Examining phonological processing in the healthy and damaged brain

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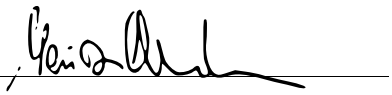
I, Marion Oberhuber, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: 

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Abstract

In this thesis I explore the neural signature of different types of speech sound processing, in the healthy brain and after damage through stroke.

The first two Experiments applied a newly developed fMRI language paradigm in healthy controls to study phonological retrieval from speech, orthography and semantics. This showed that there are at least two types of phonological processing that can be dissociated on a neuronal level. Bilateral superior temporal gyri were associated with processing auditory (phonological) representations of speech, consistent with the notion of input to phonology. In contrast, left putamen and precentral cortex/pars opercularis were associated with pre-articulatory activity, and thus with outputs from phonology. The validation of the results in a separate, larger sample increased confidence that these findings are robust rather than false positives.

Experiment 3 was concerned with examining the role of a “key player” in phonological processing, which revealed that different parts of the supramarginal gyrus differ in their response profile during a set of language tasks. This is in accordance with cytoarchitectural and connectivity studies demonstrating the structural variability of the region, and has implications for prior imaging studies considering the supramarginal gyrus as a uniform entity in the phonological network.

The final experiment revealed that the loss of supramarginal gyrus through stroke has inconsistent effects on language abilities, possibly due to other brain regions or white matter tracts that were damaged in some patients but not in others. It also showed that additional brain regions were recruited in patients compared to controls, which might reflect compensatory brain activation that supports recovery.

Taken together, this work proposes a new way of interpreting phonological effects, in particular within the supramarginal gyrus, and new insights into how the brain supports phonological processing after stroke-induced damage.

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Abbreviations

a	Anterior
ANG	Angular gyrus
Aud	Auditory
BA	Brodmann area
BOLD	Blood-oxygen-level-dependent
CB	Cerebellum
d	Dorsal
DCM	Dynamic causal modelling
EEG	Electroencephalogram
EPI	Echo-planar imaging
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FWE	Family-wise error
GLM	General linear model
Hb	Haemoglobin
Hipp	Hippocampus
HRF	Haemodynamic response function
INS	Insula
IPS	Intraparietal sulcus
ISI	Inter-stimulus interval
IFG	Inferior frontal gyrus
ITG	Inferior temporal gyrus
LH	Left Hemisphere
MFG	Middle frontal gyrus
MNI	Montreal Neurological Institute
OBM	One-back matching
OCC	Cccipital cortex
p	Posterior
PET	Positron emission tomogoraphy
PM	Premotor cortex
pOrb	Pars orbitalis

PostC	Postcentral gyrus
PreC	Precentral gyrus
pOp	Pars opercularis
pTri	Pars triangularis
PUT	Putamen
RH	Right hemisphere
RF	Radiofrequency
ROI	Region of interest
RT	Response time
SD	Standard deviation
SMA	Supplementary motor area
SMG	Supramarginal gyrus
sMRI	Structural magnetic resonance imaging
SP	Speech production
SPM	Statistical parametric mapping
STG	Superior temporal gyrus
STS	Superior temporal sulcus
tDCS	Transcranial direct current stimulation
TE	Echo time
TMS	Transcranial magnestic stimulation
TPJ	Temporo-parietal junction
TPole	Temporal pole
TR	Repetition time
v	Ventral
Vis	Visual
VLSM	Voxel-based lesion symptom mapping
VBM	Voxel based morphometry
vOT	Ventral occipito-temporal
Zsc	Z-score

1. INTRODUCTION

1.1. Motivation and aims

Phonology is defined as the branch of language concerned with the function, behaviour and organization of speech sounds (Lass, 1984). Phonological processing involves detecting, dissociating, manipulating and articulating speech sounds. It therefore underpins multiple functions that are fundamental to speech comprehension, production and reading. The brain areas involved in phonological processing have been studied extensively using neuroimaging methods such as PET (positron emission tomography) and fMRI (functional magnetic resonance imaging). It is now accepted that phonological processing needs to be supported by many different non-phonological processes, such as sensory processing, working memory, "higher-order" executive functions, and more. As a consequence, it can be difficult to dissociate phonological processing from that involved in other types of processing. This is likely to explain why neuroimaging studies of phonology have collectively associated phonology with many different brain regions in temporal, frontal and parietal areas (Demonet et al., 1992; 1994; Dietz et al., 2005; Graves et al., 2007; Heim et al., 2013; McGettigan et al., 2011; Mechelli et al., 2003; Peschke et al., 2012; Poldrack et al., 1999; Schwartz et al., 2012; Twomey et al., 2015). Critically, the results are often specific to the input modality (e.g. visual versus auditory input), task-specific (e.g. decision making tasks versus speech production tasks) or do not replicate across studies. Thus, one of the aims of this thesis was to identify the neural architecture underlying phonological processing, within and across modalities, by using a novel, comprehensive fMRI language paradigm. This fMRI paradigm allowed me to distinguish between different types of phonological processing and the underlying neuronal networks, which is also crucial for hypothesis-guided testing of "abnormal" activation during speech in clinical populations. Moreover, I attempted to validate these findings in a separate, larger sample of healthy controls, which is particularly important in the light of the recent "replication crisis" in social and cognitive science (Eklund et al., 2016; Open Science, 2015).

The neuroimaging literature has been particularly inconsistent in describing which part of the supramarginal gyrus (SMG) is important for "phonological processing". Despite being frequently associated with tasks that increase phonological demands, the reported locations of the activation peaks within SMG show a great deal of variability. Using the language paradigm mentioned above, I set out to explore functional specialisation within SMG, and the contribution of these subregions to different types of phonology.

The results from Experiments 1, 2 and 3 were the basis for the patient study I report in Experiment 4. Armed with predictions from healthy controls, I investigated how phonological processing is affected if there is damage to the SMG regions associated with phonological processing. In those patients who had preserved or recovered phonological processing abilities, I investigated how this recovery took place by comparing brain activation of stroke patients and healthy controls during the same experimentally manipulated conditions. This allowed me to reveal recovery mechanisms and potential compensatory activity in brain regions that might or might not be, part of the existing language network in healthy controls.

1.2. Summary of the core aims

i. Dissociating the neural signatures of different types of phonology in the healthy brain, using a new fMRI language paradigm that also allows different language properties (i.e. sublexical and lexical phonological and semantic processing) to be dissociated from non-speech effects. (**Experiment 1**)

ii. Validating the results from Experiment 1, using slightly modified presentation parameters, in a separate, larger sample of neurologically healthy subjects to increase confidence that the results are not false positives but real effects. The increased power also revealed additional regions within the phonological network that did not reach the required statistical threshold in Experiment 1. (**Experiment 2**)

iii. Applying the fMRI paradigm to dissociate functionally-distinct subregions within the supramarginal gyrus (SMG) and test their contribution to word processing. Re-interpreting “phonological” effects that have been associated with SMG. (**Experiment 3**)

iv. Exploring post-stroke language re-organisation in stroke patients with good phonological abilities despite parietal lesions, taking into account inter-subject variability that was observed in the control sample. (**Experiment 4**)

1.3. Phonological processing

1.3.1. Definition & theoretical models

Phonology (from Greek *phone* for “voice, sound”; and *logos* for “word, speech”) is concerned with the study of speech sounds and is one of the fundamental pillars of language. Without the ability to map the sound structure of speech, we would not be able to understand, manipulate or articulate spoken or written language. The other pillar of language is semantics, which is concerned with meaning, or content. In this thesis, I will also use the terms *lexical* and *sublexical* to further characterize phonology or semantics. Lexical processing refers to representations at the whole-word level, whilst sublexical concerns sub-units of a word (or nonword) such as phonemes or syllables. In language research, it has always been a central subject of interest to understand how phonological processing supports and complements semantics, and how it is represented in the brain.

When looking at theoretical models of word processing, it becomes apparent that most modern researchers propose that phonological and semantic functions are distributed in a parallel hierarchical fashion across the brain. From a computational point of view, a parallel processing structure makes sense because it is faster than serial processing. For instance, Gaskell and Marslen-Wilson (1995) hypothesized in their *connectionist model of phonological representation in speech perception* that incoming low-level sensory representations (e.g. spoken words that we hear) are mapped simultaneously, but separately, onto a semantic or phonological representation. This is already similar to the dual-pathway idea that most modern models of speech processing are based on (e.g. Hickok and Poeppel, 2000). In analogy to the visual “where” and “what” pathways in the brain (Milner and Goodale, 1993), language processing is thought to be supported by a ventral stream, that maps sensory input onto meaning, and a dorsal stream that maps sound onto articulatory representations (Hickok and Poeppel, 2000, 2004; Parker et al., 2005; Saur et al., 2008). Anatomically, the ventral stream projects from the bilateral middle temporal gyrus to ventrolateral prefrontal cortex, whilst the dorsal stream connects the posterior part of the sylvian fissure to premotor regions via the

arcuate and superior longitudinal fascicle (see Figure 1.1). Both pathways are supposed to operate bi-directionally, for instance in word repetition, a feedback loop provides post-articulatory auditory or sensorimotor feedback. In the DIVA model of speech output, Guenther et al. (2006) proposed that there are "error cells" located in the superior temporal gyrus (STG), firing when the expected and actual speech output do not match. Similarly, there is a somatosensory error control system, involving the supramarginal gyrus (SMG), which is activated when the speaker's tactile and proprioceptive output differs from the expected output.

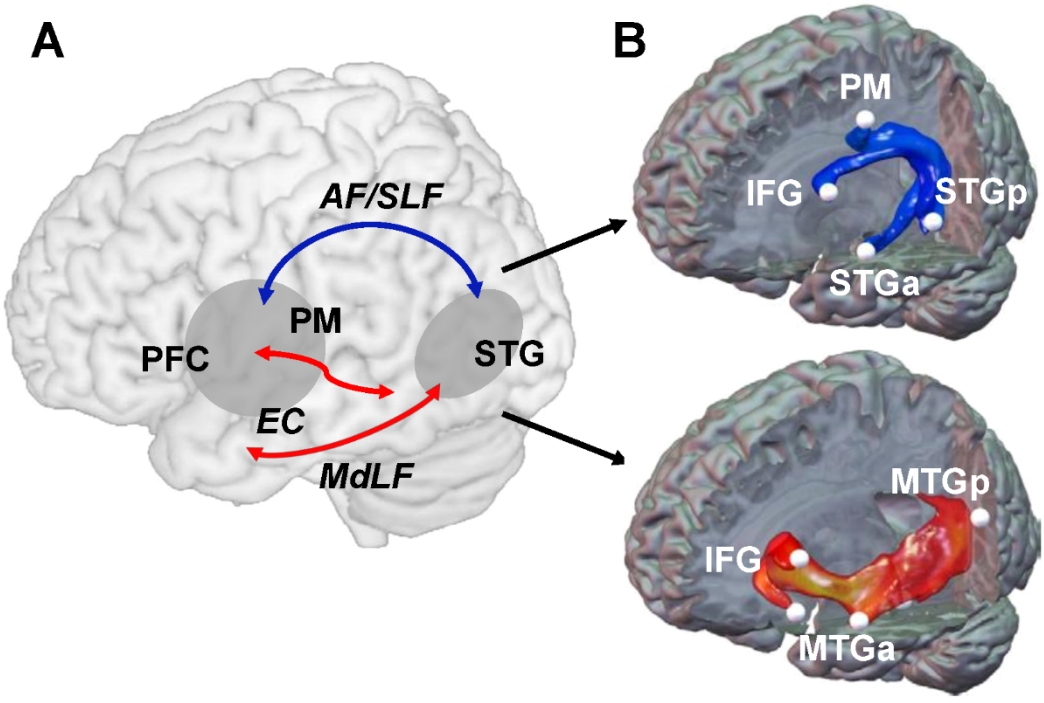


Figure 1.1: (A) Dual-route model of auditory language processing. The ventral stream (in red) is dedicated to transforming sound-to-meaning and the dorsal stream (in blue) is involved in mapping sound to articulatory representations. (B) Tractography results illustrating the fibre tracts connecting anterior and posterior brain regions that are part of the dorsal/ventral stream. 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 & Hartwigsen (2012). Reprinted with permission. © 2012 American Congress of Rehabilitation Medicine.

Gow (2012) extended the dual-pathway model of Hickok and Poeppel (2000) by proposing that word forms are stored in two separate lexicons. In his dual-lexicon model of spoken language, the posterior temporal lobe and superior temporal sulcus (STS) provide a ventral lexicon that supports the mapping from sound to meaning. The SMG and adjacent parietal operculum form the dorsal lexicon for mapping acoustic-phonetic representations to articulation.

In 2012, Price (2012) integrated previous findings from brain imaging studies of language conducted between 1992 and 2011 into a functional-anatomical model of word processing (see Figure 1.2) that described phonological processing in sensory and motor terms that are not specific to speech. According to the model, an incoming visual or auditory stimulus (e.g. a written or spoken word) is first processed in the primary sensory areas of the brain. By integrating these sensory features with prior knowledge, we form a visual or auditory mental image of the presented stimulus. Auditory images of speech are equivalent to phonological (input) representations but the model uses generic terms to emphasize that the same brain regions are involved in auditory images of non-speech sounds. If the sensory inputs carry semantic cues (e.g. familiar words, pictures or sounds of familiar objects), semantic associations can be retrieved and linked to the articulatory patterns associated with the word or object name (word retrieval stage). If there are no semantic cues available, articulatory plans can only be retrieved from non-semantic parts, e.g. the sublexical parts of an unfamiliar pseudoword (a pronounceable nonword). This non-semantic route to articulation is referred to as “articulatory recoding” in the model but is equivalent to phonological recoding (or output phonology) in other cognitive models (see below). Finally, the articulatory plans are used to initiate orofacial motor activity when the task involves a speech response. This generates an auditory stimulus (the speech response) and somatosensory processing (i.e. we can feel the movement in the speech articulators). The self-produced stimuli result in auditory and somato-sensory processing that is predicted by the speaker (from past experience particularly during language acquisition). The predicted auditory and somatosensory processing can therefore be directly compared to the experienced auditory and somatosensory

processing. If they differ, an error signal is generated that can be used to make necessary adjustments in subsequent speech production.

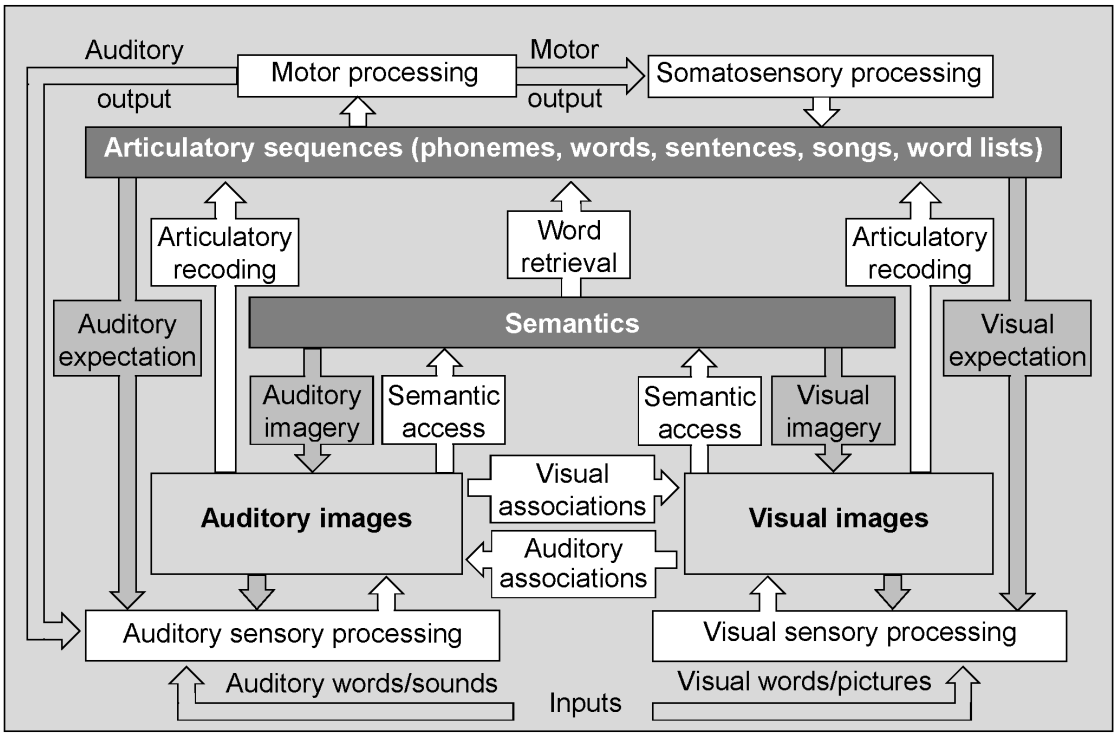


Figure 1.2: Model of language processing (adapted from Price, 2012). Dark box: Prior knowledge (multimodal representations). White boxes: Bottom-up processing from sensory inputs. Light grey boxes: Top-down processing from prior knowledge. Other boxes: sensory inputs and motor outputs.

1.3.2. Input versus output phonology

In addition to separate processing streams for semantic and phonological information, it is evident that there are different types of phonological processing. Howard and Franklin (1993) distinguish between an input phonology buffer, which is required for the decoding, segmenting and manipulating of phonological codes, and an output phonology buffer, which stores whole-word phonology and is necessary for speech production. To rehearse phonological input, the relevant information is cycled between the two stores (phonological or articulatory recoding). This proposal is supported by reports of impaired performance in a rhyming judgment task (that focuses on the sublexical phonological inputs) when output phonological processing is not available, for example, when participants are instructed to count at the same time as making the rhyming judgements (Richardson, 1987).

Evidence for different types of phonological processing has been derived from single case patient studies. For example, Martin et al. (1999) presented an interesting case study of a patient with intact pseudoword reading but impaired word reading. The authors suggest that the patient had a deficit in retrieving phonology from semantics, whilst his sublexical phonological processing was preserved. More recently, Howard et al. (2005) presented two case studies further supporting the view of two phonological stores. Patients MMG and HB showed relatively intact performance in tasks requiring the phonological output buffer (e.g. homophone judgments and pseudoword reading) but impaired performance when the task required analysis of the sublexical structure of representations in the phonological input buffer (e.g. during visual rhyme judgments, pseudohomophone detection and phonological manipulation tasks with nonwords). Both patients showed unimpaired speech comprehension and production skills.

1.3.3. Phonological versus semantic processing in patient studies

Most models on speech processing assume that both semantic and phonological processing complement each other when we are processing speech, but that the underlying neural architecture for each processing stream differs. We know from pathological findings that patients with focal damage can have selective deficits in either semantic or phonological tasks, or both. For instance, patients presenting with “semantic dementia” have difficulties with semantic memory, e.g. failure to recognise familiar objects. This impairs their ability to read familiar words that have atypical spellings that do not allow direct (non-semantic) links between orthography and phonology. On the other hand, they are still able to produce spontaneous speech and read regular words, a dissociation characteristic of surface dyslexia (Jefferies et al., 2004; Patterson et al., 1994). Neuro-anatomically, patients with semantic dementia and surface dyslexia show loss of grey matter (atrophy) mainly in the anterior temporal lobe (Ogar et al., 2011; Wilson et al., 2009). This contrasts to the temporo-parietal and frontal lesions that have been observed in patients with phonological dyslexia (Coltheart et al., 2001; Marshall and Newcombe, 1973) who have the

reverse dissociation (i.e. more difficulties reading pseudowords than familiar words with atypical spelling).

A third patient group presents with word finding difficulties (anomia) after stroke, tumour resection or epilepsy. Anomia is often associated with lesions in the left posterior inferior temporal gyrus (Herbet et al., 2016; Hillis et al., 2005; Ogar et al., 2011). Further evidence for distinct neural systems supporting semantic and phonological processing comes from a voxel-based lesion symptom mapping (VLSM) study of stroke patients, which associated different brain regions with semantic and phonological errors (Schwartz et al., 2012).

1.3.4. Phonological versus semantic processing in imaging studies

Functional neuroimaging studies of healthy populations have investigated the neural systems involved in many different types of phonological tasks. Chapter 3 reviews the results of studies that have compared phonological to semantic or perceptual processing and discusses how some of the results may be confounded by activation related to perceptual or higher order cognitive processing. Thus, the first aim of this thesis was to map the “phonological system” in the brain, and to dissociate different types of phonological processing, such as input and output phonology, by manipulating task and stimulus content (phonology and semantics) within one fMRI paradigm. As apparent from the literature, few studies have addressed the question of the neural basis of input and output phonology. Our knowledge is mainly based on pathological findings (Howard and Nickels, 2005; Martin et al., 1999; Wilding and White, 1985) rather than on controlled manipulation of experimental conditions in neurologically healthy participants. Moreover, there are inconsistencies in how phonological processing can be tested and interpreted, which might be one of the reasons that some results have not replicated across previous studies. Therefore, the second aim of my work was to validate the results from Experiment 1 in a separate sample, to reduce false positives/negatives and to increase confidence in my findings (see Experiment 2).

In the literature review conducted for Chapter 3 (Experiment 1), one region has emerged as particularly important for phonological processing: the left supramarginal gyrus (SMG) in the inferior parietal lobe. However, reports of SMG involvement in phonological tasks are inconsistent regarding the type of phonology they concern, and often spatially inconsistent. One of the aims of this thesis was to investigate the contribution of SMG to phonological processing, and to potentially find alternative interpretations for SMG activation in phonological tasks, as it has been reported in prior studies (see Experiment 3). In the following paragraphs, I will summarise the involvement of SMG in language and non-language functions, and finally illustrate its structural diversity by presenting findings from anatomical, cytoarchitectural and connectivity studies.

1.4. Supramarginal gyrus (SMG)

1.4.1. SMG involvement in language functions

The hypothesis that SMG is involved in the processing of speech sounds dates back to early studies reporting greater SMG activation for auditory speech sounds compared to non-speech sounds, during active tasks such as phonological decisions (Demonet et al., 1992; 1994) as well as during passive listening tasks (Celsis et al., 1999). Activation increase in SMG has also been found for extracting speech sounds from visually presented stimuli, i.e. during reading and lexical decisions on unfamiliar pseudowords compared to familiar words (Binder et al., 2005; Ischebeck et al., 2004; Thompson et al., 2007; Vigneau et al., 2005; Xu et al., 2001). Studies that kept the stimulus material constant while manipulating the task further contributed to our understanding of the role of SMG. For instance, SMG is more active for phonological than semantic decisions on written words (Devlin et al., 2003; Mummery et al., 1998; Price et al., 1997; Scott et al., 2003; Seghier et al., 2004). Importantly, however, there is evidence that SMG is also activated for basic auditory tasks such as detecting auditory change in pitch (Zevin et al., 2010) and for discriminating onsets in tones versus syllables (Hutchison et al., 2008). This emphasizes that SMG is involved in the processing of both speech and non-speech sounds, and

might suggest a more general role of SMG in directing attention towards a salient (auditory) stimulus.

Other studies associated SMG with amodal verbal working memory, based on findings that activation in an anterior ventral part of SMG increased when participants were performing short term memory tasks on visual letter strings (Paulesu et al., 1993) and auditory words or syllables (Buchsbaum and D'Esposito, 2009; Koelsch et al., 2009). A study addressing the question of functional dissociation in verbal working memory within SMG (Ravizza et al., 2004) found that the dorsal part of SMG is sensitive to load in working memory tasks, but not to the stimulus type, i.e. verbal or non-verbal stimuli, and suggested that dorsal SMG might be involved in domain-general, executive functions such as attention switching or task preparation. In contrast, ventral SMG was sensitive to stimulus type manipulation (greater activation for verbal than nonverbal stimuli) and might therefore support phonological encoding and basic speech processes. Hope et al. (2014) provide support for a role in domain general processing of dorsal SMG by reporting dorsal SMG activation across a series of language tasks versus fixation, independent of speech production demands.

1.4.2. TMS findings on phonological processing in SMG

The contribution that SMG makes to phonological processing has also been investigated with TMS, a technique which selectively and temporarily influences brain activation while participants are engaged in specific cognitive functions. Repetitive bursts of TMS (rTMS) to bilateral ventral SMG have been found to disrupt performance in a phonological task as well as in an n-back task on the same auditory stimuli, independent of phonological complexity (Deschamps et al., 2014). This was interpreted as evidence that SMG is part of the verbal working memory network without being involved in encoding/decoding phonological information per se. Slower and less accurate responses after SMG stimulation have also been reported for phonological tasks on visual stimuli (Romero et al., 2006; Sliwinska et al., 2012; 2015). Finally, Hartwigsen et al. (2010) found impaired phonological processing in both modalities after TMS to

dorsal SMG, whereas Deschamps (2014) applied TMS to a ventral part of SMG, and included auditory stimuli only. This suggests that there might be a ventral part of SMG that is important for working memory processes related to auditory stimuli, but a more dorsal part of SMG involved in amodal phonological processing. In addition, the studies mentioned above differ in their choice of baseline, which might affect the results. A thorough review of the cognitive processes that have been associated with different SMG subregions is provided in Chapter 5, when I investigate functional specialisation within SMG for different types of phonological processing.

1.4.3. Non-language functions of supramarginal gyrus

Although the SMG, particularly in the left hemisphere, has repeatedly been shown to be activated during tasks that involve phonological processing, it has also been associated with other non-linguistic functions (Humphreys and Lambon Ralph, 2014). For example, the posterior SMG has been associated with long-term memory functions (Henson et al., 1999; McDermott et al., 2000). This is supported by observations of strong functional connectivity between the inferior parietal cortex and classic memory regions in the hippocampal and parahippocampal cortex (Daselaar et al., 2013; Vincent et al., 2006). TMS (transcranial magnetic stimulation) and neuroimaging studies also support the notion that inferior parietal activation is involved in memory retrieval (see meta-analysis by Vilberg and Rugg, 2008). In an attempt to further characterise the role of SMG specifically in memory processes, it has been demonstrated that the retrieval of memories (i.e. remembering items) activates the more ventral part of SMG, while the more dorsal intraparietal sulcus is sensitive to the familiarity of the stimulus (Wheeler and Buckner, 2004). However, a meta-analysis of memory retrieval, combining resting state functional connectivity data and fMRI, did not identify the SMG (Nelson et al., 2010), apart from a significant cluster in the posterior part of inferior parietal lobe, including angular gyrus (ANG). The hypothesis of an essential role of SMG in episodic memory retrieval is also inconsistent with the observation that lesions to SMG do not reliably lead to episodic memory impairment (for a review, see Cabeza et al., 2008; Hower et al., 2014).

A possible alternative interpretation for SMG involvement in memory tasks comes from studies of attentional functions. In a review of episodic memory retrieval, Ciaramelli et al. (2008) found that SMG, and the surrounding ventral part of the inferior parietal lobe, are most consistently activated when memory tasks had a strong attentional component, e.g. for strong versus weak memories, more vivid versus less vivid recollection memory, and high versus low confidence memory retrieval. The authors propose an “attention-to-memory” hypothesis, suggesting that ventral parietal cortex plays a particular role in automatic, bottom-up attention allocation during memory processes rather than being involved in retrieval per se (see also Cabeza et al., 2008). Functional neuroimaging studies and tractography studies that aimed to dissect the executive components of working memory provided further evidence that SMG, in particular its anterior dorsal part, is predominantly involved in attentional shifting (for a meta-analysis, see Nee et al., 2013).

Other studies showed that the SMG is activated for both observing and imitating the actions of others, particularly hand movements (Caspers et al., 2006; 2010). A common theory suggests that SMG is part of the mirror neuron system that responds when observing the action of others (Hamilton and Grafton, 2006; Rizzolatti and Luppino, 2001). From a predictive coding perspective, mirror properties have also been interpreted as representing the link between sensory input and motor acts, whereby the observer infers the most likely goal of the observed action by minimising the prediction error (Kilner et al., 2007). Together with premotor cortex and superior temporal sulcus, SMG might represent the neuronal circuit that translates observed actions into motor representations (Buccino et al., 2001; 2004). Reports of SMG involvement in visuo-spatial working memory tasks, such as block tapping (Metcalfe et al., 2013), fit with this account since these tasks are based on action imitation between tester and test subject.

Left SMG and the adjacent intraparietal sulcus are also involved in number processing and arithmetic, e.g. in judgements of quantity on numbers or number words (Cappelletti et al., 2010), mental subtraction of Arabic numbers (Simon et al., 2002), and determining the distance between two numbers

(Fulbright et al., 2003). A large-scale meta-analysis based on key-word search in the neurosynth database revealed that maths cognition functions showed most overlap with reasoning tasks in posterior SMG, suggesting a common underlying process such as rule-based mental logic (Wendelken, 2015). Others argue that parietal activation during numerical tasks is instead indicating parietal involvement in stimulus- and response-selection functions (Fiez et al., 1996; Gobel and Rushworth, 2004).

Clearly, SMG is involved in multiple functions, therefore one of my aims was to be precise about which parts of SMG are involved in phonological processing – and how these parts differ in their functional contribution to language. To emphasize the versatility of the SMG also on a structural level, I will give an overview of the anatomical location, connections and cellular composition of the SMG in the following paragraphs.

1.4.4. Anatomical location and connections

The supramarginal gyrus is a structure in the inferior parietal lobe and can be defined by anatomical landmarks and cytoarchitectural properties. According to Brodman (1909), *area supramarginalis*, or BA 40, borders anteriorly with the somatosensory cortex/postcentral sulcus, caudally with the ANG and ventrally with the lateral sulcus (see Figure 1.3).

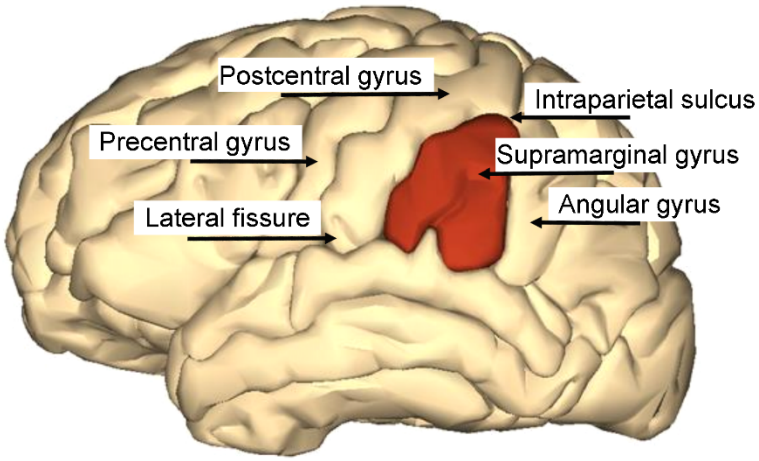


Figure 1.3: Supramarginal gyrus (in red) with surrounding structures on lateral view of left hemisphere of the human brain. Figure adapted form Wikimedia Commons (BodyParts3D, © The Database Center for Life Science licensed under CC Attribution-Share Alike 2.1 Japan).

Based on cytoarchitectonic characteristics, such as cell density, type and shape, the SMG can be divided into five different subregions (Caspers et al., 2006). Receptor density mapping techniques clustered these 5 regions into a rostral and middle group (with an additional caudal cluster comprising two areas in the ANG) (Caspers et al., 2013). Importantly, there is considerable variability between subjects, as well as between the two homologues in each hemisphere within subject (see Figure 1.4). This variability seems to be independent of anatomical landmarks and is therefore important to consider when mapping fMRI activation onto an anatomical template brain across a group of subjects.

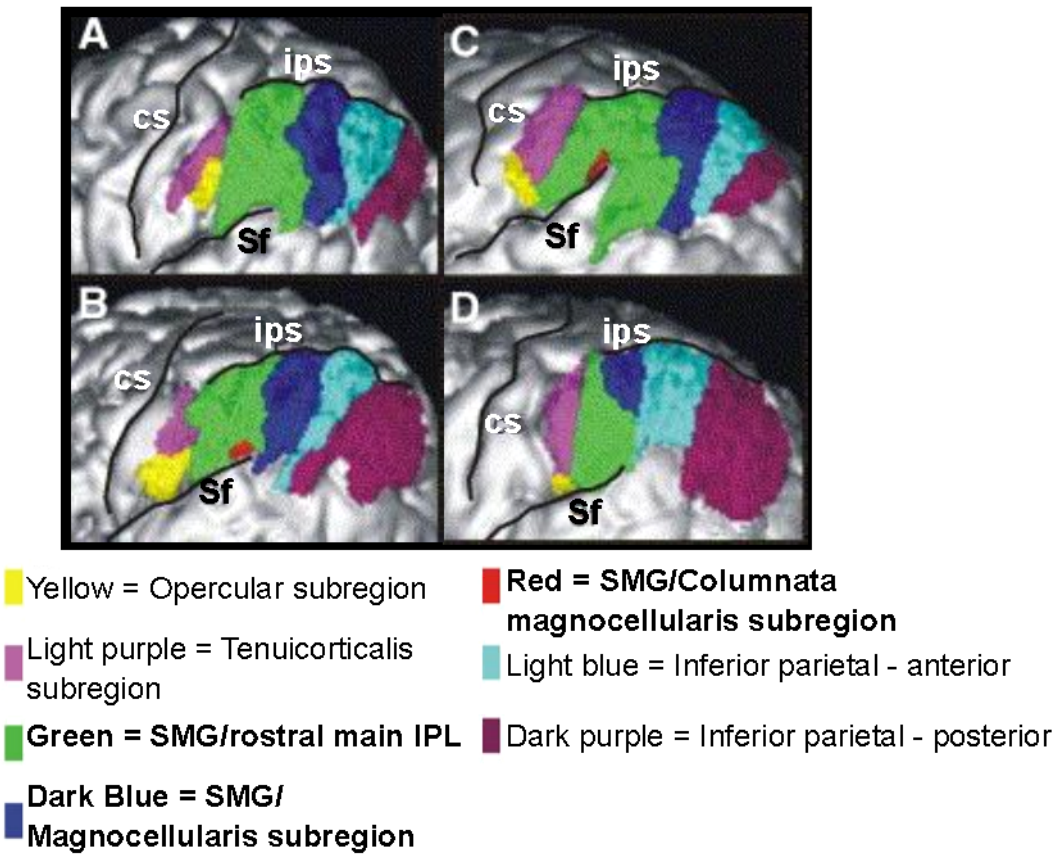


Figure 1.4: Inter-subject variability in inferior parietal subregions across four healthy subjects (A, B, C, D) (Caspers et al., 2006). Same colours correspond to the same subregion across subjects. SMG consists of green, dark blue and red subregions (in bold). Parcellation is based on cytoarchitectonic characteristics, and the nomenclature is adopted from von Economo and Koskinas (1925). Note that there is no obvious correspondence between macroanatomical landmarks and cytoarchitectonic subregions. cs = central sulcus, Sf = Sylvian fissure, ips = intraparietal sulcus. Figure adapted from Caspers et al. (2006). Reprinted with permission. © 2006 Elsevier Inc.

