An Investigation of Phonological and Semantic Control Using TMS and fMRI

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Abstract

This thesis aimed to investigate the neural basis of linguistic and semantic control across brain networks, using fMRI and TMS. Firstly we assessed the contribution of premotor cortex (PMC) to speech perception: TMS disrupted phonological but not semantic judgments, indicating a constrained role for PMC in tasks involving explicit access to phonemic representations, but not in accessing meaning. Chapter 3 examined the role of brain regions within the language network to both domain (phonological/semantic) and executive control demands. The results suggest that there are specialisations at the extreme ends of LIFG for phonology (PMC/BA 44) and semantics (BA 47), as well as contributions from posterior temporal and parietal cortex to both domains. Furthermore, Chapter 4 investigated the role of these brain areas to amodal semantic cognition using picture and verbal semantic associations which varied in their difficulty (to manipulate semantic control demands). The findings suggest that while BA45/44 respond to control demands across modalities, there are specialisations within the semantic control network; for example, bilateral BA 47 showed a verbal semantic preference. Chapter 5 used TMS to further probe the role of BA 44, 47 and pMTG across domain (phonology/semantic) and modality (picture/verbal), confirming a preference for verbal semantic material in BA 44 and 47, and highlighting an amodal contribution of pMTG to associative semantic judgments. Lastly, Chapter 6 focussed on semantic control and manipulated retrieval and selection demands using a cyclical picture naming paradigm. We found that TMS to LIFG caused a specific disruption of naming at the point at which the demands on both selection and retrieval were maximal, while TMS to pMTG caused no disruption of retrieval or selection processes. The findings of this thesis shed additional light on the role of various areas throughout the language networks to domain, modality and control.

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Parts of this thesis were conducted in collaboration with others:

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Chapter 1: Introduction and Review of the Literature

Language Networks

The ease with which we use language belies the complicated processes that support it. For example, not only do we effortlessly produce and perceive speech sounds, but we also rapidly map them onto meaning (i.e., semantic knowledge). Models of language help to capture the complicated nature of what underlies such a seemingly simple process and reveal a distributed network of brain areas that support language processing across various dimensions (i.e., speech sound segmentation, meaning across modalities (e.g., words and pictures), resolving increased perceptual and conceptual difficulty/ambiguity, etc.).

Many models advocate two processing streams: a ventral speech perception route along the temporal lobe and a dorsal auditory-motor stream for auditory-motor integration (Hickok & Poeppel, 2000, 2007; Rauschecker & Scott, 2009). Combining evidence from humans and non-human primates, Rauschecker and Scott (2009) suggest that the two streams originate in auditory cortex, and processing is both hierarchical and parallel, such that 'lower' cortical areas project to and from 'higher' areas (e.g., in frontal cortex) that have more complex response properties: posterior superior temporal sulcus (STS) projects to the intraparietal lobe (IPL) and premotor cortices (PMC) as part of the 'what' stream for 'lower level' speech perception; and the anterior STS projects to inferior frontal cortex (IFC) for 'higher level' speech comprehension. As such, anterior STS has been shown to be more sensitive to the intelligibility of speech, while posterior STS (e.g., planum temporale) may act as a computational hub for processing spectro-temporally complex sounds (like music). Likewise, many speech perception tasks have required participants to identify/segment specific speech sounds (e.g., 'pa' embedded in white noise) and Hickok and Poeppel (2000, 2007; Poeppel & Hickok, 2004) propose that the dorsal stream is engaged for tasks such as these serving a role in auditory-motor integration (e.g., in the perceived difficulty of producing a sound, silent articulation and gestural processing of speech; Scott, McGettigan, & Eisner, 2009), while the ventral stream is involved in comprehension of auditory input (i.e., whole words). Paus, Perry, Zatorre, Worsley, and Evans (1996) have shown a motor – to – auditory flow in speech production, with increased activation in auditory speech areas (i.e., superior temporal cortex) during the articulation of speech sounds (masked by noise so as to ensure that activation in auditory cortex is due to articulation not the perception of speech sounds).

Some models view perception and production as two separate and distinct processes, while theories such as the motor theory of speech perception tightly couple the two (Pulvermuller & Fadiga, 2010): this account suggests that the processes involved in producing speech are also involved in perceiving it (Liberman & Mattingly, 1985). For example, Wilson, Saygin, Sereno, and Iacoboni (2004) provide support for this theory with their study which found that the same motor areas used in speech production (i.e., PMC) were also activated in speech perception. It seems reasonable to assume that production and perception are not mutually exclusive, given that perception must inform motor articulatory learning, as accounted for in neurocomputational models that also couple action and perception in language acquisition (Garagnani, Wennekers, & Pulvermuller, 2008; Pulvermuller & Preibl, 1991). In these models, any activation of auditory cortex leads to spreading activation across all regions, including motor areas (Garagnani, Shtyrov, & Pulvermuller, 2009; Garagnani, et al., 2008). Neuroimaging studies also reveal activation for both speech listening and covert speech production in pSTG/Spt (Buchsbaum, Hickok, & Humphries, 2001; Hickok, Buchsbaum, Humphries, & Muftuler, 2003; Hickok, Okada, & Serences, 2009; Okada & Hickok, 2006). Taken together, the literature suggests an integrated view in which motor and sensory processes interact.

Another key part of language is understanding the meaning (and context) of the words we use both in perception and production (e.g., as indicated in the ‘ventral stream’ above). A large network of areas has been implicated in this ‘higher order’ use of language – with different brain areas reserved for storage of semantic representations and access to and appropriate use thereof. For example, when a listener hears the word ‘bank’, they must access the stored semantic meaning of this word in memory – and this store is thought to involve the anterior temporal lobes (ATL; Jefferies & Lambon Ralph, 2006; Lambon Ralph, Pobric, & Jefferies, 2009; Pobric, Lambon Ralph, & Jefferies, 2009). Furthermore, the word ‘bank’ has more than one meaning (e.g., money-bank, river-bank) and the appropriate meaning must be selected for the given context (example taken from: Whitney, Jefferies, & Kircher, 2011). In this case, a distributed network of brain areas is engaged to ensure that the ‘correct’ meaning is activated. However, such processes are not specific to language – for example, objects also have more than one meaning or use, and when we are required to selectively focus on the less frequent or non-canonical meanings of objects, this may involve the recruitment of the same cortical network associated with linguistic semantic control.

This thesis explores the recruitment of specific areas within frontal cortex during explicit semantic and phonological judgements. First, it examines whether premotor cortex is essential for speech perception in the context of explicit phoneme decisions and semantic judgements. Secondly, it looks at semantic judgements in more detail and considers the extent to which the brain networks that contribute to executive control of phonological, verbal semantic and picture semantic tasks overlap. This chapter will discuss the brain areas contributing to these language networks in an effort to elucidate their role in speech perception and comprehension. We will start with the contribution of motor areas such as PMC to speech perception and progress towards the many areas recruited for semantic cognition/control.

Coupling of speech perception and production

The motor theory of speech perception lost popularity due to the apparent inconsistency with neuropsychological evidence (i.e.,Basso, Casati, & Vignolo, 1977), but the debate was reinvigorated by the discovery of mirror neurons in monkeys (Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). The advent of neuroimaging has also provided a new way of examining this issue, whereby researchers can see which areas of the brain are active in both the production and the perception of speech (e.g., Wilson, et al., 2004).

Neuropsychological indications

While Liberman's motor theory (Liberman & Mattingly, 1985) states that the motor cortex is crucial to speech perception, the neuropsychological literature, in particular, studies of expressive and receptive aphasia suggest that the motor cortex is not essential for speech perception. Patients with Broca's (also known as expressive or non-fluent) aphasia have lesions to left inferior frontal cortex (LIFC), typically including ventral premotor areas that are thought to be crucial for the production of speech, and thus these patients show marked impairment in language production. The motor theory of speech perception would predict that these patients should also suffer from impaired comprehension, but this is often not the case (Alexander, 1997). Additionally, the reverse pattern is shown by patients with Wernicke's aphasia (also known as receptive, sensory or fluent aphasia), who have lesions to areas crucial for language perception, and thus suffer a loss of auditory comprehension: their spoken language is fluent, however, it does lack meaning (Geschwind, 1971). This suggests that the inability to produce language does not affect global comprehension and vice-versa. However, these patients *do* show impairment on explicit perceptual categorization tasks (e.g., identifying the acoustic boundary between two phonemes), *but these impairments are not reflected in general comprehension* (Basso, et al., 1977; Bishop, Brown, & Robson, 1990; Blumstein, Cooper, Zurif, & Caramazza, 1977; Miceli, Gainotti, Caltagirone, & Masullo, 1980; Moineau, Dronkers, & Bates, 2005). Patients with inferior frontal lesions (Broca's aphasia), *can* show impaired single word comprehension if speech is accelerated or overlaid with noise, supporting the view that LIFC may only play a vital role in speech perception for particularly difficult tasks (Moineau, et al., 2005). Additionally, dysarthria and anarthria are both disorders of language production with no impairment in general comprehension (Scott, et al., 2009). However, like aphasia, when individuals with dysarthria are tested specifically on language control, a deficit is seen. For instance, Bishop et al. (1990) found that phoneme discrimination using novel letter strings resulted in impaired performance, while comprehension and even discriminating phoneme contrasts showed no impairment. This suggests that they may have impaired memory for novel phonological strings, possibly because this sort of task requires covert repetition of the novel material inherent in this task type (Bishop, et al., 1990). Taken together, the neuropsychological literature suggests that speech motor knowledge may not be necessary for normal comprehension, but it may be recruited for certain features of language processing, such as explicit phoneme segmentation.

Evidence from Mirror Neurons

While it is clear that the patient literature provides little support for the motor theory (Liberman & Mattingly, 1985), the discovery of mirror neurons in monkeys reinvigorated the debate over the necessity of speech motor areas to perception. Single cell recordings of 'mirror-neurons', in monkey area F5, fire both when performing an action and when watching others perform that action (Rizzolatti, et al., 1996). There is also some evidence to suggest that these mirror neurons are multi-modal, in that they also seem to respond to the consequential sound of an action (Kohler et al., 2002). These findings are important for theories of language because monkey area F5 is considered to be the homologue of left inferior frontal gyrus (LIFG) in humans - i.e., BA 44, BA 45 and ventral PMC (PMv).

