2016). Consequently, the concordance between fMRI and DES is considered to be relatively low for language compared to sensorimotor mapping (Colle, Muller, & Robert, 2005; Duffau, 2007; Tonn, 2007); the sensitivity of fMRI being only 66% for language mapping (Lurito, Lowe, Sartorius, & Mathews, 2000; Roux et al., 2003b; Spena et al., 2010), compared 82-100% for motor and sensorimotor mapping (Boatman, 2004; Gil-Robles & Duffau, 2010; Ng, Mukhida, & Rutka, 2010; Quinones-Hinojosa, Ojemann, Sanai, Dillon, & Berger, 2003; Spena et al., 2010; Tharin & Golby, 2007). A recent meta-analysis confirmed that fMRI has only a moderate sensitivity and specificity for language mapping compared to DES, and that sensitivity is increased for studies that apply higher DES currents (Holloway et al., 2022). Furthermore, although there are numerous factors that can interfere with the validity of the BOLD signal, in healthy populations it is generally considered an accurate indicator of neuronal activity. However, in glioma patients, neurovascular decoupling due to tumour presence can compromise the BOLD signal (Pak et al., 2017; Pallud et al., 2017).

It is for these reasons that performing craniotomies under general anaesthesia, or awake surgery that is informed solely by functional imaging, is not ideal for brain tumour or epilepsy resections. However, general anaesthesia may be required in situations where it is anticipated that awake surgery may lead to complications, e.g., seizures, patient distress. Complications can also occur unexpectedly during awake surgery that require the patient to be re-anesthetised without completing intraoperative mapping or before further comprehensive intraoperative testing could have been administered (Gernsback, Kolcun, Starke, Ivan, & Komotar, 2018). In these situations, preoperative functional imaging, especially that combined with other techniques such as magnetoencephalography or importantly, transcranial magnetic stimulation (TMS; Cargnelutti & Tomasino, 2023; Haddad, Young, Berger, & Tarapore, 2020), as discussed in the next section, may offer the next best option for guiding the surgeon around

potential language sites. However, the absence of DES mapping may lead to a suboptimal rate of resection and less desirable oncological and neuropsychological results (Bu et al., 2021; De Witt Hamer et al., 2012).

1.4.3. Language mapping with navigated transcranial magnetic stimulation

Due to its non-invasive nature, TMS has demonstrated a useful application in presurgical planning for both motor and language mapping of cortical structures (De Witte & Marien, 2013; Haddad et al., 2020; Natalizi, Piras, Vecchio, Spalletta, & Piras, 2022). In motor mapping single pulse stimulation is used to excite motor neurons and induce movement (e.g., of the tongue or finger) to test regional functionality in motor responses; however, mapping language requires repeated pulses (repetitive TMS, rTMS) which elicits an inhibitory effect on neurons, causing a temporary lesion and a reversable disruption of function, similar to that of DES (Coburger et al., 2013). Earlier studies in epilepsy patients where rTMS was delivered without the aid of precise neuroanatomical guidance have found inconsistent results in terms of its language mapping capabilities (see Haddad et al., 2020 for a review). Initial studies found that rTMS could successfully determine hemispheric language dominance by inducing reproduceable speech arrests in line with results of the intracarotid amobarbital test (Jennum & Winkel, 1994; Pascual-Leone, Gates, & Dhuna, 1991). On the contrary, later studies suggested that unnavigated rTMS has less predictive value for postoperative language impairment than the intracarotid amobarbital test (Epstein et al., 2000), as well as imposing an increased rate of false-positive speech arrests when mapping the non-dominant hemisphere (Pelletier, Sauerwein, Lepore, Saint-Amour, & Lassonde, 2007; Tarapore et al., 2013). In recent years, advances in the field have since improved the anatomical accuracy of this stimulation method through the combination rTMS and MRI-guided neuronavigational technology, i.e., navigated rTMS (nrTMS). This offers a more precise approach that targets stimulation to anatomically specified cortical regions (Natalizi

et al., 2022; Picht et al., 2013; Tarapore et al., 2013). Furthermore, it is known that transcranial methods of stimulation are limited in relation to intracranial stimulation methods; although TMS may indirectly influence subcortical electrical activity, it can only directly depolarise cortical neurons (Allen, Pasley, Duong, & Freeman, 2007). However, the application of nrTMS can be further optimised in consideration of this disadvantage through the addition of tractography – a diffusion MRI technique that allows the visualisation of the subcortical white matter language networks that underpin cortical language sites (Negwer et al., 2017; Ohlerth et al., 2021; Raffa et al., 2017; Silva, Tuncer, Vajkoczy, Picht, & Rosenstock, 2022; Sollmann et al., 2016). This provides further advantageous data that can inform presurgical planning and has, crucially, been shown to increase the extent of resection and reduce the occurrence of postoperative impairments (Raffa et al., 2017; Sollmann et al., 2018; Sollmann, Meyer, & Krieg, 2017).

As nrTMS shares similar underlying principles to DES in terms of inducing a temporary lesion to assess functional involvement, it may provide a more comparable cortical map for intraoperative mapping than other techniques, such as fMRI. Indeed, nrTMS for language mapping has been found have greater correlation with DES than fMRI in terms of sensitivity (although notably lower specificity) to detect language areas (Ille et al., 2015). Furthermore, Ille et al. (2015) found that the concordance with DES was even higher when nrTMS and fMRI were used in conjunction. Therefore, nrTMS may provide a suitable adjunctive tool, as opposed to purely fMRI-informed resection, for patients who do not meet the criteria for awake surgery or may be unable to proceed with intraoperative testing (e.g., fatigue, complications). Importantly, recent studies have focused on preoperative nrTMS mapping with picture naming tasks commonly employed in awake surgery (objects and actions), in candidates for both awake and fully anaesthetised surgery (Bastiaanse & Ohlerth, 2023; Ille et al., 2019; Ntemou et al., 2023a; Ohlerth et al., 2021; Reisch et al., 2022).

Despite technological advancements, a key limitation of this mapping method is the variable concordance between nTMS and DES language mapping (Haddad et al., 2020; Ille et al., 2015; Jeltema et al., 2021). In comparison, the concordance between nTMS and DES for motor mapping is significantly higher (Picht et al., 2011; Weiss Lucas et al., 2020). A recent systematic review by Jeltema et al. (2021) assessed the degree of consistency between nTMS and DES for both motor mapping and language mapping. For motor mapping, concordance between the methods was measured spatially in terms of distance between cortical representation of muscle groups; it was reported that these distances varied by 2 and 16 mm between nTMS and DCS. For language, concordance was measured by sensitivity (ability to correctly detect object naming sites) and specificity (the ability to correctly identify non-object naming sites); this was reported as ranging from ranging from 10-100% and 13-98%, for sensitivity and specificity, respectively. Owing to this considerable variability, nrTMS cannot, at present, be substituted in place of DES. Further, the data available for language is currently limited, mostly to object naming tasks, although emerging research is demonstrating the application of preoperative nrTMS with other tasks, such as action naming with finite verbs (ANFV; Ntemou et al., 2023a; Ohlerth et al., 2021); further investigations are warranted to determine the suitability of administering a range of linguistic protocols for perioperative nrTMS mapping.

1.4.4. Intraoperative language testing

Structural/functional imaging and nrTMS can both be useful adjuncts for preoperative planning and navigating potentially positive language sites where intraoperative mapping is restricted, however, confirmation with DES mapping - the gold-standard mapping technique in neurosurgery - is necessary where permitted to make critical decisions regarding the resection of tissue; this will be discussed in more detail in the sections below.

1.4.4.1. Surgical procedure

Before discussing the DES technique, it is necessary to contextualise the neurosurgical procedure of awake craniotomy. Although the layout and contents of the operating theatre may vary between hospitals around the world, a diagram of a typical surgical set-up is provided in **Figure 1.1**. The exact protocol is variable, although the most common practice is the asleep-awake-asleep regime. In the first phase, the patient is anaesthetised and intubated. Rigid pin fixation, whereby the patient's head is immobilised using a Mayfield clamp, prevents any voluntary or involuntary movement of the head during surgery. Once the surgical area is prepped, the surgeon performs the craniotomy (opening of the scalp, skull, and dura mater). When the brain is exposed over the tumour site, the patient is awoken, although their head remains locally anaesthetised with a scalp blocking agent. During this awake phase, the patient completes cognitive and/or language tasks to enable the surgeon to map the cortical and subcortical functional areas. Once mapping is complete, the surgeon will begin debulking the tumour, with the aim of maximising resection while avoiding the functional boundaries identified during mapping, a margin of (usually) 1cm. The patient will often remain awake during the debulking of the tumour so that their functions can be continuously monitored

through language tasks and conversation. In the last phase, the patient is returned to sleep while the surgical site is closed and dressed.

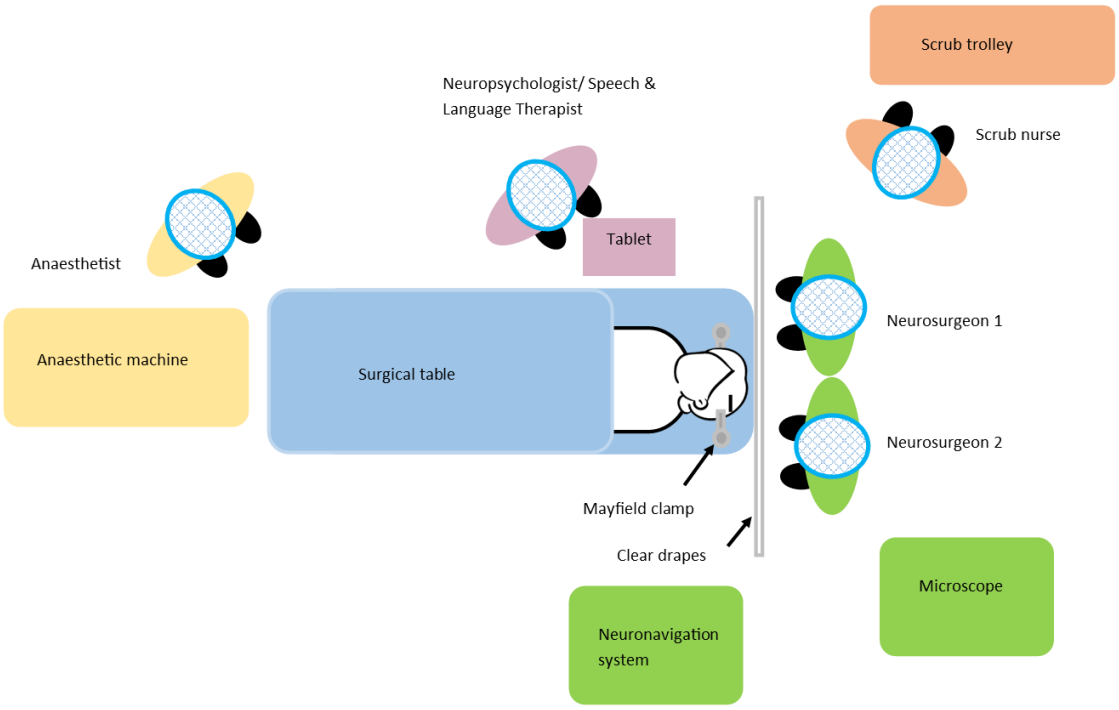

Figure 1.1. Diagram of the surgical setting in awake craniotomy. The patient is placed on the surgical table (blue). Depending upon which hemisphere the tumour is in, the patient will be positioned on their right side (left hemisphere) or left side (right hemisphere) with their head titled in the same direction. The head will be fixed in position using a Mayfield clamp and surgical drapes separate the sterile (surgical field) areas from the non-sterile areas. The neurosurgeons (green) remain in the sterile surgical area and members of the neurosurgical team will fetch surgical tools (from the scrub nurse; orange) and equipment as needed. The language clinician (pink) will position themselves at the side of the operating table near the patient's head. Language tasks will be delivered using a tablet or other device (or sometimes using paper materials). The anaesthetist (yellow) is responsible for the patient's wellbeing and safety during the procedure. They will remain near the bedside to administer anaesthesia for pain management, other medications, and fluids as necessary. They will also continuously monitor the patient's vital functions (e.g., breathing, heart rate, blood pressure etc.).

1.4.4.2. Principles of cortical and subcortical DES mapping

Language testing with DES is considered the gold-standard approach for performing awake craniotomy for tumours that infiltrate language areas of the brain. This is not only advantageous in terms of passively monitoring for deterioration of language as the surgery progresses, but crucially, the addition of DES allows the surgeon to test potentially functional

areas before resection begins. In many cases, gliomas permeate surrounding healthy brain tissue that is functional for language (as well as sensorimotor and wider cognitive processes) and has been identified in 46% and 35% of perilesional cortical and subcortical sites, respectively (Spena et al., 2010). Applying electrical stimulation to either a cortical or subcortical area of the brain will, at the correct pulse frequency (as described in the next section) temporarily supress its function, creating a localised "knock out" effect. Hence, the neurosurgeon can test whether a given area is essential (primary) for language function (as opposed to secondary/modulatory) by having the patient simultaneously perform a variety of language tasks (usually counting, repetition, object naming, phonological/semantic fluency, reading). If the patient shows any disturbance to speech or language during stimulation (e.g., speech arrest, errors, delays) during at least 2/3 non-consecutive stimulations, this would be considered a language-positive site; if there is no change to performance, the site would be considered negative for language. However, this may not always be the case, depending on the sensitivity and limited range of tasks used to test language – a limitation that this thesis aims to address.

1.4.4.3 Electrodes, stimulation parameters and protocol

DES is delivered using electrodes that apply electrical currents directly to the brain; the method for doing so is variable – it may involve electrode grids that are arranged on the surface of the brain, or the surgeon may manually stimulate cortical regions using a monopolar or bipolar stimulator. Both monopolar and bipolar stimulation can penetrate into the subcortical tissue, which is particularly important for mapping in glioma cases, as these masses are known to protrude into the white matter tracts (Bello et al., 2008; Duffau, 2007; Duffau et al., 2005; Duffau, Velut, Mitchell, Gatignol, & Capelle, 2004; Zemmoura, Herbet, Moritz-Gasser, & Duffau, 2015). While monopolar stimulation may be used for mapping language (Riva et al., 2016b; Verst et al., 2019), it is more commonly applied for motor mapping as it has a greater

sensitivity over bipolar stimulation in terms of accessing even deeper subcortical structures such as the cortico-spinal tract (Landazuri & Eccher, 2013; Seidel, Beck, Stieglitz, Schucht, & Raabe, 2013). Bipolar stimulation using Ojemann's protocol has become the primary approach for language mapping (Ojemann, 1991; Ojemann & Whitaker, 1978). This method is preferable over monopolar stimulation for mapping language structures as it can offer greater precision by focussing the dispersion of the electrical current to within the cortico-subcortical area between the two poles (Schucht, Seidel, Jilch, Beck, & Raabe, 2017); with monopolar stimulation the electrical current is applied over a much more limited surface area and is propagated subcortically in a radial fashion, resulting in reduced specificity or precision (Schucht et al., 2017; Szelenyi et al., 2011).

For bipolar stimulation a two-tip probe with 5mm separation is the standard instrument for high precision mapping (Pallud et al., 2017). Depending on the positioning of the probe in relation to the axon tract, bipolar stimulation can offer either greater sensitivity or greater specificity in mapping tract fibres (Mandonnet & Pantz, 2011; Schlosser-Perrin, Rossel, Duffau, Bonnetblanc, & Mandonnet, 2023). When the probe is positioned orthogonally to the tract, each pole stimulates a different subpart of the tract, increasing its sensitivity; when the probe is placed in a parallel orientation to the tract, each pole stimulates the same subpart of the tract, increasing specificity. The usual parameters for stimulation are biphasic rectangular pulses of 1ms accumulating to a pulse train frequency of 50-60hz. The current intensity for language mapping is generally between 1 and 10mA, which is increased by 0.5mA increments. The stimulation duration lasts around 4s and is applied shortly before the presentation of the visual stimulus (e.g., an object picture). The patient will usually be asked to read a short introductory phrase before completing linguistic tasks (e.g., "This is a…") to differentiate any seizure-induced speech disturbances from that of the stimulation-induced task interference. The role of the attending language clinician, who may be a neuropsychologist, speech, and

language therapist (SLT) or other clinician (e.g., anaesthetist) is to relay to the surgeon any disturbances that arise during mapping, and ideally decipher the category of the interference or error produced (e.g., semantic paraphasia, speech arrest). Language disturbances are usually captured by the language clinician through qualitative observation. However, some centres may additionally incorporate more automated methods to monitor neuropsychological function intraoperatively. For example, one new testing platform, NeuroMapper, has recently been licensed for use in the UK NHS and is increasingly being used for both low-grade glioma and epilepsy surgeries (Smith et al., 2022; Suarez-Meade et al., 2022). NeuroMapper not only detects intraoperative disturbances in the form of errors but also captures patients' response times to stimuli and compares them with preoperative baseline performance.

In some centres, the neurosurgeon will first mark out the areas to be stimulated surrounding the tumour by arranging sterile tags over each square centimetre of the exposed cortex (Sanai, Mirzadeh, & Berger, 2008). In other centres the surgeon may use sterile numbered/coded tags to mark positive sites following the stimulation protocol (see **Figure 1.2** for an example); with the availability of newer neurotechnology, some surgeons may alternatively mark sites digitally on a computer screen (Colle et al., 2005) .

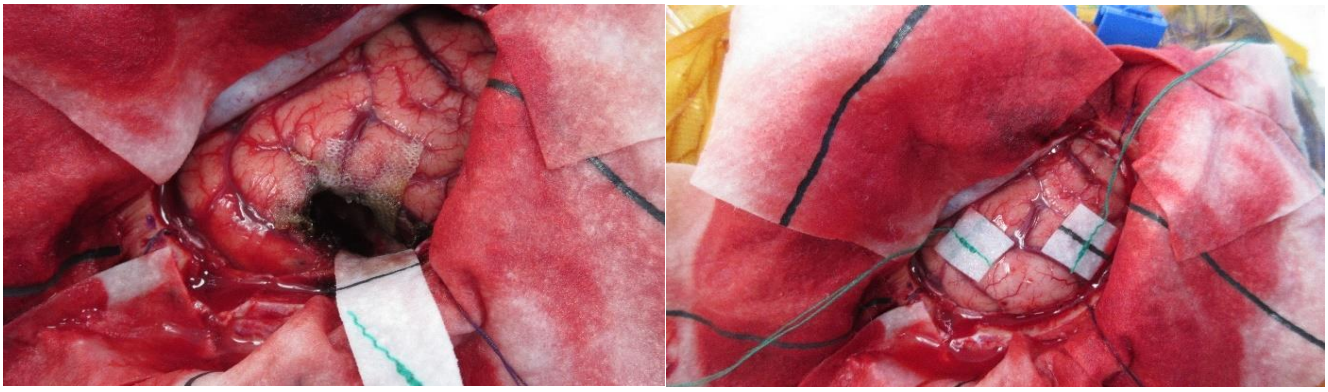

Figure 1.2. Photographs of exposed brain during awake craniotomy. Sterile tags mark locations of positive stimulation sites.

1.4.4.5. Language personnel

The expertise and background of the attending clinician is variable (O'neill et al., 2020). In many cases, the primary role of the clinician is not in awake craniotomy *per se*; they may be SLTs or occupational therapists who predominantly carry out neuropsychological rehabilitation, or clinical neuropsychologists that have developed expertise in both intraoperative and perioperative testing for awake craniotomy (Rofes et al., 2017a). In some hospitals there may be no dedicated intraoperative language clinician, but another clinician (e.g., the anaesthetist), may take on the role of assessing language as required (Bilotta et al., 2014). It has been demonstrated that the presence of a dedicated clinician such as a neuropsychologist, leads to increased rates of resection (Kelm et al., 2017). As well as administering sensitive tests, it is important that the clinician delivering them is adequately trained and able to accurately discern deterioration in language function, from that of other intraoperative events (e.g., pain, stress, fatigue etc.).

1.4.4.6. Considerations and limitations of DES

When applied according to the specific practice guidelines, DES is considered a safe method of mapping with no lasting negative effect on neuropsychological, sensory, or motor functions (Pallud et al., 2017). However, precautions must be taken to avoid the induction of seizures that can occur with repeated consecutive stimulations of the same site within a short

timeframe. Still, it is necessary to stimulate a site more than once to reliably determine function; it is thus accepted that disturbances must be observed at a particular site on three separate occasions of stimulation for its functional status to be accurately determined. While this does not pose a major limitation, it can significantly increase the length of the procedure compared to using general anaesthetic. For this reason, a multifaceted test that can incorporate the assessment of several components of language concurrently within the same task would provide a more efficient solution to intraoperative testing by reducing mapping time needed for several tasks. For example, using action or object naming in sentence context combines the assessment of both visual naming and reading within one task (e.g., "This is a… dog" or "Daily she… sings"). This is more concise than using object/action naming tasks that assess noun/verb production in isolation (e.g., "dog" or "sing") accompanied by a separate word/sentence reading task.

A major advantage of DES, as previously mentioned, is the high sensitivity to detect relevant language areas – those which functional imaging techniques are unable to delineate (Brennan et al., 2016). Assuming that stimulation is applied within the specific guidelines, there should be zero chance of false negative results pertaining to the stimulation itself. However, other factors may increase the chances of false negatives arising, including, but not limited to: sub-threshold stimulation (i.e., stimulation at a lesser intensity/duration required to suppress function (Mandonnet, Winkler, & Duffau, 2010); desynchronisation between stimulation timing and task delivery, or indeed, as is the focus of this thesis, task sensitivity to probe language functions (De Witte & Marien, 2013).

While the sensitivity of DES is considered 100%, the specificity of the technique is debateable. There are a variety of factors which may confound the effects of stimulation and it is crucial that these are controlled to avoid false positives during mapping and ensure the accuracy of DES (De Witte & Marien, 2013). Importantly, the patient's language status must

be thoroughly evaluated preoperatively and considered during intraoperative testing. While steps can be taken to avoid the confounds of mild preoperative language problems (e.g., omitting incorrect items from the intraoperative protocol), other factors such as tiredness and acute analgesic effects can be particularly difficult to control, which may invalidate the patient's performance on language tasks.

1.4.5. Postoperative and follow-up testing

Assessment is typically the same standard assessment that is completed preoperatively (although not always) and should take place within the immediate postoperative period (within 24 hours of surgery). Importantly however, any language impairment observed in this period can be due to factors such as swelling, residual anaesthesia, pain relief medication, and fatigue (O'neill et al., 2020; Rofes et al., 2017a). A follow-up assessment around 1-2 weeks will confirm whether acute postoperative deficits were indeed transient post-surgical effects, or whether they were a result of surgical damage to functional tissue. If the patient displays clear language difficulties, they will be referred for speech and language therapy and usually followed up every 3-6 months.

1.5. Chapter summary

This chapter has provided a general introduction to the neurosurgical field of awake craniotomy. Neurolinguistic testing is an integral part of awake surgery offering many advantages and has revolutionised the craniotomy by improving neurological and neuropsychological outcomes for patients. However, there remains limitations in terms of both theory and practice surrounding neurolinguistic testing. In particular, the use of more traditional language tasks (e.g., counting, object naming) introduced through the seminal work of Penfield have remained largely unchanged in many neurosurgical centres; this is despite greater advancements in other areas of neurosurgery (e.g., iMRI) and the study of language

disorders more generally. The next chapter (Chapter 2) will set out the general and specific aims for the thesis.

Chapter 2: Research aims and hypotheses

2.1. Chapter overview

The present chapter will set out the general and specific aims and objectives for the current thesis, based on the limitations of intraoperative language assessment identified in Chapter 1.

2.2. General aims

While there have been recent advances in understanding the subcortical pathways that underpin the signalling between cortical language regions, awake craniotomy remains anchored to the localisationist perspective in terms of tasks used (i.e., counting, object naming reading etc.). As will be explored in Chapter 3, these tasks are insensitive at capturing all language functions within the wide ranging cortico-subcortical language networks. For example, when comparing object and action naming during stimulation of frontal regions, some sites have been identified as specific for objects or actions (domain-specific), while others have been identified for both (domain-general; Rofes et al., 2019; Rofes et al., 2015c; Rofes et al., 2017b). It is generally accepted that the perisylvian language regions can be mapped with domain general tasks such as object naming, however, there may also be specialist language sites (domain-specific; e.g., nouns, verbs) that require targeted testing (Benetello et al., 2016; Crepaldi, Berlingeri, Paulesu, & Luzzatti, 2011; Delikishkina, Lingnau, & Miceli, 2020; Matzig, Druks, Masterson, & Vigliocco, 2009; Rofes & Mahon, 2021).

The general aim of this thesis is to improve postoperative outcomes for people undergoing awake craniotomy via the administration of a three-task naming in sentence context protocol before, during, and after surgery. A two task approach using nouns and ANFV has been used in awake craniotomy for low-grade glioma in other countries around Europe for more than 15 years (Bello et al., 2008; Havas et al., 2015; Lubrano, Filleron, Demonet, & Roux,

2014); specifically, this protocol has been applied intraoperatively and perioperatively in frontal patients across several studies (Rofes, de Aguiar, & Miceli, 2015b; Rofes et al., 2019; Rofes et al., 2015c; Rofes et al., 2017b). However, the present thesis aims to introduce this protocol for the first time in the UK NHS with English-speaking patients and for tumours within a variety of locations. In particular, this thesis also aims to explore the potential performance differences between ANFV in the past and present tense, both intraoperatively and perioperatively, which are yet to be examined in relation to awake surgery.

2.3. Specific research aims

Each chapter within the thesis will address specific research aims that are set out below:

(1) To synthesise the results of brain stimulation mapping studies to better understand the range of language and cognitive tasks used and types of errors/disturbances evoked by DES across various cortical and subcortical sites. This will be explored in **Study 1** (Chapter 3) through a systematic review of the literature. The findings of this study informed task selection for comprehensive intraoperative and perioperative testing in the subsequent studies (Chapters 4 & 5).

(2) To implement a comprehensive linguistic protocol encompassing object naming and ANFV in sentence context (Verb and Noun Test for perioperative testing, VAN-POP) for DES language mapping in an NHS neuro-theatre. In **Study 2** (Chapter 4) the VAN-POP was administered alongside currently used language tasks within the NHS centre (e.g., counting, object naming, reading) during awake craniotomy. Intraoperative data for both mapping and monitoring with both sets of tasks were collected from four low grade glioma patients (frontal, temporal, parietal and fronto-temporal).

(3) To investigate the use of the VAN-POP as a pre- and post-operative linguistic assessment tool for assessing both accuracy and reaction time in speeded naming tasks. In

Study 3 (Chapter 5), three low-grade glioma patients were tested on VAN-POP preoperatively, postoperatively and at three-month follow-up to observe changes in accuracy and reaction time in comparison to both their own performance and that of healthy controls.

2.4. Hypotheses

To address the aims outlined above, specific hypotheses for Studies 2 and 3 (Chapters 4 & 5) have been generated and are presented within each respective chapter. Hypotheses have been formulated, where possible, according to previous awake surgery studies that have implemented object and action naming. However, in the absence of direct evidence from the awake craniotomy/low-grade glioma literature in relation to a specific hypothesis, evidence will be drawn from the wider aphasia literature where damage due to other neurological conditions or injuries affects similar brain areas to the patients within the present thesis.

2.5 Chapter summary

The primary aims of this work as outlined above are to further investigate the contribution of comprehensive testing practices in awake craniotomy to improve language outcomes for patients. Chapter 3 will begin by evaluating the cognitive-linguistic tasks that have previously been used during awake craniotomy through a systematic review of studies targeting different brain regions with both traditional and more specialist tasks.

Chapter 3: A review of cognitive and linguistic tasks for direct electrical stimulation mapping in awake craniotomy

3.1. Chapter overview

Awake craniotomy with intraoperative mapping is the gold-standard procedure for brain tumour resection (Berger & Ojemann, 1992; De Benedictis, Moritz-Gasser, & Duffau, 2010; De Witt Hamer et al., 2012; Duffau, 2005; Duffau, 2007; Hervey-Jumper et al., 2015; Mandonnet et al., 2010). This technique uses DES to cortical (and often subcortical) brain regions to identify areas of sensorimotor, language and cognitive processing with a view to preserving these functions post-surgery. This involves administering a series of tests (e.g., counting, object naming, reading) whilst perilesional tissue is stimulated, during which time the patients' responses are observed and functional brain areas mapped. Postoperatively, patients may present with neuropsychological disorders such as aphasia – a language and communication syndrome which may affect the ability to speak, read, write, and comprehend. There is currently a lack of standardisation amongst intraoperative tests with many protocols developed *ad-hoc* by surgical teams.

A wealth of published data is available for cortical and subcortical mapping across a variety of tasks used in various tumour locations. The review presented in this chapter aims to: (1) unify this data to assist clinicians in selecting appropriate tasks based on anatomical knowledge of their successful application and type of functional disturbances evoked; (2) summarise key theoretical findings and issues arising from research in the field of cognition and language mapping during awake surgery. Crucially, leading to new recommendations for implementing comprehensive protocols for intraoperative mapping and monitoring.

3.2. Introduction

Primary brain cancer is a major cause of mortality and disability, world-wide. In 2016 the global incidence of central nervous system cancers (e.g., meningioma, glioma) was 330,000 with a 69% mortality rate of 227,000 (Patel et al., 2019) - the leading cause of death in people under 40, including children (Cancer Research UK, 2017). An estimated 40% of other cancers (e.g., lung, breast) metastasise to the brain (Cancer Research UK, 2017) . Additionally, a 6% rise in hospitalisations for brain cancer is expected by 2035, with the ageing population being of major significance. Over the same period, the number of survivors living with the effects of brain cancer will also rise (Cancer Research UK, 2017). To reduce mortality and maximise oncological outcome in patients, the preferred option is to perform a craniotomy to remove as much cancerous tissue as possible, whilst safeguarding neuropsychological function. The traditional craniotomy, performed under general anaesthesia, involves exposing the brain, followed by careful extraction of the tumour while avoiding functional areas through surgical markers, that may or may not have been predefined with fMRI. The aim of resective surgery in lower-grade cases is to limit the progression of the tumour in its course to becoming malignant or anaplastic, in which the prognosis for the patient is ultimately fatal. Total or subtotal resection is often achievable, however, even when combined with adjuvant therapies (e.g., chemotherapy or radiotherapy) surgical treatment may not provide a cure for the disease and tumours may reoccur either at the same or higher grade than before, potentially requiring reoperations and other subsequent treatments (Hoover et al., 2013; Martino, Taillandier, Moritz-Gasser, Gatignol, & Duffau, 2009). Despite this, surgical intervention for the removal of gliomas is often a safe and effective treatment option often with low morbidity, providing good long-term functional outcomes (Yang et al., 2023); however, for the more diffuse tumours, resection may pose significant implications for preserving neuropsychological function, especially language (De Witte & Marien, 2013; Rofes & Miceli, 2014). This presents

a paradox for surgeons – limited resection may not achieve the desired oncological outcome, while a more aggressive approach risks impairing function.

Whilst some impairments can be physical (e.g., hemiparesis, fatigue), many are hidden, meaning that survivors may experience cognitive challenges that impede daily functioning. For example, language impairments can range from mild word finding difficulty (anomia) to total loss of function (e.g., inability to read, write, or speak). Dyslexia, for instance, can affect patients in several ways – from understanding written information relating to appointments, transport, or prescriptions, to communicating through messages, email, or social media, and of course, reading for pleasure. These impairments can affect quality of life, relationships, social engagement, education, and employment prospects. Some patients may also be aware of their decline in linguistic function and studies have described patients' subjective complaints of language and communication impairments, most notably, word-finding difficulties (Ake, Hartelius, Jakola, & Antonsson, 2023; Antonsson, Lundholm Fors, & Hartelius, 2024; Brownsett et al., 2019). Although improving the patient's prognosis is the primary treatment objective of a traditional craniotomy, this often sacrifices neuropsychological function and may require lengthy rehabilitation (e.g., physiotherapy, speech, and language therapy). As neuroscience and medical technology has advanced, multidisciplinary clinical teams are better equipped to avoid postoperative complications through improved preoperative planning, state -of-the-art technology and crucially, the application of awake craniotomy with DES.

Originally championed by Wilder Penfield (Penfield & Rasmussen, 1950), awake craniotomy is the gold-standard neurosurgical approach for tumours infiltrating cognitive and linguistic structures, with several advantages over traditional craniotomies. Performed under local anaesthesia, it offers improved surgical precision through *in vivo* cortical and subcortical mapping of the brain. Mapping is achieved by repeatedly applying DES to areas surrounding the tumour, whilst the patient simultaneously performs cognitive and/or linguistic tasks

(traditionally object naming, counting, and reading delivered and monitored by a clinician (e.g., a neuropsychologist). If the stimulated region is functionally involved in the processes underpinning the task, performance inhibition is observed. For instance, disturbance of function that typically inhibits speech output (although often in addition to other linguistic functions) is broadly termed "speech arrest". This allows the surgeon to pinpoint specific areas controlling important functions. For example, DES applied to and around Broca's area usually affects speech and should thus be avoided during resection. Unlike preoperative mapping with fMRI for traditional craniotomies, which comes with many limitations for identifying language areas (e.g., functional eloquence, homogeneousness; Brennan et al., 2016), using DES allows greater precision in determining the areas to be avoided, and those that can be resected with minimal consequence. Hence, awake craniotomy allows a bespoke neurosurgical approach that considers and tests for functional heterogeneity of the brain, with critical areas spared from resection facilitating preservation of neuropsychological function.

The major disadvantage of awake surgery is that clinicians are ill-equipped with an effective, standardised neuropsychological protocol; many rely on the traditional "Penfield" tasks of counting, reading, and object naming that may be limited in their capacity to assess the breadth and depth of the more complex linguistic functions that are essential to real-world language use (De Witte & Marien, 2013; Rofes & Miceli, 2014; Rofes et al., 2015c). For example, although automatic speech tasks such as counting may access phonology (i.e., the phonological output lexicon), they may or may not access semantics (retrieval of conceptual knowledge from the semantic lexicon); this is due to the fact that overlearned information, such as chronological number sequences, do not pose significant demands on the linguistic system and may bypass complex language components (i.e., semantics, morphology, and syntax; Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 2000). While counting is considered a linguistic assessment, testing is targeted to surface level linguistic functions, i.e., speech and

articulatory processes and is therefore likely an inadequate task for assessing functions beyond simple speech production (Rofes et al., 2015c). While object naming is more linguistically taxing than counting, i.e., it requires structural description (visual decoding of the object picture), access to semantics (retrieval of object knowledge) and phonological access (sounds for speech output), it still remains limited in terms of being unable to directly assess other crucial everyday linguistic functions (e.g., morphosyntax; Rofes et al., 2015c). If intraoperative assessment is limited to tasks such as object naming, other linguistic functions may be at risk of becoming damaged during surgery. This may lead to the development of unforeseen postoperative language impairments (e.g., agrammatic aphasia) that may have otherwise been avoided with more extensive testing (e.g., the addition of grammatical tasks; Rofes et al., 2015b; Rofes et al., 2017b).

Clinicians often opt for chronological/reverse counting (or reciting other overlearned information, e.g., the alphabet) or *ad-hoc* versions of naming and reading tasks adapted from aphasia screening tests. These tasks are favoured because they are: (1) easily administered and performance is easily monitored; (2) well tolerated by patients; (3) time and cost effective; (4) fast paced (i.e., providing instant and continuous feedback to the surgeon). Despite their merits, these tasks also remain vastly limited by a lack of theoretical rationale and rigorous methodology (e.g., psycholinguistic item matching [frequency, familiarity etc.] and validation with neurologically intact participants) which is problematic for inferring specific functions (Rofes et al., 2015c). Upon inspection of the neurosurgical literature, it is clear that many studies do not report whether a standardised assessment was used or how materials were developed. While reporting inconsistencies exist, *ad-hoc* testing and lack of standardisation is commonplace, both pre-, intra-, and post-operatively, as confirmed in recent UK and European-wide surveys among language clinicians involved in awake craniotomy (O'neill et al., 2020; Rofes et al., 2017a; Sierpowska et al., 2022).

Furthermore, with the advancement of neuroanatomical knowledge, the traditional counting, object naming, and reading tasks are becoming increasingly redundant. As discussed above, visual object naming (and indeed reading) can engage some core language processes such as structural decoding, comprehension, and phonological output; however, the naivety of these tasks may mask subtler processes that support, for instance, naming objects and reading. For example, some DES-induced object naming and reading disturbances may be underpinned by lower-level shape processing, thus affecting a variety of visual stimuli (Roberts et al., 2015; Roberts et al., 2013), that within the limits of current testing cannot be probed.

Although there are several studies demonstrating the incorporation of updated versions of traditional tests (Duffau et al., 2005), along with specialised novel tests (De Witte et al., 2015b; Rofes et al., 2015c), many intraoperative, as well as pre- and post-operative neuropsychological protocols are limited in several respects: (1) an inability to capture the scope and complexity of cognition and language; (2) a lack of valid scientific and methodological bases; (3) an absence of, or inadequate pre- and/or post-operative assessment; and (4) a failure to specify guidelines for testing during awake interventions.

The focus of the present review is a thorough consideration of the sensitivity of the intraoperative tasks currently used. Since there are few experimental comparisons of different tasks or protocols in terms of their brain mapping capabilities, or effects on postoperative neuropsychological outcomes, it is problematic to make reliable evidence-based task recommendations. While previous work has summarised the range of neuropsychological tasks, pertaining to both the assessment of language and other cognitive functions, that have been reported within the awake craniotomy literature to date (Bello et al., 2008; De Witte & Marien, 2013; Połczyńska, 2009; Rofes & Miceli, 2014; Ruis, 2018), a clearer understanding of those that have successfully mapped various brain areas and the types of errors observed, is necessary and will advance the field by: (a) improving detection of cognitive and linguistic

disturbances through a more tailored approach based on tumour location and patients' clinical profiles; (b) minimising postoperative neuropsychological impairments; and (c) maximising prognosis and therapeutic efforts. One group has made progress in a review of 25 linguistic mapping studies within the literature (Rofes et al., 2019). While the present review has been in progress since 2017, a similar review has since been published, although focussing exclusively on mapping speech and language error patterns as opposed to linguistic and cognitive tasks (Collee et al., 2023). The present review has focussed primarily on utilising the profusion of bihemispheric cortical and subcortical mapping data that is available for a variety of cognitive and linguistic tasks, with the mapping of interference and error types as a secondary outcome.

The primary aim of this review is to assist clinicians and researchers in selecting appropriate tasks for testing in awake craniotomy, to facilitate preservation of cognitive and linguistic functions. Firstly, the available mapping data will be qualitatively combined and presented schematically by displaying positive DES sites for different tasks, and the types of behavioural interferences produced (e.g., anomia, semantic paraphasia). Secondly, the range of cognitive and linguistic tasks identified will be discussed in terms of their theoretical relevance and empirical support. Finally, recommendations will be made for optimising task selection towards developing a standardised, universal protocol for mapping and monitoring function during awake craniotomy.

3.3. Methods

3.3.1. Search strategy

Databases were searched via PubMed and the Liverpool John Moores University "Discover" tool. The search was applied to abstracts and keywords to identify studies of awake craniotomy for brain tumour (Appendix 1). Relevant review papers were checked for additional eligible studies (e.g., De Witte & Marien, 2013; Rofes & Miceli, 2014; See Appendix 1).

3.3.2. Inclusion and exclusion criteria

Studies were included if all of the following applied: (1) full text published in English; (2) one or more patient(s) had a diagnosis of a central nervous system tumour; (3) patient(s) underwent awake craniotomy with language and/or cognitive DES mapping; (4) positive mapping results were reported; (5) location(s) of DES were stated (e.g., Brodmann area/subcortical tract).

Studies were excluded if one of the following applied: (1) awake craniotomy was for other purposes, e.g., treatment of intractable epilepsy; (2) mixed cohort data was undifferentiable (e.g., collective results for epilepsy and tumour patients); (3) location(s) of DES were not reported/clearly defined; (4) tasks(s) were not reported/not clearly defined.

3.3.3. Screening and data extraction

Studies were first screened by title and abstract by the first author and retained for full text screening. 10% of studies were randomly selected for additional screening by two independent reviewers at each stage. Relevant information from each study was extracted (Appendices 3 and 4). Positive mapping results were extracted for each patient/group consisting of anatomical location(s) of stimulation site(s), task(s) detecting interference, and additional specific type(s) of interference/response error observed, if this information was available.

3.4. Results

3.4.1. Summary of studies

A total of 114 studies across 16 different countries reporting DES mapping data were included (see **Figure 3.1** for the screening process). Of these, 85% presented individual cases or case series and 16% reported data collectively for larger groups or cohorts (one study presented both a cohort and a single illustrative case). Left and right hemisphere data were reported in 96% and 11% of studies respectively, with only 4% focussing exclusively on right

hemisphere patients. Studies reporting data for cortical mapping was 86%, subcortical mapping data was 42%, and 29% reporting data for both. **Table 3.1** provides a reference key for subsequent Figures and a breakdown of the number of studies, cases and cohorts in which mapping has identified positive sites according to each Brodmann area or subcortical tract/region.

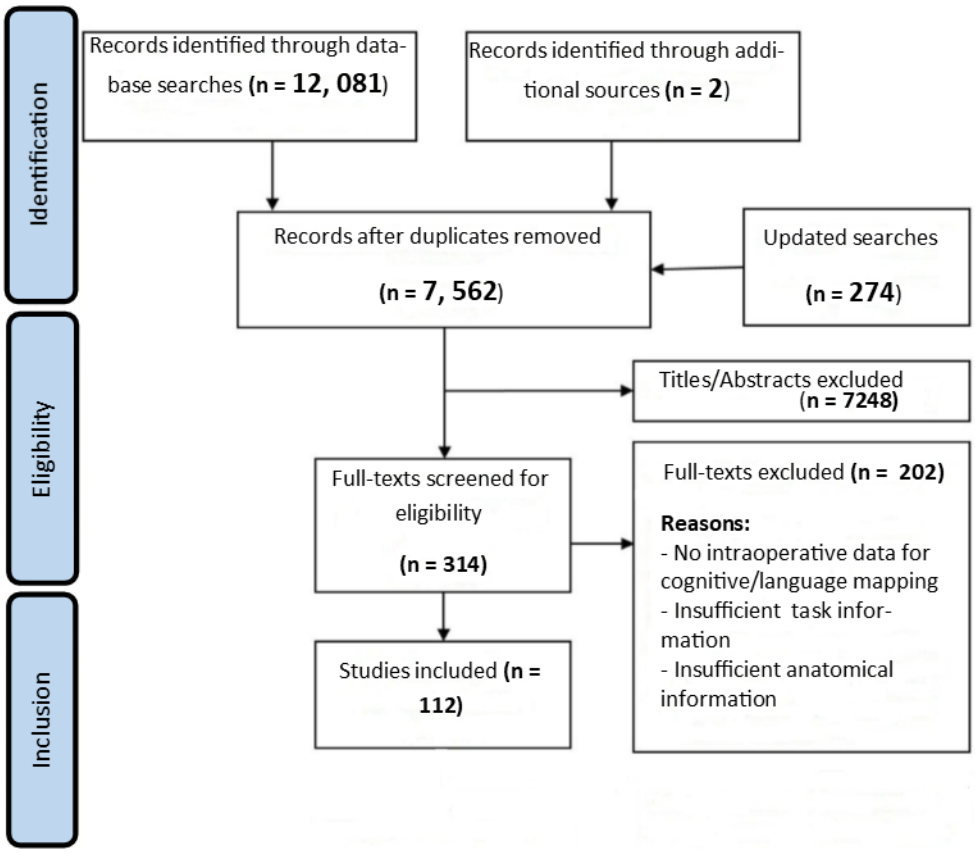

Figure 3.1. The screening process for results returned from database searching and additional sources. In the full-text screening stage, studies were excluded on the basis that they either, did not present any intraoperative data, or the intraoperative data provided was insufficient for the review purpose (i.e., specific tasks used were not stated and/or specific brain areas stimulated were not clear). Some studies that provided exposed brain diagrams of functional sites were not adequately labelled and therefore could not be included in the review.

Table 3.1. Number of studies and cases reporting positive language and/or cognitive sites in cortical and subcortical locations in the left and right hemispheres.

Anatomical region	Brodmann	No. studies		No. cases/cohorts*	
		L	R	L	R
Precentral gyrus	4	23	1	33/8*	1*
Dorsal premotor cortex	6a	12	4	41/2*	5
Ventral premotor cortex	6b	22	4	94/2*	10/2*
Superior frontal gyrus	8	7	1	5/2*	1*
Middle frontal gyrus	9/46	15	5	26/3*	35/2*
Inferior frontal gyrus	44	31	4	45/5*	2/2*
Posterior inferior frontal gyrus	44	22	3	55/9*	8
Middle inferior frontal gyrus	45	7	2	16/5*	5
Anterior inferior frontal gyrus	47	3	1	3/1*	2
Cingulate gyrus	24/32/33	2	1	7	2
Insula cortex	13-16	3	1	7	1*
Superior postcentral gyrus	1-3	6	-	7/2*	-
Inferior postcentral gyrus	43	9	2	11/4*	2
Supramarginal gyrus	40	27	4	45/8*	6/7*
Parietal lobule	5/7	7	1	8/2*	1
Angular gyrus	39	21	5	26/6	5/2*
Visual cortex	19	3	-	3	-
Heschl's gyrus	41/42	2	-	14	-
Temporal pole	38	2	-	2	-
Superior temporal gyrus	22	19	2	63	4
Anterior superior temporal gyrus	22a	7	-	6/2*	-
Middle superior temporal gyrus	22b	10	1	11/2*	1*
Posterior superior temporal gyrus	22c	23	2	31/7*	3/1*
Middle temporal gyrus	21	14	1	24	1
Anterior middle temporal gyrus	21a	7	-	2/5*	-
Middle middle temporal gyrus	21b	6	1	2/4*	1*
Posterior middle temporal gyrus	21c	13	-	13/6*	-
Inferior temporal gyrus	20/37	3	-	3	-
Anterior inferior temporal gyrus	20a	1	-	1*	-
Middle inferior temporal gyrus	20b	3	-	1/2*	-
Posterior inferior temporal gyrus	37	5	-	6/2*	-
Uncinate fasciculus (UF)		2	-	2	-
Arcuate fasciculus (AF)		24	1	78/2*	1
Frontal aslant tract (FAS)		2	-	6	-
Inferior longitudinal fasciculus (ILF)		4	-	13	-
Inferior fronto-occipital fasciculus (IFOF)		23	1	83/2*	2
Superior fronto-occipital fasciculus (SFOF)		5	-	5/2*	-
Superior longitudinal fasciculus (SLF)		12	-	39	-
Cortico-spinal tract (CST)		1	-	1	-
Striatum	S	9	2	24/1*	4
Frontal white matter** (F)	F	7	2	28/2*	10
Parietal white matter** (P)	P	5	1	5	2
Temporal white matter** (T)	T	4	1	19	2

Overall	No. studies	No. cases	No. cohorts
Left hemisphere	109	402	18
Right hemisphere	13	61	3
Cortical	99	378	17
Subcortical	48	212	2
Single case/case series	97	463	-
Cohort	18	-	18

*Number of cohorts or patient groups in which the respective site has been positively mapped (larger studies that present group data for mapping and do not indicate in how many patients the site has been mapped). **Non-specific subcortical white matter tract of the particular lobe. Anatomical regions presented in italics are subsections of larger gyri that were specified in some studies.

3.4.2. Cognitive and linguistic tasks and interference types

Table 3.2 and **Table 3.3** display a summary of mapping results for each cortical and subcortical site by task and interference type, respectively. Object naming, counting, and reading are the most popular tasks administered, with speech disturbances and anomia being the most reported types of interference (see **Appendix 2** for more specific information for individual studies/cases). Figure **3.2** provides a schematic representation of the results displayed in **Table 3.3** and **Table 3.3**. Different tasks and interference/errors have been plotted onto each cortical and subcortical brain area. Cortical regions are plotted according to nearest Brodmann area, while subcortical areas are colour coded (see **Figure 3.2** legend for corresponding shapes/icons and **Table 3.1** for an anatomical reference key).

Table 3.2. Number of cases by Brodmann area in which different linguistic and cognitive tasks have identified interference during cortical and subcortical mapping in the left and right* hemispheres.

Brodmann	Task																								
	Object naming	Face naming	Naming to definition	Colour naming	Action naming	Action naming finite verbs	Pyramid & palm trees	Semantic picture out	Sentence completion	Semantic comprehension	Reading	Non-word reading	Score reading	Writing	Repetition	Counting	Language switch	Translation	Symbol recognition	Stroop	Colour-shape switch	Spontaneous speech	Singing	Rhythm judgement	Calculation	Mentalising	Short-term verbal memory
4	32/**1**								1		4/**1**		1		1	8							3				
6A	38/**4**								1		2/**2**			4/**1**	3	2		**1**									1
6B	83/**12**										17					26/**1**						**1**				**1**	
8	3/**1**					2					**1**			2													1
9/46	21/**3**					3	**6**				3/**1**			4		5							1			**30**	1
44/5/7	42/**4**	1		2	1	2					9			3	1	5	1					**1**					**1**
44	40/**1**								1		5				2	25		1						1		**6**	1
45	4						**1**									17										**3**	1
47	4															1										**2**	
24/32/33	1																			6/**2**							
13-16	7/**1**															6											
1-3	3								1		4	4		1													
43	8							1	1		11	5		4/**1**		2											
40	31/**3**	1		1	1			1	1		23	6	3	8/1	3	1									5/**3**		
5/7	3	1									1		2		1										3/**1**		
39	14/**7**	1		4			**1**	1	1		11/**1**		1	7	2										12/**3**	**2**	2
19	2										2					1											
41/42	4										9	3		11													
38	8								1		1			1	1	6											
22	46/**4**		1	1					1		23	5		14	3	5			1								
22A	8										1					2											
22B	10/**1**						1				4/**1**		1			3											1
22C	30/**1**	1		1	1		**1**		1		6/**1**				1	4			2							**3**	
21	21/**1**			1							6	1		3		1											
21A	5	1							1		1																
21B	3/**1**	1							1																		1
21C	13			1	1			1	1	2	1				2	1											
20/37	2										1																
20A	1																										
20B	2										1																
37	3										6			1					2								
UF	1	1																									
AF	62/**1**								1		3				4	29						1					
FAS	6															1											
IFL	1										12								1								
IFOF	77/**2**	2				1	10	1	2							3											
SFOF	4															6						1					
SLF	38	3			3											24											
CST															1												
S	23/**4**															15/**2**	1				1						
F*	28/**10**					5					**1**					14		**1**									
P*	3/**2**								1						1	1								1	2		
T*	17/**2**															8						1					

Right hemisphere studies are indicated in Red. *Non-specific subcortical white matter tract.