The diversity in microstructure is also reflected in the connectivity. Fibre tracts from SMG are mainly connected to inferior frontal, postcentral and superior parietal regions, and follow the course of superior longitudinal and arcuate fascicles (Caspers et al., 2011) (see Figure 1.5). There is also an indirect pathway running parallel to the arcuate fasciculus from Broca's territory (posterior inferior frontal gyrus) to an anterior part of the intraparietal sulcus, and from a posterior part of inferior parietal lobe (closer to the ANG) to Wernicke's area in the posterior STG (Catani et al., 2005). Direct and indirect pathways are supposed to represent the anatomical correlates of semantically-mediated

versus phonologically-mediated processing. The connectivity pattern of SMG in humans corresponds largely to the one observed in macaque monkeys, however, humans compared to monkeys seem to differ in two ways: they have stronger connections between the anterior inferior parietal lobe and temporal lobe (which are stronger in the left than in the right hemisphere), which might be related to the development of human language skills (Caspers et al., 2011; Catani et al., 2005; Ruschel et al., 2014), as well as stronger interactions with anterior prefrontal cortex, an area that has been associated with higher cognitive control functions (Mars et al., 2011).

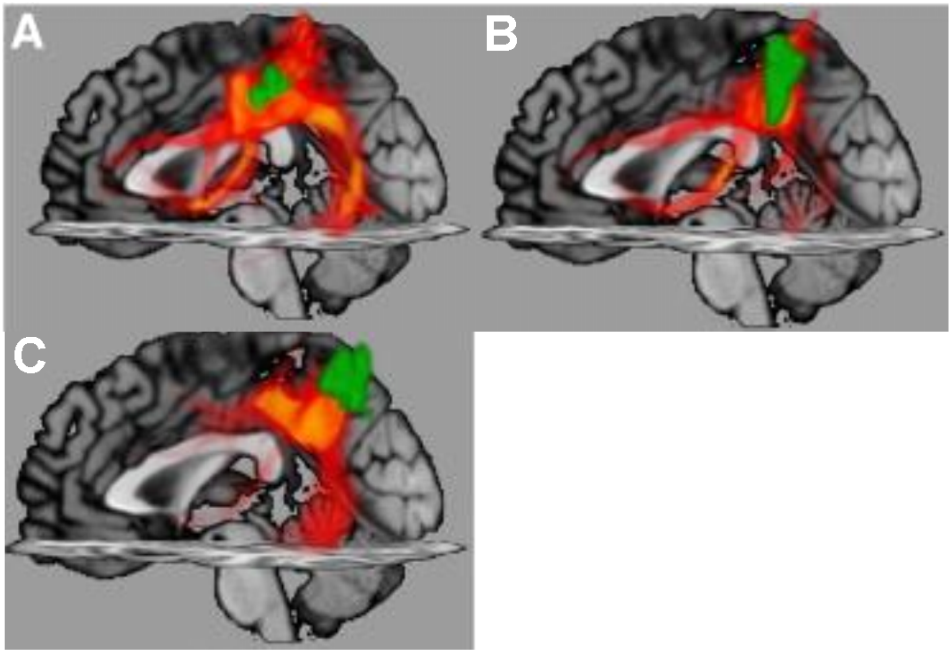


Figure 1.5: Illustration of three subregions (A, B, C, in green) within SMG and corresponding fibre tracts as identified through probabilistic tractography. Opaque yellow means low uncertainty, transparent red means high uncertainty. Figure adapted from Caspers et al. (2011). Reprinted with permission. © 2011 Elsevier Inc.

To summarise, I have reported that (i) there are multiple different types of phonological processing, (ii) tasks requiring phonological processing also require other higher cognitive functions including attention and memory retrieval, (iii) it can be difficult to segregate phonological processing from other types of cognitive processing, (iv) left SMG is considered to be an important site for phonological processing but (v) SMG is also activated by other cognitive

processes. The relationship between different types of phonological processing and different parts of SMG is therefore unclear. In my first three experiments (Chapters 3 to 5), I used functional imaging of healthy participants to investigate different types of phonological processing with a particular interest in the response in different parts of SMG. In my final experimental chapter, I investigated the effect of SMG damage on phonological processing in patients (a lesion-deficit study). On finding that some patients had good phonological skills despite damage to SMG regions that are normally activated during phonological processing, I investigated whether good phonological skills after SMG damage involved activation in (A) other brain areas (i.e. other brain regions could compensate for the phonological function of SMG); or (B) activation in a subset of the normal phonological areas – suggesting that SMG was not critical to phonological processing.

1.5. Parietal stroke & language impairment

A stroke occurs when the blood supply to a part of the brain is disrupted or severely reduced. This can be caused by a blood clot blocking a vessel (ischemic stroke) or by a leaking or bursting artery (haemorrhagic stroke). It is a devastating condition, affecting more than 150.000 people in the UK alone every year, and 15 million people worldwide. Approximately 1/3 of stroke survivors are left with language difficulties, or aphasia, which has a severe impact on their social life, work life and general well-being (Laska et al., 2001; Pedersen et al., 2004). Understanding the neural basis of aphasia, and post-stroke recovery, is essential and will provide the basis for developing better treatment in the future. In this work, I am focussing on patients who had a stroke in their parietal lobe, the impact of their lesion on phonological processing abilities, and functional reorganisation that potentially supports recovered phonological functions.

1.5.1. Lesion-behaviour correlations

It has been known for a long time that the location of the lesion is a crucial factor for the understanding of language outcome and the course of post-stroke recovery. However, other factors such as initial severity of the (aphasic)

symptoms, demographic factors, lesion volume, or the combination of lesion locations play additional important roles (Lazar and Antoniello, 2008; Plowman et al., 2012). Nevertheless, studies looking at the correlation between lesion location and related symptoms provide valuable insight into the functional role of a brain region, and the mechanisms of reorganisation and plasticity. Outlined below are the most commonly reported implications of parietal, including SMG, stroke in different patient groups.

In acute stroke patients, i.e. less than 24 hours post-stroke, it has been shown that left parietal lesions correlate strongly with nonword reading deficits (Cloutman et al., 2011; Hillis et al., 2001; Philipose et al., 2007), which suggests the parietal lobe is important for translating orthography to phonology. In chronic stroke patients, phonological awareness/abilities, measured for example with a rhyme judgement task, correlate with lesions in the perisylvian region (including posterior SMG, anterior ANG and STG), even after controlling for working memory demands, articulation, word comprehension, orthographic access, lesion volume and demographic factors (Pillay et al., 2014). Pillay et al. (2014) conclude that these regions represent the key network for pre-articulatory phonological access. A study that aimed to identify the neural network involved in inner speech used a similar silent rhyme judgement task, compared to an overt homophone-reading task, and found a correlation between task impairment and integrity of the white matter tract adjacent to SMG. In addition, they reported a significant correlation between task performance and the structural integrity of the inferior frontal gyrus, a region that has been associated with the conscious monitoring of inner speech (Geva et al., 2011). The white matter tracts connecting inferior frontal gyrus and SMG that have been identified by Geva et al. (2011) are likely to be part of the dorsal language stream, where the phonological output code is transferred to for further processing.

A study by Schwartz and colleagues (2012) measured phonological access for speech production by analysing the different types of errors in a picture naming task. They included aphasic stroke patients that were at least one month post stroke, which resulted in a group of 106 patients. The highest correlation between phonological errors in picture naming and lesion site was

found in left SMG, premotor cortex, pre-and postcentral regions, which represent the key components of the classic dorsal language stream (Murakami et al., 2015; Parker et al., 2005; Saur et al., 2008). Another lesion-deficit analysis including a small sample of 11 subacute patients (<5 weeks post stroke) found that poor performance on a rhyming task correlated with a broad range of left hemisphere regions including SMG, STG, Insula and temporal pole (Boukrina et al., 2015). However, the authors do not know which type of phonological deficit was causing the phonological errors. Nor can they exclude the possibility that other cognitive deficits that co-occur with phonological errors (e.g. verbal working memory impairments) were driving the correlation with the identified regions during the phonological task.

Turning to studies that correlated brain damage with impairments on tasks with auditory pseudowords, there is evidence that impaired nonword repetition correlated with damage to SMG, postcentral gyrus, STG and the temporo-parietal junction (Dell et al., 2013). Interestingly, the only area that was associated with phonological errors during naming and pseudoword repetition was the SMG, extending into the postcentral gyrus. According to the authors this cluster might be involved in the common underlying process of extracting phonological representations. Another study (Fridriksson et al., 2010b) found that low scores on speech repetition correlated with structural damage to the white matter tract surrounding SMG, i.e. arcuate fasciculus, in acute stroke patients. A follow-up analysis by the same authors revealed, however, that grey matter damage in the inferior portion of SMG has the highest predictive value for repetition impairment, rather than the underlying white matter fibres. Speech comprehension performance was factored out as regressor of no interest.

In summary, lesion-behaviour analyses consistently identified damage to inferior parietal lobe as key locus for phonological processing deficits, independent of input modality. However, the small number of patients available often makes it difficult to identify patients with focal lesions, and most analyses included patients with larger lesions spreading over to neighbouring parietal, temporal, occipital and frontal regions. Another point worth noting is that some patient studies report that the strongest correlation with phonological deficits

appears with ANG rather than SMG, which is inconsistent with the neuroimaging literature. Plausibly, this finding might be due to vascular properties, i.e. a stroke often affects both territories (e.g. Cloutman et al., 2011; Philipose et al., 2007; Pillay et al., 2014), rather than reflecting a key role of ANG in phonological processing. There are few studies that have included a comprehensive assessment of phonological abilities in stroke patients, in particular in the acute phase, and the results have only limited predictive value, when not controlled for factors such as working memory, attention or articulation. The patients that I included in my analysis had damage to the same part of SMG, underwent a comprehensive language assessment in the fMRI scanner, and their data are compared to a large control sample, who underwent the same experimental manipulation. The availability of both structural and functional data will allow me to test for the degree of structural damage within a region of interest, as well as for task-related BOLD signal. This should provide novel insights into structure-function relationships in stroke patients who have suffered damage to the SMG.

1.5.2. Recovery mechanisms

Modern neuroimaging and other brain mapping methods provide a much better understanding of how the brain adapts and recovers language after a stroke, in response to classic behavioural interventions, TMS, drugs or spontaneous recovery (Berthier et al., 2011; Crinion and Leff, 2007; Hartwigsen, 2016). Studies including acute stroke patients provide insight into brain functions after stroke before re-organisation or recovery has taken place. On the other hand, to understand the long-term neural changes that occurred when language functions have been recovered, longitudinal studies with repeated measurements from the same patient are conducted, or imaging data from chronic patients are compared to early stage patients or to neurologically healthy subjects. Critically, samples are often too small to generalise to the larger patient population, and the results might be biased due to unpublished null-results. Nevertheless, the wealth of research has established three main theories aimed at explaining the mechanisms of post-stroke recovery in the brain. First, the peri-lesional hypothesis, second, the laterality-shift hemisphere hypothesis, and third,

the disinhibition/malfunctioning theory (Geranmayeh et al., 2014; Hamilton et al., 2011; Warburton et al., 1999). Figure 1.6 illustrates the three theories.

The **peri-lesional hypothesis** states that the regions immediately adjacent to the damaged area play a key role in mediating compensatory activity after stroke (Heiss and Thiel, 2006; Hillis et al., 2008; Teasell et al., 2005; Warburton et al., 1999). Studies have shown that increased activation in the tissue surrounding the lesion is associated with better performance in picture naming (Cornelissen et al., 2003; Fridriksson et al., 2010a; Meinzer et al., 2008), word-stem completion (Rosen et al., 2000) and cued word production (Warburton et al., 1999). There is evidence from animal studies for axonal sprouting from the intact cortex to peri-infarct regions, as well as strengthening of existing synapses in rats, which is associated with better (motor) recovery (Carmichael, 2006; Murphy and Corbett, 2009; Uryu et al., 2001). Dendritic and synaptic changes in perilesional tissue in human stroke survivors have also been reported, although the exact mechanisms are not yet well understood (Brown and Murphy, 2008). Whilst it has been shown that neuronal activity in the ischemic penumbra can be initiated and stimulated through task-induced activation, the ideal timing and dose of behavioural training still remains to be determined (Cooke et al., 2010).

According to the **laterality-shift hypothesis**, right hemisphere homologue regions are recruited in order to compensate for functional loss in the left hemisphere. A meta-analysis across fMRI studies of chronic stroke patients found that in addition to spared left hemisphere language regions patients consistently activated right homologues. However, some right hemisphere regions were functionally homologues with left hemisphere regions, such as right pars opercularis, while others were not, such as right pars triangularis (Turkeltaub et al., 2011). Saur et al. (2006) reported that shortly after stroke, an upregulation of right hemisphere regions is observed, which correlated with language improvement. In the chronic phase, surprisingly, activation peaks re-shifted to left hemisphere language areas, associated with further behavioural improvement in an auditory comprehension task. A recent VBM (voxel based morphometry) study (Xing et al., 2016) found that grey matter volume in the right

hemisphere correlated with language outcome in stroke survivors, after controlling for lesion and demographic factors. The result suggests that structural changes in the right hemisphere may indicate the recovery potential of the patient (Xing et al., 2016). Overall, there is yet no consensus over the role of the right hemisphere in language recovery (e.g. Crinion and Leff, 2007; Turkeltaub et al., 2012), and there are numerous studies associating right hemisphere involvement after stroke with a negative impact on recovery (see below).

The **disinhibition theory** is an alternative account of interpreting right hemisphere involvement after stroke, suggesting that increased right hemisphere activation in language tasks in stroke survivors indicates inefficient or maladaptive reorganisation. This is possibly due to a reduction of inter-callosal inhibition from the affected (left) hemisphere to the unaffected (right) hemisphere. Studies have indeed shown that increased right hemisphere activation after stroke is correlated with decreased performance in language tasks, e.g. with more errors in a picture naming task (Postman-Caucheteux et al., 2010). A number of TMS and tDCS (transcranial direct current stimulation) studies targeting the right hemisphere have demonstrated that cortical inhibition in human stroke patients, applied alone or in combination with behavioural interventions, can lead to a significant improvement of language skills (Hamilton et al., 2010; Monti et al., 2008; Naeser et al., 2005). The findings suggest that the modulation of cortical activity through non-invasive brain stimulation is a promising tool for enhancing language recovery, possibly by suppressing the dysfunctional over-activation from the contralateral hemisphere, (for reviews, see Hamilton et al., 2011; and Schlaug et al., 2011). It is also possible that some areas in the right hemisphere support and some inhibit recovery, whereas others have no impact at all.

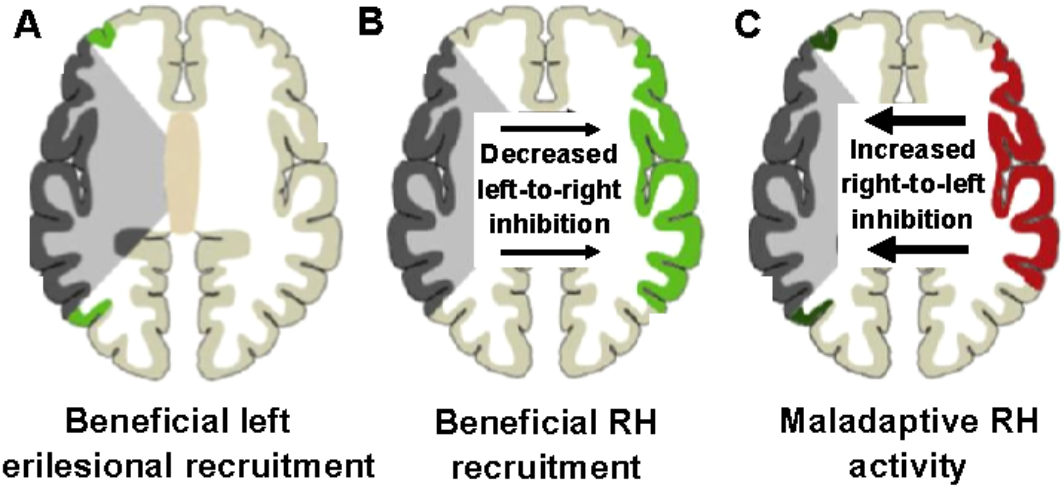


Figure 1.6: Three established theories of plasticity and re-organisation after left hemisphere stroke (grey area). A. Peri-lesional hypothesis; B. laterality-shift theory; C. disinhibition theory. Figure adapted from Hamilton et al. (2011). Reprinted with permission. © 2011 Elsevier Inc.

Finally, there are some attempts to integrate the hypotheses stated above. For instance, it is possible that lesion volume is one of the deciding factors in re-organisation, i.e. smaller lesions are more likely to lead to recruitment of the peri-lesional area, whilst larger regions are more often associated with a functional shift to right hemisphere regions (Schlaug et al., 2011). Recovery was found to be better in patients who recovered their left hemisphere language functions, compared to those who showed compensatory activation in the non-dominant hemisphere (Winhuisen et al., 2005). Another possibility is that pre-morbid language lateralisation determines the degree to which the contra-lateral hemisphere will be involved in the recovery phase, i.e. more evenly distributed language functions (i.e. weaker lateralisation) seem to correlate with better compensation through the unaffected hemisphere (Knecht et al., 2002; but see Thiel et al., 2006b for different results). As discussed above, the timeline of recovery also seems to have an effect on the course of recovery, with a shift in activation from the affected hemisphere to the contra-lateral hemisphere in the subacute phase, and back to the language-dominant hemisphere during the chronic phase (Saur et al., 2006; Winhuisen et al., 2007). Support for this theory comes from a study comparing slowly and rapidly growing

brain tumours in the left hemisphere. They found that right hemisphere compensatory activation was only observed during language tasks in those who had tumours that were growing slowly (Thiel et al., 2006a).

Despite enormous progress in imaging and cortical stimulation studies in patient cohorts over the last few decades, the exact biological mechanisms that underlie post-stroke recovery remain poorly understood. Variability between patients is large, and whilst averaging across patient groups can be beneficial for creating recovery predictions (e.g. Hope et al., 2013; 2017; Tilling et al., 2001), it is also crucial to understand how re-organisation works in individual patients. In Experiment 4 I will address the questions of how SMG damage after stroke affects phonological abilities of stroke survivors, if and how compensatory activity takes place, and if effects of plasticity are observed within or outside “normal” language nodes as observed in controls.

2. METHODS

2.1. Summary

In this chapter, I am going to introduce the two main methodologies used for my work: structural magnetic resonance imaging (sMRI) and functional MRI (fMRI). The former (sMRI) is widely used to investigate brain structure and was applied here to identify lesions to the supramarginal gyrus and improve the spatial normalisation of my fMRI studies. Most of my studies used fMRI because it allowed me to look at metabolic processes associated to brain functions over time, while participants completed specific cognitive tasks in the scanner. sMRI and fMRI were the most suitable neuroimaging techniques for this work, because they are non-invasive and have high spatial resolution across the whole brain, despite this coming at the expense of lower temporal specificity. I will explain how these methods work and describe the pre-processing pipeline and statistical analysis that I used for my experiments with healthy populations as well as stroke patients. I also introduce the tasks and methods for a new comprehensive fMRI paradigm that was tested in both healthy participants and stroke survivors. Any deviation from the standardised procedures outlined below is explained in each experimental chapter individually.

2.2. The basic physics of structural magnetic resonance imaging (sMRI)

sMRI relies on the magnetic properties of the hydrogen nuclei (single protons) in water. Since two thirds of the body consists of water, it makes it an easy and available target to measure throughout the human body. Under normal circumstances, hydrogen protons are spinning randomly on their axis, cancelling out each other's magnetic moment without creating an overall magnetic field. However, when exposed to a strong external magnetic field, such as an MRI scanner, the precession of the proton spins align and a magnetic vector is created (Berger, 2002). The speed at which the aligned protons spin depends on the strength of the static magnetic field of the scanner. This is usually as strong as 1.5 Tesla or 3 Tesla (I used 3T in all of my experiments).

If an electromagnetic pulse (radiofrequency pulse, or RF pulse) is fired at the protons in the magnetic field, with the appropriate frequency (Larmor frequency), it causes them to flip (usually by 90 degrees) into a high-energy anti-parallel state. This is called excitation. As soon as the pulse is switched off again, the hydrogen protons gradually “relax” back to their equilibrium state, emitting radiofrequency energy. The time it takes the protons to re-align with the magnetic field, along the axis that they have been excited, is determined using a time constant known as T1. The relaxation time T1 depends on the type of tissue the protons are in (e.g. grey matter, white matter, cerebrospinal fluid), and differences in T1 can therefore be used to create a “map”, or image, of different tissue types (Logothetis, 2002). Simultaneously, the time it takes for magnetisation (around the flipped protons) to decay due to the protons spinning out of sync again, the spin-spin relaxation, is measured through a time constant referred to as T2. However, the protons actually dephase quicker than T2 due to inhomogeneities in the magnetic field. An additional time constant T2* was therefore introduced, to accommodate these field inhomogeneities. T2*-sensitive sequences form the basis for fMRI. See Figure 2.1 for an example of an anatomical image based on T1 values.

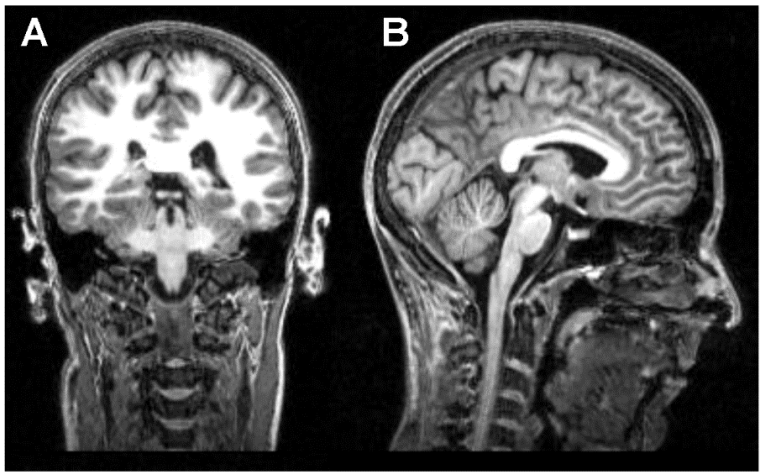


Figure 2.1: Example of T1 weighted structural image (courtesy of Suz Prejawa) on the coronal plane (A, from back to front) and on the sagittal plane (B, from side to side). Cerebral spinal fluid appears black, fat (e.g. white matter) appears bright.

In summary, an MRI scanner applies a strong magnetic field to the body, prompting hydrogen protons to line up in a specific direction. Repeated energy pulses cause the protons to flip into an anti-parallel state, whereby the time it takes them to return to their resting state is measured through a receiver coil positioned above the participant's head. The scanner processes this raw data (using a Fourier Transformation) to produce MRI images. sMRI scanning provides (T1 or T2/T2* weighted) images of the *structure* of the brain and is particularly useful in clinical settings to detect abnormalities, e.g. damage to the brain after a stroke. In order to measure the *function* of the brain, several images need to be captured sequentially to identify changes over time. This technique is called fMRI, which I am going to explain in the next section.

2.3. Functional magnetic resonance imaging (fMRI)

fMRI works by detecting changes in the paramagnetic properties of oxygenated and deoxygenated haemoglobin. The measurement of interest is commonly known as the blood-oxygen-level-dependent (BOLD) signal (Ogawa et al., 1990). It is based on the assumption that brain regions that work harder use more energy (Logothetis, 2008). As a consequence, local blood flow increases in order to meet this increase in demand. This leads to a higher proportion of oxygenated haemoglobin (Hb) than deoxygenated Hb in the active brain region. Importantly, oxygenated and deoxygenated Hb have quite different magnetic properties: while oxygenated Hb is not significantly different to other tissues or water, deoxyhaemoglobin is paramagnetic and more susceptible to magnetic fields (Gore, 2003). Just before returning to baseline, the level of oxygenated Hb briefly falls below the original level (called undershoot). With fMRI, using the T2* contrast, we can measure inhomogeneities in the magnetic field due to changes in the ratio of paramagnetic deoxygenated Hb, and slightly magnetic, oxygenated Hb, i.e. the BOLD signal. In an experimental setting, a series of stimuli, e.g. in form of written words, is presented to a participant in the scanner, and we can measure the BOLD signal repeatedly to reveal the underlying haemodynamic response of a particular region over time (see Figure 2.2). The modelling of the haemodynamic response function (HRF) is illustrated in the statistical analysis section.

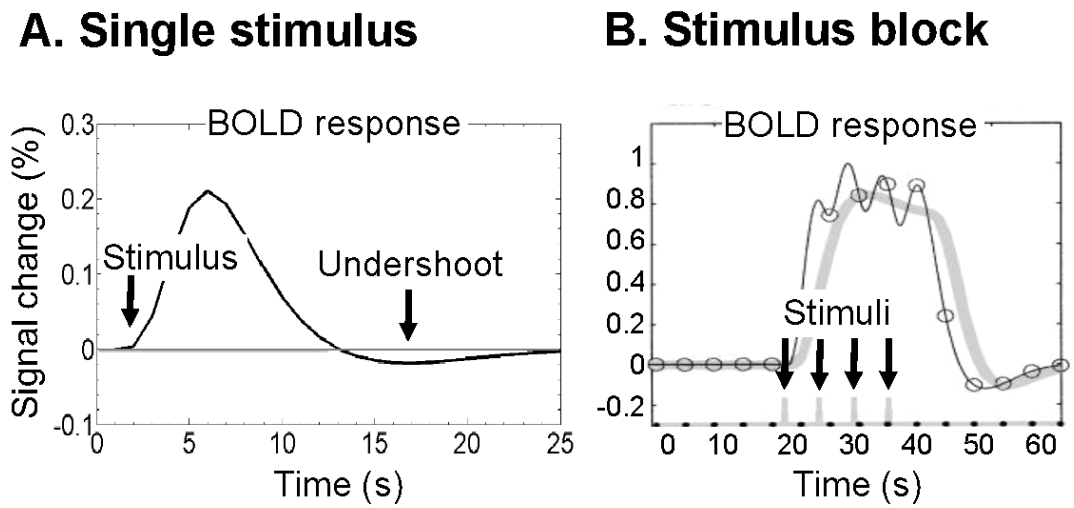


Figure 2.2: A. The haemodynamic response function (HRF) as measured with BOLD after a stimulus is presented (e.g. a written word). The peak BOLD value is reached after about 5-7 s, followed by the undershoot after around 12 s and returns to baseline over the course of 12-20 s. B. In comparison, presentation of a block of stimuli (i.e. a series of written words), as it was the case in my fMRI experiments, results in a stronger and longer lasting BOLD response. Figure adapted from Price et al. (1999). Reprinted with permission. © 1999 Academic Press.

2.4. Scanning parameters

All structural and functional MRI data described in this thesis were collected on one of two available 3T scanners (both Trio, made by Siemens, Erlangen, Germany), using a 12 channel head coil. In the following paragraph, I will explain the main parameters for the applied scanning sequence. Any deviance from the standard sequence is described in the respective experimental chapter.

For the functional images I used echo-planar imaging (EPI), a fast MRI technique (Mansfield, 1977), 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) refers 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) describes the time in ms between the radiofrequency pulse and MR signal sampling. Longer TR and TE result in higher resolution (measured in voxels, which are essentially 3D pixels) but at the cost of longer total scanning

time. In my case, the TR was chosen to achieve whole brain coverage (i.e. 44 slices) and to ensure that slice acquisition onset was de-synchronized with each stimulus onset for distributed sampling of slice acquisition across each scanning session (Veltman et al., 2002). The flip angle determines the degree to which the net magnetization is rotated relative to the main magnetic field. The field of view (FOV), defined as the spatial encoding area of the image, was 192mm, when the matrix size was 64 × 64, and there were 44 slices, with a slice thickness of 2 mm and an inter-slice gap of 1 mm. I used a total of 62 volumes in Paradigm 1 and 66 in Paradigm 2). Each set of volumes is referred to as a "time series".

Whole brain anatomical images were high-resolution T1 weighted structural scans, acquired with a standard sequence known as MDEFT (a three dimensional modified driven equilibrium Fourier transform) 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.

2.4.1. Image pre-processing

Before any statistical analysis can be applied, the imaging data need to be pre-processed. All pre-processing steps were completed with the software SPM12 (statistical parametric mapping, Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm).

2.4.2. Realignment/unwarping

The realignment step corrects for motion artefacts created by head movements. This is particularly important when the participants are producing speech, which involves orofacial muscle activity.

The first 5 images in each time series are always removed because the magnetic field takes approximately 10-15s to reach equilibrium. The removed images are referred to as "dummy scans". The 6^{th} scan is now the first image in the time series and is used as a reference image to which all subsequent images are spatially aligned. This is done by estimating 6 movement parameters for each subject over time, relative to the reference image: translation and rotation in

the x, y, and z directions (see an example of these movement parameters in Figure 2.3). The optimum value for each of these movement dimensions will minimise the difference to the reference image (using minimum square difference).

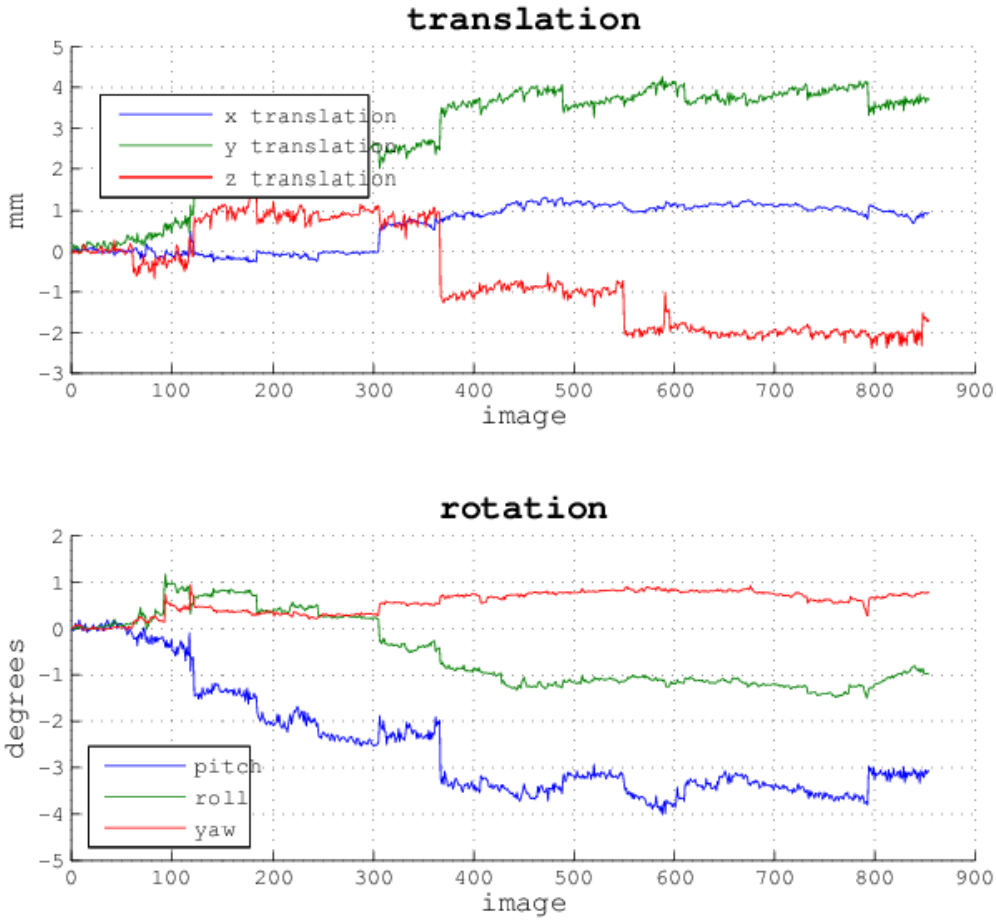


Figure 2.3: Six movement parameters for a single subject over several scan runs. This subject took part in Experiment 2 and completed several speaking and one-back matching tasks.

Within the same realignment pre-processing step, I used the unwarping option. This compensates for distortions caused by head movement or magnetic field inhomogeneity. I chose the unwarping procedure rather than including realignment parameters as linear regressors in my first level analysis because unwarping accounts for non-linear movement effects by modelling the interaction between movement and any inhomogeneity in the T2* signal. When unwarping has been used, it is not appropriate to add movement in the first level analyses.

However, the effect of differences in movement between subjects can be investigated in second level analyses.

2.4.3. Co-registration of functional and structural images

After realigning all the functional images, a similar realignment procedure is applied to functional and structural images to ensure they are in the same standard space. Co-registration works by comparing voxel intensities between images from different modalities (i.e. the structural and mean functional image), resulting in a joint histogram of the normalised mutual information. An example is shown in Figure 2.4. The sharpness in the histogram correlates with image re-alignment, the sharper the histogram, the more mutual information between the images of different modalities. 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 established transformation matrix is then applied to all functional images to align them with the structural image.