There have been some attempts to mimic single cell recording using behavioural measures in human subjects whereby use-induced motor adaptation is produced through repeated movements (e.g., repeated firing of motor cortex). Glenberg et al. (2010) blindfolded participants while they made arm movements away (from the body) and toward (the body); despite being blindfolded when making the movements (ensuring that adaptation is motor rather than visual perception), the motor adaptation biased subsequent ambiguous movement perception toward the direction of the repeated movements made. Additionally use-induced motor plasticity has been used in studies of language. In one study, participants performed 10 minutes of repeated lip or tongue movements and then performed a 2AFC syllable decision task (masked by white noise). Repeated tongue movements produced a bias to respond ‘ta’, while the repeated lip movements created the same congruent bias for ‘pa’, this, the authors argue, reflects the motor system’s role in mediating top down processes in higher level categorization tasks (Sato et al., 2011). Support was also provided by Yuen, Davis, Brysbaert, and Rastle (2009), where participants were required to produce syllables in the face of auditory or written distractors which were either congruent or incongruent to the syllable to be produced (i.e., the target). The incongruent auditory stimulus modified the participant’s production of the target syllable, while the congruent syllables did not affect articulation (nor did the written distractors). The authors argued that when encoding an auditory stimulus, encoding the articulatory information is automatic, and therefore reflected in the modified speech output for incongruent trials in this experiment. These studies suggest that the mirror neurons found in monkeys can be successfully mimicked in humans using behavioural studies in both action and language perception, and thus help implicate the motor cortex in some aspects of speech perception.

Neuroimaging

***Passive speech listening*.** While mirror neurons reinvigorated the debate over the motor theory of speech perception, neuroimaging techniques have helped researchers to test its predictions, namely that the motor areas involved in articulation are also involved in speech perception. As such, passive listening to speech sounds has been shown to activate motor speech areas. Uppenkamp, Johnsrude, Norris, Marslen-Wilson, and Patterson (2006) found that the premotor area was ‘*slightly*’ more active during vowel listening than listening to matched non-speech sounds; a finding which is in line with

Wilson et al.’s (2004) finding that the same motor areas involved in producing monosyllables were also active when passively listening to them, as well as other findings of increased PMC activation for listening to monosyllabic words (e.g., Okada & Hickok, 2006). Furthermore, TMS studies have shown that listening to speech sounds that require strong articulation activates the motor system. For example, using a combination of TMS and tongue motor evoked potentials (MEP), Fadiga, Craighero, Buccino, and Rizzolatti (2002) found that when participants passively listened to words and pseudowords the tongue area of the motor cortex showed an increase in MEPs for words with an embedded double ‘r’ consonant (requiring tongue articulation) compared with those with a double ‘f’ consonant (no tongue articulation). Likewise, Watkins, Strafella, and Paus (2003) found that stimulation of the left face motor area increased MEPs for speech sounds and speech-related lip movements, but not for non-speech sounds or eye movements. Additionally, not only did Pulvermuller et al. (2006) find differential fMRI activation for lip and tongue movements, as well as tongue versus lip articulated phonemes - but also differential activation in the same areas for the *perception* of these syllables, with stronger [p] activation in ventral motor areas and stronger [t] in dorsal precentral areas (i.e., fine grained activation by phoneme type). This receives further support from a study which used online double TMS pulses to the lip or tongue areas of motor cortex immediately preceding stimulus onset, identifying speech sounds as either [b] / [p] (lip articulated) or [d] / [t] (tongue articulated). This resulted in faster identification of congruent phonemes (i.e., perception of ‘pa’ following TMS to lip area) and inhibition of incongruent phonemes (i.e., perception of ‘pa’ following TMS to tongue area). The authors suggest that stimulation might pre-activate/prime the area increasing the excitability of the neurons therein, and the reduction in performance may be due to lateral inhibition between competing representations (D'Ausilio et al., 2009). Taken together, these studies suggest fine-grained organisation by phoneme type in the motor cortex for both speech production and perception (tasks).

*Specific Roles in Speech Perception***.** Although some studies have shown fine-grained phoneme representations for passive listening to speech stimuli (Pulvermuller, et al., 2006; Wilson, et al., 2004), most early neuroimaging studies have not reported motor cortex activation for general speech perception; if this area were crucial to speech perception it should show strong and consistent activation across speech perception tasks, and therefore may only be recruited for specific types of tasks (Scott et al. 2009). For example, Buchsbaum et al. (2001) reported a more sluggish BOLD response for auditory stimuli in PMC compared to the response for production, perhaps indicating its ‘optional’ use in perception. Furthermore, Rogalsky, Love, Driscoll, Anderson, and Hickok (2011) argue against a strict motor theory of speech perception, with motor cortex involvement in speech perception reserved for 1) strategic modulation of the speech perception process in non-natural/challenging conditions, 2) providing a back-up mechanism for processing degraded auditory stimuli, or 3) non-natural language tasks such as explicit phoneme judgements, when *metalinguistic knowledge about speech sounds*, not words, is used to guide phoneme segmentation. This suggests that the motor cortex may only be involved in “meta-linguistic task-specific aspects of performance rather than fundamental processes.” (p.185). In addition, Scott et al. (2009), suggest a further role in which the motor cortex is recruited for conversational turn taking whereby motor areas are responsible for “convergence, interactional synchrony and ensuring smooth turn transition” (p. 301).

This distinction between general speech comprehension and tasks that manipulate certain aspects of perception is seen in early research by Zatorre, Evans, Meyer, and Gjedde (1992) who sought to investigate the brain regions involved in speech perception using PET. In passive listening, activation was seen in the superior temporal gyrus bilaterally, *but not in motor areas*. However, when participants made perceptual decisions on speech syllables, activation was seen in LIFG bordering PMC, again suggesting motor recruitment for specific perceptual tasks, but not passive speech listening. Similarly, same/different decisions to stimuli that required overt segmentation, produced motor activation consistent with that reported in Zatorre, et al. (1992), but not when the same decisions were made to stimuli that did not require overt segmentation (Burton, Small, & Blumstein, 2000). Other research suggests that perceiving phonetically ambiguous speech recruits motor areas, but phonetically unambiguous speech does not (Gow Jr & Segawa, 2009). These studies support the notion that motor areas may be recruited under certain circumstances, for instance, where speech discrimination is particularly challenging (e.g., explicit phoneme judgements, increased perceptual difficulty).

TMS has been used to confirm the involvement of speech motor areas in speech perception as it is a useful technique due its ability to produce focal stimulation of brain areas purportedly involved in a certain cognitive function. This means that TMS can be used to help confirm whether activation seen in particular brain areas is functionally relevant (or not). Meister et al. (2007) disrupted speech discrimination relative to baseline following

TMS to PMC for tasks that required participants to identify syllables embedded in noise (with no TMS disruption for colour or tone discrimination control tasks). Similarly, Mottonen and Watkins (2009) applied rTMS pulses to the lip area of the motor cortex (left M1) to measure the contribution of motor articulatory representations to the categorical perception (CP) of speech. They impaired CP for speech sounds involving the lips (/pa/-/ta/), but not a continuum supported by tongue articulation (/ka/-/ga/). In contrast, Raizada and Poldrack's (2007) fMRI study of categorical perception did not report motor cortex activation, suggesting that the recruitment of PMC is dependent on the demands of the speech perception task. Scott & Evans (2010) point out that the task type can strongly influence whether effects are seen (i.e., 2AFC vs. 4AFC), and Raizada and Poldrack (2007) did not require participants to make discriminations while in the scanner, as they were interested in the brain areas that 'amplify' the boundary differences (e.g., supramarginal gyrus), and PMC activation was not elicited in this case therefore suggesting that PMC recruitment may not be necessitated when no *explicit* perceptual categorisation is required. Other research has demonstrated PMC involvement in segmenting speech input, using the 'virtual lesion' rTMS method: with results suggesting that PMC is not recruited for simple phoneme and syllable discriminations, rather it is only essential when segmentation is necessary as in some difficult phoneme discrimination tasks (Sato, Tremblay, & Gracco, 2009). Sato et al. (2009) suggest that these findings align with the Hickok and Poeppel (2007) dual stream model of speech perception in that the dorsal auditory-motor circuit is not considered to be a crucial component of adult speech processing, its involvement is necessitated whenever a 'translation of phonological information to an articulatory code is required' (p.6), as is seen in these results where the simple tasks were not affected by TMS to PMC. Further research is necessary to disambiguate aspects of speech perception and speech comprehension in PMC. The literature indicates a role for PMC in some aspects of speech perception such as phoneme segmentation tasks (e.g., Burton, et al., 2000; D'Ausilio, et al., 2009; Sato, et al., 2009), however, it has not addressed whether this area is crucial to speech comprehension, despite the neuropsychological literature indicating that this is not likely to be the case (e.g., Bishop, et al., 1990; Miceli, et al., 1980; Rogalsky, et al., 2011).

There is some indication that motor cortex activity contributes to phonological but not semantic processing. One TMS-MEP study found larger MEP's in motor cortex for both pseudo and rare words, than frequent words (Roy, Craighero, Fabbri-Destro, & Fadiga, 2008; see also Fadiga et al. 2002); therefore this site may be less interested in meaning analysis, rather it may be recruited for phonological processing of rare/new speech stimuli. Kotz et al. (2010) provide compelling support for this interpretation showing that PMC was selectively active for 'meaning-independent' 'phoneme analysis' (e.g., perception of meaningless syllables; Meister, Wilson, Deblieck, Wu, & Iacoboni, 2007; Wilson, et al., 2004), while neighbouring area BA 44/45 was involved in higher level word analysis, activated by real words, not pseudowords. Therefore it may be the case that PMC serves a domain specific function in phoneme analysis (e.g., segmentation, perception of degraded speech, etc.), while the recruitment of LIFG (BA 44/45) may serve a separate function, possibly in accessing lexical/semantic representations and/or difficulty resolution, given that activity in LIFG is often reported when task demands increase (e.g., Duncan & Owen, 2000). There is some indication that the two sites may work in concert with a study showing that activity in BA 44 was a significant predictor of PMC activation for speech listening, suggesting that LIFG may modulate PMC (Watkins & Paus, 2004). Thus, we will now turn to a discussion of the role of LIFG in language processing.

