# IMPROVING OUR UNDERSTANDING OF SPEECH AND LANGUAGE OUTCOME IN NEUROSURGERY PATIENTS

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"The brain is the organ of destiny. It holds within its humming mechanism secrets that will determine the future of the human race."

Wilder Penfield

### DECLARATION

I, Justyna Ekert confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Scientific research is a team endeavour and this thesis would not have been possible without many people that I was fortunate to work with. All structural and functional MRI data used in the experimental chapters were collected and pre-processed by the PLORAS team. I gained experience with the acquisition and pre-processing of fMRI and structural imaging in studies that are not reported in this thesis. I performed all second level analyses reported in this thesis, generated the statistics of interest, and produced all the figures. The results and interpretations in the experimental chapters were developed based on discussions with my supervisor and feedback from collaborators. I wrote the first draft of all chapters. Experiments 1 and 2 have been combined into a single paper (in submission) and were subsequently revised following co-author comments. Likewise, with co-author comments, Experiments 3 and 4 have been converted into two further papers (one in submission and one in revision). Experiment 5 has not yet been converted into a paper, but I incorporated many suggestions from my supervisor and another colleague.

> Justyna Ekert July 2021

### ABSTRACT

Malignant gliomas remain incurable and result in more years of life lost than any other tumours. Surgical resection is strongly recommended but carries a risk of causing functional impairment. This thesis aims to demonstrate how state-of-the-art functional magnetic resonance imaging (fMRI) language paradigms can contribute to neurosurgical planning. The first three experiments use a multitask fMRI language paradigm to functionally segregate left posterior temporal and left posterior frontal regions involved in the perception and production of speech. Experiment 1 demonstrated three functionally distinct responses in the left posterior superior temporal sulcus (STS), left temporo-parietal junction and anterior ascending terminal branch of the left STS. Experiment 2 validates these findings in an independent group of participants, increasing confidence that they are robust. Experiment 3 dissociates the response of three different parts of the left premotor cortex during speech production.

Experiment 4 shows that left posterior temporal regions are more consistently activated, in neurotypical controls, when a picture naming task presents pairs of objects rather than single objects. Further work could therefore test whether paired object naming is a more sensitive task for preand intra-operative language mapping. Finally, Experiment 5 found that successful reading before and after surgery, in two patients with gliomas affecting the left temporo-parietal junction, enhanced activation in bilateral perirhinal regions that were associated with semantic identification of visually presented objects in neurotypical controls. Future studies can now test whether patients who undergo resection of the left temporo-parietal junction have better reading, post-surgery, when bilateral perirhinal activation is enhanced prior to surgery. Taken together, this work expands our knowledge of the functional anatomy of language, proposes a new way of utilising fMRI data from neurotypical controls to tailor pre- and intra-operative language mapping strategies and provides an insight into how the reading system reorganises itself after brain damage.

#### **IMPACT STATEMENT**

Each day approximately 15 patients receive a diagnosis of a brain tumour and only 12% of them survive over 5 years despite optimum treatment (Cancer Research UK). Surgical intervention followed by radiotherapy is the standard of care for the majority of brain tumours (Rampling et al., 2004). A growing body of evidence suggests that more extensive resection is associated with longer life expectancy (lus et al., 2012; Jakola et al., 2012; Jakola et al., 2017; McGirt et al., 2009; Sanai et al., 2008; Sanai & Berger, 2008). The benefit of more aggressive resection in prolonging survival needs to be balanced with the risk of life-changing neurological deficits to maintain the patient's quality of life.

Brain networks supporting language processing are incredibly complex and widely distributed, thus preservation of linguistic abilities is particularly challenging. Non-invasive mapping methods such as functional magnetic resonance imaging (fMRI) transformed the practice of neurosurgery, allowing for enhanced operative strategies and meticulous pre-operative planning. The incorporation of newly acquired knowledge of functional correlates of language in pre-surgical planning can permit the surgeon to maximise the extent of resection, while minimising post-operative impairments. The overarching goal of this thesis was to improve our understanding of speech and language outcome after neurosurgery by utilising functional neuroimaging data from neurotypical controls.

From a research perspective, the reported findings resolve previous inconsistencies in the literature, characterise the response profiles of multiple regions in the posterior superior temporal lobe (Experiments 1 and 2) and posterior frontal lobe (Experiment 3), and present novel hypotheses about the contribution of each region to speech production or speech perception. From a clinical perspective, a better understanding of the functional anatomy of

language will facilitate more targeted brain mapping strategies in patients undergoing resective surgery. For instance, a clinician managing a patient with a tumour close to the left precentral gyrus could opt for intra-operative testing with a pseudoword reading task, given the strong response to pseudoword reading that I (and others) have observed in this area.

Experiment 4 demonstrates how maps of the consistency of activation across neurotypical cohorts could be used to further optimise the choice of tasks and stimuli for pre-surgical and intra-operative language mapping. Specifically, naming pairs of objects in pictures was found to elicit more robust responses in putative language regions than naming single objects in pictures, suggesting that the paired object naming paradigm might show higher sensitivity for detecting language disturbances during surgery. Finally, Experiment 5 shows how data from neurotypical controls can be used to interpret functional reorganisation of language that occurs before and after surgery in patients with tumours that have infiltrated language areas.

Overall, this thesis provides the initial building blocks of an integrated clinical tool for predicting language outcome and recovery after neurosurgery. The proposed tool will combine fMRI activation maps from large numbers of neurotypical controls with measures of inter-subject consistency and information about potential compensatory mechanisms. The product of this work would support clinical decision making and empower patients to make informed choices about their care.

#### ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisor, Professor Cathy Price, for her invaluable advice, continuous support, and patience during my PhD. As a medical student just starting the fourth year of my undergraduate study, Cathy gave me an opportunity to join the language group and, since then, has invested countless hours of her time into my education and taught me everything I know about functional MRI techniques. Cathy's immense knowledge and expertise have encouraged me in both my academic research and daily life. I could not have wished for a better supervisor and a mentor, and I can only aspire to become such an accomplished scientist.

I would like to express my sincere gratitude to Mr George Samandouras, who has been a true inspiration and taught me to always work hard, aim high and never give up. I am highly grateful for the innumerous opportunities to develop my interest and grow as a person and for helping me keep a perspective on where my research fits into the bigger picture and its clinical relevance.

I have been privileged to have been welcomed into the PLORAS team and met so many great colleagues at the FIL. Special thanks to go the collaborators who contributed to the work presented in this thesis, in particular, Professor David Green for his generous help and constructive feedback on my work, as well as Andrea and Diego, who were always happy to answer my endless streams of questions at the start of my PhD.

I also wish to acknowledge the MBPhD program for giving me the chance to pursue my passions. I would like to extend my sincere thanks to Professor Áine Burns and Carolyn Cohen for their kindness and unwavering guidance during my PhD years. I would certainly not miss to mention the funders of my PhD, the Middlesex Hospital General Charitable Trust, without whom this work would not be possible.

I am very fortunate to have wonderful friends and family who supported me throughout the years. In particular, my deepest appreciation belongs to my parents, Gosia and Roman, for their endless love and for always encouraging me in my studies, and my best friend and sister by heart, Ritika, for being my person and for standing by me through the good times and the bad. Finally, I also wish to thank Amelia, Łukasz and Noor for the countless moments of joy and happiness, and Matt for his unrivalled sense of humour and the numerous pieces of advice over the years.

### DEDICATION

To Mum and Dad,

My beloved parents who have raised me to be the person I am today

### STATEMENT OF PUBLICATIONS

The work I have been involved in during my PhD has resulted in the following peer-reviewed publications:

- Ekert, J.O., Lorca-Puls D.L., Gajardo-Vidal, A., Crinion J. T., Hope, T. M. H., Green D. W. & Price C. J. (2021). A functional dissociation of the left frontal regions that contribute to speech production during reading, repetition and object naming. In revision, *NeuroImage.*
- Ekert, J.O., Gajardo-Vidal, A., Lorca-Puls D. L., Hope, T. M. H., Dick, F., Crinion J. T., Green D. W. & Price C. J. (2021). Dissociating the functions of three different left posterior superior temporal regions that contribute to speech perception and production. Under review, *NeuroImage*.
- Ekert, J.O., Kirkman, M. A., Seghier, M. L. Green D. W. & Price C. J. (2021). A data-based approach for selecting pre-operative language mapping tasks. Under review, *Frontiers in Neuroscience*.
- Klitsinikos, D., Ekert, J. O., Carels, A., & Samandouras, G. (2021). Mapping and anatomo-surgical techniques for SMA-cingulum-corpus callosum gliomas; how I do it. *Acta Neurochirurgica*, *163*(5), 1239-1246.
- Sefcikova, V., Sporrer, J. K., Ekert, J. O., Kirkman, M. A., & Samandouras, G. (2020). High Interrater Variability in Intraoperative Language Testing and Interpretation in Awake Brain Mapping Among Neurosurgeons or Neuropsychologists: An Emerging Need for Standardization. *World Neurosurgery*, *141*, e651-e660.
- Sajid, N., Friston, K. J., Ekert, J. O., Price, C. J., & W Green, D. (2020). Neuromodulatory Control and Language Recovery in Bilingual Aphasia: An Active Inference Approach. *Behavioral Sciences*, *10*(10), 161.
- Leon-Rojas, J. E., Ekert, J. O., Kirkman, M. A., Sewell, D., Bisdas, S., & Samandouras, G. (2020). Experience with awake throughout craniotomy in tumour surgery: technique and outcomes of a prospective, consecutive case series with patient perception data. *Acta Neurochirurgica*, *162*(12), 3055-3065.

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### LIST OF ABBREVIATIONS AND ACRONYMS

ALI	Automated Lesion Identification
atSTS	Anterior ascending terminal branch of the left superior temporal sulcus
BOLD	Blood oxygenation level dependent
CAT	Comprehensive Aphasia Test
CNS	Central nervous system
CS	Central sulcus
CSF	Cerebrospinal fluid
DES	Direct electrical stimulation
dPCg	Dorsal precentral gyrus
DTI	Diffusion tensor imaging
EPI	Echo-planar imaging
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
FWHM	Full-width at half maximum
GBM	Glioblastoma multiforme
GLM	General Linear Model
GM	Grey matter
Hb	Haemoglobin
HCP	Human Connectome Project
HGG	High-grade glioma
HRF	Haemodynamic response function
IFJ	Inferior frontal junction
IFS	Inferior frontal sulcus
LGG	Low-grade glioma
LOM	Lesion overlap map
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MTG	Middle temporal gyrus
NMR	Nuclear magnetic resonance
PET	Positron emission tomography
рОр	Pars opercularis
pOrb	Pars orbitalis

PSL	Perisylvian language area					
pSTS	Posterior superior temporal sulcus					
pTri	Pars triangularis					
RF	Radiofrequency					
ROI	Regions of interest					
RT	Response time					
SD	Standard deviation					
sMRI	Structural magnetic resonance imaging					
SP	Speech production					
SPM	Statistical Parametric Mapping					
Spt	Sylvian parietal temporal					
STG	Superior temporal gyrus					
STSdp	Dorsal surface of the horizontal stem of posterior superior temporal sulcus					
STSvp	Ventral surface of the horizontal stem of posterior superior temporal sulcus					
TE	Echo time					
ТΙ	Inversion time					
TLE	Temporal lobe epilepsy					
TMS	Transcranial magnetic stimulation					
TPJ	Temporo-parietal junction					
TPOJ1	Temporal-parietal-occipital junction 1					
TR	Repetition time					
vPCg	Ventral precentral gyrus					
vPCs	Ventral precentral sulcus					
Vx	Number of voxels					
WHO	World Health Organisation					
WM	White matter					

# 1. INTRODUCTION

The overarching goal of my PhD is to investigate how functional magnetic resonance imaging data could contribute to neurosurgical planning by improving understanding of (i) the functional anatomy of language, (ii) the language tasks that activate regions targeted for neurosurgery, (iii) normal inter-subject variability in language processing and (iv) how language processing changes in the context of brain tumours and surgical resection.

#### 1.1. MOTIVATION

Primary brain tumours are a heterogenous group of benign or malignant neoplasms affecting a disproportionately large number of young and healthy individuals (Cancer Research UK). Despite the progress in treatment and survival rates, brain cancer remains the second leading cause of death in adolescents and young adults aged 15-39 (Miller et al., 2020). The incidence of brain tumours in the United Kingdom is projected to rise by 6% between 2014 and 2035, leading to an estimated number of 14,281 new cases in 2035 (Figure 1.1; Smittenaar et al., 2016).

The mean survival durations for patients who develop high-grade glioma range from 12 to 16 months after initial diagnosis (Gilbert et al., 2014). Even the less aggressive tumours can be lethal due to their ability to infiltrate surrounding brain regions and the propensity to transform to malignancy (Murphy et al., 2016). The burden of the disease on the individuals, their families and the healthcare system is substantial (Kutikova et al., 2007; Lacy et al., 2012). Neurosurgical resection is the standard of care for the majority of newly diagnosed gliomas. Mounting evidence suggests that greater extent of resection confers survival benefit in both low- and high-grade gliomas (Capelle et al., 2013; lus et al., 2012; Jakola et al., 2012; Jakola et al., 2017; McGirt et al., 2009; Roelz et al., 2016; Sanai et al., 2008; Sanai & Berger, 2008; Smith et al., 2008; Wijnenga et al., 2018). To achieve optimal outcome, the benefit of more extensive resection must be balanced with the risk of post-operative deficits. Preservation of language abilities is particularly challenging due to a wide network of distributed cortical hubs involved in language processing.

**Figure 1.1:** Observed and projected age-standardised incidence rates of brain, other CNS and intracranial tumours



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#### **1.2.** PLAN OF INTRODUCTION

In this chapter, I contextualise the relevance of my PhD work by providing the necessary background information and identifying areas that functional neuroimaging has the potential to contribute to. In the first half of the introduction, I briefly describe the epidemiology and the surgical management of gliomas of adulthood, specifically high- and low-grade gliomas. The second half focuses on the clinical applications of functional magnetic resonance imaging (fMRI) in brain tumour patients, including (i) pre-surgical planning, (ii) intra-operative language mapping and (iii) detection of recovery mechanisms. Lastly, I define the research problem and outline how I aim to address these challenges by studying neurotypical controls in my experimental work.

#### 1.3. GLIOMAS OF ADULTHOOD

Gliomas are the most common type of primary brain tumour, accounting for almost 30% of all cases (Ostrom et al., 2014). Tumours in this heterogenous group are thought to originate from neural stem or progenitor cells and are classified based on their molecular and histological features according to the 2016 World Health Organisation (WHO) classification of the Central Nervous System (CNS) (Louis et al., 2016). On the basis of their anaplastic features, they are assigned WHO grades I-IV (see Table 1.1), with grade IV gliomas, also known as glioblastomas, representing the least differentiated and most malignant of the tumours (Weller et al., 2015).

	Α	strocytoma	Oligoastrocytoma	Oligodendroglioma	Mixed neuronal-glial tumours
WHO grade	         V	Pilocytic astrocytoma Diffuse astrocytoma Anaplastic astrocytoma Glioblastoma	Oligoastrocytoma Anaplastic oligoastrocytoma	Oligodendroglioma Anaplastic oligodendroglioma	Central neurocytoma

Table 1.1: WHO	grading	of selected	brain	tumours
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#### 1.4. GLIOBLASTOMA

Glioblastoma multiforme (GBM) is a rapidly progressing, high-grade tumour that develops de novo (primary) or through progression from low-grade or anaplastic precursor lesions (i.e., astrocytomas or oligodendrogliomas) (Ohgaki & Kleihues, 2007). Despite optimal treatment, the prognosis remains very poor (Tan et al., 2020). Depending on the severity of mass-effect, the survival period of untreated GBMs is usually no longer than a few weeks. A randomised phase III clinical trial showed that supportive care with high-dose dexamethasone extended survival by approximately 3-4 months, while surgical resection with concomitant chemotherapy increased the survival rate to 14.6 months, on average (Stupp et al., 2009). The same study found that patients who had complete resection survived longer than those with partial resection or biopsy (Stupp et al., 2009). Internationally agreed clinical practice guidelines recommend attempting maximum safe resection as the initial therapeutic approach in patients with high-grade gliomas (HGGs) including GBMs (Stupp et al., 2014). Although complete tumour resection may not always be feasible (e.g. due to location of the tumour or low performance status), cytoreductive surgery, performed according to functional boundaries, can alleviate symptoms associated with tumour-related mass effect and provide tissue sample for diagnosis (Ryken et al., 2008). A study of a consecutive series of 306 GBM patients investigated the association between surgically acquired speech deficits and overall survival (McGirt, Mukherjee, et al., 2009). Median survival was found to be significantly lower in patients with new-onset speech impairments, despite matching for extent of resection, age, and pre-operative performance status (McGirt, Mukherjee, et al., 2009). While this effect is difficult to interpret, it emphasises the importance of pre-operative neuroimaging techniques in minimising the risk of new-onset post-operative language deficits (McGirt, Mukherjee, et al., 2009).

#### 1.5. LOW-GRADE GLIOMAS

Low-grade gliomas (LGGs; WHO grade I-II) are generally considered less aggressive than their high-grade counterparts. LGGs predominantly affect young and otherwise healthy patients (mean age= 41 years) with survival averaging approximately 7 years (Claus et al., 2015). The natural history of LGGs is characterised by three stages: (1) steady and slow growth at a rate of about 4mm/year; (2) infiltrative progression along white matter tracts; and finally (3) malignant transformation, defined as a process by which a LGG transforms into an aggressive high-grade glioma (WHO grade III/IV) (Duffau, 2006). Previous studies have demonstrated that the median time to malignant transformation ranges from 2.7 to 5.4 years after the diagnosis (Vertosick Jr et al., 1991; McCormack et al., 1992; Van den Bent et al., 2005; Chaichana et al., 2010). The unpredictability of the clinical course renders the management of LGGs one of the most controversial areas in neuro-oncology.

The available surgical options include biopsy only, early surgery or deferred surgery. To determine the optimal course of treatment, a number of factors is taken into consideration, including the patient's wishes, age, performance status, location of the lesion, and presence or absence of seizures (van Veelen-Vincent et al., 1998). While some patients may choose to defer surgery and opt for active monitoring, an increasing amount of evidence shows that early maximum safe resection is associated with a benefit in progression-free survival, overall survival, and rates of malignant transformation. A population-based cohort study comparing biopsy and watchful waiting with early resection found that the estimated 5-year survival in the biopsy and watchful waiting cohort was 60% (95% Cl, 48-72%) compared with 74% in the early resection group (Jakola et al., 2012).

Another favourable prognosticator for survival is the extent of surgery. In a retrospective study of 216 patients with hemispheric LGGs, Smith et al. (2008) showed that patients with the extent of resection of at least 90% had 5and 8-year survival rates of 97% and 91%, whereas patients with less than 90% extent of resection had 5- and 8-year survival rates of 76% and 60%, respectively. An increasing amount of evidence shows that greater extent of resection is associated with improved survival (Claus et al., 2005; Leighton et al., 1997; Nakamura et al., 2000; Smith et al., 2008; van Veelen-Vincent et al., 1998; Yeh et al., 2005). The main limitation of the vast majority of these studies is their retrospective design. At present, there are very few randomised controlled trials (Class I evidence) investigating the value of glioma surgery and it is unlikely that such studies will be reported because randomisation of patients to different degrees of extent of resection is considered unethical (Sanai & Berger, 2008b). Nevertheless, early surgery to excise as much tumour tissue as possible, while minimising the risk of poor functional outcome (i.e. maximum safe resection) is currently regarded as the primary recommended treatment for LGGs (National Comprehensive Cancer Network, 2018).

In LGG patients, achieving maximum safe resection without impairing function and quality of life is challenging due to the preferential "eloquent" cortico-subcortical location of these tumours. Considering that LGGs mainly affect people of working age, preservation of communication skills is crucial in minimising the impact of treatment on the patient's quality of life and optimising the timing of surgery. Previous studies have demonstrated that glioma patients with language difficulties had higher rates of distress and were less likely to return to professional activity (Gabel et al., 2019; Moritz-Gasser et al., 2012). While the exact prevalence of language impairments is difficult to establish, the need for comprehensive and patient-tailored language mapping has been highlighted in a series of 250 consecutive patients, which reported that 58% of patients had at least one site with an intra-operative stimulation-induced speech arrest (Sanai et al., 2008). It is therefore clear that sensitive language mapping strategies are needed.

#### 1.6. PRE-SURGICAL PLANNING

The first stage of any neuro-oncological surgery is operative planning. An assessment of risk versus benefit of surgery is governed by the topographic relationship between the tumour and the functionally eloquent areas. Once the decision is made to proceed with resection, the eloquent regions that might be encountered intra-operatively, need to be carefully evaluated so that they can be identified and preserved.

There are three main sources of information that are commonly considered, prior to surgery, to predict the effect of resection on linguistic function in patients with tumours affecting language regions. The first source is theoretical knowledge of the neural basis of language (e.g. Wernicke's area is important for speech comprehension). As our understanding of the language system is constantly evolving and new cognitive theories emerge, the neurosurgeon needs to continuously update their knowledge and incorporate it into clinical decision-making. The second and third source of information comes from the results of pre-operative fMRI and diffusion tensor imaging (DTI) studies. Pre-operative fMRI studies show how the patient responds to language tasks in the scanner (e.g. when they are generating speech) to localise function in or adjacent to the regions affected by the tumour. The anatomical relationship between white matter tracts and the lesion can be visualised using DTI. Pre-operative fMRI and DTI assists in defining the resection boundary and are often combined with neuronavigation to guide awake brain mapping. Yet, even when all three sources are combined, the effect of neurosurgery on language abilities cannot be accurately predicted.

In the next sections, I describe how knowledge of the functional anatomy of language and fMRI contribute to identifying linguistic function before surgery, and discuss the challenges associated with different approaches. Finally, I outline how the predictions from pre-operative planning are tested during awake brain mapping with intra-operative stimulation to localise and preserve language regions; and highlight the importance of neuroplasticity mechanisms in the context of post-operative functional recovery.

#### 1.6.1. KNOWLEDGE OF THE FUNCTIONAL ANATOMY OF LANGUAGE

Knowledge of the neural basis of language is vital to planning safer tumour resection and preservation of function. Traditionally, surgical approaches were based on the classic "localisationist" anatomical model, in which functions were ascribed to specific brain regions. Tumours in these regions were therefore considered inoperable. Here, I briefly describe (i) the classic neurological model that remains popular in the neurosurgical community, (ii) more recent discoveries and (iii) the limitations of these current models.

The historical accounts of Broca, Wernicke, Lichtheim and Geschwind form the basis of the classic model of neural basis of language. The model, composed of Broca's area, as the core of expressive language, and the Wernicke's area, as the speech comprehension centre, connected by the arcuate fasciculus, is still widely used today. In the 1861, Paul Broca, a French surgeon and anatomist, described two patients with clinically apparent speech disturbance (Broca, 1861b, 1861c, 1861a). One patient, Lelong could only produce five words and the other, Leborgne could only utter a single syllable, "tan". Based on assessment of macroscopic anatomy, Broca concluded that speech production impairments resulted exclusively from lesions to the frontal lobe, specifically the pars opercularis and pars triangularis in the left inferior frontal gyrus (Figure 1.2). This region is now known as Broca's area and the disorder. characterised by diminished speech output with intact comprehension, as Broca's aphasia (Acharya & Wroten, 2017). In 1906, Pierre Marie challenged Broca's claims, suggesting that damage to more medial structures such as the insula and the basal ganglia can result in the syndrome first described by Broca (Marie, 1906). Since then, the localisation of the seat of speech has been continuously debated (Gajardo-Vidal et al., 2021).

About 10 years after Broca's discovery, Carl Wernicke described lesions in "an area of word images" located in the posterior superior temporal lobe that caused paraphasic errors with impaired naming, repetition and comprehension but with preserved fluent speech (Wernicke, 1874). Wernicke believed that this region was connected to Broca's area and severing these connections results in repetitions errors with intact fluency and comprehension, a syndrome termed "conduction aphasia" (Hickok, 2009). The elements of conduction aphasia were further described by Ludwig Lichtheim and reaffirmed by Norman Geschwind, leading to the proposal of the Broca-Wernicke-Lichtheim-Geschwind (Geschwind, 1972). According to this model,

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upon hearing a word, the sound is sent to the auditory cortex and then Wernicke's area, where the meaning of the word is extracted and sent to Broca's area, via the arcuate fasciculus (Figure 1.2).



**A.** The original model of language from Wernicke, 1874. **B.** An updated classic model, known as the Broca-Wernicke-Lichtheim-Geschwind model (Geschwind, 1972). Reproduced from Tremblay and Dick (2016). © Elsevier.

#### 1.6.2. BEYOND BROCA'S AND WERNICKE'S AREAS

Although the classic model of language still dominates textbooks and is deeply ingrained in medical education, it is no longer an adequate explanation of how the brain processes language (Chang et al., 2015; Mandonnet & Duffau, 2021). A survey conducted within the neurobiology of language community showed that while 90% of respondents considered the classic model outdated, 47% acknowledged its heuristic function (Tremblay & Dick, 2016). A major limitation of this model is the inclusion of two main "language epicentres" that participate in speech production and comprehension (Papathanassiou et al., 2000). This concept of anatomical modularity does not explain the mechanisms underlying brain plasticity and recovery after brain injury nor does it acknowledge the large-scale distribution of language networks (Price, 2012). Advances in neuroimaging techniques provided an opportunity to revisit the classic model of language neurobiology. In 2007, Dronkers and colleagues scanned the original brains of Lelong and Leborgne (Dronkers et al., 2007). Consistent with modern lesion studies (Basso et al., 1985; Kertesz et al., 1979; Mohr et al., 1978; Naeser & Hayward, 1978; Schiff et al., 1983), a threedimensional reconstruction showed that the lesions extended far beyond Broca's area, to the inferior parietal lobe, the insula, subcortical structures and white matter tracts (Dronkers et al., 2007). More recently, Gajardo-Vidal and colleagues examined the effect of damage to Broca's area on long-term speech production outcome in 134 stroke survivors (Gajardo-Vidal et al., 2021). They concluded that damage to Broca's area, defined as Brodmann areas 44 and 45, does not contribute to speech production outcome after stroke but instead, the degree of damage to the anterior part of the arcuate fasciculus, just above the insula.

Over the years, researchers attempted to produce more reliable models of language by shifting from modular to network-based representations. Language in the human brain has now been investigated extensively using methods such as PET (positron emission tomography) and fMRI, providing evidence that language processing involves multiple, parallel, hierarchically organized pathways (Scott & Johnsrude, 2003). The tenets of these models guide clinical practice. For example, the popular "dual stream" model (Figure 1.3) emphasises two different pathways to speech processing, a concept similar to the widely accepted theory of dual stream processing in the visual domain (Hickok & Poeppel, 2004, 2007; Scott & Johnsrude, 2003).

The initial stages of speech sound processing involve spectro-temporal and phonological analyses in the superior temporal gyrus and the superior temporal sulcus. The ventral stream, or "what" pathway involves the superior and middle portions of the temporal lobe and supports auditory comprehension by mapping sound representations of speech to their conceptual representations. The dorsal or "where" stream extends from the

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posterior superior temporal gyrus to the intraparietal lobule and the premotor cortex. It is believed to be involved in mapping sensory input onto articulatory representations, a process crucial for acquisition of new vocabulary and speech development. While the ventral stream is thought to be bilaterally organised, the dorsal stream is strongly left-hemisphere dominant (Hickok & Poeppel, 2007).



Figure 1.3: Dual-route model of auditory language processing

**A.** The ventral stream (in red), involved in transforming sound-to-meaning, projects ventro-laterally toward posterior and anterior parts of the middle temporal gyrus. The dorsal stream (in blue), dedicated to mapping sound to articulatory representations, projects dorso-posteriorly, involving area Sylvian-parietal-temporal (Spt), and ultimately the premotor areas in the frontal cortex, including the posterior aspect of Broca's area (i.e. pars opercularis of the inferior frontal gyrus). **B.** AF/SLF = arcuate fasciculus/longitudinal superior fasciculus, EC = extreme capsule, MdLF = medial longitudinal fasciculus, STG = superior temporal gyrus, PM = premotor, PFC = prefrontal cortex, IFG = inferior frontal gyrus, MTG = middle temporal gyrus. a = anterior, p = posterior. Figure adapted from Saur and Hartwigsen (2012). © 2012 American Congress of Rehabilitation Medicine.

#### 1.6.3. LIMITATIONS OF CURRENT ANATOMICAL MODELS

The recent models have made a major contribution to our understanding of the neural basis for language. Anatomical knowledge of how language is processed in the brain is typically based on a combination of these theoretical frameworks and the results of multiple studies using a variety of different methodologies including lesion-deficit associations, fMRI, and direct electrical stimulation. In 2012, Price reviewed and synthesised the findings of positron emission tomography (PET) and fMRI studies from the last 20 years provided an integrated perspective on the functional anatomy of language (Price, 2012). Although there are robust and consistent findings, functional anatomical models derived from multiple different studies have two major limitations. First, anatomical regions are typically described with an anatomical name (e.g., left posterior superior temporal sulcus) and/or a single co-ordinate indicating where the region is in standard space (e.g., -53, -40, 6). These labels do not delineate the full extent of the region. Second, assimilating the results from multiple different neuroimaging studies is challenging particularly when brain regions, with the same names and peak activation co-ordinates, are associated with different functions in different studies; or conversely when the same function is associated with different brain regions. Third, many studies have highlighted significant inter-subject variability in how the human brain processes language. A multitude of factors might influence the language representation in the brain, including different cognitive strategies (Nadeau et al., 1998), age (Vandenbroucke et al., 2004), gender (Phillips et al., 2001), native language and multilingualism (Chee et al., 2001).

Even though modern neurosurgical procedures are facilitated by neuronavigation systems, this technology is expensive (e.g. in 2016 the Brainlab Curve cost more than \$400,000) and not available in many centres (Ribas et al., 2006; Severson, 2016). Knowledge of anatomical landmarks and cranio-cerebral relationships is therefore a vital part of every neurosurgical procedure (Vigo et al., 2020). Successful identification of key language areas is complicated by differences in macro- and micro-anatomy (Fedorenko &

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Blank, 2020; Ojemann, 1979; Rasmussen & Milner, 1975). For instance, an *in vivo* MRI study of the pars opercularis in 50 individuals found that in some brains the entire region was visible on the surface of the brain, appearing as a single convolution or two convolutions, while in others it was hidden within the depth of the inferior precentral sulcus (Tomaiuolo et al., 1999). Four different morphological patterns of cerebral sulci bordering Broca's have been identified using sagittal MR imaging correlated with autopsy studies (Ebeling et al., 1986). This classification was further investigated by Quiñones-Hinojosa and colleagues in a series of 33 glioma patients. Pre-operatively two of Ebeling's anatomical patterns were identified (Quiñones-Hinojosa et al., 2003). Speech arrest sites were found to confirm to these boundaries in 89 and 87% of patients, further highlighting inter-subject anatomical variability.

An additional difficulty in applying anatomical knowledge derived from neurotypical participants to patients with brain tumours stems from the masseffect associated with space-occupying lesions. Brain oedema with sulcal effacement leads to distortion of the normal cortical anatomy, making anatomy-based localisation of function extremely challenging (Silva et al., 2018). Taken together, it is very difficult to predict how a patient uses their brain for language processing, unless the patient's language regions are individually studied.

Localisation of eloquent regions might be improved by referring to databased models of language generated from neurotypical controls that completed multitask fMRI paradigms. For instance, if a patient has a brain tumour affecting the posterior superior temporal lobe, the functional anatomical map can be used to identify (a) the function that the region is normally involved in, and (b) the degree of inter-subject variability.

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#### 1.6.4. PRE-OPERATIVE FMRI

The language regions that an individual patient uses can be investigated using functional magnetic resonance imaging (fMRI), prior to surgery. fMRI is used routinely to infer brain activity and assess the spatial relationship between tumour tissue and eloquent brain regions. The underlying assumption is that performance of a cognitive task (e.g. object naming) results in higher energy consumption and an increase in cerebral blood flow, generating the blood oxygen level dependent fMRI signal (Ogawa et al., 1990). This signal is detected by an MR scanner and converted to clinical images.

A study examining the impact of pre-operative fMRI on treatment plans in neurosurgery patients found that fMRI (i) provided information about the topographic relationship between the tumour and the eloquent cortex, thereby allowing for more reliable assessment of the feasibility of surgical resection, (ii) guided the placement of the bone flap or subdural grids, (iii) helped identify patients that required further evaluation using intra-operative mapping techniques (Lee et al., 1999). The fMRI results and other MR datasets can be integrated into the stereotactic neuronavigational systems in the operating room and used to visualise the eloquent areas intra-operatively (Figure 1.4).

The complexity of the language system makes it extremely challenging to provide a thorough evaluation on all aspects of language in the clinical setting. A large number of different fMRI language testing paradigms has been reported in the literature. Speech production is typically evaluated by means of verbal fluency, verb generation and picture naming, while language comprehension tasks include semantic or grammatical judgement tasks (Deblaere et al., 2002; Roux et al., 2003; Rutten et al., 1999).

Pre-surgical fMRI mapping is useful if the results show language related neural responses in and around the regions targeted for surgery. However, the absence of language-related responses does not indicate that the regions affected by the tumour are not important for language. The function of white matter tracts, for example, cannot be measured with fMRI. Moreover, no detectible cortical activity might reflect a lack of sensitivity, or it might be the consequence of using language tasks that do not engage the regions of interest (e.g., a task like word generation will not engage all the regions needed for reading, sentence production or speech comprehension).





Pre-operative MRI imported into a neuronavigation system. fMRI and DTI overlays are manually outlined on axial slices. Scans show a non-enhancing glial tumour involving medial pre-supplementary motor area, supplementary motor area proper, cingulum and genu and body of the corpus callosum. Cyan= tumour outline, red= arcuate fasciculus, yellow= verbal fluency, white= verb generation, orange= primary motor cortex. Reproduced from Klitsinikos et al. (2021) licensed under a Creative Commons Attribution 4.0 International License.
One solution is to assess a wide range of language functions prior to surgery. However, adoption of multitask fMRI as the standard of care assessment for pre-surgical planning in patients with brain tumours might be more difficult in public healthcare systems such as the National Healthcare Service due to its relatively high cost and data acquisition time. Furthermore, the interpretation of findings from multiple fMRI tasks is often challenging. Therefore, language fMRI results are often reduced to measures of "language laterality" which simply indicate whether the patient is using the left or right side of their brain more when they are engaged in language tasks. The problem here is that global laterality measures are of limited value if patients have left lateralised responses in one part of their brain that are cancelled out by right lateralised responses in another part of their brain (Seghier et al., 2011). Despite these limitations, task-based fMRI is the most widely used tool in surgical decision-making.