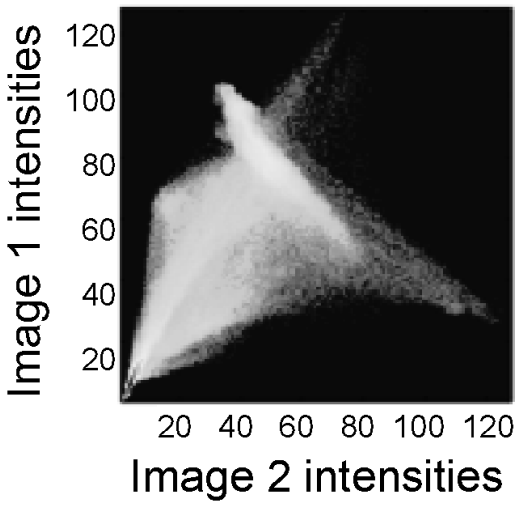


Figure 2.4: The output of the co-registration step is a joint histogram showing the mutual information between 2 images. The x and y axes show the range of voxel intensities of 2 images. The grey colour represents the voxel count. A perfectly sharp histogram would mean that the images have exactly the same signal intensity at each pair of corresponding voxels.

2.4.4. Segmentation/normalisation

The realigned structural image is then segmented into 6 tissue classes: grey matter, white matter, CSF, bone, soft tissue and air. I used the new unified normalization-segmentation function in SPM12 for this step. The segmented structural scan and the realigned functional images are all normalized to standard stereotactic space, in our case the Montreal Neurological Institute (MNI) space. The original resolution of structural and functional images (i.e. voxel size of $1mm^3$ for anatomical T1 and $3mm^3$ for functional EPI images) was maintained during normalization. Normalisation has the advantage that a signal of interest at any given voxel with the coordinates x,y,z can be compared across participants, and to other studies using the same standard space. An example of a functional image before and after normalisation is shown in Figure 2.5 (A and B).

2.4.5. Smoothing

After normalization, the images were spatially smoothed with a 6 mm full-width half-maximum isotropic Gaussian kernel (see Figure 2.5-C), to (a) reduce noise in the BOLD signal by blurring residual anatomical variability and (b) prepare the images for application of Gaussian random-field theory for statistical inference (see next section).

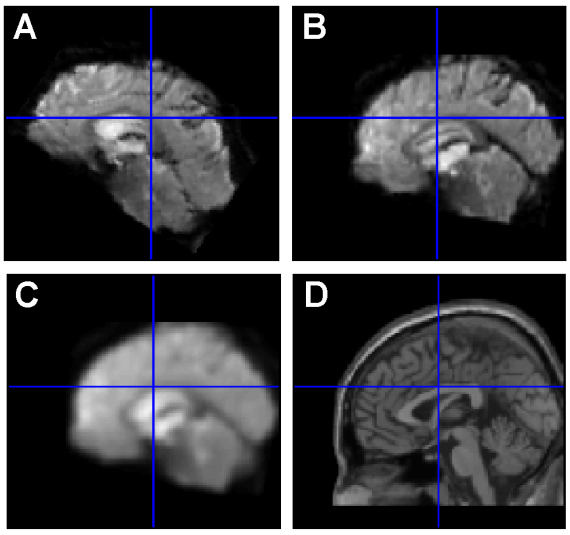


Figure 2.5: Functional images before (A) and after (B) normalisation. (C) is showing an image after smoothing. (D) is a template brain (canonical image) in standard space with the skull still visible. The crosshairs are always placed at x = 0, y = 0, z = 30 in MNI space.

2.5. Statistical analysis of fMRI data

The aim of fMRI in this work was to link cognitive (language) functions to changes in the BOLD signal. The basis of statistical inference in SPM is the General Linear Model (GLM; Friston et al., 1995), which tests for the hypothesis that the observed BOLD time-series of an individual voxel is a linear combination of explanatory variables:

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

Y is a vector containing the observed BOLD signal over time within one voxel. X is the design matrix, which contains values quantifying the experimental variables, also known as predictors or regressors, all weighted by a parameter β . ϵ is the residual error. After estimating a model for each voxel, the output is a set of estimated β values, one for each predictor of the model. This is then iterated over all voxels to obtain one beta image per predictor. As explained above, the GLM helps to determine if there is a relationship between a dependent variable and one or more independent variables. The parameter estimates β for the predictor variables are also known as betas and can also be thought of as the slope of the regression line relating X to Y. The better the estimation of β, the better the model (fits the data) and the smaller the deviations (ϵ) 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 β 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]. In my fMRI analyses I have essentially used more sophisticated versions of this "simple" contrast.

2.5.1. Thresholding and the multiple comparisons problem

The resulting t-values for each voxel are combined into a statistical map of t-values, and a threshold, or p-value, is applied across the map in order to determine which parts of the brain can be associated with the experimental manipulation. Activation at any given voxel is considered significant if the t-value is greater than the threshold defined by the p-value (e.g. $t>3.0$, $p<0.001$). The multiple comparisons problem arises from the fact that the brain consists of thousands of voxels, which means in turn that many t-tests are being performed, one for each voxel. This can lead to a number of false-positive results (type 1 errors), i.e. voxels appear to be significantly activated even though they are not. One method to control for the multiple comparison problem is to calculate the family-wise error (FWE) rate, i.e. the probability of type 1 errors. In this thesis, I have used an FWE correction that is based on a branch of mathematics called random field theory. This method corrects for the number of statistical tests being performed by taking into account the smoothness of the data (Worsley et al., 1992).

2.5.2. Group level and random effect analysis

Whereas it is important to look at single-subject activation when investigating inter-individual variability, I was interested in group effects for my experiments, which allowed me to generalise my conclusions from a sample to a larger population of healthy controls or a patient cohort. The group-level approach (also called 2nd level analysis) used here is an example of a random effect analysis, thus assuming that our group of participants was randomly drawn from a larger population. If the effect size in each subject is large enough, i.e. larger than the variance between subjects, it allows us to draw inference about the population. For each voxel, a vector of results is obtained from each participant's contrast image. The individual contrast images are entered into an ANOVA in SPM12 and a new design matrix is created. After calculating the mean and standard error for the group of participants, a simple one-sample t-test is performed. If the t-statistic is significant at the group level, we assume that this voxel was modulated by the experimental condition across participants.

2.6. Display and labeling of fMRI activation cluster

All results were displayed using MRIcroN on the ch2.better.nii.gz template brain (Version 7 July 2012, Chris Rorden, www.mricro.com/mricron). Anatomical labels were provided through the Anatomical Automatic Labeling (AAL) atlas and with reference to the *Atlas of the Human Brain* (Mai et al., 2007).

2.7. Overview of the experimental setup

For all imaging data used in this work, participants underwent a single fMRI experiment that involved either 16 conditions (Paradigm 1) or 13 conditions (Paradigm 2). Each condition presented auditory stimuli, visual stimuli or both and required participants to either speak or manually press a button to indicate they had processed the phonological or semantic content of the stimuli. There were 8 conditions that were common to Paradigm 1 and Paradigm 2; but I describe each paradigm separately to highlight their differences.

Paradigm 1 included 16 different conditions that were organised in a 2x2x2x2 factorial design. Factor I was task: with 8 speaking tasks (that were identical to those used in Paradigm 2) and 8 one-back matching tasks that required a button-press response to indicate if the current stimulus was the same as the previous stimulus. Factors II to IV manipulated the type of stimuli, within task. Factor (II) was 'modality', i.e. auditory versus visual stimuli. Factor (III) was the presence or absence of semantic cues, words, pictures and sounds of objects provide semantic cues, whereas pseudowords and meaningless baseline stimuli provide minimal or no semantic cues; and Factor (IV) was the presence or absence of sublexical phonological cues, words and pseudowords contain sublexical cues, whereas pictures and sounds of objects and baseline stimuli do not, although they do have lexical phonological associations.

Paradigm 2 consisted of the same 8 speaking tasks as paradigm 1, but did not include the 8 one-back conditions. In addition, all participants completed 5 other conditions that were not relevant to this thesis. These were visual

semantic decisions, auditory semantic decisions and production of sentences, verbs and nouns.

As described in more detail below, the stimulus selection and presentation order differed in Paradigm 1 and 2 – even for the 8 conditions used in both paradigms. In Paradigm 1, stimuli were rotated across conditions, and condition order was counterbalanced over subjects. This is standard practice to ensure that activation differences between conditions could not be the result of stimulus differences. In contrast, Paradigm 2 kept the stimuli per condition and condition order exactly the same for every participant. This was to ensure that activation differences between subjects (i.e. inter-individual differences) could not be the consequence of participants being presented with different stimuli per condition, or different condition orders.

2.7.1. Stimulus selection and creation

First, 128 pictures of easily recognizable animals and objects were created with one to four syllable names (e.g. bus, cake, duck). Written word stimuli were the written counterparts of these 128 images. Auditory word stimuli were their spoken names recorded by a native English speaker with a southern British accent approximating Received Pronunciation. Pseudowords (e.g. “appind”, or “twial”) were generated with the freely available non-word creator “WordGen” (Duyck et al., 2004) and matched to real words for spoken word length, number of orthographic neighbours and bigram frequency. Environmental sounds associated with 32 of the object concepts (e.g. the sound of a guitar playing or a cat meowing) were taken from the NESSTI sound library (http://www.imaging.org.au/Nessti; Hocking et al., 2013). Sounds for the remaining 96 objects were not easily recognizable or not available. For the auditory baseline, a male and a female voice were recorded while humming, hence removing any semantic or phonological content. 50% of the auditory baseline stimuli were matched to the duration of the environmental sounds (mean = 1.47 s) and the other 50% to the spoken words (0.64 s). Spoken words and environmental sounds could not be matched on their duration because the sounds needed to be longer to be recognizable.

For the visual baseline, the object pictures were scrambled on their global and local features and then manually edited to accentuate one of 8 colours (brown, blue, orange, red, yellow, pink, purple and green) in order to create meaningless coloured shapes. The visual form and colour shade changed on each trial, but each of the colour names appeared 4 times (32 stimuli in total per scan run). A pilot study with 19 participants was conducted (by my former colleague, research assistant and lab coordinator, Suz Prejawa) to ensure speech production responses were consistent for each colour and object. Example stimuli are shown in Figure 2.6, and stimulus properties are summarized in Table 2.2.

Figure 2.6: Example stimuli for visual conditions (reading words, reading pseudowords, naming pictures, naming colours).

2.7.2. Counterbalancing in Paradigm 1

Stimulus and task order were fully counterbalanced in Paradigm 1. Each subject was presented with the same stimuli in the speech production and one-back matching tasks. Half of the subjects completed speech production tasks first and half of the subjects performed one-back matching tasks first. Within each group, half of the subjects saw the visual conditions first, and the other half heard auditory conditions first. Hand of response for one-back matching was also counterbalanced, i.e. half of the subjects used their left hand, and half of the subjects used their right hand. Within these 8 groups, the four types of stimuli (words, pseudowords, objects and baseline stimuli) were presented in four different orders, resulting in 24 different orders in total.

2.7.3. Assigning stimuli to conditions in Paradigm 1

The 128 object pictures were divided into four sets of 32 (A, B, C, D). Within each set of 32, the items were split into 4 blocks of 8 stimuli, with one repeat in each block, making a total of 9 stimuli per block. The stimulus repeat needed to be detected and responded to during one-back tasks. Set D included all 32 object concepts that were paired with an environmental sound (e.g. a cat meowing). The remaining 96 object concepts were assigned to sets A, B and C, attempting to control for as many stimulus variables as possible. Set D was always presented for sound naming in the auditory modality and for pseudoword reading in the visual modality. Sets A, B and C were rotated across the remaining tasks (i.e. naming pictures of objects, reading words and repeating words), ensuring that these conditions were fully controlled for object names and concepts, and demands on motor execution of speech. One of these sets was repeated for pseudoword repetition. Therefore each set appeared with equal frequency within subject and across the experiment. The stimuli in set D (i.e. those presented as environmental sounds or visual pseudowords) had a slightly higher number of syllables on average (1.8) than the other stimuli (1.5). However, post hoc tests confirmed that there was no significant effect of word length on activation in any of the regions I associate with phonological processing.

2.7.4. Counterbalancing and stimulus assignment in Paradigm 2

Unlike in Paradigm 1, participants in Paradigm 2 completed all tasks in identical order without change in stimuli across participants. Keeping task order and stimulus effects constant is important when looking at inter-subject variability, which I did in Experiment 4. Because stimuli did not need to be rotated across conditions, it was possible to ensure that stimuli were assigned to conditions that maximised task accuracy. The complete task order for Paradigm 2 is listed in Table 2.1. Each condition consisted of four blocks with 10 different stimuli. The sets of pseudowords were different for the visual and auditory modalities, with half the pseudowords in each set having 1 syllable and the other half having 2 syllables.

Table 2.1: Task order in Paradigm 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 thesis are within the black box.

Object concepts were assigned to the 4 relevant conditions (i.e. naming pictures and sounds of objects, reading words, repeating words) as follows: those presented as written and auditory words had already been presented as pictures in the first 5 tasks (see Table 2.1), those presented as pictures had previously been presented as auditory words or in the sentence production task, and those presented as object sounds were a mix of those presented in other conditions. In the visual baseline, the number of colours was reduced from 8 (in Paradigm 1) to 5 (green, blue, red, orange, yellow) since some participants were struggling to name the colours purple, brown, and pink correctly in Paradigm 1. The 5 colour names were repeated 8 times (40 trials in total). In the auditory baseline, male and female hums were split equally between the 40 trials (i.e. 20 each). Within a condition, the effect of familiarity on articulation was therefore highest for gender naming (20 repetitions of each response), followed by colour naming (8 repetitions of each response).

2.7.5. Stimulus presentation

The script for stimulus presentation was written with COGENT (http://www.vislab.ucl.ac.uk/cogent.php) by Thomas Hope and Oiwi Parker Jones, and run in MATLAB 2010a (MathWorks, Sherbon, MA, USA). Visual stimuli were projected onto a screen at the head-end of the scanner bore and subjects could see them via a mirror placed on the head coil. They were each

displayed for 1.5 s. The pictures subtended a visual angle of 7.4 degrees, with a screen resolution of 1024×768 (after scaling to 350x350 pixels). Words and pseudowords were presented in lower case Helvetica. Their visual angle ranged from 1.47 to 4.41 degrees with the majority of words (with 5 letters) extending 1.84 to 2.2 degrees.

Auditory stimuli were presented via headphones (MR Confon, Magdeburg, Germany), which filtered ambient in-scanner noise. The subject's spoken response was recorded with a noise-cancelling MRI compatible microphone (FOMRI IIITM Optoacoustics, Or-Yehuda, Israel) and transcribed manually for off-line analysis.

Scanning started with the written instructions "Get ready" on the screen inside the scanner bore, while 5 "dummy" scans were acquired. This was followed by four blocks of stimuli, each of which was preceded by a written reminder of the instructions (e.g. "Name Picture") lasting for 3.085 s (i.e. the length of one TR") and followed by 16 s of fixation. Total length of each scan run (time series) was 3.2 min in Paradigm 1, and 3.4 min in Paradigm 2 (more stimuli were presented per block). Experimental details for both versions of the paradigm are presented in Table 2.2. A schematic illustration of an example task (picture naming) task is shown in Figure 2.7.

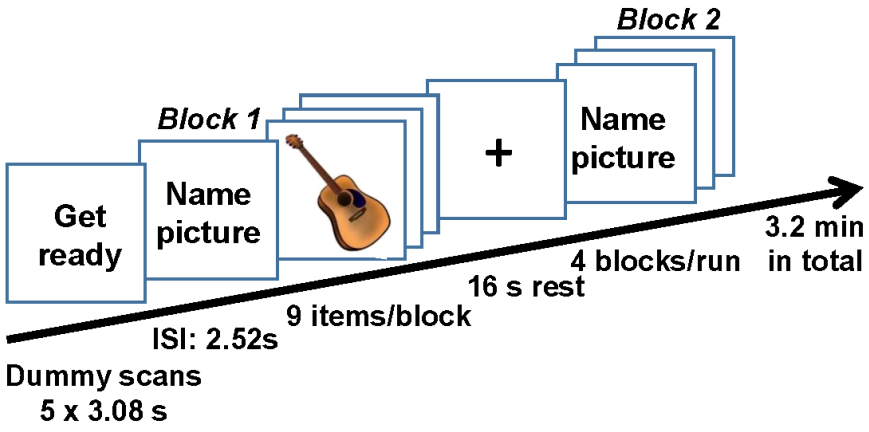


Figure 2.7: Schematic illustration of the timing of one task ("picture naming") in Paradigm 1. The participant was supposed to say out loud "guitar" in response to seeing the picture. ISI = inter-stimulus interval, i.e. the time between the presentation of 2 successive stimuli.

2.7.6. Procedure

Despite differences in the timing parameters (see Table 2.2), the procedures for the two paradigms were the same. Prior to each scanning session, each participant was given a written information sheet summarizing the purpose of our research, with the possibility to ask questions. They then gave written consent, and their MRI safety was checked for a final time (volunteers were not invited to participate if they had any known contra-indication for MRI). Each participant was trained on all tasks in a quiet testing room, using stimulus materials that were not used in the scanner, except the environmental sounds which remained the same for the training and in scanner tests because environmental sound naming was more difficult and required more practice than the other conditions. This could potentially have an impact on the fMRI activation pattern, i.e. signal increase or decrease, due to habituation. However, these effects would be specific to the auditory modality, which are not of interest for this thesis where I was investigating phonological processing that was independent of stimulus modality.

The speaking tasks required the participants to produce an overt, single word response, whereas one-back matching tasks required a button-press to indicate whether the present stimulus was the same as the one preceding it. Participants held their hand over a two buttons with instructions to press the left button if the stimulus was the “same” as the previous one and the right button if the stimulus was “different” from the previous one.

Once trained, participants were placed on a scanner bed in the head-first supine position, and the equipment was attached to them (finger pulse oximeter to monitor their well-being while being scanned, alarm bulb in the case of an emergency, button box, microphone, headphones and head coil with attached mirror). The participants were instructed to keep their head and body as still as possible and to keep their eyes open throughout. This was monitored with eye tracking (although I did not save the eye tracking data). Each task was presented in a separate scanning run, which allowed me to briefly remind the participants of the instructions before each task. Total scanning time was approximately 1.5 hours per subject, including 10 min set-up time and a 12 min structural scan.

Table 2.2: Experimental details

Participants	***Paradigm 1***	***Paradigm 2***
Number	26	59
Gender (n females/ n males)	12/14	34/25
Mean age in years (+/-SD)	31.44 (5.74)	44.5 (17.66)
Stimulus properties		
Stimulus duration in s (+/-SD)		
Visual stimuli	1.5	1.5
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 (+/-SD)		
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 (s)	2.52	2.5
Number of stimuli per block	9 (incl. one repeat)	10
Number of blocks per run	4	4
Total number of stimuli per run	36	40
Number of runs	16	8
Total time for each run (min)	3.2	3.4
Total acquisition time (min)	51.2	27.2
Scanning parameters		
TR (s)	3.085	3.085
Number of slices	44	44
Number of volumes per run	62	66
Number of dummy acquisitions	5	5

**across sets A, B, C*

2.8. Behavioural data processing

All spoken responses were transcribed online and scored-off-line supported by voice recordings where available. A response was considered "correct" if it matched the target, or was nearly identical in meaning (e.g. target = "mug", response = "cup") and "incorrect" for all other trials (i.e. when the response did not match the target, was delayed or self-corrected).

Spoken response times were not available for Paradigm 1 because, unfortunately, the incorrect audio-channel was selected for the in-scanner recording and all audio-files were lost. However, response times for spoken responses were available from the audio recordings in Paradigm 2. To compute them, I used an adaptive moving filter, tailored to each audio file (developed by Thomas Hope, Ph.D.). The optimal window length (i.e. the width which maximally smoothed the audio stream) was based on a short time period of the respective audio file collected during rest. After smoothing the whole time series, the onset of speech was defined as a rise in the absolute amplitude of the smoothed audio stream beyond 1.5 standard deviations from the mean.

All behavioural data analyses were computed in SPSS (IBM SPSS, NY, US). I tested for main effects and interactions with repeated measures ANOVA's and applied Greenhouse-Geisser correction when the assumption of sphericity was not met.

2.9. Previous reports

All imaging and behavioural data that I collected for my PhD have been integrated into the PLORAS database (Seghier et al., 2016). This database is a repository for structural and functional scans and behavioural data from controls and stroke patients and is aimed at improving recovery predictions for stroke patients.

The Paradigm 1 data have previously been reported in studies of auditory word and pseudoword repetition (Hope et al., 2014; Parker Jones et al., 2014) and sublexical reading (Oberhuber et al., 2013). The figures and tables of results in Hope et al. (2014) reference dorsal SMG activation for task difficulty/executive processing effects (at MNI [-45, -39, 42]) during auditory repetition but do not report data from other parts of the SMG because they were not activated for auditory word repetition (the focus of that study). Likewise, Oberhuber et al. (2013) report the same dorsal SMG [-42, -42, 45] area for both reading and repetition of pseudowords more than words but did not associate it with sublexical phonological processing because it was also more activated by object naming than word reading. Parker Jones et al. (2014) focus their analysis on a posterior ventral part of SMG at the temporo-parietal junction (TPJ) at MNI co-ordinates [-51, -39, 21] and associate this region with auditory imagery independent of the presence or absence auditory input. Therefore none of the data reported in these prior studies are able to answer the questions I address in this Ph.D. thesis.

3. EXPERIMENT I

Dissociating neural systems for different types of phonological processing

3.1. Summary

In the first experiment of this thesis, I tested a new fMRI language paradigm in healthy controls to dissociate the neural pathways supporting different types of phonological retrieval. Speech to phonology was tested by comparing auditory pseudowords (that carry sublexical phonological content) to sounds of objects (that have no sublexical phonological associations) during one-back matching and speech production tasks. Orthography to phonology was measured by comparing written pseudowords to pictures of objects, across tasks. Finally, activation associated with (lexical) phonological retrieval from semantics was investigated by comparing activation during object naming from pictures or sounds to reading or repeating pseudowords. I dissociated brain activation for two types of phonological processing: the bilateral superior temporal sulci were activated for auditory representations of speech, whereas the left precentral cortex, extending into pars opercularis, was associated with articulatory planning. This dissociation bears some resemblance to the notion of “input phonology”, and “output phonology”. I did not find activation that would fit with retrieval of lexical phonology, however, naming objects compared to reading or repeating pseudowords activated left hippocampus/ parahippocampus, which are semantic retrieval areas, as well as right occipital regions (calcarine sulcus and lingual gyri), that are known to support mental imagery of semantic stimuli, and bilateral cerebellum, associated with word retrieval and speech production. The novel language paradigm provides fresh insight into the conceptual understanding of phonological processing, and the neural systems supporting different types of phonological retrieval.

3.2. Introduction

Phonology is concerned with the systematic representation of speech sounds. These representations can be accessed in three different ways: (i) through speech stimuli, i.e. when we are listening to spoken language, (ii) through orthographic input, i.e. when we are reading written words or (iii) through non-verbal semantic stimuli, e.g. when we retrieve the name of a familiar object or sound. The aim of this study was to compare the pattern of brain activation for each of these routes to phonology. Accessing phonology from spoken speech was investigated using spoken pseudowords that have no semantic associations and only weak links to orthography. Accessing phonology from orthography was investigated using written pseudowords that have no semantic associations and, thirdly, accessing phonology from semantics was investigated using pictures and sounds of objects that have no non-semantic sublexical links between perceptual inputs and phonology. They therefore rely on lexical phonological retrieval.

For each stimulus type, I used 2 different tasks: speech production and silent one-back matching. The rationale being that this might help to dissociate phonological effects that are specific to speech production (i.e. output phonology) from phonological effects that are common to both speech production and silent one-back matching tasks (input phonology). Dissociating input and output phonology is difficult when only one task is used. For example, Shuster (2009) reported that repeating pseudowords increased activation relative to repeating words in the left anterior insula, superior temporal cortex, bilateral inferior frontal gyri (IFG), precentral gyri and SMA. However, I cannot infer which regions were involved in input phonology, output phonology, or attention to unfamiliar auditory stimuli.

Likewise, many prior studies have investigated the neural network supporting orthography-to-phonology by comparing activation for reading written pseudowords to that for reading written words. The rationale for this comparison is that, because pseudowords have no semantic content to guide phonological retrieval, access to phonology relies on prior learning of the relationship between sublexical letter combinations and the speech sounds associated with these

letter combinations. In contrast, because familiar words have semantic content that can drive access to phonology, they are expected to place less demands on sublexical phonological processing. The advantage of comparing pseudoword and word stimuli is that they are very well matched perceptually. On the other hand, response time and accuracy measures have shown that unfamiliar pseudowords are more difficult to read than words (Binder et al., 2005; McNorgan et al., 2015; Taylor et al., 2014). Therefore, higher activation for pseudowords than words (e.g. Taylor et al., 2013) in (a) left inferior frontal/precentral gyri, (b) left posterior fusiform and occipito-temporal gyrus, (c) bilateral SMA, (d) left insula, (e) right IFG and (f) bilateral parietal cortices – might reflect domain-general effort rather than language-specific processing.

Another approach to isolate activation specific to orthography-to-phonology is to compare word reading to object naming (Bookheimer et al., 1995; Moore and Price, 1999; Price et al., 2006). This controls for articulatory demands if speech output is matched, i.e. the same objects are presented as pictures and written words. However, in skilled readers, word reading is usually faster and more familiar than object naming (Glaser and Glaser, 1989), which could bias the activation pattern. In addition, skilled readers are more likely to read words using lexical-semantic processing rather than sublexical processing, and the lexical route is usually faster than the sublexical route (Taylor et al., 2013). Signal increase for word reading > object naming could therefore be driven by either lexical or sublexical processes. Anatomically, word reading compared to picture naming increased activation in left precentral and left superior temporal cortex (Bookheimer et al., 1995; Moore and Price, 1999; Price et al., 2006). However, the same regions were also found to be engaged during generic speech production processes (Price et al., 2006), therefore there is no evidence that these regions are specifically involved in accessing phonology from orthography.

Finally, the reverse contrast, i.e. object naming > word reading is supposed to reveal the network supporting (lexical) phonological retrieval from semantics. This contrast has previously been associated with activation increase in left occipito-temporal regions (Chee et al., 2000; Price et al., 2006) which

might reflect the visual complexity of pictures compared to orthographic stimuli. Moreover, words also provide lexical and semantic cues, and thus may (implicitly) activate semantic processing areas, weakening the association of lexical semantic activation to object naming.

In the present study, I have excluded words, which enabled me to circumvent (implicit) lexical or sublexical processing. To maximise the demands on different types of phonological access, I directly compared access to phonology from pseudowords (that have low semantic content) and objects (that carry no sublexical phonological clues). To segregate phonological from perceptual processing, I looked for effects that were common across visual and auditory modalities. Regions associated with accessing phonology from semantics were those commonly activated for naming objects from (A) their pictures compared to pseudoword reading and (B) their sounds compared to pseudoword repetition. Areas that were common to the reverse contrasts were associated with non-semantic sublexical phonological processing.

A similar approach was adopted by Thierry and Price (2006) who compared (A) conceptually rich spoken sentences to object sounds and (B) conceptually rich written sentences to pictures of events, and found greater activation in middle and posterior STS in both the auditory and visual comparisons (peak coordinates at MNI [-56, -24, -6] and [-60, -38, 0] respectively). However, because all their stimuli had high semantic content and because the task was semantic decisions rather than speech production, the Thierry and Price (2006) study does not tap into processing related to the retrieval of phonology from semantic versus non-semantic stimuli, nor does it allow us to distinguish regions associated with “input phonology” versus “output phonology”. Instead the conclusions focus on the dissociation of verbal and nonverbal semantics. The current study allows me to test whether the same middle and posterior parts of left STS are also activated for non-semantic phonological processing.

In addition, the current study investigated the functional dissociation in anterior and posterior left STS areas that have been associated with speech processing by Scott et al. (2000; 2006). Specifically, Scott et al. found that only

the anterior part of STS (at MNI [-54 +6 -16]) was sensitive to the intelligibility of speech sounds, whilst the posterior part ([-64 -38 0]) was activated by more basic phonetic cues and might be involved in maintaining short-term representations of sound sequences, underlying our ability to rehearse novel words.

3.3. Methods

3.3.1. Participants

26 participants were originally involved in this experiment. One subject was excluded from all analyses because their data for one task (one-back matching on heard words) were incomplete due to technical failure of the stimulus presentation computer. All participants were native English speakers, right handed (assessed with Edinburgh Handedness Inventory, Oldfield, 1971) and had normal or corrected-to-normal vision and hearing. They did not report any neurological or psychiatric conditions. Prior to the experiment, they gave written informed consent for participation and received financial compensation for their time. The study had approval from the London Queen Square Research Ethics committee.

3.3.2. Experimental design

All experimental details are explained in the general methods part (Chapter 2). The 8 tasks of interest for this study were (1) reading pseudowords, (2) repeating pseudowords, (3) naming pictures of objects and (4) naming sounds of objects and (5-8) one-back matching on the same stimuli. These 8 tasks enabled me to manipulate 3 factors: (I) modality (auditory versus visual), (II) semantic versus sublexical phonological content and (III) response modality (speech production versus one-back matching task). Behavioural data analysis, preprocessing and first-level analysis steps of the imaging data are explained in the general methods section.

3.3.3. Effects of interest

At the second level, 16 contrasts, one for each task, were entered into an ANOVA in SPM12. Factorial main effects and interactions were entered at this stage, where P = pseudoword, W = word, R = rest, VIS = visual, AUD = auditory, SP = speech, OBM = one-back matching. Activation related to:

1. **Speech to phonology** was identified by comparing activation for auditory pseudowords to object sounds that was common to speech production and one-back matching tasks. This involved four contrasts, the main effect of auditory pseudowords > object sounds across tasks, inclusively masked with (i) the same contrast for the speech production task only, (ii) the same contrast for the one-back matching task only, and (iii) auditory pseudowords versus rest. The significance of the main effect was set at $p<0.05$ corrected for multiple comparisons across the whole brain and $p<0.001$ in the left superior temporal sulci, which have been associated with speech processing in previous studies (Thierry et al., 2003). The threshold for the inclusive masks was set at $p<0.05$ uncorrected because this was simply to ensure that the same pattern of effects was observed during both tasks, and that deactivated voxels were excluded.

2. **Orthography to phonology** was identified by comparing written pseudowords to pictures of objects, across tasks, and inclusively masking with the same contrast for each task separately, as well as written pseudowords versus rest. The thresholds for reporting significant effects were the same as for speech to phonology.

3. **Semantics to phonology** was identified where activation was higher for pictures and sounds of objects compared to pseudowords (across visual and auditory modalities) during the speech production tasks. To ensure the effects were common to both stimulus modalities, I inclusively masked this main effect with (i) naming objects from pictures compared to reading pseudowords; and (ii) naming objects from sounds compared to auditory repetition of pseudowords. To ensure that positively activated rather than deactivated

voxels were included, I additionally masked with (iii) naming objects from pictures greater rest, and (iv) naming objects from sounds greater rest. The threshold for these inclusive masks was set at p<0.001 uncorrected to ensure that the effects we report at independent of modality. I also report the interaction between task (speech production > one-back matching) and stimulus type (objects > pseudowords).

3.4. Results

3.4.1. Behavioural results

Accuracy scores were high with an average of 89% or above per task. RTs for one-back matching tasks (including correct trials only) showed a main effect of modality, i.e. longer response times for auditory stimuli than visual stimuli ($F(1,21)=150.51$, $p<0.001$). This is likely due to longer stimulus durations for auditory than visual stimuli (see Figure 3.1 for details).

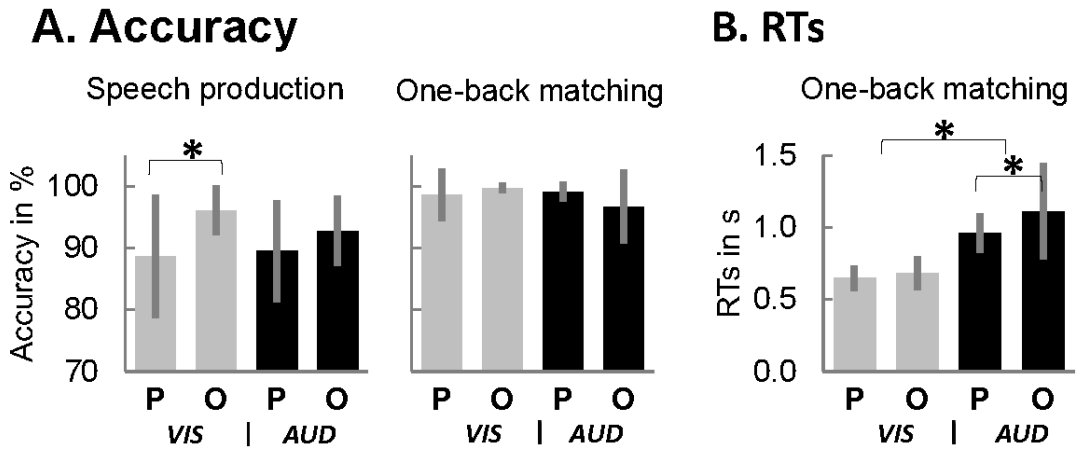


Figure 3.1: Behavioural results. A. Accuracy for speech production and one-back matching tasks and B. RTs for one-back matching tasks. RTs for speech production tasks were lost due to technical problems (see general methods chapter). Accuracy scores for speech production tasks are based on 24 subjects, after 2 outliers (47% correct in pseudoword reading) were excluded. Behavioural results for one-back matching tasks are based on 22 subjects because button press responses were lost in one or more one-back matching tasks for 3 subjects. * Significant at $p < 0.001$.

3.4.2. fMRI results

1. Speech to phonology [auditory pseudowords > object sounds]

As expected, activation in bilateral superior temporal sulci (STS) was higher for auditory pseudowords [P] than object sounds [O], even though the duration of auditory inputs was greater during O than P. The Z scores for this effect were higher during one-back matching (OBM) than speech production (SP) (see Figure 3.2-A) but this task (OBM>SP) by condition (P>O) interaction did not reach significance. See Figure 3.2.