*Divisions within LIFG***.** The LIFG is often separated into three subdivisions as described by Broadmann: BA 44, 45, 47. The specific function of these LIFG regions has received much attention and there is a body of evidence suggesting that phonological tasks activate posterior parts of LIFG (PMC/BA 44), while anterior LIFG (BA 45/47) is often activated by semantic tasks. LIFG has been the focus of much research and has been shown to be active for language tasks across domains such as phonology, semantics, and syntax (Bookheimer, 2002). A great deal of research has been dedicated to the role of LIFG in phonological processing, and has shown activation in posterior LIFG (BA 44 sometimes extending into BA 45) for a wide variety of phonological tasks. Some of these studies have found very similar results to those reported in the PMC literature, for instance, one study reported activation of BA 44/45 for long vowel discrimination to both auditory and visual presentation of words and for explicit acoustic analysis of stimuli (e.g., parsing rapidly changing spectra within tens of ms), but not passive speech listening; thus implicating a possible role for this site in retrieving internal representations about the sound of the stimulus, independent of input modality (Fiez, Raichle, Miezin, & Peterson, 1995). Similarly activation has been reported when participants heard *comprehensible* compressed speech, as well as for (written) rhyme judgements, but, like Kotz et al. (2010), not for incomprehensible speech processing (Poldrack et al., 2001).

Research as early as Ojemann and Mateer (1979) has shown that direct cortical stimulation of pLIFG during surgery disrupts phoneme monitoring; and Bookheimer (2002) presents two main arguments as to the role of pLIFG in phonological processing suggesting that it is either 1) crucial for phonological articulatory rehearsal (e.g., Baddeley's (1992) articulatory loop) or 2) that pLIFG is recruited for processes such as phoneme discrimination and sequencing (Bookheimer, 2002). In line with a role for LIFG in phonological rehearsal, Démonet, Price, Wise, and Frackowiak (1994) found LIFG to be activated by tasks that required participants to sequence phonologically ambiguous stimuli, but this site was not recruited for less complex conditions such as simple phoneme detection, phonetically ambiguous stimuli, or sequential phoneme detection alone, therefore the authors suggest that BA 44/45 is recruited as part of the verbal rehearsal strategy for completing the sequencing task. Similarly, one study forced participants to engage in phonological rehearsal by presenting stimuli visually with either same/different stress assignment or initial vowel sound, and found that TMS to BA 44 significantly disrupted these phonological decisions, but not a pattern span control task (TMS to BA 44 also disrupted a digit span task; Romero, Walsh, & Papagno, 2006). Stimulation of this site has also resulted in disruption of phonological working memory performance for a delayed phonological matching task, but not a visual matching control task (Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004).

In line with a 'higher-level' role for LIFG in phoneme discrimination (etc.), one study varied VOT along a continuum and found that PMC/LIFG was significantly active for higher-level phonological processing (i.e., making decisions on phonetic category structure/resolving phonetic category membership/selection between competing phonetic categories), while, in contrast, STG was activated for lower level processing and was less sensitive to category structure as, the authors suggest, activity is redirected to other higher level processing areas (i.e., LIFG) for such tasks (Blumstein, Myers, & Rissman, 2005). Similarly, Wright, Randall, Marslen-Wilson, and Tyler (2011) report that passive listening of morphologically complex words activated BA 44, indicating, they argue, a role for this region in 'automatic segmentation of spoken words with specific morphological properties' (P.408). Furthermore, one study suggests that pLIFG may be differentially specialised for phoneme *monitoring* near the border with the motor cortex, and phoneme *discrimination* in a slightly more inferior and medial part of pLIFG (Zatorre, Meyer, Gjedde, & Evans, 1996).

LIFG has also long been implicated in semantic processing (Binder, Desai, Graves, & Conant, 2009; Bookheimer, 2002; Noonan, Jefferies, Visser, & Lambon Ralph, submitted; Price, 2010; Vigneau et al., 2006) and some studies have attempted to establish whether functional specialisations within LIFG exist for phonological and semantic processing. Demonet et al. (1992) required sequential phonological monitoring of non-words, and semantic monitoring for positive associations (e.g., ‘mouse’ - ‘smaller than a chicken’), and found BA 44/45 to be active for the phonological task, but no activation for the semantic task in this area (while both tasks activated other parts of the network such as STG for phonology and the temporal lobe and angular gyrus (AG) for semantics). Similarly, Devlin, Matthews, and Rushworth (2003) found enhanced activation in BA 44 for phonological relative to semantic decisions and the reverse for BA 47. They confirmed these findings with a TMS study where stimulation of aLIFG produced a reliable increase in RTs when subjects made semantic decisions, but not for phonological or perceptual control tasks. Although they did not test pLIFG, these results couple nicely with those of Nixon et al. (2004) who produced an increase in error rates for a phonological matching task following pLIFG stimulation, but no disruption following TMS to aLIFG.

Other studies have directly compared the roles of pLIFG and aLIFG in phonological and semantic processing. For example, one fMRI study showed that for passive listening of morphologically complex words pLIFG (BA 44) was selectively activated, while lexical decisions increased activation in BA 47 (Wright et al. 2011). Likewise, Gold and Buckner (2002) found increased activity in posterior LIFG (BA 44/6) for controlled phonological retrieval (decisions about short/long vowel sounds of visually presented words and pseudowords) and BA 45/47 for abstract/concrete semantic decisions. Poldrack et al. (1999) made a similar distinction with BA 47/45 activated for concrete/abstract decisions and BA 44/45 for syllable counting. Gough, Nobre, and Devlin (2005) used TMS to establish this double dissociation within LIFG, requiring participants to make phonological or semantic decisions on pairs of words presented simultaneously. TMS to pLIFG disrupted homophone judgements, reflecting, the authors argue, its role for integrating sensory and motor information. In contrast, TMS to aLIFG disrupted performance for their synonym judgement task, confirming a role for aLIFG in the semantic executive system. This is consistent with Sharp et al.’s (2010) finding that activity increased in aLIFG (BA 47/10) as a function of semantic difficulty and pLIFG (BA 45) for perceptual difficulty. This is complemented by Bokde, Tagamets, Friedman, and Horwitz (2001) who showed functional connectivity of dorsal LIFG (BA 44/45) to posterior brain areas for accessing phonological representations and ventral LIFG (BA 47/11) connections to temporal areas facilitating semantic access.

Fiez (1997) suggests that the ‘neural theme’ of control ties together these LIFG regions, with aLIFG (BA 45/47) contributing to semantic control and pLIFG (BA 44/45) contributing to controlled phonological processing. This is supported by connectivity studies which show pathways between the subdivisions of LIFG to ‘lower level’ posterior brain areas specialised by language domain (e.g., ATL for semantic store); and as with the models of language discussed above (Language Networks), these are described in terms of dorsal and ventral pathways for language. The dorsal pathway along the arcuate fasciculus (AF) and the superior longitudinal fascicle (SLF) has been shown to specifically connect BA 44 and premotor cortices (dorsal PMC and pars opercularis), not extending into the ventrolateral prefrontal cortex, with perisylvian language areas and the parietal lobe (Anwander, Tittgemeyer, von Cramon, Friederici, & Knosche, 2007; Parker et al., 2005; Saur et al., 2008). It should also be noted that there are also less dominant connections along the Extreme Capsule (EmC) from BA 44 to ATL (Anwander, et al., 2007). The ventral ‘comprehension’ pathway has been shown to connect ventrolateral prefrontal cortex (BA 45/47) with the ATL via the EmC and the uncinate fascicle (Anwander, et al., 2007; Friederici, 2009; Saur, et al., 2008). This is also supported by functional connectivity studies which have shown BA 44 to be connected to posterior, dorsal areas such as pSTG, superior pMTG and aIPL, while BA 47 connectivity was to more inferior temporal regions and pMTG/AG (Xiang, Fonteijn, Norris, & Hagoort, 2010). Additionally, BA 45 has been shown to be more strongly connected to the ATL via the EmC, and less dominantly, but similar to BA 44, to parietal and perisylvian language areas via the AF and SLF (Anwander, et al., 2007). Short fibres link BA 44-45 and BA 45-47/12, which some authors suggest provides an anatomical substrate for integrating semantic and phonological information (Gough, et al., 2005; Ihara, Hayakawa, Wei, Munetsuna, & Fujimaki, 2007).

Semantic Network

Semantic Processing in LIFG

The aforementioned studies demonstrate that LIFG is involved in semantic processing, but do not necessarily indicate which aspect it contributes to (e.g., representation, control). Semantic cognition involves both storage of semantic knowledge/representations and control processes that direct our use of language in a context appropriate and time sensitive manner. The literature, which includes studies of patients with various semantic deficits and neuroimaging techniques (such as fMRI, TMS, MEG) implicate a semantic network that includes both a semantic store and a control network that acts upon this store. Patients with semantic dementia (SD), who have atrophy to the anterior temporal lobes (ATL), are highly sensitive to item frequency and are not sensitive to the effects of cueing (i.e., the cue ‘t..’ does not help to retrieve the response ‘tiger’): both of these findings suggest a degraded store of semantic knowledge; thus the ATL are thought to act as a semantic hub for storing semantic representations (Corbett, Jefferies, Ehsan, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006; Lambon Ralph, et al., 2009). In contrast, patients with semantic aphasia (SA) who typically have lesions in frontal or temporoparietal brain areas *do* show effects of cueing and as such are not believed to have degraded knowledge, but rather, show deficits in controlled access to intact semantic representations (Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006). Specifically, their deficit reflects impaired semantic control, which guides access to semantically stored representations about the meanings of words, pictures, sounds, and objects. As such, patients with SA have trouble selecting/detecting relevant semantic associations and rejecting distractor items (Jefferies & Lambon Ralph, 2006). The data from patients with SA is corroborated by fMRI and TMS studies that have shown LIFG to be involved in tasks that increase the demands on semantic control (e.g., Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Whitney, Jefferies, et al., 2011; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2012). For example, TMS to LIFG disrupts judgments on weak, but not strong, semantic associative relationships, indicating a role for this site when top-down processes are engaged to establish the semantic relationship (Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011); and there is a large number of studies showing LIFG recruitment for tasks that manipulate semantic control in various ways (e.g., homonym judgments: Hoenig & Scheef, 2009; Whitney, Grossman, & Kircher, 2009).