Table 3.3. Number of cases by Brodmann area in which different linguistic and cognitive interferences have been observed irrespective of task during cortical and subcortical mapping in the left and right hemispheres.

Brodmann	Interference																			
	Speech	Motor speech	Perseveration	No response	Phonological error	Semantic error	Grammatical error	Response error	Response delay	Anomia	Agraphia	Acalculia	Alexia	Comprehension	Language switch	Speech-Sing switch	Circumlocution	Monotone singing	Sign block	Stroop effect	Unspecified**
4	18	11			1	1			1	1								1	1		7/**1**
6A	5	3	1		2	1	1			27	3/**1**										3/**1**
6B	49/**1**	42/**10**	1							7											3/**2**
8						2		1		1	1				1						1/**1**
9/46	7		1/**9**		3	3/**1**		**17**	2	7	4				1						5/**15**
44/45/47	21	1	1		1	12	3	3		10/**1**						**1**			1		8/**2**
44	25/**1**	1			2	2		2/**2**	1	27											6/**5**
45	17				1			**2**													3/**3**
47	1						2														1/**2**
24/32/33																1				6/**2**	
13-16	1/**1**									1											5
1-3		1			1			2	1	1			2								2
43	1	1			2/**1**	1		3	1	1			3	1							8/**1**
40	5				7/**3**	4		9	2	7			2	1							26/**4**
5/7	1				2	1		1													7/**1**
39	2	1			6	1		2/**2**	2	3											21/**5**
19	1				1				1	1			1								
41/42					5	4		2					2	2							6
38														1							1
22	16	2	2		10	13/**4**		10	4	15			2	7	2	1					20
22A					1				3	3											7
22B	2				2	1		1		5				1							10/**1**
22C	5				1	6		2/**3**	1	18			2		1						23/**1**
21	2				4	3/**1**			4	5			2		2						14
21A	1								1	2											7
21B	1								1	1											6/**1**
21C	2					1	2	1	2	6				2							13
20	1								1	1			1								
20A																					1
20B	1																				2
37					1					2			1								5
UF	1		1			1		1													
AF	3	1			55/**1**	2	1	4		9											2
FAS	6																				
IFL					5								8								
IFOF	1			4	2	76/**2**			1	18	1		1	2							1
SFOF	6																				1
SLF	19	13			7					3					1						
CST		1																			
UF	1	10	11/**4**				2			1											2
F*	13/**8**				2/**3**	13/**2**	1		1	5											1
P*			1		1/**2**				2	2		1									
T*					8	10/**2**	1						1								1

Right hemisphere studies are indicated in Red. *Non-specific subcortical white matter tract. **No error type specified.

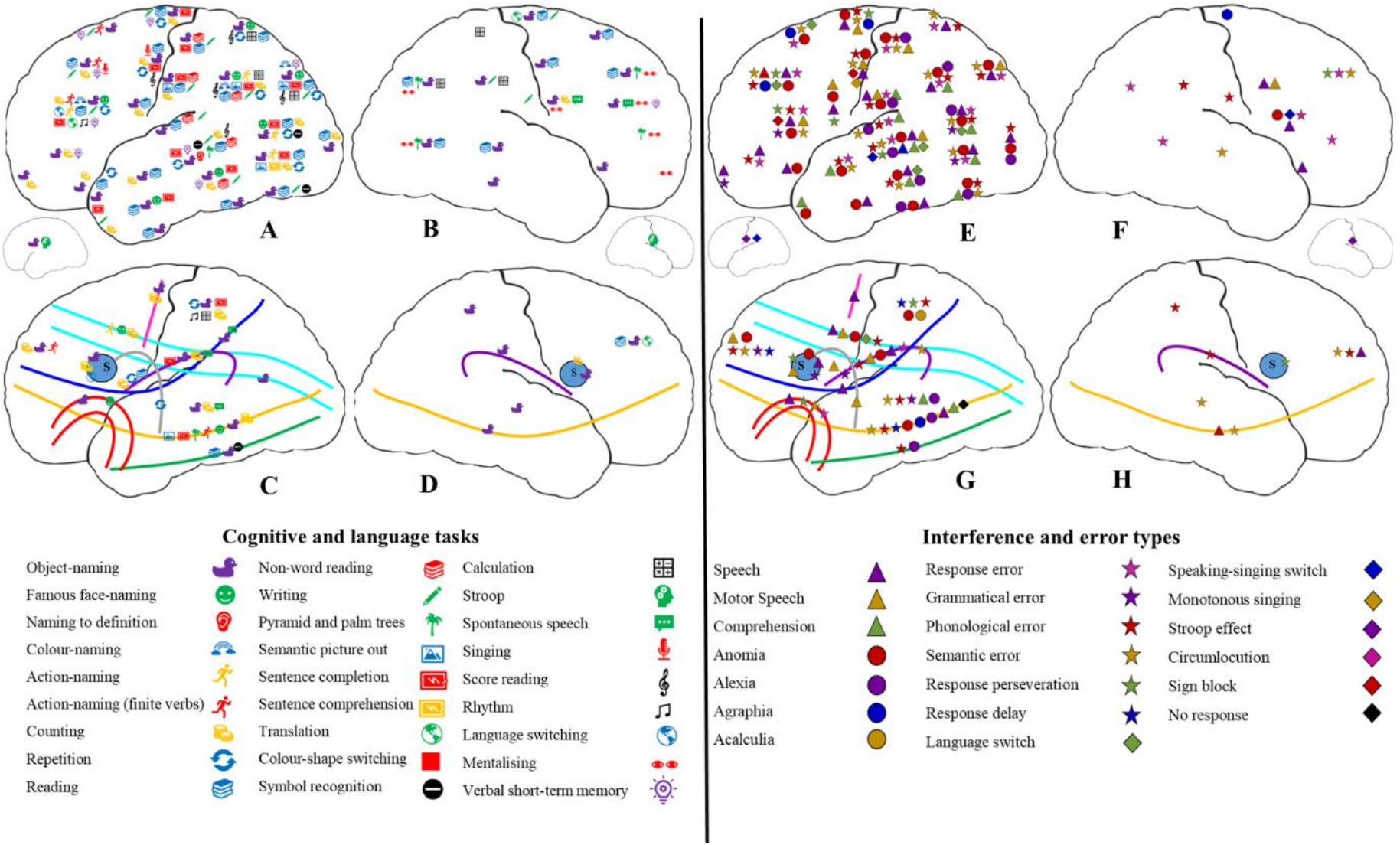

Figure 3.2. Cortical and subcortical brain maps of cognition and language tasks/interferences. Left section: Brain areas in which DES induced interference across different tasks. Left cortical areas (A); right cortical areas (B); left subcortical areas (C); and right subcortical areas (D). Right section: Brain areas in which DES induced a specific type of language/cognitive interference or error. Left cortical areas (E); right cortical areas (F); left subcortical areas (G); and right subcortical areas (H). Smaller brains below A/B/E/F display the cingulate cortex (Brodmann area 24/32/33). Cortical areas are alphanumerically labelled according to Brodmann areas and subcortical tracts are colour-coded/labelled (see table 1 for key). Each language and cognitive task/interference type is denoted by a different coloured icon/shape (see key above). Positioning of icons/shapes is approximate according to the nearest anatomical landmark and does not represent the specific location of stimulation. Note: for subcortical diagrams, shapes not directly placed on the tracts represent the subcortical white matter below the particular area (e.g., parietal white matter). Negatively mapped areas were not presented here as these are not consistently reported in the literature. Unpopulated structures therefore refer to areas in which task interference has not been found/reported.

This review describes 28 cognitive and linguistic tasks reported in the literature for which DES mapping data has been provided, although more are in use for which mapping data is unavailable (De Witte & Marien, 2013; O'neill et al., 2020; Rofes et al., 2017a; Rofes & Miceli, 2014). Mapping data for object naming were reported in 89% of studies, followed by counting and word/sentence reading in 37% and 18%, respectively. **Table 3.4** provides a summary of each task and example associated interferences that have been reported. As a broad range of both specific (e.g., semantic paraphasia) and non-specific (e.g., anomia/naming difficulty) task interferences were identified, they have been condensed into 21 categories (**Table 3.2**; see **Appendices 3, 4** and **6** for further details).

Table 3.4. Descriptions of cognitive and linguistic tasks, associated interference types induced by DES, and the number of studies reporting mapping results for each task.

Task	Description	Types of interference	N*
Object naming	Naming pictures of objects: "this is a… cat"	Anomia; alexia; speech/motor speech disturbance; response delay, perseveration; errors (response, phonological, semantic, grammatical) circumlocution; speaking-singing switch	101
Face naming	Naming pictures of famous faces	Speech disturbance; anomia; errors (semantic, phonological, response)	2
Naming to definition	Verbal description of object (e.g., four legs, furry, barks)	Speech disturbance; response errors	1
Colour naming	Name colours	Anomia	2
Action naming	Name action pictures using isolated verbs (e.g., [to] "run")	Speech disturbance, anomia; errors (semantic, phonological, response) response delays	2
Action naming finite verbs	Name action pictures using inflected verbs (e.g., [he] "runs")	Errors (response, semantic grammatical); response delays, perseveration; anomia	3
Pyramid & palm trees	Picture matching: e.g., pyramid to either palm tree (correct) or conifer	Anomia; semantic errors; comprehension interferences	3
Semantic picture out	Identify picture not semantically associated with the other two	Anomia; comprehension interferences; errors (semantic, phonological); response delays	2
Sentence completion	Provide word to complete sentence (e.g., "the dog chased the… [cat]"	Speech disturbance; anomia; response delay	2
Word production	Manipulate target to fit sentence "This is the **apples**" (apple)		1
Semantic comprehension	Match spoken sentence to associated picture	Comprehension interference	2
Reading/Non-word reading	Read words, sentences or nonwords (e.g., lorge)	Alexia; response errors/delays; speech disturbance	20/1
Score reading	Read musical notes (musicians)	Music reading interferences	2
Writing	Write words or sentences usually from dictation	Agraphia; errors (response, phonological, semantic); response perseveration	6
Repetition	Repeat words or phrases	Anomia; speech/motor speech disturbance; errors (phonological, response)	7
Counting	Sequential counting	Speech/motor speech disturbance; response perseveration	42
Language-switch/translation	Switch task language; translating words or sentences	Unable to switch/involuntary switch; translation interference	1
Symbol	Name symbols (e.g., +)	Comprehension interference	1
Stroop	Name print colour, ignore word (e.g., BLUE)	Stroop effect/unable to ignore written word	1
Colour-shape switch	Switch between colour and shape naming	Task switching interference	1
Spontaneous	Conversation	Anomia; reduced spontaneous speech; comprehension interference.	3
Singing	Sing a familiar song (amateur singers)	Speech disturbance, involuntary speaking-singing switch	1
Rhythm	Decide if melodies match (musicians)	Response errors	1
Calculation	Mental arithmetic (e.g., multiply, add, subtract)	Acalculia	8
Mentalising	Judging emotion through only the eyes	Response errors, no response/inability to complete task	3
Short-term verbal memory	Recall whether a picture has been previously seen	Recall errors (yes/no)	1

*Number of studies reporting positive mapping for each individual task.

3.5. Discussion

Selecting the most optimum cognitive and linguistic tasks for awake surgery plays a significant role in facilitating the preservation of neuropsychological function and improving resection precision. The present review has systematically collated evidence from the existing observational literature to guide clinicians and researchers in understanding which brain areas can be successfully mapped with a given task. While there was no single task or protocol that offers the best solution for mapping the brain, the results have demonstrated that a wide range of language tasks can successfully map a variety of regions during awake craniotomy, with non-linguistic cognitive tasks (e.g., calculation, cognitive control etc.) also being used in mapping and preservation of function. A rich taxonomy is also emerging beyond the crude descriptors such as "speech arrest", that has historically been assigned to intraoperative language interferences. This results in more accurate classification of different cognitive or language interferences that can selectively manifest in various tasks due to disruptions to specific regions or fibre connectivity (Catani et al., 2012). For example, consistent observation of phonological errors when the arcuate fasciculus is stimulated (Table 2.3, Figure 2.2).

Considering the surgical cases in the literature, one limitation identified from this review is that specific disturbances or errors often go unreported or are dismissed, possibly due to medical training which encapsulates the traditional "localisationist" approach. This localisationist view proposes that cognition is conceptualised in terms of domains of functioning corresponding to specific brain regions, with some brain areas considered ***silent cortex***. This data, however, becomes conspicuously useful in furthering our understanding of the neural basis of cognition and language systems to develop more optimal and targeted tools for intraoperative, as well as pre-and post-operative, testing. It would be useful for the clinician to document any specific intraoperative disturbances (e.g., errors) in case they persist postoperatively. Depending on the subtlety of the impairment, language problems may go

undetected during standard neuropsychological assessment, and it is recommended that postoperative assessment could include further tailored assessment based on any disturbances arising intraoperatively.

3.5.1. Beyond Penfield

The review identified that object naming, counting, and reading remain the most prominent tasks for identifying language regions. This is consistent with a recent survey conducted by the European Low Grade Glioma Network (ELGGN) in which all respondents reported using an object naming task intraoperatively (Rofes et al., 2017a). This task is used because it assesses three core linguistic processes – visual/object processing, phonology, and semantics (Rofes et al., 2015c). Variations include colour, symbol, and famous face naming that aim to detect subtler interferences in the retrieval of more specific semantic categories (Bello et al., 2008; Gil-Robles et al., 2013; Giussani et al., 2009; Roux, Boetto, Sacko, Chollet, & Tremoulet, 2003a). While these components (visual/object processing, phonology, semantics – as well other cognitive systems such as memory) are integral to the language system, they do not encompass all aspects of everyday conversational language, such as morphosyntax. The sensitivity of most currently used linguistic protocols is therefore deemed to be low, due to their failure to assess a wide range of mental processes (De Witte & Marien, 2013; Rofes & Miceli, 2014). This may also explain why, in some individuals, counting and object naming tasks do not detect any disturbances during mapping in suspected language areas, rendering them ***silent cortex***.

Some clinicians have used picture naming variations, such as action naming in addition to standard object naming, to assess understanding of verb concepts (Bello et al., 2008; Lubrano et al., 2014). Often, however, such tasks only assess verb production in isolation and not in relation to a subject or tense (e.g., the verb [to] run) – something that is central to our everday language use. A variation of this task that incorporates grammatical processes has been

implemented by clinicians across Europe, pre-, intra-, and post-operatively (De Witte et al., 2015b; Ohlerth et al., 2020; Rofes et al., 2015c; Rofes et al., 2017b), as discussed in more detail later.

Moreover, although naming tasks can identify language disruption generally, it is not possible to isolate specific processes. For instance, in some cases it would be difficult to determine if anomic responses are caused by visual, phonological, or semantic disruption (e.g., naming a *zebra* "horse" – both are visually similar and semantically related). Indeed, some studies have attempted to isolate specific language processes by adopting more sensitive tasks.

Semantics can be probed through non-verbal associative knowledge tasks (e.g., The Pyramids and Palm Trees Test, PPTT; Howard & Patterson, 1992) whereby a target picture is matched to a picture of an associated item in the context of two semantically similar items (e.g., *pyramid, palm tree*, fir tree). This is more cognitively taxing than naming since the task involves assessing the relatedness of stimuli without verbal expression. This would be more useful for isolating a comprehension disturbance, since anomias or paraphasias elicited during object naming might reflect a variety of disrupted processes (e.g., anomia could stem from visual, phonological, or semantic disturbance).

These tasks are similar to object naming in terms of their ease of administration and would require no extra time in theatre. To date, only a handful of studies report their use, however they collectively demonstrate the clear capabilities of semantic association tasks in detecting semantic disturbances and paraphasias in parieto-temporal cortical regions, as well as subcortically in the inferior fronto-occipital fasciculus (De Witte et al., 2015a; De Witte et al., 2015b; Gatignol, Capelle, Le Bihan, & Duffau, 2004; Moritz-Gasser, Herbet, & Duffau, 2013; Zemmoura et al., 2015). The use of this more stringent option is reccomended for assessing semantics, either in addition to, or instead of object naming. Optionally, these picture materials can double as an object naming task at a later stage, or following each trial; if the

patient becomes fatigued or less compliant with the demands of the PPTT, for example, the language clinician can easily request them to name the objects instead.

Although most intraoperative tasks are focussed on the visual modality, one study included naming to verbal description (Kin et al., 2013). One advantage of auditory naming is that it can impose different demands on the cognitive-linguistic system than its visual counterpart (i.e., phonological decoding rather than structural decoding). By virtue of delivering this naming task via the auditory modality, there also presents the opportunity to test the retrieval of abstract nouns that could otherwise not be accurately depicted through visual stimuli. While this task is not widely used in the reviewed literature, administration of both tasks during awake surgery may allow the clinician to identify potential disociations in auditory and visual naming interferences; this may be particularly useful within temporal lobe resections in which auditory naming has shown to be more impaired than visual naming (Hamberger, Heydari, & Seidel, 2024; Hamberger & Seidel, 2003). Furthermore, auditory naming may be complementary to visual naming, particularly when trying to unpick lower level visual disturbances that result in naming errors during posterior temporal/occipital stimulation (i.e., the patient can name objects auditorilly but not visually; Gil-Robles et al., 2013; Mandonnet et al., 2009). Further evidence of this task in practice is necessary before making more specific recommendations; however, as it requires no visual materials, this task can be easily implemented *ad-hoc*, making it ideal for clinicians who are unable to dedicate further time or resources to develop or prepare materials.

Following a similar process to visual naming, the second most common visual task is *reading*. Both single-word and sentence-based reading are routinely used and according to the present findings, reading interference is frequently associated with DES to left cortical and subcortical temporo-parietal regions (Roux et al., 2009b). Stimulation to these regions disrupts the cognitive mechanisms that underpin reading, including vision (orthographic), semantics,

and phonology (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001). While we predominantly read text for the purpose of extracting meaning, not all words, however, engage these systems in the same way, allowing some words and sentences to be read without engaging semantics. For regular, familiar, and highly frequent words (e.g., cat, sun) where the mapping between letters and sounds (vision and phonology) is regular and predictable, reading may not require access to semantics, as it invariably does for object naming. Consequently, word items that elicit letter-sound congruence may limit the incidence of speech and language errors during DES. Conversely, irregular words in which the mapping between letters and sounds is incongruent (e.g., colonel) often require access to semantics to support the correct pronunciation. Semantically induced interference with DES would result in slow or inefficient reading of irregular words, with patients attempting to read phonetically (e.g., colonel -> "colernel"; yacht -> "yatched"; sugar -> "sudger"). Hence, locating the semantic system with DES may be overlooked using non-standardised reading tasks, particularly if they do not contain ambiguous or irregular items; these patients may be at risk of developing postoperative surface dyslexia (i.e., intact reading of regular vs. irregular words).

Furthermore, administering only words during intraoperative testing may mask a DES induced phonological interference due to reliance on the lexico-semantic reading route rather than the sub-lexical phonological route. Roux et al. (2012) compared real word and pseudoword (non-word) reading in an attempt to isolate semantic and phonological sites. This study identified dissociated sites for word and non-word reading (the superior temporal gyrus and supramarginal/postcentral gyri, respectively) in some patients. This suggests that while assessment with real words may uncover lexico-semantic or shared sites, it may not always detect phonology-specific interferences that may only be mapped with non-word stimuli. However, some patients within this study demonstrated the opposite dissociation (i.e., word reading interferences in the supramarginal gyrus and non-word reading interferences in the

superior temporal gyrus) or an overlap between tasks in these regions. Therefore, while these two reading systems may be at least partially distinct, there is no clear functional neuroanatomical basis for implementing phonologically targeted reading assessment (i.e., there may be individual differences in subregions involved in lexico-semantic and sub-lexical processes). Furthermore, Sierpowska et al. (2017) used a non-word repetition task map the arcuate fasciculus; non-word repetition was shown to be advantageous in detecting subtle phonological errors compared to either object naming or word reading tasks. The addition of non-word reading, or non-word repetition tasks may thus be useful in testing for phonological interferences during surgery and may help to reduce the chances of patients acquiring phonological dyslexia postoperatively. This specific reading disorder has been characterised by normal reading of irregular words (intact semantic route), but impaired reading of non-words (damaged phonological route), which may result from damage to inferior parietal and inferior frontal structures (Beauvois & Derouesne, 1979; Fiez, Tranel, Seager-Frerichs, & Damasio, 2006; Funnell, 1983; Rapcsak et al., 2009).

Whilst it is acknowledged that efficient reading relies on the interactions of visual, phonological, and semantic systems (Coltheart et al., 2001), comprehensive testing for subtle reading disturbances during language mapping is vital, owing to brain heterogeneity. Consequently, standard reading tasks alone (i.e., those that use real words with regular grapheme-phoneme mapping) may not reliably and simultaneously capture the full range of processes (i.e., lexico-semantic and phonological) involved in the complex reading activities encountered in daily life (e.g., reading unfamiliar words). It is thus recommended that intraoperative protocols (particularly in temporo-parietal regions underpinned by the arcuate fasciculus) in addition to standard reading tasks, also incorporate irregular words, non-words, and an increased task difficulty (i.e., including less frequent/familiar words), to reveal more

specific reading sites and better preserve reading abilities underpinned by both semantic and phonological reading routes postoperatively.

The adoption of visual tasks as opposed to auditorily delivered tasks is essential during resections in posterior temporal and occipital regions. The results revealed visual object recognition problems during object naming following DES to posterior temporal cortex (Wang, Wang, Jiang, Wang, & Wu, 2013), and anomia/speech arrest during reading and object naming following DES to visual association cortex (Gil-Robles et al., 2013). These visually evoked disturbances are consistent in patients with posterior lesions in whom secondary language deficits stem from low-level visual impairment (Roberts et al., 2015; Roberts et al., 2013). While language tasks appear capable of detecting these disturbances in some cases, they are nonetheless masking a more generalised visual disruption. Hence, if such an impairment is induced during resection, there may be a more severe impact on a range of cognitive functions beyond language. It is therefore recommended that a more targeted assessment of visuospatial functions for patients undergoing posterior resections is carried out. Indeed, some clinicians are already considering the visuospatial domain in awake craniotomy by introducing tasks such as line bisection, which have a useful application for ruling out spatial neglect manifesting in the linguistic domain (De Witte et al., 2015b).

Some surgical teams have begun to implement a *tailored* approach to mapping, whereby the traditional "Penfield" tasks (object naming, counting, and reading) and more specialised materials are selected from a battery and prescribed according to each patient's tumour location in relation to the functional neuroanatomy of language (e.g., semantic tasks for tumours infiltrating the inferior fronto-occipital fasciculus). The Dutch Linguistic Protocol, for instance, contains several tasks that cover a range of processes, including grammar (De Witte et al., 2015b). While a targeted approach has theoretical significance in terms of functional localisation and connectivity (Catani et al., 2012), employing several tasks at one

site remains important in accounting for differences in language organisation across patients. As can be seen in Figure 2.2, DES to the arcuate fasciculus consistently produces phonological paraphasia, or speech/articulatory problems in the majority of patients; however, semantic paraphasia may also be observed. Despite this, repetition and counting tasks are typically selected to map the arcuate fasciculus, which are unable to capture semantic disruptions, potentially leading to false negative mapping. Hence, considering a wider range of language processes when devising the intraoperative protocol and retesting each site across multiple tasks can improve the reliability of mapping, as demonstrated in previous studies (Rofes et al., 2015c; Rofes et al., 2017b).

Clinicians are now recognising the importance of cognitive processes beyond language during awake surgery, including memory and executive function (Bello et al., 2008). Postoperative acalculia, the inability to perform mathematical calculations, may be as functionally detrimental as losing language, hence testing for such functions during parietal resections is highly recommended (De Witte et al., 2015b; Roux et al., 2003a). Likewise, inhibitory control tasks such as the Stroop and colour-shape switching would be useful for bilateral anterior cingulate and left striatal resections, respectively (Wager et al., 2013; Wang et al., 2013). Verbal short-term memory assessment may have an application across a variety of left frontal, temporal, and parietal regions (Martino, Gomez, de Lucas, Mato, & Vazquez-Bourgon, 2018). Finally, considering the right hemisphere specifically, assessment of emotional abilities, such as that with mentalising tasks may prove useful for mapping in socioemotional brain areas (Yordanova, Cochereau, Duffau, & Herbet, 2019).

The decision to incorporate cognitive tasks requires consideration. While potentially optimising the protocol, additional tasks require greater effort from the patient and place further demands on clinicians performing this already complex procedure. However, patient-tailored approaches may not only consider the neuroanatomical relevance of certain tasks, but also the

functional significance to the individual patient. One group, for example, emphasise the importance of tailoring tasks on the basis that certain individuals have particular occupational expertise that rely on higher cognitive functions (Herbet, Rigaux-Viode, & Moritz-Gasser, 2017). In addition to standard linguistic testing, they report employing additional cognitive testing as required, such as a calculation task to assess numerical cognition in mathematicians, as well as the *n*-back task to assess working memory in individuals employed in cognitively demanding office-based roles such as management assistants. Patient-tailored approaches are becoming increasingly common among glioma patients, not just to preserve higher cognitive functions, but a range of different functions that are relevant to the occupation, skills, or hobbies of the patient. A few examples include: singing tasks for amateur singers (Roux, Borsa, & Démonet, 2009a), score reading for musicians (Roux et al., 2007), and translation or language switching tasks for bilinguals and professional translators (Borius, Giussani, Draper, & Roux, 2012; Wang et al., 2013). Clinicians should continue to explore novel approaches to optimising intraoperative assessment according to their patients' individual needs. However, preserving the most functionally important linguistic abilities in all patients, regardless of skills, occupation or hobbies, should be the first priority in awake craniotomy. Such patient-tailored approaches therefore must be considered as a secondary outcome in preserving function and additional tasks should only be implemented in the case that core linguistic functions have been reliably and comprehensively mapped. It is imperative that neurosurgical clinicians aim to minimally test for and preserve basic speech production (phonological and articulatory processes), comprehension (semantic processes) and ideally morphosyntax (grammatical processes). This would maximise the chances of keeping essential communicative abilities intact, which are most crucial to maintaining functional quality of life postoperatively. Furthermore, it would be futile to preserve additional, presumably less essential functions, such

as the ability to perform mental calculations, if expressive and receptive language abilities become severely damaged, rendering the patient unable to communicate.

3.5.2. A comprehensive approach

Assessing the entire spectrum of cognitive functions within the brief surgical window is something that is currently both theoretically and practically impossible, and so patient-tailored protocols, such as those outlined above, strive to provide a personalised and thorough assessment for each patient. While this may be more beneficial for outcomes, implementing bespoke strategies may be unfeasible for some neurosurgical departments due to time constraints and the increased clinician workload. Underfunded and understaffed NHS hospitals in the UK, for example, rely heavily on resource utilisation and cost-effective interventions, therefore, clinicians might be disinclined to lengthen the procedure to accommodate re-testing of sites with multiple tasks. Delivering a more concise protocol (encompassing a smaller number of tasks) that is functionally comprehensive (collectively targets numerous processes) may be a suitable alternative. This approach would aim to detect more functions in comparison to traditional tasks, as well as offering a more practical solution to providing comprehensive testing. Efforts to develop comprehensive linguistic protocols have focused on incorporating the assessment of grammar, particularly for mapping frontal regions, which despite being an integral component of the language system, has been overlooked in awake craniotomy until recently (De Witte & Marien, 2013; Rofes et al., 2015c).

Picture-based grammatical production tasks, such as action naming with finite verbs (ANFV), have mapped a variety of frontal lobe sites, including Broca's area, as well as middle frontal gyrus sites that were undetectable with object naming in some patients (De Witte et al., 2015b; Rofes et al., 2015c; Rofes et al., 2017b). Unlike object naming tasks, or indeed standard action naming, ANFV requires morphosyntax – the production of the correct verb in its appropriately inflected form ("eats" or "ate"; Rofes et al., 2015c). Grammatical assessment for

language mapping is further supported by evidence from fMRI, which has demonstrated greater bilateral language activation than standard presurgical mapping tasks (Połczyńska et al., 2017). Grammatical tasks may therefore be a more optimal choice for concise and comprehensive assessment, both pre-, intra-, and post-operatively, particularly when the use of more extensive protocols is impractical.

Furthermore, traditional and more specialist intraoperative language tasks focus on testing language from the perspective of microlinguistics, for example, identifying and coding for linguistic errors within a word or sentence (e.g., semantic error, phonological error, syntax error etc.). While more specialist tasks, particularly tasks of naming in sentence context (as described above), generate multiword responses that enable a fuller assessment of lexical and grammatical production, they are limited in their assessment of macrolinguistic processes. Macrolinguistics refers to the assessment of language at the pragmatic and discourse level, which is crucial to the narrative or "storytelling" abilities that we rely on during everday language exchanges. Macrolinguistic impairment may result from neural damage and has been shown to occur in both patients who are non-aphasic and those who are aphasic with respect to microlinguistic assessment (lexical and grammatical abilities; Marini et al., 2011). Importantly, in individuals with anomic aphasia, there is also evidence to suggest that errors produced at the lexical level are associated with impairments in the coherence of global language discourse (Andreetta, Cantagallo, & Marini, 2012; Linnik, Bastiaanse, & Höhle, 2015).

Whilst macrolinguistic abilities may be difficult to assess during the brief window of DES language mapping, language monitoring during the resection phase of surgery is not limited by the same time constraints and so may accommodate a more exhaustive and comprehensive neuropsychological protocol. This may provide an opportunity to assess the more global structure and coherence of the patient's narrative linguistic abilities that bears a closer resemblance to the multifaceted nature of real world language (McCarron et al., 2017).

Using a more composite task that recruits the wider cognitive-linguistic network will undoubtably broaden the scope for both micro- and macro-linguistic error detection. Importantly, it may also facilitate a deeper understanding of the delicate relationship between the patient's intraoperative language/cognitive status and postoperative impairments (Collee, Vincent, Dirven, & Satoer, 2022a), as well as an early indication of implications for rehabilitation of impaired function. One practical option is a task integrating multiple visual stimuli, such as *The Cookie Theft* picture description task (Roth, 2011), which may be a more effective approach for continuous assessment of phonology, semantics and morphosyntax as well as pragmatic linguistic abilities. One shortcoming to using complex visual tasks during monitoring, is that prolonged testing may be more mentally taxing for the patient. However, this can be attenuated by alternating delivery with easier tasks (e.g., picture naming) or conversation to avoid fatigue. Delivering formal testing in conjunction with conversation may be a useful approach; Collee et al. (2022a) recommend monitoring spontaneous speech through conversation during resection to guide further formal testing; for example, if the language clinician observes that a patient produces a phonemic paraphasia during spontaneous speech, a repetition task may be subsequently implemented to assess this error more specifically.

3.5.4. Limitations, future directions, and conclusions

This review evaluated data from cortical and subcortical mapping studies for a range of cognitive and linguistic tasks in awake tumour surgery. One limitation, however, is the exclusion of cases for awake epilepsy resections; this decision was taken to avoid the effects of potential heterogeneities in functional organisation between these different patient populations. However, the epilepsy literature may provide further insights into optimising DES mapping, and future work should aim to investigate this separately.

The DES mapping phase of surgery has taken precedence in this review, however, the tumour resection itself is a critical period for neuropsychological function that remains largely

understudied in the awake neurosurgical literature. During this delicate phase of surgery, the patient may be engaged in conversation to assess spontaneous speech and/or formal neuropsychological testing in an effort to continuously monitor function (Bartha, Knosp, Pfisterer, & Benke, 2000). Studies of spontaneous speech in glioma patients have been conducted in the perioperative stages of awake surgery (Satoer, Vincent, Smits, Dirven, & Visch-Brink, 2013), however, there is a lack of research attention focussed on testing and reporting the results of spontaneous speech monitoring during tumour resection, an issue which has been recently raised (Collee et al., 2022a). Consequently, the present review could only focus on linguistic testing in relation to the mapping phase of surgery. Importantly, Collee et al. (2022a) found that spontaneous speech deficits were observed most frequently following the production of linguistic errors intraoperatively, suggesting that this phase of surgery should be considered more closely in future work.

The current work intends to provide a useful guide for task selection based on what is known from intraoperative mapping, rather than what is theorised from fMRI and lesion-symptom mapping – the underlying principles of which are inherently different from that of DES. Functional neuroanatomical approaches are a crucial way forward, however, their hypotheses should be formulated through direct evidence from intraoperative mapping comparing multiple tasks, for which there is currently insufficient data. To generate such evidence would require a concerted collaborative effort from the clinical and academic communities to both implement and document the outcomes of variable task protocols across different cortical and subcortical brain regions. Researchers could then begin to generate anatomical maps and perform meta-analytics to empirically establish optimal tasks for specific regions.

As acknowledged, practical, financial and time constraints may hinder such data collection. However, clinicians should aim to optimise assessment by replacing “home-made”

tasks with validated mapping tasks and/or adding complimentary tasks, where possible, to better capture the breadth of cognitive and linguistic functions. Likewise, researchers developing new tests should closely liaise with the clinical community, ensuring the accessibility of materials and supporting clinicians in their implementation. For example, researchers and clinicians of the ELGGN are currently implementing a new dual approach (ANFV and object naming) across multiple languages, including the English version (VAN-POP; Ohlerth et al., 2020), both in-theatre and as a preoperative mapping tool.

It is imperative that researchers and clinicians continue working together to improve approaches for awake craniotomy at pre-, intra-, and post-operative stages. The integrity of DES mapping rests largely on the rigour of the intraoperative protocol and remains fundamental to both neuropsychological and quality of life outcomes.

3.6. Chapter summary

Chapter 3 has reviewed intraoperative brain mapping studies of patients undergoing awake craniotomy for the resection of brain tumours. DES mapping data has been synthesised to generate neuroanatomical maps of areas that have shown to be involved in a variety of cognitive and linguistic tasks, and the types of errors and interferences arising from these sites. Use of these intraoperative tasks was discussed in terms of their theoretical and practical merits, and recommendations were made about how to optimise protocols for different brain regions using a variety of approaches (e.g., comprehensive, patient-tailored etc.). Consideration was given towards practical constraints (i.e., time, resources, staff etc.) and potential solutions by using more concise assessments (e.g., VAN-POP). The resection phase of surgery was also discussed, and how to better monitor language deterioration by combining more comprehensive formal testing and conversation to preserve function and maintain patient wellbeing and co-operation. The VAN-POP identified during this systematic review is the

focus of Chapter 4 – trialling this new protocol for the first time in The Walton Centre NHS Foundation Trust neurosurgical hospital.

Chapter 4: Direct electrical stimulation mapping using the Verb and Noun test for Perioperative testing (VAN-POP) in awake craniotomy for resection of low-grade gliomas

4.1. Chapter overview

Chapter 3 evaluated the range of cognitive and linguistic tasks that are in use around the globe for mapping and monitoring in awake craniotomy. At least 28 tasks were identified, with the most popular being counting and object naming. One of the most practical and far-reaching tests of assessing a complex range of linguistic processes was ANFV – a task that recruits the grammatical components of the language system. The present chapter describes the use of the VAN-POP (Ohlerth et al., 2020), comprising a validated English version of the original ANFV and object naming counterpart developed specifically for perioperative assessment in Italian awake craniotomy patients (Rofes et al., 2015b). This novel test was implemented along with standard intraoperative assessment during awake craniotomy for four low-grade glioma patients at one of the UKs leading neurology and neurosurgery hospitals – the Walton Centre NHS Foundation Trust. A detailed case report of each patient is described, discussing the cortical mapping results using the VAN-POP, including novel grammatical errors that have not previously been reported intraoperatively. Finally, the findings will be discussed in the context of previous research that used similar tasks, as well as the wider neuropsychological and neuroscientific literature.

4.2. Introduction

The ability to produce nouns and verbs plays a pivotal role in our everyday use of language, without which we would not be able to form even the simplest of sentences (Aggujaro, Crepaldi, Pistarini, Taricco, & Luzzatti, 2006; Berlingeri et al., 2008; Crepaldi et al., 2011; Rofes, Capasso, & Miceli, 2015a). Confrontational naming tasks involving the

production of either nouns (objects), or verbs (actions) are widely used in neuropsychological research, and for clinical diagnostics and interventions with language disordered patients. These assessments are often used intraoperatively due to their ease of administration in-theatre and ability to detect speech arrest, word retrieval difficulties, and paraphasias (errors). The use of object naming is well-documented and is often the primary task for detecting language function (see Chapter 3); its counterpart, however, is not widely reported, with only a few studies reporting action naming (Corina et al., 2005; De Witte et al., 2015b; Lubrano et al., 2014; Rofes et al., 2015c; Rofes et al., 2017b).

The lack of acknowledgement in the role of verb assessment to preserve linguistic function is rather surprising considering the ongoing debate within the literature concerning the frontotemporal dichotomy hypothesis (Crepaldi et al., 2011; Matzig et al., 2009; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). This account speculates that verbs and nouns are localised to the left prefrontal cortex and anterior temporal region, respectively. Patients with damage to left prefrontal areas (including Broca's area) should show selective deficits for verbs, but preserved noun processing, while those with more anterior temporal lesions should demonstrate the opposite pattern of impairment (Damasio & Tranel, 1993). Studies of aphasic patients with circumscribed lesions have supported this localisationist view of a double-dissociation (Damasio & Tranel, 1993; Daniele, Giustolisi, Silveri, Colosimo, & Gainotti, 1994). However, other studies have found that lesions in the more posterior temporal (Wernicke's area) and inferior parietal regions (Geschwind's territory), also produce impairments in verb retrieval (Aggujaro et al., 2006; Tomasino et al., 2019). Evidence from neuroimaging on healthy individuals is inconsistent, with a metanalysis by Crepaldi et al. (2013) unable to separate any clear frontal and temporal patterns of activation for verbs and nouns. Crepaldi and colleagues (2013) offered several explanations for such inconsistencies including input modality of the task (i.e., visual vs. auditory), the nature of experimental stimuli

and responses required (e.g., picture naming, lexical decision; verbalised vs. subvocal responses), imaging method (i.e., PET vs. fMRI), and selection of baseline task (i.e., linguistic vs. non-linguistic control); none fully accounted for discrepancies in the data. A more recent meta-analysis by Faroqi-Shah, Sebastian, and Woude (2018), aimed to control for the potential confounds in Crepaldi et al. (2013), by excluding studies using tasks that generate both noun and verb activations within the same trial (e.g., verb generation tasks from which verbs are generated from a presented noun). Unique clusters of activation were found in the posterior middle temporal region (fusiform gyrus) for nouns, and in the inferior frontal (pars opercularis and orbitalis) and middle temporal regions for verbs; however, an inferior region of the fusiform gyrus showed overlapping activation for nouns and verbs. While this suggests that noun and verb activation patterns may be at least partially separatable, it fails to support the view of a clear-cut fronto-temporal dichotomy for noun and verb processing.

An alternative explanation to the localisationist account is that regions underpinning noun and verb processing are dispersed around the cortex constituting interconnecting neural networks, supported through signalling between various subcortical white matter pathways (Crepaldi et al., 2013; Crepaldi et al., 2011). Faroqi-Shah et al. (2018) argue that the overlapping left fusiform activation for nouns and verbs is due to the region being recruited for single-word processing independent of grammatical class or task modality. The notion of class independent regions is further supported by a recent meta-analysis confirming the left inferior frontal gyrus as a neural substrate of inflectional morphology in both nouns and verbs (Bulut, 2022). The author suggests that the left posterior inferior frontal gyrus is recruited into the linguistic network to aid complex morphological processing, irrespective of grammatical word class, as opposed to subserving verb-specific processing.

The heterogeneity of such neural networks in terms of structure-function may explain the variation in patterns of impairment for verb and noun processing abilities. Damage to a

particular structure may manifest differently across patients depending upon the specific role it plays in each network. Crepaldi et al. (2011) suggest that the internal vicariousness of the verb network allows spared regions to compensate for functions primarily underpinned by those which have become damaged. Thus, intraoperative assessment of one specific lexical category targeted to a particular tumour location may not be the optimal choice for reliable detection of functional tissue during awake craniotomy. Indeed, Ojemann et al. (2002) reported that both object naming and verb generation interferences could be produced from stimulation in any perisylvian site. Furthermore, noun and verb naming sites have been observed across several frontal, temporal, and parietal locations, some that are unique to either grammatical category, or shared by both (Corina et al., 2005; Havas et al., 2015).

Specifically, Havas et al. (2015) found that within the middle and inferior frontal regions, 86% of sites were either verb-specific or general to both nouns and verbs. This suggests, anatomically speaking, while verb and noun networks could be at least partially separable, the evidence of shared noun-verb disruptions in certain stimulated regions refutes the idea of regional specialisation. The occurrence of anatomical overlaps between these networks, however, does not necessarily suggest that they are shared at the functional level. Crepaldi et al. (2011) highlight that functional independence does not always imply anatomical independence. Rather, such regions may be independently recruited for different linguistic subprocesses that are common to both noun and verb production, such as phonological encoding.

Regardless of the frontotemporal dichotomy debate, reports of selective language impairments in lesioned patients calls for the consideration of language organisation at the individual level, particularly when the aim of assessment is maximal preservation of language function. Anatomically targeted assessment is based on an inconclusive evidence base, which may result in false negative mapping, and thus the assumption of ***silent cortex***. Hence, dual

noun-verb assessment, irrespective of craniotomy location, aims to improve the validity of mapping by disentangling selective disruptions at any given stimulated area. Another advantage of using verb assessment, is that verb retrieval is inherently more challenging than noun retrieval due to its weaker association with semantics, and stronger association with motor representations (van Dam, Rueschemeyer, & Bekkering, 2010).

One limitation of confrontational naming tasks is that they are unrepresentative of everyday language use. For example, action naming using only isolated verbs does not capture the cognitive processes required for manipulation of verb forms that we use to produce more complex language for speech. In terms of verb assessment through action naming, recent awake studies have begun to retreat from simple assessment of isolated verbs (e.g., in their infinite form – [to] jump/jumping) and introduce more complex variations (ANFV). These involve assessing the production of verbs in sentence context by prompting responses in past and present tense finite forms (e.g., [he] jumps/jumped).

Similarly to standard action naming, ANFV involves the presentation of action pictures, but with the addition of an introductory phrase containing a determiner to denote the tense of the verb to be produced (e.g., "daily" or "yesterday") and a subject (he/she/it). ANFV additionally recruits grammatical processes, since responses require the manipulation of verb tense to produce a grammatically correct sentence. Rofes et al. (2015a) found that performance on ANFV tasks are more representative of patients' real world language functioning and can be easily incorporated into the intraoperative linguistic protocol alongside traditional object naming. Moreover, ANFV can identify positive language sites that are undetectable with object naming, as well as shared verb and object sites (Rofes et al., 2019; Rofes & Miceli, 2014; Rofes et al., 2015c; Rofes et al., 2017b). However, this relatively new task has not yet been widely used during awake craniotomy, and existing studies mostly provide data for frontal patients and not those with tumours in other language regions.

The present study aims to further explore the dual application of ANFV and object naming in patients with tumours affecting different locations (frontal, temporal, and parietal) to expand its application in the awake neurosurgical procedure. Previous research examined the use of an ANFV and object naming battery in Italian speaking patients and these tasks have recently been translated and validated for use in the English language (including Dutch and German), in the form of the VAN-POP (Ohlerth, Valentin, Vergani, Ashkan, & Bastiaanse, 2020). Importantly, in other languages, only one ANFV task has been used to trigger the production of finite verbs in the present tense. Languages such as Italian, Dutch and German have more complex verb inflection regardless of tense, and so production of the present tense is sufficient to assess complex inflectional morphology. However, in English, verb inflection for present tense is inherently less complex; hence, triggering only the present tense may not fully capture complex inflectional abilities that are only required with production of the past tense, particularly the irregular past tense. Therefore, for the English VAN-POP only, an additional past tense variation was introduced to trigger the production of both the regular and irregular past tense. The current study, for the first time, evaluates the use of the VAN-POP for linguistic assessment during awake craniotomy in the UK, and novelly assesses finite verb production in both the past and present tense. The next sections will describe how this test battery has been implemented into the awake protocol at The Walton Centre NHS Foundation Trust and present the findings in four low-grade glioma patients with frontal (RS), frontotemporal (JLR), temporal (MW) and parietal (GD) tumours.

The study is largely exploratory to assess the feasibility of using the VAN-POP and provide preliminary mapping data to support its wider application. However, the hypotheses for this study regarding the functional representation of object and action naming sites using the VAN-POP were generated based on previous similar studies cited above that have used object naming in conjunction with ANFV or standard action naming intraoperatively.

In prefrontal tumour patients (RS and JLR), based on previous work by Rofes et al. (2017b), it was predicted that there may be sites for both object naming and ANFV within frontal cortex, in particular, the inferior and middle frontal gyri (H_1, H_2). Some of the possible DES interferences that were expected following stimulation of these regions were phonological paraphasia, semantic paraphasia, anomia and delayed responses.

Based on the findings from the parietal patient in Rofes et al., as well as several other studies (for example, De Witte et al., 2015a; De Witte et al., 2015b; Roux et al., 2014; Signorelli, Guyotat, Schneider, Isnard, & Bret, 2003; Vidorreta, Garcia, Moritz-Gasser, & Duffau, 2011), it was predicted that object naming sites would be present in the inferior parietal region (patient GD), specifically within the angular gyrus (H_3). Stimulation of this region may generate semantic paraphasia and anomia during object naming. Action naming sites were not found within the inferior parietal region in Rofes et al., although they have been found within the neighbouring region of the supramarginal gyrus (Lubrano et al., 2014), therefore it was predicted to be possible to observe action naming sites within the angular gyrus also (H_4).

Within the temporal cortex object naming sites have frequently been found in several previous studies (see those cited above for examples or Chapter 3 for a review); therefore, stimulation of the superior/middle temporal regions in the two temporal patients (MW and JLR) was predicted to return language positive sites during object naming (H_5), with a range of possible interference types including, anomia, paraphasias, delays etc. Sites have also previously been found within the temporal regions for standard action naming, resulting in speech arrest, anomia and neologisms (Lubrano et al., 2014), suggesting that superior temporal stimulation may also reveal ANFV sites in the present cases (H_6).

Due to the nature of the study which did not always allow for direct comparison between tasks at the sites of stimulation, no specific predictions could be made regarding

specificity or overlap of sites, or whether one task could identify more sites than another. Data for each task was collected to identify the types of errors produced at various sites of stimulation across patients.

4.3. Methods

4.3.1. Participants

Four patients undergoing awake craniotomy for excision of low-grade gliomas (WHO Grades I-II) infiltrating anticipated language regions in the left-hemisphere participated. Patients were recruited during their preoperative appointment with the SLT, around one week before surgery. Further details of the recruitment process can be found in Chapter 5. Comprehensive case reports detailing background information regarding each patient are presented below.

4.3.2. Preoperative neuroimaging

MRI and fMRI were administered on three out of four patients to identify the tumour location and potential language areas in proximity; the other patient underwent cerebral perfusion. Patients completed three tasks to assess language activation: verb generation, word generation, and rhyme judgement (see **Figure 4.1**).

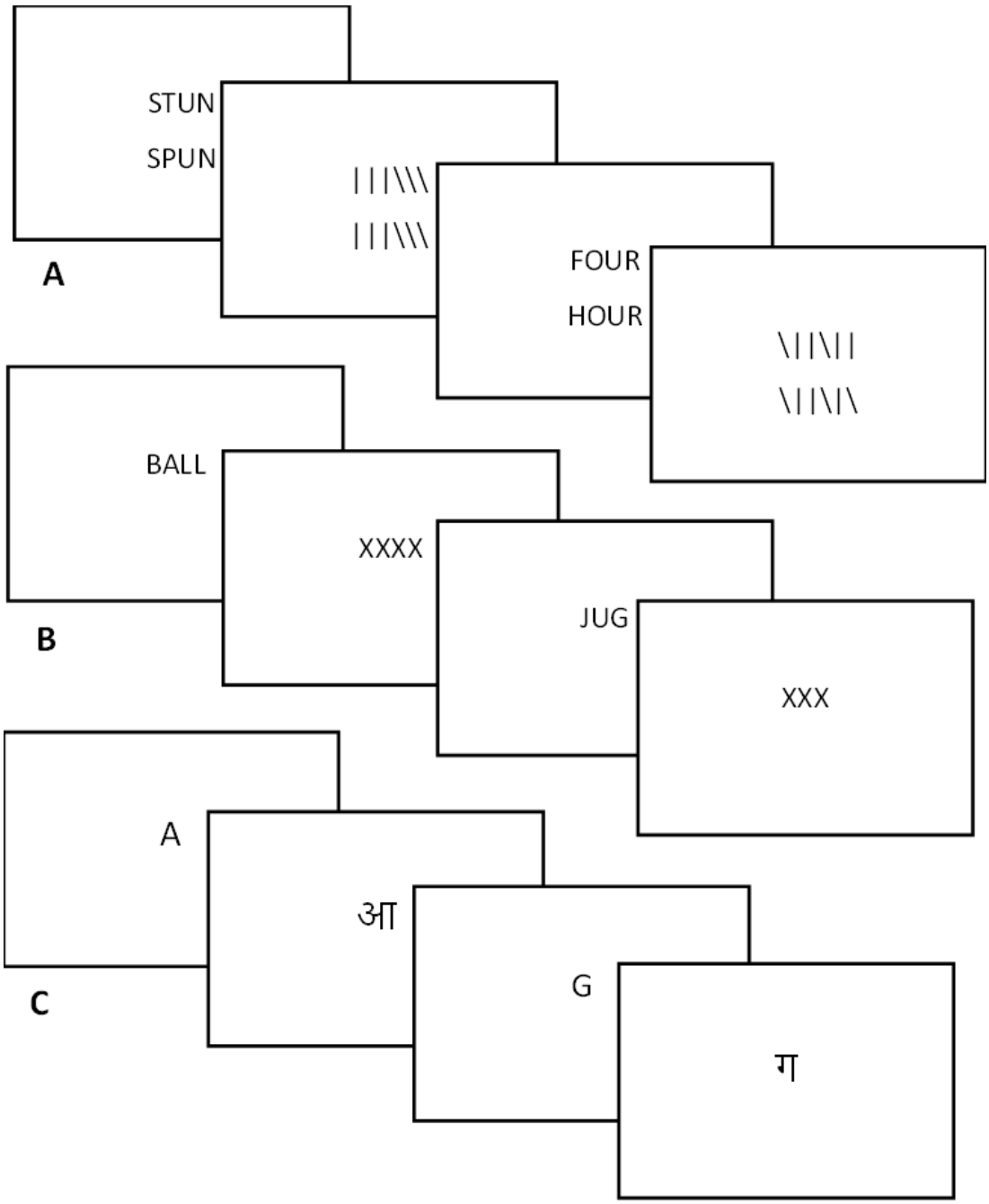

Figure 4.1. Preoperative language mapping tasks administered during fMRI. A) Rhyme judgement: participants are presented with two words and respond via button press when the words rhyme; for control trials participants press the button when the orientation of two sets of lines is congruent. B) Verb generation: participants are presented with object words and instructed to generate (mentally) as many verbs as possible that are associated with the object, e.g., ball – throw, bounce, kick, catch etc. For control trials, the participants observe letter strings. C) Word generation: participants are presented with a letter on the screen and are instructed to generate (mentally) as many words as possible beginning with that letter; during control trials the participants observe Hindi letters.