The efficiency and the precision of pre-surgery fMRI testing paradigms could be optimised by referring to whole-brain activation maps from neurotypical controls. Understanding the normal patterns of activation for a wide range of tasks is crucial to optimising the selection pre-surgery fMRI tasks and thus, ensuring that function of the region affected by a brain tumour is accurately investigated.

# 1.7. AWAKE BRAIN MAPPING

Awake brain mapping with direct electrical stimulation is the gold standard used to map the function of eloquent cortical regions and subcortical white matter tracts in neurosurgery patients, thereby allowing for maximum, safe resection (Hamer et al., 2012; Mandonnet et al., 2010). There are three different anaesthetic techniques that can be used for patients undergoing awake craniotomy, which include "asleep-awake-asleep", "awake throughout" and "asleep-awake". An example operating theatre layout for an awake craniotomy is shown in Figure 1.5.



Figure 1.5: Theatre layout for an awake craniotomy

Configuration of the operative room for awake mapping for a left sided tumour performed at University of California, San Francisco. The positioning of the equipment and personnel is tailored to the available space and specific mapping needs. ECOG = electrocorticography, OR = operating room. Reproduced from Gogos et al. (2020). © Springer Nature.

Direct electrical stimulation (DES) was pioneered in the 20<sup>th</sup> century and subsequently refined by Penfield and colleagues for use in epilepsy surgery (Erickson, 1941; Penfield & Boldrey, 1937; Penfield & Welch, 1951). The application of direct electrical stimulation (DES) for mapping of motor and

sensory pathways in neuro-oncological surgery was described by Mitchel Berger in the nineties and it has subsequently become a part of the neurosurgeon's armamentarium (Berger et al., 1989; Berger & Ojemann, 1992).

The functional and survival benefit of intraoperative mapping with DES has been demonstrated in a number of studies. A meta-analysis of 8,091 patients with infiltrative gliomas, found that gross total resection in patient cohorts with and without intra-operative stimulation mapping, were 75% and 58%, respectively (Hamer et al., 2012). Furthermore, resective surgery with the use of intra-operative functional mapping using DES was associated with lower risk of persistent neurological deficits (3.4%) in comparison to surgery without DES mapping (8.2%).

To identify language regions during surgery, the patient must be awakened or remain awake throughout so that they can engage in cognitive tasks while the cortical or subcortical region of interest is stimulated with a bipolar electrode to transiently disrupt its function. The response is evaluated by a member of a multidisciplinary team (e.g. a speech and language therapist or a neuropsychologist). The contact with the neural tissue is maintained for 3 seconds at a time with ice-cold saline irrigation between each stimulation episode to prevent intra-operative seizures (Karkar et al., 2002). Positive stimulation sites are identified and labelled with sterile tickets (see Figure 1.6).

If stimulation to a targeted region impairs the patient's responses, this serves as evidence the region supports a given function. There are two main factors that the DES response critically depends on: (1) the patient's ability to focus and remain engaged throughout surgery; and (2) the selection of the appropriate task to map a given function. The challenge here is that the language tasks need to be very carefully selected as each region can only be stimulated for 3-4s at a time. If the results of intra-operative mapping are unclear, additional testing is required, which may lead to further prolongation of the procedure and contribute to patient fatigue (Bertani et al., 2009). A "failed awake craniotomy" is defined as an inability to complete brain mapping and tumour resection, usually secondary to intraoperative seizures or patient's emotional intolerance or conversion (Leon-Rojas et al., 2020; Nossek et al., 2013). To prevent this, it is recommended that only a limited number of tasks is administered (Bertani et al., 2009). The surgeon therefore needs to plan in advance (using prior knowledge of functional anatomy and the patient's preoperative fMRI results) which tests should be used during intra-operative stimulation.







A. Stimulation of areas marked with sterile tickets #3 and #4 produced a consistent inability to complete sentences but had no effect on counting, articulation and object naming in a patient with a tumour involving the medial pre-supplementary motor area, supplementary motor area proper, cingulum, genu and body of the corpus callosum. Intraoperative language testing paradigms were selected based discussion of on а а multidisciplinary team and results of pre-operative fMRI and DTI.

**B.** Schematic illustration showing positive the location of sites. stimulation #1 M1, movement of elbow, monopolar stimulation at 5 mAmps; #2 SMA, twitching of foot, monopolar stimulation at 5 mAmps; #3 and #4 SMA, inability to complete sentences, bipolar stimulation at 5 mAmps.

Reproduced from Klitsinikos et al. (2021) licensed under a Creative Commons Attribution 4.0 International License. Despite the importance of awake brain mapping in maximising extent of resection while limiting surgical morbidity, intraoperative language mapping techniques remain extremely variable and are often left to the discretion of the surgeon and support teams. At present, no standardised protocol exists to reliably test and identify language regions in neurosurgery patients (De Witte & Mariën, 2013). For instance, Ruis found that from 232 identified brain mapping studies, 207 reported language testing with extreme variability ranging from counting to translation or semantic association and from experimental paradigms to standardized, neuropsychometric tests (Ruis, 2018).

A survey of specialists involved in awake brain mapping showed a striking lack of consensus in intraoperative language task selection, irrespective of specialism or years of experience (Sefcikova et al., 2020). The current practice highlights the lack of data-driven approach to sensitively test the sub-components of language and the need for lesion-site dependent testing paradigms. The selection of intra-operative tasks could be improved by integrating the results of pre-operative fMRI with detailed models of language function from neurotypical controls that account for inter-subject consistency. This will direct the neurosurgeon to a set of tasks that robustly probe the function of the regions targeted for surgery.

# **1.8.** FUNCTIONAL REORGANISATION

Predicting the effect of glioma surgery on language abilities is key to shared decision-making and optimising the surgical strategy. Neurosurgeons are faced with a herculean task of foreseeing the post-operative functional status in patients, often resorting to relying on pure intuition or empirical evidence (Jakola et al., 2020). This single surgeon experience is subject to a significant learning curve and is not a reliable method for estimating postoperative levels of functioning (Katlic & Coleman, 2018). Therefore, establishing the lesion site-dependent neuroplasticity mechanisms is of paramount importance.

Traditionally, the brain was viewed as a static organ with limited capacity to alter its structure and function (De Carlos & Borrell, 2007). Recent advances in neuroimaging provide evidence that brain networks undergo reorganisation to overcome injury and relearn skills lost due to structural damage. The reshaping of neural networks, also referred to as neuroplasticity, has been extensively documented in patients with ischaemic stroke (Freundlieb et al., 2015; Small et al., 2002), congenital malformations (Lewine et al., 1994; Vikingstad et al., 2000) or following brain injury. Patients harbouring gliomas represent another group that can provide a unique insight into the neural basis of brain plasticity. While the traditional neurosurgical approach is based on classic "topological" model, several studies have demonstrated that LGG patients with lesions in eloquent brain regions show no detectable deficits (Duffau et al., 2001; Fandino et al., 1999; Seitz et al., 1995). If brain functions are assumed to remain within the bounds of their classical anatomical locations, then tumours in eloquent areas might be deemed inoperable.

Neuroplasticity in brain tumour patients has been described in direct electrical stimulation studies with language mapping during repeated awake craniotomies (Duffau, 2014; Krieg et al., 2014; Picart et al., 2019; Southwell et al., 2016). Functional reorganisation is extremely important when considering resection in glioma patients and with some studies suggesting its inclusion as a surgical planning parameter (Duffau et al., 2002). Duffau (2005) proposed a multistage approach to tumours in eloquent regions, where an initially partial resection tailored according to functional boundaries could be followed by second surgery after evidence of reorganisation has been observed on longitudinal fMRI data or TMS sessions (Duffau et al., 2003). The underlying premise is that surgery may lead to unmasking of brain latent networks by facilitating cortical excitability through GABAergic inhibition and NMDA receptor-mediated excitation (Duffau et al., 2002). The interval between the two surgeries allows for functional recovery that evolves gradually over time and might minimise the risk of major neurological sequelae (Duffau, 2005). During the same surgery, repeated stimulation of the same area (marked with

a sterile ticket) produced the same result, while stimulation 5 mm away from the first point yielded a different result (Figure 1.7) (Duffau et al., 1999; Duffau et al., 2002; Duffau, Capelle, et al., 2000). The results however might have been confounded by the technical limitations of DES as current can spread along the axon, leading to false positive results (Mandonnet et al., 2010). While these intra-operative findings need to be taken with caution, the long-term reshaping of functional networks is a widely described phenomenon in both stroke and brain tumour patients.



Figure 1.7: Intra-operative view before and after surgical resection.

Motor cortical mapping was performed using DES with a bipolar 5-mm tipped probe using 60Hz biphasic square wave pulses with a 16mA amplitude. **Left:** Motor areas were marked using sterile tickets, indicating the motor arm site (2), the motor hand site (1), and the motor finger sites (A). The boundaries of the arteriovenous malformation are indicated with tickets (B) and (C). **Right.** Stimulation following resection of arteriovenous malformation showed two new and redundant motor areas (tickets 3 and 4, blue arrows) in front of the sulcus (dashed line). The numbers 1 and 2 were swapped for technical reasons, with tag 1 representing the motor arm site and tag 2 the motor hand site. Stimulation of the new site marked by tag 3 induced the same arm movement as stimulation of tag 1, and stimulation of site 4 elicited the same hand movement as site 2. F = forward, B= backward, L= left, R= right. Adapted from Duffau et al. (2000). © John Wiley & Sons Ltd.

Over the decades, three main theories have been proposed to explain the mechanisms of recovery from aphasia: (A) the peri-lesional hypothesis, (B) the laterality shift hypothesis, and (C) the disinhibition theory (see Figure 1.8).



Figure 1.8: Theories of functional reorganisation after brain damage.

**A.** Recruitment of ipsilesional cortical areas may compensate for damage to left hemisphere language centres. **B.** Some language functions may be subserved by homotopic right hemisphere regions, normally masked by transcallosal interhemispheric inhibition. **C.** Increased recruitment of right hemisphere regions may have a deleterious effect on language skills due to inhibition of more efficient left hemisphere language networks. Reproduced from Hamilton et al. (2011) © Elsevier.

(A) The **peri-lesional hypothesis** proposes that recovery is attributable to functionality in and around the lesion (Heiss & Thiel, 2006; Hillis et al., 2006; Kong et al., 2016; Warburton et al., 1999). "Peri-lesional reorganisation" has also been used to describe the enhanced participation of regions adjacent to the tumour. For example, Duffau et al., (2003) demonstrated that patients with LGGs around the Broca's area (BA 44, BA 45) showed compensatory activity in the adjacent regions, including the precentral cortex, the middle frontal gyrus and the inferior frontal gyrus (pars orbitalis, BA47) (Duffau et al., 2003). Following resection of the tumour, these patients were only observed to have transient speech disturbances suggesting that the surrounding regions were sufficiently able to take on the expected function of the tumour.

In aphasic stroke patients, increased activation in the peri-lesional tissue has been associated with better performance in picture naming (Cornelissen et al., 2003; Fridriksson et al., 2010; Meinzer et al., 2008), cued word production (Warburton et al., 1999) and word-stem completion (Rosen et al., 2000). Changes at a cellular level must also occur in the central nervous system to support recovery (Wang & Sun, 2011). Upregulation of signalling

pathways involved in promotion of axonal growth factor responses, intracellular growth and cytoskeletal arrangement leads to axonal growth and synapse formation in the peri-infarct tissue (Joy et al., 2019; Li et al., 2010, 2015; Overman et al., 2012). Studies in animal models of ischaemic stroke have provided evidence for axonal sprouting from the intact cortex to peri-infarct brain areas (Carmichael, 2006; Murphy & Corbett, 2009). Furthermore, strengthening of existing synapses in tissue surrounding the lesion was associated with better motor recovery in rats (Uryu et al., 2001).

(B) The **laterality-shift hypothesis** proposes that homotopic regions in the right hemisphere are recruited (or upregulated) to compensate for damage in the left hemisphere. In the context of language, right-sided activation has been reported in aphasic stroke survivors (Blasi et al., 2002; Crinion & Price, 2005; Heiss et al., 1999; Karbe et al., 1998; Ohyama et al., 1996; Richter et al., 2008; Warren et al., 2009) and brain tumour patients. An fMRI longitudinal case study of a patient with a temporo-frontal glioma, showed that language-related laterality in the inferior frontal gyrus (IFG) shifted from strongly left-lateralised in the first fMRI scan to bilateral prior to surgery (Rosenberg et al. 2008). This theory is further supported by evidence from studies on stroke survivors, for instance, a meta-analysis of fMRI studies of chronic stroke patients showed that, aphasics consistently recruited right homologues of the damaged areas in addition to spared left hemisphere language regions (Turkeltaub et al., 2011).

(C) According to the **disinhibition theory**, the right hemisphere overactivation following left hemisphere brain damage is a manifestation of maladaptive reorganisation. It is thought to occur as a result of reduction of inter-callosal inhibition from the affected (left) to the (unaffected) hemisphere (Geranmayeh et al., 2014). For example, LeRoux et al., (1991) reported recovery of the central facial palsy and hypophonia after resection of the nondominant M1 of the face. The authors hypothesised that this finding resulted from the disinhibition of the contralateral homologues sites via the transcallosal pathways (LeRoux et al., 1991). Non-invasive brain stimulation with the use of

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TMS or tDCS (transcranial direct current stimulation) has been proposed as a tool for enhancing language recovery, possibly by supressing the dysfunctional over-activation from the right hemisphere (Hamilton et al., 2011; Schlaug et al., 2011). However, opposing evidence suggests that the role of the right hemisphere in functional recovery may be not maladaptive but instead, it may reflect either error processing (Garavan et al., 2003; Robertson, 2014) or, as discussed above, compensatory activity (Finger et al., 2003). It is also possible that the role of right hemisphere regions in recovery depends on which brain areas are being studied. For examples, some regions may support recovery, some inhibit it, while others have no impact at all (Turkeltaub et al., 2011).

Despite decades of neuroimaging research, the exact neural mechanisms underlying recovery after brain injury, stroke or glioma surgery remain elusive. More research is needed to provide an indication of which language regions can be compensated for and therefore, resected without long-term deficits and which areas are critical to linguistic abilities.

# 1.9. CONCLUSION

In summary, modern gliomas surgery has evolved around the central dogma of avoiding injury to critical brain structures, while aiming to maximising the extent of resection. However, the current pre- and intra-operative language mapping strategies often rely on empirical evidence and lack standardisation. I propose that language mapping in glioma patients could be facilitated by integrating: (1) detailed anatomical models of language function to guide the selection of sensitive and lesion-site dependent pre- and intra-operative testing paradigms, (2) measures of inter-subject variability or consistency, and (3) understanding of recovery mechanisms. Below, I discuss how the work presented in this thesis might contribute to addressing those issues.

# 1.10. THESIS OVERVIEW

(1) To improve our knowledge of the neural basis of language, my first three experimental studies used a comprehensive, multitask language fMRI paradigm to investigate and validate the functional contribution of left temporoparietal regions to speech perception and production and the left posterior frontal lobe to speech production. Validation was included given the current reproducibility crisis in research (Eklund et al., 2016; Open Science Collaboration, 2015; Poldrack et al., 2017).

(2) To improve our understanding of inter-subject consistency for different language tasks, my fourth experimental study demonstrates how functional consistency maps can be used to visualise inter-subject consistency in activation for four different object naming tasks in neurotypical controls. Taken together, the selection of pre-and intra-operative mapping paradigms could be facilitated by the findings from (1) and (2).

(3) To gain insight into the recovery mechanisms in glioma patients, my fifth experimental study demonstrates how fMRI can be used to understand how the brain reorganises in patients with tumours in, and surgical resection of, a temporo-parietal area that I associated with phonological processing in an earlier study.

## **SUMMARY OF EXPERIMENTAL OBJECTIVES**

- Experiment 1 (Chapter 3): Functionally dissociating left temporo-parietal regions involved in speech perception and production, using a multi-task fMRI language paradigm.
- Experiment 2 (Chapter 4): Validating the response properties of regions from Experiment 1 in an independent, larger group of participants to increase confidence that the original results were not false positives.

- Experiment 3 (Chapter 5): Segregating the function of left frontal regions that contribute to speech production during reading, repetition and object naming in a cohort of 84 neurologically intact participants who performed 8 tasks of interest embedded within one of two different experimental paradigms.
- Experiment 4 (Chapter 6): Comparing inter-subject consistency of activation for four different object naming paradigms to identify which paradigm activates classical language regions most robustly and consistency and may therefore improve the sensitivity of language mapping in brain tumour and epilepsy patients.
- Experiment 5 (Chapter 7): Illustrating how data from neurotypical controls could be used to predict post-operative speech and language impairments and investigating the neural systems that support successful reading performance in two patients with tumours in a temporo-parietal region that is normally activated when neurologically intact controls are reading words.

# 2. GENERAL METHODS

# 2.1. SUMMARY

In this chapter, I am going to outline the experimental methods used to acquire and process magnetic resonance imaging data presented in my thesis. Structural magnetic resonance imaging (sMRI) is a widely used imaging technique for examining brain structure and was applied here to identify the location of brain tumours in patients and improve spatial normalisation of the functional magnetic resonance imaging (fMRI) data. Most of my experiments used fMRI because it allowed me to infer brain function by detecting haemodynamic changes related to enhanced neural activity (i.e., performance of cognitive tasks). sMRI and fMRI are non-invasive and have high spatial resolution across the whole brain, which made them particularly suitable to study the research questions posed in my thesis. In the next sections, I will explain the basic principles of these methods and the data preprocessing steps that I used for my experiments with neurotypical controls and brain tumour patients. I will also describe an automated algorithm that was applied to detect lesions in Experiment 5. Methodological details that don't generalise across experiments are provided in other chapters.

# 2.2. STRUCTURAL MAGNETIC RESONANCE IMAGING (SMRI)

Magnetic resonance imaging (MRI) is commonly applied in the clinical and research setting to produce detailed images of the organs and tissues within the human body. To acquire an MRI scan, the patient is placed within the MRI system, consisting of a set of main field coils, gradient coils, shim coils and a radiofrequency coil (Figure 2.1). The superconductive portions of the main magnet coils are made up of a metal-alloy, mostly niobium-titanium and have no resistance at temperatures around absolute zero (-273.15°C, 0 K) (Aarnink & Overweg, 2012). Cryogenic liquid helium is usually used to maintain low temperature that secures superconductivity and enables generation of a strong, constant magnetic field ( $B_0$ ). This field is distorted, in a predictable manner, by three gradient coils, which allows for spatial encoding. Radiofrequency (RF) coils serve two main purposes: (i) to generate an oscillating magnetic field perpendicular to  $B_0$  and (ii) capture the induced RF signal back from the tissue (Jacobs et al., 2007).



Figure 2.1: Schematic diagram of an MRI scanner

MRI exploits the interaction between the magnetic fields generated by an MRI system and the nuclei of hydrogen atoms, occurring abundantly in the human body. As shown in Figure 2.2, a hydrogen nucleus is composed of a single proton, with a positive charge that generates a magnetic momentum and rotates around its axis giving rise to a property known as "spin" (Grover et al., 2015). Under normal circumstances, hydrogen protons spin in random directions around their axis, cancelling each other's magnetic moment without creating a net magnetic field. Upon application of a strong external magnetic field by an MRI scanner, the hydrogen nuclei align parallel or antiparallel to the direction of the magnetic field and precess around it, creating a magnetic vector (Berger, 2002). The frequency at which protons precess, also known as the resonant frequency, is proportional the strength of the applied magnetic

The volunteer is positioned within the bore of the magnet and a radiofrequency coil is placed around the person's head to improve signal to noise ratio. Reproduced from Currie et al. (2013). © BMJ Publishing Group Ltd.

field (Grover et al., 2015). Most clinical research is conducted at a field strength of 1.5 Tesla or 3 Tesla (T). The described experiments used 3T (Experiments 1-4) and 1.5T (Experiment 5) systems.



#### Figure 2.2: Larmor frequency

A. Positively charged protons spin around their axes, generating a magnetic field. B. When an external magnetic field  $(B_0)$  is applied, protons align either parallel or antiparallel to B<sub>0</sub> and precess along the axis of the magnetic field (z-axis) with an angular frequency known as the Larmor frequency. For a field strength of 1 Tesla the Larmor of hydrogen frequency is 42 Megahertz or 42 million rotation cycles per second. Reproduced from Currie et al. (2013). © BMJ Publishing Group Ltd.

The magnetic resonance signal is generated by subjecting protons, aligned with the magnetic field (B<sub>0</sub>), to an electromagnetic pulse (radiofrequency pulse or RF pulse) with the appropriate frequency (Larmor frequency). This manipulation causes the protons to flip, usually by 90° into a high-energy anti-parallel state. This phenomenon is known as excitation. After the RF pulse is switched off, the magnetic moment vector returns to its resting state and the proton emits the absorbed energy in the form of an RF signal. The process by which the net magnetisation returns to its maximum value parallel to B<sub>0</sub> is known as T1 relaxation. In 1946, Felix Bloch, described the origin of nuclear magnetic resonance (NMR) signal using a set of equations that modelled the relaxation process with T1 as a first-order time-constant (Bloch, 1946). After time T1, longitudinal magnetisation (z-component, see Figure 2.2) has reached 63% of its maximum value (Figure 2.3). A few years after publication of his landmark paper, Felix Bloch received a joint award of the Nobel Prize for Physics for the developments of NMR and nuclear

induction (Hofstadter, 1984). The T1 relaxation time depends on the type of surrounding tissue. For example, substances whose molecules are further apart (e.g., cerebrospinal fluid) transfer energy less efficiently and will therefore have longer T1 times.

In contrast, tissues with higher density such as grey matter and white matter have short T1 relaxation times due to the tight packing of molecules. The differences in T1 relaxation times can be used to create an image (Grover et al., 2015). Likewise, the time taken for the transverse component of magnetisation to decay to approximately 37% of its initial value is governed by a time constant referred to as T2 (Figure 2.3). However, there is also an additional dephasing effect caused by inhomogeneity of the main magnetic field. An additional time constant, T2\* has been introduced to account for these effects. T2\* sequences form the basis for fMRI (Figure 2.3).





**A.** T1 describes the time required for the z-component (longitudinal magnetisation) of net magnetisation to reach approximately 63% of its original value after the RF pulse has been switched off. **B.** T2 relaxation is the time required for the transverse magnetisation to fall to approximately 37%. **C.** T2\* is a combination of T2 relaxation and dephasing effects caused by local field inhomogeneities. T2\* determines the observed rate of decay in transverse magnetisation and is always less than or equal to T2. Reproduced from Currie et al. (2013). © BMJ Publishing Group Ltd.

The acquired raw data is processed by the scanner using a Fourier Transformation to produce MRI images. sMRI provides information to qualitatively and quantitatively describe the structure of the brain and is particularly useful in diagnosing brain abnormalities e.g. damage to the brain after tumour resection.

# 2.3. AUTOMATED LESION IDENTIFICATION

To identify lesions in pre- and post-neurosurgery patients (Experiment 5), each of the T1-weighted images was processed using the Automated Lesion Identification (ALI; Seghier et al., 2008) toolbox in the Statistical Parametric Mapping software (SPM; Wellcome Centre for Human Neuroimaging, London, UK) running on Matlab 2014a (MathWorks, Natick, MA). ALI is an unsupervised method that performs outlier detection using a fuzzy c-means algorithm. The procedure involves four steps:

- Modified unified segmentation-normalisation: the unified procedure combines segmentation, bias correction and spatial normalisation (for more details, see Seghier et al., 2008). The T1-weighted images of each brain tumour patient are segmented into four tissue classes: grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), and an "extra" tissue class. The inclusion of the "extra" tissue class provides more flexibility in the segmentation procedure, when dealing with damaged tissue, and allows for explicit modelling of the atypical voxels.
- 2. Smoothing: the normalised and segmented GM and WM images from each subject are smoothed by replacing each voxel with the weighted average of the surrounding voxels using an isotropic Gaussian kernel of 8mm full-width at half maximum to supress fine-scale inter-subject anatomical variability. The smoothed images of a lesioned brain can then be compared with those of neurotypical controls.
- Outlier detection: to identify abnormal voxels, an outlier detection algorithm is applied according to the fuzzy logic clustering principle (for details, see Seghier, Friston, & Price, 2007). The underlying assumption is

that, at the global level, a lesioned brain is an outlier in relation to neurotypical brains. The smoothed GM and WM images from each patient are compared to normative data from 64 neurotypical controls. This creates fuzzy images (one for GM and one for WM), representing voxels that had a low probability of being GM and WM, in comparison to the neurotypical controls (see Figure 2.5).

4. Lesion definition (grouping): the two fuzzy GM and WM images generated in the previous step are combined to form a single fuzzy image that codes the degree of abnormality at each voxel on a continuous scale from 0 (completely normal) to 1 (completely abnormal) relative to normative data from neurotypical controls. A binary mask of the lesion (i.e. lesion/no lesion), can then be generated by applying a threshold (typically 0.3) to each image (see Figure 2.5). As the resultant lesion images are in MNI space, they can be overlapped to create a lesion overlap image.

To ensure high accuracy of lesion definition in brain tumour patients, ALI was run twice, using the fuzzy set lesion image obtained during the first run as an additional patient-specific prior in the second run (Sanjuán et al., 2013). The resulting three-dimensional (3D) binary lesion images were used in this thesis to (i) delineate the lesions, and (ii) generate lesion overlap maps (LOMs; see Figure 2.4).



#### Figure 2.4: Lesion overlap map

Lesion overlap map for two patients with temporo-parietal damage from Experiment 5 at z =+6 and z = +29 overlaid on a standard structural scan. Green indicates voxels damaged in one patient only and red shows the overlap of lesions. To measure the function of the brain, a series of sequence images needs to be acquired over time. This technique is called fMRI, which I am going to explain in the next section.





**A.** A schematic view of the steps involved in the automated lesion identification method. **B.** An illustration of the output for each step. Reproduced with permission from Seghier et al. (2008). © Elsevier.

# 2.4. FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

fMRI measures brain activity by detecting changes in the paramagnetic properties of oxygenated and deoxygenated haemoglobin (Hb). The blood oxygenation level dependent (BOLD) signal is the measure of interest (Ogawa et al., 1990). When a region in the brain is activated by a cognitive task, the energy requirement increases. This leads to a vasomotor reaction resulting in increased blood flow to the affected area. As oxygen is utilised, the concentration of deoxyhaemoglobin increases. Importantly, Hb has different magnetic properties in its oxygenated and deoxygenated forms: deoxygenated Hb is paramagnetic and more susceptible to magnetic fields, while oxygenated Hb is diamagnetic and not significantly different to other tissues or water (Gore, 2003).





**A.** The haemodynamic response function (HRF) as measured with BOLD after a stimulus is presented (e.g., a picture of an object). The peak BOLD value is usually reached within 4-6s of the stimulus onset time, followed by the undershoot after around 12s and return to baseline over the course of 12-20s. **B.** Presentation of a block of stimuli (i.e., a series of object pictures), as in my fMRI experiments, results in a stronger and longer lasting BOLD response. Reproduced with permission from (Price et al., 1999). © 1999 Academic Press.

Differences in the ratio of oxygenated and deoxygenated haemoglobin induce changes in the magnetic signal, which are then detected by the MRI scanner and reconstructed in 3D space (Greve, 2011). In an experimental setting, a series of stimuli, e.g., in the form of written words, is presented to the participant and the BOLD signal measured to reveal the underlying haemodynamic response of a particular region over time (see Figure 2.6). The modelling of the haemodynamic response function (HRF) is described in the statistical analysis section.

## 2.5. SCANNING PARAMETERS

All structural and functional data reported in this thesis were collected on one of two available 3T scanners (both Trio, Siemens, Erlangen, Germany), using a 12-channel head coil, or a 1.5T scanner (Sonata, Siemens, Erlangen, Germany). The main parameters for the applied scanning sequences will be described in the next sections.

For the functional images acquired on the 3T scanners, echo-planar imaging (EPI; Mansfield, 1977) a fast MRI technique was used with a 3 x 3 mm in-plane spatial resolution and TR/TE/flip angle of 3080 ms/30 ms/90°. The repetition time (TR) describes to the amount of time required to collect a complete brain volume, i.e. the period of time between two successive radiofrequency pulses to the same brain region. The echo time (TE) refers to the time in milliseconds between the radiofrequency pulse and MR signal sampling. Longer TR and TE result in higher image resolution but at the cost of longer scanning time. For the purpose of this work, the TR was chosen to achieve whole brain coverage (44 slices) and to ensure that slice acquisition was not correlated with the stimulus onset time (Veltman et al., 2002). The flip angle determines the amount of rotation the net magnetisation experiences during application of a RF pulse. The field of view (FOV), defined as the spatial encoding area of the image, was 192mm, when the matrix size was  $64 \times 64$ , and there were 44 slices, with a slice thickness of 2 mm and an inter-slice gap of 1 mm. A total of 62 volumes per run were acquired in Experiment 1 and 66

volumes per run in Experiment 2. Each set of volumes is referred to as a "time series". The T1-weighted structural scans were acquired after the subjects completed the fMRI tasks, using a MDEFT sequence (Deichmann et al., 2004) with the parameters TR/TE/TI set at 7.92/2.48/910 ms, flip angle 16°, 176 slices and a voxel size of 1×1×1 mm.

The anatomical and functional images reported in Experiment 5 were acquired using a Siemens 1.5T Sonata scanner. The anatomical T1-weighted images were acquired using a 3D modified driven equilibrium Fourier transform sequence and 176 sagittal partitions with an image matrix of 256 × 224 and a final resolution of 1 mm<sup>3</sup> [repetition time (TR), 12.24/echo time, 3.56/inversion time, 530 ms]. Functional T2\*-weighted echoplanar images with blood oxygenation level-dependent contrast comprised 40 axial slices of 2 mm thickness with 1 mm slice interval and 3 × 3 mm in-plane resolution. One-hundred and three volumes were acquired per session, leading to a total of 412 volume images across four sessions. Effective TR was 3.6 s/volume. TR and stimulus onset asynchrony did not match, allowing for distributed sampling of slice acquisition across the experiment (Veltman et al., 2002). To avoid Nyquist ghost artefacts, a generalized reconstruction algorithm was used for data processing. After reconstruction, the first four volumes of each session were discarded to allow for T1 equilibration effects.

#### 2.5.1. IMAGE PRE-PROCESSING

Before performing any statistical analyses, raw fMRI data needs to be pre-processed. All pre-processing steps were completed with the software SPM12 (Statistical Parametric Mapping, Wellcome Centre for Human Neuroimaging, UCL, London, UK; <u>http://www.fil.ion.ucl.ac.uk/spm</u>).

#### 2.5.2. REALIGNMENT/UNWARPING

The purpose of realignment is to correct for motion artefacts created by head movements. This step is particularly important when the participants are producing speech. The first five images in each time series, referred to as "dummy scans", are always removed as the magnetic field takes approximately 10-15s to reach equilibrium. The sixth scan is used as the reference image to which all subsequent images are spatially aligned. This is done by estimating the optimum value for six movement parameters (translation and rotation in the x,y and z directions) for each subject and applying them as transformations to the functional images. The images were unwarped in the same realignment pre-processing step. The unwarping procedure is used to correct for distortions caused by head movement or magnetic field inhomogeneity.







The unwarping option was chosen rather including realignment parameters as linear movement regressors in the first level analysis because it accounts for non-linear movement effects by modelling the interaction between movement and any inhomogeneity in the T2\* signal. Following realignment and unwarping, the realignment parameters are visually inspected to ensure that the subject's movement within each scanning run was less than one voxel (3mm) (see Figure 2.7).

#### 2.5.3. CO-REGISTRATION OF FUNCTIONAL AND STRUCTURAL IMAGES

After realignment, a similar procedure, referred to as co-registration, is performed on the structural and functional images to ensure that they are in the same standard space. Co-registration works by comparing voxel intensities between the structural and mean functional and producing a joint histogram of the normalised mutual information. SPM tries to optimise the shared information between the structural and mean functional image, and to minimize the amount of uncertainty between any two voxels between the two images. The resulting transformation matrix is then applied to all functional images to align them with the structural image. This procedure ensures: (i) a more accurate spatial normalisation of functional images using the subject's anatomical image as a reference, and (ii) the anatomical localisation of single subject activations.

#### 2.5.4. NORMALISATION

Spatial normalisation is a process that aims to align images between different subjects to a common stereotactic standard space (i.e., the Montreal Neurological Institute, MNI space). Deformation field parameters, obtained during normalisation of the structural T1 scan, are applied to all EPI images. The original resolution of the images was maintained during normalisation (voxel size of 3mm<sup>3</sup> for EPI images and 1mm<sup>3</sup> for structural T1 images).

#### 2.5.5. SMOOTHING

Following the normalisation procedure, the images were spatially smoothed with a 6mm full-width at half maximum (FWHM) isotropic Gaussian kernel to (a) reduce noise in the BOLD signal by blurring anatomical variability (b) prepare the images for application of Gaussian random-field theory, which will be discussed in the next section. Each pre-processed volume was inspected for oddities before statistical analyses.

#### 2.5.6. STATISTICAL ANALYSIS OF fMRI DATA

The aim of fMRI in this work was to relate changes in neuronal activity, measured by the BOLD contrast to the underlying cognitive functions. Statistical inference in SPM is based on the General Linear Model (GLM; Friston et al., 1995), which tests for the hypotheses that the observed BOLD time-series of an individual voxel can be explained by a linear combination of explanatory variables:

$$Y_i = x_{i1}\beta_1 + \dots + x_{ij}\beta_j + \epsilon_i$$

Where, *Y* is a vector containing the BOLD signal in a single voxel across all acquired volumes. *X* is the design matrix, which contains values quantifying the experimental variables, also known as predictors or regressors. A set of regression coefficients  $\beta$  is estimated, one for each predictor of the model, to account for structure in the residual error  $\epsilon$  (Glaser & Friston, 2004). This is then iterated over all voxels to obtain one beta image per predictor. The GLM helps to establish whether there is a relationship between a dependent variable and one or more independent variables. The parameter estimates  $\beta$  for the predictor variables, also known as betas, can be thought of as the slope of the regression line relating *X* to *Y*. The better the estimation of  $\beta$ , the better the model (fits the data) and the smaller the deviations ( $\epsilon$ ) from the line (i.e. minimum sum of squared residuals). The neural response (HRF) is modelled in SPM using prior knowledge about haemodynamics and convolved with the design matrix. The  $\beta$  at each voxel can then be transformed into a t-value by dividing it by the standard error. In

other words, the t-value gives a measure of the ratio of explained to unexplained variance of the entire model. In order to compare parameter estimates of interest (to test for a certain hypothesis), a *contrast,* or linear combination, of the parameter estimates can be created. To compare two parameters, one is assigned a '+1' and the other a '-1', written as [1 -1].