There are two main arguments as to the mechanisms that guide context - appropriate semantic processing: the selection (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) and the retrieval (e.g., Wagner, Desmond, Demb, Glover, & Gabrieli, 1997) hypotheses. Thompson-Schill et al. (1997) have advocated a role for LIFG in which control mechanisms play a crucial role in selecting amongst competing alternatives. Across three different semantic tasks (generation, classification and comparison), all varying in their selection demands (hard vs. easy), they consistently showed increased activity in LIFG (BA 44/45) for selection from amongst competing semantic alternatives. Similarly, priming studies have used competitor priming of related semantic material in order to create increased competition/selection, whilst holding retrieval demands constant using repetition conditions, and have reported increased activity in LIFG for selection, but not retrieval (Moss et al., 2005; Thompson-Schill, D'Esposito, & Kan, 1999). While the selection hypothesis suggests that LIFG is only necessary when there are competing representations vying for selection, the retrieval hypothesis suggests that, when automatic processes are insufficient, top-down processes guide controlled retrieval of task relevant information (e.g., in tasks with increased difficulty or ambiguity; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001). For example, manipulating associative strength has been argued to measure/modulate demands on retrieval and in one study participants were required to make strong/weak associative judgments with two or four possible targets (i.e., two manipulations of semantic retrieval: associative strength, number of targets), and found pLIFG to be active across all of their retrieval conditions, but aLIFG was specifically active for the conditions where the cue-target associative relationship was weak (Wagner, et al., 2001), perhaps indicative of a functional dissociation within LIFG, but their data could not speak to this possibility. The retrieval hypothesis has received support from a variety of studies suggesting that LIFG works as part of the executive system contributing to semantic *retrieval* of relevant information (Buckner, Raichle, Miezin, & Petersen, 1996; Demb et al., 1995; Fiez, 1997; Gabrieli, Poldrack, & Desmond, 1998; Kapur et al., 1994; Peterson, Fox, Posner, Mintum, & Raichle, 1988; Wagner, Koutstaal, Maril, Schacter, & Buckner, 2000), in an amodal fashion (Wagner, et al., 1997). As such, the retrieval hypothesis guides selection when cue-target associations are weak, regardless of competition.

In a study that tried to tease apart retrieval and selection, Badre, Poldrack, Pare-Blagoev, Insler, and Wagner (2005) demonstrated a dissociation of the two processes within LIFG: manipulations of associative strength, judgment specificity, congruency and number of targets (i.e., retrieval demands) increased activation in BA 45, while associative strength selectively activated BA 47. This shows, they argue, a graded distinction within LIFG for different aspects of semantic control, with BA 47 recruited exclusively for semantic retrieval and BA 45 for selection (see also: Gold et al., 2006). Other studies have used this dissociation to explain their findings, for example, one study which found increased LIFG activation in response to sentences that ended with an incongruent homonym (Hoenig & Scheef, 2009) claimed that this reflected controlled retrieval processes engaging aLIFG (Bedny, McGill, & Thompson-Schill, 2008; Wagner, et al., 2001; Whitney, et al., 2009), and selection in pLIFG (Bedny, et al., 2008; Devlin, et al., 2003; Thompson-Schill, et al., 1997; Thompson-Schill, et al., 1999). Despite the attempt to tease apart selection and retrieval, it may be more accurate to say that these tasks load these two components differently (i.e., load more heavily on selection or retrieval). Accordingly, Snyder, Banich, and Munakata (2011), showed that when retrieval demands were high, selection did not modulate activity in LIFG, while when the demands on retrieval were low, modulation of activity was seen in LIFG when the demands on selection increased – suggesting that the two processes may interact. Nevertheless, the role for LIFG in semantic control has been shown in numerous studies that have not specifically attempted to manipulate retrieval and selection demands.

It should also be noted that Gold, Balota, Kirchhoff, and Buckner (2005) suggest that LIFG acts as a domain general control centre, with specialisation by domain reserved for posterior brain areas (i.e., BA 6/40 for phonology; posterior temporal lobe for semantics), based on their results where LIFG showed a significant response across phonological and semantic tasks (although there was a greater response in aLIFG for semantic tasks and in pLIFG (near BA 6) for phonological tasks; Gold, et al., 2005; Snyder, Feigenson, & Thompson-Schill, 2007). Rajah, Ames, and D'Esposito (2008) also advocate a domain general role in cognitive control for LIFG, reporting motor (BA 6/8) activation when stimulus number increased, while BA 44/45 was activated for increased response number. In line with these domain general interpretations of LIFG, this site has also been implicated in the Stroop task, the anti-saccade task, choosing context sensitive responses (other than the prepotent response), weighting of information in working memory, competing information in working memory, selection from working memory, and as a supervisory attentional system (Thompson-Schill, 2003). Despite these studies implicating LIFG in other areas of executive processing, it is clear that LIFG plays an important role in the semantic executive control network, regardless of domain specificity. Badre and Wagner (2007) do point out that while other parts of LIFG (i.e., BA 45) are perhaps domain general (Duncan & Owen, 2000); BA 47 may be specific to the semantic domain. This is supported by a recent meta-analysis reporting activation in LIFG across language tasks, but with subtle specialisations along LIFG for phonological and semantic control (Noonan, et al., submitted; also Devlin et al. 2003, Gough et al. 2005).

The larger semantic control network

Posterior Middle temporal Gyrus

Data from patients with SA also indicate a semantic control network that extends beyond LIFG to the inferior parietal cortex (IPS), including angular gyrus (AG), and posterior middle temporal gyrus (pMTG). These patients have lesions to frontal cortex (encompassing LIFG), temporoparietal cortex (encompassing AG and pMTG), or both, and have deficits across a wide range of semantic control tasks spanning modalities (environmental sounds, pictures, object use, and verbal material; Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Corbett, Jefferies, & Ralph, 2011; Jefferies & Lambon Ralph, 2006). Despite very different lesion locations (frontal vs. posterior), the two patient groups manifest very similar deficits of semantic control (Corbett, et al., 2011; Jefferies & Lambon Ralph, 2006; Noonan, Jefferies, Corbett, & Lambon Ralph, 2010); motivating the use of neuroimaging techniques which provide better spatial precision to investigate their relative roles in semantic cognition. Perhaps most strikingly, a recent meta-analysis of fMRI studies revealed pMTG as the second largest cluster (after LIFG) in a comparison of high over low semantic control (Noonan, et al., submitted). Accordingly, many studies have reported activation in both LIFG and pMTG for tasks manipulating semantic control (e.g., Badre, et al., 2005; Whitney, Hymers, Gouws, & Jefferies, submitted; Whitney, Jefferies, et al., 2011). For instance, a recent double prime study found both LIFG and pMTG to be active when the demands on semantic control increased (Whitney, Jefferies, et al., 2011). Furthermore, a recent TMS study found that TMS to either LIFG or pMTG disrupted processing for weakly associated cue-target matching, but not for the strong associations – presumably retrieved automatically, not requiring semantic control (Whitney, Kirk, et al., 2011), complementing fMRI studies showing pMTG and LIFG involvement in semantic association tasks (Badre, et al., 2005; Noppeney, Phillips, & Price, 2004; Wagner, et al., 2001). One study found that when TMS was applied to LIFG, compensatory activity was elicited in pMTG for control demanding semantic tasks (Whitney, et al., submitted). This suggests that the two sites work together in order to retrieve/select semantic information for the given context.

Despite the evidence suggestive of similar pMTG and LIFG involvement in the semantic executive system, there is some evidence to suggest that there are some differences between LIFG and pMTG in their contributions to semantic control. For example, patients with semantic aphasia have lesions in either frontal or temporoparietal areas, but for the most part exhibit similar deficits in semantic control (Jefferies & Lambon Ralph, 2006). However, differences in performance do seem to emerge on some tasks, such as tasks requiring cyclical/repeated access to semantically related items. This task requires participants to identify items that occur in a cycle, where the current target becomes the distractor on subsequent trials and vice versa. The cycles are presented in blocks of either semantically related or unrelated items, where semantically related items show an increase in competition (relative to mixed blocks). While patients with frontal lesions show a decrease in performance across cycles, patients with temporoparietal lesions perform consistently across cycles on these tasks (Gardner et al., 2012; Jefferies, Baker, Doran, & Lambon Ralph, 2007). Therefore, while both LIFG and pMTG contribute to semantic control, their roles may differ in discrete, yet distinct, ways and further research is needed to clarify these roles.

Accordingly, a recent meta-analysis found that while LIFG was involved in tasks requiring either production or comprehension, pMTG seemed to be more specialised to the receptive domain (see also: Price, 2010). Additionally, while LIFG was activated by tasks across language domains (e.g., phonology and semantic), pMTG was highlighted as domain specific (semantic only; Noonan, et al., submitted; see also: Gold et al., 2005; Gold & Buckner, 2002). These findings are in line with a dorsal production route, including LIFG, and a ventral comprehension route – possibly through pMTG as a comprehension hub/interface (e.g., Turken & Dronkers, 2011), to the ATL (Hickok & Poeppel, 2007). However, it should be noted that some studies *do* show pMTG activation in generation tasks (e.g., Martin et al., 1995) and so, the specificity to the receptive domain found in the aforementioned meta-analysis may reflect either a genuine comprehension specialisation or a reporting bias based on task type (Noonan, et al., submitted). As such, this is a possible avenue for further exploration with tasks that make similar demands on semantic control to directly compare the recruitment of pMTG for production and comprehension.