4.3.3. Neuropsychological assessment

4.3.3.1. Preoperative and postoperative language assessment

During the patients' preoperative appointment, their SLT performed the Comprehensive Aphasia Test (CAT; scores are displayed in Table 3.1) and collected information about the patients' personal and professional lives, hobbies, interests etc. to use for conversation during the awake phase of surgery. The SLT also administered the standard and new VAN-POP intraoperative tasks (Figure 3.2) so patients could familiarise themselves with the procedure and remove any stimuli in which the patient presented any existing difficulties (details to follow). The SLT met with the patient on the day of surgery to practice the tasks again. Following surgery, the SLT performed a postoperative language assessment using the CAT, within 24 hours or the next working day if the surgery took place on the last day of the working week.

4.3.3.2. Intraoperative language assessment

Standard tasks

The intraoperative language protocol was administered via an iPad, typically by the same clinician as the preoperative assessment. The standard battery consisted of *ad hoc* or 'home-made' tasks as well as validated assessments, including counting, object-naming (Snodgrass & Vanderwart, 1980), automatic speech (e.g., push and ….. [pull]), word repetition, sentence completion, reading and calculation.

The Verb and Noun Test for Peri-operative Testing (VAN-POP)

The VAN-POP test (**Figure 4.2**) is a linguistic protocol for assessing retrieval of nouns and verbs in sentence context. It has been validated in several languages, including English, Dutch and German for use during perioperative rTMS, and intraoperative DES mapping, with

items matched and balanced for psycholinguistic variables that influence lexical retrieval of nouns and verbs (Ohlerth et al., 2020).

Consisting of two picture naming in sentence context tasks, the VAN-POP was administered to each patient in addition to the standard protocol. ANFV comprised two sets, one in the past tense (27 items), and one in the present tense (23 items), and the object naming task consisted of a 50-item set. Only the English version of VAN-POP contains both past and present subsets of ANFV. In both ANFV sets the patient is presented with an action picture (e.g., a drawing of a man eating), a lead-in phrase containing a determiner (*"yesterday"* or *"daily"*) to indicate the target tense, and a pronoun (*"he", "she"* or *"it"*) to indicate the subject of the sentence. For each item the patient is required to read the lead-in phrase and provide the correct verb in the correct tense (e.g., *"Daily, he… eats"* [present] or *"Yesterday, he… ate*" [past]). For the object naming set the patient would be presented with a picture of an object (e.g., an apple) along with a lead-in phrase (e.g., *"This is a/an…"*); the patient is simply required to read the lead-in phrase and name the object (e.g., *"This is an…apple"*). The VAN-POP object-naming set differed from the standard object naming set in the sense that the patient would read the introductory phrase themselves, whereas in the standard protocol it would be read by the SLT, and the patient would only respond with the name of the object.

Figure 4.2. Example items from the VAN-POP test in which patients were required to read the lead-in phrase and name the picture on the screen in the context of the sentence. **Top**: object naming task; produce the correct object noun. **Bottom**: past and present tense action naming tasks; produce the action-verb using the correct inflected form (past or present) as indicated by the introductory sentence (i.e., "Yesterday he… ate", "Daily he… climbs").

Spontaneous speech

In addition to formal testing the SLT would use conversation to prompt the production of spontaneous connected speech; this would take place during the monitoring phase of surgery (resection) but also between tasks to keep the patient alert and calm. Typically, the SLT would make conversation with the patient about topics such as their spouses, children, work, and happy memories or upcoming events in their lives.

4.3.4. Intraoperative procedure

All patients underwent iMRI guided awake craniotomy with DES cortical mapping via the asleep-awake-asleep regime. Once the scalp, bone flap and dura mater were removed to expose the brain, the patient was awoken and cortical mapping was performed using a bipolar stimulator with standard stimulation parameters (1-10mA, 60hz, 4s pulse duration). Tasks were

selected and administered by the SLT on an *ad hoc* basis depending on the tumour location, needs and tolerance of the patient, and the length of the mapping and monitoring phases of surgery (i.e., more tasks would be used if time permitted). Typically, assessment for cortical mapping would commence with counting or object-naming, followed by more demanding tasks such as the VAN-POP.

Functional areas were marked by placing sterile white tags on the surface of the site (see Figure 3.6). Once the surgeon was satisfied the with identification (or non-identification) of functional areas (typically 2/3 non-consecutive stimulations), dissection of the cortex and debulking of the tumour would take place. The SLT continued to monitor language using both formal testing and conversation, feeding back to the surgeon should any deterioration of performance occur. Once a significant portion of the tumour was extracted, iMRI would be conducted to determine if any further resection could take place to optimise oncological outcomes whilst considering the functional limits confirmed during mapping. Once resection was deemed complete the patient would be returned to sleep and the wound closed.

4.4. Case reports and results

The following sections present the case reports and results of language mapping and monitoring for the four patients. Results are summarised collectively at the anatomical level by task and error type (**Figure 4.3.**).

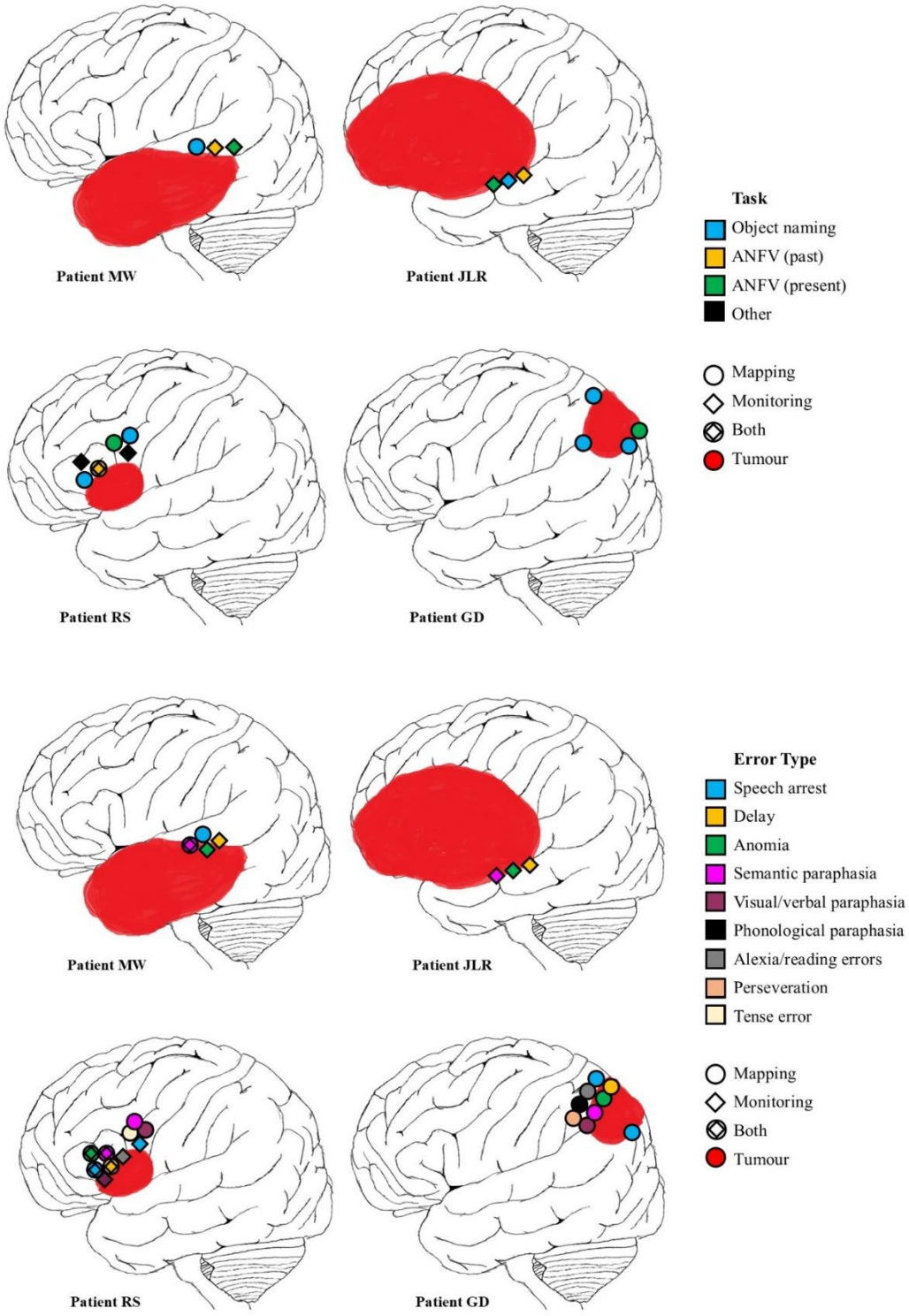

Figure 4.3. Summary of the anatomical distribution of language sites for each patient by task (top) and error type (bottom) during DES mapping and monitoring during resection.[1]

[1] Adapted from the original image by Mike Birkhead (2015) under the license of CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons: https://commons.wikimedia.org/wiki/File:Brain_-_Lateral_Left.png. Summary of the anatomical distribution of language sites for each patient by task (top) and error type (bottom) during DES mapping and monitoring during resection © 2024 by Rhiannon Mackenzie-Phelan is licensed under Creative Commons Attribution-ShareAlike 4.0 International. To view a copy of this license, visit https://creativecommons.org/licenses/by-sa/4.0/.

4.4.1. RS

4.4.1.1. Presentation and diagnosis

RS was a 23-year-old right-handed male with 17 years of education. He had previously completed a bachelor's degree in graphic design and worked as a retail assistant. Approximately two years prior to the study (2017) the patient was travelling to work and began experiencing dizziness, nausea, and vomiting that lasted for approximately one week. Although he had no true vertigo, the patient reported mild balance problems that lead to a diagnosis of labyrinthitis treated with medication. He was later admitted to his local Accident and Emergency department after complaining of headache and slurred speech; however, no neurological abnormalities were found. There was no significant medical or psychiatric history, although he had recently been prescribed propranolol for a mild anxiety disorder. During that time, he experienced a reduced appetite which led to weight loss. The patient was referred for a structural MRI that revealed a left frontal signal abnormality indicative of cortical dysplasia. Advanced MRI showed that the abnormality was likely a low-grade glioma (**Figure 4.3**). No neuropsychological impairments in short-term memory or language, including that of more complex grammar and syntactic abilities, were apparent. RS's condition was monitored with regular MRI scans and neurological examinations until he was referred for surgery in August 2019. Preoperative neuropsychological assessment one week before surgery did not reveal any significant language or motor deficits, although the patient displayed a few errors across several domains (**Table 4.1**).

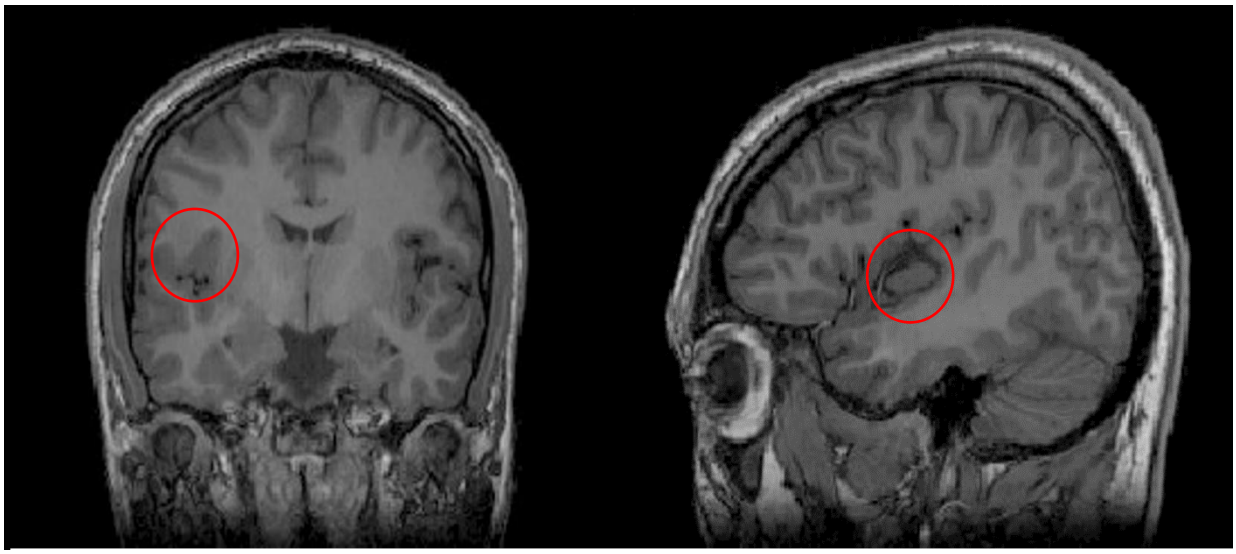

Figure 4.3. Structural Magnetic Resonance Imaging (MRI) of lesion in patient RS. Left frontal mass in inferior frontal gyrus (pars triangularis/opercularis; coronal and sagittal view).

4.4.1.2. Operation

Stimulation (2-5mA, 60Hz) applied anteriorly to the tumour, corresponding to the middle portion of the inferior frontal gyrus (pars triangularis), produced speech arrest, semantic paraphasias (e.g., *"bolt"* instead of *"screw"*) and word retrieval difficulties (delay and anomia) during object naming, and verbal and semantic paraphasias during past tense ANFV. Stimulation applied superior to the tumour, corresponding to the middle frontal gyrus and posterior inferior frontal gyrus, produced verbal/visual paraphasia on present tense ANFV (e.g., *"daily she drinks"* instead of *"daily she sings"*), and switches in tense (e.g., *"daily he shot"* instead of *"daily he shoots"*) that although remained grammatically correct, were errors in terms of the aim of the task; the patient also previously produced these response correctly during preoperative testing. Semantic and verbal paraphasias were also observed for object naming.

During resection within the middle portion of the inferior frontal gyrus, the patient produced incorrect verbs during past tense ANFV (e.g., "*yesterday she flowered*", instead of

"*yesterday she watered [the flowers]"*); semantic and verbal paraphasias, and word-finding difficulties (delay and anomia) during object-naming; reading errors were observed during sentence completion. Resection near the posterior inferior frontal and middle frontal gyri induced speech arrest when the patient recited the months of the year, while no language interference was observed for object naming, repetition, or other automatic speech tasks.

4.4.1.3. Postoperative course

Imaging confirmed residual tumour in the motor cortex, as planned, to avoid any postoperative motor impairments. Histological examination confirmed a low-grade oligodendroglioma (WHO Grade II) and the patient was referred for chemotherapy and radiotherapy to treat the remaining tumour. Postoperative neuropsychological assessment 24 hours after surgery found that performance was similar to that preoperatively, however, the patient did show both improvements and new errors on certain language components (**Table 4.1**).

4.4.2. GD

4.4.2.1. Presentation and diagnosis

Patient GD was a 39-year-old right-handed male with 14 years of education who worked as an IT Manager. He initially presented with headaches and episodes of expressive aphasia where he would experience a transient impairment in both verbal and written language (see **Figure 4.4**). During the episodes he reported becoming "confused" and unable to produce meaningful speech, despite knowing what he wanted to say. MRI scan showed an abnormality in the left temporo-parietal region indicative of a low-grade glioma (**Figure 4.5**), leading to referral for an exploratory awake craniotomy in September 2019. As the patient experienced transient aphasic episodes as opposed to persistent speech and language deficits, formal language assessment taking place one day before surgery deemed him largely unimpaired except for a few errors (**Table 4.1**).

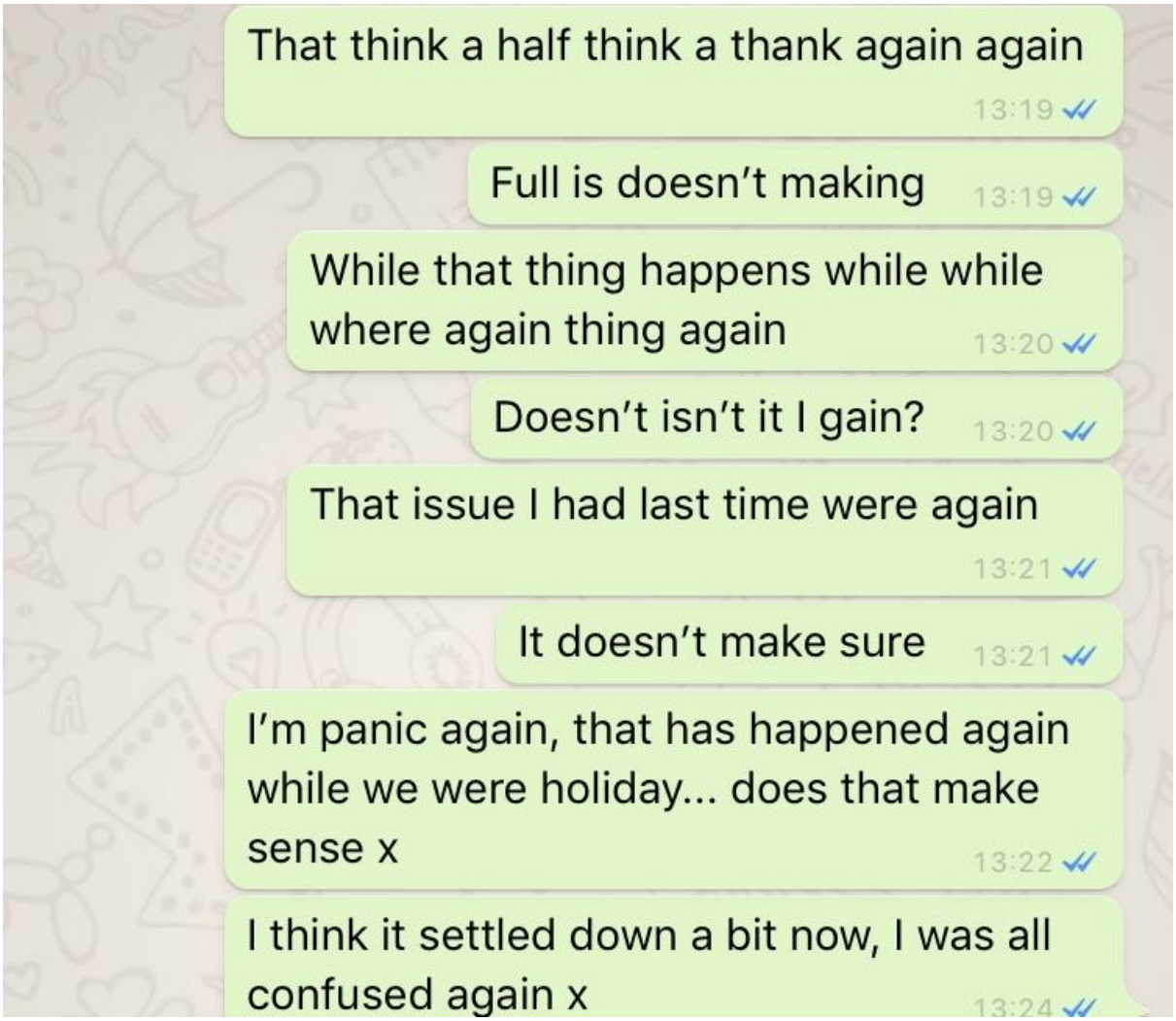

Figure 4.4. Screen shot of messages from Patient GD to partner during a transient aphasic episode. GD was texting partner to say that he was experiencing a similar aphasic episode that he had previously experienced while they were away on holiday. He described these episodes as "becoming confused" and said that this would affect both his verbal and written speech, before resolving after a few minutes.

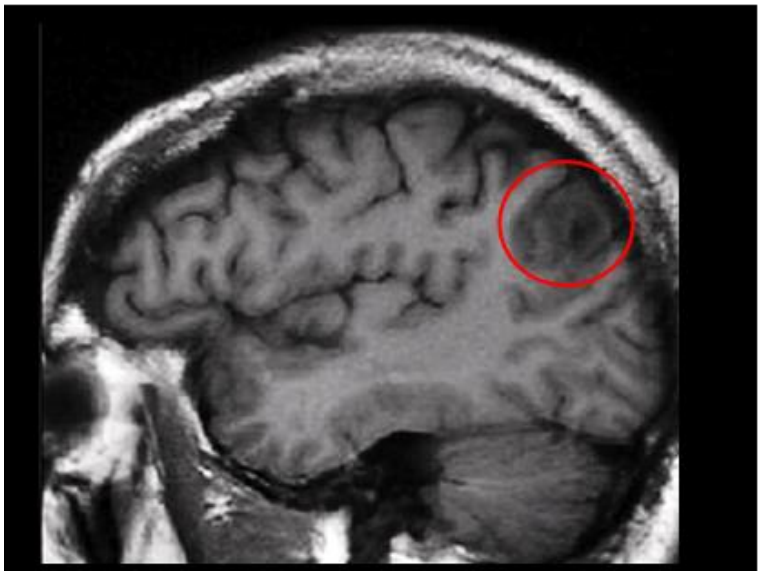

Figure 5.5. Structural Magnetic Resonance Imaging (MRI) of lesions in patient GD. Left parietal mass in angular gyrus (sagittal view).

4.4.2.2. Operation

Two sites in the angular gyrus, one anterior to the tumour and the other inferior to the tumour (**Figure 4.6**) produced language interferences when stimulated. During object naming the patient experienced receptive and expressive difficulties after stimulation of both sites. At both sites, some of the errors and disturbances noted were speech arrest, word-finding difficulties (delay and anomia), complete alexia, inability to follow simple instructions from the neuropsychologist (e.g., *"squeeze my hand"*), phonological, semantic, and verbal paraphasia (naming an unrelated object - *"omelette"*) when trying to name objects. GD also perseverated words including a recurrent perseveration of a previous verbal error (*"omelette")* when attempting to form a sentence. Further stimulations of a site in the angular gyrus posterior-superior to the tumour (**Figure 4.6**) produced speech arrest during both the object naming and present tense ANFV sets of the VAN-POP. No deterioration in language occurred during resection.

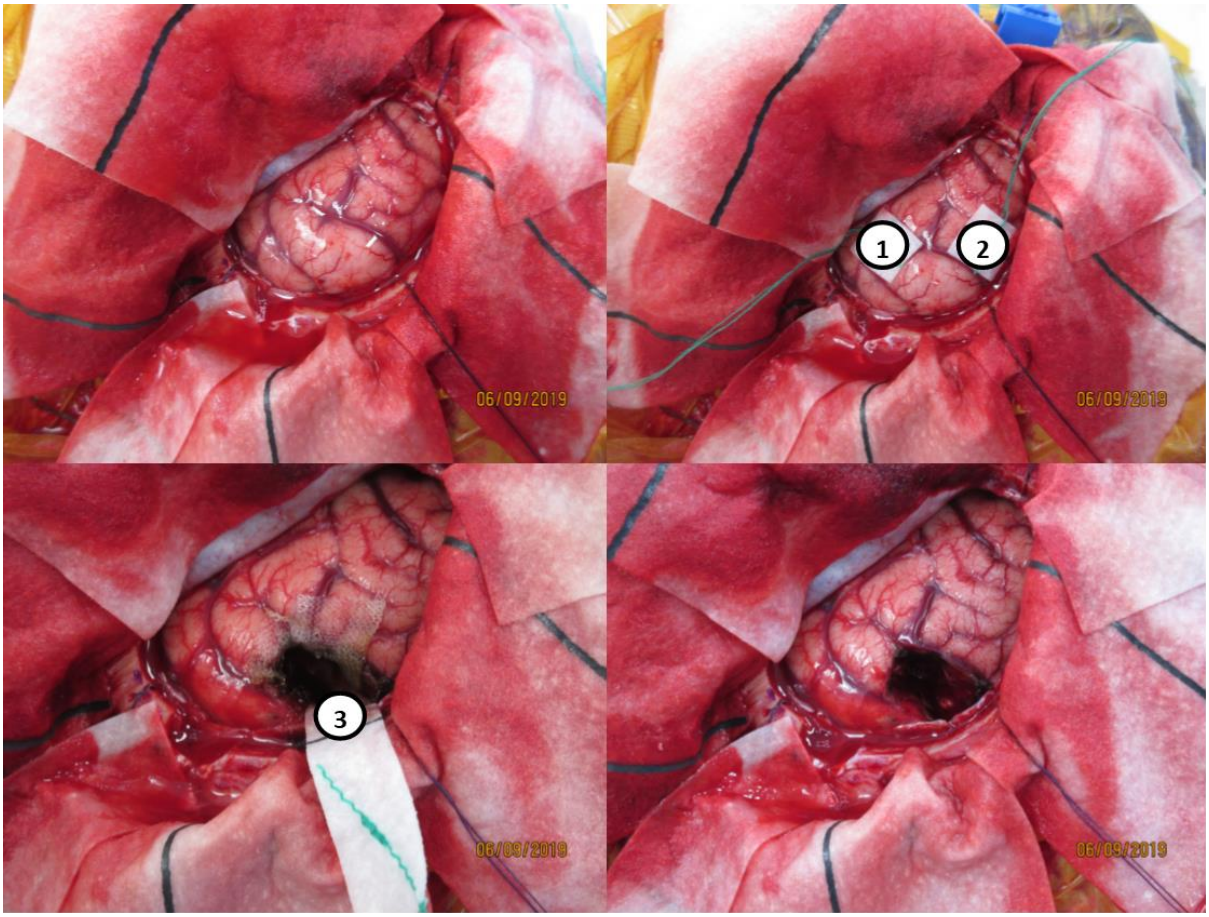

Figure 4.6. Intraoperative photographs (patient GD). Top left: craniotomy exposing part of the parietal cortex including the angular gyrus; top right, two positive language sites around the angular gyrus, one inferior (1) and the other anterior (2) to the tumour location that when stimulated produced expressive and receptive speech and language disturbances during object naming; left, positive language site in angular gyrus posterior-superior to tumour (3) that produced speech arrest when stimulated during object naming and present tense ANFV; bottom right, tumour cavity after debulking to functional boundaries

4.4.2.3. Postoperative course

GD recovered quickly and was discharged four days after surgery with no obvious deficits. Histological examination of the tumour confirmed a low-grade (WHO Grade II) oligodendroglioma and the patient was referred for chemotherapy to treat residual tumour that was unable to be removed due to the identified functional boundaries.

Postoperative neuropsychological assessment three days after surgery showed both improvements and some new errors across certain language domains (**Table 4.1**).

4.4.3. MW

4.4.3.1. Presentation and diagnosis

Patient MW was a 47-year-old right-handed male with 12 years of education, who worked as a Site Manager in a Primary School. The patient, who had no history of epilepsy, experienced a seizure one month prior to diagnosis. He began taking antiepileptic medication and steroids, and underwent further investigation via neuroimaging, although there were no subsequent seizures. The patient was otherwise fit and healthy apart from a history of hypertension, although reported use of an e-cigarette and consumption of around 100 units of alcohol per week. Neuroimaging revealed a left posterior-anterior temporal abnormality suggesting a low-grade glioma (**Figure 4.7**); the patient was referred for an awake craniotomy in September 2019.

Preoperative neuropsychological assessment by the SLT took place three weeks prior to surgery due to postponement of the craniotomy. Assessment did not reveal any major language impairments or motor deficits; however, MW did show a few errors across cognitive and language domains (**Table 4.1**).

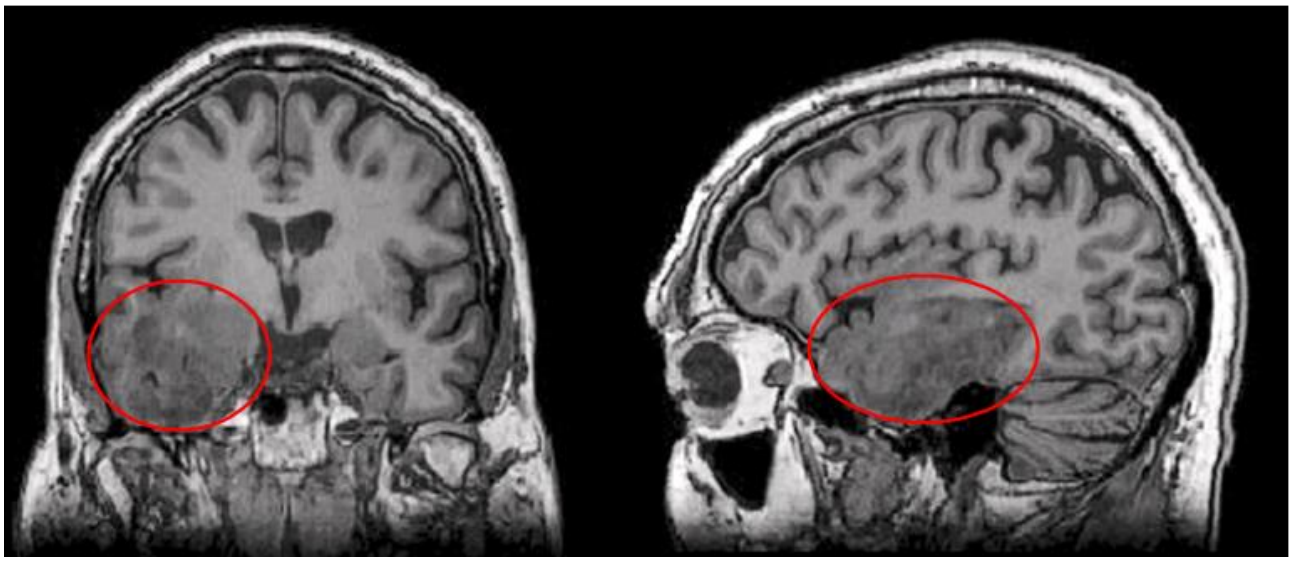

Figure 4.7. Structural Magnetic Resonance Imaging (MRI) of lesions in patient MW. Left temporal mass (coronal and sagittal view).

4.4.3.2. Operation

Stimulation (2-8mA; 60Hz) of the posterior superior temporal gyrus during object naming produced speech arrest and semantic paraphasias (e.g., "*emu"* instead of "*kangaroo"*), as well as an error in describing the colour of the object despite naming the object itself correctly (i.e., the patient said *"red pepper"* in response to a *green pepper*).

During dissection of the posterior superior aspect of the tumour, MW's language was monitored with the past and present ANFV sets of the VAN-POP. The patient made a semantic error in the past tense set similarly to patient RS (i.e., *"yesterday she flowered"*, instead of *"yesterday she watered [the flowers]"*), as well as showing significant response delays. On the present tense set the patient showed some word-finding difficulties (i.e., they reported that they knew what the action was but struggled to recall the verb). MW showed no errors during the automatic speech task. The patient was re-anaesthetised during resection of the tumour and the anterior temporal lobe was removed, although the posterior tumour portion was left intact due to removal being high risk for language impairment.

4.4.3.3. Postoperative course

Postoperative imaging suggested a resection rate of 85-90%. Although the working diagnosis was low-grade, the histological examination of the extracted tumour revealed a higher grade anaplastic oligodendroglioma (WHO Grade III), and the patient was referred for chemotherapy and radiotherapy.

Neuropsychological assessment 24 hours postoperatively found no major language impairments and performance was largely similar to the preoperative assessment; however, MW improved on some cognitive and linguistic domains (arithmetic, comprehension of spoken words, comprehension of spoken sentences), and showed some new errors on others (comprehension of written words, comprehension of written sentences), that were not apparent

preoperatively (**Table 4.1**). It was not clear at this point whether errors may have resulted from the resection of the anterior temporal lobe, or the acute effects of undergoing surgery (e.g., brain swelling, anaesthesia, fatigue etc.).

4.4.4. JLR

4.4.4.1. Presentation and diagnosis

JLR was a 28-year-old right-handed female with 14 years of education who worked as a Barista in a coffee shop but at the time of recruitment was on maternity leave. Shortly after giving birth in hospital, the patient began experiencing seizures, leading to neurological investigation. MRI revealed a large left frontotemporal tumour (**Figure 4.8**). The patient was submitted for surgery in January 2020.

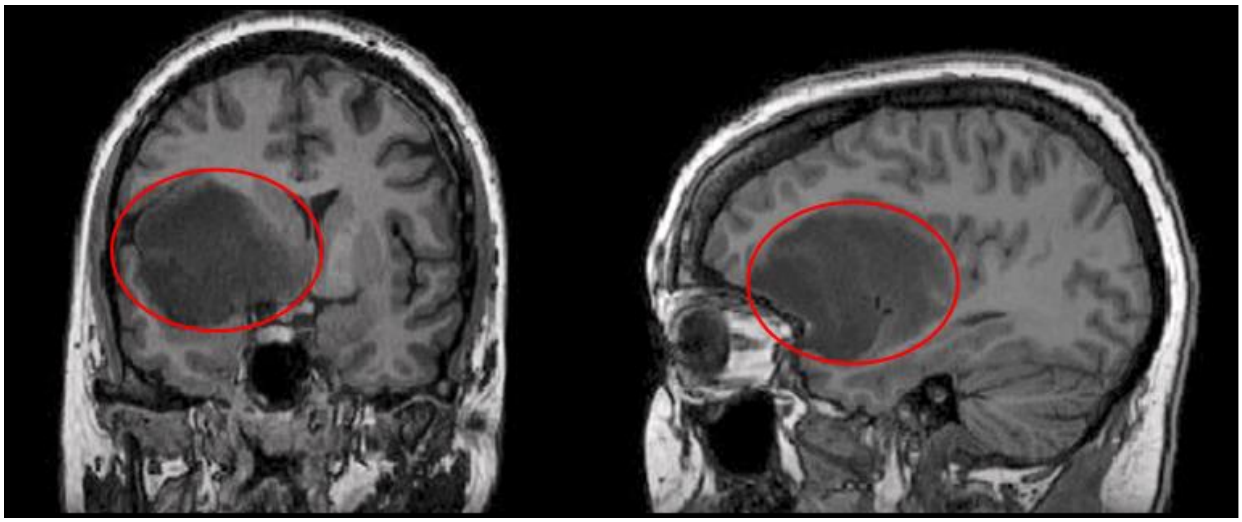

Figure 4.8. Structural Magnetic Resonance Imaging (MRI) of lesions in patient JLR. Left frontotemporal mass (coronal and sagittal view).

Preoperative language assessment one week before surgery identified some errors across a variety of language components suggesting mild aphasia (**Table 4.1**). Difficulties were prominent during object naming which required the use of phonological cueing at times, and during picture description where the patient showed repetition of information despite language structure appearing intact.

4.4.4.2. Operation

Stimulation of sites in the superior temporal region during counting did not produce any interference. Administering further tests during mapping was not possible as the patient was uncooperative due to possible fatigue and analgesic effects. However, during dissection of this region the patient showed several disturbances and errors across different tasks. During object naming she produced word-finding difficulties (delays and anomia) and semantic errors (e.g., "*ostrich"* instead of "*peacock"*, "*moustache"* instead of "*beard"*). During present tense action naming JLR made semantic errors (e.g., *"he raises his hands"* instead of *"he waves"*). On the past tense ANFV set, the patient made further semantic errors with verbs *("yesterday he sailed"* instead of *"yesterday he surfed"*).

4.4.4.3. Postoperative course

Postoperative language assessment showed both improvement and worsening of language problems across several domains (**Table 4.1**); the object naming difficulties remained. Histological examination revealed a high-grade (WHO grade III) oligodendroglioma and the patient was referred for chemotherapy and radiotherapy.

Category	*RS*		*GD*		*MW*		*JLR*	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Semantic memory	9/10	9/10	10/10	10/10	10/10	10/10	9/10	9/10
Word fluency	30	28	53	68	-	-	13	17
Recognition memory	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Gesture object use	12/12	12/12	12/12	12/12	12/12	12/12	12/12	12/12
Arithmetic	6/6	6/6	4/6	6/6	4/6	5/6	5/6	6/6
Spoken word comp	30/30	30/30	30/30	30/30	26/30	30/30	26/30	28/30
Spoken sentence comp	31/32	32/32	30/32	32/32	30/32	32/32	30/32	26/32
Spoken paragraphs comp	4/4	4/4	4/4	4/4	4/4	4/4	3/4	4/4
Written word comp	27/30	26/30	30/30	30/30	30/30	29/30	26/32	28/30
Written sentence comp	32/32	32/32	30/32	26/32	32/32	31/32	24/32	26/32
Word repetition	32/32	32/32	32/32	32/32	32/32	32/32	32/32	32/32
Complex word repetition	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Non-word repetition	10/10	10/10	10/10	10/10	9/10	9/10	10/10	10/10
Digit string repetition	12/14	12/14	14/14	14/14	12/14	12/14	14/14	14/14
Sentence repetition	12/12	12/12	12/12	12/12	12/12	12/12	12/12	12/12
Naming objects	46/48	45/48	48/48	48/48	48/48	48/48	42/48*	41/48*
Naming actions	8/10	8/10	10/10	10/10	10/10	10/10	10/10	10/10
Spoken picture description	N	N	N	N	N	N	MA*	N
Reading words	48/48	48/48	48/48	48/48	48/48	48/48	46/48	46/48
Reading function words	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Reading complex words	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Reading non-words	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Writing-copying	-	-	27/27	27/27	27/27	27/27	27/27	27/27
Writing picture names	-	-	21/21	20/21	21/21	19/21	21/21	21/21
Writing to dictation	-	-	28/28	28/28	27/28	27/28	24/28	24/28
Written picture description	N	N	N	N	N	N	N	N

Table 4.1. Scores for each patient on the Comprehensive Aphasia Test (CAT) at pre- and post-operative (1-3 days after surgery) timepoints. All patients, apart from JLR, performed within the normal range across all subsets and were not deemed to be impaired at the clinical level. N, normal performance. Clinical impairment is marked with an asterisk (*). Phonological cues were used to prompt during difficulties with object naming. MA, mild aphasia – JLR's general language structure was intact although some repetition in picture description.

4.5. Discussion

The present study assessed, for the first time, the application of the VAN-POP during intraoperative linguistic mapping in English patients with suspected low-grade gliomas. This novel test battery comprising picture naming in sentence context tasks (ANFV and object naming), was delivered during DES mapping and language monitoring during resection, alongside standard tests already in use. Results for each patient were described in terms of the location of stimulation/resection and the types of linguistic disturbances and errors produced. One or more language-positive sites were successfully mapped with DES in all but one case (JLR), using ANFV (RS and GD) or object naming (RS, GD, and MW). Monitoring of

language with VAN-POP detected at least one occurrence of functional deterioration during resection in all but one case (GD) using both tasks. However, monitoring of language through spontaneous speech during conversation, did not indicate any deterioration of language.

The inferior frontal regions were mapped with object naming and ANFV, consistent with H_1 and H_2. Positive language sites were observed in the angular gyrus during object naming and ANFV, consistent with H_3 and H_4. Object naming and ANFV sites were observed either following DES or monitoring during dissection within the superior temporal regions, in accordance with H_5 and H_6. These general findings are consistent with previous awake neurosurgical studies using picture-based action naming and object naming tasks that have successfully mapped regions throughout the cortex (Bello et al., 2008; Havas et al., 2015; Lubrano et al., 2014; Rofes et al., 2015c; Rofes et al., 2017b). The next sections will discuss the findings for each case in more detail and interpret them in relation previous research and neuroanatomical theories surrounding the nature of the verb and noun networks.

4.5.1. The prefrontal cortex

The involvement of middle inferior frontal (Broca's area) and the middle frontal gyri in noun and verb retrieval is well documented, and studies show that in some patients regions can be mapped with either object or action naming tasks (Havas et al., 2015; Lubrano et al., 2014; Ojemann et al., 2002; Rofes et al., 2019; Rofes et al., 2015c; Rofes et al., 2017b). However, other studies have found that the majority of action-specific sites were located in the middle and posterior sections of the middle frontal gyrus, while the inferior frontal gyrus plays host to sites specific to both object and action naming (Havas et al., 2015; Lubrano et al., 2014). While both frontal regions in RS were positively mapped in noun and finite verb tasks, the types of errors produced during the stimulation of each site may reveal more about their underlying subprocesses recruited for the variable demands of each task used.

4.5.1.1. Middle frontal gyrus

Stimulation of the middle frontal gyrus produced a novel grammatical (tense) error during action naming with finite verbs, in which the verb was semantically correct, but was produced in the incorrect tense. Rofes and colleagues were the first to assess ANFV in the frontal cortex, however, the errors and interference types they reported following DES were response latencies, semantic paraphasias and anomias (Rofes et al., 2015c; Rofes et al., 2017b). This novel finding in patient RS may suggest that this area is not just simply involved in retrieval of verbs as a grammatical category, but more specifically supports morphosyntactic processing necessary to produce verbs in the tense appropriate to the sentence.

Damage to frontal structures can induce agrammatic aphasia that is characterised by impaired verb inflection abilities, which may result in poorer performance in verb retrieval compared to nouns during spontaneous speech (Valinejad, Mehri, Khatoonabadi, & Shekari, 2022). However, it is not necessarily the inability to retrieve verbs that results in agrammatic responses, rather the inability to produce the verb in the correct inflected form, causing the completed sentence to be grammatically incorrect. For example, Druks and Carroll (2005) reported a post-stroke aphasic patient who was impaired in producing past tense, relative to present tense verbs, due to the inability to inflect the verb in the past tense. Therefore, it is possible that such patients may show normal performance on standard action naming tasks using infinite verbs, where the inflection of verb tense is not required for the task, however, it remains unknown whether this would have been the case in the present patient.

While the observation of semantic paraphasia during object naming in the middle frontal gyrus implies the region's involvement in semantics, components of the noun and verb networks may be functionally segregated, without being completely anatomically segregated (Crepaldi et al., 2011). This raises the question of why semantics was disrupted during object naming (semantic error), but not ANFV (grammatical error) following stimulation of the

middle frontal gyrus. A possible explanation is that noun and verb semantics are spatially separable. Considering the anatomical distribution of noun and verbs, the location of semantic representations may be driven by factors such as age of acquisition and imageability (Colombo & Burani, 2002; McDonough, Song, Hirsh-Pasek, Golinkoff, & Lannon, 2011). Verb and noun concepts are acquired at different stages of development and therefore their cortical representations may differ, particularly as the lexico-semantic processing of action verbs is reliant on embodied motor representations (Andres, Finocchiaro, Buiatti, & Piazza, 2015; van Dam et al., 2010).

4.5.1.2. Inferior frontal gyrus

Interference was observed during ANFV (verbal and semantic paraphasia) and object naming (speech arrest, semantic paraphasia and anomia) following inferior frontal gyrus stimulation; this was consistent with findings from Rofes and colleagues (Rofes et al., 2015b; Rofes et al., 2019; Rofes et al., 2015c; Rofes et al., 2017b). Furthermore, the neuropsychological literature shows that agrammatic aphasics typically present with lesions in inferior prefrontal regions (Shapiro & Caramazza, 2003), and grammatical processing is consistently linked with inferior frontal gyrus activation in fMRI studies (Bulut, 2022; Crepaldi et al., 2013; Rogalski et al., 2011). Moreover, various white matter pathways have been shown to be implicated in grammatical processing (Akinina et al., 2019). This includes association fibres connecting Broca's and supplementary motor areas (the frontal aslant tract), which has been mapped as a subcortical substrate of grammatical abilities during verb generation and sentence production (Chernoff, Sims, Smith, Pilcher, & Mahon, 2019; Sierpowska et al., 2015).

Interference during ANFV suggests this area may play a role in grammatical processing, however, a variety of errors were observed following DES, including semantic paraphasia, anomia and speech arrest. It is difficult to decipher whether interference arose from grammatical, semantic, or phonological disruption, unlike the tense errors arising at the middle

frontal gyrus, which were more suggestive of agrammatism. In particular, the semantic paraphasia observed within pars triangularis was the direct opposite of the tense error observed within the middle frontal gyrus, whereby the response was correctly inflected to the past tense, but the verb produced was semantically incorrect ("She flowered" instead of "She watered [the flowers]"). This could suggest that while the ability to inflect the verb to the past tense remained intact, semantic retrieval of the correct verb (watered) was impaired. A simple explanation may be owed to the idea that nouns are more ingrained in the semantic system than verbs (Colombo & Burani, 2002; McDonough et al., 2011); accordingly, the patient may have been able to access and retrieve the object concept more quickly, which may have led to the substitution of the noun for the verb, and subsequent inflection. However, when exploring the nature of this error in more detail, the underlying mechanism may actually be more complex; potentially reflecting an impairment in the production of verb phrase structures for transient verbs (Thompson & Meltzer-Asscher, 2014). The past tense verb "watered" is a transitive verb and must be accompanied by two arguments (the agent [She] and the theme [the flowers]) and produced as a noun phrase to be considered grammatically correct, i.e., "She watered the flowers". Building these verb phrase structures is thus more linguistically complex in comparison to intransitive verbs, e.g., "She cries", that only require one argument (She). A body of neuroimaging studies have demonstrated increased activation in areas including the inferior frontal gyrus for transitive verbs relative to intransitive verbs (for a review see Friederici, 2011; Friederici, 2017). This is consistent with the post-stroke aphasia literature which shows that agrammatic patients, who commonly have lesions to the inferior frontal regions, present with greater impairments in producing transitive or ditransitive over intransitive verbs (Dragoy & Bastiaanse, 2010; Thompson, Lange, Schneider, & Shapiro, 1997); the difficulty of which tends to increase as a function of the number of arguments required (Kemmerer & Tranel, 2000; Kim & Thompson, 2000, 2004). Thompson and Meltzer-

Asscher (2014) suggested that the inferior frontal cortex may be recruited for accessing verb argument structure necessary for phrase structure building that precedes sentence construction. This notion is further supported by recent evidence from nTMS in both glioma patients and healthy subjects (Ntemou et al., 2021; Ntemou et al., 2023a), which demonstrates that temporary suppression of this region induces more errors for transitive over intransitive verbs. Furthermore, excitatory stimulation of inferior frontal cortex induced through Transcranial Direct Current Stimulation (tDCS) has a facilitatory effect on accuracy for transitive over intransitive verbs (den Ouden & Zhu, 2022). Therefore, in the present case, resection within the inferior frontal gyrus may have prevented access to knowledge of phrase structure, impairing the ability to build the phrase and in turn, construct the sentence. While this error was identified by the neuropsychologist as a semantic paraphasia, in the context of the above literature, it is possible that the error may have occurred due to a disruption of the syntactic system rather than semantics; hence semantic retrieval of the object concept (flower) pertaining to the noun phrase remained intact but was produced in a syntactically incorrect position within the sentence.

Furthermore, the nature of the patient's error may also be further considered within the context of a neurocomputational model that proposes two interconnected systems: hierarchical structuring and morphosyntactic linearisation (Matchin & Hickok, 2020). According to this model, in production tasks such as past tense ANFV, the visual representation of an action may access and retrieve lexico-syntactic information from distinct hierarchical systems pertaining to *event knowledge* and entity *knowledge* within the temporal regions. Therefore, at the initial conceptual level, lexico-syntactic knowledge is not accessed in a serial fashion (i.e., the woman > the watering can > the flowers), but rather in terms of a hierarchical structure of knowledge concerning the individual linguistic components within each argument of the sentence (e.g., the noun phrase (she); and the verb phrase (verb [watered] and noun phrase [the flowers])).

Therefore, linguistic output processes require hierarchical lexico-syntactic information to be transformed into sequential morphemes via a linearisation process. Matchin and Hickok (2020) proposed that the pars triangularis of the inferior frontal gyrus may govern this process given it's consistent role in sentence production tasks (for a review see Meyer & Friederici, 2016), suggesting that in the present case of RS, resection of the pars triangularis, may have resulted in a failure of linearisation of the verb phrase. In turn, according to the model, this failure of linearisation would lead to the production of an incorrect sequence of morphemes, and therefore in the present case caused the noun to be substituted for the verb.

When interpreting patterns of impairment, it is important to consider differences between patients with different neurological lesions, and cortical degeneracy which may a play a role in how various functions are organised within the brain (Price & Friston, 2002). In patients with slow-growing masses such as low-grade gliomas, the organisation of language may be atypical in comparison to the healthy brain and other neuropathologies (e.g., stroke), due to preoperative plasticity. For example, there may be multiple neurocognitive systems in place for completing a given task, consequently, when one component within a preferred network becomes damaged, other back-up regions can be recruited for processing (Price and Friston (2002). A classic example of this is reading according to the dual-route cascaded model, in which the processing of regular words is possible via two separate routes should one becomes dysfunctional – the non-lexical (grapheme-phoneme conversion) and lexical route (Coltheart et al., 2001). As is mentioned in patient RS's case report, the progression of the patient's tumour was being monitored for two years prior to surgery, during which time the gradual infiltration of the tumour within Broca's area may have caused a shift in functioning towards neighbouring frontal regions that are also equipped for linguistic (grammatical) processing, such as middle frontal gyrus.

Whilst speculative, this view does stress the importance of acknowledging compensatory structure-function changes in patients with evolving lesions, particularly when delivering more concise anatomically targeted assessment. Fortunately, the regions in question were detectable with a range of tasks used and there was no risk of false negative mapping.