#### 2.5.7. THRESHOLDING AND MULTIPLE COMPARISONS PROBLEM

Analysis of fMRI data involves a mass univariate approach, which means that several thousands of voxels in the brain are modelled independently from each other. This can lead to a number of false positive results (type I error) i.e. voxels appear to be significantly activated even though they are not. Different approaches can be employed to control for multiple comparisons. The challenge lies in finding an appropriate balance between trying to minimise false positives (Type I error) while not omitting true effects (Type II) error. The Bonferroni correction is one of the most commonly used approaches to correct for the multiple comparisons problem, in which the significance threshold (p=0.05) is divided by the number of statistical tests performed. As the number of voxels included in fMRI analyses is large (≈20,000), the chance of Type II errors increases dramatically. The Bonferroni method would be a valid approach to correcting for multiple comparisons if the voxels were truly independent from each other. However, neighbouring voxels show similar response patterns and therefore, the Bonferroni correction is considered too conservative. An alternative method to control for the multiple comparisons problem is to calculate the family-wise error rate, i.e. the probability of type I errors. The family-wise error (FWE) correction, based on a branch of mathematics called random field theory, was used to control for the number of statistical tests being performed by taking into account the smoothness of the data.

#### 2.5.8. GROUP LEVEL AND RANDOM EFFECT ANALYSIS

Single-subject activation provides valuable information about interindividual variability, while group-level analysis (also referred to as 2nd level analysis) allows us to generalise the conclusions from a sample to a larger population of healthy controls or a patient cohort. The experiments presented in this work employed both single-subject as well as group-level analyses. The group level analysis approach was modelled using the random effects method, thus assuming that the group of participants included in the study was randomly drawn from a larger population. Inferences about the population can be drawn from group-level analyses if the effect size in each subject is larger than the variance between subjects. It does not necessarily mean consistency across subjects, as I address in Experiment 4.

#### 2.5.9. DISPLAY AND LABELLING OF ACTIVATION CLUSTERS

Anatomical and functional data were displayed using the MRIcroGL software (Version 2-September-2019 v1.2.20190902++, Chris Rorden, https://www.nitrc.org/projects/mricrogl) on the mni152 template brain or the structural scans of study participants. To ensure high precision of anatomical localization for effects of interest, a combination of four different atlases was used, including the Jülich histological (cyto- and myelo-architectonic) atlas (Eickhoff et al., 2005), the Human Brainnetome Atlas (Fan et al., 2016), the Harvard-Oxford cortical atlas (Desikan et al., 2006), and the volumetric projection of the Human Connectome Project Multi-Modal Parcellation version 1.0 (HCP-MMP1.0; Glasser et al., 2016; Horn, 2016). The anatomical parcels of interest were visualised using FSLeyes (0.22.6; FMRIB, Oxford, UK, https://git.fmrib.ox.ac.uk/fsl/fsleyes/fsleyes/).

# 3. DISSOCIATING THE CONTRIBUTION OF THREE DIFFERENT LEFT POSTERIOR SUPERIOR TEMPORAL REGIONS TO SPEECH PERCEPTION AND PRODUCTION

# 3.1. SUMMARY

Prior studies have shown that the left posterior superior temporal sulcus (pSTS) and left temporo-parietal junction (TPJ) both contribute to phonological short-term memory, speech perception and speech production. This within-subjects multi-factorial fMRI study dissociated the response profiles of these regions and a third region – the anterior ascending terminal branch of the left superior temporal sulcus (atSTS), which lies dorsal to pSTS and ventral to TPJ.

First, the results show that each region was more activated by (i) 1-back matching on visually presented verbal stimuli (words or pseudowords) compared to 1-back matching on visually presented non-verbal stimuli (pictures of objects or non-objects), and (ii) overt speech production than 1-back matching, across 8 types of stimuli (visually presented words, pseudowords, objects and non-objects and aurally presented words, pseudowords, object sounds and meaningless hums). The response properties of the three regions dissociated within the auditory modality. In left TPJ, activation was higher for auditory stimuli that were non-verbal (sounds of objects or meaningless hums) compared to verbal (words and pseudowords), irrespective of task (speech production or 1-back matching). In left pSTS, activation was higher for non-semantic stimuli (pseudowords and hums) than semantic stimuli (words and object sounds), irrespective of task. In left atSTS, activation was not sensitive to either semantic or verbal content. Furthermore,

each region was found to participate in a non-overlapping network of frontal, parietal and cerebellar regions.

These results challenge previous claims about functional specialisation in the left posterior superior temporal lobe and motivate future studies to determine the timing and directionality of information flow in the brain networks involved in speech perception and production.

# **3.2.** INTRODUCTION

The goal of this study is to investigate functional subdivisions for speech processing within the left posterior superior temporal lobe. Many prior studies have already identified a range of functions that activate this part of the brain. However, integrating the results from a large number of independent neuroimaging studies is challenging. This is particularly true when brain regions - with the same anatomical labels and peak activation co-ordinates are associated with different functions, or conversely, when the same function is associated with different brain regions.

The current fMRI study addresses this problem by using a withinsubjects, multi-factorial design to functionally segregate the response profiles in different left superior temporal lobe regions during auditory speech processing, short-term memory and speech production. The following sections focus on the functions often assigned to two distinct parts of the left posterior superior temporal lobe, namely: (1) the posterior portion of the left superior temporal sulcus (pSTS); and (2), a region in the left temporo-parietal junction (TPJ) that lies at the boundary of the posterior superior temporal lobe with the supramarginal gyrus. This part of the left TPJ has also been labelled as Spt (Sylvian parietal temporal) in studies where it has been reported to respond independently to speech production and speech comprehension (Buchsbaum et al., 2001; Hickok et al., 2003; Hickok & Poeppel, 2004).The location of Spt corresponds to the perisylvian language area (PSL) defined in the Human Connectome Project multi-modal parcellation (HCP-MMP1.0; Glasser et al., 2016). The HCP atlas also distinguishes three different parts of pSTS including: (i) the dorsal surface of the horizontal stem of pSTS (STSdp), (ii) the ventral surface of the horizontal stem of pSTS (STSvp) and (iii) the ascending branch of the left superior temporal sulcus that is referred to as the temporal-parietal-occipital junction 1 (TPOJ1) in the HCP atlas but, more precisely, as the anterior ascending terminal branch of the superior temporal sulcus (atSTS) in Ochiai et al. (2004) and Liebenthal et al. (2014). These anatomical regions of interest are illustrated in Figure 3.1, projected onto the mean structural image from 24 neurotypical controls included in this study. As can be seen, the four regions of interest align well with the sulcal morphometry of the study participants.

In what follows, the inconsistencies in the conclusions drawn to date about the functional contribution of left pSTS and left TPJ will be highlighted, along with and an outline of how the current analysis attempted to reconcile these inconsistencies.

## Figure 3.1: Anatomical regions of interest



Regions of interest (ROIs) from the HCP-MMP1.0 atlas (Glasser et al., 2016) overlaid on the mean structural scans from 24 healthy participants. Green = the perisylvian language area (PSL) at the temporo-parietal junction (TPJ). Red = the dorsal surface of the horizontal section of pSTS. Blue = the ventral surface of the horizontal section of pSTS. Yellow = the anterior ascending terminal branch of the superior temporal sulcus (atSTS) that is referred to as the temporal-parietal-occipital junction 1 (TPOJ1) in the HCP atlas.

# 3.2.1. THE CONTRIBUTION OF LEFT pSTS TO SPEECH PROCESSING

Early functional imaging studies demonstrated that left pSTS activation is almost invariably observed during speech perception, even when acoustic processing is controlled by comparing speech to complex unintelligible sound stimuli, and irrespective of whether the speech is intelligible or not (Benson et al., 2006; Giraud et al., 2004; Hugdahl et al., 2003; Narain et al., 2003; Rimol et al., 2006; Scott et al., 2000). As part of left pSTS was also shown to be activated during verbal fluency (word generation without stimuli), Wise et al. (2001) proposed that the left pSTS is involved in transiently representing the temporally ordered sound structure of phonetic sequences (phonological short-term memory), whether heard or internally generated. The authors also highlighted the importance of phonological short-term memory for guiding speech production, and implicated left pSTS in both mimicry and language acquisition.

A role in phonological short-term memory does not, however, mean that the underlying function is specific to speech. Indeed, left pSTS activation increases with familiarity to non-verbal sounds (lacking any phonological content) even when auditory input is controlled (Dehaene-Lambertz et al., 2005; Dick et al., 2011; Leech et al., 2009; Liebenthal et al., 2003, 2010; Margulis et al., 2009; Meyer et al., 2005). A parsimonious explanation, that would account for the response to both verbal and non-verbal stimuli, is that left pSTS contributes to the short-term retention of auditory representations that underpins speech perception, speech production and other non-linguistic auditory tasks. Another possibility is that left pSTS might be a heterogeneous region with multiple functional subdivisions that have been conflated in prior studies. For example, Liebenthal et al. (2014) distinguished the posterior portion of the stem of STS, from the anterior terminal ascending branch of the STS (atSTS) which lies dorsal to pSTS and ventral to TPJ. Specifically, in a large-scale meta-analysis of 253 studies, Liebenthal et al. (2014) found that pSTS activation was more frequently associated with non-linguistic than linguistic stimuli, whereas atSTS was most sensitive to linguistic material (although also activated by a range of executive and motor planning tasks).

The current within-subjects study tests whether different parts of left pSTS respond to the demands on: (1) auditory short-term memory (that is not specific to speech sounds); (2) phonological short-term memory (greater for

speech than non-speech) and/or (3) retrieval of phonological representations that can be integrated with the articulatory system.

# 3.2.2. THE CONTRIBUTION OF LEFT TPJ TO SPEECH PROCESSING

As reported for pSTS, part of left TPJ (also known as Spt) is independently activated by speech perception and production and during auditory-motor tasks on non-verbal sounds (Hickok et al., 2003; Buchsbaum et al., 2001; Hickok et al., 2004). Hickok and colleagues therefore proposed that Spt plays a role in auditory-motor integration (Hickok et al., 2003). The same part of left TPJ has also been associated with short-term memory of verbal (Buchsbaum & D'Esposito, 2009, 2019; Koelsch et al., 2009; Kraemer et al., 2005; McGettigan et al., 2011) and non-verbal sounds (Koelsch et al., 2009; Kraemer et al., 2005). Drawing this work together, Buchsbaum & D'Esposito (2019) have described how Spt could support the temporary maintenance of auditory speech representations via feedforward and feedback pathways that connect the auditory- and motor-speech systems.

On the other hand, activation in the same part of left TPJ has also been observed in the absence of auditory stimuli, speech production or a motor task. For example, left TPJ activation has been reported for imagining music, tones or environmental sounds (Aleman et al., 2005; Bunzeck et al., 2005; Zatorre & Halpern, 2005; Xu et al., 2006) or viewing visual stimuli that had previously been paired with sounds, music or rhythms (Jäncke & Shah, 2004; Pekkola et al., 2006; Wheeler et al., 2000; Hasegawa et al., 2004).

As with pSTS, this experiment tested whether TPJ was sensitive to the demands on: (1) auditory short-term memory (that is not specific to speech sounds); (2) phonological short-term memory (greater for speech than non-speech) and/or (3) retrieval of phonological representations that can be integrated with the articulatory system.

#### 3.2.3. EXPERIMENTAL RATIONALE

By using a multi-factorial within-subjects design, this study aimed to dissociate different parts of the left posterior superior temporal lobe on the basis of their response profiles. The choice of conditions is founded on the type of processing that I expect to be engaged by the regions, stimuli and tasks. Once different response profiles are segregated, hypotheses about the function of each region for a given task can be generated and tested, in the acknowledgement that the function of a region may vary depending on the network of regions it contributes to during any given task (Price & Friston, 2005).

To dissociate the response profile of different regions, the experimental design presented eight different stimulus types with two different tasks: overt speech production (e.g. repeating aloud, reading aloud, naming aloud) or silent 1-back matching, with a finger press response. Half the stimuli were verbal and half the stimuli were non-verbal. The auditory verbal stimuli were (1) spoken words or (2) spoken pseudowords. The visual verbal stimuli were (3) written words or (4) written pseudowords. In the current work, these stimuli are described as verbal rather than phonological because (i) phonological processing will be activated by non-verbal stimuli during speech production tasks (e.g., picture naming) and (ii) the term "verbal" is broader than phonological, incorporating the specific experiences we have with speech sounds and written material compared to other types of stimuli. The auditory non-verbal stimuli were (5) sounds of animals and objects or (6) meaningless vocal humming sounds. The visual non-verbal stimuli were (7) pictures of animals and objects or (8) meaningless coloured non-objects (see Figure 3.2). A task analysis of the types of processing that might be tapped by each of the 16 conditions is provided in Table 3.1 and detailed below.

In all the auditory conditions, the expectation was that (i) auditory shortterm memory would be required until a speech production or 1-back matching response had been made, (ii) the demands on auditory short-term memory would be greater when auditory stimuli lacked semantic content (pseudowords and humming) compared to stimuli that have rich semantic content (words and object sounds) that can be used to support task performance, (iii) speech processing would be engaged by verbal more than non-verbal stimuli in the auditory modality, and (iv) the demands on phonological encoding/retrieval would be greater for non-verbal than verbal stimuli because heard speech is available to guide the production of speech from verbal but not non-verbal stimuli.

The visual conditions contributed to the functional definition of regions by identifying processing that was, or was not, specific to the auditory modality. The expectation was that 1-back matching of visual words and pseudowords would involve phonological processing (encoding and short-term memory) because (1) even when the task does not require speech production, skilled readers are highly trained to rapidly link phonologically legal written text (words or pseudowords) to higher level representations of speech sounds (phonological encoding/retrieval) and articulation (articulatory recoding), and (2) these phonological representations can be held in short-term memory to support 1-back matching. The demands on phonological retrieval were expected to be higher for visual words and pseudowords than auditory words and pseudowords (because speech sounds are provided by auditory verbal stimuli but need to be retrieved from visual stimuli).

To further investigate functional distinctions between left posterior superior temporal lobe regions of interest, a covariance analysis was used to examine whether the regions differed in the networks of regions in which they participate (Seghier & Price, 2009).

/Sensory perceptual processing	Visual Conditions							Auditory Conditions								
Task set	Speech production				1-back matching				Speech production				1-back matching			
Type of stimulus	W	Ρ	0	С	W	Ρ	0	С	W	Ρ	0	Η	W	Ρ	0	Н
Speech acoustics from stimulus									Α	Α			Α	Α		
Hearing own speech	Α	Α	Α	Α					Α	Α	Α	Α				
Visual short-term memory	Α	Α	Α	Α	Α	Α	Α	Α								
Auditory short-term memory									Α	Α	Α	Α	Α	Α	Α	Α
Semantic retrieval/memory	Α		Α		Α		Α		Α		Α		Α		Α	
Phonological retrieval	Α	Α	Α	Α	Α	Α	i	i			Α	Α			i	i
Phonological short-term memory	A	Α	Α	Α	Α	Α	i	i	Α	Α	Α	Α	Α	A	i	i
Articulatory recoding	Α	Α	Α	Α	Α	Α	i	i	Α	Α	Α	Α	i	i	i	i
Motor control of speech	Α	Α	Α	Α					Α	Α	Α	Α				

#### Table 3.1: Task analysis

For each of the 16 different conditions (16 columns), "A" indicates whether different types of processing (rows) are expected to be activated. i = not required but may occur implicitly. W = words; P = pseudowords; O = objects; H = humming; C = coloured non-objects.

# 3.3. METHODS

## 3.3.1. PARTICIPANTS

Twenty-four, healthy, right-handed English speakers (12 female, 12 male) participated in the study. All participants were neurologically healthy and had normal or corrected-to-normal vision and hearing. Their mean age was 31.4 years, standard deviation (SD) = 5.9 years; range = 20–45. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects gave written informed consent prior to scanning and received financial compensation for their time. This study was approved by the London Queen Square Research Ethics Committee.

## 3.3.2. EXPERIMENTAL DESIGN

The fMRI paradigm comprised a 2x2x2x2 factorial design, with 16 conditions and 8 types of stimuli (see Table 3.1). Factor 1 was stimulus

modality (auditory versus visual). Factor 2 was the presence or absence of sublexical phonological content (i.e. verbal versus nonverbal stimuli). Factor 3 was the presence or absence of semantic content (i.e. semantic versus non-semantic stimuli). Factor 4 was response modality with two tasks: overtly producing speech (i.e. speech production, SP), or 1-back matching with a finger press response.

### 3.3.3. STIMULUS SELECTION AND CREATION

Pictures of 128 easily recognisable objects with one to four syllable names (e.g. tap, cat, pizza) and their written word counterparts were created. The auditory words and pseudowords were recordings of a male, native English speaker (with a Southern British accent approximating Received Pronunciation) reading aloud the written versions of the same stimuli. The auditory semantic non-verbal stimuli (sounds of animals and objects e.g. the sound of a guitar playing or a cat meowing) associated with 32 of the 128 concepts from the NESSTI were taken sound library (http://www.imaging.org.au/Nessti; Hocking et al., 2013). The remaining 96 auditory semantic non-verbal stimuli were not easily recognisable from their sounds (e.g. motorbike and telephone but not suitcase or banana). All participants were therefore presented with the same set of 32 object sounds.

The auditory non-semantic, non-verbal stimuli (auditory baseline) were created by male and female voices humming with no phonological or semantic content. Critically, stimulus duration was longer for non-verbal sounds (objects and humming) than verbal (words and pseudowords) sounds because when the stimulus duration was shortened, participants were unable to name the source of animal and object sounds. The duration of half the auditory baseline stimuli was matched to the duration of the environmental sounds (mean = 1.47s) and the other half to the spoken words (0.64s). Longer stimulus durations were expected to increase the demands on acoustic processing, auditory attention and auditory short-term memory.
Written pseudowords (e.g. "grack" or "koucan") were created using a non-word generator "WordGen" (Duyck et al., 2004). To ensure that the pseudoword stimuli were balanced with the word stimuli, we generated 128 written pseudowords that were matched to the 128 objects names for bigram frequency, number of orthographic neighbours and word length. The visual non-semantic, non-verbal stimuli were coloured non-objects. They were created from the object pictures by scrambling the global and local features to render them unrecognisable and then manually editing the images to accentuate one of eight colours (brown, blue, orange, red, yellow, pink, purple and green) to create meaningless coloured shapes. The colour of the shape and its visual form changed on each trial. Each of the colour names appeared four times per scan run (32 stimuli in total). To ensure that speech production responses were consistent for each colour and object, a pilot study with 19 participants was conducted (by a former research assistant and lab coordinator, Suz Prejawa). Examples of the visual stimuli are presented in Figure 3.2 and details of the stimulus properties (average number of syllables, average number of letters, and average stimulus duration) can be found in Table 3.2.

#### Figure 3.2: Examples of visual stimuli



Verbal (words/pseudowords) and non-verbal (pictures of objects and non-objects) visual stimuli.

Stimuluo	Syllables	Lattora	Duration	RT
Sumulus	(SD)	Letters	(seconds)	1-back
Visual words	1.53 (0.68)	5.24 (1.68)	1.5	0.655 (0.11)
Visual pseudowords	1.94 (0.92)	5.28 (1.94)	1.5	0.648 (0.09)
Visual objects	1.55 (0.69)	5.30 (1.75)	1.5	0.683 (0.12)
Visual colours	1.36 (0.49)	4.89 (1.04)	1.5	0.762 (0.11)
Auditory words	1.53 (0.68)	5.24 (1.68)	0.64 (0.10)	0.880 (0.11)
Auditory pseudowords	1.90 (0.84)	5.35 (1.72)	0.68 (0.12)	0.959 (0.14)
Auditory objects	1.81 (0.92)	5.64 (2.21)	1.47 (0.12)	1.111 (0.33)
Auditory humming	1.50 (0.51)	5.00 (1.01)	1.04 (0.43)	1.125 (0.23)

Table 3.2: Stim	ulus presenta	ation and res	ponse times
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The average number of syllables and letters (standard deviation in brackets) for each word, pseudoword, object name, colour name or gender name. The duration of these stimuli is in seconds. The response time (RT) from stimulus onset to finger press response is also in seconds with standard deviation shown in brackets. Response times were not available for the speech production conditions.

#### 3.3.4. COUNTERBALANCING

Stimulus and condition order was fully counterbalanced across participants. Half the subjects performed the 8 speech production tasks first, followed by the 1-back matching tasks. The others performed the 1-back matching tasks first, followed by the speech production tasks. Stimuli for the speech production conditions were identical to those for the 1-back matching conditions. Hand of response was counterbalanced evenly across participants, i.e. half of the subjects used their left hand, and half of the subjects used their right hand. Within task, the order of other variables was counterbalanced (stimulus modality, semantics and phonology), which resulted in 24 different orders in total.

#### 3.3.5. STIMULUS PRESENTATION

Stimulus presentation and response recording was controlled by the COGENT toolbox (<u>http://www.vislab.ucl.ac.uk/cogent.php</u>) in MATLAB 2010a (MathWorks, Sherbon, MA, USA). Visual stimuli were projected onto an MRI-compatible LCD screen positioned at the head-end of the scanner bore and viewed via a mirror attached to the head coil. Each stimulus was displayed for 1.5s and subtended a visual angle of 7.4 degrees (10cm on screen, 78cm

viewing distance) with a pixel size of 350 × 350, and a screen resolution of 1024 × 768. Visual verbal and non-verbal stimuli (words and pseudowords) were presented in lower case Helvetica. The visual angle for the written words ranged from 1.47 to 4.41°, with the majority of words (with five letters) extending 1.84–2.2°.

Auditory stimuli were presented via MRI-compatible headphones (MR Confon, Magdeburg, Germany), which also attenuated the noise of the magnetic gradients and the helium pump. Volume levels were adjusted for each participant before scanning. Spoken responses were recorded via a noise-cancelling MRI microphone (FOMRI IIITM Optoacoustics, Or-Yehuda, Israel), and transcribed manually for off-line analysis.

Scanning started with the instructions 'Get Ready' written on the inscanner screen while five dummy scans were acquired (15.4s in total). This was followed by a written instruction (e.g. 'Repeat'), lasting 3.085s, which indicated the forthcoming start of a new block and reminded participants of the task that needed to be performed.

#### 3.3.6. Assigning stimuli to conditions

The 128 object stimuli were divided into four sets of stimuli (A, B, C, D). Within each 3.2-minute run, there were four blocks of stimuli, alternating with rest. Each block presented nine stimuli including 1 repeat, with an interstimulus interval of 2.52 seconds. The repeat was present for speech production and 1-back matching conditions and was only used to assess accuracy in the 1-back matching condition. Set D always presented auditory non-verbal semantic stimuli (object sounds). The remaining 96 object concepts were assigned to sets A, B and C and presented as pictures, written words and heard words, with items rotated, across subjects such that all 96 objects were presented in each condition to all participants with no repeats within task (each participant experienced 32 items per condition). This ensured

that the speech production responses (i.e. object names) were identical for reading, repetition and object naming when averaging across participants.

#### 3.3.7. PROCEDURE

Prior to scanning, each participant was trained on all tasks in a quiet testing room using a separate set of stimuli that were not used in the scanner, except for object sounds which remained the same. Participants were familiarised with the auditory objects sounds to facilitate object recognition and ensure high accuracy for naming objects from sounds.

For the speech production tasks, participants produced a single overt spoken response. In the visual modality, they: 1) named objects or animals in pictures; 2) read written object names; 3) read pseudowords; and 4) named the colour of meaningless nonobjects (see Figure 3.2). In the auditory modality, participants 1) named objects/animals after hearing environmental sounds associated with those objects; 2) repeated heard object names; 3) repeated pseudowords; and 4) named the gender of the voice ('male' or 'female') after hearing male or female humming sounds.

For the 1-back matching task, participants placed two fingers of the same hand over an fMRI compatible button box to indicate whether or not the stimulus was the same as the one preceding it (left button for 'same', right button for 'different'). There was no overt speech production involved in any 1-back matching condition.

After completion of the training task, participants were positioned on a scanner bed in the head-first supine position and the equipment was attached (head-coil with attached mirror, button box for the 1-back matching tasks, microphone for speech production tasks and pulse oximeter to monitor their vital signs during scanning). An alarm bulb was given to each participant in case of an emergency.

During both visual and auditory conditions, participants were instructed to respond as fast as possible, keeping their body and head as still as possible, and their eyes open and fixated on a cross in the middle of the display screen. This was monitored with an eye tracker throughout the experiment. There were separate runs for each of the 16 conditions. Total scanning time was approximately 1.5 hours per subject, including 10 min set-up time and a 12 min structural scan.

#### 3.3.8. IN-SCANNER BEHAVIOUR

In-scanner behaviour was measured for each of the 16 conditions. Correct responses were those that matched the target or were nearly identical in meaning, without delay or self-correction. For some stimuli, more than one response was considered correct. All other responses were categorised as incorrect. For 1-back matching, accuracy, and response times (from stimulus onset to button press) were computed automatically, according to the button pressed in response to each trial. For speech production, spoken responses were recorded via a microphone and monitored by the experimenter who either (i) ticked a check list to confirm that the expected response had been made or (ii) recorded an alternative (or null) response. For example, a picture of a mug could be named "cup" or "mug". The same criteria were used for all participants.

Due to technical failure, response times were only available in the 1back matching task. A repeated measures 2×2×2 ANOVA was conducted in SPSS (IBM SPSS Statistics, Version 22.0, Armonk, NY: IBM Corp) to test for main effects and interactions. Factor 1 was stimulus modality (visual vs. auditory), factor 2 was semantic versus non-semantic stimuli (words and objects versus pseudowords and baseline) and factor 3 was verbal versus non-verbal stimuli (words and pseudowords versus objects and baseline).

Data acquisition and preprocessing steps are explained in the general methods section (Chapter 2).

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#### 3.3.9. FIRST LEVEL STATISTICAL ANALYSES OF fMRI DATA

Each pre-processed functional volume was entered into a subjectspecific fixed effect analysis using the general linear model (Friston et al., 1995). Stimulus onset times were modelled as single events with two regressors per run, one modelling the instructions and one modelling all stimuli of interest. Stimulus functions were convolved with the SPM canonical haemodynamic response function and high-pass filtered with a cut-off period of 128 s to exclude low-frequency confounds.

For each scanning session/run (that alternated one condition of interest with fixation), a single contrast that compared activation in response to the stimuli and task of interest to resting with fixation was generated. This resulted in 16 different contrasts (one per condition) for each participant. Each contrast for each individual was inspected to ensure that there were no visible artefacts (e.g. edge effects, activation in ventricles) that might have been caused by within-scan head movements.

#### 3.3.10. SECOND LEVEL STATISTICAL ANALYSES OF fMRI DATA

At the second level, the 16 contrasts for each participant were entered into a within-subjects one-way ANOVA in SPM12, with factorial analysis conducted at the contrast level.

Within the eight auditory conditions, the statistical contrasts reflected the conventional analysis of a factorial design - main effect of (1) verbal versus non-verbal stimuli; (2) semantic versus non-semantic stimuli and (3) speech production versus 1-back matching (see Table 3.3). Each effect was tested in both directions (i.e. verbal >non-verbal; non-verbal > verbal; semantic > non-semantic; non-semantic > semantic; speech production > 1-back matching; and 1-back matching > speech production).

		Stimulus	Abb	Verbal	Semantic	Speech Production
		Words	W	+	+	+
	Speech	Pseudowords	Ρ	+	-	+
	production	Objects	0	-	+	+
Visual		Colours	С	-	-	+
modality		Words	W	+	+	-
	1-back	Pseudowords	Ρ	+	-	-
	matching	Objects	0	-	+	-
		Colours	С	-	-	-
		Words	W	+	+	+
	Speech	Pseudowords	Ρ	+	-	+
	production	Objects	0	-	+	+
Auditory		Hums	Н	-	-	+
modality		Words	W	+	+	-
	1-back	Pseudowords	Ρ	+	-	-
	matching	Objects	0	-	+	-
		Hums	Н	-	-	-

#### Table 3.3: Experimental design

Abb = abbreviations used in all tables and figures: W = words; P = pseudowords; O = objects; C = coloured non-objects, H = humming sounds. The plus signs were the activation conditions (weighted +1 in the statistical contrast) and the negative signs were the baseline (weighted -1 in the statistical contrast).

#### 3.3.11. STATISTICAL CONTRASTS

The rationale for the statistical contrasts is based on the task analysis (see Introduction and Table 3.1). In the visual modality, 1-back matching on verbal stimuli was compared to rest and non-verbal stimuli. In the auditory modality, I compared (1) verbal to non-verbal stimuli, and vice versa, (2) semantic to non-semantic stimuli and vice versa, and (3) speech production to 1-back matching and vice versa.

Responses that were not specific to the auditory modality (i.e. involved in higher level processing) were identified by reporting activation that was common for (1) visual 1-back matching on verbal compared to non-verbal stimuli and (2) each of the auditory contrasts (see above).

#### 3.3.12. ANATOMICAL REGIONS OF INTEREST

An anatomical region of interest was used to avoid any bias towards particular parts of left pSTS and left TPJ. After considering several different atlases, the most fine grained partitions were provided by the HCP-MMP1.0 (Glasser et al., 2016). The surface-based HCP-MMP1.0 parcellation was projected onto volumetric MNI ICBM non-linear asymmetric 2009a space (Horn, 2016). The region of interest for this study was the combination of the four areas illustrated in Figure 3.1, namely the perisylvian language area (PSL) in TPJ and three different parts of pSTS: (i) the dorsal surface of the horizontal stem of pSTS (STSdp), (ii) the ventral surface of the horizontal stem of pSTS (STSvp) and (iii) the ascending branch of the left superior temporal sulcus that is referred to as the temporal-parietal-occipital junction 1 (TPOJ1) in the HCP atlas but, more precisely, as the anterior ascending terminal branch of the superior temporal sulcus (atSTS) in Ochiai et al. (2004) and Liebenthal et al. (2014).

#### 3.3.13. STATISTICAL THRESHOLDS

Voxel-wise correction for multiple comparisons was either (i) across the whole brain or (ii) within a single anatomical region (the four regions of interest illustrated in Figure 3.1 combined into a single binary mask). For the conjunctions of visual and auditory contrasts, the global conjunction in SPM was used with a statistical threshold of p<0.05 after family-wise error correction for multiple comparisons across the whole brain (in height). The auditory contrast that entered the conjunction was computed across tasks and for each task separately.

#### 3.3.14. DISSOCIATING THE WHOLE BRAIN NEURAL SYSTEMS ASSOCIATED WITH DIFFERENT LEFT POSTERIOR SUPERIOR TEMPORAL LOBE REGIONS

The brain networks associated with different regions were dissociated using a covariance analysis. The rationale for the covariance analysis is that regions belonging to the same network are expected to have more similar response variation (across subjects, conditions or time) than regions belonging to different networks (i.e. the strength of the activation going up or down will be more similar across regions in the same network than regions in different networks). Here, inter-subject variability across tasks was treated as a valuable source of information rather than noise. Previously, inter-subject variability was not only shown to reveal the same functional networks as within-subject condition comparisons but also "hidden" networks that are masked when activation is averaged over subjects in classic subtraction methods/factorial designs (Seghier & Price, 2009). Therefore, in addition to showing that different regions are associated with different networks, the results can also help infer the type of processing that different regions contribute to.

Procedurally, the whole-brain second level analysis was repeated (with 16 different conditions). This time, the parameter estimates (activation compared to rest for each subject in each condition) at the co-ordinates for the peak voxels were entered into the analysis as separate covariates. The number of regressors was equal to the number of posterior superior temporal lobe regions of interest. Variance associated with each regressor is therefore a combination of condition effects and inter-subject variability effects. A comparison of each regressor to all others, within the same analysis, identified the sets of distributed regions (across the whole brain) that covaried with one region more than the others. These effects are reported after family wise error correction for multiple comparisons across the whole brain, in height.

#### 3.3.15. PREVIOUS REPORTS

Data from this paradigm have previously been reported in: Oberhuber et al. (2013) to demonstrate a functional posterior-anterior subdivision in the putamen; Hope et al. (2014) to dissect the functional anatomy of auditory word repetition; Oberhuber et al. (2016) to investigate functional subdivisions within the supramarginal gyrus; and Yamamoto et al. (2019) to highlight a special role for the right posterior superior temporal sulcus during speech production. The current focus on auditory short-term memory in the left posterior superior temporal lobe yields novel findings that were outside the scope of all previous analyses of the same dataset.

## 3.4. RESULTS

#### 3.4.1.IN-SCANNER BEHAVIOURAL DATA

As reported in detail for the same dataset in Yamamoto et al. (2019), inscanner accuracy was above 90% for each of the 16 conditions, except for 1back matching on auditory humming (89%), repeating heard pseudowords (88%) and reading written pseudowords (86%). Reaction times during 1-back matching were slower for: (i) auditory > visual stimuli, because auditory features were delivered sequentially whereas visual features were delivered simultaneously; (ii) non-verbal > verbal auditory stimuli, because non-verbal stimuli had longer delivery duration than auditory speech stimuli; and (iii) nonsemantic > semantic visual stimuli (written pseudowords > words, and colour > object stimuli) plausibly because on-line retention of non-semantic stimuli, until the matching decision, is not facilitated by semantic memory. The mean response times for each 1-back matching condition can be found in Table 3.2.

#### 3.4.2. fMRI DATA

#### 1. Visual 1-back matching on words and pseudowords (W&P)

When correcting for multiple comparisons within the region of interest (binary mask composed of the four anatomical regions), there were three spatially distinct activation peaks for 1-back matching on verbal stimuli more than rest. These were located in left pSTS (dorsal surface), left atSTS and left TPJ (see Figure 3.3 and Table 3.4A). All three regions were also activated by (i) visual 1-back matching on words and pseudowords compared to objects and coloured non-objects (p<0.001 uncorrected) and for speech production on all visual stimuli more than 1-back matching on all visual stimuli (p<0.05 after

correction for multiple comparisons within regions of interest), see plots in Figure 3.3.