One possibility is that pMTG is recruited for tasks that load on semantic retrieval, while LIFG works on ‘post-retrieval selection’ (Badre, et al., 2005; Bedny, et al., 2008; Gold, et al., 2006). Some studies have reported greater activation in LIFG for tasks with a high degree of semantic competition, and no pMTG modulation by competition, but rather by increased demands on retrieval. For example, Badre et al. (2005) showed increased activation in pLIFG for tasks requiring selection, and in contrast, activation in aLIFG and pMTG for tasks loading on semantic retrieval. This has also been shown in double prime studies – where pMTG has been found to be activate across conditions due to its putative role in retrieval, while LIFG activation is seen only in the high competition conditions (Bedny, et al., 2008; Gold, et al., 2006; Whitney, Jefferies, et al., 2011). It has therefore been suggested that pMTG may act as an 'entry point' for semantic knowledge, by activating semantic representations when automatic retrieval fails/is not possible, working in concert with the LIFG which selects/inhibits amongst competing semantic alternatives (Badre, et al., 2005; Gold, et al., 2006). Therefore, while it is clear that pMTG plays a role in semantic control, its exact contribution is yet to be clarified.

Parietal Cortex

Angular gyrus (AG) and intraparietal sulcus (IPS) have often been reported for tasks requiring semantic control, and as such were key regions to emerge from a recent meta-analysis contrasting high and low semantic control (Noonan, et al., submitted), as well as other meta-analyses of semantic processing (Binder, et al., 2009; Vigneau, et al., 2006). fMRI and TMS studies often report activation on the boundary of AG/IPS for tasks that require some aspect of semantic control such as homonym judgments (e.g., Hoenig & Scheef, 2009; Whitney, Jefferies, et al., 2011), featural semantic judgments (e.g., Sharp, et al., 2010; Whitney, et al., 2012), and other aspects of semantic control (e.g., Bedny, et al., 2008; Hirshorn & Thompson-Schill, 2006; Lee & Dapretto, 2006; Seghier, Fagan, & Price, 2010; Xiang, et al., 2010). One study showed that stimulation of IPS disrupted difficult semantic feature selection tasks and non-semantic feature selection, but not semantic associative judgments, suggesting that the more dorsal aspects of parietal cortex (dAG/IPS) may be sensitive to featural integration (Whitney, et al., 2012). Moreover, a recent fMRI study revealed three segregations within this AG/IPS region, such that: dAG was activated across semantic and non – semantic tasks, mid AG was sensitive to semantic tasks and was overlapping with the default network (i.e., showing deactivations for meaningless tasks), and ventral AG was specifically active for semantic matching (Seghier, et al., 2010). Likewise, dAG/IPS and mid AG emerged as significant clusters in Noonan et al.'s (submitted) contrast of studies requiring high over low semantic control, while vAG emerged when the semantic domain was contrasted with the phonological domain, perhaps due to its role in semantic conceptual identification (Seghier, et al., 2010). Accordingly, AG/IPS has also been shown to be part of the frontoparietal control network (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), and has functional connections to other parts of the semantic control network, with the strongest connections running between: dAG/IPS and BA 45; mid AG and BA 47; and vAG to ATL (Xiang, et al., 2010). These functional connections align well with the aforementioned roles emerging from Seghier et al.'s (2010) study, and as such AG/IPS is an interesting area to study with regard to its specific role in language processing.

Empirical Questions for this Thesis

In view of the literature, this thesis sought to answer questions as to language specialisation along the dimensions of domain (phonological and semantic), modality (verbal and picture) and control (e.g., retrieval and selection), across a distributed network of brain areas. The first question to arise was that of motor cortex contributions to speech perception, in light of recent support for the motor theory of speech perception (e.g., Fadiga, et al., 2002; Meister, et al., 2007; Wilson, et al., 2004). Recent TMS studies have indicated a role for PMC in speech perception, but have only tested the claims of the motor theory along one dimension, namely phonology (e.g., D'Ausilio, et al., 2009; Fadiga, et al., 2002; Wilson, et al., 2004). Therefore they cannot speak to the necessary role of PMC in speech comprehension, which given the literature suggesting a specific role for this site according to task type, is an important empirical question. If motor areas (i.e., PMC) are crucial to speech perception, then stimulation of this area should cause disruption across language domains (i.e., phonological and semantic), therefore, in order to confirm the motor theory, TMS to PMC would need to disrupt processes engaged in more naturalistic speech conditions, such as accessing meaning. We started our exploration of the language network with this question, in order to assess the necessary contribution of PMC to other aspects of speech perception (Chapter 2).

Moreover, while domain specificity has received some attention (e.g., the dissociation within LIFG between phonological and semantic processing; e.g., Devlin, et al., 2003; Gough, et al., 2005; Nixon, et al., 2004), the interaction between domain and control has not been concurrently assessed. For example, many studies have separately shown the phonological/semantic dissociation, and that LIFG is involved in semantic control, but they have not concurrently tested how activation is modulated when the demands on both increase within the same experiment. Therefore, we turned our attention to assessing any specialisations by domain, control and the interaction of the two, across a network of areas previously shown to be involved in linguistic control (LIFG, pMTG, AG/IPS; Chapter 3). Furthermore, while patients with SA show multimodal deficits in semantic control (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Corbett, et al., 2011), there has been no study, to our knowledge, that has simultaneously manipulated the demands on semantic modality and control within the same experiment. Therefore, we again investigated the distributed network of brain areas reported to be involved in semantic control to assess their contribution to semantic control across modality (Chapter 4). Moreover, TMS can be a useful technique when confirming fMRI findings, because often different tasks can elicit large swathes of activation in similar areas, with very subtle specialisation (e.g., phonological and semantic tasks in LIFG), which TMS can help to clarify/confirm. Therefore, we used TMS to probe the role of BA 44, BA 47 and pMTG in phonological and amodal semantic control (Chapter 5).

While the literature clearly indicates that some areas are involved in semantic control (i.e., LIFG, pMTG; e.g., Badre, et al., 2005; Corbett, et al., 2011; Whitney, Jefferies, et al., 2011; Zempleni, Renken, Hoeks, Hoogduin, & Stowe, 2007), the exact control process engaged is still under debate (e.g., selection, retrieval; Badre, et al., 2005; Snyder, et al., 2011; Thompson-Schill, et al., 1997). Therefore, we attempted to disambiguate retrieval and selection processes using a cyclical naming paradigm: we used TMS to investigate the role of LIFG and pMTG in semantic control, specifically along the dimensions of retrieval and selection, as well as the interaction between the two processes (Chapter 6).

Chapter 2: The Selective Role of Dorsal Premotor Cortex in Speech Perception - A role in explicit phoneme judgements but not speech comprehension

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Introduction

A key controversy within the neuroscience of language concerns whether speech perception relies on purely *auditory* mechanisms or *sensorimotor* processing. One account, the motor theory of speech perception, states that brain areas involved in *producing* speech, such as the premotor cortex (PMC), necessarily participate in *understanding* spoken language under normal circumstances (Galantucci, Fowler, & Turvey, 2006; Liberman & Mattingly, 1985; Rizzolatti & Craighero, 2004). On the other hand, many current models of language propose two parallel processing streams: one that runs dorsally for auditory motor integration, and a second, ventral route for 'comprehension' (Hickok & Poeppel, 2004, 2007; Rauschecker & Scott, 2009). Tasks involving speech perception differentially recruit these two routes depending on the extent to which they involve access to articulatory representations and concepts. Crucially, these accounts do not regard PMC as a core part of the ventral stream, which may be sufficient for comprehension of clear auditory input without the involvement of a motor code.

Neuroimaging studies have provided support for the motor theory, reporting motor cortex recruitment during tasks involving phonemic judgements (D'Ausilio, et al., 2009; Meister, et al., 2007; Mottonen & Watkins, 2009), passive speech listening of meaningless monosyllables (i.e., Pulvermuller, et al., 2006; Uppenkamp, et al., 2006; Wilson, et al., 2004), and contrasts of synthetic vowel sounds over non speech stimuli (musical rain; Uppenkamp, et al., 2006). However, functional neuroimaging studies cannot determine whether this motor activation is *essential* to speech perception and the neuropsychological literature largely contradicts this view. Patients with expressive aphasia have severe deficits of language production following lesions to left frontal cortex and the motor theory would predict that these patients should also be impaired on auditory comprehension, however this is often not the case (e.g., Miceli, et al., 1980). They *do* show impairments on explicit perceptual categorisation and phoneme awareness tasks (e.g., identifying the boundary between two phonemes; performing explicit phoneme segmentation), which require access to explicit/categorical phonological representations, but these impairments are not reflected in general comprehension (Basso, et al., 1977;

Bishop, et al., 1990; Blumstein, et al., 1977; Miceli, et al., 1980; Moineau, et al., 2005; Rogalsky, et al., 2011). This dissociation is captured by studies in which patients were impaired on judgements based on perceptual features (same/different judgements), but showed no deficit for spoken word-picture judgements based on the semantic content of the word (Bishop, et al., 1990; Rogalsky, et al., 2011).