4.5.2. The parietal cortex

4.5.2.1. Angular gyrus

As identified in Chapter 2, the angular gyrus has been mapped with a variety of language tasks including object, face, and colour naming, sentence completion, reading, writing, semantic association, and repetition, as well as other cognitive tasks such as calculation, mentalising, and short-term memory. Although previous intraoperative studies have not mapped the angular gyrus with action naming tasks, the neighbouring supramarginal gyrus has shown to be an action naming site suggesting there may be some overlap in function (Lubrano et al., 2014). However, it is argued that the angular gyrus, within the inferior parietal region, is a crucial node in the network for verb processing (Crepaldi et al., 2011; Matzig et al., 2009; Vigliocco et al., 2011). Some neuroimaging studies have demonstrated greater activation for verbs compared to nouns (Berlingeri et al., 2008; Fujimaki et al., 1999; Perani et al., 1999; Saccuman et al., 2006; Shapiro, Moo, & Caramazza, 2006). Further, patients with lesions to inferior parietal region have shown selective difficulties with verbs (Aggujaro et al., 2006; Tomasino et al., 2019; Tranel, Manzel, Asp, & Kemmerer, 2008). The present study has, for the first time, found both ANFV and object naming during stimulation of the angular gyrus which induced speech arrest and other interferences. Like other linguistic tasks such as object naming and reading, ANFV has also been able to detect speech output disruption in this parietal region. Moreover, all the error types observed were consistent with those reported in studies summarised in the review. The diverse nature of ANFV in terms of the range of linguistic functions it can detect, allows it to be applied in a variety of regions including the angular

gyrus. Therefore, in line with the literature elucidating the role of inferior parietal involvement in verbs and mapping of angular gyrus sites in the present study, clinicians may wish to incorporate this task into intraoperative testing for parietal patients.

4.5.3. The temporal cortex

4.5.3.1. Posterior superior temporal gyrus

Consistent with previous mapping studies in the superior temporal regions, the object naming task detected speech arrest and semantic paraphasia in patient MW. Interestingly, although the object naming task did not require them to name the colours of the objects, the set that was already in use as part of the standard protocol contained coloured stimuli, as opposed to the black and white drawings of the VAN-POP. The patient incorrectly named the colour of the object ("red pepper", when the object was a green pepper).

Disturbances in colour naming during DES of the posterior superior temporal gyrus has previously been reported (Roux et al., 2003a) although colour anomia is more common in patients with damage to occipital-temporal areas (Damasio & Damasio, 1983). Colour naming has not been extensively examined during awake craniotomy with only two studies identified in Chapter 2 (Roux et al., 2003a; Roux, Lubrano, Lauwers-Cances, Mascott, & Demonet, 2006). Data from patient MW demonstrates that object naming tasks may be able to double as colour naming tasks – requesting the patient to name the colours of the objects, either independently or as part of naming the objects. This would be useful, both for collecting additional data on the neural correlates of object naming, but also for improving mapping by testing for additional naming functions that may be overlooked by standard object naming.

The VAN-POP was not used for mapping in MW; however, it was used for monitoring during resection in the posterior superior temporal regions. Interestingly, the same semantic error was observed during past tense ANFV as in the frontal patient, RS, ("she flowered",

instead of "she watered [the flowers]"), as well as word-finding difficulties on the present tense set. Semantic paraphasia has been widely observed during object naming in the posterior superior temporal gyrus (Chan-Seng, Moritz-Gasser, & Duffau, 2014; De Benedictis et al., 2014; Duffau et al., 2004; Lubrano et al., 2014; Mandonnet et al., 2007; Robles et al., 2008; Sarubbo et al., 2012; Tate, Herbet, Moritz-Gasser, Tate, & Duffau, 2014). Lubrano and colleagues (2014) also observed semantic paraphasia during action naming in this region, consistent with the findings. However, as discussed previously in relation to patient RS, while categorised clinically as a semantic paraphasia, this identical error in MW may have arisen due to an impairment in the mechanisms underlying the production of transitive verbs – verb argument structure (Thompson & Meltzer-Asscher, 2014). In addition to inferior frontal regions, neuroimaging evidence demonstrates that the posterior perisylvian regions, including the superior temporal gyrus, are activated for transitive over intransitive verbs, suggesting involvement in processing and integrating verb argument structure required for sentence production (Meltzer-Asscher, Schuchard, den Ouden, & Thompson, 2013; Shetreet, Palti, Friedmann, & Hadar, 2007). The fact that the same error was produced during resection of both frontal and temporal tumours provides further evidence to the contrary of a frontal-temporal dichotomy for nouns and verbs (Crepaldi et al., 2011; Matzig et al., 2009; Vigliocco et al., 2011). It may also further suggest a dispersed network of regions that interact to support the integration of noun and verb arguments for sentence production (Matchin & Hickok, 2020; Walenski, Europa, Caplan, & Thompson, 2019).

As described previously in relation to RS, the neurocomputational model proposed by Matchin and Hickok (2020) may attempt further explain why this error occurred during resection in the inferior frontal gyrus; however, in the case of the superior posterior temporal resection in patient MW, the model may not be strictly applied, anatomically speaking. According to the model, frontal and temporal subdivisions of the language network

interconnect to give rise to syntax by way of two distinct processes: syntactic linearisation and hierarchical phrase structuring, respectively. Concerning production tasks, it is postulated that these processes are subserved by the interplay between the posterior middle temporal gyrus and the inferior frontal gyrus, connected via the arcuate fasciculus (Yagmurlu, Middlebrooks, Tanriover, & Rhoton, 2016). The posterior superior temporal gyrus is reserved for auditory comprehension in terms of relaying phonological representations for decoding within the middle temporal gyrus (Hickok & Poeppel, 2007); accordingly, the superior temporal region is deemed to serve no function in syntax, at least for sentence production. These neurocognitive systems proposed are consistent with meta-analytic evidence showing that the posterior middle temporal region (but not the superior temporal region), is implicated in production tasks (Walenski et al., 2019). Notwithstanding, the relevance of the superior temporal regions may be further understood in relation to syntactical processing within comprehension tasks. Matchin, Hammerly, and Lau (2017) argued that while the superior temporal regions may not be essential to syntactic processing, the superior temporal sulcus may be specifically recruited for top-down support in simple sentence processing. Moreover, Lopopolo, van den Bosch, Petersson, and Willems (2021) also implicate the superior temporal gyrus in an ancillary capacity for phrase-structure processing, to which they further suggest may be interconnected with syntactic functions of the inferior frontal gyrus (for a review see Meyer & Friederici, 2016). However, these neuroanatomical structure-function associations of sentence comprehension may not necessarily translate to the differential processes driving sentence production; Matchin and Hickok (2020) discuss the structural and functional asymmetries of syntactic processes between comprehension and production. The computational task in sentence production is to access and retrieve ingrained phrase structure knowledge and linearise the information to form a sequence of morphemes for articulatory/phonological output processes. For sentence comprehension, on the other hand, phonological or visual phrase

structure information transduced through the auditory or visual modalities is decoded hierarchically and relayed to conceptual networks to be processed within the context of entity and event knowledge. Therefore, in terms of this neurocomputational model, the posterior superior temporal gyrus is not required for accessing hierarchical phrase structure knowledge for sentence production.

However, concerning gliomas, this model might be applied more loosely in terms of neuroanatomy given that preoperative structural damage may provoke functional reorganisation of language (Duffau, 2005; Ho et al., 2021; Piai, 2019). In the case of MW, the tumour was considerably large and in addition to the superior temporal gyrus, also infiltrated the anterior and posterior segments of the middle and inferior temporal lobe. Owing to potential preoperative neuroplastic changes, it is possible that syntactic functions initially ascribed to the posterior middle temporal portion may have shifted upwards to the remaining healthy tissues in the posterior superior temporal gyrus. Therefore, based on this notion, the posterior superior temporal gyrus may have assumed the role of the posterior middle temporal gyrus in hierarchical lexico-syntactic retrieval. Damage to posterior temporal structures is known to produce grammatical deficits (Wilson, Eriksson, Schneck, & Lucanie, 2018; Wilson, Yen, & Eriksson, 2018; Yagata et al., 2015). Therefore, resection of the superior temporal area in patient MW may have resulted in an error of verb phrase structure, rather than semantics. While the linearisation process of the inferior frontal cortex would have remained intact, failure of the hierarchical system to retrieve and relay the verb to frontal structures would mean that only the available morphemes could be linearised. In other words, as the noun phrase (the flowers) was the next morpheme in the sequence after the verb (to water) was omitted, the noun (flower) would have taken the position of the verb in the sentence. Matchin and Hickok (2020) suggest that because lexical and syntactic systems are intertwined within the posterior temporal cortex, impairment of lexico-syntactic retrieval can result in lexical substitutions, which have also been

observed in the case of paragrammatical speech in fluent aphasia (Bastiaanse, Edwards, & Kiss, 1996; Casilio, Rising, Beeson, Bunton, & Wilson, 2019). Therefore, in the present patient, the error may not be dichotomously categorised as either a semantic or syntactic disruption; rather, the error may be both lexico-semantic and lexico-syntactic in nature, reflecting a retrieval failure within a shared lexico-syntactic system.

4.5.3.2. Anterior superior temporal gyrus

JLR produced word-finding difficulties and semantic errors during object naming, although this disturbance was observed during dissection, rather than stimulation of the anterior temporal gyrus (De Witte & Marien, 2015; Riva, Casarotti, Comi, Pessina, & Bello, 2016a; Rosenberg et al., 2008; Roux & Tremoulet, 2002). Disruptions were also observed during ANFV in the form of semantic errors for verbs, suggesting that this region played a role in retrieval of both verbs and nouns. Similarly, as in patient MW, production of verb tense remained intact, while the semantic content of the verb was incorrect. Within the anterior temporal lobes of these patients, it appeared that impaired semantics during mapping/monitoring was affecting both noun and verb production.

This region has been proposed as a transmodal semantic hub for integration of conceptual information that is relayed from modality-specific association cortex (Farahibozorg, Henson, Woollams, & Hauk, 2022; Patterson, Nestor, & Rogers, 2007; Patterson & Ralph, 2016). While such semantic errors can be detected with object naming tasks alone, using the ANFV tasks in the anterior temporal lobe may be important for mapping grammatical sites. While this did not seem evident in the present patient cases, it is possible that the anterior temporal lobe may play a role in grammatical processing. One study found that following rTMS, there was a selective delay in the ability to produce irregular past tense verbs (Holland & Lambon Ralph, 2010). In the present study, however, regular, and irregular items were not directly compared during the ANFV task.

4.5.4. Limitations, future directions, and conclusions

Although the collaborating neurosurgical team and clinicians welcomed this research involvement, control over many aspects of the intraoperative mapping and monitoring protocol was limited, as was the data available. For example, the attending clinicians who primarily delivered tasks already had an established protocol containing tests they found useful for mapping. While they did understand the value of the more comprehensive testing and agreed to incorporate the VAN-POP battery into their protocol, they did not wish these to replace their current "standard" tasks. Adding more tasks to the protocol created a dilemma for the surgeons, who were conscious of increasing mapping time to accommodate retesting of each site for each task in the protocol. This meant sites were not always mapped using both object and ANFV tasks, or indeed both subsets of ANFV (past and present), making it difficult to directly compare their use at a particular site, in all cases. Furthermore, the contribution of spontaneous speech monitoring through conversation during resection was not able to be thoroughly considered. Patients did not show any deterioration that was detectable through their spontaneous speech, however, this may have been due to the fact that conversation was only used intermittently, primarily to maintain the patients' engagement and provide reassurance in between the delivery of tasks.

Given the restrictive conditions within which the study was conducted, valuable data has been collected which has yielded novel findings that have further contributed to the complex field of language testing in awake craniotomy. This study has expanded on the previous work by Rofes and colleagues (Rofes et al., 2015b; Rofes et al., 2019; Rofes et al., 2015c; Rofes et al., 2017b), by not only introducing the VAN-POP into a UK NHS neurosurgical theatre, but also applying it to temporal and parietal tumour patients. The VAN-POP was easily incorporated into the awake protocol, suggesting that this test battery can be

rolled out for use with frontal, temporal and parietal low-grade glioma patients undergoing awake craniotomy in neurosurgical centres both nationwide and worldwide.

Future research should aim to pool the intraoperative data collected using this battery to gain a better understanding of the regions it can identify, and the types of disturbances/errors produced. Experimental approaches may wish to directly compare the VAN-POP with other tasks in different regions, to gain a quantitative understanding of how well these tasks perform on a region-by-region basis, as well as exploring the impact of psycholinguistic factors in particular regions (e.g., verb regularity distinctions in the anterior temporal lobe).

4.6. Chapter summary

The present Chapter has explored the use of the VAN-POP across four patients undergoing awake craniotomy for resection of suspected low-grade gliomas. Errors were observed in all patients during either cortical mapping, monitoring, or both; in particular, a novel grammatical error was observed in the frontal patient, in which DES of a site located in the middle frontal gyrus during ANFV caused the verb to be produced in the incorrect tense. This grammatical (tense) error was exclusive to the frontal patient, while other patients produced more common errors such as anomia, speech disturbances and paraphasias. However, another novel error was also observed in both the frontal and temporal patients, which although was coded by the neuropsychologist as a semantic paraphasia, may have been grammatical in nature. Chapter 4 comprises an experimental study in which the VAN-POP was adapted for use as a set of speeded naming tasks. Reaction times and accuracy were explored across three timepoints, preoperatively, postoperatively and at 3-month follow-up and compared with the performance of healthy control groups.

Chapter 5: Postoperative language changes following awake craniotomy for glioma resection: examining lexical retrieval speed and accuracy in object naming and action naming with finite verbs

5.1. Chapter overview

Chapter 3 explored the implementation of the VAN-POP in awake craniotomy for resection of low-grade glioma and was demonstrated to be a valuable addition to the awake protocol (Ohlerth et al., 2020). The present chapter describes the adaptation of the VAN-POP as a pre- and post-operative assessment tool for monitoring linguistic changes in lexical retrieval. The object naming and ANFV (past and present tense) tasks were modified for use as computerised naming tests measuring accuracy and reaction time. In a case-control study of three glioma patients from Chapter 3 (RS, GD, MW), VAN-POP performance was compared to healthy controls at three timepoints: preoperative, postoperative (2-4 weeks) and follow-up (3-months). This study further evaluates the glioma language profile and for the first time, reports data on postoperative changes in lexical retrieval speed and accuracy on linguistically complex tasks that assess morphological production abilities.

5.2. Introduction

Awake surgery for low-grade gliomas has received recent attention from clinicians and scholars to update and optimise intraoperative language mapping protocols in line with current perspectives in functional neuroanatomy and the specific needs of the patient (De Witte & Marien, 2013; De Witte et al., 2015b; Rofes et al., 2017a; Rofes & Miceli, 2014; Rofes et al., 2015c). However, there remains a lack of in-depth understanding regarding postoperative linguistic changes and the variable patterns of impairment that emerge from different lesion locations, in the acute and longitudinal recovery phases.

Pre- and post-operative language profiles of glioma patients are typically assessed using materials that have been developed specifically for the purpose of post-stroke aphasia. Whilst the discrepancies between language impairments in stroke versus tumour patients have not been extensively examined, the underlying differences in terms of the nature of the lesions suggests that the two groups may present with distinct language profiles (Anderson et al., 1990; Duffau et al., 2008; Satoer et al., 2013) .

Low-grade gliomas are slow-growing masses that develop from mutations in the glial cells of the brain, causing gradual shifts in the organisation of language function (Duffau, 2005; Ho et al., 2021; Piai, 2019; Price & Friston, 2002). As the tumour expands and perilesional tissue becomes damaged, recruitment of neighbouring, or more remote regions, may compensate for functional loss, although the mechanism for how this occurs remains unknown. A case study of a tumour in the left frontal lobe of a right-handed patient with presumed left-lateralised language function (Fisicaro et al., 2016), illustrates how the linguistic functions of Broca's area can be assumed contralesionally (i.e., the right inferior frontal lobe). While gliomas commonly develop in the frontal lobe near Broca's (approximately 40%), they also develop in other cortical (temporal, 29%; parietal, 14%; occipital, 3%) and subcortical (14%) regions supporting language function, including Wernicke's (Larjavaara et al., 2007), which may also be subject to functional reorganisation. Regardless of where linguistic functions may relocate, the process of plasticity aims to preserve language and in many cases impairment may only be subtle (e.g., mild anomia), or may appear non-existent (Anderson et al., 1990; Duffau et al., 2008).

Structural damage from a stroke is typically sudden and more extensive, affecting a larger portion of the brain. This often results in severe and widespread language impairments including expressive and/or receptive aphasia. In contrast, even when gliomas are similar in size and location to stroke lesions, the resulting language impairments are generally less severe

(Anderson, 1990). A recent study comparing language profiles in stroke and glioma patients found that post-stroke impairments are usually selective, affecting specific linguistic components such as phonology. In contrast, post-surgical glioma impairments often manifest as moderate global aphasia or generalised decline of language processing abilities (Zyryanov et al., 2022). Although there is much to learn about the functional differences between stroke and low-grade glioma profiles, these distinctions suggest that pre- and post-operative assessment and treatment in low-grade glioma should be approached independently from stroke aphasia.

Neuropsychological batteries used to assess post-stroke language status are often based on classical models of aphasia syndromes (Tremblay & Dick, 2016). Consequently, the generalised language impairment observed in glioma patients may not be interpreted as being as severe as a dissociation of language function in stroke. Brownsett et al. (2019) compared the performance of glioma patients on the Western Aphasia Battery (WAB) and the Comprehensive Aphasia Test (CAT), finding that patients who were regarded as unimpaired on the WAB, produced language errors on the CAT. Whilst it was apparent from Chapter 4 that some of the awake patients made a small number of errors across several domains (often anomic) in the postoperative CAT, these impairments were not deemed severe by clinical standards to require speech and language therapy. Indeed, apart from JLR, all patients were deemed clinically unimpaired.

Routine pre- and post-operative linguistic assessments typically focus on accuracy, potentially missing subtler lexical retrieval deficits that manifest as processing delays. However, glioma patients who self-report word-finding problems often do not show significant error production during formal clinical testing (Brownsett et al., 2019; Satoer et al., 2012). In a recent study, while 58% of the patient group reported word-retrieval problems, there was no correlation with a reduced accuracy on a sentence judgement task (Mooijman et al., 2021).

When considering slowed reaction times as a measure of language abilities, a significant association emerged. This suggests that including reaction time as a measure of task performance may be important for diagnosing subtler pre- and post-operative language (and potentially other cognitive) impairments in glioma patients. The present study will explore the importance of this largely unexamined facet of the glioma language profile.

From a clinical standpoint, reduced lexical retrieval speed may not be as functionally detrimental as more severe aphasic disorders, since general communicative abilities appear to remain intact. However, a recent qualitative study examining long-term language experiences reported that postoperative glioma patients often felt frustrated with their communication abilities, which require greater effort than before treatment (Ake et al., 2023). Even minor cognitive impairments can significantly impact an individual's ability to perform their job, partake in hobbies, engage socially, and so on, thus reducing quality of life. Moritz-Gasser et al. (2012) found that that reaction time, not accuracy, in object naming tasks was the best predictor of a patients' ability to return to work. This is supported in a systematic review by Pascual and Duffau (2022) who found that slower lexical retrieval speed was correlated negatively with the ability to return to work.

Extended periods of absence from work can impact on quality of life due to a variety of factors including changes to lifestyle (e.g., reduced exercising), and emotional/mental health problems due to boredom and reduced social contact (Vingård, Alexanderson, & Norlund, 2004). There may also be a significant impact on personal finances due to reduced income, as well as future earning potential resulting from missed career advancement opportunities. There may also be financial impact due to reduced income and missed career advancement opportunities. The impacts are often more significant for low-grade glioma patients who are generally diagnosed between their 20s and 40s, with a mean age of 41), a period where many are in early-mid stages of their careers (Claus et al., 2015). Conversely, stroke patients, with a

mean age of diagnosis approximately 69, are typically nearing retirement or already retired (Kissela et al., 2012). Younger patients are often building careers and raising families, so even subtle cognitive impairments may have a considerable impact on quality of life. A recent systematic review found that cognitive functioning in glioma patients remains poor over time, particularly among those with low-grade glioma (Rimmer et al., 2023).

Linguistic assessments developed for post-stroke aphasia (e.g., the CAT) may be less suitable for pre- and post-operative assessment in low-grade glioma (Mooijman et al., 2021). These tests need to be adapted to detect the subtler and seemingly milder disturbances in language retrieval abilities. Incorporating measures of reaction time as well as accuracy, may therefore capture a more representative picture of real-world language abilities. Reaction times on productive (object naming) and receptive language tasks (sentence judgement) are significantly slower in preoperative low-grade glioma patients relative to healthy controls (Mooijman et al., 2021; Ras et al., 2020). However, no studies have investigated reaction times on other picture naming tasks, such as action naming, or whether these reaction time impairments improve or decline postoperatively.

In healthy individuals, reaction times in verb production tasks are typically longer than those for noun production (Arevalo, Wulfeck, & Bates, 2002; Szekely et al., 2005), due to verbs' weaker relationship with semantics (van Dam et al., 2010). Moreover, naming actions in the past tense is more linguistically challenging and usually yields longer reaction times, even in healthy participants. Post-stroke aphasic patients, especially those with frontal lesions, often perform worse on verb compared to noun tasks (Crepaldi et al., 2011; Matzig et al., 2009; Vigliocco et al., 2011), and agrammatic aphasics may struggle more with past tense verb retrieval (Bastiaanse et al., 2011; Jonkers & de Bruin, 2009). Some frontal low-grade glioma patients have shown greater impairments in finite verb production accuracy relative to noun production on picture naming (Rofes et al., 2017b). Incorporating ANFV tasks to assess

reaction time as well as object naming will improve the sensitivity of pre- and post-operative testing. Particularly, through the additional assessment of morphosyntactic language components, and also because ANFV performance is strongly correlated with performance in real-world daily communication abilities than object naming (Rofes et al., 2015a).

In Chapter 4, the dual application of object naming and ANFV was explored as part of an intraoperative neurolinguistic mapping protocol during awake craniotomy, with four low-grade glioma patients using the VAN-POP. The present study adapts the VAN-POP for computerised assessment, measuring accuracy and reaction time at various timepoints pre- and post-operatively in three patients from Chapter 3 (RS, GD, MW). Performance of each patient will be compared to a group of age- and education-matched neurologically intact individuals. Changes from preoperative baseline to acute postoperative (2-4 weeks) and follow-up (3-months) will be compared, with additional analysis of impairment patterns across object naming and ANFV tasks, depending on lesion location.

Patients' linguistic performance across the course of surgery and recovery typically follows a V-shape, with normal preoperative function, worsening in the acute postoperative period (first few weeks after surgery) and recovery to near baseline within the follow-up period (3-6 months postoperatively). However, findings by Moritz-Gasser et al. (2012) suggest reduced naming speed, not accuracy, is a better predictor of return to work, suggesting that reaction times may be more impaired than accuracy at follow-up. Similarly, post-stroke aphasia studies highlight that verb tasks are often more impaired than noun tasks, suggesting that the patients in the present study may show greater impairments for verbs, in particular the patient with the inferior frontal lesion (Crepaldi et al., 2011; Matzig et al., 2009; Vigliocco et al., 2011). Furthermore, theories regarding time reference suggest patients may be more impaired on past tense subset of the ANFV task, compared to the present tense subset (Bastiaanse et al., 2011; Jonkers & de Bruin, 2009). Accordingly, while it was expected that patients' language function

would improve at the 3-month follow-up compared to the 1-month postoperative assessment, the degree of impairment at follow-up, relative to controls and preoperative baselines, was expected to vary depending om: (1) the type of performance measure (accuracy vs. reaction time); and (2) the type of language task (object naming, past tense and present tense ANFV). Several hypotheses were formulated in relation to patient performance at follow-up relative to controls and preoperative baseline:

(H_1) patients would be more frequently impaired on reaction time measures than accuracy measures across tasks.

(H_2) patient performance would be more impaired on either one or both ANFV tasks compared to object naming.

(H_3) patient performance would be more impaired on past tense ANFV compared to present tense ANFV.

5.3. Methods

5.3.1. Ethics

Ethical approval for the study was granted by the NHS Health Research Authority as part of the wider NHS project (approval reference number: 15/NW/0461) and also by the University Research Ethics Committee for collection of healthy control data (approval reference number: 23/PSY/067). All participants were provided with information sheets during the recruitment process and given the opportunity to ask questions. All participants provided written consent to participate in the study. Healthy participants received either a £10 or £5 retail voucher (depending upon whether they completed only the VAN-POP or additional tasks as part of a separate study) for their time after completing a single session and patients received a £30 retail voucher after completing testing at preoperative, postoperative and follow-up stages.

5.3.2. Participants

5.3.2.1. Recruitment

Patients

The researcher was notified about eligible patients who were approached with details of the study (supplemented by a patient information leaflet) by their oncology nurse at The Walton Centre NHS Foundation Trust. The researcher attended the preoperative appointment if the patient expressed an interest in participating (with patient consent and clinician approval) and provided further information about the study.

Healthy controls

Healthy participants were recruited in 4 main ways: (1) emails targeted to LJMU students and staff; (2) social media adverts; (3) externally through the LJMU Research Participants Panel - a system in which subscribers of the panel agree to be contacted about studies they may be eligible for; and (4) poster advertisements in the psychology department.

5.3.2.2. Inclusion Criteria

Patients

Individuals were required to be adults (aged 18 or over) with left hemisphere language-infiltrating brain tumours. Patients needed to be at the preoperative stages of treatment and due to undergo an awake craniotomy with DES language mapping.

Healthy controls

Individuals were required to meet the following inclusion criteria: (1) English as a first language; (2) be right-handed; (3) no history of developmental language difficulties (e.g., dyslexia) or acquired brain disorders (e.g., stroke, tumour) that affect cognition or language; and (4) normal or corrected to normal vision and hearing.

5.3.2.3. Demographics

Patients

Patients were three of those detailed in Chapter 4 (RS, GD, and MW), who were undergoing awake craniotomy for excision of suspected low-grade gliomas (WHO Grades I-II) infiltrating anticipated language regions in the left-hemisphere. Patient demographic information is displayed in **Table 5.1**.

Healthy controls

Each patient was matched to an individual group of five healthy controls based on age and level of education. For age, all healthy participants were matched within a six-year range of the patient (+/- 3 years) and each group had a similar mean age to their respective patients. For education level, all subjects were matched exactly to the patient's number of educational years (see **Table 5.1** for details of control samples for each patient across tasks).

Table 5.1: Patient and healthy control characteristics and demographics

	Cases							Control Groups		
	Age	Gender	Handedness	YOE	Lesion (LH)	Language Status (CAT)		Age Range	Mean Age	Mean YOE
						Pre-op	Post-op			
RS	23	Male	Right	17	Frontal	Normal	Normal	21-26	23.20	17.00
GD	39	Male	Right	14	Parietal	Normal	Normal	36-42	37.80	14.00
MW	47	Male	Right	12	Temporal	Normal	Normal	44-50	48.80	12.00

LH, left hemisphere; CAT, Comprehensive Aphasia Test; YOE, number of years of education.

5.3.3. Materials

The Verb and Noun test for Perioperative Testing (VAN-POP)

The VAN-POP comprised three sets of black and white line drawings (400x400 pixels): 50 objects, 23 present tense actions and 27 past tense actions (see **Figure 5.1** for description). All participants received items in the same randomised order (using a random number generator).

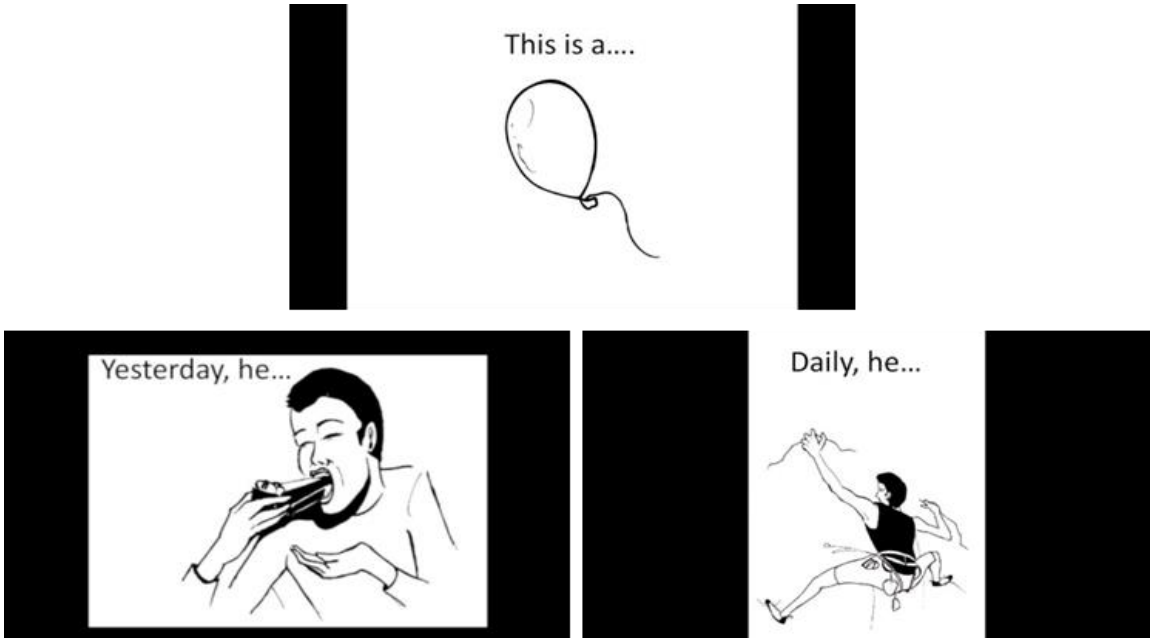

Figure 5.1. Example items from the VAN-POP in which participants are required to name objects or actions on as quickly and as accurately as possible. **Top**: object naming task; participants are required to respond with the correct noun. **Bottom**: past and present tense action naming tasks; participants are required to produce the verb corresponding to the action using the correct inflected form (past or present) as indicated by the introductory sentence (i.e., "Yesterday he../ Daily he..").

5.3.4. Procedure

Tasks were presented in E-Prime 2.0 software (MacWhinney, St James, Schunn, Li, & Schneider, 2001), with a display resolution of 1366x768 and refresh rate of 60hz. Each stimulus was presented for an unlimited duration until terminated by the researcher, and only after the participant's response was detected by a microphone. Participants were instructed to name the object or action on the screen as quickly and as accurately as possible using a hand-held microphone. For all tasks, participants were instructed *not* to read the introductory sentences aloud and produce only the relevant noun/verb depicted in the image, as per the procedure of Ohlerth et al. (2020) during the original validation of the test battery. The purpose of requesting participants to respond in this way was to ensure that the reaction time (which was captured by the first sound detected by the microphone on each trial) was recorded for the onset of the noun/verb being produced and not at the onset of the patient reading the sentence. Participants

were encouraged to position the microphone approximately 6 inches from their mouth and to speak into it using a loud and clear voice so that responses could be accurately detected.

The microphone and Serial Response Box (Psychology Software Tools) were programmed to detect the onset time of the participants verbal responses using a voice key. As participants named each item, the researcher coded responses as either correct, incorrect or a microphone error via the response box. Once the response was coded the next trial would begin automatically. If no response was detected by the microphone, the researcher would request the participant to repeat the response more clearly and code the response as a microphone error that would be excluded from the analysis. For object-naming and ANFV tasks there was some variation in correct responses accepted in cases where there may be more than one name for an item (e.g., picture and painting, swept and brushed [the floor]), or in cases where the specifics that define a given item cannot be accurately conveyed by a line-drawing and so prompt various likely responses (e.g., rat or mouse, alligator, or crocodile).

Tasks were delivered consecutively although the order was counterbalanced across the healthy control sample. Patients completed the object naming task first, followed by action naming tasks. Healthy participants and patients completed tasks (as well as other tasks as part of a separate study) during a 45-minute to 1-hour testing session. The tasks in the present study took approximately five minutes each to complete, along with a short microphone test before the experimental tasks begun. Healthy participants attended single testing session at a laboratory in the School of Psychology at LJMU. Patients attended three separate testing sessions where they completed tasks in a quiet room, either in their own home or at The Walton Centre NHS Foundation Trust. The first session took place preoperatively and was planned for approximately one week prior to surgery to coincide with the time that clinical neuropsychological assessment was delivered. RS was tested one week preoperatively, however the preoperative testing time differed for patients GD and MW due to factors beyond

the researcher's control. GD was submitted for surgery at short notice and so was tested by the researcher during the preoperative appointment taking place one day before surgery, coinciding with the time of clinical assessment. MW was initially tested at one week before his planned surgery, coinciding with the clinical assessment, however, his surgery was rescheduled for two weeks later, meaning that the testing time was three weeks before surgery. Postoperatively, testing for all patients took place approximately four weeks after surgery, to ensure they were feeling well enough. The postoperative testing session did not coincide with the clinical assessment, which took place at the bedside 1-3 days following surgery. The follow-up assessment for all patients took place approximately three months after surgery. No further clinical assessments were completed by the language clinicians during this time. Initially, a second follow-up had been planned to be completed at approximately six months postoperatively, however, due to the national UK lockdown implemented in response to COVID-19 in March 2020, this was not possible.

5.3.5. Data analysis

5.3.5.1. Data preparation

For reaction time and accuracy data, prolonged reaction times due to microphone errors were coded at the time of testing and removed from the analysis. Response times with durations lower than 250ms that were likely the result of microphone errors were also removed from the reaction time data. However, it the response was correct (as confirmed by audio recording during testing), it was included in the accuracy analysis. For reaction time data, all item errors were removed to ensure that averaged reaction times were based on correct responses only.

5.3.5.2. Statistical tests

5.3.5.2.1. *Within-patient analyses*

To examine changes in performance for each individual patient across the three timepoints (preoperative, postoperative and follow-up) tests were conducted in JASP (Version

0.18.3) and IBM SPSS Statistics (Version 29) for reaction time and accuracy. By-item repeated measures analyses were performed using Freidman's test. Post-hoc pairwise comparisons were conducted using Conover's test. For accuracy, by-item analyses were conducted using Cochran's Q test and McNemar's test for pairwise comparisons. Further analyses using a Kruskal-Wallis test were conducted to examine between-task differences in baseline-endpoint change scores for reaction time (changes between preoperative baseline and follow-up). Post-hoc pairwise comparisons were performed using Dunn's test. The Holm-Bonferroni procedure was applied to adjust for multiple comparisons in all the above analyses.

5.3.5.2.2. Case-control analyses

Analyses for examining differences between cases and control groups on reaction time and accuracy measures across the VAN-POP tasks were conducted using statistical tests designed for single-case methodology. To analyse the differences in scores for each task at each timepoint and test for impairment relative to controls, modified *t*-tests were conducted using the computer program Singlims_ES.exe (Crawford, Garthwaite, & Porter, 2010). This tests whether an individual case's score differs significantly from the mean score of their control sample. Further analyses to test for dissociations in the patients' 3-month follow-up reaction time scores between the three VAN-POP tasks were conducted using RSDT.EXE (Revised Standardized Difference Test; Crawford & Garthwaite, 2005). This tests for differences in an individual case's scores on two separate tasks, accounting for the differences between task performance within the control sample. As multiple analyses were necessary to compare the three tasks, the Bonferroni correction procedure was applied to adjust for multiple comparisons.

5.4. Results

The following subsections present the performance results for each patient on the VAN-POP tasks across three timepoints (preoperative, postoperative and follow-up), as well as comparing performance to healthy control groups. **Table 5.2** provides a summary of errors displayed by each patient during completion of each task. Descriptive statistics for within-patient task reaction time performance across timepoints are displayed in **Table 5.3**. Repeated measures analyses of performance across timepoints are described within each subsection. Descriptive and inferential statistics for each case versus their control performance at each timepoint are displayed in **Table 5.4** (reaction time) and **Table 5.5** (accuracy). Results for dissociations in reaction time performance between tasks at follow-up are displayed in **Table 5.6**. Performance for each patient relative their control group are also plotted graphically in separate figures within each subsection. **Figures 5.2** (RS), **5.3** (GD) and **5.4** (MW).

Table 5.2. Language disturbances and errors produced by patients during VAN-POP tasks at pre-, post-operative and follow-up testing stages.

	Preoperative			Postoperative			Follow-up		
Case	Item	Response	Error	Item	Response	Error	Item	Response	Error
RS	Swings	*Swung*	TEN	Watered	[…] *Watered*	DEL	Watered	[…] *Watered*	DEL
	Counts	*Counted*	TEN	Digs	*Digged*	INF			
				Hides	*Hidded*	INF			
MW	Counts	*Counted*	TEN	Bucket	*ff..ff.. bucket*	PHON/HES	Sewed	*Sss…sss.. Sewed*	HES
	Sleeps	*Slept*	TEN	Sewed	*ss..ss.. Sewed*	HES	Watered	*Flowered*	SEM (SC)
	Waves	*Raises hand*	SEM				Sleeps	*Sss..slept*	HES/TEN
							Swept	*Scrubbed*	SEM (SC)

[…], delay or hesitated speech before response; HES, hesitation; TEN, incorrect tense produced for task; SEM, semantic error/paraphasia; DEL, delayed response; INF, inflection error/agrammatic response; PHON, phonological/phonemic error/paraphasia; SC, self-corrected error.

Table 5.3. VAN-POP reaction time scores at pre-, post-operative and follow-up timepoints and change scores at follow-up compared to preoperative baseline.

			RT (ms)		*RT change scores (ms)*	
Case	Task	Timepoint	Median	IQR	Median	IQR
RS	Object naming	Pre	908.50	180.00	43.00	197.00
		Post	922.50	167.25		
		Follow-up	975.00	173.75		
	ANFV (past)	Pre	1406.00	308.00	220.50	541.00
		Post	1216.50	387.25		
		Follow-up	1613.00*****	350.25		
	ANFV (present)	Pre	1191.00	304.00	234.00	384.00
		Post	1736.00	1300.00		
		Follow-up	1448.00	612.00		
GD	Objects	Pre	553.00	151.00	78.00	141.00
		Post	659.00*****	199.50		
		Follow-up	652.50*****	159.75		
	ANFV (past)	Pre	833.00	203.50	162.00	250.00
		Post	1100.00*****	336.00		
		Follow-up	1019.00*****	285.00		
	ANFV (present)	Pre	877.00	194.00	35.00	219.00
		Post	966.00	218.50		
		Follow-up	899.00	305.00		
MW	Objects	Pre	1010.00	269.50	-75.50	508.500
		Post	908.00	215.00		
		Follow-up	908.50	256.50		
	ANFV (past)	Pre	2056.00	691.00	-582.00	768.00
		Post	1974.00	784.00		
		Follow-up	1559.00	766.250		
	ANFV (present)	Pre	1889.00	815.00	-359.00	850.50
		Post	1559.00	551.50		
		Follow-up	1416.00	358.50		

RT, Reaction time; Median; IQR, Inter-quartile range. Significant worsening of performance (RT increase) at postoperative or follow-up timepoints relative to preoperative baseline is marked with an asterisk (*). RT change scores were calculated based on the by-item differences between baseline and follow-up performance, with positive values reflecting an increase in RT (worsening) and negative values reflecting a decrease in RT (improvement) by follow-up.

Table 5.4. Case vs. control reaction times on VAN-POP tasks across timepoints.

		Control RT group scores (ms)			*Case's RT scores (ms)*		*Sig. test*[a]		*Estimated % of control population obtaining a higher reaction time than the case*[b]		*Estimated effect size* (z_{cc})[c]	
Case	*Task*	*n*	*M*	*SD*	*Timepoint*	*M*	*t*	*p*	*Point*	*(95% CI)*	*Point*	*(95% CI)*
RS	Object naming	5	814.90	53.93	Pre-op	962.26	2.496	.03*	3.35	0.00 to 23.99	2.735	0.706 to 4.737
					Post-op	1002.50	3.177	.02*	1.68	0.00 to 15.56	3.481	1.013 to 5.946
					Follow-up	1037.84	3.775	**.01***	0.98	0.00 to 10.21	4.135	1.270 to 7.019
	ANFV (past)	5	1243.57	95.53	Pre-op	1436.44	1.843	.07	0.90	0.02 to 34.83	2.019	0.390 to 3.597
					Post-op	1298.31	0.520	.32	31.53	6.72 to 66.07	0.570	-0.414 to 1.497
					Follow-up	1901.65	6.291	**.002***	0.04	0.00 to 1.09	6.891	2.294 to 11.572
	ANFV (present)	5	1103.97	145.41	Pre-op	1409.33	1.915	.06	6.40	0.01 to 33.49	2.098	0.427 to 3.722
					Post-op	1992.14	5.572	**.**003*	0.25	0.00 to 2.24	6.103	2.007 to 10.266
					Follow-up	1657.57	3.473	**.01***	1.28	0.00 to 12.70	3.805	1.141 to 6.476
GD	ON	5	883.00	168.65	Pre-op	596.53						
					Post-op	697.38						
					Follow-up	691.00						
	ANFV (past)	5	1327.51	189.85	Pre-op	876.52						
					Post-op	1248.81						
					Follow-up	1092.74						
	ANFV (present)	5	1307.52	116.21	Pre-op	915.43						
					Post-op	1041.78						
					Follow-up	1041.61						
MW	ON	5	774.35	69.33	Pre-op	1072.74	3.928	.009*	0.86	0.00 to 9.12	4.303	1.334 to 7.294
					Post-op	1008.57	3.084	.02*	1.84	0.00 to 16.55	3.379	0.972 to 5.781
					Follow-up	938.18	2.157	**.05***	4.90	0.00 to 29.26	2.363	0.546 to 4.141
	ANFV (past)	5	1320.98	94.46	Pre-op	2125.63	7.776	.001*	0.74	0.00 to 0.20	8.518	2.880 to 14.274
					Post-op	2185.87	8.358	.001*	0.06	0.00 to 0.09	9.156	3.108 to 15.336
					Follow-up	1633.96	3.025	**.02***	3.30	0.00 to 17.22	3.314	0.946 to 5.674
	ANFV (present)	5	1293.88	224.53	Pre-op	1911.89	2.512	.03*	2.39	0.00 to 23.77	2.752	0.714 to 4.765
					Post-op	1651.04	1.451	.11	11.01	0.17 to 42.74	1.590	0.183 to 2.933
					Follow-up	1504.14	0.854	.22	22.07	2.40 to 57.00	0.935	-0.176 to 1.977

n, number of control cases for each task; SD, standard deviation; RT (ms), reaction time in milliseconds; *t*, *t*-test statistic; *p*, significance value. Significant *p*-values are marked with an asterisk (*).

[a] Modified *t*-test for single case-control studies according to Crawford & Howell (1998); one-tailed test.

[b]Note: since the abnormality of the case's reaction time is dependent on an increase (as opposed to a decrease in the case accuracy scores (Crawford & Garthwaite (2002)) relative to controls, the inverse point and interval values were calculated from the original statistical output (estimated percentage of normal population falling below case's score: lower) to reflect the estimated percentages for controls obtaining higher reaction time scores than the case.

[c]Point and interval estimates of effect size (z_{cc}) for reaction time differences between control group and case as per the method outlined in Crawford, Garthwaite & Porter (2012).

Table 5.5. Case vs. control accuracy on VAN-POP tasks across timepoints.

		Control group scores				*Case's scores*			*Sig. test*[a]		*Estimated % of control population obtaining a lower score than the case*[b]		*Estimated effect size (z_{cc})*[c]	
Case	*Task*	*n*	*M*	*SD*	*%*	*Timepoint*	*Score*	*%*	*E*	*t*	*p*	*Point*	*(95% CI)*	*Point*	*(95% CI)*
RS	Object naming	5	49.20	1.30	98	Pre	50	100							
						Post	50	100							
						Follow-up	50	100							
	ANFV (past)	5	25.80	0.84	96	Pre	27	100							
						Post	26	96	1						
						Follow-up	26	96	1						
	ANFV (present)	5	22.60	0.55	98	Pre	21	91	2	-2.656	**.03***	2.83	0.00 to 21.78	-2.909	-5.018 to -0.780
						Post	21	91	2	-2.656	**.03***	2.83	0.00 to 21.78	-2.909	-5.018 to -0.780
						Follow-up	23	100							
GD	Object naming	5	50	0	100	Pre	50	100							
						Post	50	100							
						Follow-up	50	100							
	ANFV (past)	5	25.80	0.84	96	Pre	27	100							
						Post	27	100							
						Follow-up	27	100							
	ANFV (present)	5	22	0	96	Pre	23	100							
						Post	23	100							
						Follow-up	23	100							
MW	Object naming	5	49.80	0.45	99.60	Pre	50	100							
						Post	49	98	1	-1.623	.09	8.10	0.06 to 39.14	-1.778	-3.221 to -0.276
						Follow-up	50	100							
	ANFV (past)	5	26.40	1.34	97.80	Pre	27	100							
						Post	26	96.3	1	-0.272	.40	39.94	11.89 to 73.15	-0.299	-1.181 to 0.617
						Follow-up	24	88.9	3	-1.635	.09	8.87	0.06 to 38.89	-1.791	-3.242 to -0.282
	ANFV (present)	5	22.20	1.10	96.52	Pre	19	87	3	-2.656	**.03***	2.83	0.00 to 21.78	-2.909	-5.018 to -0.780
						Post	23	100							
						Follow-up	22	95.7	1	-0.166	.44	43.81	14.55 to 76.23	-0.182	-1.056 to 0.714

n, number of control cases for each task; *M*, Mean score; *SD*, standard deviation; %, percentage correct; Score, number correct out of 50 (object naming), 27 (past tense action naming), 23 (present tense action naming); *E*, number of errors; *t*, *t*-test statistic; *p*, significance value. Significant *p*-values are marked with an asterisk (*).

[a]*t*-test for single case-control studies according to Crawford & Howell (1998); one-tailed test.

[b]Point and interval estimates of effect size (z_{cc}) for reaction time differences between control group and case as per the method outlined in Crawford, Garthwaite & Porter (2012).

Table 5.6. Dissociations in reaction time performance on VAN-POP tasks at follow-up relative to control performance.

Case's score			*Comparison*	*Difference*	*X and Y correlation in control sample*	*Sig. test*[a]				*Estimate of the control population exhibiting a difference more extreme than the case*
Case		*z*	*Tasks X vs. Y*	$z_{(x-y)}$	*r*	*t*	*df*	*p*	$p_{corr.}$	*%*
RS	Object naming	4.133	ANFV (past) – Object naming	2.77	.875	3.349	4	.01*	.04*	1.43
	ANFV (past)	6.889	ANFV (present) – Object naming	.326	.688	0.300	4	.39	1.17	38.95
	ANFV (present)	3.807	ANFV (past) - ANFV (present)	3.09	.900	3.953	4	.008*	.02*	.84
MW	Object naming	2.364	ANFV (past) – Object naming	.95	.791	1.039	4	.18	.54	17.87
	ANFV (past)	3.314	ANFV (present) – Object naming	1.43	.564	1.113	4	.16	.49	16.41
	ANFV (present)	0.936	ANFV (past) - ANFV (present)	2.38	.946	4.062	4	.008*	.02*	.77

z, patient's score represented as a standardised *z*-score; *X/Y* first/second task per comparison; *z* (*x*-*y*), differences in z-scores between tasks X and Y; *r*, Pearson correlation coefficient for relationship between tasks *X/Y* in control sample; *t*, *t*-test statistic; df, degrees of freedom; *p*, uncorrected *p*-value; $p_{corr,}$ Bonferroni corrected *p*-value. Significant *p*-values are marked with an asterisk (*). [a] Revised standardised difference test (Crawford & Garthwaite, 2005) for testing for dissociation of impairment on two tasks relative to control population.

5.4.1. RS

5.4.1.1. Object naming

5.4.1.1.1. Reaction time

Within-patient

While object naming speed became slower than baseline at postoperative and follow-up testing (**Table 5.3, Figure 5.2**), the changes were not significant across the three timepoints ($\chi^2(2) = 5.08$, $p > .05$).

Case vs. controls

RS's preoperative object naming speed was significantly slower than control performance by 147ms ($p = .03$; **Table 5.4, Figure 5.2**). Following surgery, object naming speed became slower than controls at postoperative (188ms; $p = .02$) and follow-up testing (223ms slower; $p = .01$).

5.4.1.1.2. Accuracy

Within-patient

RS performed at ceiling accuracy at all timepoints (**Table 5.5, Figure 5.2**), therefore no within-patient analyses were conducted.

Case vs. controls

Controls performed the object naming task with a mean accuracy of 98%, demonstrating that RS outperformed the controls at all timepoints (**Table 5.5, Figure 5.2**). Therefore, no case-control analyses were conducted.

5.4.1.2. ANFV (past tense)

5.4.1.2.1. Reaction time

Within-patient

There was a significant main effect of timepoint on RS's past tense ANFV speed ($\chi^2(2) = 25.00$, $p = .001$; **Table 5.3, Figure 5.2**). Relative to baseline, RS showed a small improvement of ~200ms in ANFV speed at postoperative testing, although this change was not significant ($p > .05$). At follow-up testing, action naming speed decreased by ~600ms, which was significantly slower than both postoperative ($p = .001$) and preoperative reaction time ($p = .01$).

Case vs. controls

RS's preoperative past tense ANFV speed was slower than controls, although not statistically significant (~200ms slower; $p > .05$; **Table 5.4, Figure 5.2**). Postoperatively, performance improved to near control level (~50ms slower; $p > .05$). By follow-up, naming speed declined significantly below control level (650ms slower; $p = .002$).

5.4.1.2.2. Accuracy

Within-patient

Preoperatively, RS performed the task with 100% accuracy (**Table 5.5, Figure 5.2**). At postoperative and follow-up timepoints, the patient produced a delayed response each time on the same item ("*Yesterday she… watered [the plants]*"). While these errors placed the postoperative and follow-up accuracy levels at 96%, there was no significant effect of timepoint ($\chi^2(2) = 2.00$, $p > .05$).

Case vs. controls

Preoperatively, RS performed above the control level of 96%. At postoperative and follow-up timepoints, RS's accuracy reduced slightly, but remained at control level (**Table 5.5, Figure 5.2**).

5.4.1.3. ANFV (present tense)

5.4.1.3.1. Reaction time

Within-patient

Compared to baseline, RS's present tense ANFV speed decreased by ~550ms postoperatively (**Table 5.3, Figure 5.2**). At follow-up, ANFV speed improved substantially by ~300ms. However, there was no significant effect of timepoint ($\chi^2(2) = 5.16$, $p > .05$).