Figure 3.3: Condition-specific responses in three left posterior superior temporal regions



The peak effects were all significant at p<0.05 FWE-corrected for multiple comparisons within the anatomical regions of interest (see Table 3.4A), and the extent of the effect is illustrated at a height-level threshold of p<0.001 uncorrected. The plots show the relative activation per condition, with standard error of the mean across conditions. The colour around and within each plot indicates which brain region it refers to. The coloured bars show the activation conditions used to test for the effect, the grey bars show the baselines, and the hashed bars were not included in the statistical contrasts. Green is activation for auditory non-verbal > verbal stimuli; Red is activation for auditory non-semantic > semantic stimuli. Yellow is activation for visual verbal > non-verbal stimuli (yellow). W = words; P = pseudowords; O = objects; H = humming; C = coloured non-objects. SP = speech production tasks; 1-back = 1-back matching tasks.

Across the whole brain, the only other areas to show higher activation for visual 1-back matching on words and pseudowords compared to objects and coloured non-objects were the left frontal operculum and left pars opercularis (Table 3.4A). This was significant after correction for multiple comparisons across the whole brain in extent, when the height-level statistical threshold was set at p<0.001 uncorrected. According to the task analysis (Table 3.1), the processing associated with visual 1-back matching of verbal (words and pseudowords) > non-verbal (objects and coloured non-objects) stimuli could reflect phonological processing (encoding/retrieval and/or short-term memory) or orthographic processing. To determine which parts are associated with phonological processing, I consider the results of the auditory contrasts.

# 2. Verbal (words and pseudowords) versus non-verbal (object and humming) auditory conditions

The only temporal lobe region to show more activation for verbal than non-verbal auditory conditions was located in the middle part of the STS [peak at -57, -18, -6] consistent with previous studies of acoustic speech processing (Dick et al., 2011; Norman-Haignere et al., 2015; Specht et al., 2009; Liebenthal et al., 2014). Within the left posterior superior temporal regions of interest, left TPJ activation was higher for non-verbal than verbal auditory conditions (see Figure 3.3). As the same left TPJ was also more activated by visual 1-back matching on verbal more than non-verbal stimuli (see Table 3.4B), there was a highly significant interaction between [verbal versus nonverbal] and [visual versus auditory]; p<0.05 corrected in height for multiple comparisons across the whole brain (peak co-ordinates for the interaction at: -57, -36, +21, z-score = 5.1 and -54, -42, +18, z-score = 5.0).

To summarise, contrary to expectation, the analysis did not reveal any left posterior superior temporal lobe regions that could be associated with phonological short-term memory that was common to the auditory and visual modalities. Instead, the results showed that the part of left TPJ that corresponds to the putative Perisylvian Language area (PSL) and Spt (see above) is more strongly activated by non-verbal than verbal auditory conditions. This cannot be explained in terms of the demands on phonological retrieval because activation was higher for auditory verbal stimuli than visual verbal stimuli (see Figure 3.3).

#### Table 3.4: Statistical details for effects of interest

**A.** Visual 1-back matching on words (W) and pseudowords (P) compared to (i) rest and (ii) visual 1-back matching on objects (O) and coloured non-objects (C).

		MNI	Z-sc	ores
Anatomical Region (abbre	eviation)	co-ordinates	W&P > rest	W&P > O&C
Left temporo-parietal junction	(L TPJ)	-54, -42, +21	5.2 *	3.1
Left anterior ascending	(Laters)	-51, -45, +9	4.2 *	3.2
terminal branch of the STS	(L als 15)	-51, -45, +6	3.9	3.7
Left posterior STS		-54, -30, 0	3.5 *	4.0
(dorsal surface)	(L p313)	-57, -30, -3	3.1	4.3
Right posterior STS	(R pSTS)	+57, -30, 0	3.3	3.2
Left frontal operculum	(L FO)	-42, +30, -3	3.8	4.3
Left pars opercularis	(L pOp)	-48, +15, +12	4.4	3.7

**B.** Conjunctions of Auditory effects and visual 1-back matching on verbal > non-verbal stimuli (W&P>O&C).

Auditory contrast	ast Region V		Region Vy MNI		Z-scores		
Additory contrast			co-ordinates	Con.	Aud.	Vis.	
Non-verbal > Verbal	L TPJ	182	-54, -42, +21	4.8	4.7	3.1	
Non-semantic > Semantic		140	-57, -27, 0	5.9	4.0	4.3	
	L p313	142	-54, -42, +3	5.3	3.2	cores           ud.         Vis.           1.7         3.1           4.0         4.3           3.2         3.9           5.2         3.5           5.1         3.2           3.9         4.2           3.4         3.4           3.3         3.1           3.3         3.1	
	Decto	071	271 +57, -24, -3 +54, -36, -3	5.3	6.2	3.5	
	R poro	271		4.8	5.1	3.2	
	L pSTS		-60, -30, 0	6.0	3.9	4.2	
Speech production >	L atSTS	231	-57, -42, +9	4.9	3.4	3.4	
1-back matching	L TPJ		-54, -42, +21	4.8	3.3	3.1	
	R pSTS	40	+57, -30, 0	4.8	3.3	3.1	

In Part A, Z-scores that reached significance at p<0.05 corrected for multiple comparisons within the anatomical region of interest (see Figure 3.1) are masked with an asterisk (\*). In part B, Con. = Z-scores for conjunction of the auditory contrast (Aud) listed in column 1, and the visual contrast (Vis) which was always visual 1-back matching on words and pseudowords > objects and coloured non-objects (Vis). The z-scores for the conjunctions were all significant at p<0.05 FWE-corrected for multiple comparisons across the whole brain. Vx = number of voxels at p<0.001.

# 3. Non-semantic (pseudowords and humming) versus semantic (words and objects) auditory conditions

Within the anatomical regions of interest, activation was higher for nonsemantic than semantic auditory conditions in left pSTS, with a corresponding effect in right pSTS (RpSTS). There were no effects of non-semantic > semantic (or semantic > non-semantic) in either left TPJ or left atSTS (p>0.05 uncorrected). A conjunction analysis confirmed that there were 142 left pSTS voxels and 271 right pSTS voxels that were activated by (i) non-semantic > semantic auditory conditions and (ii) verbal more than non-verbal visual 1-back matching (see Table 3.4B).

# 3.4.3. DISSOCIATING THE WHOLE BRAIN NEURAL SYSTEMS ASSOCIATED WITH pSTS, TPJ AND atSTS

To dissociate the networks of regions associated with TPJ, pSTS and atSTS, the parameter estimates (activation for each condition compared to rest for each subject) were extracted, averaging over voxels within 3mm of the peak co-ordinates for left TPJ [-54, -42, 21], left pSTS [-57, -30, -3] and left atSTS [-51, -45, 6], reported for visual 1-back matching on verbal > non-verbal stimuli (see Table 3.4A). The analysis focused on brain regions where activation, across conditions, co-varied with one region more than the other two.

The results dissociated three different networks (see Figure 3.4). The network associated with left TPJ primarily included bilateral postcentral gyri, SMA and bilateral superior cerebellum, with a smaller area in the left ventral premotor cortex [-57, 9, 6]. The network associated with left pSTS primarily included the left anterior superior temporal cortex, the pre-SMA and two small regions in the dorsal and ventral premotor cortex ([-42, 3, 54] and [-54, 0, 12]). The network of regions associated with left atSTS primarily involved bilateral inferior frontal gyri and sulci (left hemisphere peak at [-54, 27, 18]) and bilateral anterior insulae/frontal opercula (left hemisphere peak at [-30, 24, 9] / [-42, 27, 3]).



Figure 3.4: Regions that covary with left pSTS, left TPJ and left atSTS

Regions where activation co-varied with each of the three regions of interest illustrated in Figure 3.3. Green = network associated with left TPJ, red = network associated with left pSTS and yellow = network associated with left atSTS. Top row: x = -/+ 56; second row x = -/+ 48; bottom row x = -/+ 6. All coloured voxels (a) covaried positively and significantly with the corresponding region, (b) covaried significantly more with the corresponding region compared to the others and (c) were activated across all tasks compared to rest, with the threshold for both (a), (b) and (c) set at p<0.05 corrected for multiple comparisons across the whole brain. The threshold for the extent of the cluster was set to >20 voxels.

### 3.5. DISCUSSION

The main contribution of this study is to dissociate the response profiles of three different left posterior superior temporal lobe regions, using a withinsubjects multifactorial design. Furthermore, the results show that the three regions co-activate with different neural systems that include different frontal, parietal and cerebellar regions. Below, the response profile of each region is considered in detail, along with plans for further investigations of their functional role in future studies.

#### 3.5.1.LEFT pSTS

Here left pSTS is distinguished from the adjacent anterior terminal ascending branch of the superior temporal sulcus (i.e. left atSTS). The results demonstrated that the response in left pSTS was higher, when the auditory stimuli were non-semantic compared to semantic, irrespective of task. According to the task analysis (Table 3.1), the enhanced activation could be a consequence of an increased reliance on auditory short-term memory when facilitation from semantic processing is not available. Indeed, the peak coordinates of this effect [-57, -30, -3/-54, -30, 0] are in close proximity to the brain region [-56, -30, 1] where Richardson et al. (2011) showed that grey matter increased with digit span (a classic verbal short-term memory task) in neurotypical individuals.

The results elucidate the functional contribution of left pSTS in two ways. First, we show that left pSTS activation is not sensitive to the phonological content of stimuli because activation was <u>not</u> higher for verbal compared to non-verbal auditory stimuli, or vice versa. Second, we show that, left pSTS activation is not specific to auditory input because activation was also observed for silent 1-back matching on visual stimuli with verbal content (i.e. words and pseudowords). A parsimonious explanation is that left pSTS may support the short-term retention of auditory representations that can be derived from either auditory or visual inputs. If the study design had not included the auditory non-verbal conditions, higher activation for verbal than non-verbal stimuli in the visual modality might have been interpreted as reflecting the demands on phonological processing. By showing that pSTS activation is higher for non-semantic, non-verbal humming than spoken word processing, the findings are more consistent with a role for left pSTS in short-term representation of sound features relevant to the task (Liebenthal et al., 2010), with demands on these short-term auditory representations increasing when the retention of auditory stimuli cannot rely on semantic memory.

This explanation can help interpret a range of prior findings. For example, reliance on auditory short-term memory may increase during audiovisual integration (Erickson et al., 2014; Szycik et al., 2012) and the attention, memory and executive tasks included in the meta-analysis conducted by Liebenthal et al. (2014) who reported greater left pSTS activation for nonlinguistic than linguistic stimuli. It is also possible that, in the absence of a behavioural task, the reliance on short-term representation of relevant sound features increases when passively listening to (1) non-verbal sounds as they become familiar (Dehaene-Lambertz et al., 2005; Dick et al., 2011; Leech et al., 2009; Liebenthal et al., 2010) and (2) non-semantic speech sounds compared to complex unintelligible sounds (Benson et al., 2006; Giraud et al., 2004; Narain et al., 2003; Rimol et al., 2006; Scott et al., 2000).

#### 3.5.2. LEFT TPJ

The response observed in left TPJ fits with two non-mutually exclusive perspectives on left TPJ (Spt) reported in the prior literature: (A) left TPJ/Spt plays a role in auditory-motor integration (Hickok et al., 2003; Buchsbaum et al., 2001; Hickok et al., 2004; Buchsbaum and D'Esposito 2019); and/or (B) it plays a role in short-term memory of auditory representations (Buchsbaum & D'Esposito, 2009, 2019; Koelsch et al., 2009; Kraemer et al., 2005; McGettigan et al., 2011) that are not necessarily linked to phonology or auditory-motor integration (Aleman et al., 2005; Bunzeck et al., 2005; Zatorre

& Halpern, 2005; Xu et al., 2006; Jäncke & Shah, 2004; Pekkola et al., 2006; Wheeler et al., 2000; Hasegawa et al., 2004).

The contributions of the current study are as follows. First, left TPJ activation was observed for silent 1-back matching on visual words and pseudowords. Its response is therefore not specific to auditory inputs or attention. Second, we found that activation was higher for non-verbal than verbal auditory stimuli. This is difficult to explain in terms of the demands on auditory-motor integration, but it might be a consequence of the non-verbal auditory stimuli having longer durations than the verbal stimuli, which necessitates more auditory processing, more auditory attention and more auditory short-term memory. Third, we found that left TPJ was more activated by auditory verbal stimuli than visual verbal stimuli. This is not consistent with the demands on phonological retrieval (or phonological processing more generally) because phonological representations are primed by hearing speech in auditory words and pseudowords but need to be retrieved for written words and pseudowords. Together these results are most consistent with left TPJ playing a role in auditory short-term memory, which is not specific to speech perception or speech production. We are therefore cautious about defining the response in left TPJ as an auditory-motor integration area but, like many other areas, it may contribute to auditory-motor integration, indirectly.

If left TPJ plays a role in auditory short-term memory, how does this differ from that in left pSTS? This study provides three distinguishing pieces of evidence. In TPJ, activation is higher for non-verbal than verbal auditory stimuli but is not higher for non-semantic than semantic auditory stimuli. As nonverbal auditory stimuli had longer durations and took longer to process than verbal stimuli (see Table 3.2), enhanced left TPJ activation for non-verbal compared to verbal auditory stimuli may reflect either the load on memory encoding or the prolonged maintenance of information in auditory short-term memory until the task is completed. In contrast, left pSTS activation was higher for non-semantic than semantic auditory stimuli but was not higher for nonverbal than verbal auditory stimuli. This may reflect demands on auditory short-term memory when there is no support from semantic memory.

The whole brain activations associated with left TPJ and left pSTS also suggest that these regions participate in partially non-overlapping neural systems (Figure 3.4). Left pSTS co-activated with extensive parts of the superior temporal gyrus (consistent with attention to auditory input), whereas left TPJ co-activated with extensive parts of the postcentral gyri that are associated with the sensory consequences of motor activity rather than motor planning. Although further studies are required to understand how these neural systems function, co-activation in left TPJ and the postcentral gyri raises an interesting hypothesis. Rather than driving motor responses (as implied from the auditory-motor integration hypothesis), left TPJ may contribute to speech production, at a post-articulatory stage, by holding auditory representations of expected speech on-line until the spoken output is matched to the intended speech. This hypothesis could be tested in future, using directional connectivity studies to determine whether left TPJ drives articulatory planning or is involved in sustaining auditory representations for post-articulatory processing.

In summary, the response observed in left TPJ is most consistent with encoding and sustaining auditory representations on-line. This is required for both speech perception and speech production but is not limited to language tasks. Future studies are required to test whether left TPJ contributes: (i) directly to motor planning (e.g. driving premotor/motor regions), (ii) indirectly to motor planning (e.g. by sustaining activity in other regions that drive the motor response) and/or (iii) to post-articulatory processing of the spoken response.

#### 3.5.3. LEFT atSTS

A distinction between the function of left atSTS and left pSTS was previously reported in a large-scale meta-analysis of 253 studies by Liebenthal et al. (2014) who found that left pSTS activation was more frequently associated with non-linguistic stimuli than linguistic stimuli whereas left atSTS was most sensitive to linguistic material (although also activated by a range of executive and motor planning tasks).

This within-subjects study indicates that activation in left atSTS increased for (i) verbal more than non-verbal visual stimuli, (ii) speech production more than 1-back matching and (iii) auditory more than visual stimuli. In these ways, the response in atSTS was similar to those in pSTS and TPJ. However, unlike left pSTS, left atSTS did not respond differentially to semantic versus non-semantic auditory stimuli; and unlike TPJ, atSTS did not respond differentially to verbal versus non-verbal auditory stimuli. We therefore found no evidence to suggest that left atSTS was sensitive to the demands on auditory or phonological short-term memory.

Based on connectivity patterns, Glasser et al., (2016) report that atSTS (corresponding to area TPOJ1 in HCP-MMP1) is one of three temporo-parietooccipital regions that link higher auditory and higher visual areas,. In addition, the same authors report that, relative to the dorsal surface of left pSTS, left atSTS is more activated by motor tasks involving tongue movements, finger tapping and toe squeezing; and less activated for listening to stories compared to answering arithmetic questions ("LANGUAGE STORY-MATH" contrast).

The covariance analysis demonstrated that activation in the left frontal operculum and left middle frontal gyrus/inferior frontal sulcus covaried more strongly with left atSTS than either left pSTS or left TPJ. This provides regions of interest for future connectivity analyses to investigate whether left atSTS is driven bottom-up from the auditory cortex and/or top-down from left frontal

regions. It will also be of interest to understand the direction of information flow between atSTS, pSTS and TPJ.

#### 3.5.4. CONCLUSIONS

The novel contribution of this study is the demonstration that pSTS, atSTS and TPJ each have distinct response properties, with left TPJ responding to non-verbal more than verbal auditory stimuli and left pSTS responding to non-semantic more than semantic stimuli; and left atSTS being significantly less sensitive to the verbal and semantic content of the stimuli.

The current work provided some speculative hypotheses about how each region might contribute to language processing but most importantly, the findings strongly motivate and guide future studies to probe the function of each region further and to use effective connectivity analyses (e.g. as in Parker Jones et al., 2013) to improve our understanding of how different parts of the speech and language network interact with one another to support speech comprehension and drive speech production. For example, how do the left posterior superior temporal lobe regions interact with each other and the rest of the brain during sensory, motor and higher-level processing? More specifically, is left temporo-parietal activation driven bottom-up from auditory inputs in the auditory cortex or top-down from the left posterior inferior frontal cortex; and how does this depend on stimulus modality, stimulus content and task? In addition, a greater understanding of inter-subject variability in the response of each region will also be essential for building maps of the functional anatomy of language that can be used to predict the behavioural consequences of brain damage or neurosurgery

# 4. VALIDATING THE FUNCTIONAL DISSOCIATION OF LEFT POSTERIOR SUPERIOR TEMPORAL LOBE REGIONS

#### 4.1. SUMMARY

The aim of this chapter was to cross-validate the response properties of the three regions of interest (ROIs) from Experiment 1 -TPJ, pSTS and atSTS in an independent group of neurotypical controls (n= 59). The paradigm used in the current study involved the same eight speech production conditions as Experiment 1 but differed in three notable ways: (i) it did not include any 1-back matching tasks; (ii) instead it included five tasks that were not used in Experiment 1 (e.g. semantic matching); and (iii) the order of conditions and stimuli within conditions were held constant for all participants in Experiment 2, rather than being counterbalanced as in Experiment 1.

The analysis focused only on the eight speech production tasks with the goal of identifying whether the left TPJ-ROI was activated by nonverbal compared to verbal auditory conditions, the left pSTS-ROI was activated for non-semantic more than semantic auditory conditions; and left atSTS-ROI was activated by verbal more than nonverbal visual conditions.

The effects of interest from Experiment 1 were found to be present in a new, larger sample of 59 participants and can be dissociated using region by condition interactions. Successful validation of these results provides evidence that the findings are more likely to reflect true effects, rather than false positives.

#### 4.2. INTRODUCTION

In the last decade, the "reproducibility crisis" has become apparent in a broad range of scientific disciplines, raising concern about the reliability of published findings (Baker, 2016; Munafò et al., 2017; Nature-Editorial, 2017; Open Science Collaboration, 2015). According to the Committee on Reproducibility and Replicability in Science, "Reproducibility is obtaining consistent results using the same input data; computational steps, methods, and code; and conditions of analysis" (National Academies of Sciences and Medicine, 2019). While it is widely acknowledged that independent verification of experimental results is an essential part of scientific methods, the reproducibility rates remain low. For instance, the Reproducibility Project, a crowdsourced collaboration of 270 contributing authors sought to replicate 100 psychological experiments published in three different journals. Although 97 of the 100 original studies obtained significant results, only 35 (36.1%) replicated with the average effect sizes in replication studies declining to almost half the magnitude of effect sizes reported in original studies (Open Science Collaboration, 2015). The strength of initial evidence (e.g., original pvalue) was found to be a better predictor of replication success than the expertise of teams conducing the research. Subsequently, a survey of 1576 Nature readers revealed that 70% of respondents failed to reproduce another researcher's experiments, while less than 31% agreed that failure to replicate a result means that the result is most likely wrong (Baker, 2016).

The problem of low reproducibility rates has been widely discussed in relation to neuroimaging, in particular functional magnetic resonance imaging (fMRI), where the costs associated with data collection, storage and processing are high in relation to other methods (Button et al., 2013; Carp, 2012; Cremers et al., 2017; Poldrack et al., 2017; Szucs & Ioannidis, 2017; Thirion et al., 2007). Differences in experimental procedures (Carp, 2012), software packages (Bowring et al., 2019), statistical analysis methods (Eklund et al., 2016; Nieuwenhuis et al., 2011; Woo et al., 2014), high variability in fMRI responses (Bennett & Miller, 2010; Dubois et al., 2018) and low statistical

power (Button et al., 2013; Lorca-Puls et al., 2018) are only a few reasons that could explain why some positive findings may not have been replicated.

In a controversial study, Eklund and colleagues (2016) used restingstate fMRI data from 499 healthy controls to investigate the validity of three most widely used software packages - SPM, FSL and AFNI. In brief, the authors showed that the parametric methods of controlling for familywise error across different software packages were valid at a voxel level but invalid for clusterwise inference, leading to high rates of false positive findings (up to 70%). Strong claims were made in the paper, such as its results "question the validity of some 40,000 fMRI studies and may have a large impact on the interpretation of neuroimaging results". This drew negative attention from the media and sparked discussions beyond the scientific community. While the overstatements from the paper have been corrected, the impact of publication was more far-reaching - it challenged the neuroscience community to develop practices that lead to reproducible science. More recently, 70 independent research teams analysed the same fMRI dataset as part of the Neuroimaging Analysis, Replication and Prediction Study (NARPS). The results showed that no two teams employed the same analysis methods, at least four different workflows could be used for every hypothesis and yield significant results (Botvinik-Nezer et al., 2020). In the light of the current discussion, the conductance of validation studies is strongly recommended.

Cross-validation is a common technique for assessing if the results of a statistical analysis will hold at the population level (Altman & Royston, 2000). In contrast to reproducibility/replicability, cross-validation relies on independence between the original and validation sets (Varoquaux et al., 2017). An experiment that has been "validated" shows greater generalizability than a "replicated" experiment. The goal of this study is to cross-validate the findings from Experiment 1 by conducting an independent analysis of data from a new group of 59 participants who performed the same eight speech production tasks as participants in Experiment 1. Focusing on these eight tasks, the response properties of the three regions of interest (ROIs) – TPJ, pSTS and atSTS can be further examined, specifically: (1) is the TPJ-ROI more activated by nonverbal compared to verbal auditory conditions? (2) is the pSTS-ROI more activated by non-semantic than semantic auditory conditions? (3) is atSTS-ROI more activated by verbal more than nonverbal visual conditions? In addition, because the data in Experiment 2 are independent of the data used to identify effects of interest in Experiment 1, the significance of these effects can be tested in a larger cohort of participants. However, due to differences in experimental designs discussed below (Table 4.1), a direct comparison of effect sizes is not possible.

Successful out-of-sample validation will provide further evidence about the generalisability of the findings from Experiment 1. On the other hand, if the results from the Experiment 2 differ from those reported in Experiment 1, I will gain further insights into the technical aspects of my data, which will serve to improve future analyses. There were many differences in the paradigm used for Experiments 1 and 2 that might explain a failure to cross-validate (Table 4.1). These differences included:

- the additional conditions that participants were engaged in. The participants in Experiment 1 performed 8 x 1-back matching tasks (see Chapter 3) that were not included in Experiment 2. In contrast, the participants in Experiment 2 performed 5 tasks that were not included in Experiment 1 (for detailed description, see Sanjuán et al., 2015). Plausibly, exposure to other tasks may influence how the set of common tasks were performed.
- the order of conditions, and the order of stimuli within conditions, were held constant for all participants in Experiment 2, rather than being counterbalanced as in Experiment 1. When stimuli and conditions are not counterbalanced, effects may be confounded by variance related to processing different stimuli in different conditions. The order of conditions will also be confounded by a reduction in effort and attention over time as participants adapt to the scanning environment.
- the participants in Experiment 2 were on average 13 years older than those in Experiment 1, and the age range was also substantially greater in Experiment 2 than Experiment 1. Age and other sources of inter-

subject variability will increase error variance, reducing signal-to-noise and potentially desensitising the experiment to effects of interest.

		Experiment 2	Experiment 1
	Size	59	24
Sample	Mean age (+/-SD)	44.5 (17.66)	31.44 (5.74)
Sample	Gender (females/males)	34/25	12/13
	Per condition	40	36
	Within condition	Identical for each participant	Rotated across conditions
	Pseudowords	Always novel	Novel during the
Stimuli	Objects	Not novel as performed after 5 other conditions with object names	speech production conditions in half the participants but not in the other half
	Colours	8 possible colours	5 possible colours
Conditio	n order	Identical for all participants	Rotated across participants
Respons	se	Speech production only	Speech production and finger-press response

SD = standard deviation.

#### 4.3. METHODS

#### 4.3.1. PARTICIPANTS

Fifty-nine neurotypical, right-handed, native English speakers were included in this study. There was no overlap between these volunteers and the 24 participants in Experiment 1. A comparison of the available information about the two participant groups is included in Table 4.1 Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the London Queen Square Research Ethics Committee. All participants gave written informed consent prior to scanning and received financial compensation for their time.

#### 4.3.2. EXPERIMENTAL SETUP

Experiment 2 consisted of the same 8 speaking tasks as Experiment 1 but did not include the 8 one-back conditions. The conditions of interest were: (1) Reading aloud familiar words, (2) Reading aloud unfamiliar pseudowords, (3) Naming objects from pictures, (4) Naming the colour of a non-object, (5) Repeating heard words, (6) Repeating heard pseudowords, (7) Naming objects from sounds, and (8) Naming the gender of a female or male voice humming. These eight tasks comprised a 2x2x2 factorial design. Factor I was stimulus modality (auditory versus visual), factor II was verbal versus nonverbal stimuli (words and pseudowords versus objects and baseline stimuli), and factor III was the presence or absence of semantic content (familiar words and object names versus unfamiliar pseudowords and baseline stimuli). In addition, the participants in Group 1 performed five other conditions that will not be analysed in this Chapter. The additional conditions (Task 1-5) involved seeing pictures of two objects and (a) deciding whether they were semantically related or not, (b) naming both objects in a noun phrase, (c) naming the verb that described how to objects interacted with one another, (d) naming both objects in a sentence (e.g. "the witch is jumping over the fire"), and hearing names of two objects and (e) deciding whether they were semantically related or not. The complete list of tasks in Experiment 2 is provided in Table 4.2.

#### Table 4.2: Task order in Experiment 2

- (1) Semantic decisions on pictures of objects
- (2) Naming two objects from pictures
- (3) Naming the action between 2 objects (e.g. eating)
- (4) Producing a sentence from pictures
- (5) Semantic decisions on heard object names
- (6) Reading words
- (7) Repeating words
- (8) Naming pictures of objects
- (9) Naming colours
- (10) Naming sounds of objects
- (11) Reading pseudowords
- (12) Repeating pseudowords
- (13) Naming gender of voice humming

The tasks of interest for this chapter are shown in bold.

#### 4.3.3. COUNTERBALANCING AND STIMULUS SELECTION

Unlike to Experiment 1, the stimulus and task order were kept identical for all subjects in Experiment 2. Each condition consisted of four blocks with 10 different stimuli. Participants were presented with a different set of pseudowords in the visual and auditory modalities. Half the pseudowords in each set had one syllable and the other half had two syllables. Object concepts were assigned to four relevant conditions (i.e. naming pictures and sounds of objects, reading words, repeating words). Stimuli presented as written and heard words had already been presented as in the picture naming tasks (Task 1-5) and those presented as pictures had previously been presented in the sentence production task (Task 4) or the word repetition task (Task 7). Object sounds (Task 10) were a mix of object concepts presented in other conditions. In the colour naming condition (visual baseline) the number of possible colours to be named was reduced from eight in Experiment 1 to five in Experiment 2 (green, blue, red, orange, yellow). Each colour name was repeated eight times (40 trials in total). In the gender naming condition (auditory baseline), there were 20 male and 20 female hums, split equally between 40 trials.

#### 4.3.4. PROCEDURE AND IN-SCANNER BEHAVIOUR

Despite differences in the presentation parameters (see Table 4.3), the procedures for Experiment 1 and Experiment 2 were the same (see Chapter 3, Methods for details). Response times for speech production conditions were not available in Experiment 1 due to technical failure. In Experiment 2, spoken responses were transcribed online and scored during off-line analysis of voice recordings. Response times (RTs) were computed from the audio recordings using an adaptive moving filter tailored to each audio file (developed by Thomas Hope, PhD). The optimal window length (i.e. the width which maximally smoothed the audio stream) was based on a sample of the respective audio file collected during rest. After the entire audio recording was smoothed, to reduce high-frequency noise in the signal, the onset of speech was defined as the first rise in the absolute amplitude of the audio stream above one standard deviation from the mean. All behavioural data analyses

were computed in SPSS (IBM SPSS Statistics for Macintosh, Version 25.0, Armonk, NY: IBM Corp).

	Experiment 1	Experiment 2
Stimulus properties		
Stimulus duration in sec (+/–SD)		
Visual stimuli	1.5	2.5
Auditory words	0.64 (0.10)	0.63 (0.09)
Auditory pseudowords	0.68 (0.12)	0.65 (0.08)
Sounds	1.47 (0.12)	1.45 (0.15)
Hums	1.04 (0.43)	1.05 (0.51)
Average number of syllables (+/–Sl	D)	
Reading words	1.53 (0.68)	1.55 (0.68)
Repeating words	1.53 (0.68)	1.68 (0.73)
Reading pseudowords	1.94 (0.92)	1.50 (0.51)
Repeating pseudowords	1.90 (0.84)	1.50 (0.51)
Naming pictures	1.55 (0.69)	1.48 (0.72)
Naming sounds	1.81 (0.92)	1.88 (0.94)
Naming gender	1.50 (0.51)	1.50 (0.51)
Naming colours	1.36 (0.49)	1.40 (0.50)
Average number of letters (+/–SD)		
Reading words	5.24 (1.68)	5.08 (1.61)
Repeating words	5.24 (1.68)	5.28 (1.38)
Reading pseudowords	5.28 (1.94)	4.40 (1.03)
Repeating pseudowords	5.35 (1.72)	4.35 (1.08)
Naming pictures	5.30 (1.75)	5.28 (1.75)
Naming sounds	5.64 (2.21)	5.65 (2.40)
Naming gender	5.00 (1.01)	5.00 (1.01)
Naming colours	4.89 (1.04)	4.80 (1.18)
Timing parameters		
ISI (sec)	2.52	2.5
Number of stimuli per block	9 (& 1 repeat)	10
Number of stimulus blocks per run	4	4
Total number of stimuli per run	36	40
Number of runs included/total	8/16	8/13
Total time for each run (min)	3.2	3.4
Total acquisition time (min)	25.6	27.2
Scanning parameters		
TR (sec)	3.085	3.085
Number of slices	44	44
Number of volumes per run	62	66

 Table 4.3: Methodological details for Experiment 1 and Experiment 2

ISI = inter-stimulus interval, SD = standard deviation, TR = repetition time.

#### 4.3.5. FIRST LEVEL STATISTICAL ANALYSES

After running the same pre-processing and first level analysis steps as in Experiment 1, each preprocessed functional volume was entered into a subject specific fixed effect analysis using the general linear model. For Experiment 1, two regressors per task were used, one modeling instructions, and the other modeling each stimulus. For Experiment 2, four regressors per task were used to model: (i) instructions, (ii) stimuli with correct responses, (iii) stimuli with incorrect responses and (iv) "other" responses (delayed, no response, or self-corrected).

#### 4.3.6. EFFECTS OF INTEREST

The condition specific effects of interest were investigated in SPM to illustrate their extent. The effects of interest for the current analysis were the same as in Experiment 1 after excluding the 1-back matching tasks. In the visual modality, verbal stimuli were compared to non-verbal stimuli during speech production. Similarly, in the auditory modality, the following statistical contrasts were generated for the speech production tasks: (1) non-semantic > semantic and (2) non-verbal > verbal.

As in Experiment 1, activation was limited to a region of interest comprised of four areas from the Human Connectome Project multi-modal parcellation (HCP-MMP1.0; Glasser et al., 2016), projected to the ICBM 2009a nonlinear asymmetric template (Horn, 2016), see Experiment 1 for details. The individual components of the combined region of interest are shown on the mean structural image from 59 participants included in this study Figure 4.1.



#### Figure 4.1: Regions of interest from Experiment 1

Regions of interest (ROIs) from the HCP-MMP1.0 atlas (Glasser et al., 2016) overlaid on the mean structural scans from the 59 neurotypical controls from this study. Green = the perisylvian language area (PSL) at the temporo-parietal junction (TPJ). Red = the dorsal surface of the horizontal section of pSTS. Blue = the ventral surface of the horizontal section of pSTS. Yellow = the anterior ascending terminal branch of the superior temporal sulcus (atSTS) that is referred to as the temporal-parietal-occipital junction 1 (TPOJ1) in the HCP atlas.

#### 4.3.7. REGION BY CONDITION INTERACTIONS

The second level analysis for Group 2 included eight speech production conditions. Using the F-map only (unbiased by condition), the subject specific parameter estimates were extracted for all conditions from the voxel closest to each of the co-ordinates identified in Experiment 1. Data for the eight speech production tasks were analysed in SPSS (IBM SPSS Statistics for Macintosh, Version 25.0, Armonk, NY: IBM Corp). In each of the three regions, the parameter estimates for the effects of interest from Experiment 1 were compared to the other two regions, which resulted in six 2x2 within-subject ANOVAs. The region by condition interactions were conducted to (i) confirm that the regions dissociated in Experiment 1 showed the same response profiles in the current study; and (ii) demonstrate that the response profile differed significantly between regions.

### 4.4. RESULTS

#### 4.4.1. IN-SCANNER BEHAVIOUR

The average in-scanner accuracy was above 97% for all conditions in Experiment 2. Accuracy for reading and repeating pseudowords was higher for Experiment 2 (95%) than Experiment 1 (87%) because of changes to the stimuli (see methods section). Accuracy scores for Experiment 2 were computed after two outliers (subjects with less than 50% accuracy) had been removed. Response times (RTs) were computed after two participants were excluded due to missing data. Across modality, RTs were slower for auditory than visual speech production stimuli due to sequential delivery of auditory, in contrast to simultaneous for the visual stimuli. Within modality, volunteers were slower on more demanding tasks, specifically: (a) object naming than word repetition or reading, (b) object naming than pseudoword production, and (c) pseudowords than words.