Critically, the bilateral STS areas associated with speech to phonology were not specific to speech processing because they were also activated during (i) one-back matching on object sounds – even though one-back matching of object sounds does not involve any speech inputs; (ii) the main effect of all auditory compared to all visual stimuli (Figure 3.2-A) and (iii) written pseudowords during one-back matching that does not involve any auditory input (see next section).

A

[P>O Auditory]				P>O SP&OBM		P>O SP	P>O OBM	OBM P	OBM O	Aud > Vis P	Aud > Vis O
	x	y	z	Zsc	Vx	Zsc	Zsc	Zsc	Zsc	Zsc	Zsc
L m/p STS^	-57	-24	-3	4.3	93	2.3	4.4	Inf	Inf	Inf	Inf
	-54	-39	3	3.5		1.3	4.4	Inf	5.9	4.7	4.6
R m/p STS^	57	-27	-3	4.6	37	3.0	4.0	Inf	Inf	7.6	Inf
	48	-33	0	4.1		2.0	4.4	Inf	Inf	5.7	5.3

B

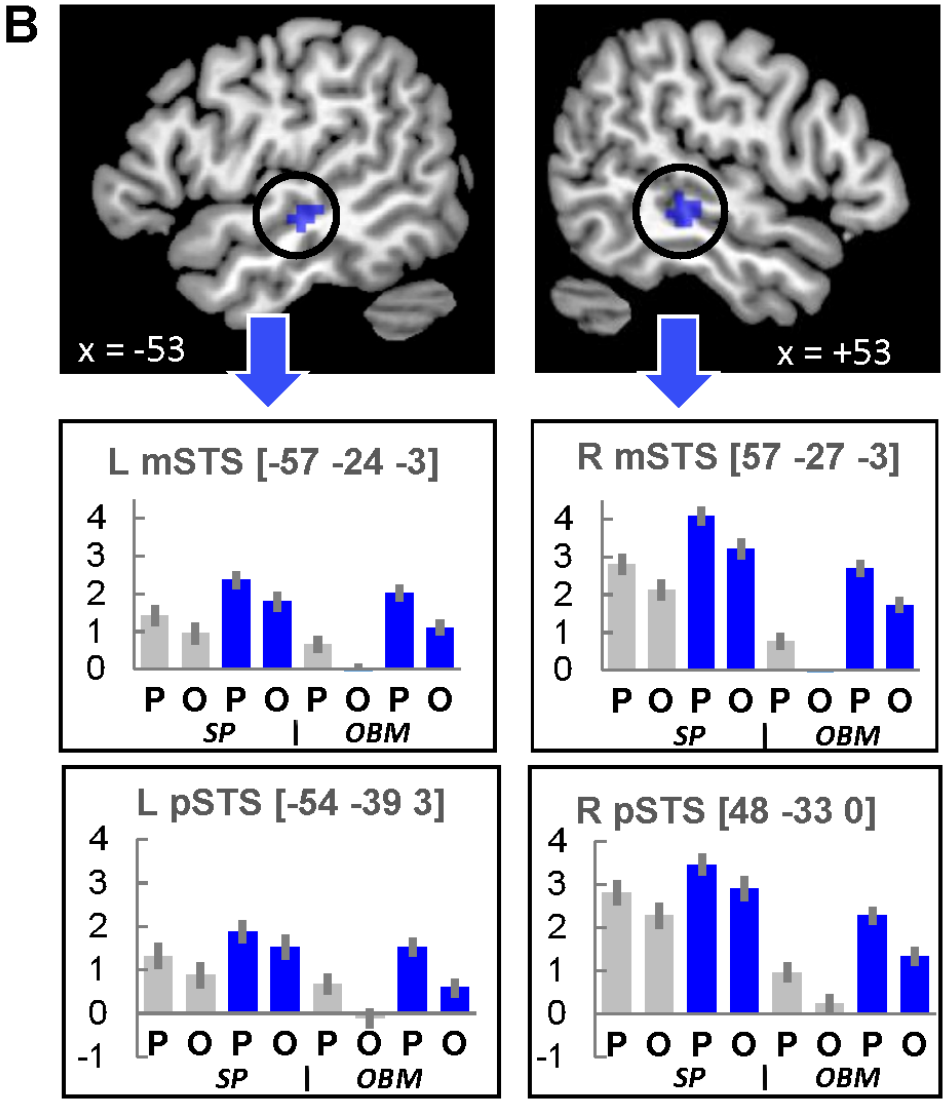


Figure 3.2: A. Peak coordinates in middle and posterior superior temporal sulcus (m/p STS) for auditory pseudowords > sounds of objects [P > O Auditory] in MNI space (xyz). ^ Significant after correcting for multiple comparisons in regions of interest from Thierry & Price (2006) but not after correcting for multiple comparisons across the whole brain. Zsc = Z-score. SP=speech, OBM=one-back matching. Aud > Vis = Greater activation for auditory than visual stimuli (P or O) across tasks. Vx = cluster size in voxels. B. Bilateral activation cluster in STS (in blue) at x = +/-53, plots show the relative activation with standard error across conditions. Grey = visual. Blue = Auditory in mSTS and pSTS, respectively.

2. Orthography to phonology [written pseudowords – pictures of objects]

The same bilateral superior temporal regions that were observed for speech to phonology were also activated by written pseudowords more than object pictures. This effect was present across speech and one-back matching tasks (and the task by condition interaction did not reach significance, see Figure 3.3-A). In addition, written pseudowords compared to pictures of objects activated the left precentral cortex (PreC), extending into the left pars opercularis (pOp), the left intraparietal sulcus (IPS) and an anterior part of left putamen (PUT) with a corresponding but less significant effect in the right putamen. These effects were observed for both tasks (with no significant task by condition interactions). See Figure 3.3.

There was no evidence that activation in these areas was dependent on orthographic inputs. To the contrary, activation in the left putamen was enhanced during all the speech production conditions, irrespective of whether the stimuli were pseudowords or objects; and activation in left PreC/pOp and IPS was observed during all conditions irrespective of the type of stimuli or mode of response. The point of interest here is that activation was higher for written pseudowords than all other stimuli but not specific to orthographic stimuli.

Activation in the left SMG was only observed (at $p<0.001$ uncorrected) in a posterior, ventral location ([-54, -39, 21] Zsc = 3.4 across tasks) that corresponded to the part of the temporo-parietal junction reported in Parker Jones et al., (2014) but does not correspond to the region associated with pseudoword reading in previous studies. I will return to consider the role of SMG activation in Chapter 5.

A

				P>O		P > O		Int	SP>OBM	
				SP&OBM		SP	OBM	SP>OBM	P	O
[P>O Visual]	***x***	***y***	***z***	***Zsc***	***Vx***	***Zsc***	***Zsc***	***Zsc***	***Zsc***	***Zsc***
*L m/p STS^*	-57	-30	0	4.1	24	2.2	3.8	ns	3.8	5.0
	-54	-21	-3	3.4		2.9	2.5	ns	4.5	4.8
	-42	-39	0	3.4	7	2.4	2.9	ns	n.s.	n.s.
R m/p STS	57	-24	-3	3.9	38	3.1	2.8	ns	6.9	7.6
	51	-33	0	3.1	5	2.5	2.7	ns	6.8	7.0
L preC	-42	-3	33	**4.9**	129	3.4	3.8	ns	3.9	5.5
L pOp	-57	6	18	4.4		4.5	2.3	ns	4.5	3.2
L PUT	-21	6	9	**4.8**	66	4.9	2.4	ns	5.9	4.2
R PUT	21	12	9	4.0	27	4.0	2.5	ns	5.4	3.7
L IPS	-36	-45	39	**4.7**	66	3.9	3.5	ns	n.s.	n.s.

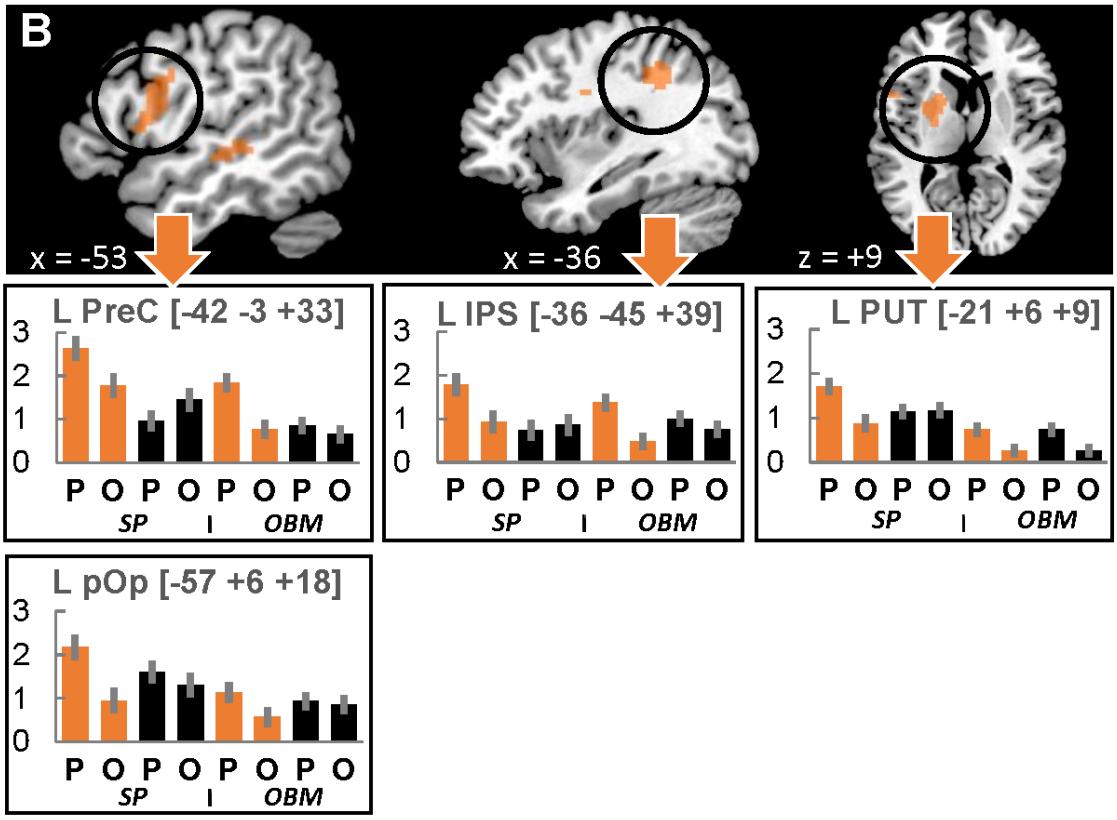


Figure 3.3: A. Peak coordinates for activation observed for visual pseudowords more than pictures of objects. Effects that were significant at p<0.05 after FWE whole brain correction (height or extent) are highlighted in bold. In STS, the effects were significant in regions of interest identified from auditory pseudowords more than objects. B. Slices and plots show relative activation across all conditions. Orange/black bars = visual/auditory. For abbreviations see Figure 3.2.

3. Semantics to phonology [naming pictures and sounds of objects > pseudowords]

Naming pictures and sounds of objects > reading/repeating pseudowords increased activation in the left hippocampus (Hipp) and parahippocampus (pHipp), and in the right lingual gyrus (Ling) and calcarine sulcus. Cerebellar (CB) activation was found in lobules [IX] and in right lobule [VI]. See Figure 3.4.

A

					Amodal			Visual		Auditory	
[O > P]					SP	OBM	Int	SP	Int	SP	Int
Amodal	x	y	z	Vx	Zsc	Zsc	Zsc	Zsc	Zsc	Zsc	Zsc
L Hipp	-21	-33	-3	13	6.1	n.s.	4.5	4.2	3.2	4.9	3.8
L pHipp	-21	-45	-6	47	7.1	3.3	4.8	Inf	3.0	4.6	4.1
R Calcarine	0	-87	-3	42	6.6	2.2	4.7	4.8	3.0	5.2	3.7
R Lingual	21	-51	-6	11	5.6	2.2	4.0	6.7	2.6	3.4	3.4
L/R CB IX	-12	-42	-42	10	6.6	n.s.	5.5	3.5	2.8	6.7	5.3
	12	-45	-45	9	6.6	n.s.	5.2	3.2	2.9	6.3	5.2
R CB VI	12	-81	-18	6	7.0	n.s.	4.5	4.5	2.7	5.7	3.7

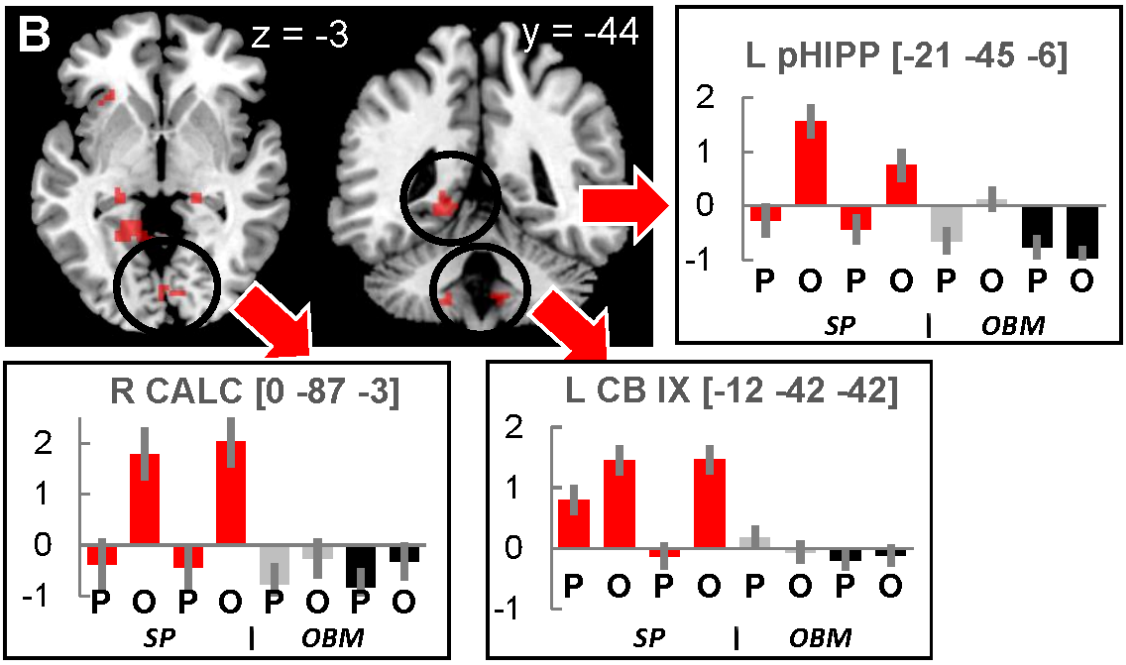


Figure 3.4: A. Peak coordinates for naming object sounds and pictures > reading/repeating pseudowords [O > P]. B. Red bars = speech production conditions, grey/black bars = visual/auditory. For abbreviations see Figure 3.2.

3.5. Discussion

With this study, I aimed to dissociate the neural systems that support access to phonology from auditory speech, orthography and semantics. Brain regions involved in accessing phonology from speech were identified by comparing activation for hearing pseudowords (which are rich in sublexical phonological associations but have no semantic content) to activation for hearing object sounds (which have semantic and lexical phonological associations but do not have sublexical phonological associations). This contrast identified bilateral middle and posterior parts of the superior temporal sulcus, which have been associated with speech processing in many other studies (e.g. Evans et al., 2014; 2016; Scott et al., 2000; Thierry et al., 2003; Thierry and Price, 2006). As discussed below, the response in these areas is enhanced by speech but not specific to speech.

Brain regions involved in accessing phonology from orthography were identified by comparing activation for written pseudowords (which carry sublexical phonological information) to activation for pictures of objects (which have semantic and lexical phonological associations but do not have sublexical phonological associations). This contrast also identified the bilateral middle and posterior parts of the superior temporal sulcus, as observed for speech to phonology and discussed below. In addition, written pseudowords enhanced activation in left frontal regions (left PreC/pOp) and the putamen that have previously been associated with articulatory decoding (see below) and the left intraparietal sulcus (IPS) that has been associated with a host of executive functions (see below).

Finally, brain areas associated with accessing phonology from semantics were identified by looking at activation that was common for naming objects from pictures and sounds compared to reading and repeating pseudowords. This identified the left hippocampus/parahippocampus and right posterior occipital regions that were only responsive when speech needed to be retrieved from semantic stimuli. Object naming also enhanced activation in inferior parts of the cerebellum that were also most activated for reading pseudowords.

The role of bilateral superior temporal sulci in sublexical phonological processing

Bilateral superior temporal sulci were more activated by visual and auditory pseudowords, compared to the respective object conditions. This was observed for two different tasks: speech production and one-back matching. The speech production task controls for “phonological output processing”. Therefore, enhanced activation for reading and repeating pseudowords is most consistent with processing “sublexical phonological inputs”. We can exclude perceptual processing because this is different for auditory and visual pseudowords and would therefore not be expected to show a common response.

Many prior studies have highlighted the importance of the superior temporal sulci for speech processing (Binder et al., 2000; Evans et al., 2014; 2016; Hickok and Poeppel, 2000; Scott et al., 2000; 2006; Uppenkamp et al., 2006). There have also been a few previous reports that, like the current study, identified the same bilateral STS regions for processing written as well as spoken language. Most recently, Oron et al. (2016) used a rhyme/consonant detection task in the visual and auditory modality (compared to visual and auditory control tasks) and found that the only region that was activated for both modalities was located at MNI [-60, -28, 0], which is close to the peak coordinate for spoken and written speech in the present study (at [-57, -24, -3]). This activation could also reflect the underlying process of audio-visual integration, as shown in a number of prior studies (Callan et al., 2006; Lee and Noppeney, 2011; Stevenson and James, 2009; van Atteveldt et al., 2004).

The location of the STS areas that I observed for pseudoword processing included posterior STS (pSTS) (i.e. at MNI [-54 -39 3] and [48 -33 0]) but not the more anterior areas that Scott et al. (2000) associated with speech intelligibility (i.e. at MNI [-54 +6 -16] and [66 -12 0]). The most likely explanation for not seeing more anterior STS is that, unlike the Scott et al. study, my stimuli did not include semantically and syntactically rich sentences. The more posterior STS regions have been associated with the maintenance phase of phonological memory (Hein and Knight, 2008; Strand et al., 2008; Wise et al., 2001). Such an

interpretation would explain the pSTS activation that I observed for visual and auditory pseudowords in terms of phonological information being held in memory while it is linked to articulatory codes (during speech production) or matched to other information (during one-back matching). In contrast, pSTS activation is less during object naming/matching, which can be based on semantic rather than phonological memory.

Although I found increased bilateral STS activation for visual as well as auditory pseudowords, the same STS regions showed a very strong main effect of all auditory versus all visual stimuli. This is not surprising given that bilateral STS are part of the auditory association cortices. However, it emphasizes that these regions are not specific to speech (Price et al., 2005) but play a role in extracting auditory representations (or “auditory images”) that can be held in memory during task performance.

In summary, the results show that middle and posterior parts of STS are more activated by phonologically rich pseudowords than semantically rich object stimuli. This was observed (i) during speech production (which controls for phonological retrieval) as well as one-back matching, and (ii) across visual and auditory modalities. I have argued that this is consistent with a role in accessing, and holding amodal phonological representations in memory. In addition, I have suggested that the same regions are also involved in representing non-phonological auditory information. Their function may therefore be more accurately defined in terms of more generic auditory representations/images.

Additional regions supporting the mapping of orthography-to-phonology

Orthography-to-phonology mapping was supported by three regions, in addition to bilateral STS: left precentral gyrus extending into the pars opercularis, left putamen (with a corresponding effect in the right putamen) and the left inferior parietal sulcus.

The activation increase in anterior bilateral putamen was a surprising finding, considering prior literature, which described the putamen primarily as a movement regulator. The demands on movement cannot account for why

putamen activation was higher for reading pseudowords than repeating pseudowords because the same stimuli (and motor response) were counterbalanced across conditions. However, many other studies have reported that the putamen is involved in higher cognitive processes such as learning, working memory and language processing (e.g. Chang et al., 2007; Crosson, 1985; Frenck-Mestre et al., 2005; Yu et al., 2013). The region has strong connections to phonological areas such as IFG and lateral temporal cortex. For instance, the putamen has been reported to have a unilateral modulatory effect on these areas during a rhyming task on visually presented words (Booth et al., 2007). In bilingual research, it has been shown that bilingual speakers have increased grey matter density in left putamen compared to monolinguals, which might reflect the higher articulatory demands that less proficient speakers face in their non-native language (Abutalebi et al., 2013). Finally, support for a specific role of the putamen in phonology comes from a cytochemistry experiment (Tettamanti et al., 2005), showing that the speed of phonological processing, but not that of syntactic processing, correlates with dopamine levels in the left putamen. Overall, these studies are consistent with putamen activity being involved in articulatory planning. This would explain why activation in the putamen was higher in all speech production tasks than the one-back matching task. It can also explain why putamen activation was observed during one-back matching on auditory and visual pseudowords, if we assume that these conditions involved some degree of “implicit” speech production (or articulatory rehearsal). This hypothesis accords well with previous studies showing that the anterior putamen is involved in the initiation of novel sequences of movements (Aramaki et al., 2011; Okuma and Yanagisawa, 2008), acquisition of sign language (Williams et al., 2016) and speaking of a second language (Klein et al., 1994). Moreover, there is further evidence from animal studies showing that the injection of the GABA agonist muscimol in the anterior part of putamen impairs the learning of novel motor sequences (Miyachi et al., 1997). In my study, activation in the anterior putamen was highest for reading aloud pseudowords which require a new motor sequence to be generated. The demands on novel motor planning will be less for repeating auditory pseudowords which can be guided by the auditory inputs (i.e. create motor outputs that match auditory inputs).

An alternative interpretation is that increased putamen activation for one-back matching on pseudowords might be a consequence of the demands on decision making. A recent study by Tremel and colleagues (2016) suggests that the putamen is involved in storing predicted item value when subjects had to learn correct choices to word pairs. When their decision-making became more skilled, this was reflected in BOLD signal changes in the putamen. However, I controlled for decision making across conditions, therefore it is unclear why there would be more decision making required for pseudowords than objects.

The precentral/pars opercularis regions (PrC/pOp) that I found more activated for reading pseudowords than object naming, have also been associated with articulatory decoding in many previous studies of speech production (Indefrey and Levelt, 2004), and reading (Burton et al., 2005; McDermott et al., 2003; see Price, 2012 for a review; Purcell et al., 2011). A recent ALE meta-analysis summarising findings from 33 fMRI studies found that the activation peak for pseudowords > words across reading and visual lexical decision tasks was in precentral gyrus at [-49, 3, 28] (McNorgan et al., 2015), which is close to the peak found in the current study [-42, -3, 33]. Premotor activation, when there is no overt speech involved, is likely to reflect sub-articulatory mechanisms that are activated irrespective of whether there is motor output required or not.

PreC/pOp activation is not specific to articulatory planning during reading. It has also been reported during other tasks that do not involve orthographic processing such as passive listening to speech and non-speech sounds (Agnew et al., 2011; Chu et al., 2013), covert syllable repetition (Wildgruber et al., 2001) and perception of spoken syllables (Pulvermuller et al., 2006). Indeed, Indefrey and Levelt (2004) refer to it as an area involved in “syllabication” which is distinct from the more precise phonetic encoding that occurs in motor cortex. Likewise, I found PreC/pOp processing for all speech production conditions including object naming. Enhanced PreC/pOp activation for pseudoword reading than object naming during speech production can be explained in terms of pseudoword reading involving the production of novel rather than familiar syllable sequences. During one-back matching, PreC/pOp activation is not needed to generate overt

speech output but subvocal articulatory activity might either be used as a memory aid (e.g. Kaan and Swaab, 2002; Koelsch et al., 2009) supplementing auditory imagery, or may occur automatically (without being necessary for task performance). It has also been shown that the functional connectivity between left pOp and STG is weaker in dyslexics than controls, which might reflect impaired access to phonetic representations in STG in dyslexics (Boets et al., 2013).

Finally, reading pseudowords compared to object naming enhanced activation in the left intraparietal sulcus (IPS) – a region associated with many domain-general functions, including attention orienting and externally or internally guided saccades (Bender et al., 2013; Corbetta et al., 2002). IPS activation was common to all conditions in my experiment but enhanced for reading pseudowords. Plausibly this is because visual attention needs to focus on sublexical parts of the stimulus during pseudoword reading. It is also interesting to note that tractography studies have identified fibre bundles connecting dorsal precentral gyrus to IPS and superior temporal gyri (Catani et al., 2005; Xiang et al., 2010). Together these regions might support a non-semantic phonological decoding route.

In summary, accessing phonology from orthography enhanced activation in (i) bilateral STS areas associated with phonological memory/auditory images; (ii) left PreC/pOp and putamen regions associated with articulatory planning of syllables and (iii) the left IPS which plays a generic role in attention/executive functions. None of these areas are specific to orthographic processing. However, the bilateral STS activations are consistent with phonological input processing (even though they are not specific to phonological processing) and the left PreC/pOp and putamen activations are consistent with what could be described as phonological output processing. The latter is likely to be (i) enhanced for reading pseudowords because the articulatory plans are novel and (ii) less activated by auditory repetition of pseudowords because the auditory inputs indicate how the output should sound.

The network supporting phonological retrieval from semantics

Object naming compared to reading or repeating pseudowords resulted in highly significant activation in the left hippocampus and parahippocampus, right occipital regions and bilateral cerebellum. The hippocampus and parahippocampus are generally not associated with word retrieval per se but rather with semantic memory functions. An increase in hippocampal activation has been reported for increased demands in speech comprehension and semantic processing (Hocking et al., 2009), for speech comprehension more than production (Awad et al., 2007) and during free verbal association tasks (Whitney et al., 2009). However, Hamamé et al. (2014) found that hippocampal iEEG activity directly predicts naming latency, and hypothesized that the hippocampus is involved in linking visuo-semantic to lexical properties of familiar object concepts.

The association of right occipital areas with accessing phonology from semantics was initially surprising given that (i) the location of these effects were in primary and visual association areas (calcarine sulcus and lingual gyrus) and (ii) activation was common to visual and auditory object naming. Right occipital activation cannot therefore be explained by greater visual complexity of object pictures. A more interesting interpretation is that activation in the right occipital regions is a consequence of visual imagery of the objects being named. This is the interpretation that was offered by Tranel et al., (2003) when they found activation in the calcarine sulcus during sound naming. It follows many other reports that the calcarine sulci are activated during visual imagery, in the absence of visual input (Klein et al., 2000; Slotnick and Yantis, 2005; Vetter et al., 2014). It may be necessary for helping to keep the object concept in short-term memory while we are retrieving its name. Thus, increased occipital activation for the semantic conditions in this experiment might be due to mental visual images of concrete semantic concepts that are created, independent of the input modality, to facilitate lexical retrieval. It has been shown that the extent of participation of visual processing areas in visual imagery depends on the vividness of the imagination (Pearson et al., 2015), which might explain why occipital activation has not been a consistent finding in other studies of picture/sound naming. This hypothesis could be tested in the future by collecting

a vividness rating of the semantic stimuli used in this study, and including the values as a covariate in the fMRI analysis.

Semantics to phonology also increased activation in bilateral cerebellum in bilateral lobule IX and right lobule VI. Activation in right lobule VI for word retrieval has been reported many times before (Frings et al., 2006; Jansen et al., 2005; Murdoch, 2010; Stoodley and Schmahmann, 2009), and is usually accompanied by left frontal activation (vice versa in subjects with right lateralised frontal activation) (Jansen et al., 2005). Involvement of lobule IX in the posterior cerebellar lobe in language tasks is less common, perhaps because it is very often excluded from the field of view to increase sensitivity in other areas. As shown by Stoodley et al. (2012), lobule IX, together with lobules V and VIIIB, show greater activation for motor tasks than cognitive tasks. Thus, it may be possible that the posterior cerebellar activation in this study is driven by semantically driven motor output. Further studies are needed to determine the role of lobule IX in speech production.

Conclusions

With this study, I sought to dissociate three different neural pathways supporting phonological retrieval from speech, orthography and from semantics. The findings make a clear distinction between two types of phonological processing: that associated with auditory representations of speech (in bilateral STS) and that associated with articulatory planning (in left PreC/pOp and putamen). Such a distinction bears similarities with the notion of input and output phonology. The input phonology areas could be re-described as “representations of heard speech” or “auditory images” that can be matched to other types of representations or stimuli. The output phonology areas could be re-described as articulatory processing that is required to overtly generate speech but which can also be used to match the articulatory content of different stimuli.

Comparing activation for object naming to reading or repeating pseudowords highlighted areas involved in semantic retrieval (hippocampal/ parahippocampal) and visual imagery (calcarine sulcus and lingual gyri) but did not identify significant activation in areas that could be considered phonological,

e.g. those involved in retrieving lexical representations (e.g. in the middle temporal regions assigned to this role in (e.g. in the middle temporal regions assigned to this role in Indefrey and Levelt, 2004) or to lexical phonological retrieval (e.g. in left middle frontal cortex, as suggested in Price, 2012).

Although the functional contributions of each language region remain poorly understood, this experiment has demonstrated how the comparison of pseudoword and object processing can be used to tease apart different phonological and semantic representations. This will be useful for investigating how phonological and semantic processing is affected by brain damage in clinical populations. In conclusion, the language paradigm applied here has a robust design providing significant results and is therefore a powerful tool for the dissociation of phonological effects in healthy and clinical populations.

4. EXPERIMENT II

Validating phonological effects in a new sample and paradigm adaptation

4.1. Summary

The aim of this chapter was to validate the phonological effects from Experiment 1 in an independent, larger sample (n=59). The effects of interest were the same as in Experiment 1, i.e. (A) speech to phonology, (B) orthography to phonology and (C) semantics to phonology, tested during 4 speech production tasks in a modified version of the fMRI language paradigm used for Experiment 1. The results show strong overlap between the activation patterns of the two studies, as well as increased effect sizes for the validation study because of the greater statistical power with a larger sample size. In addition, in Experiment 2 only, orthography to phonology increased activation in right middle frontal gyrus, right intraparietal sulcus precentral cortex/inferior frontal gyrus. After excluding factors such as stimulus and task order, inter-subject variability or stimulus priming or interference, I conclude that the additional right hemisphere clusters have been identified because of greater power in Experiment 2. Successful validation of the phonological effects from Experiment 1 increases confidence in the observed effects and helps the interpretation of the activation patterns. The modified version of the language paradigm that was tested here is an efficient and suitable tool for use in patient samples.

4.2. Introduction

Validating fMRI findings is particularly important in the light of recent publications claiming a “replication crisis” in psychology and cognitive science, suggesting that reported effects are absent, weaker or different when the same experiment is run again in a different sample. This can be due to methodological flaws, selective reporting (i.e. only positive results get written up/published), or

the lack of expertise in conducting and analysing experiments. A recent open science collaboration (Open Science, 2015) investigated the reproducibility of effects from 100 studies in psychological research, using original data when possible. They found that the average effect size between original effect and reproduced effect declined by almost half the size, and that the best predictor for reproducible results was the initial strength of the effect, i.e. the higher the original effect size (expressed through a p-value, for example), the more often the effect replicated.

Allegations of flawed study results also quickly undermine the public perception of scientific results. For example, a recent paper concerning the violation of statistical thresholding in fMRI research received major attention beyond the scientific community, potentially shedding negative light on neuroscience research. In brief, Eklund et al. (2016) claimed that many fMRI studies have not controlled for the family-wise error correctly, and that thousands of fMRI studies over the last 15 years could be flawed. Flandin and Friston (2016) published a reply soon after, explaining that drawing inference from peak thresholding is an appropriate form of correction of the family-wise error when using parametric tests, whereas parametric inference based on spatial extend (e.g. cluster-wise thresholding) requires low cluster threshold forming or correct smoothing (i.e. the data have to be smoother than the voxel size) – which has indeed been applied correctly in the majority of studies. However, a naïve use of analysis methods without appropriate control of false positive rates will continue to lead to low reproducibility rates. Replication studies in the field of brain imaging are generally rare because of the cost of scanning, and the difficulties scientists are facing when trying to publish results that are not novel. Nevertheless, researchers and publishers are increasingly acknowledging that the replication of fMRI studies is vital in order to reduce false positive (or negative) results, and to restore confidence in scientific results.

Here, I compare activation for the following tasks that were also used in Experiment 1:

(i) repeating pseudowords > naming objects from sounds (P > O Auditory),

(ii) reading pseudowords > naming objects from pictures (P > O Visual), and

(iii) naming objects (from sounds and pictures) > repeating and reading pseudowords (O > P Amodal)

Although the tasks were constant across studies, there were several differences between the paradigms, see below for details. If I identify the same activation pattern in Experiment 2 as those reported in Experiment 1, then we can be confident that the effects for speech-to-phonology, orthography-to-phonology and semantics-to-phonology are “real”. On the other hand, if the results from Experiment 1 and Experiment 2 differ, I will have the opportunity to investigate the source of the inter-study differences.

The following modifications were introduced into Experiment 2:

(i) Condition order was identical for each participant

(ii) Stimuli within condition were identical for each participant

(iii) There were no one-back matching conditions - all tasks involved overt speech production (as in half the tasks in Experiment 1)

(iv) The pseudoword stimuli were always novel

(v) The stimuli in the object naming conditions were not novel because all conditions of interest were performed after 5 other conditions with object names (see methods for details) that may have primed (reduced activation) or interfered with (increased activation) the effects of interest

(vi) The number of participants was more than doubled (n=59 versus 25)

(vii) There were 4 extra stimuli per condition (n=40 versus 36)

In contrast, in Experiment 1,

(i) Condition order was systematically rotated across participants

(ii) Stimuli were rotated across conditions (different participants performed the same condition but with different stimuli)

(iii) Half the participants were engaged in one-back matching conditions before performing the speech production conditions of interest. The other half performed one-back matching after the speech production tasks used

(iv) All the stimuli were seen twice (once for one-back matching conditions and once for speech production conditions). Consequently, all stimuli were novel during the speech production conditions in half the participants but not in the other half

(v) None of the participants were engaged in the 5 other conditions (from Experiment 2) with object names

(vi) The number of participants was less than half (n=25) than in Experiment 2 (n=59)

(vii) There were 36 stimuli per task (as opposed to 40 in Experiment 2)

To evaluate which of these paradigm differences explained any study specific differences, I tested the following hypotheses (summarised in Table 4.1):

Stimulus differences: If differences in activation between studies are due to stimulus differences, then activation should be more variable across participants in Experiment 1 than in Experiment 2 because stimuli were not varied per condition in Experiment 2 but they were in Experiment 1.