Case vs. controls

Preoperatively, RS's ANFV speed was slower than controls, with a strong trend (~300ms slower; $p = .06$; **Table 5.4, Figure 5.2**). Postoperatively, performance became significantly worse than controls (~900ms slower; $p = .003$). At follow-up, reaction time had improved, but remained significantly slower than controls (~550ms slower; $p = .01$).

5.4.1.3.2. Accuracy

Within-patient

RS's preoperative and postoperative accuracy on present tense ANFV was 91% (**Table 5.3, Figure 5.2**). Preoperatively, RS produced two tense errors (produced verbs in the past tense); whilst these responses were grammatically correct, past tense inflection was not required for this task. Postoperatively, RS produced two agrammatical responses (inflection errors) after attempting to inflect irregular verbs according to the grammatical rule for regular verbs. At follow-up, accuracy improved to 100%. However, there were no statistically significant changes across timepoints ($\chi^2(2) = 2.00$, $p > .05$; **Table 5.5, Figure 5.3**).

Case vs. controls

Controls performed the past tense ANFV task with 98% accuracy. RS performed the task with 91% accuracy at pre- and postoperative timepoints, significantly less than controls ($p < .05$). At follow-up, RS's accuracy exceeded the control level (**Table 5.5, Figure 5.2**).

5.4.1.4. Reaction time performance dissociations between tasks at follow-up

Within-patient

There was a significant effect of task on RS's reaction time change scores between preoperative baseline and follow-up testing ($\chi^2(2) = 14.49$, $p < .001$; **Table 5.3**). Pairwise comparisons revealed a significantly larger increase in reaction times on both past tense ($p = .002$) and present tense ($p = .02$) ANFV compared to object naming. However, the differences in reaction time change scores for past and present tense ANFV were not significantly different ($p > .05$).

Case vs. controls

Relative to controls, RS's reaction time at follow-up was significantly more impaired on past tense ANFV compared object naming ($p = .04$; **Table 5.6**). There was no dissociation

between present tense ANFV and object naming ($p > .05$). However, past tense ANFV was significantly more impaired than present tense ANFV ($p = .02$).

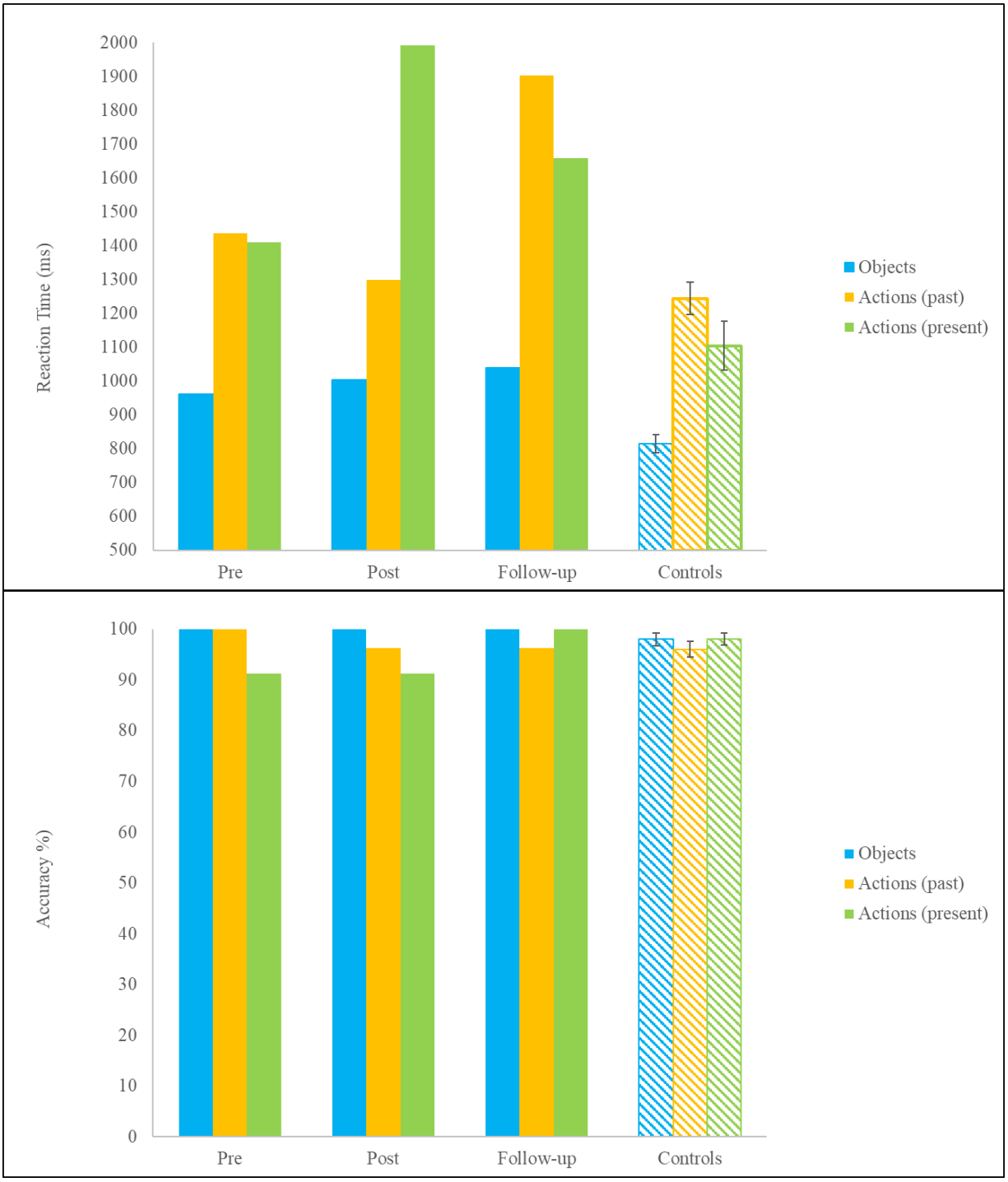

Figure 5.4. Patient RS's pre-, post-operative and follow-up performance vs. control group performance on VAN-POP tasks. **Top:** reaction time scores for object naming, past ANFV and present tense ANFV. **Bottom:** accuracy scores for object naming, past tense ANFV and present tense ANFV. Control performance is displayed in corresponding colour-coded patterned bars.

5.4.2. GD

5.4.2.1. Object naming

5.4.2.1.1. Reaction time

Within-patient

There was a significant main effect of timepoint on reaction times for object naming ($\chi^2(2) = 26.54$, $p < .001$; **Table 5.3, Figure 5.3**). In comparison to preoperative baseline, patient GD's object naming speed was significantly worse by ~100ms at postoperative ($p < .001$) and ~100ms at follow-up testing ($p < .001$).

Case vs. controls

GDs performance remained within or above the control range across all timepoints (**Table 5.4, Figure 5.3**).

5.4.2.1.2. Accuracy

GD's accuracy remained at 100% at all testing stages in line with control performance (**Table 5.5, Figure 5.3**).

5.4.2.2. ANFV (past tense)

5.4.2.2.1. Reaction time

Within-patient

There was a significant main effect of timepoint on past tense action naming speed ($\chi^2(2) = 28.22$, $p < .001$; **Table 5.3, Figure 5.3**). Compared to preoperative baseline, GD's ANFV speed significantly decreased by ~250ms at postoperative testing ($p < .001$). There was a significant improvement by ~150ms in ANFV speed between postoperative and follow-up testing ($p < .05$), although performance remained significantly slower than baseline by ~200ms ($p < .05$).

Case vs. controls

GDs performance remained within or above the control range across all timepoints (**Table 5.4, Figure 5.3**)

5.4.2.2.2. Accuracy

Accuracy remained at 100% and GD outperformed controls at all testing stages. (**Table 5.5, Figure 5.3**).

5.4.2.3. ANFV (present tense)

5.4.2.3.1. Reaction time

Within-patient

Whilst there was a slight decline of ~100ms in GD's present tense ANFV speed at postoperative testing compared to baseline, there was no significant effect of timepoint on reaction times for present tense ANFV ($\chi^2(2) = 2.44$, $p > .05$; **Table 5.3, Figure 5.3**). Speed at follow-up remained similar.

Case vs. controls

GDs performance remained within or above the control range across all timepoints (**Table 5.4, Figure 5.3**)

5.4.2.3.2. Accuracy

Accuracy remained at 100% and GD outperformed controls at all testing stages (**Table 5.5, Figure 5.3**).

5.4.2.4. Reaction time performance dissociations between tasks at follow-up

Within-patient

There was a significant effect of task type on GD's reaction time change scores between preoperative baseline and follow-up testing ($\chi^2(2) = 7.73$, $p < .02$; **Table 5.3**). Pairwise comparisons revealed no difference in change scores between object naming and both past and present tense ANFV tasks ($p_s > .05$). However, there was a significantly larger increase in reaction time on past compared to present tense ANFV ($p = .02$).

Case vs. controls

As GD's reaction time performance did not significantly differ from controls on each task, no further analyses were conducted to test for cross-task dissociations compared to controls (**Table 5.4, Figure 5.3**).

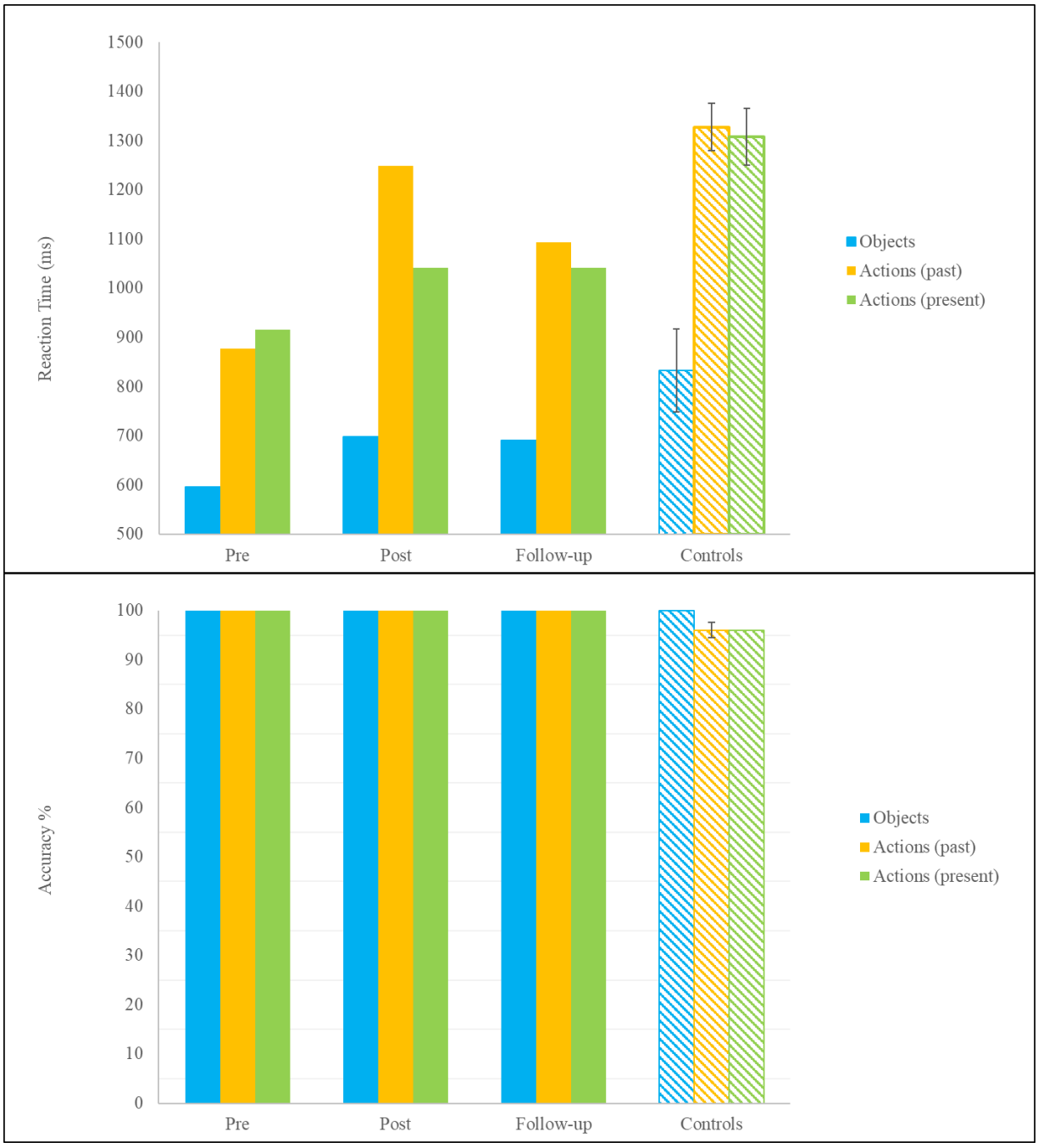

Figure 5.3. Patient GD's pre-, post-operative and follow-up performance vs. control group performance on VAN-POP tasks. **Top:** reaction time scores for object naming, past tense ANFV and present tense ANFV. **Bottom:** accuracy scores for object naming, past tense ANFV and present tense ANFV. Control performance is displayed in corresponding colour-coded patterned bars.

5.4.3. MW

5.4.3.1. Object naming

5.4.3.1.1. Reaction time

Within-patient

Compared to baseline, MW's object naming speed improved by ~50ms at postoperative and by ~150ms at follow-up (**Table 5.3, Figure 5.4**). However, there were no significant changes in reaction times across timepoints ($\chi^2(2) = 5.49$, $p > .05$).

Case vs. Controls

MW's preoperative object naming speed was significantly slower than controls by ~250ms ($p = .009$; **Table 5.4, Figure 5.4**). Despite the observed improvements at postoperative and follow-up timepoints, naming speed remained significantly slower than controls ($p = .02$, $p = .05$).

5.4.3.1.2. Accuracy

Within-patient

MW performed the object naming task with 100% accuracy preoperatively (**Table 5.3, Figure 5.4**). Accuracy was reduced postoperatively to 98% due to the production of a new error (MW hesitated with a self-corrected phonological error; **Table 5.2**). At follow-up, accuracy returned to 100%. No significant changes in object naming accuracy across the timepoints ($\chi^2(2) = 2.00$, $p > .05$).

Case vs. Control

At preoperative and follow-up timepoints, MW's accuracy remained above the control level of 99.6% (**Table 5.5, Figure 5.4**). The postoperative reduction in accuracy was not below the control level ($p > .05$).

5.4.3.2. ANFV (past tense)

5.4.3.2.1. Reaction time

Within-patient

There was a significant main effect of timepoint on MW's past tense ANFV speed ($\chi^2(2) = 7.91$, $p < .05$; **Table 5.3, Figure 5.4**). Compared to baseline, speed reduced by ~50ms postoperatively but was not significantly worse ($p > .05$). At follow-up, ANFV speed increased by ~550ms, which was a significant improvement relative to baseline ($p < .05$) and postoperative ($p < .05$) timepoints.

Case vs. Control

MWs ANFV speed was significantly slower than control ANFV speed by ~800ms preoperatively ($p = .001$; **Table 5.4, Figure 5.4**), ~850ms postoperatively ($p = .001$), and ~300ms at follow-up ($p = .02$).

5.4.3.2.2. Accuracy

Within-patient

MWs preoperative accuracy reached 100% (**Table 5.3, Figure 5.4**). Postoperatively, accuracy dropped to 96.3% following the production of a hesitant response. At follow-up, MW produced three errors (two semantic, one hesitation, **Table 5.2**), reducing accuracy to 88.9%. However, there were no significant changes in accuracy across timepoints ($\chi^2(2) = 4.67$, $p > .05$).

Case vs. Control

Preoperatively, MW outperformed the controls who completed the task with only 97.8% accuracy (**Table 5.5, Figure 5.4**). At postoperative and follow-up timepoints, while accuracy dropped below the control level, there were no significant differences ($p_s > .05$).

5.4.3.3. ANFV (present tense)

5.4.3.3.1. Reaction time

Within-patient

There was a significant main effect of timepoint on MWs present tense ANFV speed ($\chi^2(2) = 7.91$, $p < .05$; **Table 5.3, Figure 5.4**). Compared to baseline, MW's speed improved by ~250ms at postoperative testing, and a further ~150ms at follow-up testing. However, after correcting for multiple comparisons the differences fell just below statistical significance ($p_s > .05$), although a trend towards improvement was observed when comparing pre- and post-operative ($p = .06$), and preoperative and follow-up performance ($p = .06$).

Case vs. Control

Preoperative ANFV speed was significantly slower than controls by ~600ms ($p = .03$; **Table 5.4, Figure 5.4**). As postoperative and follow-up timepoints, MWs ANFV speed was ~350ms and ~200ms slower than controls, respectively; although, owing to the patient's improvements following surgery these differences were not significant relative to controls ($p > .05$).

5.4.3.3.2. Accuracy

Within-patient

MW made three tense errors preoperatively, with 87% accuracy (**Table 5.3, Figure 5.4**). Postoperatively, accuracy improved substantially to 100%. MW produced one error at follow-up (hesitation/tense error), reducing accuracy to 96.7%. However, there was no significant effect of timepoint ($\chi^2(2) = 4.67$, $p > .05$).

Case vs. controls

Preoperatively, MW performed significantly below the mean control accuracy level of 96.5% (p = .03; **Table 5.5, Figure 5.4**). Postoperatively, MW performed above the control level. At follow-up, although accuracy was slightly reduced, it was not significantly below the control level (p > .05).

5.4.3.4. Reaction time performance dissociations between tasks at follow-up

Within-patient

MW's reaction times improved across tasks at follow-up relative to baseline, with dissociations of improvement. A significant effect of task type was observed for MW's reaction time change scores between preoperative baseline and follow-up testing ($\chi^2(2) = 8.28$, $p < .02$; **Table 5.6**). Pairwise comparisons revealed a significantly greater reduction in reaction times for past tense ANFV compared to object naming (p = .04). There were no significant differences in change scores between object naming and present tense ANFV, or between past and present tense ANFV (p_s > .05).

Case vs. controls

Compared to controls, there were no dissociations in MW's reaction time performance at follow-up on object naming compared to past or present tense ANFV (p_s > .05; **Table 5.5**). However, MW's reaction time was significantly more impaired on past tense relative to present tense ANFV (p = .02).

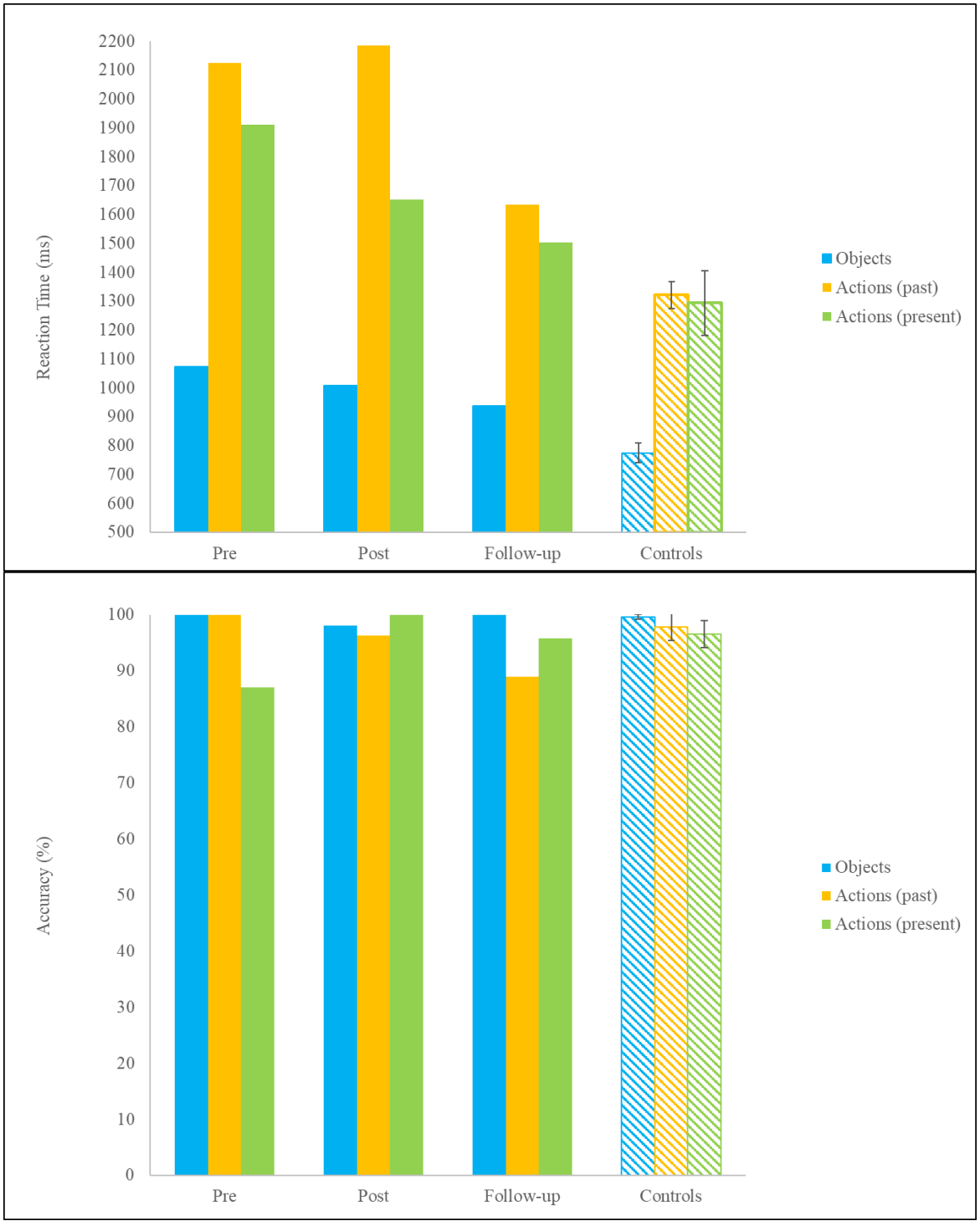

Figure 5.4. Patient MW's pre-, post-operative and follow-up performance vs. control group performance on VAN-POP tasks. Top: reaction time scores for object naming, past tense ANFV and present tense ANFV. Bottom: accuracy scores for object naming, past tense ANFV and present tense ANFV. Control performance is displayed in corresponding colour-coded patterned bars.

5.5. Discussion

Previous studies have demonstrated that preoperative glioma patients exhibit impaired reaction times on speeded object naming and receptive language tasks (Mooijman et al., 2021; Moritz-Gasser et al., 2012; Ras et al., 2020). The present study aimed to explore immediate and longer-term post-operative changes in noun and finite verb production abilities among glioma patients with variable lesion locations within the language cortex. The study assessed accuracy and reaction times across three VAN-POP tasks – object naming, past and present tense ANFV – in three patients with frontal, temporal, and parietal gliomas. These assessments were compared to healthy controls at three timepoints: preoperative, postoperative, and follow-up.

Aligned with the first hypothesis (H_1), none of the patients showed statistically significant impairments in accuracy scores on any of the VAN-POP tasks at follow-up assessment, either compared to their preoperative baseline or to the control group. However, reaction times at follow-up indicated more frequent impairments relative to both preoperative baseline and/or control group performance. Compared to preoperative baseline, RS showed impaired naming speed on 1/3 tasks, whilst GD's naming speed was impaired on 2/3 tasks. Relative to the control group, RS's picture naming speed was impaired on all 3 tasks and MW's on 2/3 tasks. This hypothesis was clearly supported by the three patient cases, demonstrating that although picture naming accuracy was not impaired on any task at 3-months following awake surgery, reaction times were impaired on at least two tasks relative to baseline or control performance. This is consistent with previous evidence showing that preoperative and postoperative glioma patients have impaired reaction times on both production and comprehension tasks (Mooijman et al., 2021; Moritz-Gasser et al., 2012; Ras et al., 2020).

The second hypothesis (H_2) predicted that at follow-up, patients' reaction time performance would be more impaired on either one or both of the ANFV tasks compared to

object naming. In RS's case, he was impaired on all three tasks at follow-up relative to controls, but he showed a significantly larger decline in naming speed for past and present ANFV tasks compared to object naming. In particular, the larger decline at follow-up in his past tense ANFV speed reduced performance significantly below the preoperative level. RS also exhibited a dissociation in reaction time performance compared to controls; he was significantly more impaired on past tense ANFV than on object naming. In contrast, neither GD or MW showed impairments on either ANFV task compared to object naming, relative to both preoperative baseline and control groups. In fact, MW showed significant improvements on past tense ANFV relative to object naming between baseline and follow-up. Thus, the hypothesis was partially supported, as only RS demonstrated impairment in past tense ANFV compared to object naming. This might suggest a pattern of impairment that is specific to more anterior perisylvian lesions, in contrast to posterior tumours in GD and MW.

The third hypothesis (H_3) predicted that at follow-up, patients' reaction times would be more impaired on the past tense ANFV task compared to the present tense ANFV task. Relative to baseline, neither RS or MW showed significant differences in performance between past and present tense ANFV at follow-up. However, when compared to controls, they were significantly more impaired on past tense ANFV compared to present tense ANFV. Moreover, although GD was impaired relative to controls, he exhibited a significantly larger decline in performance on past tense ANFV relative to present tense ANFV, when compared to his baseline.

The present study is the first (to the best of the author's knowledge) to investigate postoperative changes in glioma patients using speeded object naming and ANFV in past and present tenses. The following sections will discuss these novel findings in relation to the emerging understanding of the glioma language profile and the wider aphasia literature on noun and verb processing. The potential neural and cognitive mechanisms underpinning

performance patterns on different tasks and measures, depending on lesion location will be considered. Particular attention will be given to interpreting the dissociation of past and present tense verb production within the framework of time reference theories that explain impaired past tense processing in agrammatic aphasia.

5.5.1. The glioma language profile

5.5.1.1. Lexical retrieval: speed versus accuracy measures

The findings demonstrate that in glioma patients, linguistic production speed is more consistently impaired than accuracy across tasks and timepoints, with these impairments persisting at least three months following awake craniotomy. This is consistent with previous studies that observed slowed reaction times on object naming and sentence judgement in pre- and post-operative glioma patients (Mooijman et al., 2021; Moritz-Gasser et al., 2012; Ras et al., 2020). Moreover, reduced reaction times across multiple tasks in all three patients is consistent with a recent study of the glioma language profile suggesting a generalised decline of language processing abilities (Zyryanov et al., 2022). This was particularly true for patients RS and GD, who, by follow-up, showed significant declines in reaction time on at least one task compared to baseline. Although MW exhibited a linear improvement (except for temporary postoperative worsening on past tense ANFV) across the three timepoints, he remained impaired in naming speed on object naming and past tense ANFV relative to controls. These data suggest incorporating measures of reaction time in linguistic assessment may provide a more comprehensive understanding of the language status of glioma patients than accuracy-based assessment alone.

Further evidence comes from examining patients' pre- and post-operative performance on the CAT (Table 4., Chapter 4). All patients (except JLR, who was not part of this study), were deemed clinically unimpaired based on accuracy. This suggests that clinical accuracy-based measures (as well as experimental measures on VAN-POP) may not align with reaction

time performance. This is consistent with Ras et al. (2020), who found that significant response latencies among glioma patients on the BNT, despite their accuracy rarely showing clinical impairment. However, the present findings deviate slightly from those of (Mooijman et al., 2021), who found that patients differed from controls on both accuracy and reaction time during a sentence judgement task. These differences could be due to various factors, such as differences in task type (production as opposed to comprehension tasks), and study design (single case-control as opposed to a group study). However, Mooijman et al. (2021) found that self-reported lexical retrieval difficulties correlated with lexical retrieval speed, not accuracy. While self-reported language difficulties were not formally assessed periodically in the present study, patient GD, who performed 100% accuracy at all time points, reported that he was feeling "less mentally sharp" in the months following surgery. This self-reported assessment aligns with his decline in language performance at postoperative follow-up timepoints, despite accuracy scores remaining unchanged on the CAT and VAN-POP. Taken together with previous studies, the present findings indicate the value of incorporating speeded linguistic assessment, especially reaction time measures, into standard clinical practice. This approach may help to detect subtle retrieval delays that patients themselves might notice and report, but which often remain undetected during conventional aphasia assessments.

Furthermore, lexical retrieval speed is a predictor of the ability to return to work (Moritz-Gasser et al., 2012; Pascual & Duffau, 2022). Therefore, it remains vitally important to develop strategies to combat such barriers in glioma patients, which may include not only improving assessment, but providing therapeutic interventions to support improvement of language and cognitive function postoperatively. Importantly, cognitive functioning among glioma patients has been found to be poor and continues to remain poor in the longer term (Rimmer et al., 2023). This finding can be understood in relation to GD, who continued to show poorer reaction times at follow-up on object naming and past tense ANFV relative to

baseline. RS was also impaired on past tense ANFV at follow-up compared to baseline, and even showed a further worsening from performance at one month. It is therefore important to further understand the trajectory of lexical retrieval speed impairments in the longer-term postoperative period.

5.5.1.2. Possible mechanisms of impaired lexical retrieval speed

Low-grade glioma patients have the advantage of preoperative plasticity to maintain support for productive and receptive language functions (Duffau, 2005; Ho et al., 2021; Piai, 2019). If plasticity occurs, the patient may show no, or only a few mild anomic errors, a profile of which has historically been ascribed to this patient group (Davie et al., 2009). Reorganisation of neural connections, however, may reduce overall efficiency of the language network which may manifest as seemingly milder global language issues, including retrieval delays (Mooijman et al., 2021; Ras et al., 2020; Zyryanov et al., 2022). One recent study linked distinct patterns of resting state functional connectivity in glioma patients to preoperative language impairments and poorer 1-year outcomes for language function (Wolthuis et al., 2021), while another has found that local efficiency in the contralesional hemisphere may be associated with reaction times on cognitive tasks (De Baene, Rutten, & Sitskoorn, 2019). This raises the question of whether preoperative (and postoperative) neuroplastic changes may cause alterations in bilateral connections that affect language processing and production speeds. The extent to which functioning of the wider cognitive network influences lexical retrieval remains debatable (Mooijman et al., 2021; Moritz-Gasser et al., 2012; Ras et al., 2020). Ras et al. (2020) and Moritz-Gasser et al. (2012) did not find a relationship between lexical retrieval speed and performance on a non-verbal cognitive task (Trail Making Test, TMT). Mooijman et al. (2021) reported a correlation between reaction times in a receptive language task (sentence judgement) and completion times for the TMT, although this relationship was present in the patient group only. Further, Faroqi-Shah and Gehman (2021) assessed individuals with aphasia on a lexical

retrieval task and found that after general processing speed was controlled for, lexical retrieval delays were not observed. These conflicting findings may be explained by the different language tasks used across studies and the varying demands on cognitive function. However, as measures of reaction time performance on non-linguistic tasks were not obtained in the present study, it is not possible to investigate this further in relation to the current findings.

Patterns of performance across timepoints for accuracy and reaction times may be partially explained by deviant speed-accuracy trade-offs relative to controls and the use of cognitive coping strategies to support task completion. A speed-accuracy trade off may explain MW's performance on past tense ANFV at postoperative and follow-up timepoints. At postoperative testing, MW showed higher naming accuracy (96%), but reduced mean naming speed (~2200ms). At follow-up testing, he demonstrated the opposite performance pattern on this task - reduced naming accuracy (89%) with self-corrected errors, but increased naming speed (~1600ms). It appeared that MW struggled to complete the task both quickly and accurately at the same time, and intentionally used the coping strategy of maintaining either speed or accuracy at the detriment of the other. increasing speed or accuracy. Speed-accuracy trade-offs have previously been described by (Mooijman et al., 2021) during a speeded comprehension task. This may further support the idea that reduced neurocognitive efficiency in glioma patients may affect language performance (De Baene et al., 2019; Wolthuis et al., 2021). Furthermore, the fact that only MW showed this pattern of performance could be due to the fact that he was older than the other patients. It has been shown that on reaction time tasks, younger adults are better able to balance speed and accuracy, while older adults may prioritise minimising errors at the cost of speed (Starns & Ratcliff, 2010). However, this pattern of performance was only apparent on the past tense ANFV task, which may suggest it was also related to the greater complexity of past tense inflection. Therefore, older patients may be more likely to struggle in balancing speed and

accuracy on production tasks when a higher cognitive-linguistic load is imposed. Furthermore, this paradigm may offer a more sensitive method of error detection by testing the patient while they are under load, as opposed to conditions where response times are unrestricted. This method could be a more representative assessment of communication abilities in daily life; for example, producing language in a conversational context requires both a timely and accurate response. Speeded linguistic assessments that assess object and action naming in sentence context have already been shown to closely represent real-world language function (Rofes et al., 2015a), and may offer a more ecologically valid approach than non-speeded language testing.

5.5.1.3. Object naming versus action naming

Patient RS was the only patient that was found to be more impaired on at least one of the ANFV tasks compared to object naming. He showed a larger decrease in reaction times at follow-up compared to baseline on both past and present ANFV tasks relative to object naming. Whilst he was impaired on all tasks at follow-up relative to controls, he was significantly more impaired on past tense ANFV compared to object naming. As patient RS harboured an inferior frontal lesion, it was theoretically fitting that he showed greater difficulties on the ANFV tasks relative to object naming as patients with frontal lobe damage often show impairment on actions relative to objects (Aggujaro et al., 2006; Crepaldi et al., 2013; Crepaldi et al., 2011). Contrary to this distinction, however, recent studies in both stroke and brain tumour patients suggest that impairments to word (e.g., object naming) and sentence production (e.g., “The woman is [washing] the dishes”) do not result from circumscribed lesions to the frontal cortex, but rather through damage extending to the subcortical white matter tracts – namely the arcuate fasciculus (Gajardo-Vidal et al., 2021; Ntemou et al., 2023b). In the case of patient RS, it is not clear whether the tumour infiltrated any subcortical tracts as diffusion-weighted imaging was not available. Further research is

needed to determine whether impaired sentence production speed is a function of the inferior frontal gyrus or this subcortical region.

Patient GD presented a lesion in the inferior parietal regions but did not show the same dissociation for objects and actions; rather, he appeared to be equally impaired on both tasks following surgery, in relation to his own preoperative baseline. Evidence suggests that both nouns and verbs are underpinned by an extensive fronto-temporo-parietal network, however, it has been argued that the inferior parietal lobe may play an important role in processing of verbs over nouns (Crepaldi et al., 2011; Matzig et al., 2009; Vigliocco et al., 2011). Some neuroimaging studies have even demonstrated greater activation for verbs compared to nouns in the inferior parietal lobule across various tasks including morphological, picture naming and lexical decision tasks (Berlingeri et al., 2008; Fujimaki et al., 1999; Perani et al., 1999; Saccuman et al., 2006; Shapiro et al., 2006). It is also proposed that this region may play a role in the mirror neuron system which is recruited not only for the observation/visual processing of actions, but also for the processing of action-verbs (Wang, Zhang, & Sun, 2022). Furthermore, aphasic patients who show specific impairments for retrieving lexical representations of verbs (e.g., in naming) often have lesions within or extending to the inferior parietal lobule, i.e., Geshwind's territory (Aggujaro et al., 2006; Tomasino et al., 2019; Tranel et al., 2008). Therefore, in the context of the above literature, it may be surprising that GD did not show noun-verb dissociation. However, other studies have shown either the opposite distinction, where nouns show greater activation for verbs in the parietal lobe (Palti, Ben Shachar, Hendler, & Hadar, 2007; Sahin, Pinker, & Halgren, 2006), or indifferentiable in activation for nouns and verbs in the parietal region (Yokoyama et al., 2006). The present findings appear to align most with the latter study suggesting that the parietal lobe contributes equally to nous verbs.

The temporal and frontal lobes have often been argued to be distinctly specialised regions for the retrieval of nouns and verbs, respectively (Crepaldi et al., 2011; Vigliocco et al., 2011). Contrary to this dissociation, however, the anterior, middle and posterior regions of the temporal lobe, in which MW's tumour was situated, have shown to be associated with selective impairments for verbs (particularly irregulars) in both aphasic patients and healthy subjects with induced virtual lesions (Aggujaro et al., 2006; Holland & Lambon Ralph, 2010; Patterson, Lambon Ralph, Hodges, & McClelland, 2001). These regions have also been previously mapped as action naming sites in intraoperative studies (Corina et al., 2005; Havas et al., 2015), and may be attributed to the involvement of the semantic lexicon for irregular verb production (Okrent, 2004; Zimmermann, 2001). Similarly to GD, patient MW was equally impaired on both object naming and past tense ANFV, but in relation to the control group. In relation to baseline, however, MW showed a larger improvement by follow-up on the past tense ANFV task relative to object naming. This suggests that the temporal lobe may play a more important role in noun retrieval since a greater postoperative recovery was seen for verbs compared to nouns.

Taken together, the present findings add further evidence to the debate on the neuroanatomical distribution of noun and verb processing in the brain, demonstrating that centres within the fronto-temporo-parietal network may differentially support lexical retrieval according to grammatical class (Crepaldi et al., 2013; Crepaldi et al., 2011; Vigliocco et al., 2011). Evidence from patient RS supports the view that inferior frontal structures are more specialised for lexical retrieval of verbs over nouns (Aggujaro et al., 2006); this region may exist as an epicentre within the verb processing network, and as a supporting node within the noun network (Catani et al., 2012; Catani & Mesulam, 2008). Evidence from MW suggests that temporal structures of the language network are more specialised for noun production.

Finally, the pattern of impairment in GD indicates that the parietal regions may subserve the processing of both grammatical classes equally (Yokoyama et al., 2006).

5.5.1.4. Action naming: past tense versus present tense

Greater difficulties in producing the past tense were observed across all three patients in the form of reduced lexical retrieval speed for past tense relative to present tense ANFV. In the case of RS, although he was impaired on both past and present tense action naming at 3-month follow-up compared to controls, his performance on past tense was worse. MW was impaired on past tense but not present tense ANFV relative to controls. GD was not impaired relative to controls but showed a greater decline at follow-up on past tense compared to present tense ANFV.

While this dissociation applied only to lexical retrieval speed and not accuracy, the findings may be interpreted in line with evidence from aphasic patients demonstrating a greater difficulty in referring to the past relative to the present (Bastiaanse, 2008; Bastiaanse et al., 2011; Duman & Bastiaanse, 2009; Faroqi-Shah & Dickey, 2009; Faroqi-Shah & Thompson, 2007; Jonkers & de Bruin, 2009; Lee, Milman, & Thompson, 2008; Park, Obermeyer, Paek, & Zurbrugg, 2024). For example, Bastiaanse (2008) found that individuals with lesions to Broca's area who experienced agrammatic aphasia were more impaired on past tense than present tense finite verb production. Jonkers and de Bruin (2009) showed a similar pattern for both Broca's and Wernicke's aphasic patients, who displayed impairments in past tense processing on both production and comprehension tasks. Given that past tense production has shown to be impaired in both patients with anterior and posterior perisylvian lesions, this may explain why all three patients showed poorer lexical retrieval speed for past relative to present tense ANFV. Moreover, Jonkers and de Bruin (2009) also found those with lesions to Broca's area had more discernible impairments in the production of the past tense, while in those with lesions to Wernicke's area, the impairments were greater in the comprehension of the past tense.

Therefore, the finding that RS had the worst retrieval speed for past tense ANFV (as well as on the other two tasks, although to a lesser extent) out of all the patients may be explained in part by the location of the lesion within Broca's area. GD on the other hand, who had the most posterior lesion, demonstrated the best performance on ANFV out of all the patients. However, as the patients were not assessed on comprehension tasks, it remains unknown whether they would have shown dissociations in both production and comprehension for past tense verbs.

Impaired processing of tense morphology is commonly observed in agrammatic aphasia resulting from lesions to Broca's area. Several accounts have been proposed to explain deficits in with tense inflection, including that of the Tree Pruning Hypothesis (TPH) and the Tense Underspecification Hypothesis (TUH). The TPH suggests that in agrammatic aphasics, the erasure of the tense node within the syntactic tree results in difficulties with inflectional morphology (Friedmann & Grodzinsky, 1997). The TUH proposes that because tense inflection requires extrasentential information (i.e., reference to information outside of the sentence) processing tense is inherently more complex (Wenzlaff & Clahsen, 2004). However, these hypotheses, amongst others (for an overview see Bastiaanse, 2013; Bastiaanse et al., 2011), cannot explain dissociations in performance between past and present tense verb processing observed in the present study. The performance dissociations for past and present tense verbs have previously been attributed to theories of time reference (Bastiaanse, 2008, 2013; Bastiaanse et al., 2011; Jonkers & de Bruin, 2009). It is postulated that referring to the past is more challenging than referring to the present due to the discrepancy between the time reference for the action being depicted and the timepoint at which speech is occurring. In the case of producing the present tense, for example, "Daily she dances", the moment at which the speech output is produced is congruent with the timepoint at which the activity is occurring, i.e., the speech and the dancing are both happening in the present. In the case of past tense

production however, the speech and activity are temporally incongruent; the speech is being produced in the present, but the dancing has occurred in the past.

This idea can be further understood through the PAst DIscourse LInking Hypothesis (PADILIH) proposed by Bastiaanse et al. (2011). There are two levels of syntactic processing: narrow syntax or binding relations (relations between linguistic information within the sentence, e.g., subject-verb agreement) and discourse syntax or discourse linking (extra-sentential references to linguistic information outside of the sentence). It is argued that reference to the present constitutes a binding relation, since the speech and activity are temporally bound (Zagona, 2003); however, for referencing the past, while the activity and speech are temporally distinct, they are considered to be discourse linked (i.e., the link between speech occurring in the present and an event occurring in the past). This further explains why reference to the past is more linguistically complex than reference to the present, posing a greater linguistic challenge, and not just for patients; healthy individuals also show greater difficulty in referring to the past, evident through slower production speed for past compared to present tense production (Dragoy, Stowe, Bos, & Bastiaanse, 2012; Faroqi-Shah & Dickey, 2009; Jonkers, Boers, Koopmans, Menninga, & Zoodsma, 2007). This pattern was consistent in the healthy control groups within the present study, in which they presented with longer reaction times for past compared to present tense ANFV. Moreover, as discourse linking is more linguistically complex, it consequently imposes a greater cognitive load than narrow syntax and it has been suggested that those with agrammatic aphasia do not possess the cognitive resources necessary to concurrently execute both processes (Avrutin, 2006). Consequently, processing by way of narrow syntax may be opted for, potentially resulting in errors of tense substitution (present instead of past tense verbs; Bastiaanse, 2013; Bastiaanse et al., 2011). The glioma patents in the present study appeared to have much milder language problems than the post-stroke aphasic patients described in the above studies, and thus did not

demonstrate this pattern of errors. However, the reduced lexical retrieval speed for past tense ANFV may also suggest that glioma patients have depleted cognitive resources for dealing with these two competing linguistic processes, in line with evidence demonstrating they a have diminished neural efficiency (De Baene et al., 2019; Wolthuis et al., 2021).

5.5.1.5. Task sensitivity for error detection: object naming vs. action naming

Reduced accuracy on linguistic domains may not be the hallmark of language impairment in pre- and post-operative glioma, as is often the case in other neurological disorders such as stroke aphasia. While there was no significant impairment to accuracy at follow-up in any of the patients, preoperatively RS and MW displayed significant accuracy impairments relative to controls on the present tense ANFV task (and 1 month postoperatively for RS). In contrast, there was no significant impairments to accuracy on the object naming task, in fact 2/3 patients performed with 100% accuracy for this task at all timepoints, and MW made only one error postoperatively that was not significantly below the control level. This may suggest that ANFV tasks, which provide an assessment of verb morphology are more optimal to detect accuracy impairments than those assessing noun retrieval (Bastiaanse, 2008; Bastiaanse et al., 2011). Indeed, the majority of errors made by patients on the ANFV tasks were those relating to tense and inflection. This suggests that accuracy assessments vary in their ability to consistently detect errors in glioma patients, which may be partly dependent on the specific tasks used.

This may also be further considered by comparing the patients' pre- and post-operative accuracy on the VAN-POP with those of the CAT (**Table 4.** Chapter 4). For example, on the CAT, MW showed no errors for object or action naming (in isolation rather than in sentence context) on the CAT pre- and post-operatively, as well as displaying normal performance on the spoken picture description task; he was considered to be clinically unimpaired according to the CAT. Therefore, this may indicate that glioma patients are more likely to reveal accuracy

impairments when more linguistically demanding tasks are used that require the implementation of grammatical processes (e.g., past tense inflection) in sentence context. Contrary to this, however, the cases of RS and GD do not support this proposal. RS showed some minor errors to both object and action naming (in isolation rather than sentence context) both pre- and post-operatively, although performance on spoken picture description task was normal. GD, on the other hand, showed no errors on either the clinical assessment of the VAN-POP. Therefore, tasks that assess more complex inflectional morphology may not always be more sensitive to detect impairments than more grammatically simpler tasks. However, this does highlight the importance of testing language accuracy on a range of measures owing to the considerable variability in the nature of errors observed in glioma patients.

Furthermore, upon examining errors on the present tense task at pre- and post-operative timepoints, it was apparent that RS was attempting to inflect verbs to the past tense despite this being unnecessary for the task. The errors produced at the preoperative timepoint were not agrammatical (e.g., *"Daily he counted")* but were produced in the incorrect tense. Responses produced postoperatively became agrammatic as the patient failed to retrieve the correct irregular forms, and instead applied the rule for inflection of regular verbs (i.e., adding the affix [-ed] to the stem [dig]; (Ullman et al., 1997), resulting in an overregularisation ("Daily he digged"; "Daily he hidded"). The aphasia literature contains mixed findings regarding performance patterns for regular and irregular verbs. Some studies have reported that performance on irregular verbs is worse than regular verbs (de Diego, Costa, Sebastián-Galles, Juncadella, & Caramazza, 2004; Inglis, 2005; Kok, van Doorn, & Kolk, 2007; Miozzo, 2003); one study reported worse performance on regular verbs (Ullman et al., 1997); and others have found no difference between the two verb types (Bird, Ralph, Seidenberg, McClelland, & Patterson, 2003; Druks, 2006; Faroqi-Shah & Thompson, 2007; Wenzlaff & Clahsen, 2004). However, RS did not produce overregularisation errors (e.g., "ate" and "drank") on the past

tense task, therefore there did not appear to be a consistent issue with producing irregular verb forms.

Overall RS produced more errors on the present tense task than the past tense task at pre and postoperative timepoints; interestingly, none of the errors produced on past tense ANFV were grammatical errors, however, the majority of errors produced on the present set were grammatical. This finding was surprising given that previous studies (as described above) have shown that patients with lesions to Broca's area produce more, oftentimes grammatical, errors for past compared to present tense. However, the observation that both RS and MW made substitution errors (producing past instead of present) on the present tense task may be mediated by task order effects, in that the past tense task was always administered before the present tense task. Despite the opportunity to complete practice items and receive feedback, during the test phase the patients occasionally appeared to slip back into past tense production, particularly for items earlier on in the set. This suggests that the production of tense errors, in this case, may not have been an linguistic issue per se, but perhaps an issue with executive functions, specifically with updating to the change in task requirements and mental flexibility to switch strategies for verb retrieval and inflection (Miyake et al., 2000). This possibility is further supported by evidence showing that glioma patients have impairments to executive functions and reduced functional connectivity in the contralesional hemisphere to areas associated with cognitive flexibility (De Baene et al., 2019; Ng et al., 2019).

5.5.2. Limitations, future directions, and conclusions

Patient recruitment and data collection for this study was severely affected by the COVID-19 pandemic for the glioma patient sample. Cases included were limited to three as the fourth patient (JLR) from Chapter 4 withdrew from the study postoperatively, and further cases were unable to be recruited to enable a case-series design. The length of the follow-up

for each patient was also restricted to three months, rather than six months, as initially planned, which prevented monitoring of language function in the longer term.

Due to the single case design, recruitment of at least five control subjects that precisely matched the demographics of each individual patient was challenging. Controls were matched precisely to the patient on education level; however, the age matching was less conservative. Each control group was within a six-year range (+/- 3 years) of the respective patient's age. Although age matching may have been slightly suboptimal, within the context of the reaction measures on the VAN-POP, it is highly unlikely that there would be any significant age-related differences in performance between the patient and a control group up to three years above or below their age. Reaction time latencies on visual tasks are estimated to increase on average by only 2.80ms per year (Woods, Wyma, Yund, Herron, & Reed, 2015). Furthermore, during validation of the VAN-POP it was reported that there were no significant differences in accuracy between age groups on any of the tasks (Ohlerth et al., 2020).

Another consideration was the unknown impact of adjuvant therapies on language performance at follow-up testing, in patients RS and MW. RS was submitted for radiotherapy after postoperative testing due to subtotal resection, while MW was referred for both radiotherapy and chemotherapy after postoperative testing due to the higher grade (WHO grade III) of tumour confirmed following histological analysis. Satoer et al. (2012) found that postoperative treatment with either single or combined chemotherapy and radiotherapy did not have a significant negative impact on cognitive functioning in glioma patients at three-month follow-up. Others have reported that glioma patients in receipt of radiotherapy showed a progressive decline in attentional functioning (Douw et al., 2009), even when treatment was delivered at or below safe doses (< 2 Gy), and that combined adjuvant treatments may further affect cognitive functioning (Scheibel, Meyers, & Levin, 1996).

At three-month follow-up testing, RS's naming speed on the past tense ANFV task sharply declined, while MW's production of errors on both past and present ANFV increased. It remains unknown whether adjuvant therapies received by each patient impacted task performance at follow-up. However, as there was not a consistent decline observed across all tasks and measures, with patients' accuracy and speed improving on some tasks, this may be unlikely. However, the potential effects of adjuvant treatments on postoperative cognitive functioning provides further justification for comprehensive longitudinal monitoring of patients over the postoperative course, even if their language function appears intact in the immediate postoperative period.

The present study has contributed to the small but growing body of evidence showing impaired reaction times on language tasks in pre- and post-operative glioma patients. Evidence from the current study suggests that impaired lexical retrieval speed is more common in the glioma language profile than lexical retrieval errors. Accuracy was only impaired in the preoperative (two patients) and 1-month postoperative period (one patient), but only on the task that was considered most linguistically complex (past tense ANFV). However, impairments of lexical retrieval speed remained present at 3-month follow-up. Larger group studies are necessary to investigate language processing and production speeds in a variety of patients with different tumour locations and grades, as well as across a wider spectrum of tasks.