Recent Transcranial Magnetic Stimulation (TMS) research has confirmed a focal role for PMC in some speech perception tasks, including speech discrimination of syllables embedded in noise (D'Ausilio, et al., 2009; Meister, et al., 2007), categorical perception (Mottonen & Watkins, 2009), and phoneme discrimination of nonsense syllables (Sato, et al., 2009). While these TMS studies indicate that PMC plays an important role in explicit phoneme judgements, an important caveat remains: other aspects of speech processing, such as mapping sounds onto meaning (Marslen-Wilson & Warren, 1994; Morais & Kolinsky, 1994), may proceed without the involvement of motor speech areas. Early auditory processes do not necessarily resolve ambiguities in the input: instead, some models of speech perception suggest that uncertainty is cascaded downstream. Phonological ambiguity does not pose a problem for semantic access, at least under normal circumstances, since semantically-related items are rarely also phonologically-related and comprehension is constrained by context (for example, input which is acoustically ambiguous at the mid-point of /pa/ and /ba/ is sufficient to identify a family member). In contrast, categorical perception and explicit phoneme judgements require participants to access categorical representations of phonology in the absence of meaning. In these circumstances, the articulatory features represented within PMC may be recruited in order to ‘tune up’ phonological processing, allowing the activation within auditory and articulatory areas to settle on a specific phoneme. Similarly, Gaskell, Quinlan et al. (2008) describe a model in which categorical representations of phonemes are formed during speech perception, but are not required for word recognition, which instead relies on a non-categorical representation of speech. This view finds support in studies where ‘naturalistic’ speech comprehension (e.g., listening to intelligible natural sentences) does not recruit motor areas (e.g., Scott, Blank, Rosen, & Wise, 2000; Spitsyna, Warren, Scott, Turkheimer, & Wise, 2006); however when perceptual and also semantic difficulty increases (i.e., acoustically degraded speech where the degree of semantic relatedness between words is weak), activation can be seen in frontal and parietal areas (e.g., Sharp, et al., 2010).

The current study addressed this possibility using the 1 Hz paradigm to induce 'virtual lesions' in language areas of the left hemisphere. Repetitive trains of TMS were delivered to transiently disrupt the neural processing of the underlying tissue, manifested in the concurrent behavioural disruption of tasks reliant on this area. We examined the effects of dorsal premotor stimulation on the speech perception processes necessary to support explicit phoneme judgements, as well as the comprehension of spoken words to allow extraction of meaning. The motor theory of speech perception suggests that both tasks should show disruption (indicating that dPMC is necessary for both phoneme judgement and semantic tasks), while a selective effect on phonological decisions only would point to a more restricted role for dPMC, which would not be compatible with the view that motor processes contribute to speech perception in normal comprehension. TMS to PMC was compared with stimulation of two additional sites: 1) posterior superior temporal gyrus (pSTG), which is uncontroversially recruited during normal auditory processing (Buchsbaum, et al., 2001; Hickok & Poeppel, 2007; Scott, 2005; Scott & Johnsrude, 2003; Seghier et al., 2004) and therefore expected to disrupt performance on *both* tasks and 2) occipital pole (OP), a control site allowing us to characterise any non-specific effects of stimulation.

Method

Design

A within-subjects 2x3x3 factorial design was employed, including TMS (no stimulation vs. stimulation), task (phonological, semantic, visual control) and site (OP, PMC, pSTG) as factors. We employed an rTMS virtual lesion method, delivering a low-frequency train of rTMS pulses offline. Participants then performed the task immediately after stimulation, allowing us to rule out the possibility that the loud clicks associated with each pulse, jaw contractions, or eye blinks following peripheral nerve stimulation disrupted performance on the behavioural tasks. Participants performed the baseline testing (without TMS) either *before* TMS stimulation, or completed baseline testing 30 minutes *after* TMS stimulation (by which time the effects should no longer be present; Lambon Ralph, et al., 2009; Pobric, Jefferies, & Lambon Ralph, 2007; Pobric, et al., 2009; Whitney, Kirk, et al., 2011). The order of baseline testing was counterbalanced across sessions for each participant. The study made use of a non-linguistic control task (scrambled pictures to ensure that disruption was task-specific) and a control stimulation site (OP; to ensure that the effects were not due to non-specific effects of TMS).

Participants

Fifteen right handed, native English speakers who were recruited from the University of York student population were examined in the study (nine males; mean age = 21.8, SD = 2.4). All participants were reimbursed £30 for their time. Four participants were replaced due to difficulties co-registering brain images with scalp locations, and one due to technical problems during testing (N = 5). One participant from our final sample, who was identified as an outlier in the phonological and semantic conditions for PMC and OP, was excluded from the analysis. All participants passed safety screening for MRI and TMS, were free from any history of neurological disease or mental illness and were not taking any medication. Each participant gave their informed consent before each TMS testing session began, and the experiment was reviewed and approved by the York Neuroimaging Centre Ethics Board.

Tasks

The probe words for the phonological and the semantic tasks were presented auditorily, with the targets presented visually. A two alternative forced choice (2AFC) format was used across all three tasks (phonological, semantic, visual control; see Table 2-1). In the phonological task, participants had to decide which phoneme they had heard at the end of a word (e.g., auditory probe “cart”, with the answer choices ‘t’ and ‘p’ on the left and right hand sides of the screen; both response options produced real words). In the semantic task, participants had to make a decision about which semantic category the auditory probe word belonged to (e.g., auditory probe “cart”, with choices “manmade” and “natural”). There were six types of semantic decision within the experiment (concrete/abstract, manmade/natural, nice/nasty, hear/see, large/small, and action/object). In the visual control task, a probe image of a scrambled face appeared at the top of the screen and participants were asked which of two scrambled figures below was identical to the probe. The non-identical figures were produced by rotating the target image through 90°.

Condition	Phonological		Semantic		Control	
Probe	“cart”		“cart”			
Target	p	t	manmade	natural		

Table 2-1: Task conditions. The target item is underlined.

Stimuli

The auditory stimuli were cross-spliced spoken words taken from a previous study; these were modified in order to increase difficulty whilst minimising error rates (Gaskell, Quinlan, Tamminen, & Cleland, 2008). The stimuli were constructed from word pairs (such as job-jog): the final phoneme from one word (i.e., /b/) was attached to the onset and vowel of the second word (i.e., /jo/ of “jog”) and the final phoneme was then attenuated, in order to increase task difficulty when making explicit phoneme judgements. In pilot testing, task performance at different levels of attenuation (12.5%, 25%, 50%) was examined for each item, and the final level of attenuation was selected to maximise difficulty while minimising the error rate (given our primary dependent measure was response time; RT; median level of attenuation 12.5%). The same auditory probes were used across tasks but were never repeated within one testing session, for example, items presented in the phonological task in week 1 were not presented in the semantic task in week 1, but could occur in the opposite order (semantic/phonological) in week 2. The stimuli in the visual control task were pictures of faces, scrambled into 100 blocks rendering them unrecognisable.

Procedure

A PC running E-Prime software was used to present the tasks and record accuracy and RT. Responses were given with left and right index fingers corresponding to the positions of the two response options on the screen. The language tasks started with a fixation screen for 250ms followed by the presentation of the target and distractor (e.g., for ‘carp’, ‘p’ is the target and ‘t’ is the distractor) for 500ms, followed by the auditory probe, after which participants were required to make a response. The participant's response triggered the next trial. For the visual control task, the probe and targets appeared on screen simultaneously.

The experiment began with a practice block, to familiarise participants with the tasks (6 trials per task type). There were 30 experimental trials per task (semantic, phonological, control), with participants performing a total of 90 trials per condition (baseline, post-TMS). No trials were repeated within a session, but some trials (less than 20%) were repeated across sessions (i.e., one week later). The order in which the trials occurred was randomised and the order in which the tasks were presented was pseudo-randomised across participants. Each task block was preceded by a screen which informed participants of the new task type, and participants pressed the space bar to continue. The different categories within the semantic task were presented in mini-blocks, and again there was an instruction screen at the start of each one, indicating the type of decision participants would be making (e.g., concrete or abstract).

Selection of TMS Sites

Structural T1-weighted MRI scans were used to identify sites for stimulation in each participants' brain. Sites were identified from previous functional neuroimaging and TMS studies of speech perception and an average peak coordinate was taken. The coordinates contributing to the left PMC site came from Sato et al. (2009), Meister et al. (2007), Wilson et al. (2004), Vigneau et al. (2006) and D'Ausilio et al. (2009), producing the following coordinates: -52.67, -6.67, 43 (MNI). The left pSTG site was taken from Meister et al. (2007), Okada and Hickok (2006), Dehaene-Lambertz et al. (2005), and Zevin and McCandliss (2005) producing the following coordinates: -59.56, -30.53, 7.08 (MNI). These sites were then transformed into each participant's individual brain space. The left occipital pole was measured as 20mm superior and 10 mm left of the inion, as in previous TMS studies (e.g., Ishibashi, Lambon Ralph, Saito, & Pobric, 2011).

For 11 participants, the MRI structural image was co-registered to the participant's scalp using an Ascension Minibird magnetic tracking device (www.ascension-tech.com) in conjunction with MRIreg software (www.mricro.com/mrireg.html). Five anatomical landmarks were identified for co-registration (tip of nose, bridge of nose, vertex, left/right tragus). Stimulation coordinates were transformed into individual subject space using the transformation matrix from the 'segment' function in SPM5. For the remaining participants, Brainsight 2 (Rogue Research, Montreal Canada, www.rogue-research.com/) was used to co-register participant brains and to identify stimulation sites prior to rTMS administration. Four landmarks were used for co-registering the participants head to their brain image (tip of the nose, bridge of the nose, left/right tragus).

Stimulation Parameters

Before TMS testing began, individual active motor threshold was established in each testing session. This was determined by the lowest stimulation intensity required to elicit visible contraction of the first dorsal interosseous (FDI) muscle in the contralateral hand. Motor thresholds ranged between 38% and 65% of maximum stimulator output, with an average of 49% of stimulator output. A 70mm figure of eight coil, attached to a MagStim Rapid2 stimulator was used to deliver the magnetic pulses. Repetitive trains of TMS were applied at 1Hz for 10 minutes; participants were stimulated at 120% of their motor threshold. We used a coil orientation established as the least uncomfortable for participants prior to stimulation, as it has been shown that orientation does not reliably influence behavioural effects (Niyazov, Butler, Kadah, Epstein, & Hu, 2005).