		Accura	cy (SD)	Response times (SD
		Experiment 2	Experiment 1	Experiment 2
	W	99.9 (0.5)	99.6 (1.3)	0.74 (0.12)
Vieual	Ρ	98.2 (3.3)	85.8 (15.1)	0.88 (0.16)
visuai	0	96.7 (3.3)	96.0 (4.6)	1.00 (0.15)
	С	98.6 (4.1)	99.0 (1.9)	0.88 (0.11)
	W	99.5 (1.3)	99.5 (1.1)	1.18 (0.14)
Auditors	Ρ	97.8 (4.4)	88.3 (8.7)	1.25 (0.19)
Auditory	0	92.9 (10.0)	91.8 (7.6)	1.58 (0.25)
	Н	98.1 (5.7)	99.1 (2.1)	1.42 (0.26)

Figure 4.2: In-scanner behavioural scores



**Top:** Detailed behavioural results (mean with standard deviation in brackets) for Experiment 1 and Experiment 2. Accuracy scores for Experiment 2 are based on n = 58 after one outlier (less than 30%) was removed. Response times for the speech production tasks were only available for Experiment 2 and are reported for 57 subjects, following exclusion of two participants with missing data. Plots show mean scores with standard deviation (red bars). **Bottom left:** Accuracy scores for speech production conditions are shown for Experiment 1 (grey) and Experiment 2 (black). **Bottom right:** RTs for Experiment 2 are for correct trials only and include stimulus delivery (longer for auditory than visual). W = words, P = pseudowords, O = objects, C = colours.

#### 4.4.2. REGION BY CONDITION INTERACTIONS

The co-ordinates for data extraction were almost identical to those used in Experiment 1 (no more than 1mm difference on each axis) as shown in Table 4.5. The data from the four auditory conditions were entered into SPSS which confirmed the expected region by condition interactions: the effect of non-verbal > verbal auditory conditions was significantly higher in left TPJ than either left pSTS (F (1,58) = 19.248; p<0.001) or left atSTS (F (1,58) = 11.533; p<0.001), and the effect of non-semantic > semantic auditory conditions (across tasks) was significantly higher in left pSTS than either left atSTS (F (1,58) = 4.710; p=0.017) or left TPJ (F (1,58) = 16.907; p<0.001). The effect of verbal > non-verbal visual conditions was significantly higher in left atSTS than left TPJ (F (1,58) = 4.021; p=0.025) or left pSTS (F (1,58) = 3.885; p=0.027). The region by conditions interactions are reported in Table 4.4.

Table 4.4: Region x Condition	n analysis for	r speech p	production	tasks
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Regi	ons	Conditions	Statist	ics
TPJ vs	atSTS	Auditory non-verbal >	F(1,58)=11.533	p<0.001
	pSTS	verbal (O&H > W&P)	F(1,58)=19.248	p<0.001
pSTS vs	TPJ	Auditory non-semantic >	F(1,58)=16.907	p<0.001
	atSTS	semantic (P&H > W&O)	F(1,58)=4.710	p=0.017
atSTS vs	TPJ	Visual verbal >	F(1,58)=4.021	p=0.025
	pSTS	non-verbal (W&P > O&C)	F(1,58)=3.885	p=0.027

TPJ = temporo-parietal junction, pSTS = posterior superior temporal sulcus, atSTS = W = words, P = pseudowords, O = objects, C = colours.

#### 4.4.3. fMRI RESULTS

The results of the SPM statistical comparisons between conditions are provided in Table 4.5, and the extent of the effects within the anatomical regions of interest is illustrated in the lower section of Figure 4.3. The activation plots depicted in Figure 4.3 show that the pattern of responses in left TPJ, left pSTS and left atSTS is consistent across both groups of participants, despite differences in experimental paradigms.

**Table 4.5:** Validating Experiment 1 effects in an independent group of 59 participants

Region	L atSTS	L TPJ	L pSTS
Experiment 1 conjunction	-57, -42, 9	-54, -42, 21	-57, -27, 0
Experiment 2 F-map	-57, -43, 8	-54, -43, 20	-57, -28, -1
Visual verbal > non-verbal	4.96	3.26	2.56
Auditory non-verbal > verbal	NS	3.98	NS
Auditory non-semantic > semantic	NS	NS	3.03



Figure 4.3: Condition-specific responses in three left posterior superior temporal regions

Activation is shown on the mean of the structural MRI images acquired from the 24 participants from Experiment 1 (top left) and 59 participants from Experiment 2 (top right). For Experiment 2, activation was limited to the regions of interest from Experiment 1. The condition-specific responses for the speech production tasks from Experiment 1 (left) and Experiment 2 (right). The plots show the relative activation per condition, with standard error of the mean for each condition. The coloured bars show the activation conditions used to test for the effect, the grey bars show the baselines and the hashed bars were not included in the statistical contrasts. Green is activation for auditory non-verbal > verbal stimuli; Red is activation for auditory non-semantic > semantic stimuli. Yellow is activation for visual verbal > non-verbal stimuli (yellow). The significance threshold was set at p<0.05 uncorrected for Experiment 2 and p<0.001 uncorrected for Experiment 1. The z-scores and p values of activation within 1mm of the co-ordinates reported for Experiment 1 is shown in Table 4.5. W = words; P = pseudowords; O = objects; H = humming; C = coloured non-objects.

### 4.5. DISCUSSION

The aim of this experiment was to test whether the three regions of interest TPJ, pSTS and atSTS dissociated in Experiment 1 showed the same response properties in an independent group of 59 participants. The region by condition interactions confirmed that: (1) the left TPJ-ROI was more activated by nonverbal relative to verbal auditory conditions in comparison to left atSTS and left pSTS, (2) the left pSTS-ROI was more activated by non-semantic relative to semantic auditory conditions in comparison to left TPJ and left atSTS; and (3) the left atSTS-ROI was more activated by verbal relative to nonverbal visual conditions than left TPJ and left pSTS. Successful validation of results from Experiment 1 provided important evidence for reproducibility of our findings. This is reassuring considering the large number of possible sources of variance in neuroimaging studies, which will be discussed in relation to the current work.

As the current paradigm did not include the 1-back matching tasks, a direct comparison of the effect sizes was not possible. The plots of condition-specific responses illustrated in Figure 4.3 show that the three effects of interest correspond very well to those observed in Experiment 1, despite several differences between the experimental designs and multiple sources of variance (Table 4.1). In neuroimaging studies, variance can be considered at three different levels: (1) measurement and data acquisition, (2) experimental design, (3) participant sample (Kellmeyer, 2017).While it is clear that not all factors can be controlled for, certain steps can be taken to maximise study reproducibility. In the remaining part of this section, the steps that might have contributed to the successful replication will be considered.

First, a precise description of methodological details and results in Experiment 1 provided sufficient information to conduct a validation study. Second, high reliability of the presented fMRI data was ensured by careful evaluation and quality assessment of each processing step as recommended

by Poldrack and colleagues (Poldrack et al., 2008). This was achieved through a combination of visual inspection of results, review of movement parameters for each subject and detection of outliers. Variance at the data analysis level was minimised by utilising the same statistical software package (SPM) to preprocess and analyse data in both experiments. SPM implements the General Linear Model (GLM) to make statistical inferences about the effects of interest. The GLM framework is an elegant method for analysing data from simple fMRI experiments as well as more complex multitask designs due to its flexibility and the inherent ability to test for a number of different effects of interest (Friston et al., 1994). The conceptual simplicity of GLM and its implementation in the SPM package made it one of the most popular approaches to analysing functional neuroimaging data (Poline & Brett, 2012). A recent survey of researchers involved in collecting, analysing, and interpreting clinical language fMRI data at 63 epilepsy centres found that SPM was the most frequently used software for data analysis across all institutions (Benjamin et al., 2018). It does not however mean that GLM analyses are suitable for all types of data. As GLM is a parametric approach, it relies on the assumption of normality of data. In a non-parametric setting, other approaches might be considered, such as permutation tests (Winkler et al., 2014).

#### 4.5.1.CONCLUSION

This study demonstrated that, despite modifications to the experimental stimuli and methods, the unique response properties of three regions of interest from Experiment 1 – TPJ, atSTS and pSTS can be dissociated in a larger, non-overlapping group of 59 participants. This successful validation provides evidence that the functional dissociation within the posterior superior temporal lobe is more likely to reflect true effects rather than false positives. In addition, the current chapter highlighted the importance of a number of factors that need to be considered in both scientific research and clinical practice to ensure that the best practice guidelines for reporting fMRI studies, proposed by the Committee on Best Practice in Data Analysis and Sharing (COBIDAS) are followed (Nichols et al., 2017).
# 5. A FUNCTIONAL DISSOCIATION OF THE LEFT FRONTAL REGIONS THAT CONTRIBUTE TO SPEECH PROCESSING

# 5.1. SUMMARY

Controversy surrounds the interpretation of higher activation for pseudoword compared to word reading in the left precentral gyrus and pars opercularis. Specifically, does activation in these regions reflect: (1) the demands on sublexical assembly of articulatory codes, or (2) retrieval effort because the combinations of articulatory codes are unfamiliar?

Using fMRI, in 84 neurologically intact participants, the current study addressed this issue by comparing reading and repetition of words (W) and pseudowords (P) to naming objects (O) from pictures or sounds. As objects do not provide sublexical articulatory cues, the hypothesis was that retrieval effort will be greater for object naming than word repetition/reading (which benefits from both lexical and sublexical cues); while the demands on sublexical assembly will be higher for pseudoword production than object naming.

The results revealed that activation was: (i) highest for pseudoword reading [P>O&W in the visual domain] in the ventral precentral gyrus bordering the precentral sulcus (vPCg/vPCs), consistent with the sublexical assembly of articulatory codes; but (ii) as high for object naming as pseudoword production [O&P>W] in dorsal PCg (dPCg) and the left inferior frontal junction (IFJ), consistent with retrieval demands and cognitive control.

In addition, the response properties of vPCg/vPCs, dPCg and IFJ were dissociated from other left frontal lobe regions that are activated during single word speech production. In both auditory and visual domains: a central part of vPCg (head and face area) was activated by [P&W>O]; vPCg bordering the

central sulcus (tongue area) was activated by [W>O&P]; the pars orbitalis and inferior frontal sulcus were activated by [O>W&P]; and the left pars triangularis was equivalently activated by [W&P&O] relative to baseline conditions. The findings from this chapter help to resolve a previous discrepancy in the literature, dissociate four functionally distinct parts of the precentral gyrus, and refine our knowledge of the functional anatomy of speech production in the left frontal lobe.

# 5.2. INTRODUCTION

The left frontal lobe plays a well-researched role in speech production (Basilakos et al., 2018; Flinker et al., 2015; Long et al., 2016; Mugler et al., 2018). However, there is controversy as to the specific roles that distinct left frontal regions play in the generation of a speech plan. For example, as detailed below, some studies have associated the assembly of sublexical articulatory codes (e.g. phonemes and syllables) with activation in the left dorsal precentral gyrus whereas others have claimed that sublexical assembly is supported by a more ventral region of the precentral gyrus (see Table 5.1). Here, the challenges of assigning specific functions to discrete regions are considered, along with a plan of how to tackle this problem by using a multifactorial design that allows the demands on articulatory planning to be dissociated from more general, non-linguistic processes such as working memory, attention and cognitive control.

From an extensive literature review (see Table 5.1 for details), it can be noted that the majority of the functional neuroimaging studies investigating neural processing related to sublexical assembly compared activation for reading unfamiliar "pseudowords" to reading familiar words. Pseudowords (e.g. pholat) can only be read successfully by applying sublexical spelling to sound associations (e.g. ph+o+l+a+t or ph+ol+at or pho+lat). In contrast, reading familiar words (e.g. photos) is not dependent on sublexical assembly because it is facilitated by lexical (i.e. whole-word) knowledge. Thus, although reading words and pseudowords both involve the conversion of orthographic input into articulatory codes, the demands on integrating sublexical articulatory codes are higher when reading pseudowords.

A critical limitation of this approach is that enhanced activation for reading pseudowords compared to familiar words may not necessarily reflect increased demands on sublexical assembly. Instead, activation may reflect slower, more demanding speech production when the stimulus is unfamiliar. Indeed, the results detailed in Table 5.1 illustrate that an area in the left ventral precentral gyrus/pars opercularis, where activation is higher for pseudoword than word reading, also shows increased activation when people are reading aloud familiar words with "irregular" spelling-to-sound correspondences that are "inconsistent" with other words in the same language (e.g. yacht which is pronounced "yot" not "yatched") compared to "regular" spelling-to-sound correspondences that are "consistent" with most other words in the same language (e.g. mint, hint, tint, flint, stint, print, splint). A plausible explanation for the contrasting activation pattern for pseudowords and irregularly spelled words more than regularly spelled words is that it might reflect the demands on executive control, which are higher for pseudowords and irregularly spelled words than regularly spelled words (Fiez et al., 1999). In both cases (pseudowords and irregularly spelled words), there is a conflict between lexical and sublexical processing – and the reader therefore has to attend to one and inhibit the other. For example, when reading the word "yacht", the sublexical spelling-to-sound association ("yatched") is inconsistent with the lexical spelling-to-sound association ("yot"). The output from sublexical assembly ("yatched") therefore needs to be inhibited. Conversely, when reading the pseudoword "chiden", the reader must inhibit the production of real words that look alike (e.g. children and chicken).

Several studies have attempted to dissociate processing related to sublexical assembly and generic processing demands during speech production, but the conclusions have been inconsistent. For example, Fiez et al. (1999) and Mechelli et al. (2005) found that, compared to regular words, reading pseudowords and irregularly spelled words increased activation in the vicinity of the pars opercularis (Table 5.1), consistent with generic demands on mapping orthography-to-phonology, as opposed to sublexical assembly. In contrast, Mei et al. (2014) and Twomey et al. (2015) showed that activation at the same site (in standard space) is involved in sublexical assembly even when response times (reflective of general processing demands) are controlled. The role of the left dorsal precentral gyrus is also unclear. While Mechelli et al. (2005) and Twomey et al. (2015) associated it with sublexical processing; Binder et al. (2005) reported increased activation in this region for irregular than regular word reading, which is more consistent with generic demands. Further investigation is therefore required to understand these inconsistent conclusions.

The current study design provides an opportunity to consider how areas that were more activated for pseudoword than word production responded during object naming. Considering their response to object naming provides three advantages. First, object naming relies on lexical retrieval of articulatory codes and can be compared to reading and repeating the same object names, thereby controlling for speech output. Second, it is slower and more attention demanding than reading (Glaser & Glaser, 1989), and can therefore be used to segregate activation related to: (i) generic processing demands (object naming and pseudoword reading > word reading), (ii) sublexical assembly (pseudoword reading > object naming); (iii) lexical retrieval (object naming > pseudoword reading); (iv) processing that is enhanced by the combination of potentially conflicting lexical and sublexical codes (words > pseudowords and object naming) and (v) phonological-to-articulatory recoding (words and pseudowords > object naming). Third, pictures or sounds of objects do not provide any sublexical clues as to how the name is pronounced. This contrasts to irregular word reading, where high activation may reflect automatic but unsuccessful attempts at sublexical assembly. By including repetition of heard words and pseudowords, and naming objects from their sounds (i.e. corresponding conditions in the auditory and visual modalities), enabled me to

dissociate articulatory processing that does or does not depend on stimulus modality. For example, the demands on the assembly and production of articulatory plans are assumed to be higher for reading written words/pseudowords compared to repeating spoken words/pseudowords because the sounds that need to be produced are provided by the stimuli during repetition but need to be abstracted from the stimulus during reading and object naming.

In summary, the literature review (Table 5.1) highlights a lack of clarity in how activation in and around the dorsal versus ventral left precentral gyrus contributes to speech production. Using a multi-factorial design, this experiment investigated which parts of the left precentral gyrus were most consistent with: (1) the demands on sublexical assembly of articulatory codes (assumed to be higher for pseudoword reading than object naming) or (2) retrieval effort (assumed to be higher for object naming and pseudoword production than word production). Although the research questions concern regions in the left frontal lobe, whole brain activation was also examined to delineate the neural networks in which different left frontal regions participate.

Table 5.1: Left precentral	gyrus	and	pars	opercularis	activation	associated
with sublexical processing.						

Task	Activation Baseline		First Author (date)	MNI Coordinates
			Herbster et al. (1997)	-44, 4, 16
			Mechelli et al. (2005)	-54, 8, 18
		Regular words	Correiros et al. (2007)	-46, 8, 28
		(consistent	Carreiras et al. (2007)	-56, 0, 34
		mappings)	Mei et al. (2014)	-52, 0, 40
	Dooudourdo	11 0 /	Binder et al. (2005)	-43, 2, 27
	FSeudowords		Fiez et al. (1999)	
Reading		Words	Mechelli et al. (2003)	-48, 8, 22
aloud		vvorus	Brunswick et al. (1999)	-48, 6, 26
		Irregular words (inconsistent	Binder et al. (2005)	-51, 2, 13 -48, 0, 28
		spelling-sound mappings)	Mechelli et al. (2005)	-56, 0, 40
			Herbster et al. (1997)	-46, 6, 16
	(inconsistent spelling-sound	(consistent	Mechelli et al. (2005)	-52, 2, 18
		spelling-sound		-50, 7, 21
	mappings)	mappings)	Binder et al. (2005)	-51, 0, 36
				-44, -4, 43
			Poldrack et al. (1999)	-47, 0, 13
	Syllables		Price et al. (1997)	-52, -2, 24
		Semantic	Devlin et al. (2003)	-30, 0, 24 -42, 0, 28
Word			Yen et al. (2019)	-52, 4, 30
matching			Mummery et al. (1998)	-52, -8, 38
	Rhyming		Roskies et al. (2001)	-49, 3, 16 -49, 1, 26
		Semantic	Yen et al. (2019)	-50, 3, 30
Attention to:	Phonology	Semantics	McDermott et al. (2003)	-55, 3, 15
	Pseudowords	Words	Fiebach et al. (2002)*	-49, 12, 12
Lexical decision	Words Sequential	Words Simultaneous	Twomey et al. (2015)	-57, 17, 7 -51, 8, 22 -54, 4, 43
	Pseudowords	Words		-48, 6, 18
Perception decision	Words (after assembled training)	Words (after addressed training)	Mei et al. (2014)	-56, 6, 24

\*Coordinates mapped from Talairach to MNI space using BioImage Suite (Lacadie et al., 2008). Studies were first grouped by task: reading aloud different types of stimuli or different matching tasks on the same (word) stimuli: Rhyming (e.g. do "whale" and "snail" rhyme?) and syllable judgements (e.g. does "snail" have 1 or 2 syllables?) focus attention on sublexical sounds compared to semantic/synonym tasks (e.g. do "kill" and "slay" have similar meanings?). ^ This effect was not observed in Fiez et al. (1999) when pseudowords were compared to low frequency consistent words (or low or high frequency inconsistent words).

# 5.3. METHODS

The data used in this chapter have previously been reported in Oberhuber et al. (2016) where the goal was to dissociate the function of different parts of the left supramarginal gyrus. The focus of the current experiment is to tease apart how distinct left frontal lobe regions contribute to speech production.

# 5.3.1. PARTICIPANTS

Data from a combined total of 84 participants was included in this study (Experiment 1, n=25; Experiment 2, n= 59) and re-analysed for Experiment 3. All subjects were neurologically healthy, right-handed, English speakers with normal or corrected-to-normal vision. Participant and experimental details for each group of subjects are reported in Experiment 2.

# 5.3.2. EXPERIMENTAL DESIGN

To restate, two non-overlapping participant groups (n=25 and 59) performed the same 8 tasks of interest embedded within one of two different experimental paradigms (described in Chapters 3 and 4). The 8 conditions of interest for this study were: (1) reading words, (2) reading pseudowords, (3) naming objects from pictures, (4) naming colours, (5) repeating heard words, (6) repeating heard pseudowords, (7) naming objects from sounds and (8) naming gender of humming voices. These 8 tasks comprised a 2x2x2 factorial design (Table 5.2) that manipulated 3 factors: Factor I was stimulus modality (auditory versus visual); Factor II was verbal versus nonverbal stimuli (words and pseudowords versus objects and baseline stimuli); Factor III was the presence or absence of semantic content (familiar words and object names versus unfamiliar pseudowords and baseline stimuli). In addition to the 8 speech production conditions examined in the current analysis, Group 1 completed 1-back matching tasks on the same 8 stimulus sets; while Group 2 completed 5 tasks that involved sentence production, verb production, noun

production and semantic decisions on pictures of objects or their heard object names. These additional tasks were presented in separate scanning sessions and were not examined in the current analysis.

	Factor I			Factor II	Factor III
	Input	Stimulus		Verbal vs.	Semantic vs.
	mput		Nonverbal	Nonsemantic	
		Written object names	W	$\checkmark$	$\checkmark$
	Viewel	Written pseudowords	Ρ	$\checkmark$	×
	VISUAI	Pictures of objects	0	×	$\checkmark$
		Coloured patterns	В	×	×
		Heard object names	W	$\checkmark$	$\checkmark$
	Auditory	Heard pseudowords	Р	$\checkmark$	×
		Sounds of objects	0	×	$\checkmark$
		Humming (male or female voice)	В	×	×

#### Table 5.2: Experimental design

**Factor IV** = Task: Speech production or 1-back matching. Key: W= words, P = pseudowords, O = objects, B = baselines.

Although the presentation parameters in the two paradigms were not identical (see Experiment 2), the focus of this study is on results that were observed across both datasets. Direct comparison of the same effects in the 24 participants from Experiment 1 and 59 participants from Experiment 2, did not reveal any significant differences in activation.

Data preprocessing and first level analysis steps are explained in the general methods section and Chapters 3-4, respectively.

#### 5.3.3. SECOND LEVEL STATISTICAL ANALYSIS

The first level analysis for each participant yielded 8 separate contrasts (one per condition > fixation), i.e. words (W), pseudowords (P), objects (O) and baseline (B) in the visual and auditory modality (see Table 5.2). The second level analysis modelled 16 conditions; 8 for each group of participants. Contrasts were computed across group and effects that were common across groups are demonstrated in the figures illustrating the results. The two effects of interest (A and B below) will be described first, followed by a report of how left precentral gyrus activation changes for four other effects (C-G) that might provide insight into the results of prior and future studies.

Contrast A [P>W&O] identified activation that was higher for pseudoword reading/repetition compared to word reading/repetition and object naming (i.e. consistent with the demands on sublexical assembly). Contrast B [O&P>W] identified activation that was higher for object naming and reading/repetition compared to word reading/repetition pseudoword (consistent with generic demands on articulatory planning). Contrast C [W>P&O] identified activation that was higher for word reading/repetition compared to pseudoword reading/repetition and object naming. Contrast D [O>W&P] identified activation that was higher for object naming compared to word reading/repetition and pseudoword reading/repetition. Contrast E [W&P>O&B] was the main effect of verbal compared to non-verbal stimuli. Contrast F [W&O>P&B] was the main effect of semantic compared to nonsemantic stimuli. Contrast G [W&P&O>B] searched for activation that was higher for words, pseudowords and objects compared to the baselines (colour and gender naming).

Each of these six contrasts was repeated three times: once across modality, once in the visual modality and once in the auditory modality. The results are reported at p<0.05 after family wise error correction in height. To ensure that there was no overlap in the areas identified, the inclusive and exclusive masking options in SPM were used (all thresholded at p<0.05 uncorrected). Table 5.3A summarises all the main contrasts (A-G) and the inclusive and exclusive masks used for each effect. The type of processing that was expected to be probed is indicated in Table 5.3B and rationalised in the Discussion.

#### Table 5.3: Task analysis

		loolate ent		1 11110	1000						
		Main Contrast	l P>W	nclus P>O	s <b>ive (</b> v W>P	✓) and W>O	<b>d excl</b> O>W	usive O>P	<b>; (×)</b> ∣ P>B	<b>mask</b> O>B	<b>∖s</b> W>B
А	Sublexical assembly	P>W&O	<b>√</b> √	$\checkmark\checkmark$					√√		
В	Retrieval demands	P&O>W	$\checkmark\checkmark$				$\checkmark\checkmark$		$\checkmark\checkmark$	$\checkmark\checkmark$	
С	Highest for words	W>P&O			$\checkmark\checkmark$	$\checkmark\checkmark$					$\checkmark\checkmark$
D	Highest for naming	O>W&P	××				$\checkmark\checkmark$	$\checkmark\checkmark$		$\checkmark\checkmark$	
Е	Verbal > nonverbal	W&P>O&B	××	$\checkmark\checkmark$	××	$\checkmark\checkmark$			$\checkmark\checkmark$		$\checkmark\checkmark$
F	Semantic > nonsemantic	W&O>P&B			√√	××	××	√√		√√	<b>√√</b>
G	All > baselines	W&P&O>B	××	xx	xx	xx	××	××	$\checkmark\checkmark$	$\checkmark\checkmark$	$\checkmark\checkmark$

A. Contrasts used to isolate effects of interest.

#### **B.** Interpretation.

	Effect of interest	Main Contrast	Type of processing that might be probed
A	Sublexical assembly	P>W&O	Sublexical assembly of speech sounds (g-o-l-m)
в	Retrieval demands	P&O>W	Highest demands on retrieving articulatory plans
С	Highest for words	W>P&O	Lowest demands on retrieving articulatory plans
D	Highest for naming	O>W&P	Retrieving whole word articulatory plans
Е	Verbal > nonverbal	W&P>O&B	Speech representations to articulatory plans
F	Semantic > nonsemantic	W&O>P&B	Stimulus recognition & semantic associations
G	All > baselines	W&P&O>B	Higher demands on response selection

Key: W = words, P = pseudowords, O = objects, B = baseline.

✓✓ Inclusive masks (visual &/or auditory), **××** Exclusive masks (visual &/or auditory)

# 5.4. RESULTS

Details of the in-scanner behavioural performance for the 24 participants and 59 participants are documented and illustrated in Experiment 2 and in (Oberhuber et al., 2016).

#### 5.4.1. SUBLEXICAL ASSEMBLY (P>W&O)

Activation that was higher for pseudowords than both words and objects was observed for visual stimuli only, in the left ventral precentral gyrus (head and face area), bordering the ventral precentral sulcus (Table 5.4; red in Figure 5.1 and Figure 5.2). There was no corresponding effect in the auditory modality, which is not surprising given that the spoken response for pseudoword repetition, but not pseudoword reading, can be guided by the stimulus. The difference between the visual and auditory modalities was confirmed by a modality by condition (P>W&O) interaction that was significant at p<0.001 uncorrected: z-scores = 4.1 at [-57, +9, +18]; 4.1 at [-54, +6, +27]; 4.2 at [-48, 0, +33]. The same pattern of effects was also observed in the left anterior putamen (as reported in Oberhuber et al., 2013) and the left postcentral sulcus (Figure 5.1).

### 5.4.2. GENERIC DEMANDS ON ARTICULATORY PLANNING (P&O>W)

Activation was higher for pseudowords and objects than words deep in the inferior frontal junction, extending laterally into the superior precentral sulcus and inferiorly into pars opercularis (Table 5.4; blue in Figure 5.1 and Figure 5.2), with no significant difference between the visual or auditory modalities in any of these areas (p>0.05 uncorrected). The same pattern of effects (P&O>W) was also observed in the bilateral anterior insula/frontal operculum and pre-SMA.

# 5.4.3. HIGHEST ACTIVATION FOR WORD READING AND REPETITION (W>P&O)

Activation was higher for words than both pseudowords and objects on the posterior surface of vPCg, bordering the central sulcus (Table 5.4; green in Figure 5.1 and Figure 5.2), with no significant difference between the visual or auditory modalities (p>0.05 uncorrected). The same pattern of effects (W>P&O) was observed in the left posterior putamen (as reported in Oberhuber et al., 2013), left middle temporal gyrus, left posterior SMG/angular gyrus, SMA and cingulate motor area.

#### 5.4.4. HIGHEST ACTIVATION FOR OBJECT NAMING (O>P&W)

Activation was higher for objects than pseudowords and words in the left inferior frontal sulcus and left pars orbitalis (Table 5.4; magenta in in Figure 5.1 and Figure 5.2), with no significant difference between the visual or auditory modalities (p>0.05 uncorrected). The same pattern of effects was also observed in the left middle temporal sulcus (pink in Figure 5.2), left fusiform, bilateral visual cortices and bilateral cerebellum.

### 5.4.5. THE MAIN EFFECT OF VERBAL > NONVERBAL STIMULI (P&W>O&B)

Activation was higher for pseudowords and words than objects and baselines in a third part of the left ventral precentral gyrus (Table 5.4; yellow in Figure 5.1 and Figure 5.2), with no significant difference between the visual or auditory modalities (p>0.05 uncorrected). The same pattern of effects was also observed in the left putamen and the left postcentral gyrus.

### 5.4.6. THE MAIN EFFECT OF SEMANTIC > NON-SEMANTIC STIMULI (O&W>P&B)

The only voxels in the left frontal lobe that were sensitive to semantic processing common to words and objects were located close to the left dorsal motor cortex (z-score = 5.4 at [-33, 9, 54]). Other more extensive effects of semantic processing were observed in bilateral angular gyri and the posterior temporal lobe.

## 5.4.7. COMMON ACTIVATION COMPARED TO BASELINE (W&P&O>B)

All conditions (W&P&O) showed common activation compared to the baseline conditions in left pars triangularis (Table 5.4, cyan in Figure 5.1 and Figure 5.2), with no significant difference between the visual or auditory modalities (p>0.05 uncorrected). The same pattern of effects (W&P&O>B) was also observed in the left ventral anterior supramarginal gyrus (as reported in Oberhuber et al., 2016) and the supplementary motor cortex.

Effect of interest	Main contrast	x	у	z	Vx	Zsc	Location
A Sublexical assembly	P>O&W	-57 -54 -51	9 6 0	18 27 33	30	5.7 5.9 4 8	Ventral precentral gyrus/sulcus
B Retrieval demands	P&O>W	-39 -48	6 3	27 48	88	>8 5.4	Inferior frontal junction Dorsal precentral gyrus
C Highest for words	W>P&O	-54	-9	30	89	5.3	Ventral precentral gyrus/ Central sulcus
D. Highost for paming		-39 -45	15 24	24 18	28	7.4 5.8	Inferior frontal sulcus
	U-VVQF	-30 -30	33 33	-9 0	34	7.6 4.9	Pars orbitalis
E Verbal > nonverbal	W&P>O&B	-57 -54	3 -3	27 33	24	6.2 6.2	Ventral precentral gyrus (head and face area)
F Semantic > nonsemantic	W&O>P&B		ns		ns	ns	ns
G All > baselines	W&P&O>B	-51	33	9	50	7.5	Pars triangularis

Table 5.4: Left frontal regions	associated with different contrasts
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W = words, P = pseudowords, O = objects, Int. = interaction of semantics and verbal input, Vx = number of contiguous voxels at p<0.001 uncorrected, Zsc = Z-score, ns = not significant at p<0.001 uncorrected. All effects were significant after voxel-level correction for multiple comparisons across the whole brain.

**Figure 5.1:** Functional dissociations in, and around, the left ventral precentral gyrus



Axial slices (left z= +24, right z= +27) showing the relative location of each effect on a standard structural template in MNI space. vPCg/vPCs = ventral precentral gyrus/sulcus; IFJ/IFS = Inferior frontal junction/sulcus; CS = Central sulcus. Regions associated with sublexical assembly (P>O&W) are shown in red; lexical retrieval (O>W&P) in magenta; lexical and sublexical (W>P&O) processing in green; lexical or sublexical (P&O>W) in blue; verbal > nonverbal (W&P>O&B) in yellow.



Figure 5.2: Anatomical location of effects of interest and their condition dependent responses

Relative location of each effect shown on a standard structural template in MNI space. The estimated effect size is illustrated for Words (W), Pseudowords (P), Object naming (O) and Baseline conditions (B) in the visual (columns 1-4 and 9-12) and auditory modalities (columns 5-8 and 13-16). Columns 1-8 are from Experiment 1. Columns 9-16 are from Experiment 2. The coloured bars highlight the activation conditions using the same colour scheme as the images above. The names of the anatomical regions associated with the co-ordinates in the plots are in Table 5.4. The error bars are standard error. Although each effect of interest was highly significant and mutually exclusive of all other effects, these plots show that there is high selectivity without specificity (i.e. all regions were activated across conditions).

# 5.5. DISCUSSION

Prior studies have reported that increased demands on sublexical assembly of speech sounds increases activation in either dorsal (Mechelli et al., 2005) or ventral (Mei et al., 2014; Twomey et al., 2015) parts of the left precentral gyrus (Table 5.1). However, possible confounds in the experimental designs of previous studies make it difficult to determine the type of processing that engages each region. To further dissociate the functional contribution of distinct left frontal regions to speech production, activation for word and pseudoword production was compared to that observed during object naming, which exerts high demands on the retrieval of whole-word articulatory plans.

The results indicate that the response in the left ventral precentral gyrus (head and face area), bordering the ventral precentral sulcus (vPCg/vPCs), is most consistent with sublexical assembly of articulatory codes, because activation was higher for pseudoword reading than object naming and word reading. In contrast, the response in the left dorsal precentral gyrus (dPCg) extending into the left inferior frontal junction (IFJ) was found to be most consistent with retrieval demands, because activation was higher for object naming and pseudoword reading/repetition.

By utilising the multi-task approach, six other functionally distinct regions in the left frontal lobe that are differentially engaged during single-word speech production were dissociated. Below, the importance of each of the findings is discussed in the context of the results of previous studies, highlighting their relevance for refining our understanding of the functional anatomy of speech production. A summary of the findings, and interpretation related to prior literature can be found in Table 5.5.

Region	Prior hypotheses	Effect	Most parsimonious explanation
vPCg/vPCs	<ul> <li>(a) Sublexical assembly of articulatory plans</li> <li>(b) Retrieval effort</li> <li>(c) Conflict resolution</li> </ul>	P>O&W	(a) Sublexical assembly of articulatory plans
dPCg	<ul> <li>(a) Sublexical assembly of articulatory plans</li> <li>(b) Retrieval effort/ executive functions</li> <li>(c) Conflict resolution</li> </ul>	P&O>W	(b) Retrieval effort/ executive functions
vPCg/CS	Motor control of tongue movements	W>P&O&B	<i>"Memory guided"</i> motor control of tongue movements
vPCg	<ul> <li>(a) Sublexical assembly of articulatory plans</li> <li>(b) Retrieval effort/ executive functions</li> </ul>	W&P>O&B	Neither hypothesis confirmed Proposed hypothesis: "phonological-to-articulatory recoding"
IFJ	Cognitive control/ attention working memory	P&O>W	Consistent with prior hypothesis
IFS	<ul><li>(a) Word retrieval</li><li>(b) Integration of information prior to response selection</li></ul>	O>W&P	(b) Integration of information prior to response selection
pOrb	Semantic retrieval	O>W&P	Semantic-to-articulatory recoding
pTri	<ul><li>(a) Semantics/ phonology</li><li>(b) Post retrieval control</li></ul>	W&P&O>B	(c) Post retrieval control of response selection

dPCg/vPCg/vPCs: Dorsal/ventral precentral gyrus/sulcus. CS: Central sulcus IFJ/IFS: Inferior frontal junction/sulcus. pOrb/pTri: Pars orbitalis/pars triangularis.