Improving perioperative language assessment for glioma patients requires the incorporation of speeded language tests into routine language assessment within clinical settings. Clinicians must also consider the wider impact of subtle retrieval delays on patients' functional quality of life and ability to resume normal daily activities after surgery (Ammanuel et al., 2022; Gabel et al., 2019; Rimmer et al., 2023). Importantly, therapeutic interventions need to be offered for lexical retrieval impairments, to promote recovery of language function

to a level conducive to returning to work and patients should be provided with practical coping strategies to aid them in moments word-finding problems.

5.6 Chapter summary

The present chapter has explored immediate and more longitudinal postoperative linguistic changes in patients who underwent awake craniotomy for the resection of frontal, temporal and parietal gliomas. Measures of both accuracy and reaction time through object naming and ANFV tasks of the VAN-POP revealed the variable nature of the glioma language profile. Specifically, at 3-month follow-up, lexical retrieval speed was impaired on at least 2/3 tasks in all patients either in relation to healthy controls or the patient's preoperative baseline. However, none of the patients were impaired on accuracy at follow-up. Further, at follow-up all patients showed a dissociation between past and present tense ANFV; lexical retrieval speed was more impaired for past compared to present tense ANFV, in relation to baseline or healthy control performance. The final chapter will constellate the findings of the three empirical studies described in this thesis and discuss implications for the field of language testing in awake craniotomy, and beyond.

Chapter 6: General discussion

6.1. Chapter overview

The final chapter will evaluate the findings of the three empirical studies presented in this thesis. Firstly, the aims and purpose of the thesis set out in Chapter 1 will be revisited followed by a summary of the key findings from Studies 1-3 (Chapters 3-5). Secondly, the findings will be discussed in terms of the theoretical implications and impact on current awake craniotomy practice at pre-, intra-, and post-operative stages. Thirdly, the main challenges encountered within this thesis will be considered and how these can be addressed with future research to improve linguistic assessment. The final section summarises the novel contribution of the work.

6.2. Aims of the thesis and summary of findings

The overarching purpose was to contribute to the growing body of work that aims to improve postoperative language outcomes in patients undergoing awake craniotomy for the resection of brain tumours, specifically low-grade gliomas. This investigation spanning over the course of three empirical studies has focused on improving linguistic assessments during preoperative, intraoperative, and postoperative phases of awake brain surgery.

Study 1 (Chapter 3) presented a systematic review of the literature. The first aim was to extract and synthesise data from brain stimulation mapping studies to provide an overview of the range of cognitive and linguistic tasks that have been used to map cortical and subcortical brain regions during awake craniotomy for brain tumour resection. The second aim was to investigate the types of cognitive and linguistic errors/disturbances induced by DES, regarded as the current gold-standard, delivered to cortical and subcortical sites, which had not yet been extensively reviewed. This work sought to provide an informative summary and a prescriptive tool grounded by DES data, rather than what is theorised from models of the functional

localisation of cognition and language. The findings were intended, not only to support clinicians and researchers in selecting appropriate tasks for optimal neuropsychological assessment in theatre; they also informed the implementation of a comprehensive protocol for pre-, intra-, and post-operative linguistic assessment in subsequent studies within the present thesis.

The review collated data from 114 intraoperative brain mapping studies conducted across 16 different countries. Mapping data was reported for 28 cognitive and linguistic tasks; the most common being object naming (89%), consistent with that reported in a survey of assessment practices in awake craniotomy (Rofes et al., 2017a), counting (37%) and reading (18%). However, these commonly used tasks may not consistently detect language positive sites across the brain, either collectively, or singularly, as they cannot assess the broader spectrum of linguistic functions that are ascribed to different regions. For example, counting may only assess lower-level speech or articulatory functions, but not morphological (grammatical) processes that require a more specialised task such as ANFV (De Witte & Marien, 2013; Rofes & Miceli, 2014). Furthermore, a composite catalogue of 19 DES-induced task interference types was developed based on a wealth of descriptors reported in the literature (e.g., anomia, speech arrest, semantic paraphasia). This provided novel insights into the variety of intraoperative disturbances beyond vague terms such as “speech arrest” that are commonplace in awake neurosurgical reports.

Theoretical and practical merits of traditional versus specifically developed tasks for awake surgery were evaluated. Based on this, recommendations were offered towards optimising the intraoperative protocol by employing comprehensive linguistic assessment (De Witte et al., 2015b; Rofes et al., 2015c; Rofes et al., 2017b). While it is crucial to firstly prioritise preservation of the most fundamental linguistic functions with comprehensive linguistic testing (i.e., phonology/articulation, semantics and morphosyntactic abilities), it was

suggested that more secondary functional outcomes may also be considered in accordance with studies that have further tailored cognitive-linguistic protocols to each patient's individual needs, e.g., skills, hobbies or occupation (Borius et al., 2012; Herbet et al., 2017; Roux et al., 2009a; Roux et al., 2007; Wang et al., 2013). Although not a primary focus of the review, the critical nature of language monitoring was also considered; suggestions were offered in terms of implementing a combination of formal and informal testing during the debulking phase of surgery. This is a considerably understudied, yet vital part of awake craniotomy, that can have significant implications for postoperative functional outcomes. Furthermore, it was recommended that clinicians and researchers should collect and report positive (and importantly, negative) DES mapping data, highlighting specific interference types, particularly for more novel (e.g., ANFV) and less commonly used tasks (e.g., PPTT, sentence judgement) for which neuroanatomical data is currently scarce (Rofes et al., 2019).

Study 2 (Chapter 4) aimed to implement a new comprehensive linguistic protocol (VAN-POP) for DES language mapping and monitoring (Ohlerth et al., 2020) at The Walton Centre NHS Foundation Trust. As demonstrated in Chapter 3, a comprehensive neuroanatomically targeted cognitive-linguistic assessment, particularly one that is bespoke where possible (i.e., focusses on functions relating to occupation, skills, and hobbies in addition to preserving essential linguistic functions), is the most favourable approach. However, optimising intraoperative testing is not simply about developing a protocol that can map the most functions. Careful considerations must be given not only to the individual needs of the patient, but the practicality of administering such assessment within the parameters of the individual surgical setting, without compromising, imperatively, the preservation of fundamental linguistic functions.

In line with findings of the review, and in consultation with neurosurgeons and clinicians, it was decided by the research team that a more concise protocol was required.

Specifically, one that (1) fits easily into existing health service care pathways and (2) provides a comprehensive assessment of cognitive and linguistic functions beyond the existing protocols. The VAN-POP presented a practical solution, offering a set of tasks that was easy for clinicians to integrate into existing protocols and assessing more complex linguistic functions such as morphosyntactic production (Rofes et al., 2015a; Rofes et al., 2015b; Rofes & Miceli, 2014; Rofes et al., 2015c; Rofes et al., 2017b).

The next phase of the research (Study 2, Chapter 4) trialled the VAN-POP among four native English-speaking patients with suspected low-grade glioma in frontal, temporal, and parietal regions. The VAN-POP comprised a standardised English version of an object naming and ANFV protocol originally developed for intraoperative mapping in Italian patients (ECCO and VISC; Rofes et al., 2015b). Previous studies using these tasks have reported their application in patients primarily with left frontal glioma, and to a lesser extent, with temporal and parietal patients. These studies were also limited to Italian and Dutch-speaking patients (Rofes et al., 2015b; Rofes et al., 2015c; Rofes et al., 2017b). Moreover, ANFV tasks in these other languages have only assessed the production of verbs in the present tense. However, for the English variation within the VAN-POP, both past and present tense ANFV are assessed on two separate tasks. Therefore, for the first time, this study assessed glioma patients intraoperatively using both past and present tense ANFV.

Using the VAN-POP, at least one or more language sites were mapped in 3/4 cases, and applying the protocol for language monitoring during tumour resection allowed detection of language deterioration in 3/4 cases. Some novel interferences, that have not yet been reported in the awake neurosurgical literature, was observed in the patients during the ANFV tasks. For example, on the present tense ANFV task, the frontal patient produced verbs in the past tense. In the past tense ANFV task, the frontal and temporal patient produced the same error, that although was classified as a semantic paraphasia by the language clinician, may have in fact

been a grammatical error. Furthermore, no deterioration of function was detected during monitoring with spontaneous speech via conversation; however, it was suggested that this may have been due to the fact that conversation was only used intermittently, primarily to keep the patient engaged in between the delivery of formal tasks. Consistent with previous studies by Rofes and colleagues, this study endorsed the VAN-POP as a practical and effective tool for mapping and monitoring during awake craniotomy in patients with perisylvian tumours. Importantly, the findings of this study have successfully expanded the application of ANFV to English patients and have for the first time, provided intraoperative data for past and present tense finite verb production. Moreover, further data for ANFV has also been obtained for temporal and parietal patients, for which previous studies have been less focussed on. Although no explicit grammatical disturbances (tense and inflection errors) were observed in these patients, other language errors (e.g., speech arrest and semantic paraphasia) using the ANFV tasks during DES and/or tumour debulking were observed, demonstrating its value in detecting not just morphosyntactic disturbances but phonological and semantic interferences as well.

Study 3 (Chapter 4) adapted the VAN-POP for speeded perioperative assessment to further understand the longer-term impact of awake surgery on cognitive and linguistic functions. Specifically, considering not only accuracy but processing speed over the postoperative course. Three patients from Study 2 were tested at three timepoints: preoperative (1 week), postoperative (1 month) and follow-up (3 months). Accuracy and reaction times were then compared to healthy controls and across timepoints.

Interindividual performance across timepoints revealed both improvements and declines in accuracy and reaction times for various tasks over the postoperative course. No patient showed exactly the same performance patterns across different tasks/timepoints, possibly owing to different lesions and individual differences. However, there were some very interesting findings observed within individual patients and some consistent patterns across all

three patients. Across all timepoints, reduced linguistic processing speed was more frequently observed across patients than accuracy-based language deficits. When errors were made, they were usually only detected with one of the ANFV tasks; indeed, none of the patients had any significant impairments with respect to object naming across any of the timepoints. Crucially, it was also demonstrated that only lexical retrieval impairments extended into the postoperative period up to at least three months following surgery. At 3-month follow-up, lexical retrieval speed was impaired in all patients on at least two tasks either in relation to healthy controls or the patient's preoperative baseline. However, none of the patients were impaired on accuracy at follow-up.

Furthermore, inter-patient differences in lexical retrieval speed were observed between object naming and ANFV that appeared to be due to heterogeneity in lesion locations. Patient RS, who possessed the inferior frontal lesion, demonstrated a dissociation in reaction time performance between the object naming and past tense ANFV, with worse performance for ANFV compared to controls. The parietal patient appeared to be equally impaired on object naming and past tense ANFV in relation to baseline performance. MW, the temporal patient was equally impaired on both tasks relative to controls, although he showed less of an improvement on object naming compared to ANFV. Finally, the most novel finding that was consistent across all patients was the dissociation between past and present tense ANFV. Lexical retrieval speed was more significantly impaired on past compared to present tense ANFV, in relation to either baseline or healthy control performance.

Taken together with recent work showing that receptive language processing speed is impaired in low-grade glioma (Mooijman et al., 2021) as well as lexical retrieval for object naming (Moritz-Gasser et al., 2012; Ras et al., 2020), slower linguistic processing may be a central characteristic of the glioma language profile that is not currently recognised in standard pre- and post-operative neuropsychological assessment. Retrieval impairments may also be

worse for either nouns or verbs depending upon the lesion location, consistent with previous neuropsychological and neuroimaging studies (Aggujaro et al., 2006; Bulut, 2022; Crepaldi et al., 2013; Crepaldi et al., 2011; Faroqi-Shah et al., 2018). The production of verbs in the past tense may be more impaired relative to present tense regardless of whether the lesion is more anterior or posterior, although worse performance may be a function of lesion proximity to Broca's area (Bastiaanse, 2008, 2013; Bastiaanse et al., 2011; Jonkers & de Bruin, 2009). Furthermore, accuracy impairments may also only be detectable with more complex linguistic tasks such as ANFV. The limitations of current clinical assessment may allow such subtle impairments to "slip under the radar"; consequently, low-grade glioma patients may not receive appropriate neuropsychological interventions, and be burdened with long-term functional impairments that affect several aspects of their personal and/or professional lives (Ammanuel et al., 2022; Pascual & Duffau, 2022).

6.3. Shifting perspectives in neurosurgical practice

Chapters 1 and 3 explored the limitations of current assessment in awake craniotomy due to the lack of standardisation among linguistic protocols (De Witte & Marien, 2013; Rofes & Miceli, 2014) and reliance on tasks based on traditional localisationist models of language (Tremblay & Dick, 2016). Contemporary connectionist language models have revolutionised our understanding of neuropsychological functions and play a key role in diagnosis, assessment, and treatment of disordered language and the understanding of how this differs from that in the healthy brain (Catani et al., 2012; Catani & Mesulam, 2008; McClelland & Rogers, 2003; McClelland et al., 1989). However, it is important to remember that while such models provide a summative representation of clinico-anatomical function, they cannot predict exactly how an individual brain will operate when intact or lesioned, due to variability of linguistic functions (Ojemann, 1979; Ojemann & Whitaker, 1978).

Reliance on traditional tasks such as counting, object naming and reading, is based on outdated models of language function (Tremblay & Dick, 2016), which may give rise to false negative mapping, especially when considering the variable nature of the glioma language profile. The distribution of lesioned language networks may be more elusive due to the influences of preoperative and postoperative plasticity (Duffau, 2005; Ho et al., 2021; Piai, 2019; Price & Friston, 2002). However, while all neural tissue should be considered as potentially functional, there may be a distinction between areas which are essential and those which are more supplementary to various linguistic processes. Within connectionist language models, essential tissue refers to that which, if damaged, prevents the function from being executed and potentially results in a profound and definitive impairment (Catani et al., 2012; Catani & Mesulam, 2008). Supplementary tissue, on the other hand may support the functions of essential areas but are not necessary in order for the function to be carried out. Therefore, damage to a participating centre within the broader language network or relevant subnetwork would result in a specific impairment to the language functions that are largely localised to that area (i.e., essential); this may only cause partial disruption to neighbouring connections and therefore present as milder impairments. For example, damage to inferior frontal structures may cause a more pronounced impairment to verb production, while noun production, which may be supported more temporo-parietally, might be impaired to a lesser extent (Crepaldi et al., 2011). Hertrich, Dietrich, and Ackermann (2020) make the distinction between the "core language networks" pertaining to the dorsal and ventral streams within the perisylvian regions, and additional regions and subnetworks that are recruited to support specific task-dependent requirements. However, they argue that the margins of these language networks are arbitrary and may vary depending on several factors, including individual variability and, importantly, damage and plasticity mechanisms imposed by neuropathologies (Duffau, 2005; Ho et al., 2021; Piai, 2019). Therefore, separating the essential and supplementary tissue within these

language networks presents a formidable challenge of awake surgery that is central to the goal of resecting maximal tumour whilst minimising the chances of severe long-term language impairments. The use of more comprehensive linguistic protocols may be able to facilitate this goal by improving the sensitivity and specificity of language mapping in terms of distinguishing essential and non-essential language sites for different functions.

The rationale behind employing the VAN-POP was to maximise the preservation of language through more comprehensive linguistic assessment. However, while optimising the assessment may support the dissociation between essential and non-essential tissue, it also may inadvertently exacerbate the central dilemma of awake surgery – the trade-off between neuropsychological function and oncological outcome (Paldor, Drummond, Awad, Sufaro, & Kaye, 2016). Improving the resolution of mapping with specialised tasks such as the VANPOP may uncover a host of potential functional consequences that makes deciding the extent of resection more demanding. However, advanced knowledge of these risks may be advantageous in guiding more thorough postoperative assessment and interventions, aiding neuropsychological recovery and rehabilitation. For instance, if interferences during a particular task are identified during DES or debulking, it would be advantageous to tailor postoperative assessment towards assessing those linguistic components in greater depth. In Study 2 (Chapter 4), for example, MW produced a semantic error ("She flowered" instead of "She watered [the flowers]") during tumour resection, that he also produced at 3-month follow-up in Study 3 (Chapter 5); this type of error may not have been observed had MW not completed the VAN-POP postoperatively. Consistency in neuropsychological assessment administered pre-, intra-, and post-operatively will allow clinicians to identify whether intraoperative disturbances have translated into postoperative impairment, and further monitor its trajectory over the postoperative course. This is particularly crucial given a recent systematic review finding that intraoperative errors, specifically anomia and speech production errors

(e.g., dysarthria), are a significant predictor of postoperative language impairments (Collee, Vincent, Dirven, & Satoer, 2022b).

Optimising assessment in awake craniotomy to minimise postoperative impairment is not a process that should be restricted to the intraoperative phase. Similar limitations are present for perioperative assessment of patients, which is often inconsistent and incomprehensive (De Witte & Marien, 2013). Improving linguistic assessment is equally crucial preoperatively to obtain a true representation of baseline level of function, including any subtle impairments (e.g., delayed responses), and postoperatively, to track short-term and longitudinal changes over the course of treatment and recovery. Adaptation of the VAN-POP into experimental reaction time tasks in the pre- and post-operative period successfully measured, for the first time, changes in linguistic processing speed across object naming and ANFV tasks in glioma patients. At 3-month follow up testing, all patients were significantly impaired on at least two tasks with regards to reaction time in relation to either their own preoperative baseline, or healthy control performance. However, patients were not impaired on accuracy for any task. These changes were too subtle to be detected by the language clinician, and consequently the language function of the three patients included in Chapter 5 was considered to be within the normal range according to their clinical assessment on the CAT. Even if subtle delays were detectable with standard aphasia assessment (which they are currently not), they may not be considered clinically relevant to the patient's functional language status, despite naming speed affecting real-world functioning, and importantly, the ability to return to work (Moritz-Gasser et al., 2012). The present findings have provided further support for the view that subtle, yet significant changes in postoperative glioma patients are often overlooked due to insensitivity of current clinical language assessment.

However, the implementation of reaction time measures in clinical practice may present a significant practical challenge for clinicians. In the present study, reaction times were

captured using a serial response box (see Chapter 5 for details) and microphone programmed in EPrime software. Processing this data was a labour-intensive task that required several steps including data extraction, preparation (e.g., filtering out responses due to microphone errors) and analysis before anything meaningful could be interpreted. In clinical practice, this approach would not be feasible, as clinicians may not have the time or specific training to be able analyse this data in this way. Therefore, future research may consider the development and implementation of software in which verbal response times can be measured and processed more automatically and can provide more instantaneous results that can be interpreted by the clinician.

As argued in Chapter 5, pre- and post-operative assessment for awake surgical candidates needs to be updated to reflect the emergent understanding of the glioma language profile, and how it differs from other aetiologies (e.g., stroke aphasia). Language impairments among low-grade glioma patients may be subtle in nature, yet affect performance across a variety of different linguistic domains; this profile has recently been described as a moderate global aphasia that results in an overall decline of linguistic abilities (Zyryanov et al., 2022). Impaired linguistic processing speed may indeed be a manifestation of this decline, while receptive and expressive abilities are generally spared, giving the appearance that language remains largely intact pre- and post-operatively.

The aetiology of this pattern of impairment is yet to be fully explored, and recent work has considered whether reduced linguistic processing speed is a function of more general cognitive slowing, the findings of which are mixed (Mooijman et al., 2021; Moritz-Gasser et al., 2012; Ras et al., 2020). Furthermore, while not necessarily mediated by processing speed, a recent meta-analysis has shown that executive functions are also affected in postoperative low-grade glioma patients, both in the immediate and longer term (Ng et al., 2019). This may suggest that executive functions could play a role in lexical retrieval impairments, especially

since everyday language may require a degree of mental flexibility (e.g., shifting between verb tenses). However, in the present study, executive functioning was not assessed, and neither was the ability to switch between verb tenses, as past and present tense subsets of the ANFV were administered separately. Future work may therefore explore this idea further in glioma patients by administering past and present ANFV subsets as part of an event-related design. Performance could then be correlated with other tasks assessing different executive functions such as set shifting, inhibition, monitoring and updating (Miyake et al., 2000). This could reveal more about how executive processes contribute towards lexical retrieval impairments in the glioma language profile. Further research is required to establish the mechanisms underlying slower performance on language tasks in low-grade glioma. This may inform cognitive training strategies that could focus on rebuilding or strengthening, for example, executive functions and general processing speed, to improve linguistic outcomes (Weyer-Jamora et al., 2021). If the low-grade glioma language profile does encompass a global aphasia, then a global approach to assessment and treatment could be a promising way forward.

The extent to which neuropsychological functions are assessed and monitored in the long-term following awake craniotomy is something that differs between neurosurgical centres, with longitudinal data rarely reported beyond 3-6 months postoperatively (De Witt Hamer et al., 2012; Ng et al., 2019). Patients are usually assessed in the immediate postoperative period (between 24 hours and seven days after surgery) and clinicians commonly observe new, or a worsening of existing preoperative deficits, classified as mild to moderate in severity (Davie et al., 2009; Wilson et al., 2015). These deficits are often transient, and are frequently attributed to factors such as swelling, fatigue and anaesthesia/analgesic medications, typically improving or resolving fully over the postoperative course by around the 3-month mark (De Benedictis et al., 2010; Duffau, 2007; Pereira et al., 2009; Reithmeier, Krammer, Gumprecht, Gerstner, & Lumenta, 2003; Spena et al., 2010; Tonn, 2007).

De Witte and Marien (2013) estimated that permanent deficits occur in less than 5% of patients. However, it is important to note here that while this figure seems relatively low, it only represents language impairments observed with clinical aphasia test batteries; these assessments will not include more complex linguistic tasks such as ANFV that have since been developed, or indeed, consideration of reaction time measures in the classification of impairment. Taken together with current findings, this suggests that more multifaceted linguistic assessments may find the occurrence of permanent language deficits to be much higher. Furthermore, patients with lasting impairments (> 3 months postoperatively) are usually submitted for speech and language therapy and regularly reassessed (around every 3-6 months); however, in patients whose language function appears intact within the short-term postoperative period (< 3 months), or in those with seemingly acute minor difficulties that fail to meet the criteria for interventions, a longer-term follow-up (> 3-6 months) assessment is not routinely performed (De Witte & Marien, 2013). Consider patient GD, for example, his language was unimpaired clinically and was thus not considered a candidate for clinical follow-up assessment. However, his reaction times on the experimental tasks remained delayed at 3-month follow-up compared to his preoperative baseline.

Regardless of whether the patient presents with impairment over the postoperative course, longer-term follow-up assessment of neuropsychological function is necessary to monitor changes. Patients' cognitive functioning may appear acceptable upon discharge with current testing; however, problems may not become apparent until patients resume activities that require greater cognitive effort (e.g., returning to employment or education, socialising etc.). Furthermore, the prospect of language function progressively worsening in the postoperative period is not something that has been acknowledged in the low-grade glioma literature. The clinical consensus is that minor neuropsychological deficits will subside over the physical recovery period without intervention. However, a recent study following patients

up to 12 months postoperatively found that both semantic fluency (animals and verbs) and verbal cognitive speed declined in the period between three and 12-month assessments (Norrelgen, Jensdottir, & Ostberg, 2020). In Chapter 5, declined performance on ANFV at follow-up relative to acute postoperative testing, was reported in two patients (RS and MW). The possible negative cognitive effects of adjuvant oncological treatments (i.e., chemotherapy and radiotherapy) were considered as a potential explanation for the selective decline on this linguistically demanding task. However, the evidence remains unclear as to whether adjuvant therapies impact neuropsychological function (Douw et al., 2009; Satoer et al., 2012; Scheibel et al., 1996), and if so, under what conditions (e.g., dosage, duration of treatment etc.) and to what extent (i.e., severity of impairments and specificity of functions). Moreover, the possible use of cognitive strategies that may have led to speed-accuracy trade-offs in MW's performance was suggested as an explanation of his differential pattern of performance (Mooijman et al., 2021).

These performance patterns may be attributable to pre- and post-operative neuroplastic changes that have adverse consequences for the overall efficiency of cognitive and language networks (Cargnelutti, Ius, Skrap, & Tomasino, 2020; De Baene et al., 2019; Krishna, Kakaizada, Almeida, Brang, & Hervey-Jumper, 2021; Piai, 2019). Such an account would fit with recent findings of a generalised decline in language function observed specifically in glioma, but not stroke (Zyryanov et al., 2022). The longitudinal impact of awake craniotomy on neuroplasticity and the trajectory of the glioma language profile remains poorly understood, particularly in relation to subtle cognitive and linguistic changes (e.g., lexical retrieval delays), which requires further research. Regardless of the causes in the decline of function, regular neuropsychological follow-up assessments in awake craniotomy patients are critical to monitor changes and determine treatments, wherever appropriate.

6.4. Limitations and future research directions

This thesis has contributed some novel insights into comprehensive language assessment in brain tumour patients undergoing awake craniotomy. Although laying foundations, there remains a long road ahead in improving neuropsychological assessment intraoperatively, as well as perioperatively, in the immediate and longer term. An important outcome of improving oncological interventions is improved life span of patients, including those with higher tumour grades (UK, 2017). Exploring new ways to maximise quality of life through improving neuropsychological interventions should be an essential goal of future work.

Whilst Study 2 (Chapter 4) demonstrated that the VAN-POP is a useful assessment tool for awake craniotomy that can be used for different tumour locations, experimental comparison of VAN-POP tasks with current tasks was not possible due to the practical constraints within the collaborating neurosurgical hospital. Further data is needed to establish neuroanatomical DES maps comparing ANFV with object naming and other tasks to empirically reinforce the advantages of using linguistically complex grammatical tasks over more basic ones, on a region-by-region basis. As highlighted in Chapter 1, new intraoperative monitoring platforms, such as NeuroMapper, allow the detection of intraoperative disturbances in the form of both errors and response times (Smith et al., 2022; Suarez-Meade et al., 2022). Recording reaction times in-theatre allows detection of subtle delays that cannot be measured by the language clinician; this may help to better identify intraoperative disturbances and reduce further postoperative declines in linguistic processing speed. Incorporating newer linguistic protocols such as VAN-POP with intraoperative measures of reaction time will revolutionise the awake mapping field, allowing highly accurate real-time detection of DES and resection-induced retrieval delays. This will allow clinicians and researchers to gather a wealth of intraoperative

data that can be used for improving patient outcomes and furthering understanding of the neural correlates of language and cognition in low-grade glioma and other neuropathologies.

Studies 2 and 3 (Chapters 4 and 5) succeeded in trialling the VAN-POP with frontal, temporal and parietal patients. However, the total number of patients included in these studies was limited due to the impact of COVID-19. Consequently, research questions concerning the factor of different lesion locations on both intraoperative and pre-/post-operative task performance was not able to be fully addressed. Future studies should aim to test a larger number of patients using the VAN-POP, pre-, intra-, and post-operatively to further understand the effects of tumour and surgical lesion location on language function.

One of the most important limitations of the present thesis was that the postoperative follow-up period was relatively short (3 months). Due to the onset of the COVID-19 pandemic, patients could not be followed-up at six months post-surgery, as originally planned. A follow-up timepoint of three months does reflect the typical length of follow-up at which patients are assessed clinically, particularly in the UK NHS. However, this timepoint is still within the relatively acute postoperative period. Therefore, functional reorganisation of neuropsychological functions may still be ongoing, suggesting that improvements (or perhaps declines/stability of functioning) may be seen within the 3-6-month postoperative period. A longer-term follow-up at six months or more postoperatively is crucial to gain a better understanding regarding the trajectory of impairments in low-grade glioma. Future studies may explore the role of a range of factors (e.g., tumour size, grade, and adjuvant therapies) and importantly, provide insights into whether lexical retrieval impairments across different tasks improve, remain stable or worsen over time, with and without therapeutic interventions.

Qualitative research enables valuable insights into the patient experience of life after awake craniotomy and how their perceptions of their own neuropsychological function may

impact their quality of life (Ake et al., 2023). Further research is needed to establish whether deficits identified through objective testing translate into functional difficulties in the real-world and how this may change over time. This would provide further justification for clinical investment in improving postoperative neuropsychological assessment.

6.5. Conclusions

The overarching purpose of this thesis was to investigate preoperative, intraoperative, and postoperative language assessment in awake craniotomy to improve language outcomes for patients. The main aims were to: (1) map, neuroanatomically, the range of tasks currently used, and types of inferences from DES to cortical and subcortical regions through a systematic literature review; (2) trial the VAN-POP for mapping and monitoring complex linguistic functions during awake craniotomy for resection of frontal, temporal and parietal glioma; (3) examine patients linguistic changes in performance (accuracy and reaction times) on the VAN-POP over the postoperative course.

The systematic review synthesised DES mapping data from the vast neurosurgical literature and provided a guide for clinicians to optimise protocols through comprehensive assessment of cognitive and linguistic mapping. The VAN-POP was demonstrated to be a valuable comprehensive approach that can detect positive language sites during mapping and/or monitoring in all patients within the study, while proving to be practical for delivery by clinicians and well-tolerated by patients. As a pre- and post-operative assessment, the VAN-POP has been capable of detecting linguistic changes in performance and providing new insights into the unique nature of the glioma language profile. Specifically, response time being a critical measure to consider, with postoperative declines in lexical retrieval speed that would otherwise have remained masked by standard clinical assessment based on accuracy.

Neuropsychological assessment in current awake craniotomy practice is insufficient and requires improved interventions to maximise postoperative outcomes and patient quality of life. This thesis has advanced improvement by demonstrating that new approaches such as the VAN-POP can optimise intraoperative and perioperative assessment and uncover subtler pre- and post-operative impairments beyond the scope of standard clinical assessments. Going forward, collaborations between clinicians and researchers on developing all stages of assessment provides the best hope of improving neuropsychological outcomes for patients.

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Appendices

Appendix 1.

Search strategy, terms and databases used for systematic review (Chapter 2)

Population	Outcome	Databases
Neoplasm AND Brain OR Brain Neosplasm OR Brain Tumor OR Brain Tumour OR Tumor AND Brain OR Tumour AND Brain OR Malignant Neosplasm AND Brain OR Brain Malignant Neosplasm OR Malignant Neosplasm AND Brain OR Neosplasm AND Brain AND Malignant OR Brain Neosplasm AND Malignant OR Malignant Brain Neoplasm OR Neosplasm AND Intracranial OR Intracranial Neosplasm OR Neoplasms AND Brain OR Brain Neosplasms OR Brain Tumors OR Brain Tumours OR Tumors AND Brain OR Tumours AND Brain OR Malignant Neosplasms AND Brain OR Brain Malignant Neosplasms OR Malignant Neosplasms AND Brain OR Neosplasms AND Brain AND Malignant OR Brain Neosplasms AND Malignant OR Malignant Brain Neoplasms OR Neosplasms AND Intracranial OR Intracranial Neosplasms OR Brain Cancer OR Cancer AND Brain OR Cancer AND Brain OR Brain AND Cancer OR Brain Cancers OR Cancers AND Brain OR Cancers AND Brain OR Brain AND Cancers OR Brain Tumors AND Recurrent OR Brain Tumours AND Recurrent OR Recurrent Brain Tumors OR Recurrent Brain Tumours OR Brain Neosplasms OR Brain Neosplasms (These terms searched for by title, abstract and key words)	Broca OR Wernicke OR Aphasia OR Anomia OR Alexia OR Dyslexia OR Language OR Linguistic OR Reading OR Writing OR Naming OR Speech OR Agrammatism OR Semantic OR Semantics (These terms were searched for by full text so as not overlook papers that may not make language assessment explicit in the title.)	The LJMU Discover tool was used for searching, allowing access to multiple databases at once 3 separate searches were performed due to the setup of this search engine: the first search applied search terms to titles; the second to abstracts; and the third to keywords
Population search terms were not used for the follow-up search as this restricted the results.	Broca OR Wernicke OR Aphasia OR Anomia OR Alexia OR Dyslexia OR Language OR Linguistic OR Reading OR Writing OR Naming OR Speech OR Agrammatism OR Semantic OR Semantics	PubMed (searched for articles published since the original search). Updated search could not be done using the LJMU discover tool as the platform changed and no longer support searching using Boolean terms.
Population search terms were not used for the follow-up search as this restricted the results.	Broca OR Wernicke OR Aphasia OR Anomia OR Alexia OR Dyslexia OR Language OR Linguistic OR Reading OR Writing OR Naming OR Speech OR Agrammatism OR Semantic OR Semantics	PubMed (searched for articles published since the original search). Updated search could not be done using the LJMU discover tool as the platform changed and no longer support searching using Boolean terms.

Appendix 2.

Information for included studies in systematic review (Chapter 2)

First author	Year	Country	Title	Study ID	Study Type	Hemisphere	Location
Abel	2009	Belgium	Cortical stimulation mapping in a patient with foreign accent syndrome: Case report	Abel2009	Single case study/case series	Left	Cortical
Alimohamadi	2016	Belgium	Application of Awake Craniotomy and Intraoperative Brain Mapping for Surgical Resection of Insular Gliomas of the Dominant Hemisphere	Alimohamadi2016	Single case study/case series	Left	Both
Amorim	2008	Belgium	Cortical stimulation of language fields under local anaesthesia.	Amorim2008	Single case study/case series	Left	Cortical
Bello	2007	Belgium	Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas	Bello2007	Single case study/case series	Left	Subcortical
Bello	2008	Brazil	Motor and language DTI Fiber Tracking combined with intraoperative subcortical mapping for surgical removal of gliomas.	Bello2008	Single case study/case series	Left	Subcortical
Bilotta	2014	Canada	Diagnostic work up for language testing in patients undergoing awake craniotomy for brain lesions in language areas	Bilotta2014	Single case study/case series	Left	Cortical
Borius	2012	China	Sentence Translation in proficient bilinguals: A direct electrostimulation brain mapping.	Borius2012	Single case study/case series	Both	Cortical
Chacko	2013	China	Awake craniotomy and electrophysiological mapping for eloquent area tumours.	Chacko2013	Group/Cohort	Left	Cortical
Chan	2019	China	Awake Craniotomy and Excision of A Diffuse Low-Grade Glioma in a Multilingual Patient - Neuropsychology and Language	Chan2019	Single case study/case series	Left	Cortical
Chan-Seng	2014	France	Awake mapping for low-grade gliomas involving the left sagittal stratum: anatomofunctional and surgical considerations	ChanSeng2014	Single case study/case series	Left	Both
De Benedictis	2014	France	Anatomo-functional study of the temporo-parieto-occipital region: dissection, tractographic and brain mapping evidence from a neurosurgical perspective	DeBenedictis2014	Single case study/case series	Left	Both
Della Puppa	2015	France	Right parietal cortex and calculation processing:	DellaPuppa2015	Single case study/case series	Right	Cortical

			intraoperative functional mapping of multiplication and addition in patients affected by a brain tumor				
De Witte	2015	France	Subcortical language and non-language mapping in awake brain surgery: the use of multimodal tests	DeWitte2015a	Single case study/case series	Left	Both
De Witte	2015	France	The Dutch Linguistic Intraoperative Protocol: A valid linguistic approach to awake brain surgery.	DeWitte2015b	Single case study/case series	Left	Both
De Witte	2015	France	Non-organic language deficits after awake brain Surgery: a case report.	DeWitte2015c	Single case study/case series	Left	Both
De Witt Hamer	2011	France	Is the human left middle longitudinal fascicle essential for language? A brain electrostimulation study.	DeWittHamer2011	Single case study/case series	Left	Both
Duffau	2002	France	Intraoperative mapping of the cortical areas involved in multiplication and subtraction: an electrostimulation study in a patient with a left parietal glioma	Duffau2002a	Single case study/case series	Left	Cortical
Duffau	2002	France	Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study	Duffau2002b	Single case study/case series	Left	Both
Duffau	2002	France	Long term reshaping of language, sensory, and motor maps after glioma resection: a new parameter to integrate in the surgical strategy	Duffau2002c	Single case study/case series	Left	Cortical
Duffau	2003	France	The role of the dominant premotor cortex in language: a study using intraoperative functional mapping in awake patients.	Duffau2003a	Single case study/case series	Left	Cortical
Duffau	2003	France	The articulatory loop: study of subcortical connectivity by electrostimulation.	Duffau2003b	Single case study/case series	Left	Cortical
Duffau	2003	France	Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation	Duffau2003c	Single case study/case series	Left	Cortical
Duffau	2004	France	Intraoperative mapping of the subcortical visual pathways using direct electrical stimulation.	Duffau2004	Single case study/case series	Left	Cortical
Duffau	2005	France	New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-	Duffau2005	Single case study/case series	Left	Both

			subcortical electrostimulations				
Duffau	2008	France	Cortico-subcortical organization of language networks in the right hemisphere: an electrostimulation study in left-handers	Duffau2008a	Single case study/case series	Both	Both
Duffau	2008	France	Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere	Duffau2008b	Group/Cohort	Left	Subcortical
Duffau	2009	France	Functional outcome after language mapping for insular world-health organisation grade II gliomas in the dominant hemisphere.	Duffau2009a	Single case study/case series	Left	Cortical
Duffau	2009	France	Is the left uncinate fasciculus essential for language? A cerebral stimulation study	Duffau2009b	Group/Cohort	Left	Cortical
Ellemore	2009	France	Relationships between essential cortical language sites and subcortical pathways	Ellemore2009	Single case study/case series	Left	Subcortical
Fuji	2015	France	Intraoperative subcortical mapping of a language-associated deep frontal tract connecting the superior frontal gyrus to Broca's area in the dominant hemisphere of patients with glioma	Fuji2015	Single case study/case series	Left	Subcortical
Gatignol	2004	France	Double dissociation between picture naming and comprehension: an electrostimulation study.	Gatignol2004	Single case study/case series	Left	Both
Gao	2016	France	Language-associated cortical regions in non-proficient Chinese–English bilinguals with glioma	Gau2016	Group/Cohort	Left	Cortical
Gil-Robles	2005	France	The role of dominant striatum in language: a study using intraoperative electrical stimulation.	Gil-Robles2005	Single case study/case series	Both	Subcortical
Gil-Robles	2008	France	Long-term brain plasticity allowing a multistage surgical approach to world health organisation grade II gliomas in eloquent areas.	Gil-Robles2008	Single case study/case series	Left	Both
Gil-Robles	2013	France	Double dissociation between visual recognition and picture naming: A study of the visual language connectivity using tractography and brain stimulation.	Gil-Robles2013	Single case study/case series	Left	Both

Giussani	2009	France	Who is who: areas of the brain associated with recognizing and naming famous faces	Giussani2009	Group/Cohort	Left	Cortical
Giussani	2011	France	Anatomical correlates for category-specific naming of living and non-living things	Giussani2011	Group/Cohort	Left	Cortical
Hayashi	2014	France	Case Reports & Case Series (CRP): Functional recovery from pure dyslexia with preservation of subcortical association fiber networks	Hayashi2014	Single case study/case series	Left	Subcortical
Henry	2004	France	Subcortical pathways serving cortical language sites: initial experience with diffusion tensor imaging fiber tracking combined with intraoperative language mapping	Henry2004	Single case study/case series	Left	Cortical
Herbert	2015	France	Disrupting the right pars opercularis with electrical stimulation frees the song: case report.	Herbert2015	Single case study/case series	Right	Cortical
Kamada	2007	France	Visualization of the frontotemporal language fibers by tractography combined with functional magnetic resonance imaging and magnetoencephalography	Kamada2007	Single case study/case series	Left	Both
Khan	2014	France	The role of the left inferior fronto-occipital fascicle in verbal perseveration.	Khan2014	Single case study/case series	Left	Subcortical
Kin	2013	France	Language areas involving the inferior temporal cortex on intraoperative mapping in a bilingual patient.	Kin2013	Single case study/case series	Left	Cortical
Kosla	2015	France	Reorganization of Language Areas in Patient with a Frontal Lobe Low Grade Glioma - fMRI Case Study.	Kosla2015	Single case study/case series	Left	Cortical
Kurimoto	2006	France	Safe removal of glioblastoma near the angular gyrus by awake surgery preserving calculation ability--case report	Kurimoto2006	Single case study/case series	Left	Cortical
Leclercq	2010	France	Comparison of diffusion tensor imaging tractography of language tracts and intraoperative subcortical stimulations	Leclercq2010	Group/Cohort	Left	Subcortical
Lee	2018	France	Neural encoding and production of functional morphemes in the posterior temporal lobe.	Lee2018	Group/Cohort	Left	Cortical
Lima	2017	France	Surgical resection of incidental diffuse gliomas involving eloquent brain areas.	Lima2017	Single case study/case series	Left	Both

			Rationale, functional, epileptological and oncological outcomes				
Lubrano	2004	France	Writing-specific sites in frontal areas: a cortical stimulation study	Lubrano2004	Single case study/case series	Both	Cortical
Lubrano	2010	France	What makes surgical tumor resection feasible in Broca's area? Insights into intraoperative brain mapping	Lubrano2010	Group/Cohort	Left	Cortical
Lubrano	2012	France	Language monitoring in a multilingual patient undergoing awake craniotomy.: A case study of German-English-French trilungual patient with WHO grade II glioma.	Lubrano2012	Single case study/case series	Left	Cortical
Lubrano	2014	France	Anatomical correlates for category-specific naming of objects and actions: a brain stimulation mapping study	Lubrano2014	Group/Cohort	Left	Cortical
Maldonado	2011	France	Does the left superior longitudinal fascicle subserve language semantics? A brain electrostimulation study.	Maldonado2011a	Single case study/case series	Left	Subcortical
Maldonado	2011	France	Surgery for gliomas involving the left inferior parietal lobule: new insights into the functional anatomy provided by stimulation mapping in awake patients	Maldonado2011b	Single case study/case series	Left	Subcortical
Mandonnet	2007	France	Does the left inferior longitudinal fasciculus play a role in language? A Brain stimulation study.	Mandonnet2007	Single case study/case series	Left	Both
Mandonnet	2009	France	Evidence for an occipito-temporal tract underlying visual recognition in picture naming.	Mandonnet2009	Single case study/case series	Left	Cortical
Martino	2018	France	Intraoperative Identification and Preservation of Verbal Memory in Diffuse Gliomas: A Matched-Pair Cohort Study	Martino2018	Group/Cohort	Both	Cortical
Matsuda	2014	France	The persistent crucial role of the left hemisphere for language in left-handers with a left low grade glioma: a stimulation mapping study.	Matsuda2014	Single case study/case series	Left	Both
Matsuda	2019	France	Subcortical calculation mapping during parietal glioma surgery in the dominant hemisphere: A Case Report.	Matsuda2019	Single case study/case series	Left	Cortical

Metellus	2016	France	Successful Insular Glioma Removal in a Deaf Signer Patient During an Awake Craniotomy Procedure	Metellus2016	Single case study/case series	Left	Both
Morits-Gasser	2009	France	Evidence of a large-scale network underlying language switching: A brain stimulation Study.	Morits-Gasser2009	Single case study/case series	Left	Both
Morits-Gasser	2013	France	Mapping the connectivity underlying multimodal (verbal and non-verbal) semantic processing: A brain electrostimulation study.	Morits-Gasser2013	Single case study/case series	Left	Subcortical
Motomura	2014	France	Association of the dorsal inferior fronto-occipital fasciculus fibres in deep parietal lobe with both reading and writing processes: a brain mapping study.	Motomura2014	Single case study/case series	Left	Both
Mukae	2017	France	The usefulness of arcuate fasciculus tractography integrated navigation for glioma surgery near the language area; Clinical investigation.	Mukae2017	Single case study/case series	Left	Subcortical
Nomura	2013	France	Possible roles of the dominant uncinate fasciculus in naming objects: A case report of intraoperative electrical stimulation on a patient with a brain tumour.	Nomura2013	Single case study/case series	Left	Subcortical
Ogawa	2014	France	Rapid and minimum invasive functional brain mapping by real-time visualisation of high gamma activity during awake craniotomy.	Ogawa2014	Single case study/case series	Left	Cortical
Ogawa	2017	Germany	Clinical impact and implication of real-time oscillation analysis for language mapping.	Ogawa2017	Single case study/case series	Left	Cortical
Parney	2010	India	Awake craniotomy, electrophysiologic mapping, and tumor resection with high-field intraoperative MRI	Parney2010	Single case study/case series	Left	Cortical
Petrovich Brennan	2007	Iran	Object naming is a more sensitive measure of speech localisation than number counting.	PetrovichBrennan2007	Single case study/case series	Left	Cortical
Plaza	2009	Israel	Speaking without Broca's area after tumour resection.	Plaza2009	Single case study/case series	Left	Both
Pu	2011	Italy	Cortical areas involved in numerical processing: an intraoperative electrostimulation study	Pu2011	Single case study/case series	Left	Cortical
Rech	2017	Italy	Intraoperative identification of the negative motor	Rech2017	Single case study/case series	Left	Cortical

			network during awake surgery to prevent deficit following brain resection in premotor regions				
Riva	2016	Italy	Brain and Music: An Intraoperative Stimulation Mapping Study of a Professional Opera Singer	Riva2016	Single case study/case series	Left	Cortical
Rofes	2015	Italy	Advantages and disadvantages of intraoperative language tasks in awake surgery: a three-task approach for prefrontal tumors	Rofes2015	Single case study/case series	Left	Both
Rofes	2017	Italy	Mapping nouns and finite verbs in left hemisphere tumours: a direct electrical stimulation study.	Rofes2017	Single case study/case series	Left	Both
Rolland	2018	Italy	Awake Surgery for Gliomas within the Right Inferior Parietal Lobule: New Insights into the Functional Connectivity Gained from Stimulation Mapping and Surgical Implications	Rolland2018	Single case study/case series	Left	Both
Rosenberg	2008	Italy	Language related reorganization in adult brain with slow growing glioma.	Rosenberg2008	Single case study/case series	Left	Cortical
Roux	2002	Italy	Organization of language areas in bilingual patients: a cortical stimulation study	Roux2002	Single case study/case series	Left	Cortical
Roux	2003	Italy	Writing, calculating, and finger recognition in the region of the angular gyrus: a cortical stimulation study of Gerstmann syndrome	Roux2003a	Single case study/case series	Left	Cortical
Roux	2003	Italy	Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation	Roux2003b	Single case study/case series	Left	Cortical
Roux	2004	Italy	Intra-operative mapping of cortical areas involved in reading in mono- and bilingual patients	Roux2004	Group/Cohort (1 illustrative case)	Both	Cortical
Roux	2006	Italy	Category-specific cortical mapping: color-naming areas	Roux2006	Single case study/case series	Left	Cortical
Roux	2007	Japan	When "abegg" is read and ("A, B, E, G, G") is not: a cortical stimulation study of musical score reading	Roux2007	Single case study/case series	Left	Cortical
Roux	2009	Japan	"The mute who can sing": a cortical stimulation study on singing.	Roux2009a	Single case study/case series	Left	Cortical
Roux	2009	Japan	The graphemic/motor frontal area Exner's area revisited	Roux2009b	Single case study/case series	Left	Cortical

Roux	2009	Japan	Cortical calculation localization using electrostimulation	Roux2009c	Single case study/case series	Left	Cortical
Roux	2012	Japan	Segregation of lexical and sub-lexical reading processes in the left perisylvian cortex	Roux2012	Single case study/case series	Both	Cortical
Roux	2014	Japan	The neural basis for writing from dictation in the temporoparietal cortex	Roux2014	Single case study/case series	Left	Cortical
Roux	2015	Japan	Electrostimulation mapping of comprehension of auditory and visual words	Roux2015	Group/Cohort	Left	Cortical
Saito	2014	Japan	Functional plasticity of language confirmed with intraoperative electrical stimulations and updated neuronavigations.	Saito2014	Single case study/case series	Left	Both
Sakurada	2007	Japan	Surgical resection of tumours located in subcortex of language area	Sakurada2007	Single case study/case series	Left	Cortical
Sallard	2012	Japan	Ultra-fast recovery from right neglect after ‘awake surgery’ for slow-growing tumor invading the left parietal area	Sallard2012	Single case study/case series	Left	Subcortical
Sarubbo	2012	Japan	Is the resection of gliomas in Wernicke's area reliable? : Wernicke's area resection	Sarubbo2012	Single case study/case series	Left	Both
Satoer	2017	Japan	Differential effects of awake glioma surgery in critical language areas on cognition: 4 case studies.	Satoer2017	Single case study/case series	Left	Both
Schapiro	2012	Japan	A technique for mapping cortical areas associated with speech arrest	Schapiro2012	Single case study/case series	Left	Cortical
Sierpowska	2013	Japan	Intraoperative electrical stimulation of language switching in two bilingual patients	Sierpowska2013	Single case study/case series	Left	Cortical
Signorelli	2003	Poland	Technical refinements for validating functional MRI-based neuronavigation data by electrical stimulation during cortical language mapping	Signorelli2003	Single case study/case series	Left	Cortical
Simos	1999	Singapore	Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping	Simos1999	Single case study/case series	Left	Cortical
Sollman	2013	Spain	Navigated transcranial magnetic stimulation for preoperative language mapping in a patient with a left frontoopercular glioblastoma	Sollman2013	Single case study/case series	Left	Cortical

Spena	2010	Spain	Preoperative and intraoperative brain mapping for the resection of eloquent-area tumors. A prospective analysis of methodology, correlation, and usefulness based on clinical outcomes	Spena2010	Group/Cohort	Left	Cortical
Spena	2015	Spain	Acute functional reactivation of the language network during awake intraoperative brain mapping	Spena2015	Single case study/case series	Left	Cortical
Tate	2014	Spain	Probabilistic map of critical functional regions of the human cerebral cortex: Broca's area revisited	Tate2014	Group/Cohort	Left	Cortical
Tiandong	2015	Spain	Glioma localization and excision using direct electrical stimulation for language mapping during awake surgery	Tiandong2015	Group/Cohort	Left	Cortical
Tomasino	2014	The Netherlands	Involuntary switching into the native language induced by electrocortical stimulation of the superior temporal gyrus: A multimodal mapping study	Tomasino2014	Single case study/case series	Left	Cortical
Van Geemen	2014	USA	Limited plastic potential of the left ventral premotor cortex in speech articulation: evidence from intraoperative awake mapping in glioma patients.	VanGeemen2014	Single case study/case series	Left	Both
Vassal	2010	USA	Crossed aphasia elicited by intraoperative cortical and subcortical stimulation in awake patients.	Vassal2010	Single case study/case series	Right	Both
Vidoretta	2011	USA	Double dissociation between syntactic gender and picture naming processing: a brain stimulation mapping study	Vidoretta2011	Single case study/case series	Left	Both
Wager	2013	USA	Intraoperative Monitoring of an Aspect of Executive Functions: Administration of the Stroop Test in 9 Adult Patients During Awake Surgery for Resection of Frontal Glioma	Wager2013	Single case study/case series	Both	Cortical
Walker	2004	USA	Intraoperative speech mapping in 17 bilingual patients undergoing resection of a mass lesion	Walker2004	Group/Cohort	Left	Cortical
Wang2013	2013	USA	Direct evidence of the left caudate's role in bilingual control: An intra-operative electrical stimulation study	Wang2013	Single case study/case series	Left	Both

Yordanova	2011	USA	Awake surgery for WHO Grade II gliomas within "noneloquent" areas in the left dominant hemisphere: toward a "supratotal" resection. Clinical article	Yordanova2011	Single case study/case series	Left	Both
Yordanova	2017	USA	Neural pathways subserving face-based mentalizing	Yordanova2017	Single case study/case series	Right	Cortical
Yordanova	2019	USA	Combining resting state functional MRI with intraoperative cortical stimulation to map the mentalizing network	Yordanova2019	Single case study/case series	Right	Cortical
Zemmoura	2015	USA	New insights into the neural network mediating reading processes provided by cortico-subcortical electrical mapping.	Zemmoura2015	Single case study/case series	Left	Both

Appendix 3.