Condition order effects: If differences in activation between studies are due to order effects, then activation should also be more variable across participants in Experiment 1 than in Experiment 2 because condition order was not varied across participants in Experiment 2 but it was varied in Experiment 1. In addition, activation might be consistently higher or consistently lower in one of the Experiments if it is influenced by whether a condition was preceded by one-back matching (Experiment 1) or other object processing conditions (Experiment 2).

Pseudoword novelty: If differences in activation between studies are due to differences in pseudoword novelty, then activation should be greater in Experiment 2 than Experiment 1, and also greater in Experiment 1 for participants who performed the speech production conditions before one-back matching.

Object name priming: If inter-study differences in P>O or O>P activation are due to object names being more familiar in Experiment 2 (because the same object names were heard during prior object processing conditions), then object naming activation should be significantly less in Experiment 2 than Experiment 1. This could result in O>P being bigger in Experiment 2 and P>O being bigger in Experiment 1.

Object name interference: If inter-study differences in P>O or O>P activation are due to interference effects in Experiment 2 (because the same names were heard during prior object processing conditions), then object naming activation should be significantly higher in Experiment 2 than Experiment 1. This could result in O>P being bigger in Experiment 2 and P>O being smaller in Experiment 1.

Power: If differences in activation between studies are due to power differences, then activation should be more significant in Experiment 2 than Experiment 1 (Experiment 2 had more participants than Experiment 1); and inter-study differences should be less significant when the number of participants was matched (e.g. using subsets of 25 participants in Experiment 2). If activation is consistently higher for Experiment 2 than Experiment 1 even when sample size is controlled, then I will also consider the influence of the number of stimuli per condition (40 in Experiment 2 and 36 in Experiment 1).

Outliers: If differences in activation between studies are due to atypical participants in one or other studies, then differences should be reduced or eliminated when participants with outlier values are removed.

Table 4.1: How inter-study differences are expected to affect activation.

Cause of inter-study differences	**Object naming (O)**		**Pseudowords (P)**	
	Mean	*Variability*	*Mean*	*Variability*
Condition order effects:		E1>E2		E1>E2
Stimulus differences:	E1 >/<E2	E1>E2	E1 >/<E2	E1>E2
Object name priming	E1 > E2			
Object name interference:	E2 > E1			
Pseudoword novelty (E2>E1, P):			E1A>E1B	
Number of subjects (E2>E1, O&P)	E2A = E1		E2A = E1	
	E2B = E1		E2B = E1	
Number of stimuli, after controlling	E2A > E1		E2A > E1	
number of subjects & outliers	E2B > E1		E2B > E1	

E1 = Experiment 1 (n=25)
E1A = E 1 (n=13 who performed speech production before one back matching
E1B = E 1 (n=12 who performed speech production after one back matching
E2 = Experiment 2 (n=59)
E2A = E 2 (n= 25, including participants 1-25)
E2B = E 2 (n= 25, including participants 26-50)

The advantages of counterbalancing stimuli and condition order are well appreciated in group level studies. However, counterbalancing stimuli and condition order is not an efficient way to study inter-subject variability – quite simply because inter-subject variability in activation could be due to inter-subject variability in stimuli and condition order. We therefore need to control for stimuli and condition order when comparing activations across participants. It is also an advantage to maximise the number of participants to increase power across participants and fully evaluate the scale of normal inter-subject variability. The adaptations to the paradigm used for Experiment 2 are therefore suitable for studying the degree to which individual stroke patients show abnormal activation patterns.

In brief, the data collected in Experiment 2 will allow each individual patient to be compared to a large sample of controls (i.e. n=59), who underwent exactly the same experimental manipulation. If the stimuli and condition order had been counterbalanced across the healthy controls, only a subset of healthy controls (who used exactly the same paradigm as the patient) could be compared to each patient. Keeping stimuli and condition order constant across all patients also allows us to compare any combination of patients to each other.

In summary, Experiment 2 tested if the results from Experiment 1 could be reproduced when stimuli and condition order were held constant. It also enabled me to test whether there were any differences between the activation patterns of the two studies, and what the cause of these differences might be.

4.3. Methods

4.3.1. Participants

A new sample of 59 participants was included in Experiment 2, compared to 25 different participants in Experiment 1. All participants were native English speakers, right handed (assessed with Edinburgh Handedness Inventory, Oldfield, 1971) with normal or corrected-to-normal vision and hearing, and without neurological or psychiatric conditions. Prior to the experiment, they gave written informed consent for participation and received financial compensation for their time. The Experiment had approval from the London Queen Square Research Ethics committee. Participant details for both samples are reported in the general methods section.

4.3.2. Experimental design

The conditions of interest were: (1) Repeating heard pseudowords, (2) Naming objects from their sounds, (3) Reading Pseudowords aloud, and (4) Naming objects from pictures. In addition, there were 4 other conditions that were included in Experiments 1 and 2 and will be analysed in Experiment 3. These are: (5) Repeating familiar words, (6) Reading aloud familiar words, (7) naming the gender of a voice humming with no semantic or phonological sounds, and (8) naming the colour of a picture with no semantic or phonological content. Finally, the participants in Experiment 2 also performed 5 other conditions that were not part of my experiments but have been reported in Sanjuan et al. (2014). Four of these extra conditions involved seeing pictures of two objects and (1) making a binary semantic similarity decision; (2) naming both objects; (3) naming the verb describing how two objects were interacting with one another and (4) producing a sentence that described how the two objects were interacting with

one another (e.g. “the donkey is eating the carrot”). The fifth of these extra conditions involved hearing two object names and making a binary semantic similarity decision. The importance of mentioning these 5 extra conditions here is that they were always performed before the conditions of interest for Experiment 2; and this exposed participants to the names of the objects used in Experiment 2, as well as half the visual object naming pictures. If this prior exposure has a notable effect on group results or inter-subject variability then we should be able to detect it by comparing the results of Experiment 1 (novel stimuli for half the participants) and Experiment 2 (repeated stimuli).

4.3.3. Effects of interest

The 8 speech production conditions were analysed separately for Experiment 1 and Experiment 2. The effects of interest were the same as in Experiment 1 after excluding the one-back matching conditions (see below for details). In addition, I combined the 8 speech production conditions from Experiment 1 and Experiment 2 into a single analysis with 16 conditions. This enabled me to test whether effects observed in one experiment but not the other resulted in a significant Experiment by condition interaction.

1. **Speech to phonology** was identified by comparing auditory pseudowords (that carry sublexical phonological content) to objects sounds (that have no sublexical phonological associations), and inclusively masking this contrast with auditory pseudowords > rest.

2. **Orthography to phonology** was identified by comparing written pseudowords (that provide phonological orthographic cues) to objects pictures (that do not provide orthographic cues), and inclusively masking this contrast with visual pseudowords > rest.

3. **Semantics to phonology** was identified by comparing pictures and sounds of objects to visual and auditory pseudowords [O>P]. Inclusive masks were [O>P] in the visual modality only, [O>P] in the auditory modality only, [O>Rest] in the visual modality only and [O>Rest] in the auditory modality only.

4.3.4. Thresholds

The statistical threshold was set to $p<0.05$ after family wise error correction for multiple comparisons across the whole brain. For signal extraction from regions of interest, the threshold was lowered to $p<0.01$ uncorrected (unless stated otherwise). Thresholds for inclusive masks was set at $p < 0.05$ for P > O and at $p < 0.001$ for O > P (to match the effects from Experiment 1).

4.3.5. Post hoc analysis to explore differences between Experiment 1 & 2

When activation was observed in one experiment more than another, I used the voxels activated in one but not the other as a region of interest and extracted the eigenvariates for each participant for each condition. Data from one-back matching tasks in Experiment 1 were not included so that all comparisons were matched for task.

Speech production data from participants in Experiment 1 were subdivided according to whether they performed the speech production conditions before (Group 1A) or after (Group 1B) the one-back matching conditions. Data from participants in Experiment 2 were subdivided into two groups of 25 (to match the total number of participants in Experiment 1). The selection of these 2 groups was based on the order in which they were scanned (participants 1-25 in Group 2A; participants 26-50 in Group 2B). For each condition, within each group, I calculated the mean value, standard deviation, minimum and maximum. In addition, I calculated the range of differences between P and O across participants.

When activation was significant for P>O and O>P in Experiment 2 but not 1, I investigated the following explanations:

1) **Lower Inter-subject variability** in Experiment 2 because stimuli and condition order were held constant. Variability was estimated from the standard deviation in condition values (P or O) and the range in condition differences (P vs. O).

2) **Power** because Experiment 2 had more participants than Experiment 1. If this is the case, inter-study differences should be less significant when the number of participants was matched (e.g. using subsets of 25 participants in Experiment 2).

3) **Number of stimuli** because Experiment 2 had more participants than Experiment 1. This should not be affected by the number of participants or the removal of atypical participants.

4) **Atypical participants:** This should result in reduced inter-study differences when atypical participants (with activation 2.5 times higher or lower than the mean of the condition) are removed.

When Experiment 2 activation was higher for P>O but not O>P, and/or when Experiment 1 activation was higher for O>P but not P>O, I additionally investigated the following explanations:

5) **Pseudoword novelty effects in Experiment 2.** This was expected to result in higher pseudoword activation for Group 1A than Group 1B.

6) **Object naming was primed in Experiment 2**. This was expected to result in less object naming activation for Experiment 2 than Experiment 1 with no significant inter-study differences for pseudowords.

When Experiment 1 activation was higher for P>O but not O>P, and/or when Experiment 2 activation was higher for O>P but not P>O, I investigated the following:

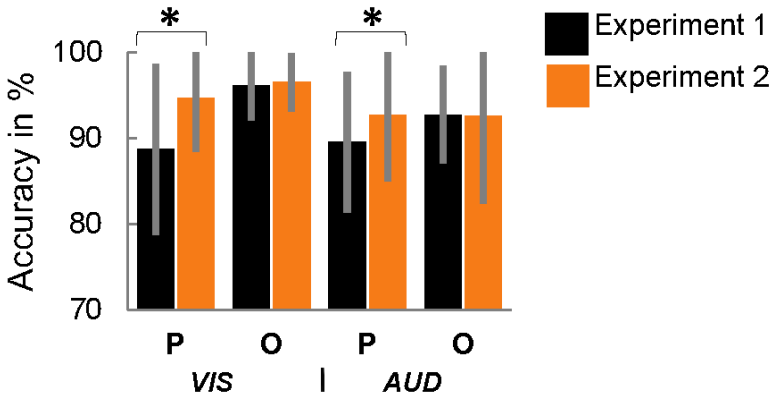
7) **Object interference in Experiment 2** reduced activation differences between P and O. If this was the case, activation would be higher for Experiment 2 than Experiment 1 for objects but not pseudowords.

4.4. Results

4.4.1. Behavioural results

In Experiment 2, average in-scanner accuracy was above 90% for all conditions. One participant was excluded from the average score for pseudoword repetition because his audio-file was corrupt and out-of-scanner scoring was not possible. His behavioural data was excluded from all subsequent analyses. Accuracy for reading and repeating pseudowords was higher for Experiment 2 (95%) than Experiment 1 (89%) ($F(80)=5.99$, (80), $p=0.017$) because of changes to the stimuli (see general methods chapter). See Figure 4.1.

A. Accuracy for Experiments 1 and 2



B. Accuracy for Experiment 2 (n=59)

	VISUAL		AUDITORY	
	P	O	P*	O
Mean (%)	94.72	96.57	92.72	92.58
SD	6.28	3.38	7.70	10.22
MIN	75	87.5	68	55
MAX	100	100	100	100

Figure 4.1: A. Accuracy scores (mean with standard deviation) for Experiment 1 (black) and Experiment 2 (orange). VIS = Visual, AUD = Auditory. B. Details on accuracy scores for Experiment 2. Scores for pseudoword repetition are based on n=58 participants. See chapter 3 for behavioural results on Experiment 1.

4.4.2. fMRI results

Speech to phonology

As in Experiment 1, pseudoword repetition, compared to auditory sound naming, increased activation in bilateral superior temporal sulci (STS). In addition, Experiment 2 found that [P > O Auditory] increased activation in bilateral posterior putamen. A post hoc analysis of Experiment 1 identified bilateral putamen activation at a lower statistical threshold; and the effects in Experiment 2 were not significantly different from those in Experiment 1. See Figure 4.2.

A	*Experiment 1 only (SP & OBM)*				*Experiment 2 only (SP only)*					*Experiments 1&2 combined (SP)*	
[P > O] AUD	***x***	***y***	***z***	***Zsc***	***x***	***y***	***z***	***Zsc***	***Vx***	***S1 > S2***	***S2 > S1***
L/R aSTS (ROI)	-57	-24	-3	**4.3**	-60	-33	3	4.0		n.s.	n.s.
R aSTS^	57	-27	-3	**4.6**	-57	-33	-3	2.4		n.s.	n.s.
Novel											
L pPUT	-24	-3	0	3.6	-24	0	0	**4.9**	63	n.s.	n.s.
R pPUT^	24	-3	-3	4.0	27	-6	3	**4.6**	39	n.s.	n.s.

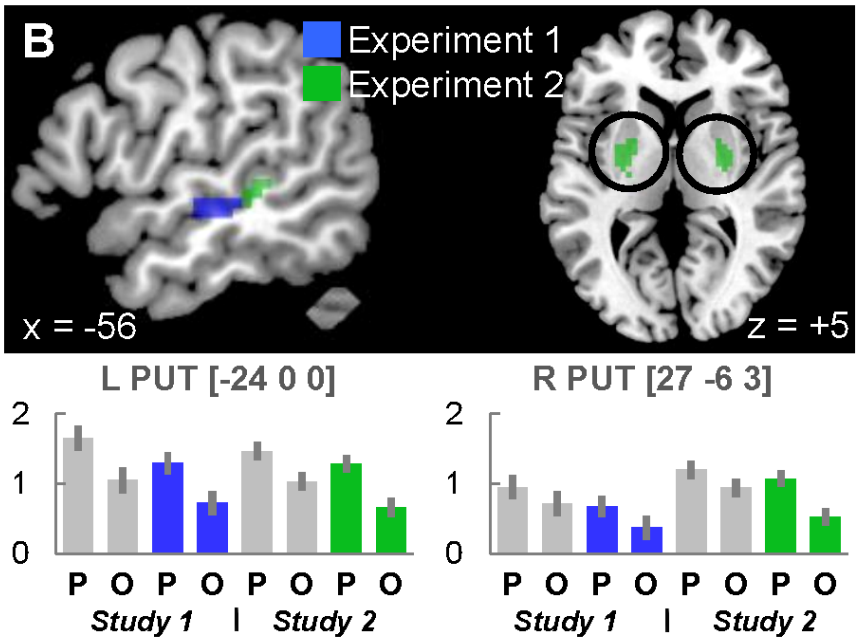


Figure 4.2: A. Peak coordinates for [P > O Auditory] in Experiment 1 and Experiment 2, and across both experiments. ROI in bilateral anterior temporal sulcus (aSTS) taken from Experiment 1. xyz = coordinates in MNI space. SP = speech production, OBM = one-back matching. n.s. = not significant. Vx = cluster size in voxels. B. Overlay of activation for [P>O Auditory] for Experiment 1 (green) and Experiment 2 (blue). Plots show contrast estimates and standard error across tasks for each experiment. Grey bars = visual tasks.

Orthography to phonology

As in Experiment 1, reading pseudowords compared to naming pictures of objects activated bilateral superior temporal sulci, left precentral gyrus, extending into pars opercularis, bilateral anterior putamen and the left inferior parietal lobe. Within these regions, activation in left pars opercularis was higher in Experiment 2, while activation in bilateral putamen was higher in Experiment 1 (see Table 4.2). In addition, Experiment 2 activated right hemisphere regions in precentral, inferior parietal and middle frontal regions, as well as left postcentral cortex. I also noted that activation in MFG was strongly deactivated in some participants in Experiment 2 but not in Experiment 1. Reasons for these inter-study differences are investigated in post hoc analyses below. See Table 4.2 and Figure 4.3.

Table 4.2: Activation cluster for Orthography to Phonology

[P > O] VIS	***Experiment 1 only (SP & OBM)***				***Experiment 2 only (SP only)***					***Experiments 1&2 combined (SP)***	
	x	***y***	***z***	***Zsc***	***x***	***y***	***z***	***Zsc***	***Vx***	***S1 > S2***	***S2 > S1***
L/R STS (ROI)	-57	-30	0	**4.1**	-60	-33	3	3.8		n.s.	n.s.
	57	-24	-3	**3.9**	60	-24	-3	3.9		n.s.	n.s.
L preC	-42	-3	33	**4.9**	-42	-3	39	3.9		n.s.	n.s.
	-48	-3	45	**4.1**	-51	-3	45	4.7		n.s.	n.s.
	-51	-3	42	2.4	-54	0	42	**5.5**		n.s.	n.s.
	-24	-18	54	2.5	-24	-12	54	**5.2**	35	n.s.	n.s.
L pOp	-57	6	18	**4.4**	-57	9	18	4.6		n.s.	n.s.
	-54	6	30	2.6	-57	9	33	**6.3**	239	n.s.	**3.2**
	-54	9	12	3.0	-51	9	12	**4.9**		n.s.	n.s.
L aPUT	-21	6	9	**4.8**	-21	6	3	4.0		**4.0**	n.s.
R aPUT	21	12	9	**4.0**	21	12	12	2.6		**2.5**	n.s.
L IPS	-36	-45	39	**4.7**	-36	-42	39	3.9		n.s.	n.s.
NOVEL											
L PostC	-57	-21	30	2.6	-57	-21	27	**6.7**	52	n.s.	n.s.
R PreC/IFG				n.s.	60	15	24	**5.4**	132	n.s.	n.s.
				n.s.	54	12	15	**4.8**		n.s.	n.s.
				n.s.	57	9	39	**3.8**		n.s.	n.s.
R IPS	39	-36	39	3.9	39	-42	39	**4.9**	118	n.s.	n.s.
				n.s.	45	-45	48	**4.3**		n.s.	**3.1**
				n.s.	54	-36	54	**3.9**		n.s.	n.s.
R MFG				n.s.	39	42	0	**5.1**	194	n.s.	**3.5**
				n.s.	21	45	-6	**4.7**		n.s.	**3.8**
	33	54	0	2.6	33	54	0	**4.5**		n.s.	n.s.

Z-scores highlighted in bold indicate which study the co-ordinates came from. For abbreviations see Figure 4.2.

Orthography to Phonology

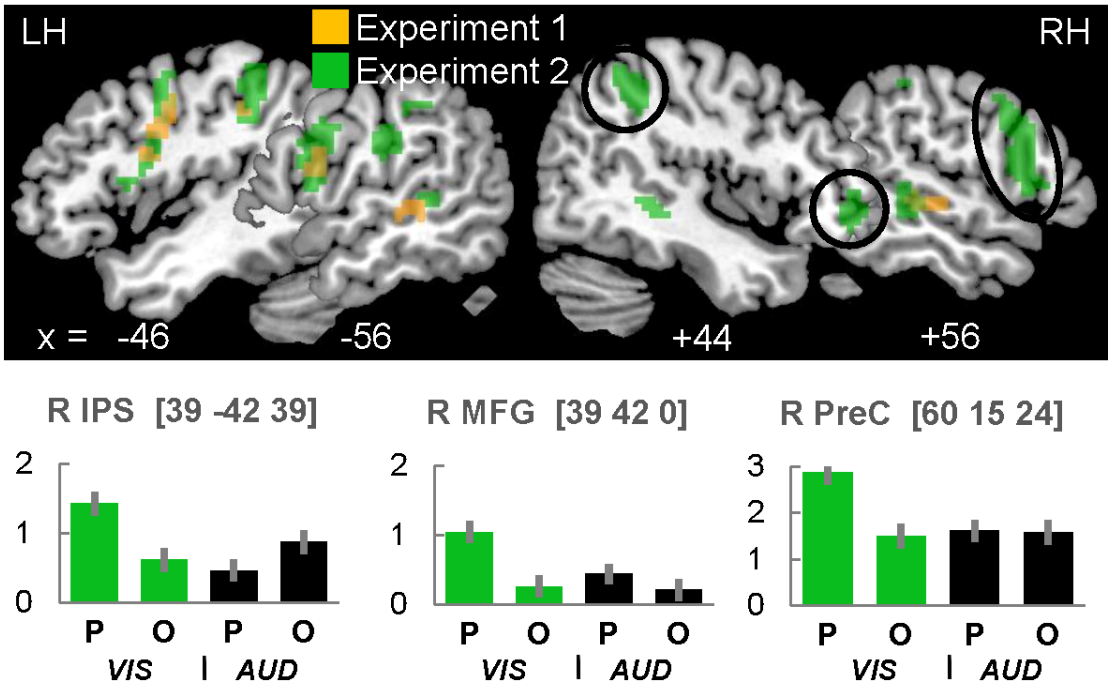


Figure 4.3: Overlay of activation cluster for [P>O Visual] for Experiment 1 (orange) and Experiment 2 (green). Plots show contrast estimates and standard error for Experiment 2 across tasks in right hemisphere regions. Green/black bars = visual/auditory. For Z-scores see Table 4.2. For display purposes only, cluster size was thresholded at 20 voxels for Experiment 1, and at 30 voxels for Experiment 2.

Semantics to phonology

Naming objects, compared to pseudoword reading and repetition activated an extensive network that was remarkably consistent across experiments. Significant differences in the strength of activation were only observed when the statistical threshold was set at p<0.001. Activation in the left middle frontal gyrus was higher in Experiment 1, whilst activation in bilateral posterior/occipital regions was higher in Experiment 2. See Figure 4.4.

A

[O > P Amodal]	*Exp. 1 only (SP)*				*Exp. 2 only (SP)*					*Exp. 1 & 2 (SP)*	
	x	*y*	*z*	*Zsc*	*x*	*y*	*z*	*Zsc*	*Vx*	*S1 > S2*	*S2 > S1*
L ITG-p	-51	-54	-12	**5.2**	-51	-54	-9	4.6		n.s.	n.s.
L MFG	-42	21	21	**6.0**	-39	18	24	3.2*		**3.7**	n.s.
L/R CB IX	-12	-42	-42	**6.6**	-12	-42	-45	7.4		n.s.	n.s.
	12	-45	-45	**6.6**	12	-45	-45	7.2		n.s.	n.s.
R CB VI	12	-81	-18	**7.0**	12	-81	-18	Inf		n.s.	n.s.
L Insula	-30	24	-3	**5.5**	-30	33	-9	6.1*		n.s.	n.s.
L pOrb	-30	33	-9	5.0	-30	33	-9	6.1	23	n.s.	n.s.
L Hipp	-21	-33	-3	**6.1**	-21	-33	-3	6.7		n.s.	n.s.
L pHipp	-21	-45	-6	**7.1**	-18	-45	-6	Inf		n.s.	n.s.
R Calcarine	0	-87	-3	**6.6**	0	-84	-3	Inf		n.s.	n.s.
R Lingual	21	-51	-6	**5.6**	21	-51	-3	Inf		n.s.	n.s.
L/R Occipital	-12	-96	6	5.1	-12	-96	6	Inf	4034	n.s.	n.s.
Cortex	12	-93	9	6.5	12	-93	9	Inf		n.s.	**3.3**
	-18	-81	-12	7.3	-18	-81	-12	Inf		n.s.	**3.8**
NOVEL											
L mCingulate	-18	-30	45	3.3*	-18	-33	42	**6.2**	20	n.s.	n.s.
				n.s.	-6	-36	30	**5.4**	11	n.s.	n.s.
L Precuneus				n.s.	-15	-39	54	**5.6**	9	n.s.	n.s.
R Amygdala	24	-3	-18	3.8	27	0	-18	**5.5**	30	n.s.	n.s.
R CB lob 6/9				n.s.	12	-69	-27	**5.7**	9	n.s.	n.s.

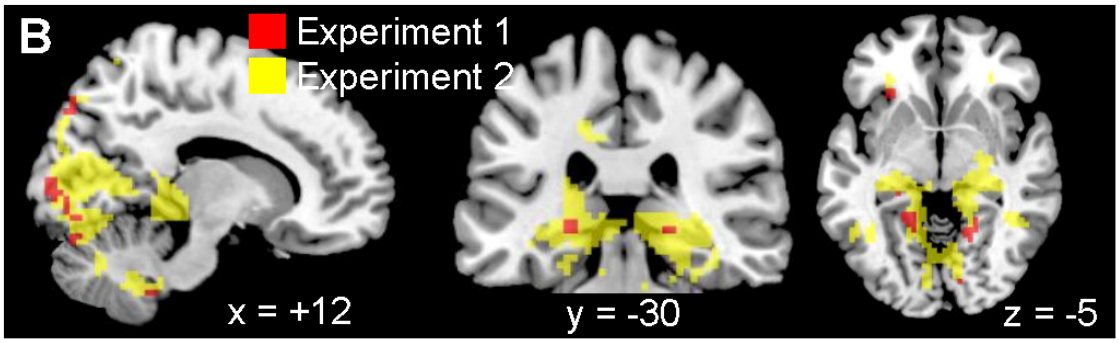


Figure 4.4: A. Peak coordinates for the replication of [O>P Amodal] for Experiments 1 and 2. * = threshold for masking lowered to p<0.05. SP = speech conditions only. B. Overlay of activation cluster for Experiment 1 (red) and Experiment 2 (yellow) during [O>P Amodal]. For abbreviations see Figure 4.2. For display purposes only, cluster size was thresholded at 5 voxels for Experiment 1 and 2.

4.4.3. Post hoc analyses to explore differences between Experiment 1 and 2

Regions of interest for the post hoc analyses were defined as areas that were activated for orthography to phonology in Experiment 2 but not in Experiment 1. This included 118 voxels in right IPS, 194 voxels in right MFG, and 132 voxels in right PreC (see Table 4.2 and Figure 4.3.). For each region of interest, mean activation for P > Rest and O > Rest was extracted across all voxels in the region for every participant. See Figure 4.5.

The inter-study differences we observed in these regions were most likely to be explained by power because inter-study differences in P>O were not significant ($p>0.05$) when the sample size was reduced to 25 in Experiment 2 ($p>0.05$ for Group 1A > Experiment 2 and Group 1B > Experiment 2) and participants with outlier values (in Experiment 2 only) were removed. There was no evidence for the following explanations:

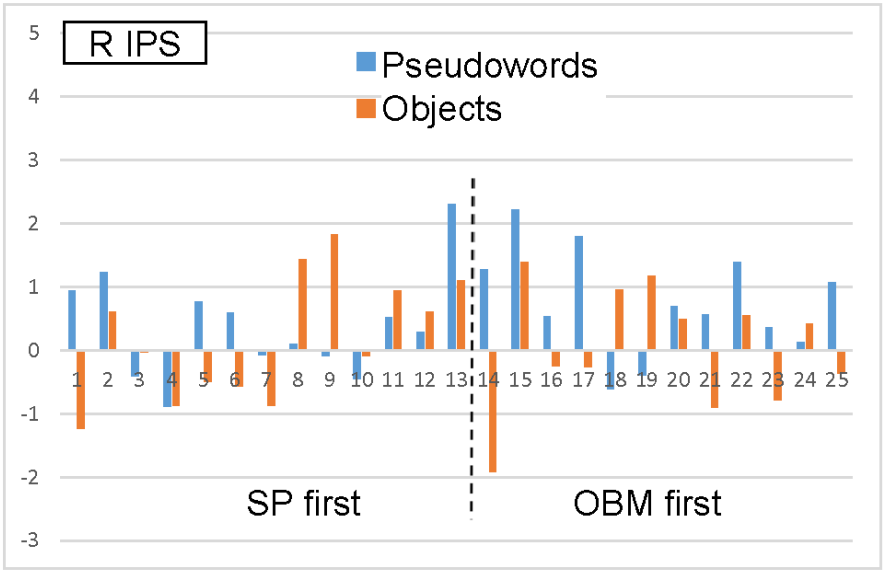
(i) **Lower Inter-subject variability** in Experiment 2 than Experiment 1 (to the contrary, variability was higher in Experiment 2 for pseudowords and P>O).

(ii) **Pseudoword novelty** in Experiment 2 because there was no significant difference between Group 1A and Group 1B (that differed in novelty) for any of the conditions including pseudowords.

(iii) **Object name priming or interference in Experiment 2** because there was no significant difference in object naming between Experiment 1 and 2 when the number of participants was matched and outliers were removed.

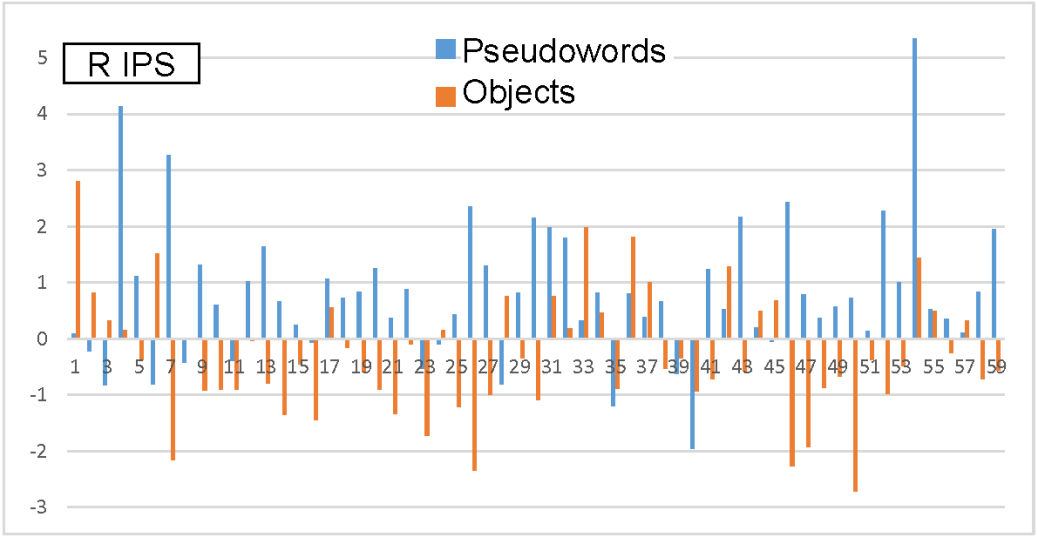
4.4.4. Post hoc analysis of inter-subject variability for reading pseudowords more than naming pictures of objects

Experiment 1: R IPS activation for reading pseudowords and naming pictures of objects relative to rest.

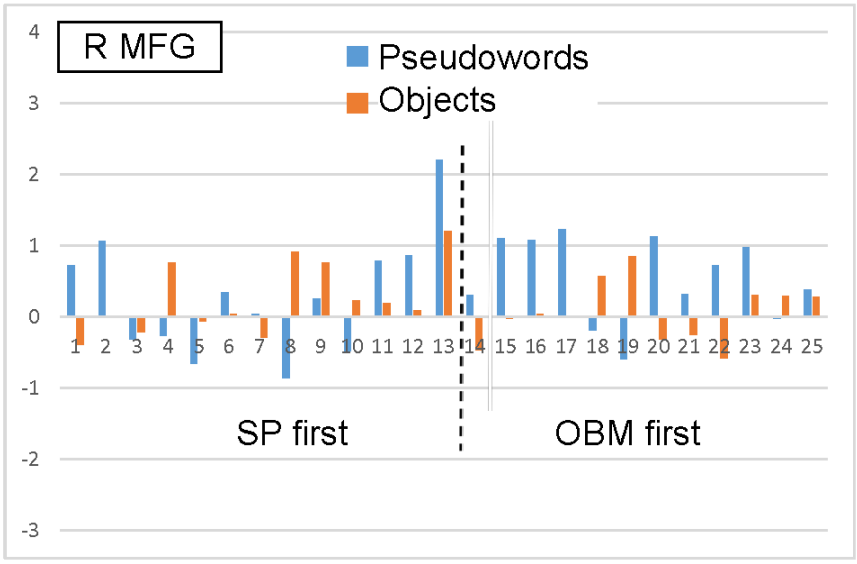


Participants #18 & #25 had 47% accuracy for reading pseudowords

Experiment 2: R IPS activation for reading pseudowords and naming pictures of objects relative to rest.

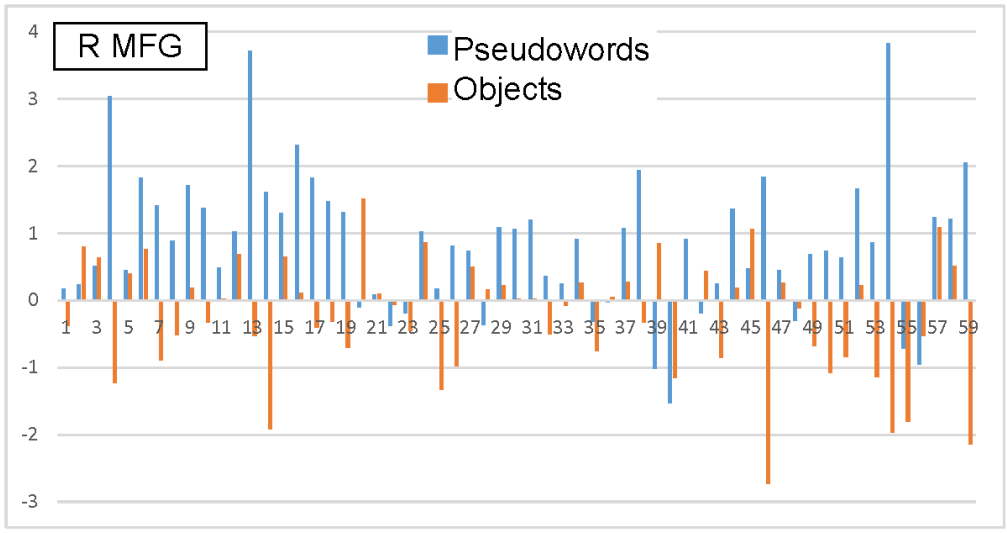


Experiment 1: R MFG activation for reading pseudowords and naming pictures of objects relative to rest.