Data Analysis

TMS disruption was expected to manifest itself in delayed RT, rather than a decline in accuracy (Walsh & Cowey, 2000), since the behavioural task was designed to be as demanding as possible whilst minimising error rates. The analyses therefore examined RT for correct responses, within 1.5 standard deviations of the mean (accuracy data are provided in Table 2-2). The predictions of this study were confirmed using paired t-tests to examine if the predicted TMS effects were significant at each site (one-tailed), along with within-participants ANOVA (all two-tailed) to test for the predicted interactions between TMS and task at each site (i.e., to establish an interaction of task and TMS for PMC). Separate ANOVAs (all two-tailed) were used to examine site x TMS interactions for each task.

	PMC		pSTG		OP	
	Baseline	TMS	Baseline	TMS	Baseline	TMS
Control	96.99	94.84	96.99	96.77	97.20	96.77
	(.92)	(2.01)	(1.2)	(1.0)	(.82)	(1.09)
Phonological	94.62	92.26	90.54	91.61	94.62	92.69
	(1.77)	(1.86)	(2.1)	(2.51)	(1.16)	(1.56)
Semantic	87.96	85.16	88.82	82.15	87.96	87.53
	(2.15)	(1.88)	(1.66)	(2.33)	(2.17)	(2.2)

Table 2-2: Accuracy Data. PMC = Premotor Cortex. pSTG = posterior Superior Temporal Gyrus. OP = occipital pole. Average accuracy, standard error in parentheses. The only paired comparison that reached significance in accuracy was between the TMS and no-TMS conditions for pSTG and the semantic task (t(14) = 2.981, p = .01).

Results

Premotor cortex

Paired sample t-tests confirmed our prediction that PMC is involved in phoneme judgements but not semantic judgements: phonological judgements were significantly slowed by TMS to this site (*t*(14) = -2.03, *p* < .05), while, crucially, the semantic task was unaffected (t(14) = 1.07, *p* > 0.1). There was also no disruption of the control task after TMS to PMC (t(14) < 1). A within-participants ANOVA was used to confirm that the two language tasks were affected differently by TMS: this analysis revealed a significant main effect of task (F(1,14) = 34.67, *p* < .001) and a significant interaction of task by TMS (F(1,14) = 4.66, *p* < .05; see Figure 2-1).

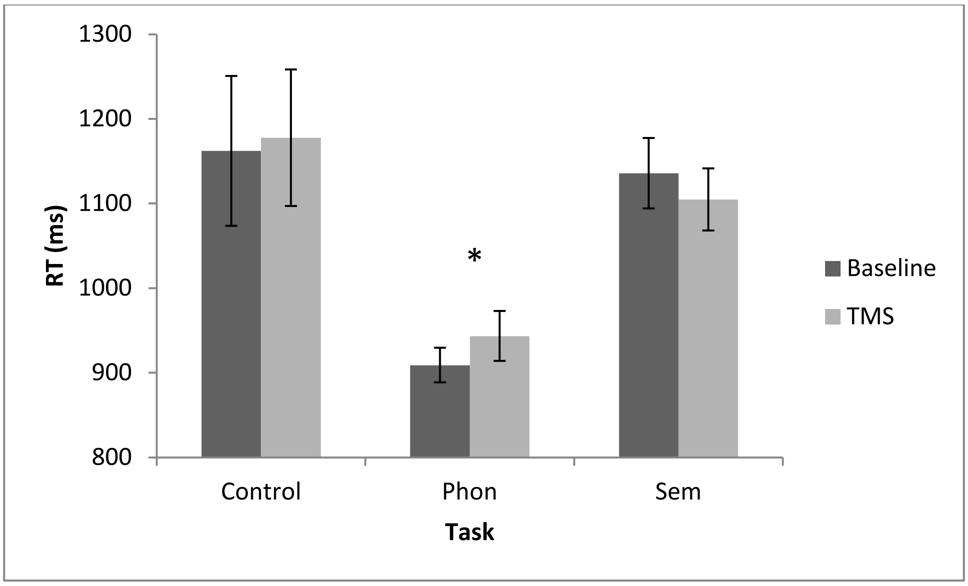

Figure 2-1: Premotor Cortex (PMC). TMS to PMC produces significant slowing of the phonological task but not the semantic task. Error bars represent standard error of the mean. Stars represent significant slowing after TMS (p < .05).

One potential concern relating to the previous analysis is that anatomical landmarks might not be a good guide to localisation of function in specific individuals, and therefore TMS may have been applied to a non-relevant site in at least some of the participants (potentially masking its effect on both tasks). To confirm that TMS failed to disrupt the semantic task, even when it was applied to a site confirmed to be functionally relevant, we selected those participants (n=11) who showed the expected TMS-induced disruption of phoneme detection for PMC (i.e., slowing of 0 ms or more). We were then able to establish if there were TMS effects on the other two tasks. Again, both the control and the semantic task showed no effect of TMS to PMC (t(10) < 1). The phonological task did, unsurprisingly, show a significant disruption after TMS to PMC (t(10) = -3.78, *p* < .01) and a direct comparison of the two language tasks confirmed a significant interaction of task by TMS (F(1,10) = 7.36, *p* < .05; see Figure 2-2).

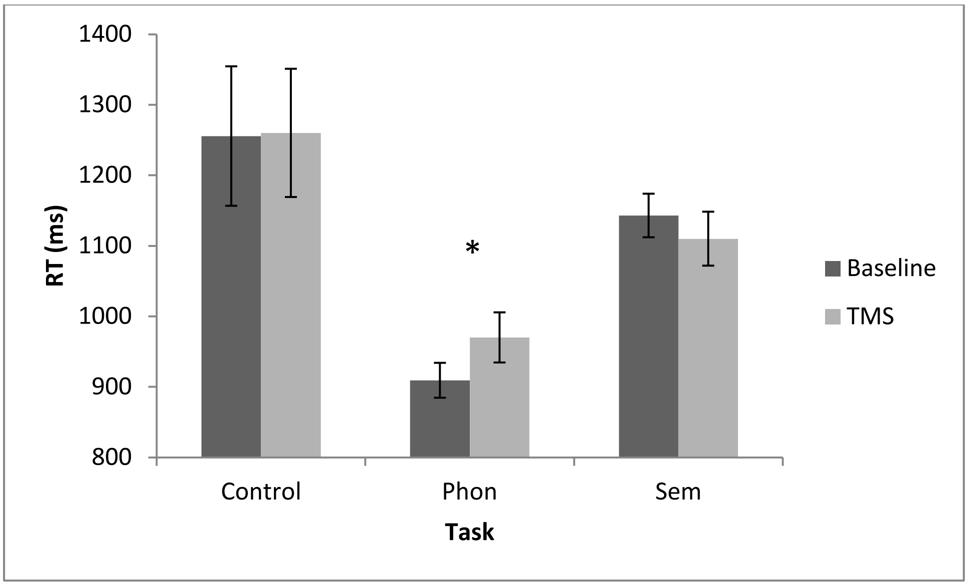

Figure 2-2: Functionally Localised Premotor Cortex (PMC). TMS to functionally localised PMC shows a significant slowing of the phonological task but not the semantic or control task. Error bars represent standard error of the mean. Stars represent significant slowing after TMS (p < .05).

Posterior Superior Temporal Gyrus

Paired sample t-tests confirmed our prediction that pSTG is involved in both phonological and semantic judgements to spoken words. TMS had a significant effect on both phoneme judgements (t(14) = -1.77, *p* ≤ .05) and semantic judgements (t(14) = -2.40, *p* < .05), but there was no effect on the control task (t(14) < 1). A within-participants ANOVA confirmed that the two language tasks were equally sensitive to disruption by TMS: there was a significant main effect of task (F(1,14) = 42.54, *p* < .001) and TMS (F(1,14) = 5.47, *p* < .05), but no interaction (F(1,14) = 2.93, *p* > 0.1; see Figure 2-3).

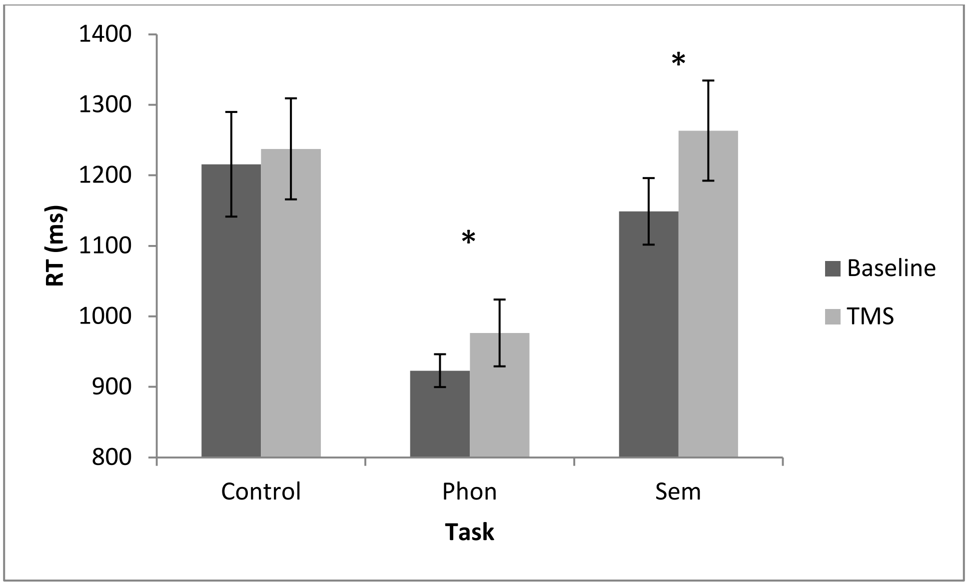

Figure 2-3: Posterior Superior Temporal Gyurs (pSTG). TMS to pSTG shows significant slowing for both phonological and semantic tasks. Error bars represent standard error of the mean. Stars represent significant slowing after TMS (p < .05).

Occipital Pole

As predicted, there was no disruption to any task after TMS to OP: paired t-tests were non-significant for all tasks (t(14) < 1 in all cases). A direct comparison between the two language tasks showed a significant main effect of task (F(1,14) = 63.62, *p* < .001), no effect of TMS (F(1,14) < 1) and no interaction (F(1,14) < 1; see Figure 2-4).