Left hemisphere DES mapping data extracted from included studies in systematic review (Chapter 2)

		Cortical Mapping					Subcortical Mapping			
Study ID	**CASE**	**Area d**	**BA**	**Task**	**Interference/error description (from paper)**	**Category**	**Area**	**Task**	**Interference/error description (from paper)**	**Category**
Individual Case Data										
Abel2009	1	Posterior Superior temporal gyrus	22(a) 21(a)	Object naming	Hesitation	Response delay				
Alimohamadi2016	1	Posterior Superior temporal gyrus	22 (a)	Counting	Conductive aphasia	Speech disturbance				
	2						Caudate head	Counting	Perseveration	Response perseveration
Amorim2008	Fig 3	Ventral premotor cortex Mid. inferior frontal gyrus (pars triangularis)	6(b)	Counting Counting	Speech arrest Speech arrest	Speech disturbance Speech disturbance				
	Fig 2	Posterior superior temporal gyrus Posterior middle temporal gyrus	22(a) 21(a)	Counting Counting	Speech arrest Speech arrest	Speech disturbance Speech disturbance				
Bello2007	Fig 2						Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming; Spontaneous speech	Semantic paraphasia Anomia; reduction of spontaneous speech	Semantic error Anomia; Reduction of spontaneous speech
	Fig 3						Subcallosal fasciculus	Spontaneous speech	Reduction of spontaneous speech	Reduction of spontaneous speech
Bello2008	Fig 4						Superior longitudinal fasciculus	Object naming; Action naming; Famous face naming	Phonological paraphasia; Anomia	Phonological error; Anomia

	Fig 4						Superior longitudinal fasciculus	Object naming; Action naming; Famous face naming	Phonological paraphasia; Anomia	Phonological error; Anomia
	Fig 5						Superior longitudinal fasciculus Inferior fronto-occipital fasciculus Uncinate fasciculus	Object naming; Action naming; Famous face naming famous face naming famous face naming	Phonological paraphasia; Anomia Semantic paraphasia Semantic paraphasia	Phonological error; Anomia Semantic error Semantic error
	Fig 5						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia	Semantic error
Bilotta2014	1	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	2	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	3	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	4	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	5	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	6	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				

	7	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	8	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	9	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	10	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	11	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	12	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	13	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	14	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
	15	Posterior/middle Inferior frontal gyrus (pars opercularis/ triangularis)	44/45	Counting	Speech arrest	Speech disturbance				
Borius2012	3	Posterior Inferior frontal gyrus (pars opercularis)	44	Object naming; Reading; Translation		Not specified				
	5	Middle superior temporal gyrus	22(b)	Object naming; Reading		Not specified				

	6	Supramarginal gyrus	40	Object naming; Reading		Not specified				
	7	Posterior inferior frontal gyrus (pars opercularis) Angular gyrus	44 39	Object naming; Reading Object naming; Reading		Not specified				
Chan2019		Ventral premotor cortex Precentral gyrus Dorsal precentral gyrus	6b 4 6a	Counting Object naming Object naming	Speech arrest Naming delay Anomia	Speech disturbance Response delay Anomia				
ChanSeng 2014	1	Ventral premotor cortex Supramarginal gyrus Middle Superior temporal gyrus	9(b) 40 22(b)	Object naming Object naming Object naming	Speech arrest Anomia Phonological paraphasia	Speech disturbance Anomia Phonological error	Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	2	Ventral premotor cortex Posterior Superior temporal gyrus Posterior Middle temporal gyrus Posterior Inferior temporal gyrus Basal temporo-occipital junction (VC)	9(b) 22(c) 21(c) 20(c) 37/19	Object naming Object naming Object naming Reading Reading	Speech arrest Anomia Anomia Alexia Alexia	Speech disturbance Anomia Anomia Alexia Alexia	Inferior fronto-occipital fasciculus Inferior longitudinal fasciculus	Object naming Reading	Semantic paraphasia Alexia	Semantic error Alexia
	3	Ventral premotor cortex Posterior superior temporal gyrus	6(b)	Object naming Object naming	Speech arrest Anomia	Speech disturbance Anomia	Inferior fronto-occipital fasciculus Inferior longitudinal fasciculus	Object naming Reading	Semantic paraphasia Alexia	Semantic error Alexia
	4	Ventral premotor cortex Posterior Middle temporal gyrus Posterior Superior temporal gyrus	6(b) 21(c) 22©	Object naming Object naming Object naming	Speech arrest Anomia Semantic paraphasia	Speech disturbance Anomia Semantic error	Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia	Semantic error
	5	Ventral premotor cortex Posterior Superior temporal gyrus	6(b) 22(c.)	Object naming Object naming	Speech arrest Anomia	Speech disturbance Anomia	Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error

	6	Ventral premotor cortex Posterior Inferior temporal gyrus	6(b) 21©	Object naming Object naming	Speech arrest Anomia	Speech disturbance Anomia	Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	7	Ventral premotor cortex Middle Superior temporal gyrus Posterior Superior temporal gyrus	6(b) 22(b) 22(c)	Object naming Object naming Object naming	Speech arrest Anomia; phonological paraphasia Semantic paraphasia	Speech disturbance Anomia; phonological error Semantic error	Inferior fronto-occipital fasciculus Arcuate fasciculus Inferior longitudinal fasciculus	Object naming Object naming Reading	Semantic paraphasia Phonological paraphasia Alexia	Semantic error Phonological error Alexia
	8	Ventral premotor cortex Posterior Superior temporal gyrus Posterior Middle temporal gyrus	6(b) 22c) 21(c)	Object naming Object naming Object naming	Speech arrest Anomia Semantic paraphasia	Speech disturbance Anomia Semantic error	Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
DeBenedictis2014	1	Ventral premotor cortex	6(b)	Counting	Speech arrest	Speech disturbance	Superior longitudinal fasciculus Arcuate fasciculus	Object naming, counting Object naming	Articulation disorders Semantic paraphasia	Speech disturbance Semantic error
	2	Ventral premotor cortex Posterior Superior temporal gyrus	6(b)	Counting/Object naming Object naming	Speech arrest Anomia; Semantic paraphasia; Reading troubles	Speech disturbance Anomia; Semantic error; Alexia	Inferior fronto-occipital fasciculus Inferior longitudinal fasciculus	Object naming Object naming	Semantic paraphasia; anomia Reading troubles	Semantic error; anomia Alexia
DeWittHamer2011	1	Ventral premotor cortex	6(b)	Object naming	Speech arrest	Speech disturbance	Inferior fronto-occipital fasciculus Arcuate fasciculus Striatum	Object naming Object naming Object naming	Dyssomnia Phonological paraphasia Perseveration	Anomia Phonological error Response perseveration
	2	Ventral premotor cortex Superior temporal gyrus	6(b)	Object naming Object naming	Speech arrest Hesitation	Speech disturbance Response delay	Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	3	Ventral premotor cortex Superior temporal gyrus	6(b)	Object naming Object naming	Speech arrest Dyssomnia	Speech disturbance Anomia	Striatum Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming Object naming	Anomia Semantic paraphasia Phonological paraphasia	Anomia Semantic error Phonological error

	4	Ventral premotor cortex Inferior frontal gyrus Middle temporal gyrus	6(b)	Object naming Object naming Object naming	Speech arrest Phonological paraphasia Semantic paraphasia	Speech disturbance Phonological paraphasia Semantic error	Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming	Anomia; Semantic paraphasia Phonological paraphasia	Anomia; Semantic error Phonological error
	5	Ventral premotor cortex Middle temporal gyrus Superior temporal gyrus	6(b) 9/46 22	Object naming Object naming Object naming	Speech arrest Anomia Semantic paraphasia	Speech arrest Anomia Semantic error	Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming	Semantic paraphasia; anomia Phonological paraphasia	Semantic error; Anomia Phonological error
	6	Ventral premotor cortex	6(b)	Object naming	Speech arrest	Speech disturbance	Striatum Inferior fronto-occipital fasciculus Arcuate fasciculus	Object naming Object naming Object naming	Speech arrest; disarticulation Semantic paraphasia; anomia Phonological paraphasia	Speech disturbance; Motor Semantic error; Anomia Phonological error
	7	Ventral premotor cortex Superior temporal gyrus	6(b) 22	Object naming Object naming	Speech arrest Semantic paraphasia	Speech disturbance Semantic paraphasia	Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia	Semantic error
	8	Ventral premotor cortex Superior temporal gyrus	6(b) 23	Object naming Object naming	Speech arrest Anomia	Speech disturbance Anomia	Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia	Semantic error
DeWitte2015a	1	Posterior Inferior frontal gyrus Superior temporal gyrus	44 22	Counting, Object naming Counting, Object naming	Speech arrest Speech arrest	Speech disturbance Speech disturbance	Below temporal region	Spontaneous speech	Auditory comprehension deficit	Auditory comprehension deficit
	2	Precentral gyrus Superior temporal gyrus Middle temporal gyrus	4 22 21	Object naming Object naming Object naming	Anarthria Delay Delay	Motor Response delay Response delay	Inferior fronto-occipital fasciculus Inferior fronto-occipital fasciculus	Semantic picture out Object naming	Semantic comprehension deficit Semantic paraphasia	Semantic comprehension deficit Semantic error
	3	Supramarginal gyrus Angular Postcentral gyrus	40 39 1-3	Object naming Object naming Object naming	Speech arrest Anomia; Delay Anomia; Delay	Speech disturbance Anomia; Response delay	Below parietal cortex Below parietal cortex	Sentence completion Calculation	Delay (reading)	Delay (reading)

DeWitte2015b	2	Inferior frontal gyrus Middle temporal gyrus	44/45/47 21	Action naming with finite verbs Object naming	Speech arrest Anomia; Delay	Speech disturbance Anomia; Response delay	Inferior fronto-occipital fasciculus Arcuate fasciculus	Semantic picture out Repetition	Phonological paraphasia; word retrieval problem Phonological paraphasia; word retrieval problem	Phonological error; word retrieval problem Phonological error; word retrieval problem
	3	Dorsal premotor cortex	6a	Sentence completion	Speech initiation difficulty	Speech disturbance	Cortico-spinal tract	Repetition	Speech arrest with motor reaction	Motor
	4	Posterior Inferior frontal gyrus Middle temporal gyrus Inferior temporal gyrus	44 21 20	Repetition Object naming Object naming	Speech arrest Anomia; Delay Anomia; Delay	Speech disturbance Anomia; Response delay Anomia; Response delay	Inferior fronto-occipital fasciculus Arcuate fasciculus	Semantic picture out; sentence completion Repetition	Word retrieval problem Phonological paraphasia	Anomia; Speech disturbance Phonological error
	5	Supramarginal/postcentral gyrus Angular/supramarginal gyrus Posterior Middle temporal gyrus	40/43 39/40 21c	Semantic picture out Semantic picture out Semantic picture out	Delay Anomia; dysarthria Anomia	Anomia; Response delay Anomia; Motor Anomia	Inferior fronto-occipital fasciculus Below parietal cortex	Sentence completion Calculation	Delay -	Response delay Not specified
DeWitte2015c	1	Precentral gyrus Anterior Superior temporal gyrus	4 22a	Object naming Object naming	Speech arrest with motor reaction Delay	Motor Response delay	Arcuate fasciculus	Object naming	Phonological paraphasia	Phonological error
Duffau2002a	1	Angular gyrus Angular gyrus Supramarginal gyrus Supramarginal gyrus	39 39 40 40	Multiplication Subtraction Counting Object naming	Speech arrest Speech arrest	Speech disturbance Speech disturbance				
Duffau2002b	Fig 1	Middle frontal gyrus	9/46	Object naming	Anomia	Anomia	Subcallosal fasciculus	Counting, Object naming	Transcortical motor aphasia	Speech disturbance
	Fig 2	Posterior Inferior frontal gyrus	44	Object naming, Counting	Speech arrest	Speech disturbance	Subcallosal fasciculus	Counting, Object naming	Transcortical motor aphasia; Speech arrest	Speech disturbance
Duffau2002c	1	Middle temporal gyrus Inferior	21b 44/45/47	Object naming Counting,	Anomia Speech arrest	Anomia Speech disturbance				

		frontal gyrus		Object naming						
Duffau2003a	1	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	2	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	3	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	4	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	5	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	6	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	7	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				

	8	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	9	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	10	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	11	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	12	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	13	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	14	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	15	Dorsal premotor cortex Ventral premotor	6a 6b 44	Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				

		cortex Posterior Inferior frontal gyrus		Object naming						
	16	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	17	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	18	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	19	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	20	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	21	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	22	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				

	23	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	24	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
	25	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Object naming Object naming Object naming	Anomia Anarthria Anomia	Anomia Motor Anomia				
Duffau2003b	1	Inferior precentral gyrus Posterior Inferior frontal gyrus Supramarginal gyrus	4 44 40	Counting; Object naming; Repetition Counting; Object naming; Repetition Counting; Object naming; Repetition	Anarthria Speech arrest; Anomia Speech arrest	Motor Speech disturbance; Anomia Speech disturbance	Below supramarginal gyrus	Counting; Object naming; Repetition	Anomia	Anomia
Duffau2003c	1	Insula cortex Dorsal premotor cortex Inferior frontal gyrus	13-16 6a 44/45/47	Counting, Object naming Counting, Object naming Counting, Object naming	Speech arrest Anarthria Speech arrest	Speech disturbance Motor Speech disturbance				
	Fig 5	Precentral gyrus Middle frontal gyrus Anterior Inferior frontal gyrus (pars orbitalis)	4 9/46 47	Counting, Object naming Object naming Counting, Object naming	Anarthria Anomia Speech arrest	Motor Anomia Speech disturbance				
Duffau2004	1	Posterior Inferior frontal gyrus Posterior	44 22c	Counting; Object naming	Speech interference with motor reaction	Motor Semantic error				

		Superior temporal gyrus		Object naming	(face) Semantic paraphasia					
Duffau2005	1	Inferior frontal gyrus	44/45/47	Object naming	Semantic paraphasia	Semantic error	White matter (below inferior frontal gyrus)	Object naming	Semantic paraphasia	Semantic error
	2	Inferior frontal gyrus	44/45/47	Object naming	Semantic paraphasia	Semantic error	White matter (below inferior frontal gyrus)	Object naming	Semantic paraphasia	Semantic error
	3	Inferior frontal gyrus	44/45/47	Object naming	Semantic paraphasia	Semantic error	White matter (below inferior frontal gyrus)	Object naming	Semantic paraphasia	Semantic error
	4	Inferior frontal gyrus	44/45/47	Object naming	Semantic paraphasia	Semantic error	White matter (below inferior frontal gyrus)	Object naming	Semantic paraphasia	Semantic error
	5	Inferior frontal gyrus	44/45/47	Object naming	Semantic paraphasia	Semantic error	White matter (below inferior frontal gyrus)	Object naming	Semantic paraphasia	Semantic error
	6						White matter (below inferior frontal gyrus)	Object naming	Semantic paraphasia	Semantic error
	7						White matter (below inferior frontal gyrus)	Object naming	Semantic paraphasia	Semantic error
	8						White matter (below inferior frontal gyrus)	Object naming	Semantic paraphasia	Semantic error
	9						White matter (below inferior frontal gyrus)	Object naming	Semantic paraphasia	Semantic error
	10						White matter (below insula cortex)	Object naming	Semantic paraphasia	Semantic error
	12	Inferior Frontal gyrus	44/45/47	Object naming	Semantic paraphasia	Semantic error	White matter below superior temporal sulcus	Object naming	Semantic paraphasia	Semantic error
	13	Inferior Frontal gyrus	44/45/47	Object naming	Semantic paraphasia	Semantic error	White matter below superior temporal sulcus	Object naming	Semantic paraphasia	Semantic error
	14	Inferior Frontal gyrus	44/45/47	Object naming	Semantic paraphasia	Semantic error	Anterior floor of the external capsule White matter below superior temporal sulcus	Object naming Object naming	Semantic paraphasia Semantic paraphasia	Semantic error Semantic error
	15	Inferior Frontal gyrus	44/45/47	Object naming	Semantic paraphasia	Semantic error	Anterior floor of the external capsule White matter below superior temporal sulcus	Object naming Object naming	Semantic paraphasia Semantic paraphasia	Semantic error Semantic error

	16						Anterior floor of the external capsule White matter below superior temporal sulcus	Object naming Object naming	Semantic paraphasia Semantic paraphasia	Semantic error Semantic error
	17						Anterior floor of the external capsule White matter below superior temporal sulcus	Object naming Object naming	Semantic paraphasia Semantic paraphasia	Semantic error Semantic error
Duffau2009a	1	Insula Cortex	13-16	Counting, Object naming		Not specified				
	2	Insula Cortex	13-16	Counting, Object naming		Not specified				
	4	Insula Cortex	13-16	Counting, Object naming		Not specified				
	8	Insula Cortex	13-16	Counting, Object naming		Not specified				
	20	Insula Cortex	13-16	Counting, Object naming		Not specified				
Ellemore2009	4						Arcuate Fasciculus	Counting, Repetition	Articulatory disturbance	Speech disturbance
Fujii2015	1						Frontal aslant tract	Object naming	Speech arrest	Speech disturbance
	2						Frontal aslant tract	Object naming	Speech initiation	Speech disturbance
	3						Frontal aslant tract	Object naming	Speech arrest	Speech disturbance
	4						Frontal aslant tract	Object naming	Speech arrest	Speech disturbance
	5						Frontal aslant tract	Object naming	Speech arrest	Speech disturbance
Gatignol2004	1	Precentral gyrus Posterior Superior temporal gyrus Middle Superior temporal gyrus	4 22c 9/46	Counting Object naming Pyramids and palms trees test	Speech arrest with motor reaction Anomia Semantic comprehension interference; semantic errors	Motor Anomia Comprehension deficit; Semantic errors	Below superior/middle temporal gyrus	Object naming		Not specified

Gil-Robles2005	1						Putamen	Counting, Object naming	Anarthria	Motor
	2						Putamen	Counting, Object naming	Anarthria	Motor
	3						Putamen	Counting, Object naming	Anarthria	Motor
	4						Putamen	Counting, Object naming	Anarthria	Motor
	5						Putamen	Counting, Object naming	Anarthria	Motor
	6						Caudate	Counting, Object naming	Perseveration	Response perseveration
	8						Caudate	Counting, Object naming	Perseveration	Response perseveration
	9						Caudate	Counting, Object naming	Perseveration	Response perseveration
	10						Caudate	Counting, Object naming	Perseveration	Response perseveration
	11						Caudate	Counting, Object naming	Perseveration	Response perseveration
	12						Caudate	Counting, Object naming	Perseveration	Response perseveration
Gil-Robles2008	1	Dorsal premotor cortex Ventral premotor cortex Posterior Inferior frontal gyrus	6a 6b 44	Counting Counting Counting	Anarthria Speech arrest Verbal paraphasia	Motor Speech disturbance	Superior fronto-occipital fasciculus Arcuate fasciculus	Counting Counting	Articulatory problems Speech arrest; verbal paraphasia	Speech disturbance Speech disturbance; response error
	2	Ventral premotor cortex Posterior Inferior frontal gyrus	6b 44	Counting, Object naming Object naming	Speech arrest Semantic paraphasia; phonological paraphasia	Speech disturbance Semantic error; phonological error	Superior fronto-occipital fasciculus Arcuate fasciculus	Counting Counting	Articulatory problems Verbal paraphasia	Speech disturbance Verbal error

Gil-Robles2013	1	Posterior Inferior temporal gyrus Superior temporal gyrus	44 22	Symbol recognition; Reading Object naming		Not specified Not specified	Inferior longitudinal fasciculus	Symbol recognition; Reading	symbol recogniti on; reading interference	symbol recognition; reading interference
	2	Posterior Inferior temporal gyrus Superior temporal gyrus	44 22	Symbol recognition; Reading Object naming; Symbol recognition; Reading		Not specified Not specified	Inferior fronto-occipital fasciculus Inferior longitudinal fasciculus	Object naming Reading	Semantic paraphasia Reading interference	Semantic error Reading interference
	3	Posterior Inferior temporal gyrus Superior temporal gyrus	44 22	Reading Object naming	- Anomia	Not specified Anomia	Inferior fronto-occipital fasciculus Inferior longitudinal fasciculus	Object naming Reading	Semantic paraphasia Reading interference	Semantic error Reading interference
Hayashi2014	1						Arcuate fasciculus Inferior fronto-occipito fasciculus	Object naming Object naming	Phonological paraphasia Semantic paraphasia	Phonological error Semantic error
Henry2004	1	Precentral gyrus	4	Object naming	Anomia; Speech arrest with motor reaction (mouth)	Anomia; Motor				
Kamada2007	21	Posterior Inferior frontal gyrus Middle frontal gyrus	44 9/46	Object naming Object naming	Speech arrest Speech arrest	Speech disturbance Speech disturbance	Arcuate fasciculus	Object naming	Paranomia (verbal paraphasia)	Paranomia (verbal error)
	22	Middle frontal gyrus	9/46	Object naming	Speech arrest	Speech disturbance	Arcuate fasciculus	Object naming	Paranomia (verbal paraphasia)	Paranomia (verbal error)
Khan2014	1						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
	2						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
	3						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration

	4						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
	5						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
	6						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
	7						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
	8						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
	9						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
	10						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
	11						Inferior fronto-occipital fasciculus	Object naming	Semantic paraphasia; perseveration	Semantic error; Response perseveration
Kin2013	1	Superior temporal gyrus Superior temporal gyrus Middle Inferior temporal gyrus	22 22 9/46	Object naming Naming to description Object naming	Speech arrest Speech arrest; Verbal paraphasia Speech arrest	Speech disturbance Speech disturbance; Response error Speech disturbance				
Kosla2015	1	Inferior frontal gyrus	44/45/47	Object naming		Not specified				

Kurimoto 2006	1	Angular gyrus Angular gyrus Supramarginal gyrus Supramarginal gyrus	39 39 40 40	Addition Subtraction Object naming Repetition		Not specified Not specified Not specified Not specified				
Lima2017	14	Ventral premotor cortex	6b	Counting, Object naming	Speech arrest; Anarthria	Speech disturbance; Motor	Arcuate fasciculus Frontal aslant tract Superior longitudinal fasciculus	Counting, Object naming Counting, Object naming Counting, Object naming	Phonological paraphasia Speech arrest Speech arrest	Phonological error Speech disturbance Speech disturbance
	17						Arcuate fasciculus	Counting, Object naming	Phonological paraphasia	Phonological error
Lubrano2004	1	Dorsal premotor cortex	6a	Writing	Substituted/omitted letters	Response error				
	2	Dorsal premotor cortex	6a	Writing	Substituted letters, Writing arrest	Response error; Agraphia				
	5	Inferior frontal gyrus	44/45/47	Object naming; Reading; Writing	Illegible script	Response error				
	6	Dorsal premotor cortex	6a	Object naming; Reading; Writing	Writing arrest; perseverated writing (words)	Agraphia; response perseveration				
	7	Temporal pole Superior frontal gyrus	38 8	Object naming; Reading; Writing Writing	- Paragraphia	Non-specific Response error				
	9	Inferior frontal gyrus	44/45/47	Object naming; Reading; Writing	Illegible script	Response error				
	10	Inferior frontal gyrus	44/45/47	Object naming; Reading; Writing	Word/letter substitution; Writing arrest	Response error				
	11	Dorsal premotor cortex	6a	Writing; Reading	Writing arrest	Agraphia				

Lubrano2012	1	Ventral premotor cortex Inferior frontal gyrus	6b 44/45/47	Object naming Object naming	Anomia Speech arrest; Anomia; Semantic paraphasia	Anomia Speech disturbance; Anomia; Semantic error				
Maldonado2011a	1						Inferior fronto-occipito fasciculus Arcuate fasciculus Superior longitudinal fasciculus	Object naming Counting, Object naming Counting, Object naming	Semantic paraphasia Phonological paraphasia Articulatory disturbance	Semantic error Phonological error Speech disturbance
	2						Inferior fronto-occipito fasciculus Arcuate fasciculus Superior longitudinal fasciculus	Object naming Counting, Object naming Counting or Object naming	Semantic paraphasia; syntax disturbance Phonological paraphasia Articulatory disturbance	Semantic error; syntax disturbance Phonological error Speech disturbance
	3						Arcuate fasciculus Superior longitudinal fasciculus	Counting, Object naming Counting, Object naming	Phonological paraphasia Articulatory disturbance	Phonological error Speech disturbance
	4						Inferior fronto-occipito fasciculus Arcuate fasciculus Superior longitudinal fasciculus	Object naming Counting, Object naming Counting, Object naming	Semantic paraphasia Phonological paraphasia Articulatory disturbance	Semantic error Phonological error Speech disturbance
	5						Arcuate fasciculus Superior longitudinal fasciculus	Counting, Object naming Counting, Object naming	Phonological paraphasia Articulatory disturbance	Phonological error Speech disturbance
	6						Inferior fronto-occipito fasciculus Superior	Object naming Counti	Semantic paraphasia	Semantic error Speech

							longitudinal fasciculus	ng, Object naming	Articulatory disturbance	disturbance
	7						Arcuate fasciculus	Counting, Object naming	Phonological paraphasia	Phonological error
	8						Arcuate fasciculus	Counting, Object naming	Phonological paraphasia	Phonological error
	9						Superior longitudinal fasciculus	Counting, Object naming	Articulatory disturbance	Speech disturbance
	10						Arcuate fasciculus Superior longitudinal fasciculus	Counting, Object naming Counting, Object naming	Phonological paraphasia Articulatory disturbance	Phonological error Speech disturbance
	11						Superior longitudinal fasciculus	Counting, Object naming	Articulatory disturbance	Speech disturbance
Maldonado2011b	1						Opercular white matter Posterior white matter	Counting, Object naming Counting, Object naming	Articulatory disturbance Syllabification; phonological problems	Speech disturbance Syllabification; phonological problems
	2						Opercular white matter Below superior temporal gyrus	Counting, Object naming Object naming	Articulatory disturbance Semantic errors	Articulatory disturbance Semantic errors
	3						Opercular white matter Posterior-superior white matter	Counting, Object naming Counting, Object naming	Articulatory disturbance Phonological disturbance	Speech disturbance Phonological disturbance
	4						Opercular white matter Anterior white matter	Counting, Object naming Counting, Object naming	Articulatory disturbance Phonological disturbance	Speech disturbance Phonological disturbance

	5						Opercular white matter Below superior temporal gyrus	Counting, Object naming Object naming	Articulatory disturbance Noun gender errors; semantic paraphasia	Speech disturbance Noun gender errors; semantic paraphasia
	6						Opercular white matter Below superior temporal gyrus	Counting, Object naming Object naming	Articulatory disturbance Semantic errors	Speech disturbance Semantic errors
	7						Posterior white matter	Counting, Object naming	Phonological disturbance	Phonological disturbance
	8						Opercular white matter Posterior white matter	Counting, Object naming Counting, Object naming	Articulatory disturbance Phonological disturbance	Speech disturbance Phonological disturbance
	9						Opercular white matter Posterior white matter	Counting, Object naming Counting, Object naming	Articulatory disturbance Phonological disturbance	Speech disturbance Phonological disturbance
	10						Below Supramarginal gyrus Posterior white matter	Object naming Counting, Object naming	Anomia Phonological disturbance	Anomia Phonological disturbance
	11						Opercular white matter	Counting, Object naming	Articulatory disturbance	Speech disturbance
	12						Opercular white matter Anterior inferior white matter	Counting, Object naming Counting, Object naming	Articulatory disturbance Phonological disturbance	Speech disturbance Phonological disturbance
	13						Opercular white matter Posterior white matter	Counting, Object naming Counting, Object	Articulatory disturbance Phonological disturbance	Speech disturbance Phonological disturbance

								naming		
	14						Posterior white matter	Counting, Object naming	Phonological disturbance	Phonological disturbance
Mandonnet2007	1						Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Counting, Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	2	Ventral premotor cortex Supramarginal gyrus Posterior Superior temporal gyrus	6b 40 22c	Object naming Object naming Object naming	Anarthria Semantic paraphasia Anomia	Motor Semantic error Anomia	Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Counting, Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	4						Arcuate fasciculus	Counting, Object naming	Phonological paraphasia	Phonological error
	5						Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Counting, Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	6						Arcuate fasciculus	Counting, Object naming	Phonological paraphasia	Phonological error
	8						Inferior fronto-occipito fasciculus	Object naming	Semantic paraphasia	Semantic error
	9						Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Counting, Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	10						Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Counting, Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	11						Arcuate fasciculus	Counting, Object naming	Phonological paraphasia	Phonological error
Mandonnet2009	1	Posterior temporal cortex Middle temporal cortex	22c/21c/37 21b/22b/20b	Object naming Object naming	Visual recognition disturbance Anomia	Comprehension disturbance				

						Anomia				
Matsuda2014	1	Ventral premotor cortex	6b	Object naming	Speech arrest	Speech disturbance	Inferior fronto-occipito fasciculus Caudate Lentiform nucleus	Object naming Object naming Object naming	Semantic paraphasia Perseveration Anarthria	Semantic error Response perseveration Motor
	2	Ventral premotor cortex Dorsal premotor cortex	6b 6a	Object naming Object naming	Speech arrest Anomia	Speech disturbance Anomia	Inferior fronto-occipito fasciculus Arcuate fasciculus Superior longitudinal fasciculus	Object naming Object naming Object naming	Semantic paraphasia Phonological paraphasia Anarthria	Semantic error Phonological error Motor
	3	Ventral premotor cortex Posterior Superior temporal gyrus	6b 22c	Object naming Object naming	Speech arrest Anomia	Speech disturbance Anomia	Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	4	Ventral premotor cortex	6b	Object naming	Speech arrest	Speech disturbance	Arcuate fasciculus Superior longitudinal fasciculus Lentiform nucleus	Object naming Object naming Object naming	Phonological paraphasia Anarthria Anarthria	Phonological error Motor Motor
	5	Ventral premotor cortex; Inferior frontal gyrus Supramarginal gyrus	6b 44/45/47 40	Object naming Object naming Object naming	Speech arrest Anomia Anomia	Speech disturbance Anomia Anomia	Inferior fronto-occipito fasciculus Lentiform nucleus	Object naming Object naming	Semantic paraphasia Anarthria	Semantic error Motor
	6	Ventral premotor cortex Posterior Superior temporal gyrus	6b 22c	Object naming Object naming	Speech arrest Anomia	Speech disturbance Anomia	Arcuate fasciculus Superior longitudinal fasciculus	Object naming Object naming	Phonological paraphasia Anarthria	Phonological error Motor
	7	Ventral premotor cortex Posterior Superior temporal gyrus	6b 22c	Object naming Object naming	Speech arrest Anomia	Speech disturbance Anomia	Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	8	Ventral premotor cortex	6b	Object naming	Speech arrest	Speech disturbance	Arcuate fasciculus Lentiform nucleus	Object naming Object naming	Phonological paraphasia Anarthria	Phonological error Motor
	10	Ventral premotor cortex Posterior Superior	6b 22c	Object naming Object naming	Speech arrest Anomia	Speech disturbance Anomia	Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Object	Semantic paraphasia Phonolo	Semantic error Phonol

		temporal gyrus						naming	gical paraphasia	ogical error
Matsuda2019	1						Below Supramarginal gyrus	Calculation	Unable to calculate	Acalculia
Metellus2016	1	Middle frontal gyrus Inferior frontal gyrus Precentral gyrus	9/46 44/45/47 4	Object naming (Sign lang) Object naming; Reading; Repetition (sign lang) Counting; Object naming (sign lang) Object naming; Reading; Repetition (sign lang)	Perseveration Sign blockage Sign blockage Sign blockage	Response perseveration Sign language blockage	Arcuate fasciculus	Object naming; Reading; Repetition (Signed)		Not specified
Morits-Gasser2009	1	Inferior frontal gyrus Middle Superior temporal gyrus Posterior Superior temporal gyrus	44/45/47 8 22c	Object naming Object naming Object naming	Speech arrest - Involuntary language switch	Speech disturbance Not specified Language switch	Superior longitudinal fasciculus	Object naming	Involuntary language switch; Phonological paraphasia	Involuntary language switch; Phonological error
Moritz-Gasser2013	1						Inferior fronto-occipito fasciculus	Object naming Pyramid & palm trees task	Anomia; Semantic paraphasia No response	Anomia; Semantic error No response
	2						Inferior fronto-occipito fasciculus	Object naming Pyramid & palm trees task	Anomia; Semantic paraphasia No response	Anomia; Semantic error No response
	3						Inferior fronto-occipito fasciculus	Object naming Pyramid & palm trees task	Semantic paraphasia Anomia	Semantic error Anomia
	4						Inferior fronto-occipito fasciculus	Object naming Pyramid & palm trees task	Anomia; Semantic paraphasia No response	Anomia; Semantic error No response

	5						Inferior fronto-occipito fasciculus	Object naming Pyramid & palm trees task	Semantic paraphasia Anomia	Semantic error Anomia
	6						Inferior fronto-occipito fasciculus	Object naming Pyramid & palm trees task	Anomia; Semantic paraphasia Anomia	Anomia; Semantic error Anomia
	7						Inferior fronto-occipito fasciculus	Object naming Pyramid & palm trees task	Semantic paraphasia Anomia	Semantic error Anomia
	8						Inferior fronto-occipito fasciculus	Object naming Pyramid & palm trees task	Semantic paraphasia; Anomia Anomia; No response	Semantic error; Anomia No response
Motomura 2014	1	Superior parietal lobule	5/7	Object naming	Phonological paraphasia	Phonological error	Inferior fronto-occipito fasciculus	Object naming Reading; Writing	Semantic paraphasia Reading; Writing interference	Semantic error Reading; Writing interference
Mukae2017	4						Arcuate fasciculus	Object naming	Anomia	Anomia
	5						Arcuate fasciculus	Object naming	Anomia	Anomia
Nomura2013	1						Uncinate fasciculus	Object naming	Verbal paraphasia; speech disturbance; perseveration	Verbal error; speech disturbance; Response perseveration
Ogawa2014	1	Inferior frontal gyrus	44/45/47	Object naming	Speech arrest	Speech disturbance				
Ogawa2017	1	Inferior frontal gyrus Superior temporal gyrus	44/45/47 22	Object naming Object naming	Speech arrest Speech arrest	Speech disturbance Speech disturbance				
	7	Inferior frontal gyrus Superior temporal gyrus	44/45/47 22	Object naming Reading		Not specified Not specified				
Parney2010	1	Inferior frontal gyrus	44/45/47	Counting; Object naming	Speech arrest	Speech disturbance				

Petrovich Brennan2007	1	Inferior frontal gyrus	44/45/47	Object naming; Counting	Speech arrest; Hesitation; Phonological paraphasia Speech arrest	Speech disturbance; Response perseveration; Response delay; phonological error				
	2	Superior temporal gyrus	22	Object naming	Word-finding difficulty; Phonological paraphasia; Circumlocution	Anomia; phonological error; circumlocution				
	11	Superior temporal gyrus Superior temporal gyrus Superior temporal gyrus	22 22 22	Object naming Object naming Counting	Speech arrest; Hesitation; Word-finding difficulty Phonological paraphasia Speech arrest; hypophonia	Speech disturbance; response delay; phonological error Speech disturbance; motor				
	12	Superior temporal gyrus Superior temporal gyrus	22 22	Object naming Counting	Speech arrest; Word-finding difficulty; Phonological paraphasia Speech arrest	Speech disturbance; anomia; phonological error Speech disturbance				
	14	Superior temporal gyrus	22	Object naming	Hesitation; Perseveration; Word-finding	Response delay; response perseveration; Anomia				
	15	Superior temporal gyrus Superior temporal gyrus	22 22	Object naming Counting	Speech arrest; perseveration; Word-finding difficulty; Verbal paraphasia; dysarthria Speech arrest	Speech disturbance; Response perseveration; anomia; response error; motor Speech				

						disturbance				
Plaza2009	1	Dorsal premotor cortex Ventral premotor cortex	6a 6b	Object naming Counting; Object naming	Semantic paraphasia Speech arrest	Semantic error Speech disturbance	Inferior fronto-occipito fasciculus Superior longitudinal fasciculus Caudate nucleus	Counting, Object naming Counting, Object naming Counting, Object naming	Semantic paraphasia Anarthria Perseveration	Semantic error Anarthria Response perseveration
Pu2011	1	Angular gyrus Horizontal intraparietal sulcus	39 5/7	Subtraction Subtraction		Not specified				
	2	Angular gyrus Horizontal intraparietal sulcus Supramarginal gyrus	39 5/7 40	Subtraction Multiplication; Subtraction Multiplication		Not specified				
	3	Angular gyrus Horizontal intraparietal sulcus Supramarginal gyrus	39 5/7 40	Multiplication; Subtraction Multiplication; Subtraction Multiplication		Not specified				
	4	Angular gyrus Horizontal intraparietal sulcus Supramarginal gyrus	39 5/7 40	Multiplication; Subtraction Multiplication; Subtraction Multiplication		Not specified				
Rech2017	1	Ventral Precentral gyrus	4	Object naming	Speech arrest	Speech disturbance				
Riva2016	1	Inferior precentral gyrus Postcentral gyrus Anterior Middle temporal gyrus Anterior Superior temporal gyrus Frontal operculum (pars opercularis)	4 43 21a 22a 44 22b	Counting, object naming Counting, object naming Object naming Object naming Rhythm task Score reading	Anarthria/dysarthria Anarthria/dysarthria Delay; Phonological paraphasia; Anomia Delay; Phonological paraphasia;	Motor Motor Response delay; Phonological error; Anomia Response delay; Phonological error; Anomi				

		Middle Superior temporal gyrus			Anomia Errors hesitations, note errors, rhythm errors, inability to read scores	a Response errors Response errors				
Rofes2015	MG	Middle inferior frontal gyrus Middle frontal gyrus	45 9/46	Object naming Object naming	Phonological paraphasia Phonological paraphasia	Phonological error Phonological error	Below prefrontal cortex	Action naming with finite verbs	Phonological paraphasia; Anomia	Phonological error; Anomia
	PR	Posterior Middle frontal gyrus Superior Middle frontal gyrus Posterior Superior frontal gyrus	9/46 9/46 8	Action naming with finite verbs Action naming with finite verbs; Object naming Action naming with finite verbs	Semantic paraphasia (self-corrected) Delays Anomia (for verb)	Semantic error Response delay Anomia	Below fronto-polar cortex	Action naming with finite verbs Object naming	Perseveration; incorrect gender pronoun Semantic paraphasia; Anomia	Response perseveration; Grammatical error Semantic error; Anomia
	TT	Superior Middle frontal gyrus Posterior Middle frontal gyrus	9/46 9/46	Action naming with finite verbs Object naming; Action naming with finite verbs	Delays; Anomia Delays; Anomia	Response delay; Anomia Response delay; Anomia	Below frontal cortex	Object naming Action naming with finite verbs	Delays; Anomia Delays; Anomia	Response delay; Anomia Response delay; Anomia
Rofes2017	CRO	Middle frontal gyrus Posterior Middle frontal gyrus	9/46 9/46	Object naming Object naming	Semantic paraphasia; Anomia Semantic paraphasia; Anomia	Semantic error; Anomia Semantic error; Anomia	Inferior fronto-occipital fasciculus	Action naming with finite verbs	Semantic paraphasia	Semantic error
	MG	Middle Inferior frontal gyrus Middle frontal gyrus Posterior Middle frontal gyrus	45 9/46 9/46	Object naming Object naming Object naming	Phonological paraphasia	Phonological error	Arcuate fasciculus	Object naming	Anomia	Anomia

	CRA						Arcuate fasciculus	Object naming	Semantic paraphasia; Anomia	Semantic error; Anomia
	TT						Below Post. Middle frontal gyrus Below Inf-Post. Middle frontal gyrus	Object naming Object naming	Anomia Anomia	Anomia Anomia
	PR	Posterior Superior frontal gyrus Post-Middle Middle frontal gyrus Post-Superior Middle frontal gyrus	8 9/46 9/46	Action naming with finite verbs Object naming Object naming; Action naming with finite verbs	Semantic paraphasia Semantic paraphasia Semantic paraphasia	Semantic error Semantic error Semantic error	Below Middle frontal gyrus Below Superior frontal gyrus	Object naming; Action naming with finite verbs Object naming; Action naming with finite verbs	Anomia	Anomia
	SO	Inferior frontal gyrus	44/45/47	Action naming with finite verbs	Anomia	Anomia	Below antero-medial insula cortex	Action naming with finite verbs	Semantic paraphasia	Semantic error
Rolland2018	1	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Superior longitudinal fasciculus	Object naming	Articulatory disorders	Speech disturbance
	2	Precentral gyrus Posterior Superior temporal gyrus	4 22c	Object naming Object naming	Articulatory disorders Naming disturbances	Speech disturbance Anomia	Inferior fronto-occipital fasciculus	Object naming	Semantic disorders	Semantic error
	3	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Superior longitudinal fasciculus	Object naming	Articulatory disorders	Speech disturbance
	4	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Superior longitudinal fasciculus	Object naming	Articulatory disorders	Speech disturbance
	5	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Superior longitudinal fasciculus Inferior fronto-occipital fasciculus	Object naming Object naming	Articulatory disorders Semantic disorders	Speech disturbance Semantic error
	6	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Superior longitudinal fasciculus	Object naming	Articulatory disorders	Speech disturbance
	7	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Inferior fronto-occipital fasciculus	Object naming	Semantic disorders	Semantic error
	8	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance				
	9	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Inferior fronto-occipital fasciculus	Object naming	Semantic disorders	Semantic error
	10	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance				
	11	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Superior longitudinal fasciculus	Object naming	Articulatory disorders	Speech disturbance
	12	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Inferior fronto-occipital fasciculus	Object naming	Semantic disorders	Semantic error

	13	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Inferior fronto-occipital fasciculus	Object naming	Semantic disorders	Semantic error
	14	Precentral gyrus	4	Object naming	Articulatory disorders	Speech disturbance	Inferior fronto-occipital fasciculus	Object naming	Semantic disorders	Semantic error
Rosenberg 2008	1	Posterior Inferior frontal gyrus Anterior Superior temporal gyrus	44 22a	Object naming Object naming	Delays Hesitation	Response delay Response delay				
Roux2002	1	Post superior temporal gyrus Ventral premotor cortex	22c 6b	Object naming Counting, reading	Anomia Speech arrest	Anomia Speech arrest				
	2	Anterior Superior temporal gyrus Middle Superior temporal gyrus Ventral premotor cortex Post .Superior temporal gyrus	22a 22b 6b 22c	Object naming Counting, reading Counting, reading Object naming	Anomia Speech arrest Speech arrest Anomia	Anomia Speech disturbance Speech disturbance Anomia				
	3	Posterior Superior temporal gyrus Anterior Middle temporal gyrus Visual association cortex	22c 21a 19	Object naming; Counting, reading Object naming Object naming; Counting, reading	Anomia; Speech arrest Anomia Anomia; Speech arrest	Anomia; Speech disturbance Anomia Anomia; Speech disturbance				
	4	Posterior Inferior frontal gyrus Posterior Middle frontal gyrus Ventral premotor cortex	44 9/46 6b	Counting, reading Counting, reading Counting, reading	Speech arrest Speech arrest Speech arrest	Speech disturbance Speech disturbance Speech disturbance				
	5	Posterior inferior frontal gyrus Ventral premotor cortex	44 6b	Counting, reading Counting, reading	Speech arrest Speech arrest	Speech disturbance Speech disturbance				
	6	Posterior middle frontal gyrus Ventral premotor cortex	44 6b	Counting, reading Counting, reading	Speech arrest Speech arrest	Speech disturbance Speech disturbance				

	7	Posterior superior temporal gyrus	22c	Counting, reading	Speech arrest	Speech disturbance				
	8	Ventral premotor cortex Posterior Inferior frontal gyrus Posterior Middle frontal gyrus	6b 44 9/46	Counting, reading Counting, reading Counting, reading	Speech arrest Speech arrest Speech arrest	Speech disturbance Speech disturbance Speech disturbance				
	9	Middle Superior temporal gyrus	22b	Object naming; Counting, reading	Anomia; Speech arrest	Anomia; Speech disturbance				
	10	Anterior Superior temporal gyrus Middle Superior temporal gyrus Postcentral gyrus Ventral premotor cortex	22a 22b 43 6b	Object naming; Counting, reading Object naming; Counting, reading Counting, reading Counting, reading	Anomia Anomia Speech arrest Speech arrest	Anomia Anomia Speech disturbance Speech disturbance				
	11	Posterior Inferior frontal gyrus Middle Inferior frontal gyrus Posterior Middle frontal gyrus Middle frontal gyrus	44 45 9/46 9/46	Object naming Object naming Object naming Object naming	Anomia Anomia Anomia Anomia	Anomia Anomia Anomia Anomia				
	12	Posterior Superior temporal gyrus Middle frontal gyrus Ventral premotor cortex Precentral gyrus	22c 9/46 6b 4	Object naming Object naming Counting, reading Counting, reading	Anomia Anomia Speech arrest Speech arrest	Anomia Anomia Speech disturbance Speech disturbance				
Roux2003a	1	Angular gyrus	39	Calculation; Writing; Colour naming		Not specified				
	2	Angular gyrus	39	Calculation; Writing; Reading		Not specified				

	3	Angular gyrus	39	Calculation; Writing; Reading; Colour naming; Object naming		Not specified				
	4	Angular gyrus Supramarginal/Superior parietal lobule Posterior Superior temporal gyrus Middle temporal gyrus Supramarginal gyrus	39 40/5/7 22c 21 40	Calculation; Writing; Reading Calculation Object naming; Colour naming Object naming; Colour naming Object naming; Colour naming		Not specified Not specified Not specified Not specified Not specified				
	5	Angular gyrus Angular gyrus Supramarginal/Superior parietal lobule Supramarginal gyrus Posterior Superior temporal gyrus Middle temporal gyrus	39 39 40/5/7 40 22c 21	Calculation; Writing; Reading; Object naming; Colour naming Calculation Calculation Object naming Object naming Object naming		Not specified Not specified Not specified Not specified Not specified Not specified				
	6	Angular gyrus Supramarginal/Superior parietal lobule Posterior Superior temporal gyrus Middle temporal gyrus Angular gyrus Superior temporal gyrus	39 40/5/7 22c 21 39 22	Calculation; Writing; Reading Calculation Object naming; Reading Object naming; Reading Colour naming Colour naming		Not specified Not specified Not specified Not specified Not specified Not specified				
Roux2003b	12	Middle superior temporal gyrus Middle temporal gyrus Posterior Middle temporal gyrus	22b 21b 21c	Object naming Object naming Object naming	Anomia Anomia Anomia	Anomia Anomia Anomia				
	6	Insula cortex	13-16	Object naming	Anomia	Anomia				

	5	Angular gyrus	39	Object naming	Anomia	Anomia				
Roux2004	Fig 4	Angular gyrus Superior temporal gyrus Supramarginal gyrus Middle temporal gyrus	39 22 40 21	Reading Reading; object naming Reading; object naming Object naming	Paraphasia - Naming hesitation -	Response error Not specified Response delay Not specified				
Roux2006	Fig 3	Inferior frontal gyrus Posterior Middle temporal gyrus	44/45/47 21c	Object naming; Colour naming Object naming	- Hesitation	Not specified Response delay				
	Fig 4	Inferior frontal gyrus Anterior Superior temporal gyrus Middle Superior temporal gyrus Posterior Superior temporal gyrus Posterior Middle temporal gyrus	44/45/47 22a 22b 22c 21c	Object naming; Colour naming Object naming; Colour naming Object naming Object naming Colour naming	Anomia; Speech arrest Anomia Anomia Anomia Anomia	Anomia; Speech disturbance Anomia Anomia Anomia Anomia				
Roux2007	1	Temporal, frontal supramarginal gyri Posterior Temporal, supramarginal, frontal gyri Superior Frontal Gyrus Middle Frontal Gyrus	40 40 8 9/46	Object naming Word reading/ Arabic number reading Score reading Score reading		Not specified Not specified Not specified Not specified				
	2	Temporal, frontal supramarginal gyri Posterior Temporal, supramarginal, frontal gyri Supramarginal gyrus Posterior Superior Temporal gyrus	40 40 40 22c	Object naming Word reading/ Arabic number reading Score reading Score reading		Not specified Not specified Not specified Not specified				

	3	Temporal, frontal supramarginal gyri Posterior Temporal, supramarginal, frontal gyri Posterior Inferior Frontal Precentral gyri Superior parietal lobe Posterior Middle Temporal gyrus	40 40 44 4 5/7 21c	Object naming Word reading/ Arabic number reading Score reading Score reading Score reading Score reading		Not specified Not specified Not specified Not specified Not specified				
	4	Temporal, frontal supramarginal gyri Posterior Temporal, supramarginal, frontal gyri Supramarginal gyrus/superior parietal lobe	40 40 40/5/7	Object naming Word reading/ Arabic number reading Score reading		Not specified Not specified Not specified				
	5	Temporal, frontal supramarginal gyri Posterior Temporal, supramarginal, frontal gyri Supramarginal/Angular gyri	40 40 40	Object naming Word reading/ Arabic number reading Score reading		Not specified Not specified Not specified				
Roux2009a	1	Precentral gyrus Inferior frontal gyrus Supramarginal gyrus	4 44/45/47 40	Singing Object naming; Reading; Object naming (French/ Rwandan) Object naming (French); Object naming (Rwandan)	Speech arrest Speech arrest; Anomia -	Speech disturbance Speech disturbance; Anomia Not specified				
	2	Precentral gyrus Inferior frontal gyrus	4 44/45/47	Singing Object naming; Reading	Speech arrest Speech arrest; Anomia	Speech disturbance Speech disturbance; Anomia				
	3	Middle frontal gyrus	9/46	Singing	Perseveration; Speech arrest	Response perseveration				