#### 5.5.1. SUBLEXICAL ASSEMBLY (P>W&O) IN THE VISUAL MODALITY

Activation associated with sublexical processing included the left ventral precentral gyrus, bordering the ventral precentral sulcus. The MNI coordinates of peak activation in this area ([-57, 9, 18] and [-54, 6, 27]) corresponds to those associated with sublexical assembly in Mei et al. (2014) and Twomey et al. (2015) using completely different experimental designs. In Mei et al. (2014), native English speakers were trained to read words presented in unfamiliar Korean Hangul characters by either recognising the words as a whole or by relying on the sublexical spelling to sound relationships. When reading the same words in the scanner, those using a sublexical assembly strategy increased activation at MNI co-ordinates [-56, 6,

24] compared to those who read the words lexically. In Twomey et al. (2015), a very similar area (MNI co-ordinates [-51, 8, 22]) was more activated when words emerged on the screen sequentially compared to when they emerged as a whole.

Other studies (Binder et al., 2005; Mechelli et al., 2005) did not associate the vPCg with sublexical assembly because activation increased for words with irregular compared to regular spellings (see Table 5.1) and irregular spellings cannot be read successfully using sublexical assembly. An alternative interpretation of the enhanced vPCg/vPCs response during irregular reading is that skilled readers will automatically engage sublexical assembly when presented with familiar orthography. Moreover, unsuccessful sublexical processing may persist for irregular word reading until the correct pronunciation is retrieved via lexico-semantics.

The vPCg activation that was associated with sublexical processing was on the anterior surface of vPCg, bordering the ventral precentral sulcus. Here, cortical activity has been related to the motor planning of vocal tract actions required to produce speech sounds (articulatory gestures) at discrete times (Mugler et al., 2018). In contrast, the same study noted that the higher-level construction of phonemes was associated with cortical activity in the inferior frontal cortex (pOp) rather than vPCg. In this context, enhanced activation for pseudoword reading compared to word reading and object naming appears to reflect the encoding of novel sequences of articulatory gestures.

#### 5.5.2. GENERIC DEMANDS ON ARTICULATORY PLANNING (P&O>W)

The area associated with generic retrieval demands was located deep in the frontal lobe, with the peak falling in the left inferior frontal junction (located at the junction of the inferior precentral sulcus and inferior frontal sulcus) and a secondary peak in the left dorsal precentral gyrus (dPCg). The inferior frontal junction (IFJ) is part of a network associated with attention, cognitive control and working memory (Roth et al., 2006; Cole and Schneider, 2007; Muhle-Karbe et al., 2016; Tamber-Rosenau et al., 2018; Zhang et al., 2018) that also includes the dorsolateral prefrontal cortex, anterior insula, and pre-SMA (Sundermann & Pfleiderer, 2012) - all regions that were co-activated with the IFJ in the current study (blue areas in Figure 5.1 and Figure 5.2).

The dPCg has previously been associated with sublexical assembly because it was more activated for reading pseudowords compared to irregularly and regularly spelled words (Mechelli et al., 2005); and for reading text delivered sequentially rather than simultaneously (Twomey et al., 2015). In the current study, the finding that activation was higher for object naming than word reading is not consistent with this claim. Instead, the results are more consistent with prior studies that demonstrated a role for the left dPCg in retrieving fine-grained motor plans and anticipating rhythms (Chen et al., 2008) during speech articulation and finger movements (Meister et al., 2009); particularly when people watch/listen to material for which they have been highly trained to generate very specific action responses, including dance movements (Calvo-Merino et al., 2005), piano music (Lahav et al., 2007) and violin music (Dick et al., 2011). According to this hypothesis, left dorsal precentral activation should be lower when retrieval demands are lower (i.e. for reading and repeating words), as observed in the current study.

# 5.5.3. HIGHEST ACTIVATION FOR WORD READING AND REPETITION (W>P&O)

Relative to all other stimuli, words enhanced activation in a posterior part of vPCg, bordering the left central sulcus (vPCg/CS). This region, previously associated with tongue movements (Schubotz et al., 2010) was not predicted on the basis of previous work. Below, three possible explanations are presented, with the most plausible considered last. The first is that lexical and sublexical speech plans may conflict during word reading and repetition, particularly in a language like English where the correct lexical pronunciation is inconsistent with the sublexical components (e.g. when reading "bowl" we must inhibit the production of "owl"). However, no prior evidence was found to suggest that left vPCg/CS reflects conflict processing. For example, the conflict between lexical and sublexical codes is expected to be highest for reading words with inconsistent compared to consistent spelling-to-sound correspondences (Fiez et al., 1999) but no previous study has reported vPCg/CS activation for reading irregularly spelled words compared to either regularly spelled words or pseudowords (Binder et al., 2005; Herbster et al., 1997; Mechelli et al., 2005). To the contrary, vPCg/CS activation [at Talairach co-ordinates: -49, -13, 34] was reported to be higher for reading pseudowords and words with consistent (regular) spellings compared to words with inconsistent (irregular) spellings (Fiez et al., 1999).

The second explanation is that increased activation in vPCg/CS is required because of lower activation in vPCg/vPCs and the left inferior frontal sulcus. Future studies could investigate this by testing whether higher activation in these regions results in lower activation in the vPCg/CS. The third (not mutually exclusive) explanation is that activation in left vPCg/CS is enhanced during "memory guided movement". This stems from observing that the posterior putamen, where condition-dependent response mirrored those in left vPCg/CS, has previously been (i) associated with "memory guided movement" (Menon et al., 2000; Oberhuber et al., 2013; Tricomi et al., 2009), and (ii) shown to interact directly with the sensorimotor and supplementary motor cortices (Fernández-Seara et al., 2009; Hikosaka et al., 2002), both of which were also more activated for words than other conditions (Figure 5.1 and Figure 5.2).

#### 5.5.4. HIGHEST ACTIVATION FOR OBJECT NAMING (O>P&W)

In contrast, retrieving articulatory plans from semantic stimuli (i.e. semantic-to-articulatory recoding) enhanced activation in (i) the left pars orbitalis (pOrb), a region already associated with controlled semantic retrieval (Sabb et al., 2007), and (ii) the left inferior frontal sulcus, a region already associated with word retrieval (Arya et al., 2019; Price, 2012). The left inferior

frontal sulcus has also been associated with the integration of bottom-up and top-down multi-sensory information (semantic, nonsemantic and nonverbal) prior to response selection (Adam & Noppeney, 2010; Gau & Noppeney, 2016; Noppeney et al., 2010).

## 5.5.5. THE MAIN EFFECT OF VERBAL > NONVERBAL STIMULI (W&P>O&B)

In a central part of vPCg, activation was higher for verbal stimuli (words and pseudowords) than nonverbal stimuli (object, colour and gender naming) in both auditory and visual modalities (yellow in Figure 5.1 and Figure 5.2). As activation in this part of vPCg was not higher for pseudowords than words, it is not consistent with the expected demands on sublexical assembly of articulatory plans. Therefore, two alternative explanations are considered. The first is that the equivalent response to words and pseudowords might be a consequence of spatial smoothing with higher activation for (i) pseudowords than words on the anterior surface of vPCg and (ii) words than pseudowords on the posterior surface of vPCg cancelling each other out. This unlikely, however, because in the auditory domain there were no precentral regions that were more activated by pseudowords than words. A second possibility is that enhanced activation in the central part of vPCg for verbal more than nonverbal stimuli reflects the retrieval of articulatory codes from phonological processing (as opposed to the assembly of these codes). Although further studies are required to investigate this, the proposed hypothesis is that phonological-to-articulatory recoding may be evoked faster and sustained longer when processing verbal stimuli, compared to non-verbal stimuli because (i) we are highly trained to link verbal stimuli to their speech sounds and articulatory codes and (ii) non-verbal stimuli may rely more heavily on perceptual and semantic processing.

#### 5.5.6. COMMON ACTIVATION COMPARED TO BASELINE (W&O&P>B)

Activation in the left pars triangularis (pTri) did not differ for words, pseudoword and objects, but was higher for each of these stimuli compared

to the baselines. Although pTri has previously been associated with word retrieval and semantics (Liuzzi et al., 2017; Malins et al., 2016; Price, 2012; Tylén et al., 2009) and phonological processing (Andin et al., 2015; Partanen et al., 2019), a more parsimonious explanation is that these effects reflect post-retrieval control demands (Barredo et al., 2016; Glaser et al., 2013). In the current design, the demands on post-retrieval control were lowest in the baseline conditions because there were only two response options for gender naming, and eight for colour naming as opposed to 36-40 different responses during the words, pseudowords and object conditions.

# 5.5.7. CONCLUSIONS

The literature review (Table 5.1) highlighted inconsistency in the brain regions associated with the demands on sublexical assembly of articulatory plans. Some studies have proposed that the left dorsal precentral gyrus (dPCg) is involved in sublexical assembly, whereas others have claimed that sublexical assembly is supported by more ventral regions. Using a multi-factorial design that included object naming conditions as well as word and pseudoword reading and repetition, the demands on sublexical assembly were associated with activation in the left ventral precentral gyrus (vPCg), bordering the left ventral precentral sulcus (vPCs). In contrast, the response in dPCg was found to be more consistent with retrieval effort and demands on executive functioning.

The contrasting response properties of other left frontal lobe regions that contribute to speech production have also been described, and the interpretation has been compared with that of previous studies (Table 5.5). Of particular interest is the dissociation of two other parts of the ventral precentral gyrus: the most posterior region (bordering the central sulcus) was more activated by word reading and repetition than all other conditions; whereas a more central region was activated by verbal (words and pseudowords) compared to nonverbal (objects, patterns and humming) stimuli. This motivates future studies using ultra-high field 7T fMRI to further investigate the contribution of different vPCg regions to speech production.

Overall, the results from this study resolve a previous discrepancy in the literature, dissociate four functionally distinct parts of the left precentral gyrus, and refine our understanding of the functional anatomy of speech production.

# 6. A DATA-BASED APPROACH FOR SELECTING PRE-OPERATIVE LANGUAGE MAPPING TASKS

Pre- and intra-operative language mapping in neurosurgery patients frequently involves an object naming task. The choice of the optimal object naming paradigm remains challenging due to lack of normative data and standardisation in mapping practices.

The aim of this study was to identify an object naming paradigm that robustly and consistently activates classical language regions and may therefore improve the sensitivity of language mapping in brain tumour and epilepsy patients. Functional magnetic resonance imaging (fMRI) data from two independent groups of healthy controls (total = 79) were used to generate threshold-weighted voxel-based consistency maps. This novel approach allowed the inter-subject consistency of activation to be visualised and compared for four different object naming paradigms. The four tasks of interest included: naming single objects in the visual and auditory modality and naming two objects in a phrase or a sentence.

The results showed that the consistency of activation in language regions was greater for naming two objects per picture than one object per picture, even when controlling for the number of names produced in 5 seconds. The more reliable performance of the two object naming paradigm in delimiting language eloquent regions indicates that use of this paradigm may improve the sensitivity of pre- and intra-operative language mapping. More broadly, these findings suggest that the precision and sensitivity of presurgical planning for a whole range of different linguistic and non-linguistic functions may be improved by referring to databased models of inter-subject consistency and variability in typical and atypical brain responses.

### 6.1. INTRODUCTION

Awake craniotomy with intra-operative stimulation mapping is strongly advocated for patients with gliomas affecting eloquent brain regions (Hamer et al., 2012; Leon-Rojas et al., 2020). A growing body of evidence suggests that more extensive resection is associated with longer survival (lus et al., 2012; Jakola et al., 2012; Jakola et al., 2017; McGirt et al., 2009; Sanai et al., 2008; Sanai & Berger, 2008). Nevertheless, to preserve the patient's quality of life, the survival benefit conferred by more aggressive surgery needs to be balanced with the risk of post-operative deficits (referred to as the oncofunctional balance) (Duffau et al., 2009). This is particularly challenging in patients with tumours in or adjacent to cortical language hubs, where resection may lead to life-changing impairments in communication skills (Gabel et al., 2019; Jakola et al., 2011). To attempt to preserve the integrity of language regions, intra-operative mapping with the use of direct electrical stimulation is performed (Ilmberger et al., 2008; Rofes, Spena, et al., 2017; De Witte & Mariën, 2013). The capacity to detect and evaluate function during surgery critically depends on the selection of sensitive and lesion-site specific testing paradigms that, at present, lack standardisation (O'neill et al., 2020; Sefcikova et al., 2020; Young et al., 2021).

The purpose of this study is to demonstrate how functional consistency maps generated from large populations of neurotypical controls can be used to facilitate the selection of pre- and intra-operative language tasks that robustly and consistently activate core language areas. The challenges related to current language mapping practices will be discussed prior to illustrating how results from functional magnetic resonance imaging (fMRI) of neurotypical participants can be used to inform decision making.

#### 6.1.1. PRE-OPERATIVE PLANNING WITH FMRI

The complexity and wide distribution of language networks make it extremely challenging to predict how resection will affect language function. This is further complicated by inter-individual structural and functional variability, commonly observed in healthy individuals (Fedorenko & Blank, 2020) and exacerbated following tumour-induced reorganisation. Before surgery, language function is commonly investigated using fMRI (Castellano et al., 2017). This provides potentially valuable, patient-specific information about the location and function of cortical language regions that may be at risk of damage, thereby enabling more targeted surgical approaches and reducing the operative duration (Sanai et al., 2008). In 2017, the American Society of Functional Neuroradiology published a white paper proposing two sets of language paradigms that balance the clinical usefulness and ease of application (Black et al., 2017). The recommended fMRI tasks for pre-surgical language assessment in adult patients included: sentence completion, silent word generation, rhyming, object naming and/or passive story listening. The extent to which these guidelines have been adopted is currently unknown (Benjamin et al., 2018).

The reliability of fMRI has been examined in a meta-analysis of studies comparing fMRI with direct electrical stimulation for language mapping. The authors found that the sensitivity and specificity of fMRI for detecting language areas ranged from 59-100% and 0-97%, respectively (Giussani et al., 2010). It is also important to acknowledge the limitations of this technique. Detection of fMRI activation in a cortical area does not mean that the region is critical for a certain function and cannot be resected without post-operative functional deficits (Duffau, 2005; Silva et al., 2018). Furthermore, the reliability of the blood-oxygen-level-dependent (BOLD) signal may be compromised by disruptions to neurovascular coupling; or a weak paradigm that does not elicit robust activation at the individual subject level (Mahdavi et al., 2015; Pak et al., 2017). Results from fMRI analyses should therefore be perceived as a source of supplementary information and not a substitute for intra-operative stimulation mapping.

#### 6.1.2. INTRA-OPERATIVE STIMULATION MAPPING

Direct electrical stimulation (DES) is the gold standard used to map the function of eloquent cortical regions and subcortical white matter tracts in neurosurgery patients, thereby facilitating maximum safe resection (Hamer et al., 2012). For intra-operative language mapping, the patient must be awakened or remain awake throughout the surgery so that they can engage in linguistic tasks such as object naming, counting, verbal fluency and other (for review, see Young et al., 2021). A neuropsychologist or speech and language therapist monitors the patient's response to the task while the peritumoral tissue is stimulated to transiently disrupt its function (Klitsinikos et al., 2021). According to the standard protocol first established by Ojemann and colleagues, each brain region should be stimulated at least 3 times, (Hervey-Jumper et al., 2015; Ojemann et al., 1989; Sanai et al., 2008; Sanai & Berger, 2008a). A positive language site is identified when stimulation to the cortical region of interest results in an inability to successfully perform the task in 66% or more of the testing (Sanai & Berger, 2010).

Functional disturbances during electrical stimulation may indicate that the stimulated region was required for the task tested, but they may also reflect false positives. For example, a reduction in speed or accuracy may not be due to disturbance at the stimulus site; it could be a consequence of (a) disruption in distant task-related regions through the spread of electrical current along connecting axons (Mandonnet et al., 2010; Matsumoto et al., 2004), (b) patient fatigue, particularly during long testing sessions (Mandonnet et al., 2010), or (c) inadequate task difficulty (Bu et al., 2021). Conversely, there are several reasons why the absence of an effect of DES may be a false negative: (1) the task was not appropriate to test the function of the stimulated region because it does not activate the region in the normal population; (2) the stimulated region was essential for the task in the patient because of normal inter-subject variability or pathology-induced functional reorganisation; and (3) the stimulated region is required for the task but the stimulation intensity was insufficient to generate a response or the effect wasn't detected e.g. if the effect was on response times or hesitation rather than speech arrest (O'neill et al., 2020; Shimotake et al., 2015). The successful interpretation of intraoperative DES is therefore critically dependent on selecting tasks that: (i) are easy to perform, particularly for patients who struggle to maintain focus during awake surgery; and (ii) robustly and consistently activate the targeted region in neurotypical individuals within the short timespan that DES can be safely applied.

At present, no standardised protocol exists to reliably identify and test language regions in neurosurgery patients with many institutions assessing only one task (Ruis, 2018; Sefcikova et al., 2020). A survey of the European Low-Grade Glioma Network showed that object naming was the most frequently utilised task for mapping language during awake surgery (Rofes, Mandonnet, et al., 2017). However, choice of the object naming paradigms is highly variable across institutions ranging from in-house designed paradigms to use of one of a number of standardised tests for intra-operative language assessments, such as DO70/DO80, Picture Naming AAT, Boston Naming Test, Reitan Indiana Aphasia screening test, BDAE and the Snodgrass and Vanderwart collection, Laiacona–Capitani test (O'neill et al., 2020; Rofes et al., 2015; Ruis, 2018).

While stimulation mapping with visual picture naming is considered the gold standard, the choice of stimulus modality should be carefully considered, taking into account the site of the lesion. Hamberger et al. (2005) showed that sparing visual naming sites, without consideration of other sites involved in naming, did not reliably prevent post-operative language decline in patients with temporal lobe epilepsy. Six out of seven patients who had auditory naming sites resected declined post-operatively, in comparison to three out of twelve patients with preserved auditory naming regions. Intra-operative language mapping may therefore require multiple tasks in order to prevent post-operative language deficits (Manan et al., 2020).

#### 6.1.3. CURRENT STUDY

The current study investigates how robustly and consistently different object naming paradigms engage sensory, motor and language regions in neurotypical individuals. BOLD fMRI was used as a proxy for neural activity. Hypotheses for optimal task selection for intra-operative and pre-operative surgical planning can be generated by identifying object naming paradigms with more robust BOLD responses. Specifically, this study compared how consistently four different object naming tasks activated sensory, motor and language regions in neurotypical individuals at the voxel/region level. Three of the object naming tasks involved visual (picture) naming, the third involved auditory object naming (from the nonverbal sounds of objects and animals). For all four tasks, the number of stimuli presented and the fMRI acquisition time was controlled but, for two of the visual naming tasks, objects in pairs were presented every 5 seconds for a duration of 2.5 seconds, whereas in the other two tasks one object was presented at a time every 2.5 seconds for a duration of 1.5 seconds (Figure 6.1).

The expectation was that the requirement to name two objects on a trial, rather than one, would increase demand on the regions involved in speech production (e.g. those required to retrieve and produce names) and so yield more robust activation at the individual level. If the naming of two objects results in more robust activation at the individual level in speech production regions compared to naming a single object, then future studies could investigate whether naming two objects increases test sensitivity for intraoperative and pre-operative language mapping.

Prior studies have aimed to compare the effectiveness of different language mapping fMRI paradigms (e.g. Unadkat et al., 2019) using traditional SPM{t} maps. However, this approach does not account for inter-subject variability (or consistency) and relies on selecting an arbitrary t-score threshold, leading to possible bias. In contrast, functional consistency maps can be used to visualise activation over a range of different statistical thresholds and provide a score to indicate how consistently activation is observed across subjects in each voxel (Seghier & Price, 2016).

### 6.2. METHODS

The data used in this chapter have previously been reported in Experiment 1 (Group 1) and Experiment 2 (Group 2). Details concerning both participant samples are included in Chapter 4. This study was approved by the London Queen Square Research Ethics Committee. All subjects gave written informed consent prior to scanning. Data preprocessing and analysis steps have been described in the General Methods section (Chapter 2) and the respective chapters. Details that are relevant to the current study are outlined in the subsequent sections.

#### 6.2.1. PARTICIPANT GROUPS

The full participant sample comprised 79 native English speakers, with normal or corrected-to-normal vision, and no history of neurological or psychiatric disorders. All were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). One group of participants (n=24) performed two different object naming tasks in addition to 14 other tasks (see Chapter 3 for details). The first object naming task (single visual object naming) involved overtly naming a single object in a picture (Figure 6.1). Successive objects were semantically unrelated. The second object naming task (single auditory object naming) involved hearing the sound of an object or animal (e.g. a dog barking) and overtly naming the object associated with the sound (e.g. "dog"). The second group of participants (n=55) performed four object naming tasks including those performed by Group 1 (single visual object naming and single auditory object naming) and two tasks that presented two semantically unrelated objects per picture (Figure 6.1). In one task, the objects were juxtaposed one above the other and participants named both objects aloud one after the other using a noun phrase (e.g. "tap and pizza"). In the other task, the objects interacted to depict an event and participants were

instructed to overtly name the two objects within a sentence that described how the objects were interacting (e.g. "*The cat is drinking from the jug*"). To do so they used one of four pre-specified verbs that described the interaction: 'eating', 'drinking', 'jumping', or 'falling' (Figure 6.1). The set of acceptable verbs was restricted to minimise inter-subject variability in verb selection. Passive constructions were ruled out by requiring the agent of the action to be named first.

#### 6.2.2. OTHER fMRI TASKS FOR GROUP 1

Group 1 participated in 16 different tasks previously described in Chapter 3, including the visual and auditory single object naming tasks of interest for the current study. The order of the 16 tasks in Group 1 was counterbalanced across 24 subjects (see Chapter 3, Methods for details). As exactly the same stimuli were used for speech production and 1-back matching tasks, a direct comparison of fMRI activation for speech production and 1-back matching identified brain regions involved in speech production, after controlling for stimuli. The main effects of stimulus modality (visual versus auditory), semantics versus non-semantic, and phonological versus nonphonological are reported in Hope et al. (2014).

The current study examines inter-subject consistency across the whole brain, and in language regions that are (a) activated by object naming compared to rest and (b) also activated when retrieving speech sounds, after controlling for task and perceptual processing (see "Regions of interest" below for details). **Figure 6.1:** Details of the experimental design with examples of stimuli and expected responses during naming single and two objects



Participants were also asked to perform a single auditory object naming task (naming objects from sounds). Note: \* = presentation parameters used in Group 2.

#### 6.2.3. OTHER FMRI TASKS FOR GROUP 2

Group 2 participated in 13 tasks reported in Chapter 4, including the four object naming tasks described above. For the purpose of this analysis, the 13 tasks have been split into two different parts, referred to as "Part 1" and "Part 2". Part 1 involved 5 tasks that each presented two objects in a trial and were always presented in the following order: (1) visual semantic matching, (2) naming two objects, (3) verb naming, (4) sentence production and (5) auditory semantic matching. Tasks 1-4 presented two objects in each picture. In the two object naming task, the two objects in the picture were unrelated and non-interacting (e.g. "Tap and Pizza"), see Figure 6.1. In the sentence production tasks, the two objects in the picture were interacting and participants produced a short sentence describing the interaction (Figure 6.1). Further details about the five tasks in Part 1 have been reported in Sanjuán et al. (2015). The tasks of interest for this study are naming two objects in a phrase or in a sentence.

Part 2 of the Group 2 paradigm involved the eight speech production tasks used with Group 1, including visual and auditory single object naming. These eight tasks were always performed after the five Part 1 tasks.

#### 6.2.4. STIMULUS SELECTION AND COUNTERBALANCING

The same set of stimuli was presented to Groups 1 and 2. Details on the stimulus selection process can be found in Chapter 3.

For Group 1, the 128 object names were assigned to four different sets of 32 stimuli (A, B, C, D) and rotated across conditions. Sets A-C were rotated across pictures of objects, written object names and auditory object names, in different participants. Within participant, no stimulus set was repeated across the speech production tasks or across the 1-back matching tasks. Set D included the sounds of 32 objects that were always used during the object sound tasks and never used in any other task. For further details, see Chapter 3. For Group 2, the 120 stimuli were assigned to six different sets of 20 stimuli (A-F), with 8 stimuli in set G. Each task, except auditory object naming, presented 2 different stimulus sets. In Part 1, the first task presented two novel sets (A&C), and the second to fifth presented one novel set (not presented in a previous task) and one repeated set (E&A, B&C, F&E, D&F for tasks 2-5). In Part 2, visual object naming presented sets D&F. The pictures in set D were novel but their names had been presented during auditory semantic matching in Part 1. The pictures in set F were not novel as they had previously been presented for sentence production. For auditory object naming, participants were presented with eight new stimuli from set G and 12 stimuli that had previously been or heard in Sets A to E.

As in Part 1, the order of the eight tasks in Part 2 was held constant. Moreover, the stimuli used in each task were identical for every subject in Group 2. This was to ensure that inter-subject variability, within task, could not be accounted for by stimulus effects. However, as Group 2 always performed Part 2 after Part 1, differences between tasks (e.g. naming two objects per trial in Part 1 versus naming a single object per trial in Part 2) could reflect task order, see section on investigating the effect of task order below.

#### 6.2.5. INVESTIGATING THE EFFECT OF STIMULUS FAMILIARITY

As described above, the stimuli presented to Group 2 during two object naming and sentence production (Part 1) were less familiar than the stimuli presented to Group 2 during auditory and visual single object naming (Part 2). Many prior studies have demonstrated how stimulus familiarity reduces neuronal responses, see Van Turennout et al. (2003) for an illustration during object naming. If the neuronal response is reduced by stimulus repetition, sensitivity to fMRI changes may be reduced possibly leading to less consistency in activation across subjects. To investigate the effect of familiarity, a comparison of inter-subject variability was conducted for single object naming in (A) Group 1 versus Group 2 and (B) subjects in Group 1 who performed speech production before (n=12) versus after (n=12) 1-back matching. For (A), the names of objects in the object naming tasks were completely novel for Group 1 but not for Group 2 (see above). For (B) the pictures of objects in the object naming tasks were completely novel for the 12 subjects who performed the speech production tasks first, but not novel for the 12 subjects who performed 1-back matching first.

### 6.2.6. PRESENTATION DETAILS

Each task (16 for Group 1 and 13 for Group 2) was presented in its own (separate) scanning run with four blocks of stimuli, each lasting 25 seconds, followed by 16 seconds of fixation. Within block, there were 9 stimuli of the same kind (8 novel, 1 repeat) for all Group 1 tasks; and 10 stimuli for all Group 2 tasks. The stimulus repeat in the Group 1 tasks only needed to be detected and responded to (with a finger press) in the 1-back matching tasks but was also present in the speech production tasks in order to keep the stimuli constant across tasks. The inter-stimulus interval was 2.52s for Group 1, 2.5s for Group 2 Part B, and 5s for Group 2 Part A (which presented pairs of object stimuli), see Table 4.3, Chapter 4 for further details of stimulus presentation parameters. The scanning procedure was identical for both groups (see Chapter 3, Methods for details).

#### 6.2.7. INTER-SUBJECT CONSISTENCY DURING OBJECT NAMING

Inter-subject consistency for all object naming tasks was evaluated, at every brain voxel, using threshold-weighted voxel-based consistency maps, as described in Seghier & Price (2016). These "functional consistency maps" quantify the proportion of subjects activating a particular voxel, and its nearest 6 neighbours, over a wide range of statistical thresholds (0.5-0.001). A low consistency value (the proportion near 0) means that the voxel was consistently not activated in almost all subjects. When the proportion is 1, the voxel was activated in each subject irrespective of threshold within the range of statistical thresholds. A proportion less than 1, indicates either consistency across subjects at a low statistical threshold or that only a subset of participants activated the voxel, irrespective of threshold (for full discussion about the interpretation of intermediate consistency values, see Seghier & Price 2016). The maps were linearly weighted towards higher statistical thresholds. To examine inter-subject consistency in activation across the whole brain, "functional consistency maps" were generated for each of the naming tasks.

#### 6.2.8. REGIONS OF INTEREST

In addition to assessing inter-subject consistency at the whole brain level, consistency in activation in the core language areas was evaluated. Using data from Group 1 only, these regions were segregated from the rest of the object naming network by searching for voxels that were activated during (A) object naming compared to rest and (B) 1-back matching of written words and pseudowords compared to visual objects and visual baselines. Contrast (B) has already been shown to activate areas involved in speech sound processing (Hope et al., 2014), consistent with expectation that skilled readers are highly trained to link written words and pseudowords to speech sounds and these "phonological codes" can be used to make 1-back matching decisions. Common activation for (Contrast A) and (Contrast B) segregates speech sound processing from the rest of the object naming system because (i) the 1-back matching task does not involve motor control of speech or auditory processing of the spoken response; and (ii) areas involved in visual perception are controlled by comparing visual 1-back matching of written words and pseudowords to visual objects and visual baselines.

Common activation for Contrasts (A) and (B) was identified by using a global conjunction in SPM with a statistical threshold of p<0.05 after family wise error correction for multiple comparisons across the whole brain (in height). Additional checks were performed to confirm that the identified voxels

were also activated by 1-back matching of words and pseudowords compared to rest. The left temporal and frontal regions activated by the conjunction are illustrated in Figure 6.2 and Table 6.1. The left frontal region included the pars opercularis (pOp) and pars triangularis (pTri). The left temporal region was in the left anterior ascending terminal branch of the superior temporal sulcus (atSTS), extending posteriorly into the left middle temporal gyrus (MTG) and dorsally into the left temporo-parietal junction (TPJ).



Figure 6.2: Regions of interest

Sagittal slices (left x= -54, right x=-48) showing the group-level SPM{t} map for language regions of interest overlaid on a standard structural template in MNI space at p<0.05 corrected for multiple comparisons. The SPM{t} map was generated using data from Group 1 only. Green = temporal regions of interest, Red = frontal regions of interest (see Table 6.1).

Region				_	Z-scores	
		MNI	V.,		Visual	
		co-ordinates		SP	1-b	Conj.
			-		W&P > 0&B	(SP & 1-b)
	nTri	-42, 30, -3		5.89	4.27	7.47
Frontal	ртп	-45, 24, 6	161	5.73	3.53	6.42
	рОр	-48, 15, 18		5.86	3.67	6.63
	atSTS	-51, -45, 6		3.61	3.71	6.06
Temporal	MTG	-60, -48, 9	69	2.55	3.65	5.80
	TPJ	-54, -42, 21		5.41	3.09	5.76

#### Table 6.1 Statistical details for regions of interest

atSTS = anterior ascending terminal branch of the superior temporal sulcus, MTG = middle temporal gyrus, pOp = pars opercularis, pTri = pars triangularis, TPJ = temporo-parietal junction, SP = speech production, 1-b = 1-back matching. W = written words; P = written pseudowords; O = objects in pictures; B = visual baseline (coloured patterns); Vx = number of voxels activated. Conj. = conjunction of SP O>rest and 1-b W&P>O&B.
### 6.3. RESULTS

#### 6.3.1. OBJECT NAMING BEHAVIOURAL DATA

Average in-scanner accuracy was 89% or above for each object naming task in both groups (Figure 6.3). Response times were only available for Group 2. Within this group, response times were slower for single object naming in the auditory than visual modality (Figure 6.3) because auditory stimuli were delivered over time (sequential) while all parts of the visual stimuli were presented at the same time point (simultaneous).



Figure 6.3: Behavioural data

The plots show mean scores with standard deviation. **Left:** Accuracy scores for Group 1 are shown in green and Group 2 in blue. RTs (right) were only available for Group 1. **Right**: Response times (RTs) for Group 2 participants. Note: RTs are for correct trials only. 1 Obj = single object naming, 2 Obj = two-object naming, Sent = sentence production.

#### 6.3.2. INTER-SUBJECT CONSISTENCY IN OBJECT NAMING ACTIVATION

For naming single objects and two objects, activation was highly consistent in sensori-motor areas, including bilateral occipital, motor and auditory cortices (see Figure 6.4). These regions were associated with the following functions in the group-level analysis reported by Hope et al., 2014: (i) bilateral occipito-temporal regions were associated with visual perception, (ii) left posterior middle temporal and parietal areas were associated with semantic associations, (iii) bilateral motor cortices, supplementary motor cortices, subcortical and cerebellar regions were associated with motor control

of speech; and (iv) bilateral auditory cortices were associated with hearing stimuli or hearing the sound of the spoken response.

In language regions of interest (left posterior superior temporal and inferior frontal regions associated with retrieving speech sounds, see Figure 6.2), activation was also highly consistent for naming two objects in a noun phrase and for naming two objects in a sentence (Group 2) but significantly less consistent for naming single visual objects in Groups 1 and 2, see Table 6.2 and Figure 6.5 for details. Auditory single object naming was significantly more consistent than visual single word object naming in temporal regions but not in frontal regions (see Figure 6.2).

There was no significant difference in the consistency of activation for producing two object names in a phrase compared to in a sentence (see Table 6.2B), nor in single object naming for (A) Group 1 (less familiar names) and Group 2 (more familiar names); or (B) subjects in Group 1 who performed speech production tasks before versus after 1-back matching on the same stimuli (mean consistency = 52% for both subgroups). Therefore, there was no evidence that differences in activation consistency for naming two objects rather than a single object arose from either familiarity or stimulus repetition.