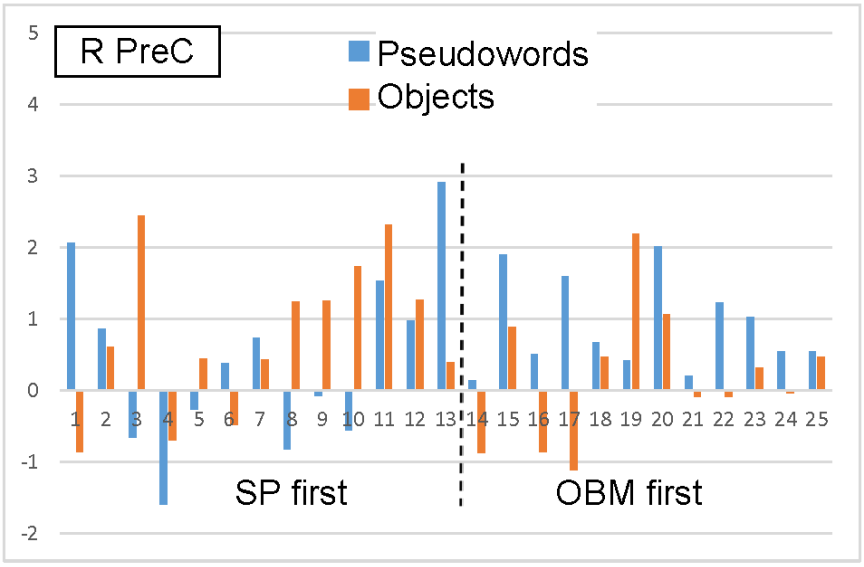


Participants #18 & #25 had 47% accuracy for reading pseudowords

Experiment 2: R MFG activation for reading pseudowords and naming pictures of objects relative to rest.



Experiment 1: R PreC activation for reading pseudowords and naming pictures of objects relative to rest.



Participants #18 & #25 had 47% accuracy for reading pseudowords

Experiment 2: R PreC activation for reading pseudowords and naming pictures of objects relative to rest.

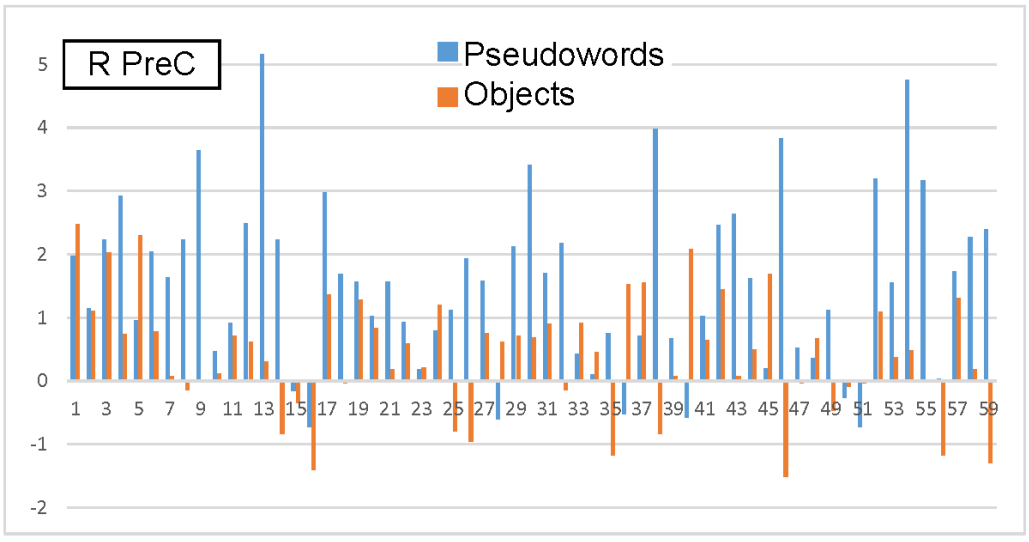


Figure 4.5: Plots show eigenvariates for [P > O Visual] for each participant within Experiment 1 and Experiment 2 for each region of interest (Right inferior parietal sulcus, right middle frontal gyrus, right precentral cortex). Blue/orange bars = reading pseudowords/naming object pictures. For Z-scores see Table 4.2.

4.5. Discussion

The aim of this study was to validate the fMRI effects for (i) speech to phonology, (ii) orthography to phonology and (iii) semantics to phonology from Experiment 1 in a new sample of participants with a modified experimental design. Given the modifications to the paradigm in Experiment 2, compared to Experiment 1, it is both surprising and reassuring that the results for both experiments were so consistent. Thus, this study provides an applied example of the theoretical principles formulated in a recent paper on best practice in neuroimaging data analysis (Nichols et al., 2017). The paper highlights that the most challenging form of reproducibility is "whether a finding holds under variation in the stimuli and experimental methods". Moreover, contrary to the findings of a recent meta-analysis on reproducibility effects (Open Science, 2015), the effect sizes in this validation study (Experiment 2) are larger than in the original experiment (Experiment 1). This is likely due to the larger sample size included in Experiment 2, which allowed for greater statistical power, and identification of novel regions for the effects of interest.

Novel effects in Experiment 2

In Experiment 2, but not Experiment 1, orthography to phonology increased activation in right middle frontal gyrus, right intraparietal sulcus and right precentral cortex/inferior frontal gyrus. These study-specific effects were thoroughly investigated in post-hoc analyses to identify potential sources of inter-study variability. These analyses revealed that differences between the two experiments are likely due to greater power in Experiment 2. None of the other factors, i.e. condition or stimulus order, pseudoword novelty, object name priming or interference, number of stimuli or inter-subject variability could have explained the observed activation pattern, i.e. greater activation in right hemisphere regions for orthographic stimuli in Experiment 2 compared to Experiment 1. This increases confidence that the differences in the design of the two paradigms (as spelled out in the introduction) have not confounded the results, and that the paradigm used for Experiment 2 is a suitable tool to investigate language functions.

The other important point to note is the significance of the sample size in fMRI studies. Button et al. (2013) highlighted that sufficient power will dramatically increase the chance of finding a statistically significant effect, particularly when the “true” effect in the population is small. Although Experiment 1 included more than 16 participants, which has been suggested as minimum sample size for fMRI studies (Friston, 2012), this number might not be enough to detect the contribution of the right hemisphere to phonological retrieval from orthography, particularly if effects are only observed in a subset of participants. Replication studies with increased power, where possible, are important to detect real effects, but also to uncover false positives.

The role of the right hemisphere in orthography to phonology

The contribution of the right hemisphere to phonological processing is generally limited to motor and auditory regions (Vigneau et al., 2011). The activation in this experiment for orthography to phonology in right middle frontal gyrus, precentral cortex, extending into inferior frontal gyrus, and intraparietal sulcus might therefore reflect non-speech functions such as additional demands on executive processes. For instance, Baumgaertner et al. (2013) suggest that right inferior frontal gyrus is recruited when attention is directed towards non-linguistic features of verbal stimuli. Activation in the right middle frontal gyrus (MFG) for orthography to phonology fits with reports of its involvement in silent syllable counting in written pseudowords (Poldrack et al., 1999) and syllable discrimination in auditory and visual stimuli (Sekiyama et al., 2003). Alternatively, it has been suggested that the right MFG is involved in auditory attention, not specific to language (Vigneau et al., 2011). Finally, the right intraparietal sulcus (IPS) is usually not directly linked to language functions but rather considered to be part of the attentional control network (Corbetta et al., 2002; Rushworth et al., 2001). More specifically, right IPS activation has been found when bottom-up attention is required, e.g. when directing attention towards salient stimuli (Geng and Mangun, 2009) or voluntary shifting of attention to visual spatial cues (Cusack et al., 2010; Ikkai and Curtis, 2008). Other neuroimaging studies identified IPS activation for number processing, including conceptual decisions on numbers (Cappelletti et al., 2010), magnitude processing during a syntactic processing task (Carreiras et al., 2010) and estimation of discrete quantities

(Castelli et al., 2006). Overall, prior findings suggest that right hemisphere regions play a supportive role for the tasks involved in this study rather than a specific role in phonological processing. Moreover, right hemisphere activation in the current experiment might be driven by a few participants who recruited additional neural resources during the more effortful task of pseudoword reading compared to object naming.

Conclusions

This validation study shows that the phonological effects found in Experiment 1 are also present in a separate, larger sample. The strong overlap of the activation cluster across studies provides evidence that the effects are "real" effects rather than false positives. The results provide strong support for the bilateral superior temporal sulci and bilateral putamen playing a key role in input phonology, independent of input modality. Right hemisphere activation for orthography to phonology, which is only present in Experiment 2 but not in Experiment 1, is likely due to increased power in the validation study (i.e. results are based on 59 participants in Experiment 2 versus 25 participants in Experiment 1). Right middle frontal gyrus and right intraparietal sulcus might play an important role in orienting attention, whilst right inferior frontal activation might reflect supportive processing of perceptual stimulus features. However, the functional roles of the identified right hemisphere regions need to be interpreted with caution since the activation pattern was not present in Experiment 1, and might be driven by a subset of participants in Experiment 2.

It has been shown that replication studies generally achieve a smaller effect size than the original experiment, and that a replication study, in order to have the same power as the original study, needs a considerably larger sample size (Button et al., 2013). In this experiment, the sample size was increased by >50% compared to the original study, and the effect sizes in most regions were indeed larger than in the original study. In addition, the validation of the results in a new sample demonstrated that the fMRI paradigm that has been used here is a suitable tool to investigate language functions in other samples, such as bilinguals or elderly participants, and in single subject studies, involving stroke or tumour patients.

5. EXPERIMENT III

Four functionally distinct regions in the left supramarginal gyrus support word processing

5.1. Summary

Here, I set out to investigate the role of the left supramarginal gyrus (SMG) in phonological processing. The anterior dorsal part of left SMG (adSMG) has commonly been implicated in phonological tasks, however, I did not find SMG activation in Experiments 1 and 2 for reading pseudowords compared to naming pictures of objects. Previously reported adSMG activation could have been driven by different processes that are not specific to phonology. These include: mapping orthography-to-phonology, planning articulatory sequences or auditory short-term memory. In order to test for each of these processes, I included words and baseline conditions in my analyses, in addition to the pseudoword and object conditions that I used in Experiments 1 and 2. The word conditions allowed me to replicate previous studies that have compared pseudowords to words. The baseline conditions (with minimal semantic and sublexical phonological cues) allowed me to look for effects that were common to pseudowords, words and objects. A sample of 85 healthy participants was included to increase power and to potentially detect subthreshold activation.

In ventral SMG, I found (A) an anterior subregion, associated with articulatory sequencing (for speech production > one-back matching tasks), and a (B) posterior ventral subregion associated with auditory short-term memory (for auditory > visual stimuli and written words and pseudowords > pictures of objects). In dorsal SMG, I found a (C) posterior subregion associated with the integration of sublexical and lexical cues, since it showed highest activation for words compared to other stimuli and finally, (D) an anterior dorsal subregion showing higher activation for both pseudoword reading and object naming compared to word reading, thus more likely reflecting executive demands rather than phonological processing.

This dissociation of four functionally-distinct regions within SMG improves our understanding of the different types of phonological processing, and the functional role of SMG, and has implications for predicting the effect of brain damage to this region. Moreover, it demonstrates the potential of the fMRI paradigm for the dissociation of different processing levels that are involved in language and beyond.

5.2. Introduction

The SMG is known to play an important role in phonological processing, as shown in numerous previous studies. It was therefore surprising that the first two experiments of this thesis did not reveal SMG activation for reading pseudowords compared to naming pictures of objects. The only inferior parietal region I identified was in the adjacent intraparietal sulcus. Several previous studies have reported that an anterior dorsal part of SMG (adSMG) is more activated for reading pseudowords compared to reading aloud words, and for phonological decisions on familiar written words compared to semantic decisions on matched words. Anatomically, there is a striking overlap between the activation peaks for pseudoword > word reading and phonological > semantic decisions, as apparent from the literature review in Table 5.1. This observation suggests that the left anterior dorsal SMG is involved in sublexical phonological processing of orthographic stimuli and is therefore not in alignment with the absence of adSMG activation for pseudoword reading in my own experiments.

Table 5.1: SMG activation reported in prior studies of phonological decisions and pseudoword reading.

Study	*Technique*	*x y z*	*Mean x y z*
Reading aloud visual pseudowords > words			
Vigneau (2005)	fMRI	-60 -28 36	
		-52 -36 44	
Binder (2005)	fMRI	-37 -37 37*	-49 -35 39
		-47 -38 41*	
Taylor (2014)[a]	fMRI	-46 -38 44	
Carreiras (2007)	fMRI	nr	
Cummine (2013)	fMRI	nr	
Fiez (1999)	PET	nr	
Herbster (1997)	PET	nr	
Mechelli (2000)	fMRI	nr	
Rumsey (1997)	PET	nr	
Phonological > semantic decisions on visual words			
Scott (2003)	PET	-60 -26 39*	
Mummery (1998)	PET	-59 -31 38*	
Seghier (2004)	fMRI	-55 -35 40*	-52 -35 40
Devlin (2003)	fMRI	-42 -40 46	
Price (1997)	PET	-42 -44 36*	
Roskies (2001)	PET	nr	
Phonological > perceptual decisions on visual words versus letter strings			
Xu (2002)	fMRI	-47 -44 33*	-43 -45 37
Seghier (2004)	fMRI	-39 -46 42*	
Gitelman (2005)	fMRI	nr	

*fMRI or PET studies were included if they used alphabetic stimuli. No SMG activation was observed when the stimuli were presented in the auditory modality (Shuster, 2009) or when reading aloud pseudowords was compared to lexical decisions on pseudowords (Carreiras et al., 2007). xyz = MNI coordinates (*translated from Talairach space using the tal2icbm transformation, Lancaster et al. 2007). nr = no SMG coordinates reported. [a] = Excluded from mean coordinates (because not cluster peak).*

In the current study, I hypothesized that the exact contribution of SMG activation to phonological decisions (versus semantic decisions) and reading aloud written pseudowords (versus reading familiar words) could arise at different levels including:

(i) The recoding of sublexical orthography-to-phonology;

(ii) phonological or auditory short-term memory to hold the sublexical phonological inputs in memory while they are integrated into a sequence;

(iii) executive processes (such as visual attention or the maintenance of task sets) that are not specific to phonological tasks but increase for more demanding tasks including phonological relative to semantic decisions (Mummery et al., 1998) and pseudoword relative to word reading (Binder et al., 2005); and

(iv) articulatory sequencing which may be more demanding for the unfamiliar phonological structure of pseudowords.

In this experiment, I examined evidence for each of the above alternatives in order to understand what is driving adSMG activation, and why this region was not activated for pseudoword reading > object naming. Moreover, I investigated the possibility that different subregions of the left SMG support word processing in different ways. Previous studies have shown that increased demands on auditory short-term memory lead to greater SMG activation at [-44, -38, 21] and [-63, -34, 19] (Buchsbaum and D'Esposito, 2009; Koelsch et al., 2009), i.e. more ventral than the cluster associated with phonological decisions and pseudoword reading (Table 5.1). In contrast, other researchers have reported that executive functions increase activation in a more posterior SMG region at [-42, -47, 38] and [-45, -39, 42] (Hope et al., 2014; Ravizza et al., 2004). (This might explain why this posterior part of SMG has been reported for phonological decisions on word stimuli when compared to perceptual decisions on letter strings (see Table 5.1), since this low-level baseline does not control for semantic, orthographic or executive processing. On the other hand, the more anterior dorsal SMG area is associated with phonological decisions *after* controlling for these factors. This functional dissociation is supported by reports of an evident heterogeneity in connectivity patterns (Mars et al., 2011), cytoarchitecture (Caspers et al., 2006) and receptor distribution within SMG (Caspers et al., 2013).

I investigated (A) the contribution of SMG to phonological tasks and (B) whether there is within-subject evidence for the apparent functional dissociation along the anterior-posterior and dorsal-ventral axes in SMG. To that end, I acquired data with the previously introduced language paradigm (see general methods section). In addition to the pseudoword and object conditions that were the focus of Experiments 1 and 2, I included words (which include semantic,

lexical and sublexical phonological cues) and baseline conditions (with minimum phonological or semantic cues) in both the visual and auditory modalities and for both speaking and one-back matching tasks (i.e. an additional 8 conditions). This design allowed me to dissociate multiple different functions by independently manipulating the presence of sublexical phonological cues (words and pseudowords relative to objects and baselines); semantic content (words and objects relative to pseudowords and baselines) and stimulus modality (visual versus auditory). By having both speaking and one-back matching tasks on the same stimuli I could test whether the observed effects in SMG were commonly or differentially involved in articulatory processes or silent matching tasks. Below I introduce the rationale for each of the hypotheses I tested for (also summarized in Table 5.3).

(A) Recoding of sublexical orthography-to-phonology

If SMG activation reflected the demands on orthographic-to-phonological recoding, I would expect activation to be higher for (a) reading pseudowords than all other conditions and (b) reading words than pictures of objects. The pattern of activation across visual conditions was therefore expected to be P>W>O, irrespective of task (speech production and one-back matching). Moreover, this pattern of effects should be significantly greater in the visual modality than the auditory modality because orthographic processing is not explicitly required for any of the auditory tasks.

(B) Phonological or auditory short-term memory

If SMG activation reflected the demands on phonological short-term memory, then I expect activation to be (a) higher for stimuli with phonological input (i.e. W&P>O&B) in both modalities and both tasks and (b) higher for pseudowords than words (P>W) because pseudowords are reliant on phonological processing whereas words are facilitated by lexical and semantic processing.

If SMG activation reflected the demands on auditory short-term memory, I would expect activation to be (a) higher for all auditory than all visual conditions in both tasks and (b) enhanced for visual stimuli that had the stronger auditory

associations (i.e. the stronger phonological associations for words and pseudowords than objects and baselines (Glaser and Glaser, 1989).

(C) Executive processing

If SMG activation reflected the demands on executive processing (e.g. attention), I would expect activation to increase for conditions that were more difficult. For example, reading pseudowords is more difficult than reading words because words but not pseudowords are facilitated by familiarity and semantic cues. Likewise, naming objects is more difficult than reading words because words but not objects are facilitated by sublexical phonological cues (Binder et al., 2005; Glaser and Glaser, 1989). Behaviourally, difficulty is reflected by increased response times and errors. Therefore, SMG activation that was related to difficulty (and executive processing) should mirror the effect on response times and errors (P>W and O>W).

(D) Articulatory sequencing

If SMG activation reflected the demands on articulatory sequencing, then I would expect speech production activation to be (a) less for the baseline conditions which involved repetition of the same articulatory outputs (colour names and genders) compared to all other conditions which involved constantly changing articulatory outputs; (b) the same for word and object naming conditions because articulatory output was controlled in these two conditions and (c) higher during speech production than one-back matching for all types of stimuli. The pattern of effects across conditions was therefore expected to be P&W&O>B and this effect was expected to be stronger during speech production than the one-back matching tasks that do not involve overt articulation.

5.3. Methods

5.3.1. Participants

Data from a combined total of 85 participants were included in this study (n = 26 from Experiment 1, n = 59 from Experiment 2) and re-analyzed for Experiment 3. They were all English speakers, right handed, neurologically healthy and reported normal or corrected-to-normal vision and hearing. They gave written informed consent for participation and were compensated financially for their time. The study was approved by London Queen Square Research Ethics Committee. Participant details are provided in the general methods.

5.3.2. Experimental design

To restate, in Paradigm 1 there were 16 conditions, 8 involving overt speech production and 8 involving one-back matching. This allowed me to look at stimulus by task interactions. The complete list of tasks from Paradigm 1 is provided in Table 5.2. Paradigm 2 included the same 8 speech production conditions (tasks 1-8 in Table 5.2) but not the 8 one-back matching conditions (tasks 9-16 in Table 5.2). The data from Paradigm 2 contributed to the results in two ways: by validating effects of interest during speech production in Paradigm 1 using different subject cohorts and presentation parameters; and by providing responses times for the overt speech production conditions which were unavailable for Paradigm 1.

Task difficulty was expected to be greater for pseudoword than word conditions (Binder et al., 2005) or for naming objects than words (Glaser and Glaser, 1989). Therefore, task difficulty was least when both semantic and phonological information were present (i.e. for words).

Table 5.2: List of tasks

	Task	*Stimulus modality*	*Response modality*
1	Reading words (W)	Vis	SP
2	Reading pseudowords (P)	Vis	SP
3	Naming pictures of objects (O)	Vis	SP
4	Naming colours (B)	Vis	SP
5	Repeating words (W)	Aud	SP
6	Repeating pseudowords (P)	Aud	SP
7	Naming sounds of objects (O)	Aud	SP
8	Naming gender of voice humming (B)	Aud	SP
9	Word matching (W)	Vis	OB
10	Pseudoword matching (P)	Vis	OB
11	Object picture matching (O)	Vis	OB
12	Colour matching (B)	Vis	OB
13	Word matching (W)	Aud	OB
14	Pseudoword matching (P)	Aud	OB
15	Sounds of objects matching (O)	Aud	OB
16	Gender matching (B)	Aud	OB

Task order as presented to participants (in counterbalanced order). Vis=visual, Aud=Auditory, SP=overt speech production, OB=one-back matching.

5.3.3. Analysis 1 - activation during 8 speech production tasks

Effects of interest

I entered 16 contrasts, 8 for each Paradigm, into an ANOVA in SPM12, with Paradigm as a between subject factor and 8 conditions as a within subjects factor. Factorial main effects and interactions were entered at the second level contrast stage. Activation related to the effects of interest are identified below where P = pseudo-word, W = word, O = object naming, B = baseline, R = rest (see Table 5.3 for summary). Activation related to:

1) **Orthographic-to-phonological recoding** was identified by comparing pseudowords to all other visual stimuli (P>WOB) and inclusively masking this contrast with P>W, P>O, P>B, P>R, W>O and W>B (see Table 5.3). I also searched for SMG activation that was higher for visual P&W than visual O&B and all auditory conditions.
2) **Phonological or auditory short-term memory** was identified by the main effect of sublexical phonological cues (i.e. W&P>O&B) inclusively masked by

W>O and P>O. Activation related to auditory but not phonological short-term memory was expected to be greater for all auditory conditions than all visual conditions.

3) **Executive processing** was identified by comparing P&O>W&B and inclusively masking this contrast with P>W, O>W, P>B and O>B.
4) **Articulatory sequencing** was identified by comparing object naming to baseline conditions (O>B) excluding activation that differed for O and W (that have matched articulatory output).

Table 5.3: Dissociating activation related to different types of processing.

Main contrasts	Orthography-to-phonology	Phonological STM	Auditory STM	Executive processing	Articulatory sequencing	Lexical/ sublexical integration
[P>WOB]	✓					
[WP>OB]		✓	✓			
[PO>WB]				✓		
[O>B]					✓	
[W>POB]						✓
Masks						
[P>W]	✓			✓		
[P>O]	✓	✓	✓			
[P>B]	✓			✓		
[P>R]	✓					
[W>P]						✓
[W>O]	✓	✓	✓		✓*	✓
[W>B]	✓					✓
[W>R]						✓
[O>W]				✓	✓*	
[O>B]				✓		
Modality effect	Vis	Vis&Aud	Vis (& Main Aud>Vis)	Vis&Aud	Vis&Aud	Vis&Aud

**exclusive masks. STM = short-term memory. P = pseudowords, W = words, O = objects, B = baselines, R = rest. Vis = visual. Aud = auditory. Main Aud>Vis = Main effect of auditory>visual stimuli.*

In addition, the experimental design allowed me to test whether any parts of SMG were more activated for words than all other stimuli (W>P&O&B), inclusively masked with W>P, W>O, W>B and W>R. Such effects cannot be attributed to semantic processing (which is expected to be higher for objects than words). Nor can it be attributed to sublexical phonological processing (which is expected to be higher for pseudowords than words). I therefore associated activation that was greatest for words with the integration of sublexical with lexical (or semantic) inputs.

Each of these effects was repeated across modalities and in each modality separately. If an effect was only found in one modality, I tested for the modality by effect interaction.

5.3.4. Statistical thresholds

For the 5 effects of interest described above, the statistical threshold was set to $p<0.05$ after family wise error correction for multiple comparisons across the whole brain. The threshold for all masks (inclusive and exclusive) was consistently set at $p<0.05$ (uncorrected).

5.3.5. Analysis 2 - identifying the effect of speech production within regions of interest from Analysis 1

This post hoc analysis was based on the subjects who performed both the speech production and one-back matching tasks (i.e. Paradigm 1). One of the 26 subjects was excluded due to a technical failure during one-back matching on auditory words. Using data from the remaining 25 subjects, I entered 16 contrasts (8 contrasts for speech production tasks and 8 contrasts for one-back tasks), into a within-subjects one-way ANOVA. Using SMG regions of interest from Analysis 1, I tested how the effects identified in Analysis 1 (see above) interacted with task (speech production > one-back tasks).

5.4. Results

5.4.1. Behavioural results

For speech production tasks (see Figure 5.1, Box A), in-scanner accuracy for both Paradigms was 98% or above for the word and baseline conditions; and 93% or above for object naming. Accuracy for pseudowords was higher for Paradigm 2 (94%) than Paradigm 1 (89%) because of changes to the stimuli (see Methods). Response times for speech production (Study 2) were slower for auditory than visual stimuli because stimulus delivery was sequential for auditory stimuli but simultaneous for visual stimuli. Within modality, response times were fastest for words and slowest for object naming.

For one-back matching (see Figure 5.1, Box B, for details), accuracy was above 98% for words, pseudowords and objects, 96% for the visual baseline and 89% for the auditory baseline. In the response times for correct trials only, there was a main effect of stimulus modality (as in speech production), presumably because auditory stimuli were delivered sequentially rather than simultaneously ($F(1,21)=150.51$, $p<0.001$). See general methods section and supplement for details.

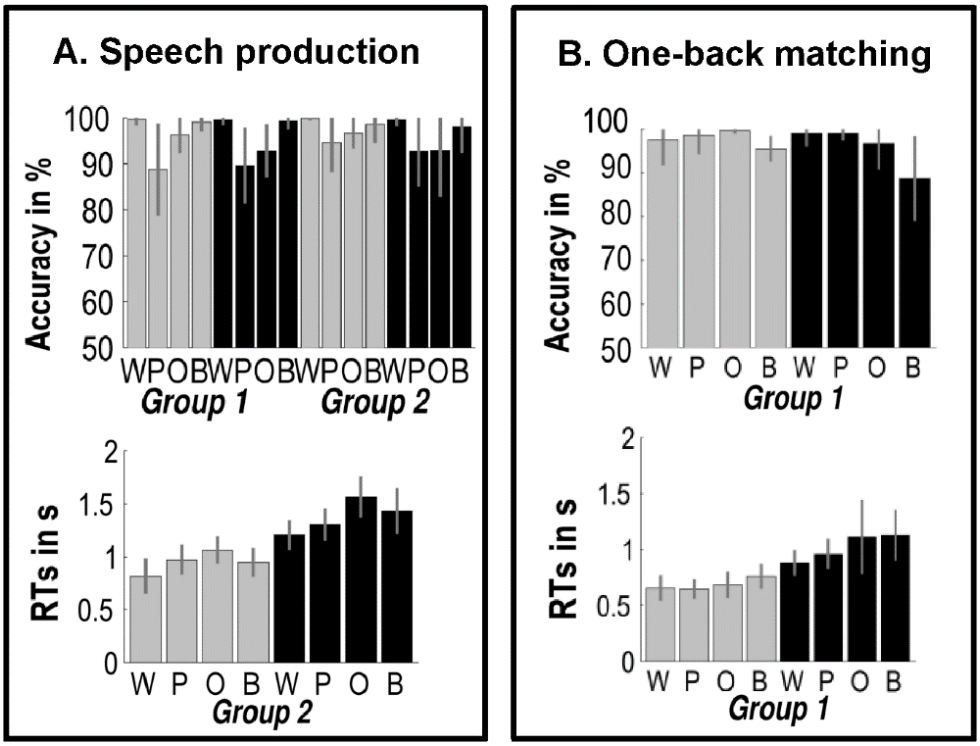


Figure 5.1: Behavioural results (mean with standard deviation). A. Accuracy scores for speech production scores are based on n = 82 after 3 outliers, i.e. subjects with less than 50% accuracy, had been removed. RTs for Paradigm 2 (based on n = 56, 2 participants were excluded because of missing data one condition) are for correct trials only and include stimulus delivery (longer for auditory than visual). The effects of [O>W] and [O>P] are stronger in the auditory modality ($F(1,56)=15.15$, $p<0.001$ and $F(1,56)=33.51$, $p<0.001$, respectively). The effect of [P>W] is stronger in the visual modality ($F(1,56)=8.92$, $p=0.004$).

B. Accuracy and RTs for one-back matching tasks (based on n = 22, 3 subjects had missing data from one of the one-back matching conditions and were excluded from all behavioural analyses). RTs are higher for the visual baseline compared to visual words ($T(21)=6.34$, $p<0.001$), pseudowords ($T(21)=5.49$, $p<0.001$) and objects ($T(21)=3.84$, $p<0.001$) and also for the auditory baseline compared to auditory words ($T(21)=6.89$, $p<0.001$) and pseudowords ($T(21)=4.93$, $p<0.001$), but not compared to objects ($T(21)=2.95$, $p=0.777$). Grey/black = visual/auditory tasks.

5.4.2. fMRI results

I focus on differential responses within SMG during speech production (Analysis 1) and then report the task by condition interactions (Analysis 2). As shown in Chapter 4, there were no significant Group by condition interactions, therefore the statistics for the effects are reported across paradigms (Table 5.4), and the validation of the effects are illustrated in the plots in Figure 5.2.

1. Recoding of sublexical orthography-to-phonology

I did not find any SMG region where the pattern of activation across conditions corresponded to that expected for processing related to the translation of orthography into phonology (i.e. P>W>O&B in the visual > auditory modalities). Nor did I find SMG activation that was higher for visual P&W than visual O&B and the auditory conditions.

2. Phonological or auditory short-term memory

Stimuli with sublexical phonological input (i.e. W&P>O&B) enhanced activation in the posterior ventral SMG (pvSMG) but only in the visual modality. This modality specific effect was confirmed by a significant interaction between [W&P>O&B] and stimulus modality. The one-back matching tasks (Analysis 2, Figure 5.3) validated the effect of sublexical phonological input (W&P>O&B) in pvSMG in the visual modality. The response in this region was more consistent with auditory short-term memory than phonological short-term memory because (a) there was a main effect of all auditory versus all visual stimuli irrespective of phonological content (Z score = Inf); and (b) activation was not higher for pseudowords (that rely on sublexical phonological processing) than words that should put less demands on sublexical phonological processing because they have useful semantic cues).

3. Executive processing

Reading pseudowords and naming objects increased activation compared to reading words and the visual baseline in an anterior part of the dorsal SMG (adSMG) that extended posteriorly into the inferior parietal sulcus. This pattern of effects was only observed in the visual modality, and consequently, there was a

highly significant interaction between P&O>W&B and stimulus modality (visual>auditory), see Table 5.4.

In the one-back matching task (Analysis 2, Figure 5.3), activation in adSMG was higher for visual pseudowords than words (as observed for speech production) but not higher for objects than words. In addition, adSMG activation was higher for conditions with longer response times including: one-back matching in the visual baseline > rest (Z score = 5.3), auditory baseline > rest (Z score = 6.4) and pseudoword reading > rest (Z score = 5.0).

4. Articulatory sequencing

I found that the greater demands on phonological output during W, P and O compared to the baseline conditions increased activation in an anterior part of ventral SMG (avSMG) for both stimulus modalities.

In addition, Analysis 2 showed that avSMG activation was significantly higher for speech production more than one-back matching (Z score = 4.5) and this was qualified by an interaction between task and condition (W&P&O>B; Z score = 4.0). There was no significant activation in avSMG for any condition during the one-back matching task. Therefore all evidence supports a role for avSMG in speech articulation.

5. The integration of lexical and sublexical phonology

Activation that was highest for words than all other stimuli, was observed in the posterior dorsal SMG (pdSMG), irrespective of whether the stimuli were presented in the visual or auditory modalities (see Table 5.4). This resulted in a two-way interaction between sublexical phonological inputs and semantics (Z score = 4.7 at [-57, -48, 45]) because the effect of sublexical phonological inputs was greater (in pdSMG) in the presence of semantics (W>O) than in the absence of semantics (P>B).

In Analysis 2, I observed a task (speech production > one-back matching) by condition (W>P&O&B) interaction (Z score = 3.4) and a three-way interaction between phonological input, semantic content (W>P) and task (speech production > one back matching) (Z score = 3.5) at [-57, -48, 42].