						; Speech disturbance				
	5	Precentral gyrus Supramarginal gyrus	4 40	Singing Object naming; Reading	Monotonous singing -	Monotonous singing Not specified				
Roux2009b	DO	Middle frontal gyrus	9/46	Writing	Agraphia	Agraphia				
	CIV	Middle frontal gyrus	9/46	Writing	Agraphia	Agraphia				
	PV	Middle frontal gyrus	9/46	Writing	Agraphia	Agraphia				
	CJB	Superior frontal gyrus	8	Writing	Agraphia	Agraphia				
	CP	Middle frontal gyrus	9/46	Writing	Agraphia	Agraphia				
	CV	Ventral premotor cortex	9b	Object naming; Reading	Speech arrest; Anomia	Speech disturbance; Anomia				
	BD	Ventral premotor cortex	9b	Object naming; Reading	Speech arrest; Anomia	Speech disturbance; Anomia				
	RJ	Ventral premotor cortex	9b	Object naming; Reading	Speech arrest; Anomia	Speech disturbance; Anomia				
	GC	Ventral premotor cortex	9b	Object naming; Reading	Speech arrest; Anomia	Speech disturbance; Anomia				
	PE	Ventral premotor cortex	9b	Object naming; Reading	Speech arrest; Anomia	Speech disturbance; Anomia				
	JG	Ventral premotor cortex	9b	Object naming; Reading	Perseveration	Perseveration				
	PE	Ventral premotor cortex	9b	Object naming; Reading	Speech arrest; Anomia	Speech disturbance; Anomia				
	AL	Middle frontal gyrus	9/46	Object naming	Speech arrest; Anomia	Speech disturbance; Anomia				
Roux2009c	Fig 2	Middle temporal gyrus Angular gyrus	21 39	Object naming; Counting Calculation	- Acalculia; calculation hesitation	Not specified Acalculia; Response delay				
	Fig 3	Middle frontal gyrus	9/46	Calculation;		Not specified				

				Object naming						
Roux2012	1	Superior temporal gyrus Heschl's gyrus Middle temporal gyrus Postcentral gyrus	22 42 21 43	Reading ; Non word reading Reading ; Non word reading Reading ; Non word reading Non word reading	Auto-corrections; letter-level errors; blockade Blockade Hesitation Letter-level errors; Slowing; Syllabation	Response error; Alexia Alexia Response delay Response error; Alexia				
	2	Supramarginal gyrus Postcentral gyrus	40 43	Reading ; Non word reading Reading ; Non word reading	Letter-level errors Slowing; Syllabation	Response error Alexia				
	3	Heschl's gyrus Superior temporal gyrus Supramarginal gyrus Supramarginal gyrus	42 22 40 40	Reading ; Non word reading Reading Reading Reading ; Non-word reading	Blockade Neologism/Jargon Neologism/Jargon Articulation/voice alteration	Alexia Response error Response error Response error				
	6	Supramarginal gyrus	40	Non-word reading	Letter-level errors	Response error				
	7	Supramarginal gyrus Supramarginal gyrus Postcentral gyrus Postcentral gyrus Superior temporal gyrus	40 40 2 43 22	Reading ; Non-word reading Reading Reading ; Non word reading Reading ; Non word reading Reading	Letter-level errors Word-level errors Slowing/ syllabation Auto-corrections Neologism/Jargon	Response error Response error Alexia Response error Response error				
	8	Supramarginal gyrus Superior temporal gyrus Postcentral gyrus	40 22 3	Reading Reading ; Non word reading Non word reading	Slowing; Syllabation Neologism/Jargon Slowing; Syllabation	Alexia Response error Alexia				
	9	Supramarginal gyrus Superior temporal gyrus Superior temporal gyrus Postcentral gyrus	40 22 22 43	Reading Non word reading Reading ; Non word reading Reading ; Non word reading	Blockade Slowing; Syllabation; Neologism/Jargon Neologism/Jargon Letter-level errors	Alexia Alexia; Response error Response error Response error				
	10	Postcentral gyrus	2	Reading ; Non	Letter-level errors	Response error				

				word reading						
	11	Postcentral gyrus	2	Reading ; Non word reading	Letter-level errors; Neologism/Jargon	Response error				
	12	Supramarginal gyrus Superior temporal gyrus	40 22	Reading ; Non word reading Reading ; Non word reading	Letter-level errors Letter-level errors	Response error Response error				
	13	Superior temporal gyrus Superior temporal gyrus Heschl's gyrus Supramarginal gyrus	22 22 42 40	Reading Reading ; Non word reading Reading ; Non word reading Non word reading	Slowing; Syllabation Letter-level errors Letter-level errors Letter-level errors	Alexia Response error Response error Response error				
Roux2014	1	Superior temporal gyrus	22	Writing; Reading	Semantic paragraphia	Semantic error; Not specified				
	2	Superior temporal gyrus	22	Writing; Object naming	Phonemic paragraphia	Phonological error				
	3	Heschl's gyrus Postcentral gyrus	42 43	Writing Reading ; Object naming; Writing	Word deafness Word deafness	Comprehension deficit Comprehension deficit; Not specified				
	4	Postcentral gyrus Heschl's gyrus Supramarginal gyrus Superior temporal gyrus	43 42 40 22	Reading ; Object naming; Writing Writing Reading ; Object naming; Writing Writing	semantic paragraphia Semantic paragraphia Semantic paragraphia Semantic paragraphia	Not specified; semantic error Semantic error Not specified; semantic error Semantic error				
	5	Supramarginal gyrus Superior temporal gyrus	40 22	Reading ; Writing Writing	Word deafness Semantic paragraphia	Not specified; Comprehension deficit Semantic error				

	6	Heschl's gyrus Angular gyrus	42 39	Object naming; Reading; Writing Object naming; Reading; Writing	Phonemic paragraphia Phonemic paragraphia	Not specified; Phonological error Not specified; Phonological error				
	8	Superior temporal gyrus Angular gyrus Middle temporal gyrus Posterior middle temporal gyrus	22 39 21 37	Writing; Object naming; Reading Object naming; Reading; Writing Object naming; Reading; Writing Object naming; Reading; Writing	Word deafness; Phonological paragraphia Phonemic paragraphia Phonemic paragraphia Phonemic paragraphia	Comprehension deficit; Phonological error; Not specified Phonological error; Not specified Phonological error; Not specified Phonological error; Not specified				
	9	Superior temporal gyrus Heschl's gyrus Supramarginal gyrus	22 42 40	Writing; Reading Writing; Reading Writing; Reading	Phonemic paragraphia Phonemic paragraphia Phonemic paragraphia	Phonological error; Not specified Phonological error; Not specified Phonological error; Not specified				
	10	Superior temporal gyrus Heschl's gyrus	22 42	Reading; Object naming; Writing Writing	Phonemic paragraphia; semantic paragraphia Phonemic paragraphia	Phonological error; semantic error; Not specified Phonological error				

	11	Supramarginal gyrus Superior temporal gyrus Heschl's gyrus	40 22 42	Reading; Object naming; Writing Reading; Object naming; Writing Reading; Object naming; Writing	Phonemic paragraphia Semantic paragraphia Semantic paragraphia	Phonological error; Not specified Semantic error; Not specified Semantic error; Not specified				
	12	Superior temporal gyrus Heschl's gyrus	22 42	Writing Writing; Reading	Word deafness Semantic paragraphia	Comprehension deficit Semantic error; Not specified				
	13	Supramarginal gyrus	40	Writing; Reading	Phonemic paragraphia	Phonological error; Not specified				
	14	Heschl's gyrus	42	Writing	Word deafness	Comprehension deficit				
	15	Supramarginal gyrus	40	Writing; Reading; Object naming	Phonemic paragraphia; Not specified	Phonological error				
	16	Superior temporal gyrus Postcentral gyrus Middle temporal gyrus	22 43 21	Reading; Object naming; Writing Reading; Object naming; Writing Reading; Object naming; Writing	Semantic paragraphia Phonemic paragraphia Semantic paragraphia	Semantic error; Not specified Phonemic error; Not specified Semantic error; Not specified				
	17	Heschl's gyrus Postcentral gyrus	42 43	Writing Writing; Reading; Object naming	Semantic paragraphia Phonemic paragraphia	Semantic error Phonological error; Not specified				

	18	Superior temporal gyrus Heschl's gyrus Middle temporal gyrus	22 42 21	Writing; Reading; Object naming Reading; Object naming; Writing Writing	Phonemic paragraphia Phonemic paragraphia Phonemic paragraphia	Phonological error; Not specified Phonological error; Not specified Phonological error				
	19	Posterior Inferior temporal gyrus Superior temporal gyrus Heschl's gyrus Supramarginal gyrus	37 22 42 40	Writing; Reading Writing; Reading Reading; Object naming; Writing Reading; Object naming; Writing	Phonemic paragraphia Phonemic paragraphia; Word deafness Phonemic paragraphia Phonemic paragraphia	Phonological error; Not specified Phonological error; Comprehension deficit; Not specified Phonological error; Not specified Phonological error; Not specified				
	20	Postcentral gyrus Supramarginal gyrus	1/2 40	Writing Writing	Phonemic paragraphia Phonemic paragraphia	Phonological error Phonological error				
	21	Superior temporal gyrus	22	Reading; Object naming; Writing	Word deafness	Comprehension deficit; Not specified				
	22	Superior temporal gyrus	22	Reading; Object naming; Writing	Word deafness	Comprehension deficit				
Saito2014a	OP 1	Dorsal premotor cortex	6a	Object naming	Speech arrest	Speech disturbance	Superior longitudinal fasciculus	Object naming	Speech arrest	Speech disturbance
	OP 2	Ventral premotor cortex	6b	Object naming; Reading	Speech arrest with motor reaction	Motor	Superior longitudinal fasciculus	Object naming	Speech arrest	Speech disturbance

Sakurada2007	1	Precentral gyrus Inferior frontal gyrus Ventral premotor cortex Superior temporal gyrus Middle temporal gyrus	4 44/45/47 6b 22 9/46	Object naming Object naming Object naming Object naming Object naming	Anarthria Speech arrest Speech arrest Speech arrest Speech arrest	Motor Speech disturbance Speech disturbance Speech disturbance Speech disturbance				
	2	Precentral gyrus Ventral premotor cortex Inferior frontal gyrus Superior temporal gyrus	4 6b 44/45/47 22	Object naming Object naming Object naming Object naming	Anarthria Anarthria Speech arrest Speech arrest	Motor Motor Speech disturbance Speech disturbance				
	3	Inferior temporal gyrus	20	Object naming	Speech arrest	Speech disturbance				
	4	Precentral gyrus Superior temporal gyrus	4 22	Object naming Object naming	Anarthria Speech arrest	Motor Speech disturbance				
Sallard2012	1						Superior longitudinal fasciculus	Counting; Object naming	Phonological paraphasia	Phonological error
	2						Superior longitudinal fasciculus	Counting; Object naming	Phonological paraphasia	Phonological error
Sarubbo2012	1						Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Counting, Object naming	Semantic paraphasia Phonological paraphasia	Semantic error Phonological error
	2	Superior temporal gyrus/Supramarginal gyrus Middle temporal gyrus	22/40 21	Object naming Object naming	Semantic paraphasia Anomia	Semantic error Anomia				
	3	Superior temporal gyrus	22	Object naming	Semantic paraphasia; Anomia	Semantic paraphasia; Anomia	Inferior fronto-occipito fasciculus	Object naming	Semantic paraphasia	Semantic error
	4	Superior temporal gyrus	22	Object naming	Semantic paraphasia; Anomia	Semantic paraphasia; Anomia	Inferior fronto-occipito fasciculus Arcuate fasciculus	Object naming Object naming	Phonological paraphasia Anomia	Phonological error Anomia
Satoer2017	1	Dorsal premotor cortex	6a	Object naming; Repetition	Anomia	Anomia				

	2	Posterior Superior temporal/Supramarginal gyrus	22c/40	Object naming; Repetition	Anomia	Anomia	Arcuate fasciculus	Object naming or Repetition	Phonological paraphasia	Phonological error
	3	Dorsal premotor cortex Parietal lobule (AG) Temporo-parietal junction (STG-AG) Inferior frontal gyrus	6a 39 22/39 44/45	Object naming; Repetition Object naming; Repetition Object naming; Repetition Object naming; Repetition	Speech arrest; Anarthria Speech arrest Phonological paraphasia; Neologisms Speech arrest	Speech disturbance; Motor Speech disturbance Phonological paraphasia; Response error Speech disturbance	Arcuate fasciculus	Object naming or Repetition	Phonological paraphasia	Phonological error
	4	Dorsal premotor cortex Inferior frontal gyrus Parietal lobule (AG) Superior temporal gyrus	6a 44/45/47 39 22	Object naming; Repetition Object naming; Repetition Object naming; Repetition Object naming; Repetition	Speech arrest Speech arrest Phonological paraphasia Speech arrest	Speech disturbance Speech disturbance Phonological error Speech disturbance				
Schapiro2012	1	Inferior frontal gyrus	44/45/47	Counting, object naming	Speech arrest	Speech disturbance				
Sierpowska2013	1	Inferior frontal gyrus Middle frontal gyrus Middle temporal gyrus	44/45/47 9/46 21	Object naming Object naming Object naming	- Involuntary language switch Involuntary language switch	Not specified Language switch Language switch				
	2	Inferior frontal gyrus Middle frontal gyrus Supramarginal gyrus Superior parietal lobule	44/45/47 9/46 40 5/7	Object naming Object naming Object naming Object naming						
Signorelli2003	1	Angular gyrus Supramarginal gyrus	39 40	Object naming Object naming	Speech arrest Semantic paraphasia	Speech disturbance Semantic error				
	2	Supramarginal gyrus	40	Object naming	Verbal paraphasia	Response error				
Simos1999	1	Posterior Middle temporal gyrus	21b	Sentence repetition;	Delayed responses	Delayed responses				

				Object naming						
	5	Posterior Middle temporal gyrus	21b	Sentence repetition; Sentence comprehension	Comprehension disturbance	Comprehension disturbance				
	6	Temporal pole Superior temporal gyrus	30 22	Sentence repetition; Sentence comprehension Sentence repetition; Sentence comprehension	Comprehension disturbance Comprehension disturbance	Comprehension deficit Comprehension deficit				
Sollman2013	1	Superior temporal gyrus Middle temporal gyrus	22 21	Object naming Object naming	Speech arrest Speech arrest	Speech disturbance Speech disturbance				
Spena2015	1	Inferior frontal gyrus	44/45/47	Counting, Object naming, Reading	Speech arrest; Anarthria	Speech disturbance; Motor				
Tomasino 2014	1	Superior temporal gyrus Inferior frontal gyrus	22 44/45/47	Counting Counting; Object naming	Involuntary language switch Speech arrest	Language switch Speech disturbance				
VanGeemen2014	1	Ventral premotor cortex	6b	Counting, Object naming	Anarthria	Motor	Inferior fronto-occipito fasciculus Superior longitudinal fasciculus	Object naming Counting or Object naming	Semantic paraphasia Anarthria	Semantic error Anarthria
	2	Ventral premotor cortex	6b	Counting, Object naming	Anarthria	Motor	Arcuate fasciculus Superior longitudinal fasciculus	Counting or Object naming Counting or Object naming	Phonological paraphasia Anarthria	Phonological error Anarthria
	3	Ventral premotor cortex	6b	Counting, Object naming	Anarthria	Motor	Superior longitudinal fasciculus	Counting or Object naming	Anarthria	Anarthria
	4	Ventral premotor cortex	6b	Counting, Object naming	Anarthria	Motor	Inferior fronto-occipito fasciculus Arcuate fasciculus Superior longitudinal fasciculus	Object naming Counting or Object namin	Semantic paraphasia Phonological paraphas	Semantic error Phonological error

								g Counting or Object naming	ia Anarthria	Anarthria
	5	Ventral premotor cortex	6b	Counting, Object naming	Anarthria	Motor	Arcuate fasciculus Superior longitudinal fasciculus	Counting or Object naming Counting or Object naming	Phonological paraphasia Anarthria	Phonological error Anarthria
	6	Ventral premotor cortex	6b	Counting, Object naming	Anarthria	Motor	Superior longitudinal fasciculus	Counting or Object naming	Anarthria	Anarthria
	7A	Ventral premotor cortex	6b	Counting, Object naming	Anarthria	Motor	Arcuate fasciculus Superior longitudinal fasciculus	Counting or Object naming Counting or Object naming	Phonological paraphasia Anarthria	Phonological error Anarthria
	7B	Ventral premotor cortex	6b	Counting, Object naming	Anarthria	Motor	Arcuate fasciculus Superior longitudinal fasciculus	Counting or Object naming Counting or Object naming	Phonological paraphasia Anarthria	Phonological error Anarthria
	8	Ventral premotor cortex	6b	Counting, Object naming	Anarthria	Motor	Arcuate fasciculus Superior longitudinal fasciculus	Counting or Object naming Counting or Object naming	Phonological paraphasia Anarthria	Phonological error Anarthria
Vidoretta2011	1	Angular gyrus Supramarginal gyrus Superior temporal gyrus Posterior Middle temporal gyrus	39 40 22 21c	Object naming Object naming Object naming Object naming		Not specified				
	2	Dorsal premotor cortex	6a	Object naming		Not specified	Caudate	Object naming	Noun gender errors	Grammatical error
	3	Inferior frontal gyrus	44/45/47	Object naming	Noun gender errors	Grammatical error				
	4	Inferior frontal gyrus	44/45/47	Object naming	Noun gender errors	Grammatical error	Arcuate fasciculus	Object naming	Noun gender errors	Grammatical error
	5	Superior temporal gyrus Posterior	22 21c	Object naming Object naming	- Noun gender errors	Not specified Gram				

		Middle temporal gyrus				matical error				
	6	Dorsal premotor cortex Inferior frontal gyrus Inferior frontal gyrus (pars orbitalis)	6a 44/45/47 47	Object naming Object naming Object naming	- - Noun gender errors	Not specified Not specified Gram matical error				
	7	Inferior frontal gyrus Inferior frontal gyrus (pars orbitalis)	44/45/47 47	Object naming Object naming	Noun gender errors -	Gram matical error Not specified				
	8	Dorsal premotor cortex	6a	Object naming		Not specified	Caudate	Object naming	Noun gender errors	Gram matical error
	9	Superior temporal gyrus Posterior Middle temporal gyrus	22 21c	Object naming Object naming	- Noun gender errors	Not specified Gram matical error				
Wager2013	1	Cingulate gyrus	25	Stroop test	Stroop effect	Stroop effect				
	2	Cingulate gyrus	25	Stroop test	Stroop effect	Stroop effect				
	3	Cingulate gyrus	25	Stroop test	Stroop effect	Stroop effect				
	6	Cingulate gyrus	25	Stroop test	Stroop effect	Stroop effect				
	5	Cingulate gyrus	25	Stroop test	Stroop effect	Stroop effect				
	7	Cingulate gyrus	25	Stroop test	Stroop effect	Stroop effect				
Wang2013	1	Inferior frontal gyrus Middle temporal gyrus Inferior frontal gyrus Superior frontal gyrus Middle frontal gyrus Cingulate gyrus	44/45/47 21 44/45/47 8 9/46 25	Object naming Object naming Language switching Object naming Object naming Object naming	- - Unable to Switch Involuntary language switch Involuntary language switch Involuntary language switch	Not specified Not specified Unable to switch Language switch Language switch Language switch	Caudate	Language switching; Colour Shape switching	Unable to switch	Unable to switch
Yordanova2011	7	Ventral premotor cortex	6b	Counting, object naming	Speech arrest	Speech disturbance	Superior longitudinal fasciculus Caudate Fibres from ventral premotor cortex	Counting, object naming	Phonological paraphasia Perseveration Speech arrest	Phonological error Response perseveration Speech disturbance

Zemmoura15	1	Ventral premotor cortex Superior temporal gyrus Middle temporal gyrus	6b 22 21	Object naming Object naming Object naming	Anarthria Anomia Involuntary language switch	Anarthria Anomia Language switch	Inferior longitudinal fasciculus Inferior fronto-occipital fasciculus Arcuate fasciculus	Reading Object naming Object naming	Phonological disturbances Semantic paraphasia Phonological paraphasia; anomia	Phonological disturbances Semantic error Phonological error; anomia
	2	Ventral premotor cortex Precentral gyrus Postcentral gyrus Superior temporal gyrus	6b 4 1/2/3 22	Object naming Object naming Object naming Object naming	Anarthria Anarthria Articulatory troubles; motor reaction (tongue) Semantic paraphasia; language switching	Motor Motor Motor Semantic error; Language switching	Inferior longitudinal fasciculus Inferior fronto-occipital fasciculus Arcuate fasciculus	Reading Object naming Object naming	Phonological disturbances Semantic paraphasia; anomia Phonological paraphasia	Phonological disturbances Semantic error; anomia Phonological error
	3	Ventral premotor cortex Superior temporal gyrus Middle temporal gyrus	6b 22 21	Object naming Object naming Object naming	Anarthria Anomia Phonological paraphasia	Motor Anomia Phonological error	Inferior longitudinal fasciculus Inferior fronto-occipital fasciculus Arcuate fasciculus	Reading Object naming Object naming	Phonological disturbance Anomia Phonological paraphasia; anomia	Phonological disturbance Anomia Phonological error; anomia
	4	Middle temporal gyrus Ventral premotor cortex Superior temporal gyrus	21 6b 22	Reading; object naming Object naming Object naming	Anomia; Alexia Anarthria Anomia	Anomia; Alexia Motor Anomia	Inferior longitudinal fasciculus Arcuate fasciculus	Reading Object naming	Phonological disturbances Phonological paraphasia	Phonological disturbances Phonological error
	5	Ventral premotor cortex Superior temporal gyrus	6b 22	Object naming Object naming	Anarthria Anomia; Semantic paraphasia	Motor Anomia; Semantic error	Inferior longitudinal fasciculus Inferior fronto-occipital fasciculus Arcuate fasciculus	Reading Object naming	Phonological disturbance Anomia; Semantic paraphasia Phonological paraphasia; Anomia	Phonological disturbance Anomia; Semantic error Phonological error; Anomia
	6	Inferior temporal gyrus Superior temporal gyrus Middle temporal gyrus Occipital lobe (Visual cortex)	20 22 21 19	Reading Object naming Object naming Object naming	Alexia Anomia Phonological paraphasia; Anomia Phonological paraphasia; Anomia	Alexia Anomia Phonological error; Anomia Phonological error; Anomia	Inferior longitudinal fasciculus Inferior fronto-occipital fasciculus Arcuate fasciculus	Reading Object naming Object naming	Alexia Anomia Phonological paraphasia	Alexia Anomia Phonological error

	7	Middle temporal gyrus Superior temporal gyrus	21 22	Reading Reading	Alexia Anomia	Alexia Anomia	Inferior fronto-occipital fasciculus	Object naming; Pyramids & palm trees task	Semantic paraphasia; Semantic association disturbance	Semantic error; Semantic association disturbance
Group Data										
Chacko2013	-	Inferior Frontal gyrus Superior Temporal gyrus	44/45/47 22	Object naming, Reading, counting Object naming, Reading, Counting		Not specified Not specified				
Duffau2008b	-						Fibres from VPMc, subcallosal fasciculus Ant. Arcuate fasciculus Ant. Inf. Fronto-occipital Fasciculus Head of the caudate nucleus Post. Inf. Fronto-occipital Fasciculus post. /Ant. AF (posterior part) deep: lentiform nucleus,	Counting, Object naming Counting, Object naming Counting, Object naming Counting, Object naming Counting, Object naming Counting Object naming		Not specified Not specified Not specified Not specified Not specified Not specified Not specified
Duffau2009b	-	Posterior Inferior Frontal gyrus Middle Frontal gyrus Lat. Precentral gyrus Posterior/Middle Temporal gyrus	44 9/46 4 22b/c	Counting, Object naming Counting, Object naming Counting, Object naming		Not specified Not specified Not specified Not specified				

Gao2016	-	Supramarginal Gyrus Middle/Posterior Superior Temporal Gyrus Posterior Inferior Temporal Gyrus Middle Superior Temporal Gyrus Posterior Superior Temporal Gyrus Posterior Inferior Frontal Gyrus Posterior Inferior Frontal Gyrus	40 22b/c 37 22b 22c 44 44	Object naming Object naming Reading Reading Counting Counting	Anomia Anomia Anomia Alexia Alexia Speech Arrest Speech Arrest	Anomia Anomia Anomia Alexia Alexia Speech disturbance Speech disturbance				
Giussani2009	-	Sup Inferior Frontal Gyrus Middle Frontal Gyrus Inferior Frontal Gyrus Anterior Superior Temporal Gyrus Posterior Superior Temporal Gyrus Anterior Middle Temporal Gyrus Middle/Posterior Mid Temporal Gyrus Supramarginal/Angular Gyrus Superior Parietal Area (Superior parietal lobule)	44/45 9/46 44/45/47 22a 22c 21a 21b/c 40/39 5/7	Famous Face naming Famous Face naming Famous Face naming Famous Face naming Famous Face naming Famous Face naming Famous Face naming Famous Face naming Famous Face naming	Speech Arrest, Anomia, Semantic Paraphasia Speech Arrest, Anomia, Semantic Paraphasia Speech Arrest, Anomia, Semantic Paraphasia Speech Arrest, Anomia, Semantic Paraphasia Speech Arrest, Anomia, Semantic Paraphasia Speech Arrest, Anomia Speech Arrest, Anomia Phonemic paraphasia, Semantic paraphasia, Neologistic paraphasia Phonemi	Speech disturbance; Anomia; Semantic error Speech disturbance; Anomia; Semantic error Speech disturbance; Anomia; Semantic error Speech disturbance; Anomia; Semantic error Speech disturbance; Anomia; Semantic error Speech disturbance; Anomia Speech disturbance; Anomia Speech disturbance; Anomia; Semantic error Speech disturbance; Anomia				

					c paraphasia, Semantic paraphasia, Neologistic paraphasia	Anomia Phonological error; Semantic error; Response error Phonological error; Semantic error; Response error				
Giussani2011	-	Post/Anterior Temporal gyri Supramarginal Gyrus Middle/Inferior Frontal gyri Supramarginal/Angular gyri Posterior Temporal/Supramarginal gyri	20/21/21 40 9/46/44/45/47 40/39 22c/40	Object naming Object naming Object naming Object naming Object naming	Anomia Anomia Anomia Phonological paraphasia Semantic Paraphasia	Anomia Anomia Anomia Phonological error Semantic error				
Lee2018	-	Ant/Mid/Posterior Middle temporal gyrus Ant/Mid/Posterior Superior temporal gyrus Posterior/Middle Inferior frontal gyrus Inferior Precentral gyrus Inferior Postcentral gyrus Supramarginal/angular gyrus	21a/b/c 22a/b/c 44/45 4 43 40/39	Word production task Word production task Word production task Word production task Word production task Word production task		Not specified Not specified Not specified Not specified Not specified Not specified				

Leclercq2010	-						Arcuate Fasciculus Inf. fronto-occipital fasciculus Subcallosal Fasciculus Insuloopercular sulcus Premotor Fasciculi	Counting, Object naming Counting, Object naming Counting, Object naming Counting, Object naming Counting, Object naming	Articulatory disorders Articulatory disorders Articulatory disorders Articulatory disorders	Speech disturbance Speech disturbance Speech disturbance Speech disturbance
Lubrano2010	-	Middle Frontal Gyrus Inferior Frontal gyrus	9/46 44/45/47	Object naming Object naming	Anomia Anomia	Anomia Anomia				
Lubrano2014	-	Inferior Frontal Gyrus Middle Frontal Gyrus Superior Frontal Gyrus Anterior Superior Temporal Gyrus Middle Superior Temporal Gyrus Posterior Superior Temporal Gyrus Posterior Middle Temporal Gyrus Supramarginal Gyrus	44/45/47 9/46 8 22a 22b 22c 21c 40	Object naming, Action naming Object naming, Action naming Object naming, Action naming Object naming, Action naming Object naming, Action naming Object naming, Action naming Object naming, Action naming	Speech arrest, anomia; semantic paraphasia, neologism; hesitation Speech arrest, anomia; semantic paraphasia, neologism; hesitation Speech arrest, anomia, neologism Speech arrest, anomia, neologism Speech arrest, anomia, neologism Speech arrest, anomia, neologism Speech arrest, anomia, neologis	Speech disturbance; Anomia; Semantic error Response error; Response delay Speech disturbance; Anomia; Response error				

					m Speech arrest, anomia, neologism					
Martino2018	Cohort 1	Dorsal premotor cortex Superior frontal gyrus (SMA) Posterior inferior frontal gyrus (pars triangularis) Posterior Middle frontal gyrus Angular gyrus Middle Superior temporal Middle temporal Precentral gyrus Dorsal premotor cortex Superior frontal gyrus Posterior Middle frontal gyrus Ventral premotor cortex Posterior inferior frontal gyrus (pars opercularis) Inferior frontal gyrus (parts triangularis) Anterior	6a 8 45 9/46 39 22b 21b 4 6a 8 21c 6b 44 45 22a 22b 22c 21c 43 40	Short term verbal memory task Short term verbal memory task Short term verbal memory task Short term verbal memory task Short term verbal memory task Short term verbal memory task Short term verbal memory task Short term verbal memory task Object naming Object naming Object naming Object naming Object naming Object naming Object		Not specified Not specified				

		Superior temporal gyrus Middle Superior temporal gyrus Posterior Superior temporal gyrus Posterior middle temporal gyrus Postcentral gyrus Supramarginal gyrus		naming Object naming Object naming Object naming Object naming Object naming Object naming		Not specified Not specified Not specified Not specified Not specified				
Martino2018	Cohort 2	Mid middle frontal gyrus Posterior Middle frontal gyrus Precentral gyrus Ventral premotor cortex Posterior Inferior frontal gyrus (part opercularis) Midt. Inferior frontal gyrus (part triangularis) Postcentral gyrus Anterior superior temporal gyrus Mid superior temporal gyrus Post superior temporal gyrus Anterior middle temporal gyrus Mid middle	9/46 9/46 4 6b 44 45 43 22a 22b 22c 21a 21b 21c 20a 20b	Object naming Object naming Object naming Object naming Object naming Object naming Object naming Object naming Object naming Object naming Object naming Object naming Object naming Object naming Object naming		Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specifi				

		temporal gyrus Post middle temporal gyrus Anterior inferior temporal gyrus Mid inferior temporal gyrus				ed Not specifi ed				
Roux2004		Superior Frontal Gyrus Superior Precentral gyrus Superior Parietal lobule Middle Frontal gyrus Middle Precentral gyrus Middle Postcentral Gyrus Supramargi nal gyrus Angular Gyrus Inferior Frontal gyrus Inferior Precentral gyrus Inferior Postcentral gyrus Anterior Superior Temporal Gyrus Middle Superior Temporal Gyrus Posterior Superior Temporal Gyrus Anterior Middle Temporal Gyrus Middle Temporal Gyrus	8 4 5/7 9/46 4 1/2/3 40 39 44/45/ 47 4 43 22a 22b 22c 21a 21b 21c 20b 37	Object naming, reading Reading Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Object naming, Reading Reading Reading Object		Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi ed Not specifi				

		Posterior Middle Temporal Gyrus Middle Inferior Temporal Gyrus Posterior Inferior Temporal Gyrus		naming, Reading		ed Not specified Not specified				
Roux2015	-	Anterior Superior Temporal/Heschl's gyrus Anterior Superior temporal gyrus Posterior Middle Temporal gyrus	22a/41/42 22a 21b	Auditory sentence picture matching Auditory sentence picture matching Auditory sentence picture matching	Comprehension disturbance (speech discrimination/word deafness) Comprehension disturbance (speech discrimination/word deafness) Comprehension disturbance (speech discrimination/word deafness)	Comprehension deficit Comprehension deficit Comprehension deficit				
Spena2010	-	Inferior Frontal gyrus (pars opercularis) Inferior Frontal gyrus (pars triangularis) Inferior parietal lobule Superior Temporal gyrus Dorsal Premotor	44 45 40 22 6a 40/39 39	Object naming Object naming Object naming Object naming Object naming Object naming Object naming	Speech arrest Speech arrest Speech arrest Speech arrest Speech arrest Speech arrest Speech arrest	Speech disturbance Speech disturbance Speech disturbance Speech disturbance Speech disturbance Speech disturbance Speech				

		cortex Supramarginal gyrus/Posterior Inferior Parietal lobe (Angular gyrus)				disturbance Speech disturbance				
Tate2014	-	Middle Superior temporal gyrus, Inferior frontal gyrus (pars opercularis) Junction of precentral gyrus/dorsolateral prefrontal cortex (middle frontal gyrus)	22 44 4/9/46	Object naming Object naming Object naming	Phonological paraphasia Phonological paraphasia Phonological paraphasia	Phonological error Phonological error Phonological error				
	-	Inferior Frontal gyrus (pars triangularis/opercularis) Posterior Middle Frontal gyrus Superior Frontal gyrus Inferior Precentral gyrus Middle/Posterior Superior Temporal gyrus Anterior/Middle/Posterior Superior Temporal gyrus Supramarginal gyrus	44/45 9/46 8 4 22b/c 22a/b/c 40	Object naming Object naming Object naming Object naming Object naming Object naming Object naming	Semantic paraphasia Semantic paraphasia Semantic paraphasia Semantic paraphasia Semantic paraphasia Semantic paraphasia Semantic paraphasia	Semantic error Semantic error Semantic error Semantic error Semantic error Semantic error Semantic error				
Tiandong2015	-	Vent. Precentral gyrus Inferior Frontal gyrus (pars opercularis) Inferior Frontal gyrus (pars triangularis) Posterior Middle Frontal gyrus Posterior Superior Frontal gyrus	4 44 45 9/46 8	Counting Counting Counting Counting Counting		Not specified Not specified Not specified Not specified Not specified Not specified				

Walker2004	-	Middle Superior Temporal gyrus Posterior Superior Temporal gyrus	22b 22c	Object naming Object naming		Not specified Not specified				

Appendix 4.

Right hemisphere DES mapping data extracted from included studies in systematic review (Chapter 2)

		Cortical Mapping					Subcortical Mapping			
Study ID	**CASE**	**Area**	**BA**	**Task**	**Interference/error description (from paper)**	**Category**	**Area**	**Task**	**Interference/error description (from paper)**	**Category**
Individual Case Data										
Borius2012	4	Dorsal premotor cortex	6a	Reading; Object-naming; Translation		Not specified				
DellaPuppa2013	1	Angular gyrus Supramarginal gyrus Superior parietal lobule	39 40 5/7	Multiplication Multiplication Multiplication		Not specified Not specified Not specified				
	2	Angular gyrus Supramarginal gyrus	39 40	Addition Addition	-	Not specified Not specified				
	3	Angular gyrus Supramarginal gyrus	39 40	Multiplication Multiplication	-	Not specified Not specified				
Duffau2008a	1	Vent. Premotor Cortex Dorsal. Premotor Cortex	6b 6a	Object-naming	Anarthria Anomia	Motor speech disturbance Anomia	Posterior pathway Head of Caudate	Object-naming	Articulatory disturbance Perseverations	Speech disturbance Response perseverations
	2	Vent. Premotor Cortex	6b	Object-naming	Anarthria	Motor speech disturbance	Posterior pathway	Object-naming	Articulatory disturbance	Speech disturbance
	3	Vent. Premotor Cortex	6b	Object-naming	Anarthria	Motor speech disturbance	Posterior pathway Head of Caudate	Object-naming	Articulatory disturbance Perseverations	Speech disturbance Response perseverations
	4	Vent. Premotor Cortex Inf. Frontal gyrus (Pars Opercularis)	6b 44	Object-naming	Anarthria Speech Arrest	Motor speech disturbance Speech deficit	Posterior pathway Medial pathway	Object-naming	Articulatory disturbance Transcorti	Speech disturbance Speech

									cal motor aphasia	disturbance
	5	Ventral PMC Dors-Lat. Prefrontal Cortex Anterior Insular Cortex	6b 9/46 13-16	Object-naming	Anarthria Semantic paraphasia Articulatory disorders	Motor speech disturbance Semantic error Speech disturbance	Posteriorly pathway Deeply	Object-naming	Articulatory disturbance Phonemic paraphasia	Speech disturbance Phonological error
	6	Vent. Premotor Cortex Supramarginal gyrus	6b 40	Object-naming	Anarthria Phonemic paraphasia	Motor speech disturbance Phonological error	Deeply	Object-naming	Phonemic paraphasia	Phonological error
	7	Vent. Premotor Cortex Supramarginal Gyrus	6b 40	Object-naming	Anarthria Phonemic paraphasia	Motor speech disturbance Phonological error	Deeply	Object-naming	Phonemic paraphasia	Phonological error
	8	Vent. Premotor Cortex Superior Temporal Gyrus	6b 22	Object-naming	Anarthria Semantic paraphasia	Motor speech disturbance Semantic error	Deeply	Object-naming	Semantic paraphasia	Semantic error
	9	Vent. Premotor Cortex Superior Temporal Gyrus/Post. Mid. Temporal Gyrus	6b 22 21c	Object-naming	Anarthria Semantic paraphasia	Motor speech disturbance Semantic error	Deeply	Object-naming	Semantic paraphasia	Semantic error
Gil-Robles 2005	7						Caudate	Counting, Object-naming	Perseveration	Response perseveration
	11						Caudate	Counting, Object-naming	Perseveration	Response perseveration
Herbert 2015	1	Ventral premotor cortex Inferior frontal gyrus	6b 44/45/47	Counting Object-naming Spontaneous speech Mentalizing	Speech arrest; Anarthria Speaking-Singing switch Speaking-Singing switch Speaking-Singing switch	Speech disturbance; Motor speech disturbance Speaking-Singing switch Speaking-Singing switch Speaking-Singing switch				
Lubrano2004	12	Dorsal premotor cortex	6a	Writing; Reading	Writing arrest	Agraphia				
Roux2012	20	Postcentral gyrus Supramarginal gyrus	43 40	Writing Writing	Phonological paragraphia Phonological paragraphia	Phonological error Phonological error				
Vassal2010	1	Dorsal premotor cortex Superior temporal gyrus	6a 22	Object-naming Object-naming	Anomia Semantic paraphasia	Anomia Semantic error				
	2	Superior temporal gyrus	22	Object-naming Object-naming	Semantic paraphasia	Semantic error	Inferior fronto-occipito fascicul	Object-naming	Semantic paraphasia Phonologi	Semantic error Phono

							us Arcuate fasciculus	Object-naming	cal paraphasia	logical error
	3	Dorsal premotor cortex Inferior frontal gyrus	6a 44/45/47	Object-naming Object-naming	Anomia Anomia	Anomia Anomia	Inferior fronto-occipito fasciculus	Object-naming	Semantic paraphasia	Semantic error
Wager2013	5	Cingulate gyrus	25	Stroop test	Stroop effect	Stroop effect				
	7	Cingulate gyrus	25	Stroop test	Stroop effect	Stroop effect				
Yordanova2017	1	Middle frontal gyrus	9/46	Pyramid & palm trees Reading the mind in the eyes	Error/no response Error/no response	Response error; No response Response error; No response				
Yordanova2017	2	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error	Response error				
Yordanova2017	4	Middle frontal gyrus	9/46	Pyramid & palm trees	No response	No response				
Yordanova2017	5	Middle frontal gyrus	9/46	Reading the mind in the eyes	No response	No response				
Yordanova2017	6	Middle frontal gyrus	9/46	Reading the mind in the eyes	No response	No response				
Yordanova2017	7	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error	Response error				
Yordanova2017	8	Middle frontal gyrus	9/46	Pyramid & palm trees	Error/no response Error	Response error; No response Response error				
Yordanova2017	9	Middle frontal gyrus	9/46	Pyramid & palm trees Reading the mind in the eyes	Error Error	Response error Response error				
Yordanova2017	10	Temporo-parietal junction	22/39	Pyramid & palm trees Reading the mind in the eyes	Error Error	Response error Response error				
Yordanova2017	11	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error	Response error				
Yordanova2017	12	Post. Superior temporal gyrus	22c	Reading the mind in the eyes	Error	Response error				
Yordanova2017	13	Inferior frontal gyrus (opercularis)	44	Reading the mind in the eyes	Error	Response error				
Yordanova2017	14	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error/no response	Response error; No response				
Yordanova2017	15	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error	Response error				
Yordanova2017	16	Inferior frontal gyrus (opercularis)/Middle frontal gyrus Inferior frontal gyrus (triangularis)	44/9/46 45	Pyramid & palm trees Pyramid & palm trees	Error Error	Response error Response error				

Yordanova2017	17	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error	Response error				
Yordanova2017	18	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error/no response	Response error; No response				
Yordanova2017	19	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error	Response error				
Yordanova2017	20	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error	Response error				
Yordanova2017	22	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error/no response	Response error; No response				
Yordanova2017	23	Inferior frontal gyrus (triangularis)	45	Reading the mind in the eyes	Error	Response error				
Yordanova2017	24	Middle frontal gyrus	9/46	Reading the mind in the eyes	no response	No response				
Yordanova2017	25	Temporo-parietal junction	22/39	Reading the mind in the eyes	Error	Response error				
Yordanova2017	26	Middle frontal gyrus	9/46	Reading the mind in the eyes	Error	Response error				
Yordanova2017	27	Middle frontal gyrus Middle frontal gyrus	9/46 9/46	Pyramid & palm trees Reading the mind in the eyes	Error Error	Response error Response error				
Yordanova2019	1	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	2	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	3	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	4	Inferior frontal gyrus (triangularis)	45	Reading the mind in the eyes		Not specified				
Yordanova2019	5	Middle frontal gyrus (middle)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	6	Inferior frontal gyrus (opercularis)	44	Reading the mind in the eyes		Not specified				
Yordanova2019	7	Inferior frontal gyrus (opercularis)	44	Reading the mind in the eyes		Not specified				
Yordanova2019	8	Inferior frontal gyrus (orbitalis)	47	Reading the mind in the eyes		Not specified				
Yordanova2019	9	Inferior frontal gyrus (opercularis)	44	Reading the mind in the eyes		Not specified				
Yordanova2019	10	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	11	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	12	Inferior frontal gyrus (triangularis)	45	Reading the mind in the eyes		Not specified				
Yordanova2019	13	Middle frontal gyrus (middle)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	14	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				

Yordanova2019	15	Inferior frontal gyrus (orbitalis)	47	Reading the mind in the eyes		Not specified				
Yordanova2019	16	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	17	Inferior frontal gyrus (opercularis)	44	Reading the mind in the eyes		Not specified				
Yordanova2019	18	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	19	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	20	Inferior frontal gyrus (triangularis)	45	Reading the mind in the eyes		Not specified				
Yordanova2019	21	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	22	Middle frontal gyrus (anterior)	9/46	Reading the mind in the eyes		Not specified				
Yordanova2019	23	Inferior frontal gyrus (opercularis)	44	Reading the mind in the eyes		Not specified				
Group Data										
Martino 2018	-	Ventral premotor cortex Inferior frontal gyrus Middle frontal gyrus Ant. Middle temporal gyrus Mid middle temporal gyrus	6b 44/45/47 9/46 21a 21b	Object-naming Object-naming Object-naming Object-naming Object-naming		Not specified Not specified Not specified Not specified Not specified				
Martino 2018	-	Ventral premotor cortex Inferior frontal gyrus	6b 44/45/47	Object-naming Object-naming		Not specified Not specified				
Roux2004	-	Sup. Frontal Gyrus Angular Gyrus Supramarginal gyrus Mid. Precentral gyrus Mid. Frontal Gyrus Inf. Precentral gyrus Inf. Postcentral gyrus Inf. Frontal gyrus Post. Sup. Temporal Gyrus Mid. Sup. Temporal Gyrus	8 39 40 4 9/46 4 43 44/45/47 22c 22b	Object-naming, reading Reading Object-naming, Reading Object-naming, Reading Object-naming, Reading Object-naming, Reading Object-naming, Reading Object-naming, Reading Object-naming, Reading Object-naming, Reading		Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified Not specified				

Appendix 5.

Cognitive and linguistic tasks used by studies included in systematic review (Chapter 2)

Study ID	Object naming	Famous face naming	Naming to description	Colour naming	Action naming	Action naming (finite verbs)	Pyramids & palm trees	Semantic picture out	Sentence completion	Word production	Sentence comprehension	Reading	Non-word reading	Score reading (music)	Writing	Repetition	Counting	Language switching	Translation	Symbol recognition	Stroop	Colour shape switching	Spontaneous speech	Singing	Rhythm judgement	Calculation	Reading the mind in the eyes	Short-term verbal memory
Abel2009	x																											
Alimohamadi2016																	x											
Amorim2008																	x											
Bello2007	x																						x					
Bello2008	x	x			x																							
Bilotta2014																	x											
Borius2012	x											x							x									
Chacko2013	x											x					x											
Chan2019	x																x											
ChanSeng2014	x											x																
DeBenedictis2014	x																x											
DellaPuppa2015																										x		
DeWitte2015a	x							x	x								x						x			x		
DeWitte2015b	x					x		x	x							x												
DeWitte2015c	x																											
DeWittHamer2011	x																											
Duffau2002a	x																x									x		
Duffau2002b	x																x											
Duffau2002c	x																x											
Duffau2003a	x																											
Duffau2003b	x															x	x											
Duffau2003c	x																x											
Duffau2004	x																x											
Duffau2005	x																											

Duffau2008a	x																x										
Duffau2008b	x																x										
Duffau2009a	x																										
Duffau2009b	x																x										
Ellemore2009																x	x										
Fuji2015	x																										
Gatignol2004	x						x										x										
Gau2016	x										x						x										
Gil-Robles2005	x																x										
Gil-Robles2008	x																x										
Gil-Robles2013	x										x									x							
Giussani2009		x																									
Giussani2011	x																										
Hayashi2014	x																										
Henry2004	x																										
Herbert2015	x																x					x				x	
Kamada2007	x																										
Khan2014	x																										
Kin2013	x		x																								
Kosla2015	x																										
Kurimoto2006	x															x										x	
Leclercq2010	x																x										
Lee2018										x																	
Lima2017	x																x										
Lubrano2004	x											x			x												
Lubrano2010	x																										
Lubrano2012	x																										
Lubrano2014	x				x																						
Maldonado2011a	x																x										
Maldonado2011b	x																x										
Mandonnet2007	x																x										
Mandonnet2009	x																										
Martino2018	x																										x

Matsuda 2014	x																										
Matsuda 2019	x																								x		
Metellus 2016	x										x				x	x											
Morits-Gasser2009	x																										
Morits-Gasser2013	x						x																				
Motomura2014	x										x			x													
Mukae2017	x																										
Nomura 2013	x																										
Ogawa2014	x																										
Ogawa2017	x										x																
Parney2010	x															x											
PetrovichBrennan2007	x															x											
Plaza2009	x															x											
Pu2011																									x		
Rech2017	x																										
Riva2016	x												x			x								x			
Rofes2015	x					x																					
Rofes2017	x					x																					
Rolland 2018	x																										
Rosenberg2008	x																										
Roux2002	x										x					x											
Roux2003a	x			x							x			x											x		
Roux2003b	x																										
Roux2004	x										x																
Roux2006	x			x																							
Roux2007	x										x		x														
Roux2009a	x										x												x				
Roux2009b	x										x			x													
Roux2009c	x															x									x		
Roux2012											x	x		x													
Roux2014	x										x			x													
Roux2015	x									x																	
Saito2014	x										x																
Sakurada2007	x																										
Sallard2012	x															x											

Sarubbo 2012	x																x										
Satoer2017	x															x											
Schapiro 2012	x																x										
Sierpowska2013	x																										
Signorelli2003	x																										
Simos1999	x										x					x											
Sollman 2013	x																										
Spena2010	x																										
Spena2015	x											x					x										
Tate2014	x																										
Tiandong2015																	x										
Tomasino2014	x																x										
VanGeemen2014	x																x										
Vassal2010	x																										
Vidorettta2011	x																										
Wager2013																					x						
Walker2004	x																										
Wang2013	x																	x				x					
Yordanova2011	x																x										
Yordanova2017							x																			x	
Yordanova2019																										x	
Zemmoura2015	x						x					x															
Total	**101**	**2**	**1**	**2**	**2**	**3**	**4**	**2**	**2**	**1**	**2**	**20**	**1**	**2**	**6**	**7**	**42**	**1**	**1**	**1**	**1**	**1**	**3**	**1**	**1**	**8**	**3**	**1**

Appendix 6.

List of DES-induced disturbance categories based on interference and error types reported by included studies in systematic review (Chapter 2)

Category	Description
Speech	Speech arrest without motor response; speech initiation deficit; articulatory disturbance
Motor-Speech	Anarthria/dysarthria; speech disturbance with motor response
Response perseveration	Perseveration of responses/errors
No response	No response to task/stimuli
Phonological error	Phonological paraphasia/paragraphia
Semantic error	Semantic paraphasia/paragraphia
Grammatical error	Syntax errors; pronoun errors; noun gender errors in foreign languages
Response error	Speech/reading/writing errors; verbal/visual paraphasias, paragraphias, Paranomia; neologisms; letter/word errors; substitutions; omissions
Response delay	Delays or hesitations in task responses
Anomia	Inability to name; difficulty naming; retrieval difficulties
Agraphia	Difficulty writing; writing arrest; inability to write
Alexia	Difficulty reading; inability to read; reading arrest
Acalculia	Difficulty calculating or complete inability to calculate
Comprehension	Auditory comprehension deficit; word deafness; semantic comprehension deficit; semantic association deficit
Language switch	Involuntary language switches to another language in bilingual patients
Speech-sing switch	Normal talking voice switches to a singing voice
Circumlocution	Using many words to describe something when fewer would do
Monotonous singing	Singing voice becomes monotone
Sign block	Inability to use sign language in deaf patients
Stroop effect	Inability to ignore the word print colour when incongruent to the colour-word being read
Not specified	Interference or error type not specified in the study