Figure 6.4: Consistency of activation across the whole brain, for each task of interest



#### Table 6.2: Functional consistency details

		Naming objects							
Region	MNI co-ordinates	Two in a sentence	Two in a phrase	Single					
		Visual Audite					itory		
		G2	G2	G1	G2	G1	G2		
pTri	-42, 30, -3	90%	89%	59%	59%	64%	58%		
	-45, 24, 6	84%	84%	53%	50%	55%	50%		
рОр	-48, 15, 18	93%	85%	53%	55%	60%	62%		
atSTS	-51, -45, 6	87%	87%	42%	47%	57%	69%		
MTG	-60, -48, 9	90%	84%	42%	53%	67%	80%		
TPJ	-54, -42, 21	92%	88%	43%	65%	75%	87%		

#### **A.** Consistency of activation in regions of interest.

#### **B.** Statistical comparison of naming one or two objects per trial.

		Odds ratios for naming two objects in a phrase compared to						
Region	MNI co-ordinates	Sentence	S	g				
			Visual	Auditory				
		G2	G1	G2	G1	G2		
pTri	-42, 30, -3	0.93*	5.87	5.44	4.67	5.87		
	-45, 24, 6	0.98*	4.58	5.11	4.26	4.93		
рОр	-48, 15, 18	0.41*	5.27	4.90	3.92	3.63		
atSTS	-51, -45, 6	0.99*	9.54	7.65	4.93	3.07*		
MTG	-60, -48, 9	0.57*	7.11	4.58	2.49*	1.28*		
TPJ	-54, -42, 21	0.64*	8.86	3.62	2.34*	1.00*		

#### C. Statistical comparison of auditory and visual single object naming.

Deview	MNI	Odds ratios for auditory compared to visual single object naming					
Region	co-ordinates	Auditor	ry G1 vs	Auditory G2 vs			
		Visual G1	Visual G2	Visual G1	Visual G2		
pTri	-42, 30, -3	1.26*	1.17*	1.00*	0.93*		
	-45, 24, 6	1.08*	1.20*	0.93*	1.04*		
рОр	-48, 15, 18	1.34*	1.25*	1.45*	1.35*		
atSTS	-51, -45, 6	1.94*	1.55*	3.11	2.49		
MTG	-60, -48, 9	2.86	1.84*	5.57	3.59		
TPJ	-54, -42, 21	3.78	1.55*	8.86	3.62		

All odds ratios, except the values indicated with an asterisk, were significant (p<0.05, 2 tailed), using both Chi Squared (Pearson) p values and Fischer's exact probability test. Consistency is expressed as a percentage (between 0-100%) rather than a value between 0 and 1. G1 = Group 1; G2 = Group 2. atSTS = anterior ascending terminal branch of the superior temporal sulcus, MTG = middle temporal gyrus, TPJ = temporo-parietal junction, pOp = pars opercularis, pTri = pars triangularis.



Figure 6.5: Consistency of activation within language regions of interest

## 6.4. DISCUSSION

To select the optimal task for intra-operative mapping, a neurosurgeon needs confidence that the selected task typically and robustly engages the function of interest. In the case of object naming, the results strongly favour use of a two object naming paradigm compared to a single object naming paradigm. Language regions are most consistently and robustly activated when participants name two objects in a picture using a phrase (e.g. "tap and pizza") or when they name two objects in a sentence (e.g. "The cat is drinking from the jug"). By contrast, activation is much less consistent when naming a single object from a picture (single visual object naming) or naming an object from its sound (single auditory object naming). These findings have implications for pre-operative and intra-operative language mapping in that such mapping may have improved sensitivity to language function if the task involves presenting two objects in the same picture rather than pictures of single objects.

Greater consistency of activation in language-related was observed for naming two objects rather than one even though the number of objects presented was held constant within 25s blocks (10 for two object naming and 10 for single object naming). Moreover, no evidence was found to suggest that this greater consistency was the consequence of familiarity effects. Instead, the proposed hypothesis is that naming two objects increases demand on processes related to word retrieval and production yielding robust languagerelated activation at the individual subject level.

In the language regions of interest used in the current study (left posterior temporal and left posterior frontal areas involved in speech processing), activation did not show significantly more consistency for producing two object names in a sentence compared to a noun phrase (see Figure 6.5 and Table 6.2). Therefore, the simpler two object naming task was sufficient for investigating activation in the chosen language regions of interest. If, on the other hand, the regions of interest chosen were those involved in syntactic processing, the sentence production task would be a better choice for pre-surgical planning. For example, in a series of 14 neurosurgery patients, Chang et al. (2018) used DES to identify stimulation sites associated with syntactic deficits during sentence production. Stimulation of regions in the pars opercularis and pars triangularis, which have not been identified during mapping with counting, naming or repetition, induced syntactic errors in 7/14 patients.

In the temporal lobe language region of interest, which included the temporo-parietal junction, middle and superior temporal cortex, activation was more consistent for auditory object naming than for visual object naming (see Figure 6.5 and Table 6.2). This is in line with prior studies (Hamberger et al., 2001, 2005) that reported a clinical benefit of utilising single auditory object naming for language mapping in patients with temporal lobe epilepsy (TLE) (Hamberger et al., 2001, 2005). TLE patients often present with word finding difficulties and conversational speech impairments, despite normal performance on visual naming tasks. Carefully planned language testing, which takes into consideration the stimulus modality, is therefore crucial in preserving a patient's quality of life, particularly since a study by Moritz-Gasser et al. (2012) demonstrated that naming ability was significantly correlated with return to work in patients with low-grade gliomas.

In addition, the results from the current experiment show how consistently sensory and motor regions are activated by all four object naming tasks (Figure 6.4). This supports the notion that object naming can be used to probe the function of many different brain regions during intra-operative mapping. An impaired response to an object naming task during DES does not, however, indicate the function of the stimulated region as so many different types of processes are involved in object naming. To determine the function of a brain region, multiple different tasks are required to systematically manipulate the demands on different types of processing. This is possible

within group fMRI studies (e.g. the 16 tasks administered to Group 1) but is not feasible for pre-operative planning because single patient pre-operative fMRI mapping needs to maximise repetitions of the same task for reliable estimation of signal to noise; and this necessitates minimising the number of tasks unless the patient can return for multiple scanning sessions. In addition, interpretation of results from multitask fMRI studies is often challenging.

Functional consistency maps offer a potential data-based solution for pre-surgical planning, accounting for inter-subject variability. Specifically, for each region of interest, functional consistency maps can be generated to calculate inter-subject consistency in response to multiple different tasks and task differences (contrasts). Neuro-surgical teams could then compare the location of regions planned for resection with the output from a database that indicates (i) which tasks engage the region; (ii) the consistency with which the region is engaged for these tasks across neurotypical individuals; and (iii) which tasks might be optimal for pre-operative fMRI or intra-operative DES.

#### 6.4.1. LIMITATIONS AND FUTURE DIRECTIONS

The current study explored the consistency of object naming activation in healthy controls. These findings may not necessarily translate to patient populations because the object naming networks may have already reorganised in patients with brain tumours or epilepsy (Fisicaro et al., 2016). To further investigate the effect of pathology on the consistency of object naming activation, future studies could investigate the consistency of language-task related activation in more heterogenous participant samples, such as patients with brain tumours or drug-resistant epilepsy.

The results suggest that successful implementation of the two object naming paradigm in the intra-operative setting may allow for more sensitive language mapping. More research is required to evaluate whether the two object naming paradigm is superior to a single object naming paradigm in clinical practice. The approach illustrated in the current study can be extended to map networks of regions activated by different language tasks. For instance, Rofes and Miceli (2014) argued that verb naming might be more sensitive than object naming due to recruitment of additional networks involved in grammatical processing. Functional consistency maps could be used to compare the consistency of activation for verb naming relative to object naming and make further recommendations for intra-operative testing. This would contribute to data-based approaches for neurosurgical planning that will provide reliable and lesion-site specific brain mapping paradigms.

#### 6.4.2. CONCLUSIONS

Object naming is a widely utilised task in patients undergoing neurosurgery and allows the mapping of a widely distributed network of speech production regions. This study examined the inter-subject consistency in activation during four different object naming tasks in neurotypical participants. Naming two depicted objects either in a phrase or in a sentence resulted in more consistent activation in core language areas (posterior temporal and inferior frontal) in comparison to single object naming (from visual or auditory stimuli). These results suggest that requiring two objects to be named on a trial may optimise sensitivity to DES effects during awake language mapping. In addition, single object naming in the auditory modality (naming object from sounds) resulted in higher consistency of activation in temporal language regions in comparison to single object naming in the visual modality (naming objects from pictures). These findings highlight the importance of selecting a stimulus modality based on lesion site.

## 7. How are patients able to read FOLLOWING RESECTION OF LEFT TEMPORO-PARIETAL READING AREAS?

This study investigated how a combination of fMRI data from 74 neurotypical controls and two patients with tumours affecting left temporoparietal areas could be utilised to explain language outcome following tumour resection. In Experiment 1 and Experiment 2, the left temporo-parietal junction (TPJ) was found to important for phonological processing. In accordance with this result, the hypothesis of the current study was that patients with damage to the left temporo-parietal cortex might show a decline in reading and object naming scores post-surgery. Despite this, they were still able to perform a simple reading task with an accuracy greater than 90%.

To establish whether their successful reading performance might be associated with atypical activation in other, intact brain regions, fMRI data from the two patients was compared to neurotypical controls. This revealed that both patients showed higher than normal activation in the left and right perirhinal cortices before and after surgical resection of their tumours. The condition-dependent responses in neurotypical controls were analysed to elucidate how enhanced activation in the perirhinal regions might be contributing to successful reading performance. The results demonstrated that activation in bilateral perirhinal cortices was enhanced by the semantic content of the visual stimuli. The current study offers a cognitive explanation of how the perirhinal cortices are contributing to task performance and proposes that the increased reading-related activation in the perirhinal cortex, in the context of dysfunctional responses in TPJ, reflects increased reliance on a whole word reading strategy. Moreover, the observation that perirhinal activation was enhanced both pre- and post-surgery suggests that both patients had changed their reading strategy prior to surgery.

## 7.1. INTRODUCTION

This study applies functional neuroimaging to gain an insight into how patients with damage to language-related brain regions are able to maintain or recover their language abilities. Understanding functional reorganisation has an important translational impact on patients. First, it might allow the neurosurgeon to resect tumours that were previously deemed inoperable. For instance, it would explain how patients are able to retain language abilities following resection of gliomas in Broca's area, Wernicke's area, Rolandic area or the insula (Desmurget et al., 2007; Duffau, 2005, 2014). Second, understanding functional reorganisation may provide evidence that a specific cortical site can be compensated for, and this could be considered during preoperative planning. Duffau and colleagues suggested a multistage approach to resection of tumours in eloquent brain regions, where a second surgery is performed after evidence of reorganisation has been observed on longitudinal fMRI data or TMS (transcranial magnetic stimulation) sessions (Duffau et al., 2003). This technique allows the margins of the initial resection to be extended without inducing post-operative sequelae (Duffau, 2005).

The current study investigated how two patients with tumours in the left temporo-parietal region, associated with auditory short-term memory in Experiment 1 and 2, were able to produce speech both before and after brain tumour resection. The goal was to use fMRI to identify whether undamaged brain regions had to work harder than normal (i.e., increased their activity more than in neurotypical controls) when patients were successfully performing tasks that activate the damaged left temporo-parietal region. Pre- and postsurgery, both patients participated in an fMRI paradigm with four different language tasks and four control conditions. Data analysis and interpretation focused on language tasks that (i) the patients performed very accurately and (ii) resulted in highly significant activation, in neurotypical controls, in the left temporo-parietal region that was damaged in both patients. In this context, regions showing increased activation in the patients compared to the neurotypical controls might be informative of how the patients retained the ability to perform the task.

To understand how regions with abnormally high activation in the patients might be contributing to their reading performance, the second part of this study investigated how these regions responded during the eight fMRI tasks in neurotypical controls. Abnormally high activation might be located (i) around the resected area (peri-lesional) as in Duffau et al., (2003); (ii) in more distant parts of the left hemisphere (e.g. functional reorganisation within hemisphere) and/or (iii) in contralateral regions (Turkeltaub et al. 2011; Yamamotto et al., in submission). Alternatively, (iii) it is possible that the same compensatory mechanisms might not be identified in both patients because they differed from one another both in the extent of their lesion and the underlying tumour histology. P1 had an anaplastic astrocytoma (WHO grade III) that infiltrated left motor regions as well as the parietal lobe. In contrast, P2 had a central neurocytoma (WHO grade II) with more temporal lobe damage than P1 but less damage to motor regions. It was therefore possible that these differences would lead to the recruitment of different compensatory strategies, despite common damage to the left temporo-parietal region.

In summary, this study investigated how a combination of functional imaging studies of patients with neurological damage and neurotypical controls may help to predict and explain neurosurgical outcome in two patients with damage to a temporo-parietal area.

## 7.2. METHODS

#### 7.2.1. PARTICIPANTS

Two patients (P1 and P2) with left temporo-parietal tumours, without any history of other neurological or psychiatric conditions; and 74 neurotypical intact controls (38 females, 36 males, mean age= 34.5; age range= 16.1-73.6).

All participants were right-handed (Oldfield, 1971), native English speakers with a normal or corrected-to-normal vision. Demographic, clinical and lesion data for each patient along with psychometric testing are presented in Figure 7.1, along with images of their structural brains scans before and after surgery. The study was approved by the National Hospital for Neurology and Institute of Neurology Joint Ethics Committee. Patients and neurotypical controls gave written informed consent prior to participation in the study and received financial compensation for their time.

#### 7.2.2. THE COMPREHENSIVE APHASIA TEST

Patients' language performance was assessed using the Comprehensive Aphasia Test (CAT; Swinburn et al. 2004). The CAT is a fully standardised test battery, which consists of a total of 27 different tasks divided into two sections - the cognitive screen and the language battery. The cognitive screen captures general cognitive capacities such as semantic memory or visual neglect, which can aid the interpretation of the language scores. The other dimensions of the CAT relate directly to language (such as 'reading words', or 'repeating non-words').

To compare performance on different tasks, raw scores are converted into T-scores, through a non-linear transformation, which represent how well the patient performed relative to a reference population of 113 aphasic patients. For instance, a T-score of 50 indicates the mean of the patient sample used to standardise the CAT, whereas a T-score of 60 represents one standard deviation above the mean. The cut-off scores for impaired performance were defined according to the CAT criteria, relative to a second reference population of 27 neurologically normal controls, and these are different for each task. Lower scores indicate poorer performance, with scores falling in the bottom 5% of the control population classified as impaired. Tscores can be compared using parametric statistics because they are normally distributed with a mean of 50 and a standard deviation of 10.



Figure 7.1: Details of patients with temporo-parietal damage

White area shows complete overlap between the damaged regions in the two patients post-surgery, purple area shows the resection cavity in one patient only.

#### 7.2.3. LESION IDENTIFICATION

To illustrate common areas of damage in both patients, a 3D binary image of abnormal tissue in each patient brain, was created using an automated lesion identification (ALI) algorithm (Sanjuán et al., 2013). This algorithm identifies abnormal tissue by first segmenting it into four classes: grey matter, white matter, cerebrospinal fluid and an atypical "extra" tissue class and subsequently comparing each voxel to grey or white matter segments from a group of 64 controls. The tissue affected by a brain tumour will be identified as an outlier and classified as atypical. The toolbox utilises the unified segmentation–normalisation routine, with the resultant lesion image is in MNI space. The ALI procedure was repeated twice to optimise accuracy of lesion definition (Sanjuán et al., 2013). The threshold used to convert the fuzzy to binary images was 0.3 as recommended in Seghier et al. (2008). Details of this procedure have been described in the general methods section (Chapter 2).

#### 7.2.4. EXPERIMENTAL SETUP

The experimental paradigm involved eight different tasks that were performed by both patients and neurotypical controls. These data were utilised to investigate which tasks activated the left temporo-parietal region that was damaged in each patient. Four tasks involved overt speech production and the other four tasks involved a finger press response to indicate semantic or perceptual relationships between stimuli. The four speech production tasks were: (1) Reading aloud written object names, (2) Naming aloud objects from pictures, (3) Saying "1,2,3" aloud while looking at pictures of non-objects, (4) Saying "1,2,3" aloud while looking at unfamiliar symbols. The four finger press tasks involved (5) Semantic matching decisions on written object names, (6) Semantic matching decisions on pictures of objects, (7) Perceptual matching of unfamiliar symbols, (8) Perceptual matching of pictures of unfamiliar objects. The list of conditions and instructions for each task are shown in Table 7.1.

Task (abbreviatio	on)	Response	On-screen instruction	Description
Reading words	(Read-W)	S	"Read"	Read all three object names
Reading baseline	(123-S)	S	"1,2,3 Symbols"	Say "1,2,3" in response to unfamiliar symbols
Picture naming	(Name-O)	S	"Name"	Name aloud all three pictures
Picture naming baseline	(123-N)	S	"1,2,3 Pictures"	Say "1,2,3" while looking at pictures of unfamiliar non- objects
Semantic decisions on pictures of objects	(SM-O)	F	"Match pictures"	Match semantically related pictures
Semantic baseline	(PM-N)	F	"Same pictures"	Match identical pictures of unfamiliar non-objects
Semantic decisions on written names	(SM-W)	F	"Match words"	Match semantically related words
Perceptual decisions on unfamiliar symbols	(PM-S)	F	"Same symbols"	Match identical string of unfamiliar symbols

#### Table 7.1 A summary of the fMRI tasks

S = speech production, F = finger-press.

#### 7.2.5. COUNTERBALANCING AND STIMULUS SELECTION

Condition order was fully counterbalanced within and across sessions. All stimuli were derived from a set of 192 easily recognisable objects with three to six letter names in English: 33 had three letter names (e.g. "hat", "jug" or "dog"), 65 had four letter names (e.g. "lamb", "bear", "piano"), 58 had five letter names (e.g. "swing", "money", "snake") and 36 had six letter names (e.g. "pencil", "window", "parrot"). A pilot study with eight participants was conducted to ensure inter-subject agreement on all object names.

The 192 object names were divided into two different sets (A, B) of 96 items. One group of selected participants was presented with set A as written words for reading aloud, set B as pictures for object naming, set B for semantic

decisions on words, and set A for semantic decisions on pictures. The other group was presented with set B as written words for reading aloud, set A as pictures for object naming, set A for semantic decisions on words, and set B for semantic decisions on pictures. Each word or picture was presented only once, although the object concept was repeated twice (once as a word and once as a picture).

To control for visual information across conditions, all stimuli were presented in triads with one item presented above and two items presented below (Figure 7.2). Stimuli within a triad were always of the same type (pictures of objects, written object names, meaningless combinations of Greek letters or pictures of meaningless, and unfamiliar nonobjects). During the semantic and perceptual decision tasks, the item positioned above the other two acted as a target that was related to one of the items below. There was no semantic or perceptual relationship between any of the three items in the speech production conditions.



#### Figure 7.2: Examples of stimuli

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#### 7.2.6. PROCEDURE AND IN-SCANNER BEHAVIOUR

To ensure that the task was understood correctly each participant completed a short training session before entering the scanner, with stimuli that were not used in the scanner. The participants were instructed to keep their body, head and mouth as still as possible. A brief instruction was presented on the screen to indicate the required response before each stimulus block.

In the scanner, stimuli were presented via a video projector, a frontprojection screen, and a system of mirrors fastened to a head coil. Written words were presented in lower case Arial font and occupied 4.9° (width) and 1.2° (height) of the visual field. Pictures of non-objects were physically bigger and subtended an angle of 7.3° × 8.5°.

There were four separate scanning runs, lasting approximately 6 min each. In two runs, the participants made semantic and perceptual decisions. In the other two sessions, participants performed four speech production tasks. Each run consisted of 24 blocks of stimuli of the same type/condition with an additional 12 blocks of fixation that were presented every two stimulus blocks. Each stimulus block lasted 18 s and consisted of four trials during which three stimuli were simultaneously presented on the screen for 4.32 s, followed by 180 ms of fixation. Every two stimulus blocks, fixation continued for 14.4 s.

For the matching tasks, participants used an fMRI compatible button box to indicate if the stimulus matching the target was in the left or right hemifield. The hand of response was rotated across participant. When the right hand was used, left and right were indicated by the index finger and middle finger, respectively. When the left hand was used, left and right were indicated by the middle finger and index finger, respectively. In the speech production tasks, verbal responses were recorded and filtered using a noise cancellation procedure to monitor accuracy and distinguish between correct and incorrect responses. Response times were available for the perceptual and semantic decision tasks but not for speech production. Speaking aloud increases the risk of task-related movement artefacts, therefore extra care was taken to limit participant movement during scanning and evaluate signs of movement in the data.

#### 7.2.7. FUNCTIONAL MRI DATA ACQUISITION, PROCESSING AND ANALYSIS

Image processing and statistical analyses were performed using standard procedures in SPM (<u>http://www.fil.ion.ucl.ac.uk/spm/</u>) and have been described in the general methods section.

In subject-specific first-level, fixed effects analyses, each stimulus onset was modelled as an event in condition-specific "stick-functions" lasting 4.32 s per trial and having a stimulus onset interval of 4.5 s. The resulting stimulus functions were convolved with a canonical hemodynamic response function that provided regressors for the general linear model. For each task condition there were three regressors: instruction, correct trials, and incorrect trials. For speech production, correct trials were defined as all three trial responses were correct. One or two correct response per trial (i.e. one or two errors) were categorised as incorrect trials. Time-series from each voxel were high-pass filtered (1/128-Hz cut-off) to remove low-frequency noise and signal drift. Contrast images computed where activation was higher for each of the eight conditions, compared to resting with fixation.

#### 7.2.8. TASK SELECTION AND PATIENT ANALYSIS

Although all participants performed all eight tasks, the analysis of the patient data focused on a task that met two criteria that are essential for further interpretation. First, in neurotypical participants, the task must robustly and consistently activate the left temporo-parietal region that was damaged in both patients (Figure 7.1). Second, the patients must be able to perform the selected task(s) with high accuracy before and after surgery, despite having damage to regions activated in neurotypical controls.

In-scanner behavioural accuracy is a crucial consideration when analysing fMRI data from patients with lesions (Price & Friston, 1999), even when the analysis is limited to correct trials only (as in the current study). A low number of correct trials will reduce the reliability of the estimated response, potentially resulting in both false positive or false negative results (Amaro & Barker, 2006). In the context of high accuracy, the fMRI analysis can be used to investigate how patients are able to perform the task despite damage to regions that are typically activated by the task. Contrast images for the task of interest compared to fixation (from the first level fMRI analysis) were entered into the second level fMRI analysis, modelling five "groups": (1) all neurotypical controls; (2) P1 pre-surgery; (3) P1 post-surgery; (4) P2 pre-surgery; (5) P2 post-surgery. Effects of interest were identified in voxels where patient activation was greater than neurotypical controls. Because the patient lesions were very variable, the results focus on effects that were consistent across the two patients as these are more likely to be a consequence of loss of function in the temporo-parietal region that was damaged in both patients. There were three statistical contrasts of interest, each thresholded at p<0.05 after family wise error (FWE) correction for multiple comparisons across the whole brain: Contrast 1 = P1 pre-surgery and P2 pre-surgery > Controls, Contrast 2 = P1 post-surgery and P2 post-surgery > P1 pre-surgery and P2 pre-surgery, Contrast 3 = P1 pre-surgery and P2 pre-surgery > P1 post-surgery and P2 post-surgery.

To ensure that these effects were driven by both patients, the inclusive masking option in SPM was used to limit the results to voxels that were activated by the same effects in individual patients, thresholded at p<0.001 uncorrected. Contrast 1 (pre-surgery only) was inclusively masked with the following four contrasts: P1 pre-surgery > Controls; P2 pre-surgery > Controls: P1 pre-surgery alone; and P2 pre-surgery alone. Contrast 2 (post-surgery >

pre-surgery) was inclusively masked with the following contrasts: P1 postsurgery > pre-surgery; P2 post-surgery > pre-surgery; P1 post-surgery alone; and P2 post-surgery alone. Contrast 3 (pre-surgery > post-surgery) was inclusively masked with the following contrasts: P1 pre-surgery > post-surgery; P2 pre-surgery > post-surgery; P1 pre-surgery alone; and P2 pre-surgery alone. Finally, the corresponding effects for each patient separately were examined using a statistical threshold of p<0.05 corrected for both the group difference (patient > controls) and patient activation (reading > fixation) alone.

#### 7.2.9. INTERPRETING AREAS OF ATYPICAL ACTIVATION IN THE PATIENTS.

The activation differences across all 8 tasks of the fMRI paradigm were studied in neurotypical controls to interpret the findings of the patient analysis described above. Figure 7.3 offers a schematic of the basic phonological and semantic processing pathways implicated and their expected recruitment in each task. Table 7.2 overviews expected pathway activation for each task as the rationale for the statistical analysis.

In the schematic, a distinction is made between accessing phonological associations and phonological memory. For reading and object naming, the three visual items in the display need to be linked to their phonology (either directly or indirectly via semantics) and held in memory during speech production. In contrast, saying "1,2,3" to meaningless pictures does not depend on the content of the visual input– but the phonology driving speech production ("1,2,3") still needs to be held in memory throughout the trial. The schematic also distinguishes between (i) accessing semantics from vision, (ii) linking semantics to phonology, and (iii) making semantic associations for matching decisions. Access to semantics from vision is expected for all four conditions with written object names and pictures of objects. Linking semantics to phonology is expected during object naming and reading aloud; and semantic association matching is expected during the semantic matching tasks.



Figure 7.3: Schematic of the functional analysis of the fMRI tasks.

Top (in grey) overviews the expected phonological and semantic processing pathways involved in the fMRI tasks. The eight smaller boxes below focus on the processing expected for each task separately, with different colours and spatial positioning of the boxes corresponding to those in the overview above. Boxes and arrows indicate flow of information but do not imply either strict seriality or a dissociation between grey and white matter. a = linking orthographic visual stimuli to phonological associations, b= linking familiar visual stimuli to semantic associations, c = linking semantics to phonology, d= linking phonology to semantics, e = semantic association matching.

The underlying assumption is that activation of phonology and semantics will differ for written words and objects in two ways, depending on the task (Glaser & Glaser, 1989). First, the engagement of phonology is expected to be higher during semantic matching on words than semantic matching on objects because of learnt associations between spelling and sound (i.e. orthographic to phonological associations). Second, during speech production, the links between vision and phonology are expected to be indirectly mediated via semantics for objects. In contrast, words can also access phonology without semantics because of the learnt associations between spelling (lexical and sublexical) and sound.

Following the schematic and tabulation of the pathways expected to be recruited for each task (Figure 7.3 and Table 7.2, respectively) the statistical analysis dissociated brain activation related to each type of processing. Multiple contrasts were tested, for each effect, to ensure that the main effect was not driven by any particular condition, sensori-motor processing or deactivation in the non-semantic conditions. Details of the dissociated phonological and semantic effects are presented in the Appendices A1-A4.

	Name	Read	123	123	SM	SM	ΡM	ΡM
lask	: O	W	Ν	S	0	W	Ν	S
Phonological and semantic processing								
Accessing phonology (a or c)	$\checkmark$	$\checkmark$	×	×	~	$\checkmark$	×	×
Phonological memory*	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$	~	$\checkmark$	×	×
Accessing semantics (b or d)	$\checkmark$	$\checkmark$	×	×	$\checkmark$	$\checkmark$	×	×
Semantics-to-phonology (c)	$\checkmark$	$\checkmark$	×	×	×	×	×	×
Semantic matching (e)	×	×	×	×	$\checkmark$	$\checkmark$	×	×
Sensori-motor processing								
Visual processing	$\checkmark$	✓	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$
Speech production	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$	×	×	×	×
Matching decision and finger press	× ;	×	×	×	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$

 Table 7.2: Overview of processing pathways for each task

\* = phonological associations and short-term memory,  $\checkmark$  = process is expected. ★ = process is not expected. ~ = access to phonology without semantics is expected to be less for objects than for words. Letters (a to e) refer arrows in Figure 7.3. For abbreviations see Table 7.1. **1. Accessing phonology:** Activation that was observed for (i) semantic matching on words more than objects; (ii) object naming more than saying "1,2,3" to nonobjects; and (iii) reading aloud more than saying "1,2,3" to symbols. Common activation for these three tasks does not involve speech production (semantic matching is silent); or visual, orthographic or semantic processing.

**2. Phonological memory:** Activation that was observed for (i) semantic matching on words more than objects; (ii) saying "1,2,3" to nonobjects and symbols more than perceptual decisions on non-objects and symbols and (iii) saying "1,2,3" to non-objects and symbols more than fixation.

**3. Accessing semantics:** Activation that was observed for: (i) the main effect of semantics (i.e. the comparison of semantic compared to non-semantic stimuli across task); (ii) semantic compared to non-semantic stimuli during speech production; (iii) semantic compared to non-semantic stimuli during semantic matching and (iv) each of the four semantic tasks relative to fixation.

**4. Semantics to phonology:** Activation that was observed for (i) semantic speech production tasks compared to the semantic matching tasks, which controls for stimuli; (ii) the semantic by task interaction, i.e. [semantic production more than saying "1,2,3"] more than [semantic > perceptual matching] which controls for the motor response; and (iii) each semantic speech production task compared to fixation.

**5. Semantic matching:** Activation that was observed for (i) semantic matching compared to speech production on semantic stimuli; (ii) the second tail of the semantic by task interaction, i.e. [semantic > perceptual matching] more than [semantic production > saying "1,2,3"] which controls for the motor response; and (iii) each semantic matching task compared to fixation.

The threshold was set at p<0.05 FWE corrected for the first contrast in each effect. The other tasks were entered as inclusive masks with a statistic threshold of p<0.001 uncorrected.

### 7.3. RESULTS

## 7.3.1. THE EFFECT OF TUMOURS AND RESECTION ON LANGUAGE PERFORMANCE

Prior to surgery both P1 and P2 performed in the normal range for almost all the CAT tasks, with the exception that P1 had impaired recognition memory and arithmetic and P2 had difficulty naming actions (Table 7.4). After surgery, P1 had aphasic scores on (i) spoken and written sentence comprehension, and (ii) all spoken and written production tasks (repetition, naming, reading, writing), with the exception of reading short function words (e.g. "and") and nonword repetition that was impaired relative to pre-surgery but just within the normal range. In contrast, P2 was only impaired when reading complex words (such as "president") and on the visual recognition task. The effect of surgery was also observed on the performance of the inscanner tasks. As shown in Figure 7.4, both patients were within the normal range of accuracy prior to surgery. After surgery, P1 was impaired (more than 2.5 standard deviations from normal) for all tasks, except those with nonobjects. P2 was impaired for object naming, after surgery, but still within the normal range. The in-scanner object naming task may have been more sensitive to impairments than the CAT object naming task because, in the scanner, three objects needed to be named within 4.5s (i.e. a limit of 1.5s per object).

Response times were only available for the matching tasks. Before surgery, P1 was more than 2.5 standard deviations slower than normal on semantic matching of words and perceptual symbols and after surgery this patient was also 2.5 standard deviations slower on semantic matching of objects (Table 7.3).

				Stimulus					
			-	W	0	S	Ν		
		С		99.7 ± 1.1	$94.9 \pm 4.9$	99.8 ± 1.5	99.8 ± 2		
		D1	PreS	100	96	100	100		
	Speech	FI	PostS	90*	65*	83*	100		
		<b>D</b> 2	PreS	100	97	100	100		
Accuracy		FZ	PostS	99	84*	100	100		
	Matching	С		93.2 ± 4.2	91.3 ± 5.7	98.0 ± 3.5	98.9 ± 3		
		D1	PreS	84	87.5	94	100		
		F I	PostS	75*	72*	87.5*	100		
		<b>D</b> 2	PreS	87.5	87.5	100	100		
		FZ	PostS	87.5	87.5	100	94		
		С		1.68 ± 0.27	1.77 ± 0.31	$1.10 \pm 0.22$	$1.18 \pm 0.38$		
		D1	PreS	2.47*	2.52	1.95*	1.82		
RTs	Matching	FI	PostS	2.62*	2.78*	2.13*	1.97		
		<b>D</b> 2	PreS	2.06	1.99	1.03	1.09		
		Г2	PostS	1.84	1.94	1.10	1.25		

#### Table 7.3: In-scanner behavioural scores

Scores in bold with an asterisk are below the cut-off for unimpaired performance. PreS = pre-surgery, PostS = post-surgery, C = controls. For other abbreviations see Table 7.1.



Figure 7.4: Accuracy scores and response times for controls and patients

The red bars show standard deviation for 74 controls. Lighter colours refer to presurgery scores and darker colours indicate performance post-surgery. Threshold for impairment was defined as mean value in controls minus 2.5\*standard deviations. Note: RTs were only available for the matching tasks and include correct trials only. For abbreviations see Table 7.1.

		P1	P2		
	PreS	PostS	PreS	PostS	
Cognitive					
Line bisection	59	59	59	66	
Semantic memory	60	60	60	60	
Recognition memory	43*	48	48	43*	
Total memory	50	54	54	50	
Word fluency	68	62	70	/5	
Gesture	68 40*	68 50	68 65	60 65	
Arithmetic	40"	53	65	65	
Comprenension	0.5		07		
Spoken total	65	5/	67	63	
Spoken sontoncos	00 65	50 60*	00 70	20 72	
Spoken paragraphs	60	<b>6</b> 0	7 Z 7 Q	60	
Written total	65	53	73	61	
Written words	65	55	65	55	
Written sentences	64	51*	72	62	
Repetition		-		-	
Total	72	52*	72	72	
Words	65	50*	65	65	
Complex words	62	38*	62	62	
Non-words	67	58	67	67	
Digit strings	66	50^	66	66	
Sentences	63	56^	63	63	
Naming					
Total	69	56*	69	74	
	74 60	50*	/U 56*	00 60	
Actions Spokon picturo	69	59	<b>30</b>	69	
description	65	59*	64	66	
Reading	74	40*	74	05	
l Otal Words	60	49 <sup>~</sup> 10*	60	60 64	
Complex words	67	49 19*	67	04 57*	
Function words	62	62	62	62	
Non-words	68	40*	68	68	
Writing					
Total	69	44*	61	64	
Copying	61	46*	61	61	
Picture naming	67	38*	58	62	
Dictation	68	38*	63	63	
Written picture	69	NC	73		
description	00	NC	15	NC	

#### Table 7.4: CAT scores for patients pre- and post- surgery

NC = Task not completed. All scores are t-scores, as recommended by the CAT. Those in bold with an asterisk are below the cut-off for impaired performance.

#### 7.3.2. SELECTION OF TASK OF INTEREST FOR fMRI ANALYSIS

The in-scanner task results described above indicated that the most accurate language task, for both patients, was reading aloud. Post-surgery, all three words in a trial were read aloud accurately, within 4.5s, on 90% of trials for P1, and 99% of trials for P2 (Table 7.3). This high accuracy ensures that the sensitivity of the fMRI analysis for reading data was not compromised for the patients compared to the neurotypical controls.