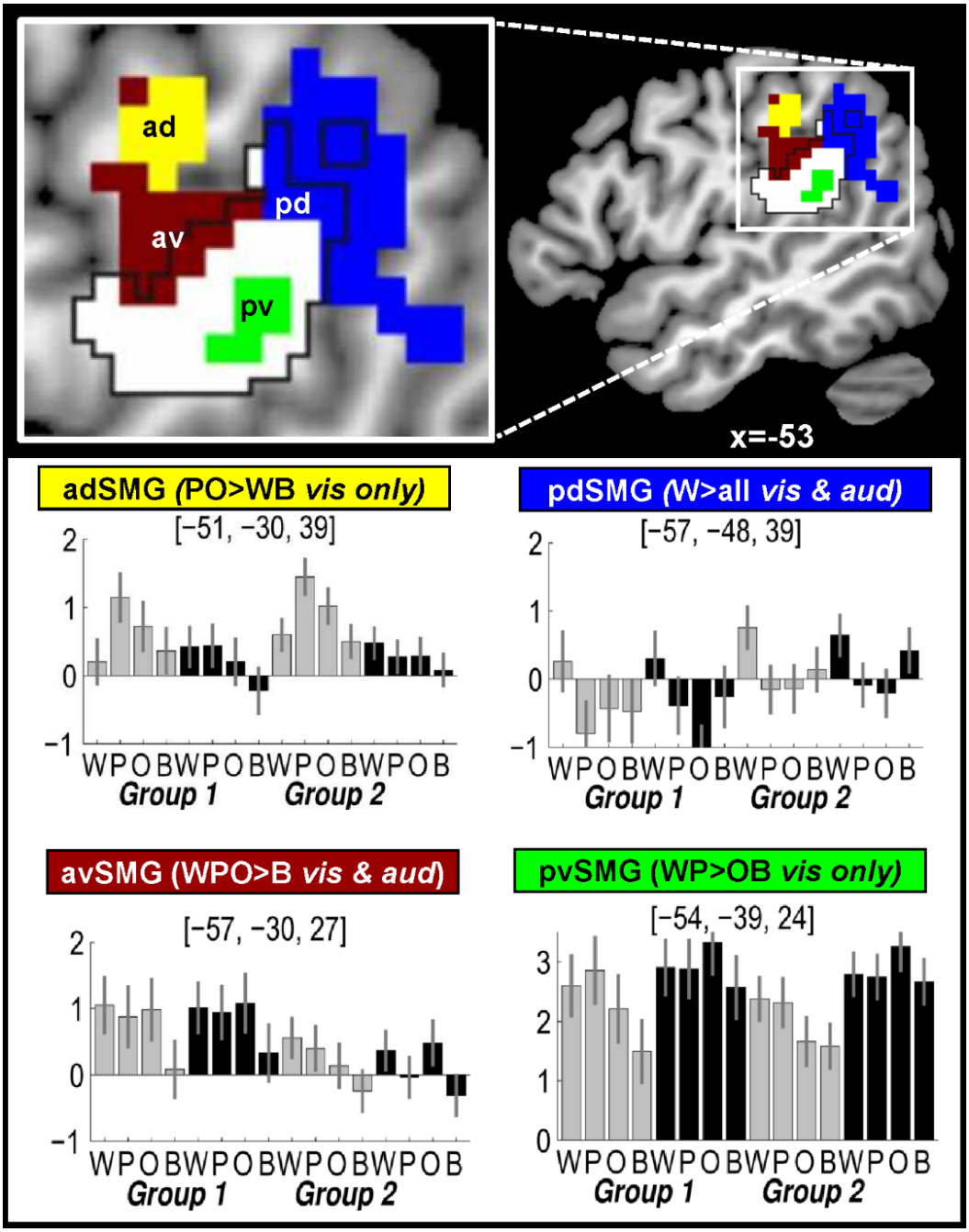


Figure 5.2: Top row shows the activation clusters (yellow, blue, brown, green) within the left SMG for each effect of interest (see plots for anatomical region and condition effects). The white area (outlined in black) shows the borders of the SMG according to the IBASPM software in SPM 12 (http://www.thomaskoenig.ch/Lester/ibaspm.htm) but other studies (see Table 5.1) include more anterior areas as shown in yellow. Peak coordinates for each effect are reported in Table 5.4. The extent of activation includes voxels that were significant at $p<0.001$ for the main effect of interest, and inclusive/exclusive masking at $p<0.05$ uncorrected. Plots show the relative activation (with 90% confidence intervals) across all 8 conditions for Group 1 and Group 2. Grey/black bars = visual/auditory tasks.

Table 5.4: Location and significance of fMRI activation within left SMG for each type of processing during speech production conditions.

1) Auditory short-term memory (main effect of sublexical phonological input in the visual modality)												
	k	**x**	**y**	**z**	**[WP>OB]**	*Int.*	*[P>O]*	*[P>B]*	*[W>O]*	*[W>B]*	*OB Aud>OB Vis*	
pvSMG	189	-54	-39	24	5.2	*4.2*	*3.3*	*5.3*	*3.1*	*5.0*	*Inf*	

2) Executive processing (visual pseudowords & objects > words & baselines)										
	k	**x**	**y**	**z**	**[PO>WB]**	*Int.*	*[P>W]*	*[P>B]*	*[O>W]*	*[O>B]*
adSMG	191	-51	-30	39	7.8	*4.8*	*7.0*	*6.9*	*3.5*	*4.5*
		-39	-33	42	6.6	*4.5*	*7.5*	*5.1*	*3.7*	*3.8*

3) Articulatory sequencing (All conditions > baselines)							
	k	**x**	**y**	**z**	**[O>B]***	*[W>B]*	*[P>B]*
avSMG	106	-54	-33	27	6.7	*7.4*	*5.5*

4) Integrating lexical and sublexical phonological inputs (Words > all other)												
	k	**x**	**y**	**z**	**[W>POB]**	*[W>P]*	*[W>O]*	*[W>B]*	*[W>R]*	*[R>P]*	*[R>O]*	*[R>B]*
pdSMG	250	-57	-48	39	7.7	*7.1*	*7.4*	*5.2*	*5.5*	*4.1*	*4.1*	*n.s.*
		-54	-51	42	7.7	*6.9*	*7.5*	*4.4*	*4.3*	*3.5*	*4.2*	*n.s.*

*The columns show, from left to right, the location of the effect in left SMG (a=anterior, p=posterior, d=dorsal and v=ventral), k = cluster size, x y z = MNI coordinates. Z scores for statistical comparisons of different conditions (W=words, P=pseudowords, O=objects, B=baseline, R=rest) across auditory (Aud) and visual (Vis) modalities or for visual only (when stated). Int = Z score for the interaction of modality (i.e. visual/auditory) with the effect of interest. Inf = infinitive, n.s. = not significant, L = left hemisphere. * = exclusively masked with [O>W] and [W>O] to exclude regions showing other effects of interest. Z scores above 4.7 were significant at p<0.05 following family wise error correction for multiple comparisons across the whole brain. Those above 3.09 were significant at p<0.001 uncorrected.*

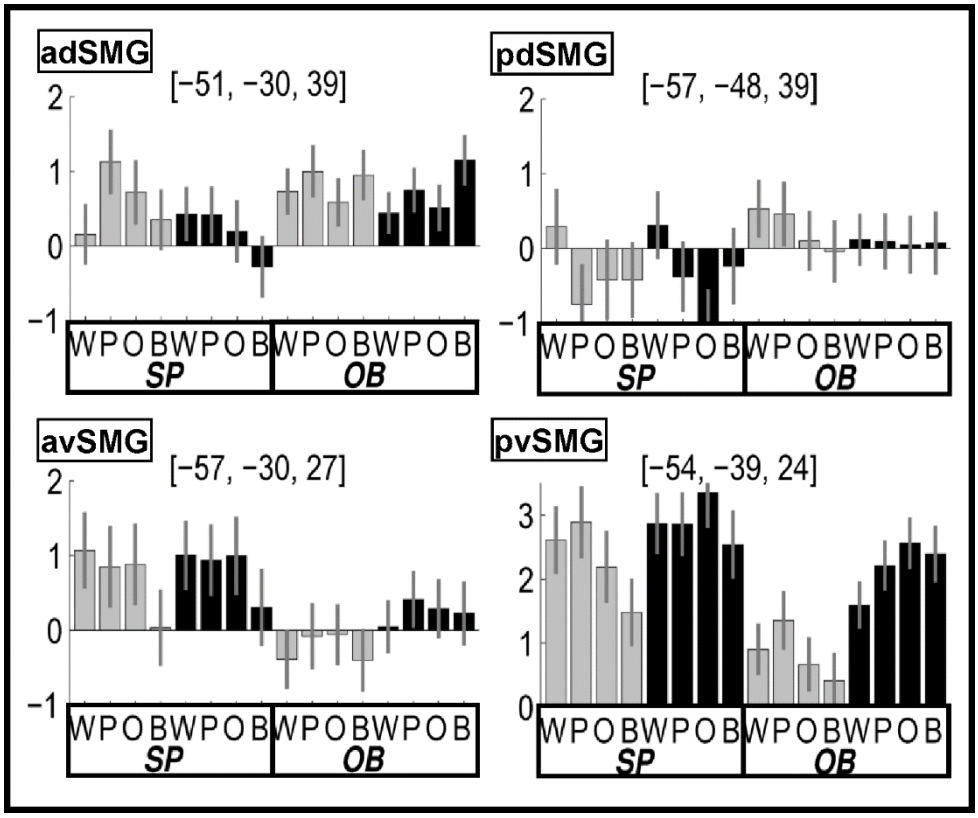


Figure 5.3: Task by condition effects in regions of interest. Plots show the relative activation (with 90% confidence intervals) during 8 speech production (SP) and 8 one-back (OB) tasks, at coordinates identified for condition effects during speech production tasks (Analysis 1). Grey/black bars = visual/auditory tasks. See Table 5.4 for abbreviations and text for significant interactions between task and condition.

In summary, I have distinguished the response in four different parts of SMG:

(1) the posterior ventral part of SMG (pvSMG) was activated for stimuli with phonological input (i.e. words and pseudowords) in the visual modality irrespective of task (speech production and one-back matching). It was also strongly activated by auditory relative to visual stimuli during the one-back matching task and for speech production relative to one-back matching on the visual stimuli. This is consistent with the expected activation pattern for auditory short-term memory.

(2) a region spreading from anterior dorsal SMG (adSMG) to the inferior parietal sulcus was more activated for reading pseudowords and naming pictures than words, This is not consistent with a role in phonological input processing but rather with a role in a more executive function.

(3) a more anterior part of ventral SMG (avSMG) was (i) associated with articulatory sequencing because it was more activated for words, pseudowords and object naming relative to the baseline conditions in both modalities during the speech production tasks, and (ii) not significantly activated during one-back matching.

(4) a lateral part of posterior dorsal SMG (pdSMG) was most activated for words (across modality) but only during the speech production tasks.

The region by condition interactions for this functional segregation are reported in Table 5.5.

Table 5.5: Region x condition analysis for speech production tasks.

Regions		***Conditions***	***Statistics***	
adSMG vs	pdSMG	P – W	F(1,84)=196.62	*p<.001*
	avSMG		F(1,84)=112.83	*p<.001*
	pvSMG		F(1,84)=93.570	*p<.001*
pdSMG vs	avSMG	W – P	F(1,84)=37.95	*p<.001*
	pvSMG		F(1,84)=15.51	*p<.001*
	pdSMG		F(1,84)=196.62	*p<.001*
avSMG vs	pdSMG	O – B	F(1,84)=10.47	*p<.002*
	pvSMG		F(1,84)=13.69	*p<.001*
	adSMG		F(1,84)=2.76	*p<.100*
pvSMG vs	pdSMG	P – O	F(1,84)=31.25	*p<.001*
	avSMG		F(1,84)=13.19	*p<.001*
	adSMG	W – B	F(1,84)=37.73	*p<.001*
	pdSMG		F(1,84)=5.18	*p<.025*

See Table 5.4 and Figure 5.2 for abbreviations.

Finally, the analysis of data from Paradigm 2 was repeated after including the mean response time per condition per subject as a covariate of interest. This did not affect the significance of phonologically driven SMG activation; and I found no evidence that SMG activation was affected by response times either across or within conditions.

5.5. Discussion

Prior studies have highlighted the importance of the left SMG for phonological processing by comparing activation for either phonological to semantic decisions or pseudoword reading to word reading. However, the first 2 experiments in this thesis did not reveal greater SMG activation for reading pseudowords than for naming object pictures. In this experiment, I investigated the cause of left SMG activation during phonological tasks in more detail after controlling for multiple types of non-phonological processing (e.g. orthographic processing, articulatory sequencing and auditory short-term memory). I found that the anterior dorsal part of SMG that has previously been associated with phonological processing (Table 5.1) was better explained by executive rather than phonological processes. In addition, three other functionally distinct regions within left SMG that all contribute to word processing were identified. An anterior ventral part of SMG responded to the demands on phonological output (articulatory sequencing) whereas a posterior ventral part of SMG was sensitive to phonological input and auditory processing of all types of stimuli, and a posterior dorsal part of SMG was most responsive to production of words that carry both lexical and sublexical phonological inputs. Below I discuss each of the four subregions in detail.

Posterior ventral SMG (pvSMG)

PvSMG was activated for the main effect of sublexical phonological input in the visual modality (i.e. more activation for written words and pseudowords than objects and baseline stimuli) irrespective of the mode of output (speech production or one-back matching). In the auditory modality, this effect was reversed with more activation for auditory object sounds than any other condition. It cannot be explained in terms of (i) orthographic-to-phonological processing because activation was not higher for visual words and pseudowords than auditory words and pseudowords; (ii) sequencing sublexical phonological codes because activation was not higher for articulating unfamiliar pseudowords than familiar words or (iii) phonological short-term memory because activation was not higher for stimuli with phonological input (i.e. words and pseudowords)

across tasks and modalities; and also not higher for pseudowords than words as expected given the greater demands on sublexical phonological cues.

When turning to the prior literature, I noted that the MNI coordinates of the pvSMG region that I found to be more activated by visual words and pseudowords than visual objects or baselines [-54, -39, 24], correspond almost exactly to those that have previously been associated with auditory imagery [-51, -39, 21] in Parker Jones et al. (2014), using the same data but a different set of contrasts (Paradigm 1, Analysis 2). In brief, in Parker Jones et al., (2014), we refer to pvSMG as TPJ (temporo-parietal junction). Our conclusion was that this region is involved in the auditory representation of sounds (verbal or non-verbal) that can either be accessed bottom up via auditory inputs or top down in the absence of auditory inputs. Evidence of bottom-up auditory processing is provided by the main effect of auditory versus visual one-back matching (Z score = Inf). Evidence for top-down auditory processing comes from the main effect of phonology during silent visual one-back matching (and prior studies of auditory imagery discussed in Parker Jones et al., 2014). The argument is that both bottom-up and top-down activation of auditory representations may contribute to pvSMG/TPJ activation during speech production.

On the basis of the conclusion that the pvSMG/TPJ region is involved in the auditory representation of sounds (Parker Jones et al., 2014), I suggest that enhanced pvSMG activation in the current study for sublexical phonological inputs in the visual modality is because written words and pseudowords have stronger auditory associations (from highly familiar sublexical phonological content) than pictures of objects or meaningless visual inputs. This interpretation is in line with other studies associating pvSMG activation with the demands on auditory memory for verbal and non-verbal material (Buchsbaum and D'Esposito, 2009; Koelsch et al., 2009) but stands in contrast to the conclusions of Papoutsi and colleagues (2009) who interpreted increased ventral SMG activation at [-56, -38, 20] for repetition of pseudowords with 4 syllables compared to 2 syllables in terms of demands on syllabification and segmentation. I do not think that pvSMG activation in the present study can be interpreted in terms syllabification and segmentation because this should result in higher pvSMG activation for

pseudoword production than object naming, which I did not observe. On the other hand, the Papoutsi et al. (2009) findings can be re-interpreted in terms of the demands on auditory short-term memory because participants in their study had to keep the desired response in mind over a delay-period, and memory load is greater for 4 compared to 2 syllables.

In summary, I am arguing that enhanced pvSMG activation for sublexical phonological cues in the visual modality reflects auditory short-term memory. Other studies have shown that pvSMG activation is also enhanced during auditory short-term memory tasks on nonverbal stimuli (Koelsch et al., 2009). It is therefore not specific to speech sounds. Indeed, I found pvSMG activation to be highest during nonverbal auditory object naming (see Figure 5.2).

Anterior dorsal SMG (adSMG)

An anterior part of dorsal SMG (adSMG) was more activated for reading pseudowords and naming objects than all other speech production conditions. The location of this pseudoword and object effect [at MNI -51, -30, 39] corresponds very closely to that reported in previous studies of phonological relative to semantic decisions on visual words [at MNI -52, -35, 40] as well as some of the studies comparing pseudoword to word reading [at MNI -49, -35, 39] (see Table 5.1). It also extended posteriorly and medially [at MNI -39, -33, 42] into the area associated with executive processing [at MNI -42, -37, 38 in Ravizza et al., 2004] and phonological decisions on words [-55, -35, 40] when semantic or executive processing is not controlled (Seghier et al., 2004). This activation pattern also explains why I did not find a significant difference in activation for pseudoword reading > object picture naming in adSMG in Experiments 1 and 2.

Enhanced adSMG activation for pseudoword reading and object naming compared to word reading cannot be explained in terms of orthographic-to-phonological recoding because object naming involves no orthographic input but word reading does. I also excluded explanations in terms of (i) phonological output, which was matched in the reading and object naming conditions; (ii) phonological short-term memory because adSMG activation was not higher for

repetition and one-back matching of auditory pseudowords than auditory object naming; and (iii) visual attention because activation was not higher for visually presented pseudowords and objects than one-back matching of the auditory baseline.

The observation that adSMG activation was as high for one-back matching of the baseline conditions (colour and gender) as it was for pseudoword reading may provide some clues to its function. Unexpectedly, the behavioural data (see results section for details) indicate that, during one-back matching, accuracy is lower and response times are highest for the baseline conditions, which involved matching two consecutive stimuli on the basis of perceptual features (colour or gender). The longer response times/loss of accuracy may have arisen because the same features were repeated multiple times in each scanning session (not just when a one-back response was required) and this might have increased the level of interference or uncertainty relative to other conditions that did not involve multiple presentations of the same feature. Likewise, enhanced activation for pseudoword reading and object naming compared to word reading may reflect ambiguous, and thus more difficult, mappings between (i) sublexical orthography and phonology in the case of pseudoword reading, and (ii) semantics and phonological outputs in the case of object naming (i.e. the same semantic concept can have multiple names). In contrast, word reading may be less ambiguous because it is constrained by both sublexical phonological cues and semantics.

Whatever its true function, the activation profile of the adSMG region across tasks cannot be explained in terms of phonological processing per se. Instead, I am proposing that previously reported adSMG activation for phonological compared to semantic decisions or pseudoword reading compared to word reading might reflect functions that are not specific to phonological processing but appear to be called on when there is ambiguity in the mapping between inputs (auditory and visual) and outputs.

Future studies could examine the function of adSMG more precisely by manipulating the ambiguity of sensory to motor mapping within task. This might

explain why increased adSMG activation for pseudoword relative to word reading has not consistently been reported (see Table 5.1). It would also be informative to use functional connectivity studies (e.g. dynamic causal modelling) to investigate how activity in adSMG links sensory inputs to motor outputs. Specifically, it would be useful to know whether adSMG is primarily driven top-down from motor and/or frontal regions and/or bottom-up from sensory input regions. For the time being, the current study contributes to our understanding by showing how adSMG activation varies across a range of different tasks; and how this pattern of response is functionally distinct from that of other SMG regions that also respond during word and pseudoword processing.

Anterior ventral SMG (avSMG)

AvSMG showed three effects that were consistent with its role in phonological output processing irrespective of the presence or absence of phonological cues: it was (i) more activated for speech production than one-back matching, (ii) speech production activation was least for the baseline conditions (i.e. naming colours and gender) that involved repeatedly saying the same spoken response in the same scanning run and (iii) activation was the same for conditions that were matched for articulatory output (i.e. word and object naming). Notably, avSMG activation did not differ significantly across object naming, reading and repetition of familiar words and unfamiliar pseudowords. This allowed me to exclude a role for this area in (i) auditory short-term memory because activation related to auditory memory should be greater during auditory object naming than visual object naming; (ii) orthographic to phonological mapping which would result in more activation for words than objects, (iii) processing semantics which would result in more activation for objects than words or (iv) managing task difficulty which would result in more activation for objects and pseudowords than words because behavioural evidence indicates that words are faster to process.

The avSMG area that I associate with phonological output processing (at MNI coordinates [-57, -30, 27]) is ventral to the more dorsal anterior SMG activations that have previously been reported for phonological relative to semantic decisions, or reading pseudowords > reading familiar words (see Table

5.1). However, it is interesting to note that the avSMG region that I associated with phonological output processing corresponds more closely with that associated with phonological versus semantic decisions in TMS studies (e.g. Romero et al., 2006 with mean coordinates at [-46, -30, 26]; Sliwinska et al., 2012 at [-52, -37, 32]). Sliwinska et al. (2015) suggest that the stimulation over avSMG [-52, -34, 30] disrupted covert articulation. In which case, the claim would be that avSMG is more important (or necessary) for phonological than semantic decisions. The absence of significant avSMG activation in the comparison of phonological and semantic decisions in fMRI studies can also be explained if covert articulation occurred during both phonological and semantic decisions even though it was only necessary for phonological decisions.

Posterior dorsal SMG (pdSMG)

A lateral part of the posterior dorsal SMG (pdSMG) was more activated for reading and repeating words than all other speech production conditions. This is consistent with a role for this region in integrating lexical and sublexical phonological cues. An explanation in terms of semantic processing can be excluded because this should result in more activation for object naming that relies on semantic mediation than word repetition and reading that is facilitated by sublexical phonological information. To the contrary, I found that pdSMG activation was less for object naming than repetition and reading. Instead, I found that increased demands on semantic processing (during object naming and word production) increased activation in the ANG as reported previously (e.g. Binder et al., 2003; Devlin et al., 2003; Diaz and McCarthy, 2007; Price et al., 1997; Seghier et al., 2010; Sharp et al., 2010). Thus, the pdSMG area that I am associating with the integration of lexical and sublexical inputs lies conveniently close but anterior to regions in the ANG that are associated with semantic processing.

Anatomically, pdSMG has been shown to have direct cortico-cortical connections linking anteriorly to SMG and posteriorly to the ANG (Lee et al., 2007). Cyto-architectonically, posterior SMG shows characteristics of both anterior SMG and anterior ANG and has therefore been described as a “transition zone” between these areas (Caspers et al., 2006). However, very little

is known about the function of lateral pdSMG during word processing because it is rarely reported in functional imaging studies of language (Richardson et al., 2010). Our lab previously reported that grey matter in this region is higher in teenagers who have richer vocabularies (Lee et al., 2007; Richardson et al., 2010) and in adults who speak more than one language (Grogan et al., 2012; Mechelli et al., 2005). In Richardson et al. (2010), they suggested that pdSMG was involved in explicit vocabulary learning but this does not explain why I am now reporting activation during word reading and repetition that do not involve such learning.

Clues to the function of lateral pdSMG come from the observation that it was as responsive during word repetition as it was during word reading. I suggest that it may be involved in the active process of integrating lexical and sublexical information during word repetition and reading, however I do not know what type of lexical and sublexical information is being integrated (e.g. articulatory sequences or auditory associations). It is unlikely that lateral pdSMG activation reflects conflict between lexical and sublexical inputs because there is no prior evidence to suggest that activation in this area increases with the known conflict between lexical and sublexical cues during irregular word reading (e.g. Binder et al., 2005; Mechelli et al., 2005; Nosarti et al., 2010). Further studies of how pdSMG activation influences, and is influenced by, activation in other regions may provide more clarity on how it contributes to word processing.

Conclusions

The results presented here have implications for differentiating different types of phonological input and output processing and the functional contributions of different SMG regions. As reported previously, I found that a posterior ventral part of SMG (on the border with the temporal lobe) is activated by tasks that increase demands on auditory short-term memory for verbal and nonverbal stimuli. In addition, I dissociate for the first time the following effects in different parts of SMG: (1) the ventral SMG region associated with articulatory output is anterior to that involved in auditory short-term memory; (2) a lateral part of posterior dorsal SMG is involved in the integration of lexical and sublexical inputs and (3) activation in the anterior dorsal SMG that has previously been

associated with phonological relative to semantic decisions and for reading pseudowords compared to words, could not be explained in terms of phonological processing but appeared to be involved in more difficult tasks, i.e. when there was ambiguity in the mapping between sensory inputs and motor outputs.

Effective connectivity studies, using techniques such as dynamic causal modelling (DCM), could take the findings from this experiment a step further and explore the connections of different parts of SMG with other cortical areas, and their precise roles within the distributed network of phonological processing. The findings could also be challenged by comparing the consequences of focal transcranial magnetic stimulation (TMS) or permanent brain damage to each of the SMG sub-regions during a range of different tasks (see Experiment 4). For example, does selective disruption to pdSMG differentially impair word repetition and reading?

6. EXPERIMENT IV

The effect of SMG damage on phonological processing

6.1. Summary

In this final experimental chapter, I investigated the effect of damage to the left anterior dorsal supramarginal gyrus (adSMG) on pseudoword reading and naming behaviour in a sample of stroke survivors who completed the same fMRI paradigm as the healthy controls in Experiment 3. I focused on pseudoword reading and object naming because these are the tasks that maximised normal adSMG activation in Experiment 3. A novel combination of structural and functional brain data was used to investigate the integrity of the region of interest. This identified a sample of 7 patients with >90% damage to adSMG and no fMRI signal during pseudoword reading. Surprisingly, 3 of these 7 patients showed good pseudoword reading abilities and all but one performed in the normal range (accuracy and response times) for object naming. These behavioural results suggest that the integrity of left adSMG is not absolutely necessary for either pseudoword reading or object naming, which challenges some prior findings. The fMRI results indicated that when patients were reading pseudowords and naming objects, they showed increased activation, compared to controls, in left subcortical areas (thalamus, caudate, putamen) and in the right pars triangularis. This might reflect compensatory activity, allowing the patients to perform well despite loss of adSMG. I will discuss the potential as well as the limitations of this type of lesion-behaviour-fMRI activation study.

6.2. Introduction

The fMRI results in Experiment 3 showed that an anterior dorsal part of left supramarginal gyrus (adSMG) is strongly activated by reading pseudowords and naming objects. Based on this fMRI finding in healthy participants, I hypothesized that damage to this part of SMG would impair the ability to read pseudowords and name pictures. In Part 1 of this chapter, I tested this prediction

by identifying stroke survivors with selective damage to the left adSMG from our sample of patients who had taken part in our fMRI experiment (n = 59), completing the same language paradigm as the healthy participants used in Experiment 2. By analysing structural and functional integrity of the region of interest, as well as their behavioural profile, I investigated how consistently damage to the region of interest would result in impaired pseudoword reading and/or object naming.

In Part 2 of this chapter, I investigated how some patients with adSMG damage were still able to read some pseudowords (i.e. what neural systems were supporting recovery). To that aim, I compared the patients' fMRI activation pattern across both tasks to the sample of neurologically healthy participants included in Experiment 3. Activation in patients was expected to be less compared to controls within the damaged region. On the other hand, increased activation for patients compared to controls was expected in either (i) a subset of the regions that are activated in controls, which are working "harder" post-stroke, or (ii) in novel regions that are potentially compensating for the loss of left adSMG. Turkeltaub et al. (2011) have shown that the most consistent compensatory activation during language tasks is found in right homologues of left hemisphere language regions. However, increased activation within left language areas in patients has been associated with better recovery (Fridriksson et al., 2010a; Meinzer et al., 2008; Saur et al., 2006).

If, on the other hand, patient activation does not differ significantly from controls, this could suggest inter-individual variability in controls, i.e. healthy participants might recruit different neural routes to achieve successful reading. For instance, Seghier et al. (2008a) found that, in a sample of 43 healthy participants, successful word reading was achieved via at least two different neural pathways. One subgroup relied more on the left inferior frontal gyrus and anterior occipito-temporal regions, whereas the other subgroup recruited the right inferior parietal and left posterior occipito-temporal cortex while reading the same word list. The preference for the respective route correlated with the subject's reading speed as measured outside of the scanner. Thus, the compensatory regions activated in patients might be part of these alternative

routes. Similarly, in a more recent study, Seghier et al. (2014) demonstrated a compensatory relationship between activation in the left premotor cortex and left putamen during reading aloud. The less the premotor cortex was activated, the more the left putamen was activated.

In Part 3 of this chapter, I investigated if the abnormal activation pattern observed in patients as they read pseudowords was also observed when they named pictures of objects. In addition, I considered how consistently patients over- or under-activated in the respective regions. It has been shown that activation related to language tasks in stroke patients is less reliable across time than in controls (Chen and Small, 2007). Moreover, these variability effects seem to be region-dependent (Eaton et al., 2008). Similarly, in a group of epilepsy patients awaiting surgery, Fernandez et al. (2003) showed that test-retest reliability within patients was higher for frontal lobe activation than for temporo-parietal activation. Finally, we know that patients differ in their language recovery trajectories over time (Hope et al., 2013; 2017; Lazar and Antoniello, 2008; Prabhakaran et al., 2008). Thus, I considered the possibility that the fMRI signal in compensatory regions is driven by a few patients rather than the whole patient group (Fedorenko et al., 2010).

The importance of combining different modalities for diagnostics and predictions in stroke patients has been highlighted recently by Pustina et al. (under review). They showed that adding fMRI data (i.e. resting state connectivity data) and virtual tractography to lesion maps improves recovery predictions significantly. My approach involved a combination of lesion data and task-related fMRI data, in addition to analysing demographics and language assessment scores from inside the scanner. Adding fMRI signal to lesion data provides a much stronger indicator of tissue properties within the damaged area than using a lesion identification algorithm alone. For instance, it is possible that a brain area appears to be damaged on the structural MRI image, but that there is still fMRI signal measured within this region, suggesting that there might be preserved tissue within the “damaged” area. If, on the other hand, an area has been labelled as damaged and there is no fMRI signal expressed within the lesioned area, it can be assumed that this region is not actively contributing to

any task-related activation. I therefore expected the activation profile and recovery prediction to depend on the degree of damage and responsivity in the lesioned area.

In summary, this chapter (Experiment 4) addresses the following research questions:

(1) How consistently does selective damage to left adSMG impair pseudoword reading in stroke survivors?
(2) How does brain activation change in patients who can read pseudowords (and name pictures of objects) after left adSMG damage?
(3) Is activation increase or decrease in patients specific to one task or present across tasks?
(4) Is there inter-patient variability in the compensatory system used?

By systematically integrating different data sources, I sought to establish whether damage to left adSMG impairs the ability to read pseudowords. Moreover, the comparison of fMRI activation during pseudoword reading and object naming from stroke patients and healthy participants, who underwent exactly the same experimental manipulations, will enable me to investigate whether, and if so which, brain regions are recruited in stroke patients for compensation. Finally, this experiment will contribute to our understanding of how inter- and intra-individual variability influences the behavioural and neural pattern in healthy participants and stroke patients, and highlight the importance of considering variability in group analyses for recovery predictions.

6.3. Methods

6.3.1. Participants

Data from stroke survivors and the healthy controls from Experiment 2 (n = 59) were included in this experiment. Details concerning the control sample are included in the general methods section and in Chapter 3. The experiments in both stroke patients and healthy participants were approved by the London

Queen Square Research Ethics Committee. All patients and healthy participants gave written informed consent prior to participation and received financial compensation for their time.

The full patient sample comprised 57 patients who had taken part in my fMRI experiment, using the language paradigm from Experiment 2. All patients were right-handed prior to their stroke, native speakers of English with normal or corrected to normal vision and hearing, and no history of neurological or psychiatric illness that were not related to their stroke. For each patient, a 3D lesion image in standard space was included, created from their T-1 weighted structural scan, and an fMRI assessment, consisting of the same 8 conditions that were included in Experiments 2 and 3. Demographic, clinical and lesion data were extracted from the PLORAS database (Price et al., 2010; Seghier et al., 2016), see Figure 6.1-A.

6.3.2. Task information

To assess the patients' phonological ability, the pseudoword reading task from the fMRI paradigm that was used in Experiment 2 was selected. This task is supposed to maximise demands on sublexical phonological processing with minimum support from semantics. The second task of interest was naming pictures of familiar objects, which does not provide sublexical phonological cues, but semantic (and lexical phonological) cues. All participants completed exactly the same tasks as the healthy participants in Experiment 2, with the same task and stimulus order. This ensured consistency between the patient and the control sample, and enabled me to identify abnormal activation patterns in patients compared to controls. The tasks that were used to test all patients were as follows: (1) Reading aloud familiar words, (2) Reading aloud pseudowords, (3) Naming objects from pictures, (4) Naming the colour of a picture with no semantic or phonological content, (5) Repeating familiar words, (6) Repeating heard pseudowords, (7) Naming objects from their sounds and (8) Naming the gender of a voice humming with no semantic or phonological sounds. Finally, like participants in Experiment 3, patients also performed 5 other conditions that

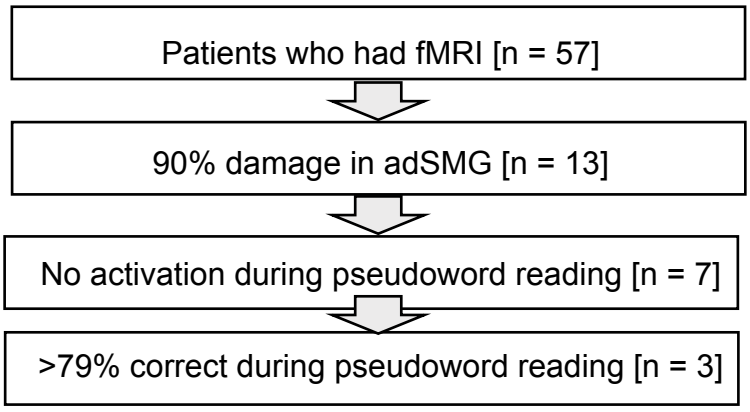
were not part of my experiments but have been reported elsewhere (Sanjuan et al., 2014).

6.3.3. Defining damage to the region of interest

Structural and functional integrity of the region of interest was investigated in a two-step procedure. First, T1-weighted high resolution anatomical whole-brain volumes were obtained for all patients, and converted to a 3D binary lesion image, using an automated lesion identification algorithm which is described in full elsewhere (Seghier et al., 2008b). This algorithm separates the image into normal and abnormal (lesioned) voxels, compared to healthy controls. As the lesion image is in MNI space, we can search for whether there is damage to a particular region of interest. In this case, my region of interest was a spherical region of interest (5mm sphere) centred on the mean fMRI coordinate in adSMG from Experiment 3 (MNI [-51, -30, 39]). I selected patients who had 90% damage to this region (n=13).

Second, to ensure that there was no preserved tissue within adSMG that could have supported the patients' performance during pseudoword reading, the fMRI signal within the adSMG region of interest measured during pseudoword reading was considered. Average eigenvariates from the adSMG sphere were extracted for each patient for pseudoword reading versus rest, and those patients with positive signal from the regions of interest were excluded.

6.3.4. Workflow summary for patient identification



6.3.5. Research questions

(1) How consistently does damage to left adSMG impair pseudoword reading in stroke survivors?

Identification of structural and functional damage to left adSMG in patients was based on two criteria: (i) >90% damage to adSMG as indicated in the lesion overlap map, and (ii) no fMRI signal expressed within adSMG during pseudoword reading, as indicated through eigenvariates with negative, or near zero, values, that were extracted from the adSMG sphere for each patient.

Impaired performance during pseudoword reading was defined relative to the mean and standard deviation of that measured in the control sample. Those patients whose accuracy was less than 2.5 standard deviations below normal, were considered impaired in pseudoword reading.

(2) How does brain activation change in patients who can read pseudowords and name objects after left adSMG damage?

To identify regions with (i) less activation for patients than controls across the whole brain, the main effect of controls > patients for reading pseudowords and naming objects was computed (and thresholded at $p<0.05$ corrected for multiple comparisons across the whole brain), and inclusively masked with four different contrasts (thresholded at $p<0.001$ uncorrected): greater activation for controls than patients for reading pseudowords; greater activation for controls than patients for naming pictures of objects; reading pseudowords relative to rest in the controls only; and naming pictures of objects relative to rest in the controls only. The latter two contrasts were to ensure that differences between controls and patients were not driven by areas that were deactivated in the patients.

Regions with (ii) increased activation for patients versus controls were identified with the reverse contrasts, i.e. activation that was greater for patients than controls for reading pseudowords and naming pictures of objects (thresholded at $p<0.05$ corrected for multiple comparisons across the whole brain), inclusively masked (thresholded at $p<0.001$ uncorrected) with greater activation for patients than controls reading pseudowords, greater activation for

patients than controls naming pictures of objects; reading pseudowords relative to rest in patients only; and naming pictures of objects relative to rest in patients only.

(3) Is activation increase/decrease for patients specific to one task or present across tasks?

To investigate specificity of the observed activation differences, the relative activation differences for each task were considered, i.e. significance of increase or decrease for pseudoword reading only or object picture naming only; and the group by task interaction.

(4) Is there inter-patient variability in the regions that were activated abnormally at the group level?

To identify inter-patient variability within the regions that showed increase or decrease for patients at the group level, the fitted responses for each subject (controls and patients) were extracted from a particular voxel and plotted for each condition.

6.4. Results

6.4.1. Lesion details and behavioural profile of patients with damage to adSMG

13 out of 57 patients who underwent fMRI scanning had more than 90% damage to left adSMG (within a 5mm sphere centred at MNI [-51, -30, 39]). However, eigenvariate extraction from adSMG during pseudoword reading showed that 6 out of these 13 patients still expressed a task-related BOLD signal. This resulted in a sample of 7 patients with damage to adSMG and no fMRI signal during pseudoword reading. See Figure 6.1 for demographics, clinical and lesion details on the selected subgroup of patients.

A *Demographics and clinical details*	*PS0539*	*PS0418*	*PS0066*	*PS0430*	*PS0127*	*PS0610*	*PS0707*
% damage to adSMG	91	98	100	93	100	100	100
Eigenvariates from adMSG							
during pseudoword reading	-0.35	-0.35	-0.86	0.34	-2.95	-0.20	-2.48
during object naming:	-1.63	3.88	3.95	6.55	1.47	1.01	5.61
Lesion volume (cm^3)	61.2	112.2	372.0	237.3	250.7	191.2	348.2
Age at scan (years)	66.09	51.48	51.54	51.91	49.65	50.7	60.59
Years since stroke	4	6	16	18	23	8	5
Gender	M	M	F	F	M	M	M

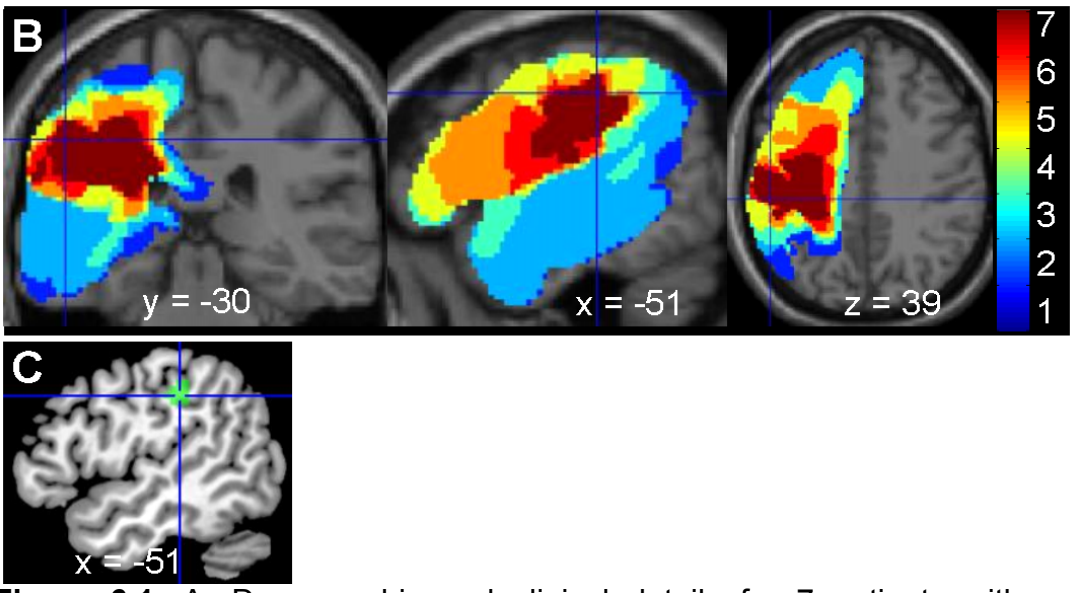


Figure 6.1: A. Demographic and clinical details for 7 patients with > 90% damage to left aSMG and no activation within adSMG during pseudoword reading (see eigenvariates). F=female, M=male. B. Lesion overlap map of those 7 patients. Crosshair placed at peak voxel in adSMG at MNI [-51, -30, 39]. Dark red area shows complete overlap across 7 patients, dark blue shows lesion that affected one patient only. C. Activation cluster in left adSMG for pseudoword reading and object naming in healthy controls.

Out of these 7 patients, 3 were able to read a high proportion of pseudowords (see Table 6.1), i.e. > 79% correct. This threshold was based on the mean accuracy score in the control group minus 2.5 standard deviations (i.e. 95% -2.5*6.3). I then considered the patients' performance during object naming, which has also been associated with left adSMG activation in controls, and found that 6/7 patients had surprisingly high accuracy (threshold for impairment defined as 97% -2.5*3.4). Remarkably, the speed of response for all patients was also within the bounds of normality but this could be governed by the slow rate of presentation in the scanner.

Table 6.1: Behavioural results of patients with damage to adSMG

	Accuracy in %		***RTs in s***	
	P	**O**	**P**	**O**
PS0539	100.0	92.5	1217.9	1272.0
PS0418	97.5	92.5	1073.9	1028.9
PS0066	90.0	97.5	1175.9	1375.8
PS0430	62.5	90.0	1085.9	1365.3
PS0127	37.5	80.0	1386.6	1656.5
PS0610	70.0	92.5	1059.7	1092.9
PS0707	42.5	92.5	1191.2	1390.1
Controls (mean)	94.7	96.6	973.8	1065.2
SD	6.3	3.4	137.7	123.8
*mean -/+ SD*2.5*	79.0	88.1	1318.0	1374.7

*Accuracy scores (in %) and RTs (in seconds) for patients and controls (mean value and standard deviation, SD) for reading pseudowords (P) and naming pictures of objects (O). Patients highlighted in green show good performance in pseudoword reading (> 79% correct). Threshold for impairment was defined as mean value in controls minus 2.5*standard deviation (for accuracy) and mean value plus 2.5*standard deviation (for RTs).*

6.4.2. Activation differences in patients versus controls

As expected, patients showed less activation than controls within the area affected by their stroke, extending over left pre- and postcentral cortex. Patients showed an increase in activation compared to controls in left subcortical regions (i.e. putamen, caudate and thalamus) and in the right pars triangularis in the inferior frontal gyrus during pseudoword reading and object naming. Activation in left globus pallidus (GP) increased for patients during object naming only (Z score for interaction with task = 4.6). See Figure 6.2.

A				Main effect		P	O	INT
	x	y	z	Zsc	Vx	Zsc	Zsc	[P > O]
[Controls > Patients]								
L PreC/PoC	-48	-13	38	Inf	104	6.6	5.3	n.s.
	-60	-7	8	5.1	7	4.1	3.3	n.s.
	-39	5	32	5.4	5	4.5	3.7	n.s.
	-24	-79	5	5.5	5	4.1	3.6	n.s.
	-15	-4	50	-		5.7	n.s.	**4.5**
L IPL	-42	-40	44	-		5.6	1.9	**3.3**
[Patients > Controls]								
L Caudate	-18	11	20	6.9	39	4.7	5.6	n.s.
L PUT	-24	17	-4	5.9		5.7	3.0	2.3
R pTri	33	29	5	6.5	27	4.8	4.8	0.4
L vThalamus	-6	-10	2	6.1	9	5.1	4.3	2.4
L GP	-15	-4	11	-		n.s.	7.2	**-4.6**

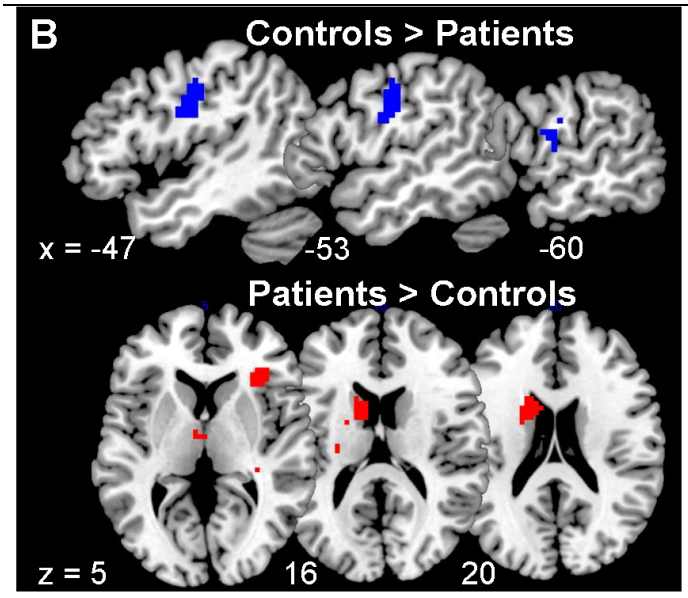


Figure 6.2: A. Peaks and extents for activation differences between patients and controls for the main effect of reading pseudowords (P) and naming pictures of objects (O), and for each task separately relative to rest. Effects were significant at p<0.05 after FWE whole brain correction. xyz = coordinates in MNI space. Vx = cluster size in voxels. Significant interactions with task are highlighted in bold. B. Activation cluster where patients showed a decrease (in blue) or increase in activation (in red) compared to controls across tasks.

6.4.3. Specificity

Activation decrease for patients versus controls in left pre/postcentral cortices was present across tasks, apart from left IPL, where activation decrease was specific to object naming (Z score for interaction = 3.3). Activation increase for patients in left subcortical regions and right pars triangularis was observed during both pseudoword reading and object naming. Activation increase for patients was only specific to object naming in the globus pallidus, as confirmed with a group x task interaction (patients > controls and object naming > pseudoword reading). See Figure 6.2-A and 6.3.

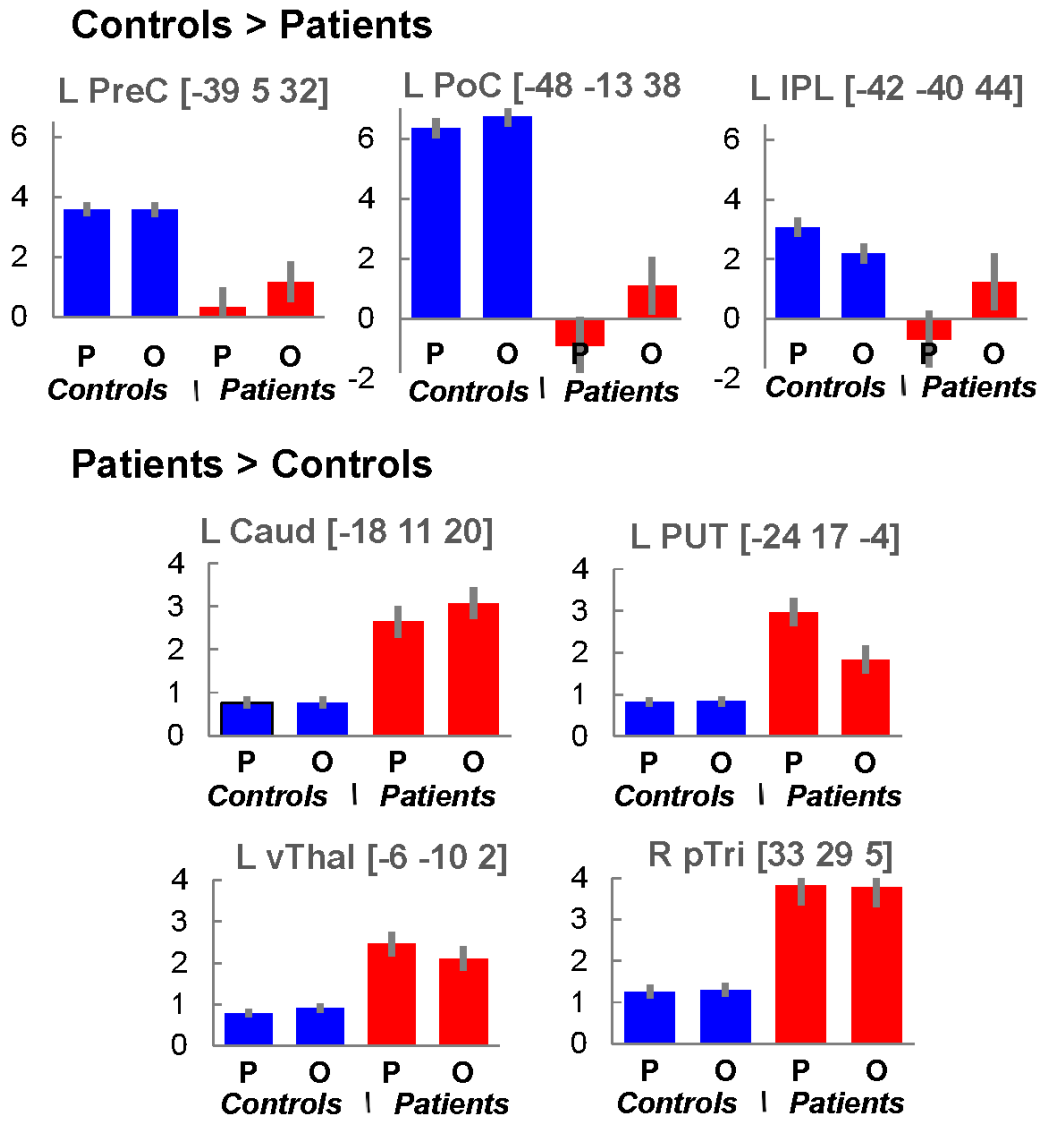


Figure 6.3: Plots show relative activation differences (with standard error) between controls (blue) and patients (red) for reading pseudowords (P) and naming pictures of objects (O).

6.4.4. Consistency

There was a high degree of variability in activation within the patient group. Even at the most significant peak that was identified at the group level (patients > controls), i.e. in the left thalamus, activation during pseudoword reading was driven by a few patients, whereas 2 patients activated within the normal range, as illustrated below (Figure 6.4).

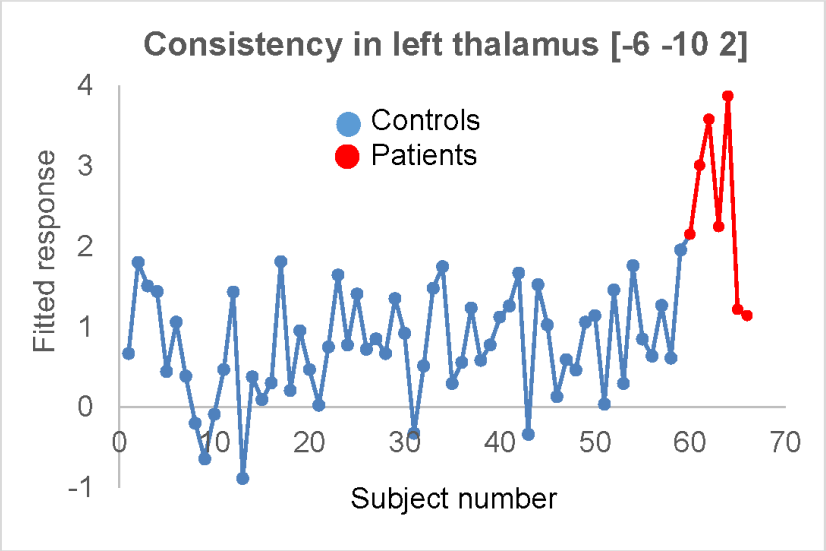


Figure 6.4: Fitted responses extracted from the left thalamus at MNI [-6 -10 2] across controls (blue) and patients (red) during pseudoword reading.

Summary of results

(1) How consistently does selective damage to left adSMG impair pseudoword reading and object naming in stroke survivors?

It was surprising to find that all patients could produce some correct responses and three had scores within the accuracy range of healthy controls, despite damage to adSMG. This effect was even more striking in object picture naming, where 6/7 patients were able to perform within normal expectations.

(2) How does brain activation change in patients who can read pseudowords/ name objects after left adSMG damage?

As expected, patients showed a decrease in activation during pseudoword reading within the area that had been affected by their stroke, centred on pre-and postcentral cortex. An increase in patient activation was observed in left subcortical areas and in the right pars triangularis.

(3) Specificity

The activation decrease in pre/postcentral cortex for patients was observed for both pseudoword reading and object naming. In contrast, activation decrease in left IPL was specific to object naming. Subcortical regions showed abnormally high activation in patients across tasks, whereas activation in left globus pallidus was increased in patients for object naming, but not for pseudoword reading.

6.5. Discussion

This study sought to investigate the effect of anterior SMG damage on phonological processing in stroke patients, and the changes that occur after stroke in order to support recovery of phonological tasks. Surprisingly, this revealed that damage to the left adSMG region that is activated when healthy participants are reading pseudowords and naming pictures does not consistently lead to persistent impairments reading pseudowords or naming pictures of objects. I was also able to show that patients over-activate a network of regions comprising left subcortical structures and right inferior frontal gyrus, which potentially compensate for the loss of adSMG and allow patients to perform well behaviourally. However, inter-subject variability in the patient group, as well as in the control group, suggests that successful cognitive performance can be achieved with different neural strategies.

Here, I provided proof-of-principle for a novel combination of structural and functional measures to test the integrity of a brain region after stroke. Surprisingly, despite the automated lesion identification algorithm showing that most or all of the region of interest was destroyed in a subsample of the patients included, the fMRI analysis revealed that there was still activation observed within left adSMG during pseudoword reading and object naming in 6 patients who were excluded from further analyses. This suggests that there was preserved tissue within the lesion, which potentially supported the tasks of interest. By excluding those patients with positive activation during pseudoword reading, I ensured that the region of interest was not contributing to pseudoword reading. Extracted eigenvariates indicated that some of the 7 patients included were able to activate adSMG during object naming but not during pseudoword reading. This might explain why patients performed better during object naming than during pseudoword reading. Regardless, this discrepancy between lesion analysis and fMRI signal has important implications for lesion-behaviour correlations. Previous studies might have overlooked preserved tissue, if no functional imaging data was considered. This study demonstrates the benefit of combining lesion and fMRI data for the characterisation of post stroke lesions, and the impact of the loss of a region on behaviour.

The remarkably good reading and naming performance that we observed after adSMG damage was at first surprising, since left adSMG has been associated with phonological tasks in numerous studies. For instance, significant activation in adMSG has been reported during reading aloud pseudowords > words (Binder et al., 2005; Taylor et al., 2014; Vigneau et al., 2005) and during phonological > semantic decisions on words (Scott et al., 2003; Seghier et al., 2004). However, as shown in Experiment 3, the response pattern in adSMG does not correspond to what I would expect for non-semantic phonological processing, because the region is most activated by the most difficult tasks (pseudoword reading and object naming) rather than by the demands on non-semantic phonological processing. In Experiment 3, I speculated that adSMG activation might reflect unspecific higher-order executive functions, supporting the input-to-output mapping for ambiguous stimuli. This lesion study suggests that whatever the function of the region, it is not absolutely necessary for pseudoword reading and object naming because some patients are still able to perform these tasks despite loss of adSMG.

Behavioural performance is not only dependent on the damaged part of the brain, but also on the integrity of the remaining tissue. Thus, I was interested in searching for compensatory regions across the brain, where activation was increased in patients compared to controls, presumably supporting their behaviour. I found significant over-activation in patients versus controls in two separate clusters: in left subcortical regions, including putamen, thalamus, and caudate and in right pars triangularis in the inferior frontal gyrus. At the same time, patients showed decreased activation in pre- and postcentral cortices in their left hemisphere. The relationship between premotor cortex and subcortical regions has been investigated by Seghier et al. (2014), who found that patients with damage to left putamen showed increased activation in left premotor cortex during reading and picture naming. Moreover, in control participants, reduced connectivity through the left putamen correlated with an increase in connectivity through the premotor cortex. The current study might have revealed the reverse effect, i.e. reduced activation in premotor cortex is compensated for by increased putaminal activation. A connectivity analysis could test this hypothesis by investigating how these two regions influence each other during the tasks of

interest. As shown in Experiment 2, the bilateral putamen is one of the key nodes within the normal network for orthography-to-phonology mapping and crucially involved in pseudoword reading (Oberhuber et al., 2013).

The other abnormal activation cluster identified at the group level was in the right hemisphere in pars triangularis. A few studies associated this regions with phonological processing, i.e. with syllable counting in pseudowords and words (Poldrack et al., 1999), syllable identification in visually and auditorily presented stimuli (Sekiyama et al., 2003) and silent repetition of pseudowords versus rest (Warburton et al., 1996). However, these studies also reported activation in the left homologue of pars triangularis, indicating that the cluster in the right frontal lobe would not be sufficient to perform phonological tasks, but is supporting left hemisphere activation. It is also possible that activation increase in the right pars triangularis might reflect maladaptive activation. According to the disinhibition theory, increased right hemisphere activation post stroke is associated with increased inter-callosal inhibition of the affected hemisphere, which interferes with beneficial reorganisation within the language network. Meta-analyses have indeed shown that abnormal right hemisphere activation is correlated with less successful recovery, whereas increased activation in left hemisphere perisylvian language regions is associated with better recovery (Turkeltaub et al., 2011). For instance, TMS suppression of the right pars triangularis resulted in improved performance and reduced reaction times in a picture naming task (Naeser et al., 2005). This experiment does not allow me to reject the hypothesis that right hemisphere activation is hindering behavioural performance, however, it is unlikely because (i) only correct trials were included in the fMRI analysis and (ii) increased right pars triangularis activation was not specific to pseudoword reading but also observed during object picture naming, which patients performed well on.

Limitations

It has been shown that the use of fMRI in stroke patients is vulnerable to biological influences, e.g. a potentially skewed time-course of hemodynamic response function, or a low signal-to-noise ratio within the lesioned area (Bonakdarpour et al., 2007). Another potential issue might arise from movement

related artefacts in the data, due to increased head motion in patients that introduces additional artefacts at the dark/light border of images (if the head moves in sync with the stimulus onsets). Some studies recommend the use of covert rather than overt speech tasks to reduce motion. However, this makes it impossible to evaluate whether the patient has performed the task correctly on each trial. I therefore used an overt response – to measure behavioural accuracy - but additionally made sure that the patients' head was carefully positioned in the head coil of the scanner. I then used post hoc tests to confirm that the motion artefacts were not observed around each patient's lesion border and not significantly greater in the patient group than the control group.

Our data did not allow the effect of therapy to be investigated. The recovery mechanisms that I have identified could therefore either be a consequence of spontaneous recovery or slow re-learning. Other studies considering pre- and post-intervention changes might find different compensatory activation patterns. Related to this issue, it has been shown that the shape of the recovery curve can change over time. I did not collect longitudinal data to investigate how the compensatory network changed over time. Moreover, premorbid data is not available and thus abnormal language organisation prior to stroke cannot be completely excluded.

Finally, the small sample size included in this study might be a point of concern. Out of 57 patients, only 13 met the criteria of having near-complete or complete damage to the region of interest; and only 7 of these patients showed no activation in adSMG during pseudoword reading. However, one of the aims of this study was to investigate individual recovery patterns and inter-patient variability, which would not be visible in group studies including large samples. Lack of specificity of the lesions included could also have biased the results. Despite the most careful selection that was possible with the data available, the patient sample included here tended to have large lesions, centered in parietal lobe, but spreading into left frontal and occipital lobe. Thus, the observed activation pattern has also been influenced by damage to the surrounding tissue, and not just to adSMG.

7. CONCLUSIONS

This thesis describes the use of structural and functional magnetic resonance imaging to investigate the neural basis of different types of phonological processing, and the effect of brain damage through stroke on phonological abilities.

In the general introduction, I reviewed the literature on theoretical models and experimental manipulations of phonological effects, the involvement of supramarginal gyrus in prior language and non-language studies, and the consequences of brain damage through stroke in terms of behavioural impairment, as well as common theories on neuro-biological recovery mechanisms after stroke.

With the first two Experiments I showed that there are at least two types of phonological processing that can be dissociated on a neuronal level. Bilateral superior temporal gyri were associated with processing auditory (phonological) representations of speech, whereas activation in left putamen and precentral cortex/pars opercularis was consistent with articulatory planning. The validation of the results in a separate, larger sample (Experiment 2) increased confidence that these findings are robust rather than false positives. In Experiment 3, I went on to study the role of a “key player” in phonological processing, which revealed that different parts of the supramarginal gyrus differ in their response profile during a set of language tasks. This is in accordance with cytoarchitectural and connectivity studies demonstrating the structural variability of the region, and has implications for prior imaging studies considering the supramarginal gyrus as a uniform entity in the phonological network.

The final experiment demonstrates the application of previously examined research questions to a clinical sample, i.e. how does damage to the supramarginal gyrus after stroke affect phonological abilities? This revealed that the loss of the supramarginal gyrus has inconsistent effects on language abilities, possibly due to other brain regions or white matter tracts that were damaged in some patients but not in others. It also showed that additional brain

regions were recruited in patients compared to controls, which might reflect compensatory brain activation that supports recovery.

Having discussed the implications of the above findings in the discussion of each respective chapter, this final chapter will allow me to discuss a few more general points and make my concluding statements.

This work demonstrates the potential of considering a range of different tasks when interpreting language, and other cognitive functions, using fMRI. When considering one experimental condition, compared to a (high or low level) baseline, it is often not possible to isolate the process of interest. In this thesis, I took into account the response pattern for a set of tasks, across modalities and response modes, which allowed me to narrow down the cognitive processes driving task-related activation, and disentangle specific processes such as articulatory planning from more domain-general processes such as attention or verbal working memory. This approach was particularly useful in Experiment 3, which revealed that four subregions within supramarginal gyrus are involved in a phonological task (e.g. pseudoword reading), but are driven by different processes (e.g. auditory short-term memory, integration of lexical and sublexical cues, articulatory sequencing or domain-general executive functions).

The fMRI paradigm introduced here is a promising tool for the investigation of different language processes. Its power lies in the choice of different task combinations to isolate the process of interest, and the comprehensive data it can provide, i.e. data from different perceptual modalities (visual and auditory input) and response modes (speech production and silent one-back matching), as well as audio recordings for response time analysis. Nonetheless, applying the current paradigm to more than 100 participants taught me that, in particular for patients, it can be challenging to complete an extensive list of language tasks while lying still in an fMRI scanner, over a prolonged period of time. From a practical point of view, it might not always be feasible to put participants through all tasks. It is therefore useful to have gathered data with an adapted version of the paradigm in Experiment 2, in which task and stimulus order were kept constant – with tasks that are easiest and most informative

being presented first. This makes it possible to stop the experiment when a patient tires and use the data that has been collected by comparing to that collected from large numbers of healthy controls who underwent exactly the same experimental manipulations up to the point that the patient tired.

One of the major findings of this thesis is that “phonological processing” is much less of a clearly defined concept than often suggested. As I alluded to in the general introduction, the processing of speech sounds involves a myriad of processes such as perceptual processing, auditory short-term memory, or motor output planning. Here, I am touching upon the need for alternative theoretical concepts to help explain activation profiles that I have observed. At a broad level, I can link some of my neuroimaging findings to cognitive definitions such as “input phonology” and “output phonology” by viewing activation in the superior temporal sulci (for speech representations) as input phonology and by viewing activation in the left precentral cortex, putamen and ventral anterior supramarginal gyrus (related to articulatory planning) as output phonology. However, although this allows me to link biological structures to cognitive functions, it is not an accurate description of what the brain regions are doing. Specifically, I am referring to the response in the bilateral superior temporal sulci. The response in these areas was consistent with the expectations of phonological processing because activation was higher for listening to speech than listening to environmental sounds (meaningful auditory inputs that are not speech) whereas other parts of the auditory cortex were more activated for listening to environmental sounds than speech. On the other hand, although I can argue that the superior temporal sulci are involved in phonological processing, I cannot say that the superior temporal sulci are specific to phonology because these regions also responded to all auditory inputs.

One explanation of the common responses that I observed for speech and nonspeech is that the superior temporal sulci are involved in an auditory function that is needed to recognise speech and nonspeech sounds, with this function being required more during speech than nonspeech. The second possibility is that parts of the superior temporal sulci are tuned to speech and the activation during non-speech sound processing occurs because the human brain is always

looking for speech clues (i.e. implicit but redundant processing). Prior attempts to distinguish these accounts have provided evidence for the common processing account. For example, Leech et al. (2009) showed that the response in the superior temporal sulci changes when participants learn to recognise non-speech sounds. Others have shown that damage to the speech parts of the bilateral superior temporal sulci impairs auditory sound recognition as well as speech recognition (Dick et al., 2007; Saygin et al., 2003).

In addition, my findings have identified phonological processes that are not in traditional cognitive models of word reading and repetition: "auditory imagery" in posterior ventral SMG (also referred to as the temporo-parietal junction) and "the integration of lexical and sublexical phonological inputs" in posterior dorsal SMG. These processes are not dissociated from speech recognition and articulatory decoding in traditional models of reading and repetition. Therefore, my observation that there are dissociable brain regions for four different types of phonology illustrates how neuroimaging can challenge and inform our understanding of cognition as well as brain structure. There have been surprisingly few examples of this (see Coltheart, 2006), perhaps because it has taken a couple of decades of experience with neuroimaging to understand how it can best be used and what the results are telling us. Hopefully, my findings will inspire future experiments to look at the different components of phonological processing.

Another point I would like to emphasize is that none of the brain regions identified in my experiments are involved in a single process only, or sufficient for any cognitive process. If anything, isolating a particular region that is crucially involved in a certain process (e.g. bilateral superior temporal sulcus as key nodes for phonological representations) helps to describe its role within the neural network that is supporting a task. For instance, the parcellation of left supramarginal gyrus into functionally distinct subregions (Experiment 3) provided important insight into the contribution of each part to phonological tasks. Importantly, each subregion co-activated with a range of other regions outside of SMG, reflecting the network nature of the brain. The results are not included in this thesis because it would go beyond the scope of Experiment 3, however, it

will be interesting in the future to investigate the direction of information flow between these areas and SMG subregions, using effective connectivity analysis.

A surprising finding was the disparity in anatomical and functional integrity of brain regions affected by stroke. In 6 out of 13 patients that took part in Experiment 4, the automated lesion identification algorithm identified a part of their supramarginal gyrus as damaged, however, I still detected fMRI signal in the region of interest. These patients were subsequently excluded from the analysis to rule out the possibility that the region was still contributing to the task of interest. In my opinion, this represents a crucial point when considering lesion-behaviour correlations, since remaining tissue might be overlooked when only taking structural MRI images as a biomarker for tissue integrity. This in turn can affect recovery predictions based on lesion size or location. It is possible that current predictions are *under*-estimating the recovery potential for specific patients. Previous studies have used different combinations of resting state fMRI and structural data for the diagnosis and prognosis of functional impairment in different neurological conditions (for reviews, see Orru et al., 2012; and Ovadia-Caro et al., 2014), and it has been suggested that resting state data might indeed reflect behavioural deficits better than structural MRI (e.g. Rehme et al., 2015). The current study contributes to this discussion by providing a first proof-of-concept for the additive value of including task-based fMRI signal from *within* the lesion, when describing language impairment in individual patients. The exact neuro-biological origin of fMRI signal that has been extracted from a structurally impaired region remains the topic of future research.

In conclusion, this work contributes to our understanding of the cognitive processes enabling us to successfully perform phonological tasks. Moreover, I have demonstrated the importance and feasibility of validating fMRI findings across samples, and the benefits of including a large group of control participants to increase statistical power, where possible. The patient data is contributing to this work in two ways: first, by revealing the consequences of stroke-related damage to the SMG, which further characterises its role in language tasks, and second, by suggesting alternative pathways that might support recovery, which could eventually be targeted with therapeutic interventions.

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