As expected from prior studies, the left temporo-parietal region that was surgically removed in the patients is activated when neurotypical controls are reading aloud (Figure 7.5). The fMRI investigation of P1 and P2 below can therefore focus on understanding how patients are able to read aloud accurately when they have a tumour in, or resection of, the left temporoparietal language areas.

#### 7.3.3. READING ACTIVATION DIFFERENCES IN PATIENTS VERSUS CONTROLS

Neither patient showed any evidence of activation in Left TPJ, either before or after surgery (Figure 7.6). Prior to surgery, both patients showed higher than normal reading activation in the (undamaged) left and right perirhinal cortices (Figure 7.6 and Figure 7.7). Post-surgery, reading activation in these regions remained higher than normal, particularly for P1 (Figure 7.6). In addition, in the post-surgery assessment, both patients showed enhanced activation in (i) the right intraparietal sulcus [38, -56, 36], (ii) right occipito-parietal junction [36, -64, 22], (iii) left dorsal supramarginal gyrus on the border with the angular gyrus; (iv) the left superior temporal gyrus (STG), bordering Heschl's gyrus, and (v) at the border of the ventricles with the resection site.



Figure 7.5: Activation for reading (>fixation) in neurotypical controls

SPM{t} map thresholded at p<0.05 FWE-corrected. T-scores are colour-coded (high = red, low = blue). Top row shows the left hemisphere and bottom row the right hemisphere.

		L PRC	R PRC
		-36, -10, -32	36, -4, -36
Controls		4.0	ns
	P1	4.0	4.1
Pre-surgery	P2	6.6	4.0
	P1	7.1	6.5
Post-surgery	P2	3.4	3.4
	P1	3.6	3.8
Pre-surgery > C	P2	6.2	3.8
	P1	8.1	6.3
Post-surgery > C	P2	3.2	3.2
Pre > Post	P1&2	ns	ns
Post > Pre	P1&2	ns	ns

**Table 7.5:** Z-scores for activation related to reading aloud in perirhinal regions

Activation is reported for reading aloud relative to fixation in each patient and in comparison to controls (C), in regions showing more activation in both patients than controls. PRC = perirhinal cortex, TPJ = temporo-parietal junction, STG = superior temporal gyrus, L = left, R = right. ns = not significant at p <0.001 uncorrected. Bold = significant at p <0.05 FWE. Negative z-scores = controls > patient.

**Figure 7.6:** Reading activation in neurotypical controls and patients, in brain regions where patients differed from neurotypical controls pre- and post-surgery.



The y-axis represents the weighted mean of activation within a 3mm radius of the peak coordinate in regions of interest summarised as the first eigenvariate for L TPJ [-46, -40, 24], R PRC [36, -4, -36] and L PRC [-36, -10, -32]. The response of each neurotypical control is shown in grey. P1 is shown in blue, P2 is shown in red. Squares pre-surgery, are triangles are postsurgery.

When the patients were considered individually, both showed abnormally high activation in and around the tumour/surgery site. This is difficult to interpret and may have been caused by speech-related movement artefacts. Outside, the tumour region, P1 showed increased activation, postsurgery, in the left hippocampus and bilateral temporal poles. P2 showed abnormally high activation pre- and post-surgery in bilateral ventral and dorsal posterior occipital regions, and bilateral superior temporal regions. Presurgery P2 also showed abnormally high activation in the left inferior frontal sulcus.

Although these patient-specific effects might indicate the type of processing that is compensating for the effect of the tumour or resection, the current study focuses on interpreting the functional contribution of regions where activation was enhanced in both patients as this is more likely to be a consequence of dysfunction in the left temporo-parietal language region that was commonly damaged in both patients.

**Figure 7.7:** Regions where activation for reading > fixation was higher in patients than controls



Red = pre-surgery, green = post-surgery, yellow = areas showing increased activation pre- and post-surgery. The effects are shown on the post-surgery patient-specific structural scans. For visualisation purposes, a threshold of p<0.05 uncorrected was used for both patients pre- and post-surgery.

#### 7.3.4. UNDERSTANDING THE NEURAL CHANGES OBSERVED IN P1 AND P2

Focusing on the neurotypical controls only, all eight conditions in the fMRI paradigm were analysed, to segregate five different types of phonological or semantic processing: (1) accessing phonology, (2) phonological processing that is independent of the stimulus, (3) accessing semantics, (4) semantic

matching and (5) semantically mediated speech production. Full details of these results are provided in the appendix. The current analysis focuses on the response in the four regions where both patients showed more or less activation than controls (Table 7.5).

At the left TPJ site where both patients had (i) tumours, (ii) subsequent surgical resection and (iii) less activation than controls, the neurotypical response pattern was highly significantly associated with phonological processing that was independent of the stimulus. As shown in the top left of Figure 7.8, this region was activated by all speech production tasks and semantic matching on written words.

**Figure 7.8:** Neurotypical activation in regions where both patients showed atypical activation during reading prior to surgery



For abbreviations see Table 7.1.

In contrast, the left perirhinal cortex was significantly activated (p<0.05 corrected) by the main effect of semantics, over task (middle plot in Figure 7.8) and associated with accessing semantics. A similar trend was observed in the right perirhinal cortex (right plot in Figure 7.8) but here the main effect of semantics was only significant at p=0.001 uncorrected (z-score = 3.1).

In summary, patients had less activation than normal in a left temporoparietal region associated with phonological processing that is independent of stimulus; with enhanced activation in bilateral perirhinal cortices associated with semantic processing, and also in a region close to left Heschl's gyrus that is expected to be involved in auditory processing of spoken responses.

## 7.4. DISCUSSION

This study sought to investigate how two patients were able to read aloud written object names following tumours in, and resection of, left temporoparietal regions that are normally involved in phonological processing. The results found no evidence of activation in the affected left temporo-parietal region in either P1 or P2, before and after surgery. As the TPJ region is highly activated (z-score = 7.8) when neurotypical controls are reading words in the same experimental paradigm, the question of interest is how patients are able to read words accurately in the absence of temporo-parietal activity. In both patients, successful reading performance, prior to surgery, was associated with abnormally high activation in parts of the left and right perirhinal cortices, which was maintained after surgery. In addition, post-surgery, both patients showed greater than normal activation in posterior right hemisphere regions associated with visual attention (intraparietal sulcus and occipito-parietal junction) and the auditory cortex that might reflect increased auditory monitoring of the spoken response to reduce errors. There were also patient specific effects for each patient that are not the focus of the current study.

The next sections consider (A) the function of left TPJ region that was dysfunctional in our patients, (B) how perirhinal activation may have contributed to reading, and (C) the presence of enhanced perirhinal activation prior to surgery.

#### (A) The function of the TPJ region that was dysfunctional in our patients

The left TPJ region that was dysfunctional in the patients was associated with phonological processing in the neurotypical controls. Specifically, our neurotypical controls activated left TPJ during (i) semantic matching on written words compared to pictures of objects, consistent with the expectation that written words are more tightly associated to phonology than objects, when no speech production response is required (W. R. Glaser & Glaser, 1989); and (ii) all speech production tasks, irrespective of whether the speech production response was related to the stimulus (as for naming objects and reading words) or independent of the stimulus (as for repeatedly saying "1,2,3" to meaningless stimuli). In the case of repeatedly saying "1,2,3" to meaningless stimuli, the phonological response needs to be held in memory throughout the scanning run. Common TPJ activation for semantic matching of written words, and saying "1,2,3" to meaningless stimuli could therefore reflect the demands on phonological memory.

Other evidence that TPJ is involved in phonological short-term memory has been reported in Oberhuber et al. (2016) using the same data that were presented in Experiment 1. Specifically, left TPJ was activated by silent 1-back matching (a classic short-term memory task) on visual words and pseudowords > objects and coloured patterns, consistent with the demands on phonological short-term memory. In addition, the findings from Experiment 1 showed that TPJ activation is not specific to phonological short-term memory. To the contrary, it was more responsive to non-verbal than verbal auditory stimuli, irrespective of task, and therefore, TPJ was associated with "auditory short-term memory" that was not specific to phonology. This is consistent with the conclusions of a study by Schulze, Vargha-Khadem and Mishkin (2012) who concluded that speech and auditory memory may be so critically dependent on each other that they had co-evolved. Other prior literature support this hypothesis (Buchsbaum & D'Esposito, 2009; Koelsch et al., 2009).

Returning to the current study, the finding that patients can read in the absence of TPJ activation suggests that TPJ was not essential for reading familiar object names (harp, oven, elephant), perhaps because the reading system had reorganised prior to surgery (Thiel et al., 2006), or perhaps because TPJ activation in neurotypical controls is superfluous (i.e. activated but not essential because the task is supported by other processing

pathways). To understand how the patients were able to retain their language, a whole-brain analysis was conducted to identify regions where brain activity was atypically high during reading. The results showed that, pre- and postsurgery, both patients showed significantly more activation than the controls in parts of the left and right perirhinal cortices.

# (B) How perirhinal activation may compensate for damage to the left TPJ?

To investigate how the perirhinal regions that were more activated in P1 and P2 than the controls might be contributing to reading, the conditiondependent response observed in neurotypical controls are explained first, followed by a review of functions assigned to these regions in prior literature. The current study found that the left perirhinal cortex showed greater activation for semantic than non-semantic stimuli in neurotypical controls. A weaker effect of semantics was also observed in the right perirhinal cortex (p<0.001 uncorrected). These findings are consistent with the association of semantic processing with fMRI activation at very similar co-ordinates, for example: [-32, 4, -36] in Crinion et al.(2006), [-39, -9, -36] in Binney et al. (2010), [-36, -10, -35] in Bruffaerts et al. (2013) and [-36, -10, -32] in Rice et al. (2015).

The specific role that the perirhinal cortex plays in semantic processing is more challenging to elucidate because perirhinal activation has also been associated with tasks that increase the demands on visual discrimination, particularly when visual features are integrated into a view-invariant representation (Devlin & Price, 2007) and when matching visual and tactile information associated with wooden blocks that have no semantic associations (Holdstock et al., 2009). These studies suggest that perirhinal cortices are involved in the integration of visual as well as semantic information. Indeed, when visual and semantic similarity were investigated independently in the same participants, Martin et al. (2018) observed that the perirhinal cortex coded both visual and semantic similarity, regardless of whether the task focused attention on visual or conceptual features. Martin and colleagues further concluded that perirhinal cortex was involved in integrating visual with semantic object features (Martin et al., 2018).

Studies of patients provide further evidence for the role of perirhinal cortex in visual and semantic integration. For example, patients with medial temporal lobe damage caused by herpes simplex encephalitis had impairments differentiating concepts that are 'tightly packed' in semantic space (Moss et al., 2005; Noppeney et al., 2007). Kivisaari et al. (2012) concluded that it was specifically the medial perirhinal cortex that was necessary for the disambiguation of perceptually and semantically confusable objects. Most recently, Douglas and colleagues reported a case of a patient with bilateral damage to perirhinal regions who was impaired at controlling interference from competing perceptual or conceptual properties (Douglas et al., 2019). The patient's errors reflected interference from (i) visual features during a conceptual task and (ii) conceptual features during a visual task.

Based on the findings from the fMRI and patient studies discussed above, the proposed hypothesis is that enhanced reading-related activation in the perirhinal cortex, in the context of dysfunctional responses in TPJ, reflects increased efforts to detect and integrate the visual features of words into coherent semantic concepts. During reading, the visual features of words are used to extract the constituent letters that are then mapped onto more coherent larger patterns such as words or phrases (McClelland, 1996; Rosa et al., 2016). Word recognition might therefore be supported by increased perceptual processing of orthographic properties (Grainger et al., 2012; Scarf et al., 2016; Vidal et al., 2021). In the context of P1 and P2, this may reflect increased reliance on a semantic reading strategy if damage to a TPJ region impairs orthographic-to-phonological processing.
#### (C) Enhanced perirhinal activation prior to surgery

It is particularly interesting that both patients showed increased activation in the bilateral perirhinal cortices prior to surgery and that these changes persisted following surgical resection of the tumours. Identification of pre-operative plasticity that persists after surgery has an important clinical impact. Specifically, it opens the possibility for extending the margins of resection, in the anticipation that the detected over-activation in intact brain regions might support behavioural performance after surgery (Ho et al., 2020). Duffau, (2008) suggested that knowledge of the mechanisms underlying cerebral reorganisation is a valuable resource that might be eventually integrated into surgical planning. In the context of the current study, if increased perirhinal activation is observed in patients with temporo-parietal tumours prior to surgery, this might reassure the surgeon that successful reading performance might still be possible, however a decline on object naming tasks is expected.

Although the concept of functional reorganisation has been extensively documented in glioma patients (Duffau, 2015; Duffau et al., 2003; Duffau et al., 2001; Fisicaro et al., 2016; Kong et al., 2016; Vassal et al., 2017), longitudinal fMRI studies are scarce and if available, the results are often difficult to interpret due to lack of data from neurotypical controls. For example, Quiñones et al. (2021) used fMRI and MEG (magnetoencephalography) to map language in five bilingual brain tumour patients, before and after surgery and identified an increase in the level of activation in the left and right middle temporal gyrus in one patient, at both time points. As this study did not include neurotypical controls, the responses in this region were not characterised in detail (Quiñones et al., 2021). In contrast, the current analysis allowed the neurotypical responses to be examined for a range of different language tasks to provide an explanation for how the two patients might be compensating for damage to the temporo-parietal cortex. Interpretation of these changes is crucial for assessing the potential of linguistic recovery following surgery and improving our understanding of the language system.

#### 7.4.1. LIMITATIONS

There are six major limitations of this study. The first is the small sample size because the current analysis included only two patients with tumours and resection in the vicinity of the left temporo-parietal reading area, with the same paradigm and the same scanner. It is therefore not clear how consistently other patients with left temporo-parietal damage will show enhanced activation in bilateral perirhinal cortices. A second limitation is that the two patients differed in the extent of their tumours. P1 had a much larger tumour that extended into motor and frontal regions. It was diagnosed as a WHO grade III anaplastic astrocytoma whereas P2 had a more focal tumour diagnosed as a WHO grade II central neurocytoma. Differences in the rate of tumour growth may therefore have influenced the location and strength of compensatory activity, resulting in inconsistent results across patients. A third limitation is that, although the patients both had (i) damage to the same left TPJ region and (ii) increased activation in perirhinal cortices, there is no evidence to conclude that enhanced perirhinal activation was the consequence of left TPJ damage. It might reflect a generic compensatory strategy when the normal reading system if damaged. This leads to the fourth limitation which is that I did not include a control group of patients with tumours and resections that preserved left TPJ. This would have allowed me to test whether increased perirhinal activation was specific to patients with left TPJ damage. A fifth major limitation is that both patients showed significantly more activation than normal in multiple regions. These effects haven't been interpreted because they were not consistent across patients and they may not have been the consequence of damage to the LTPJ region. Nevertheless, they may play an essential role in compensating for dysfunction in and around the tumour/resection site; and in this context, it cannot be concluded that the patients' ability to read was solely the consequence of enhanced perirhinal activation. A sixth limitation is that atypical activation in the patients might be the consequence of disruptions in neurovascular coupling caused by the tumour (Pak et al., 2017). This could result in false-negative results in the left hemisphere tumour area in the two patients included in this chapter. It may also result in false positive activations in undamaged parts of the left hemisphere, particularly those close to the

tumour. However, disrupted neurovascular coupling in the left hemisphere is unlikely to be the consequence of neurovascular disruption, particularly since the abnormally high activation was also observed after surgical intervention, when compression, shift and oedema around the tumour are resolved.

### 7.4.2. FUTURE DIRECTIONS

Future studies are required to increase the sample size of patients with left temporo-parietal damage. This would assess how consistently readingrelated activation in the perirhinal cortices increases in response to left temporo-parietal damage; and how specific the effect was to lesion site. An increased sample of patients would also allow an investigation into the relationship between reading performance and perirhinal activation. If perirhinal activation is higher for patients who have better reading performance after left temporo-parietal tumours and resection, a surgeon could be more confident that familiar word reading would be possible, if upregulation in perirhinal cortex is observed before surgery. Within-patient, longitudinal, fMRI investigations before and after surgery would provide an opportunity to test whether perirhinal activation increases as patients adapt to the tumour or recover after surgery.

Second, to investigate whether compensatory activation in the perirhinal cortex was specific to patients with left temporo-parietal tumours, we need to assess whether perirhinal activation is abnormally high in patients who have damage to other parts of the reading system (e.g. the left frontal or middle temporal regions). Third, Figure 7.6 illustrates inter-subject variability in the degree to which left TPJ was activated in neurotypical controls. Future studies could examine how inter-subject variability in left TPJ during neurotypical reading and relates to the degree of activation in the bilateral perirhinal cortices. This would determine whether the patients were changing how they used the normal system or adopting an atypical reading strategy. Fourth, along with a better understanding of the connectivity of the reading system, the

results of the investigations proposed above may lead to further insights into the neuroplasticity mechanisms that support functional reorganisation.

#### 7.4.3. CONCLUSIONS

This study found that two patients with tumours affecting a left temporoparietal region involved in phonological processing had impairments on phonological tasks such as reading post-operatively. Nevertheless, the patients were still able to read highly familiar object names. To gain a better understanding of how the reading system changed in the two patients, their activation patterns were compared to those observed in neurotypical controls. In the absence of activation in the left temporo-parietal region, both patients showed enhanced activation in the left and right perirhinal cortices. Based on the condition-dependent response in the neurotypical controls and prior literature, the enhanced response in the perirhinal cortices was associated with increased reliance on the whole-word semantic reading.

This proof-of-concept study demonstrates how data from neurotypical controls can be used to predict what language functions might be affected following resection of temporo-parietal tumours. More broadly, the workflow of this experiment can be applied to tumours in other language regions. Further studies of patients with a wide variety of lesions will provide a better understanding of lesion site-dependent functional reorganisation that is clinically relevant for pre-operative planning

## 8. GENERAL DISCUSSION

The dictum *Primum, non nocere – first, do no harm* is considered as the ethical and moral imperative to prevent the onset of iatrogenic effects. In glioma surgery, this principle needs to be balanced with the clinical benefit of extensive resection. The main question that imposes itself is: How can we protect functions that are extremely precious, yet poorly understood?

The aim of my thesis was to demonstrate how data from neurotypical controls could be used to improve our understanding of speech and language outcome after neurosurgery. The body of work presented progresses our understanding of the neural basis of language and suggests how this knowledge could be applied to guide the selection of tasks for neurosurgical planning. Ultimately, this will help neurosurgeons to predict whether, when and how language can be supported after neurological damage caused by tumours and neurosurgical resection.

Below, I summarise my main results and discuss how my findings provide the building blocks required for a clinical tool that will allow neurosurgeons to understand: (1) which language functions might be impaired by tumour resection, (2) how these functions could be assessed before and during surgery; (3) how consistently neurotypical individuals activate brain regions of interest when engaged in selected language tasks and (4) whether other areas can compensate for the function of the damaged region. In the last section, I describe my long-term vision to provide a clinical tool that will facilitate language mapping during surgical planning.

### 8.1. PROGRESSING OUR UNDERSTANDING THE NEURAL BASIS OF LANGUAGE

This thesis demonstrates the potential of within-subject, multi-factorial fMRI paradigms when interpreting language and other cognitive functions. Explicit inclusion of various cognitive components (factors) provides an opportunity to decompose tasks into separable processes, which can be considered as independent effects or interactions (Friston et al., 1996). For instance, activation for a language task that is common across modalities cannot be explained in terms of sensory or perceptual processing. Instead, it suggests the engagement of higher-level processing, such as covert speech production, abstract representations of speech sounds and/or auditory short-term memory. Factorial analyses allowed me to functionally dissociate three posterior superior temporal lobe regions and four subdivisions of the left premotor/motor cortex.

In Experiment 1, I investigated the functional organisation of speech processing in the temporal lobes. The results revealed that (1) there were three spatially distinct regions with unique response properties, located in left pSTS (dorsal surface), left atSTS and left TPJ, (2) left TPJ and left pSTS are not selective to phonological processing and (3) the auditory memory function in left pSTS is different from that in left TPJ. Validation of these findings in a separate, larger cohort of participants (Experiment 2) increased confidence that these findings are robust rather than false positives.

Left TPJ was more activated for nonverbal than verbal auditory stimuli but insensitive to semantic content. Its response was most consistent with encoding and sustaining auditory representations on-line. In contrast, left pSTS was more activated for non-semantic than semantic stimuli but not for nonverbal > verbal stimuli. This suggests that the role of left pSTS in auditory short-term memory increases when there is no support from semantic memory - an observation that might explain why increased activation in left pSTS was also observed during audio-visual integration (Erickson et al., 2014; Szycik et al., 2012) and attention, memory and executive tasks (Liebenthal et al., 2014).

The third region identified in Experiments 1 and 2 was in atSTS between left TPJ and left pSTS. Left atSTS was not sensitive to the demands on phonological retrieval, sublexical assembly, semantic content, or unfamiliarity. Although it was not possible to elucidate the role of atSTS based on the available data, I was able to demonstrate that left atSTS contributes to a range of language tasks with a response profile that is distinct from both left pSTS and left TPJ. This motivates further research to establish the functional contribution of atSTS to both linguistic and nonlinguistic tasks.

In Experiment 3, I re-examined the role of left frontal lobe regions in discrete aspects of generating a speech plan (before motor execution). The multifactorial design allowed me to test whether premotor activation for pseudoword compared to word production was also observed when pseudoword production was compared to object naming. I found that there are at least four different parts of the left premotor/motor cortex that differentially contribute to articulatory planning during reading, repetition, and object naming.

The results from Experiment 3 found evidence that activation in ventral but not dorsal premotor cortex is sensitive to the demands on sublexical assembly. In dorsal premotor cortex, activation was higher for object naming than word reading. Although this is not consistent with the demands on sublexical assembly as previously suggested. by Mechelli et al. (2005), the response in this region was consistent with the demands on retrieving fine-grained motor plans (Chen et al., 2008; Meister et al., 2009). The findings of Experiment 3 therefore furthered our understanding of the functional anatomy of language and resolved inconsistent claims in previous literature.

### 8.2. APPLYING KNOWLEDGE OF THE NORMAL LANGUAGE SYSTEM TO SELECT TASKS FOR NEUROSURGICAL PLANNING

In Experiment 4, I used functional consistency maps to quantify and compare inter-subject variability in activation for different object naming paradigms. In neurotypical controls, naming pairs of objects in a noun phrase or a sentence elicited a more robust response than naming single objects. This suggests that naming pairs of objects might show higher sensitivity for detection of intra-operative deficits however, this will require validation in a clinical sample.

More importantly, Chapter 6 highlights the utility of functional consistency maps in selecting lesion site-specific testing paradigms, which currently lack standardisation (Ruis, 2018; Sefcikova et al., 2020). Previous studies have mainly focused on examining the spatial overlap between different language testing paradigms (e.g. Unadkat et al., 2019). In contrast, the presented approach (i) does not necessitate the use of arbitrary t-score thresholds, thereby reducing the risk of bias; (ii) allows for visualising activation over a range of different statistical thresholds, and (iii) provides a score to indicate how consistently activation is observed across subjects in each voxel (Seghier & Price, 2016).

Functional consistency maps could enhance the precision of computerised platforms for behavioural testing by recommending lesion site-specific language paradigms. For instance, Morrison et al. (2016) utilised a novel tablet technology to administer tasks based on fMRI predictions and found that the traditional assessments, number counting and conversational speech, were not sensitive enough to detect language deficits in two cases. When these patients were evaluated with a word-generation task, previously used during pre-operative fMRI, speech arrest sites were identified. The excellent concordance between pre-surgery fMRI and intra-operative findings reported in this study might be partially due to the presentation parameters

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and the type of stimulus being identical in the two environments (Morrison et al., 2016). It is unclear however, how the pre-surgery fMRI testing paradigms were selected. I propose that the sensitivity of intra-operative testing could be maximised by integrating these testing platforms with pre-surgery fMRI tasks that have been selected using functional consistency maps.

### 8.3. HOW LANGUAGE CAN BE SUPPORTED AFTER NEUROLOGICAL DAMAGE CAUSED BY TUMOURS AND NEUROSURGICAL RESECTION

The key insight from Chapter 7 is the hypothesis that the perirhinal cortices may contribute to accurate reading performance in patients with left temporo-parietal damage. Specifically, I studied two patients who had tumours affecting the left TPJ region associated with auditory short-term memory in Experiment 1. Both patients retained the ability to read familiar words before and after surgery, with no evidence of left TPJ activation but with higher than normal activation in bilateral perirhinal cortices before and after surgery. Further research is now required to increase the sample size and ensure that these results are generalisable to other patients with damage to the left temporo-parietal language region associated with auditory short-term memory.

A second contribution of Chapter 7 was to show how abnormal activation following neurological damage could be investigated by studying neurotypical controls with multi-task fMRI. Specifically, I showed that activation in the perirhinal regions is normally enhanced by the demands on semantic processing of visual stimuli. This provides an intuitive understanding in cognitive terms: Dysfunction in regions important for phonological processing resulted in increased semantic processing, consistent with there being different neural pathways for reading.

#### 8.4. LONG-TERM VISION – AN INTEGRATED CLINICAL TOOL

The work conducted during my PhD has motivated me to develop a clinical tool that will: (i) facilitate the selection of pre-operative planning tasks; (ii) predict outcome after surgery; and (iii) provide recommendations for individualised cognitive neurorehabilitation strategies. In the next section, I will discuss how the findings from each chapter fit within the broader context of this tool and outline my plans for future research.

# (1) Which language functions might be affected by tumour resection and how could they be assessed before and during surgery?

To facilitate neurosurgeons addressing this question, I plan to create a 3-dimensional atlas of language functions in the human brain. I have to date segregated the functions of multiple posterior superior temporal lobe regions that participate in speech perception (Experiment 1) and multiple frontal regions that contribute to speech production (Experiment 3). These results will be combined with prior findings that dissociated the functions of four different parts of the supramarginal gyrus for speech production (Oberhuber et al., 2016), three different parts of the angular gyrus for semantic processing (Seghier et al., 2010), two different parts in the left anterior temporal lobe for semantic processing (Sanjuán et al., 2015) and three different parts of the left ventral occipito-temporal cortex for reading aloud (Ludersdorfer et al., 2019). The atlas will allow the neurosurgeon to establish the functional importance of the area affected by a tumour and tailor the selection of tasks for pre-surgery fMRI and intra-operative testing.

The use of functional anatomical maps that are derived from a single multitask fMRI paradigm and subsequently validated in an independent group of participants would be a stepping stone to standardisation in brain mapping practices that is currently lacking (O'neill et al., 2020; Sefcikova et al., 2020).

# (2) What degree of inter-subject variability is expected in the functional response of targeted brain regions?

The output from the previous step needs to be complemented by functional consistency measures from neurotypical controls matched for demographics (e.g., age, gender handedness) to maximise the likelihood of selecting the most reliable task for pre- and intra-operative mapping. The approach adopted in Experiment 4 needs to be extended to delineate networks of regions that respond to other linguistic tasks. Data from functional consistency maps will be particularly important for neurosurgical planning in patients who are unable to undergo pre-operative fMRI due to various contraindications. For instance, strong magnetic fields may lead to the malfunction of devices such as pacemakers or implantable cardioverter defibrillators (Ghadimi & Sapra, 2019). It is therefore not possible to obtain fMRI data in these cohorts of patients, which hinders the neurosurgeon's ability to identify the function of regions affected by the tumour.

# (3) Can other brain areas compensate for the function of the damaged region?

In Experiment 5, I demonstrated that two patients with tumours affecting a temporo-parietal region showed increased activation in the bilateral perirhinal cortices. This study was limited by the inclusion of only two patients. More research is needed to increase the dataset and enable the investigation of the functional reorganisation in patients with brain tumours affecting other regions. These findings will contribute to our understanding of which areas (a) can be compensated for and therefore, safely removed during surgery or (b) are critical because their resection leads to permanent deficits.

The long-term vision for this work is an integrated clinical tool that is able to use a single anatomical brain scan from the patients and basic demographic details to (i) indicate which brain regions are affected by the tumour; (ii) output the tasks and language functions that normally activate regions in and around the tumour; (iii) supplements each output with measures of inter-subject variability; (iv) provides information about how the brain could functionally re-organise. This project would be an adaptation of a tool that is currently being developed using the Predicting Language Outcome And Recovery After Stroke (PLORAS) database (Seghier et al., 2016).

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# APPENDICES

## A1. PHONOLOGICAL EFFECTS OF INTEREST

Region	Х	у	Z	Vx	Zsc	
Accessing phonol	ogy (g	x = -56				
atSTS	-56	-42	6		7.8	CSEC
cA22	-62	-34	4	132	7.5	
	-48	-40	2		7.1	
apsis	50	-30	0	17	5.8	
Pars opercularis	-54	12	0	7	5.1	
Phonological mem	ory (y	ello	w)			
atSTS	-58	-42	6		7.6	x = -50
vpSTS	-62	-30	-2		7.6	
	-60	-40	26		6.7	
	-54	-42	28	405	6.4	
TPJ	-52	-38	20		6.0	CAL 27 C.S.
	-64	-40	16		5.7	
	-44	-40	24		5.0	
	48	-34	18	6	5.5	
pSTS	54	-34	0	64	5.9	
Area 6r	-58	12	4	35	5.8	

Right: Sagittal slices at x = -56 and x = -50 show left hemisphere effects thresholded at p<0.05 corrected for multiple comparison across the whole brain. Green = accessing phonology, yellow = phonological memory. Left: Peak MNI co-ordinates, the number of voxels (Vx) in each cluster and z-scores (Zsc). cA22 = caudal portion of Brodmann area 22, dpSTS = dorsal posterior superior temporal sulcus, vpSTS = ventral posterior superior temporal sulcus, TPJ = temporo-parietal junction.

### A2. REGIONS ASSOCIATED WITH ACCESSING SEMANTICS

Region	v	v	7	Vv	7sc	-
Tomporol	~	У	2	**	230	-
Temporal			-			- z = -36
atSTS	-50	-42	8	11	7.4	
Inferior temporal ovrus	36	-38	-24	14	6.3	
	-44	-48	-14	~~-	8.0	
Fusiform Face Complex	-38	-44	-24	937	7.9	A BACK
Parahippocampal Area A3	-28	-42	-18		7.0	
Perirhinal cortex	-36	-10	-32	8	6.6	
Frontal						
Supplementary and	4	10	ΕA		0.0	
cinqulate eve fields	-4	12	54		0.3	
Area 32	-2	22	36	416	7.3	
Superior Frontal Language	_					6 0
area	-4	2	68		6.0	
Pars orbitalis	_3/	32	-16		8.0	x = -50
	-04	202	-10	379	7.4	× 000
Orbitofrontal cortex	-30	20	_1/	010	7.4	
DIPFC(pQAGV)	-42	20	2/		7.0	
Erontal operculum	-40	20	24	530	7.9	C 1
Pare opercularie	-42	18	20	550	7.0	
	-04	10	20		1.1	CALLY CA
	- 10					
Ventral lateral nucleus	-12	-16	10	66	6.7	
Cerebellum						
CB Crus 2	10	-80	-36		7.8	
CB Vermis 7	6	-74	-24	318	7.3	
CB Crus 2	20	-76	-42		7.3	
CB Lobule 6	34	-66	-26	79	6.2	
CB Vermis 9	-2	-58	-34	6	55	

Right: Coronal slice at z = -36 shows activation in the left and right perirhinal cortex and a sagittal slice at x = -50 shows left hemisphere effects at p<0.05 corrected for multiple comparison across the whole brain. Left: Peak MNI co-ordinates, the number of voxels (Vx) in each cluster and z-scores (Zsc). atSTS = anterior superior temporal sulcus, DLPFC = dorsolateral prefrontal cortex.

#### A3. REGIONS ASSOCIATED WITH SEMANTICS-TO-PHONOLOGY

Region	Х	У	z	Vx	Zsc	
Temporal						10
aSTG	-62 -52 58 50 62	-12 12 8 16 -12	-2 -6 -8 -14 -2	17 31 17 14 9	6.1 5.6 6.2 5.7 5.3	z = +8
Other						
Supplementary and cingulate eye fields	-4 -2	12 4	50 58	258	7.9 7.4	KCKOM
Area 32	-2	22	36		7.8	
Premotor eye field	-46	-2	42	7	5.8	
Midcingulate cortex	16	-8	30	12	5.7	
Cerebellum						x = <u>-3</u>
Crus 2	-6	-74	-38	118	6.8	
Vermis 8	4	-72	-40	74	6.5	
Vermis 4/5	2	-54	-22	74	0.0 6.3	A CARACTAR
Vermis 8	$\overline{0}$	-64	-42	15	5.9	
Lobule VI	-32	-44	-26	9	6.6	
Lobule VI	-30	-54	-22	28	5.7	
Lobule 4/5	-22	-50	-18	20	5.4	
Lobule VI	-40 -4 -8 30	-52 -68 -62 -48	-28 -12 -16 -36	ь 24 7	6.1 5.4 5.1 5.3	

Right: Coronal slice at z = +8 and a sagittal slice at x = -3 show activation in bilateral anterior superior temporal gyri, the midcingulate cortex and the cerebellum at p<0.05 corrected for multiple comparison across the whole brain. Left: Peak MNI coordinates, the number of voxels (Vx) in each cluster and z-scores (Zsc). aSTG = anterior superior temporal gyrus.

### A4. REGIONS ASSOCIATED WITH SEMANTIC MATCHING

Region	Х	У	z	Vx	Zsc	•
Temporal						x = -54
Area TE1	-52	-48	-12	173	7.3	
pMTG	-60	-44	-8	170	6.7	
Frontal						
IFS	-52	26	20		7.9	
Area 47m	-34	32	-14	1062	7.8	
Pars opercularis	-52	18	28		7.8	
	-4	24	46		7.3	- Y
Area 8 (8BM)	-2	36	42	92	6.1	
	4	26	42		5.2	x = -48
pIFS	52	32	20		6.1	
alFJ	42	20	24	140	6.0	
pIFS	46	32	12		5.9	
Inferior 6-8 Transitional Area	-26	8	54	34	5.8	8. 5
Parietal					1	
Medial IntraParietal Area	-30	-66	42	124	7.3	
Cerebellum						
Crus 2	10	-82	-34	190	7.9	- Y
Crus 1	22	-76	-26	100	5.9	
Crus 2	28	-74	-42	23	6.6	

Right: Sagittal slices at x = -54 and x = -48 show left hemisphere effects. Left: Peak MNI co-ordinates, the number of voxels (Vx) in each cluster and z-scores (Zsc). aIFJ = anterior inferior frontal junction, pIFS = posterior inferior frontal sulcus, pMTG = posterior middle temporal gyrus.