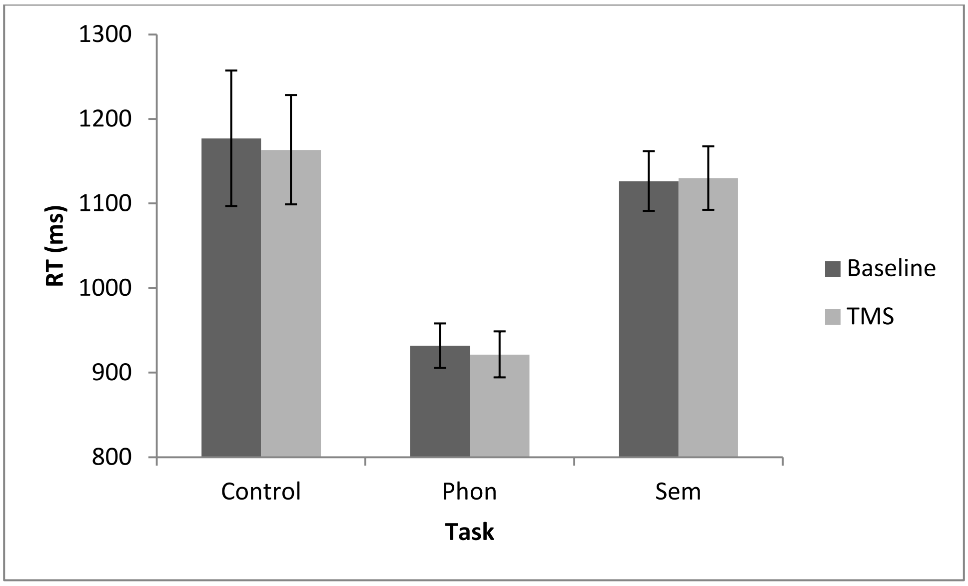

Figure 2-4: Occipital Pole (OP). TMS to OP shows no effect for any of the tasks. Error bars represent standard error of the mean.

Between Sites Comparison

As the control task revealed no significant TMS effects for any of the sites, it was not included in this analysis. A 3 x 2 x 2 within-participants ANOVA exploring the interactions between site, task and TMS revealed a significant site by TMS interaction (F(2, 28) = 5.61, $p < .01$), confirming that the TMS effects were site specific (i.e., disruption following stimulation of PMC and pSTG, not OP). There was also a significant three way interaction (F(2, 28) = 3.69, $p = .038$), confirming that the interaction of task and TMS was site specific (i.e., phonological task disruption for PMC, both language tasks disrupted by TMS to pSTG).

Discussion

This study reveals that premotor cortex (PMC) plays a restricted role in the perception of spoken language. We explored the effects of TMS stimulation on a phoneme judgement and a semantic decision task. This study also made use of a control task which required challenging visual judgements in the absence of language or auditory processing, to demonstrate that any TMS effects were specific to the auditory speech domain. The results revealed that TMS stimulation of dPMC disrupted explicit phonological judgements, but not semantic decisions to the same stimuli. Stimulation of a second region, posterior superior temporal gyrus (pSTG), containing auditory association cortex, produced disruption of *both* language tasks. Since the TMS effects at this site were equivalent for phonological and semantic decisions, we can be confident that the selective effects of PMC stimulation do not reflect general susceptibility of phoneme judgements to interference. A control site, occipital pole (OP), confirmed that the TMS effects were site-specific: TMS to OP did not affect performance on any of the tasks. Moreover, there were no effects of TMS on the visual control task at any of the sites, confirming that the effects we observed were specific to the language domain.

This study reveals that the role of dPMC is constrained to phoneme judgements. In contrast, some theories advocate a necessary and automatic role for motor speech representations in speech perception, an idea which has received support from the discovery of mirror neurons (Rizzolatti & Craighero, 2004; but see, Gallese, Gernsbacher, Heyes, Hickok, & Iacoboni, 2011), and neuroimaging studies (Fadiga, et al., 2002; Pulvermuller, et al., 2006; Uppenkamp, et al., 2006; Watkins & Paus, 2004; Watkins, et al., 2003; Wilson, et al., 2004). As functional neuroimaging methods cannot confirm that PMC activity plays a *necessary* role in speech perception, TMS has been used in several studies to show that stimulation of this region does disrupt speech perception tasks (D'Ausilio, et al., 2009; Fadiga, et al., 2002; Meister, et al., 2007; Mottonen & Watkins, 2009; Sato, et al., 2009). However, all of these TMS studies, as well as the majority of fMRI studies, have used explicit phoneme judgements which have additional metalinguistic and cognitive control demands (Pulvermuller, et al., 2006; Uppenkamp, et al., 2006; Wilson, et al., 2004). This research cannot demonstrate, therefore, that PMC plays a vital role in speech perception in simple/naturalistic situations, such as the comprehension of spoken words. Additionally, evidence from patient studies suggests that motor areas may only be crucial for tasks that require overt segmentation or explicit phoneme awareness, and not for speech comprehension (e.g., Basso, et al., 1977; Bishop, et al., 1990; Rogalsky, et al., 2011). However, patients typically have large and variable lesions and consequently these studies lack spatial resolution. Neither functional neuroimaging nor neuropsychological methods are ideally placed to confirm an essential role for a specific region such as PMC in aspects of speech recognition. In the current study, we overcame these limitations through the use of TMS to produce relatively focal disruption of processing within PMC in healthy participants.

The current findings complement previous TMS findings by confirming the role of the PMC in explicit phoneme judgement tasks (e.g., D'Ausilio, et al., 2009; Meister, et al., 2007; Mottonen & Watkins, 2009), but crucially the study reveals that dPMC is not necessary for mapping sound to meaning. A dissociation between auditory comprehension and explicit phoneme discrimination tasks fits well with a current model of spoken word recognition (Gaskell, Quinlan et al., 2008), and has clear parallels in the neuropsychological literature (Blumstein, et al., 1977; Miceli, et al., 1980). For example, Miceli et al. (1980) reported 19 patients whose performance on phonological discrimination tasks was pathological, but their performance on word (or sentence level) comprehension tasks was normal. Patient studies in which the same stimuli are used across phonological discrimination and comprehension tasks have also confirmed this discrimination/comprehension dissociation (e.g., Bishop, et al., 1990; Rogalsky, et al., 2011). Patients with impaired speech production performed more poorly than controls on syllable discrimination (i.e., same or different? “boy”-“voy”), but crucially, not on picture-syllable matching (i.e., a picture of a boy, and asked “Is this a voy?” or “Is this a boy?”; Bishop et al., 1980). The current study shows a similar dissociation but with higher anatomical specificity, confirming that this pattern follows stimulation of dPMC in healthy participants.

There is strong connectivity between pSTG and PMC (Catani, Jones, & ffytche, 2005; Osnes, Hugdahl, & Specht, 2011; Pulvermuller & Fadiga, 2010; Saur, et al., 2008): what might account for the selective recruitment of motor areas in this large-scale distributed language network? (1) dPMC may be involved in strategic modulation of the speech perception process in non-natural/challenging conditions such as repetition and learning of new words, when speech perception is challenging (Burton, et al., 2000; Demonet, et al., 1992). (2) It could also provide a back-up mechanism for processing degraded auditory stimuli. Recent support for this explanation comes from Osnes, Hugdahl et al. (2011), who saw a decrease in PMC activation as speech became less distorted (see also Devlin & Aydelott, 2009; Scott, et al., 2009). (3) dPMC recruitment may also be necessitated when explicit knowledge of phoneme segments is required (Hickok & Poeppel, 2000; Rogalsky, et al., 2011; Sato, et al., 2009), for example in non-natural language tasks such as explicit phoneme judgements, where *metalinguistic knowledge about speech sounds*, not words, is used to guide phoneme segmentation (Rogalsky, et al., 2011). Early support for this comes from Zatorre et al. (1992) who found syllable judgements, but not passive listening, revealed activation in Broca's area bordering PMC (also corroborated by Burton, et al., 2000). Difficult explicit judgements about the constituent sounds of words may be aided by mental simulation within action systems. In order to establish that there is a /t/ not a /p/ at the end of "cart", for example, participants may generate the motor plan for "cart" and decide if this overlaps with the articulation of /t/ (Halle & Stevens, 1962; Yuen, et al., 2009). In contrast, when listening to "cart" and deciding if this is a natural or man-made object, auditory representations may be mapped to meaning more directly along the ventral language route (Hickok & Poeppel, 2007).

In most circumstances, task difficulty and the requirement to employ explicit phoneme knowledge are correlated. The TMS study of Sato, Tremblay et al. (2009) revealed that PMC was *not* recruited for *simple* phoneme and syllable discriminations; it was only essential for *difficult* phoneme discrimination tasks requiring segmentation. While the results of this study are consistent with ours, difficult tasks are often thought of as more vulnerable to TMS effects in a variety of tasks (Devlin & Watkins, 2007) and Sato et al. (2009) did not include a control site to demonstrate that disruption of the difficult phonological task was specific to PMC. The current findings address this shortcoming, as the selective pattern of interference seen for PMC in the current study was not reproduced following TMS to another site within the language network (pSTG) or a non-language control site (OP).

In summary, the current study made use of two language tasks, a visual control task and three test sites (dPMC, pSTG, OP) to address the crucial question as to whether dPMC recruitment is necessary for all speech perception processes, as postulated by the motor theory of speech perception (Galantucci, et al., 2006; Liberman & Mattingly, 1985; Rizzolatti & Craighero, 2004). We revealed that although previous research has implicated PMC in speech perception, its role is confined to explicit phoneme judgement tasks and does not extend to the semantic domain.

Chapter 3: An fMRI Investigation of Phonological and Semantic Control across Language Networks

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Introduction

Two key issues concerning the language networks distributed throughout the cortex are 1) which/how these networks are specific to different types of content and 2) the modulation of the networks by task demands (i.e., difficulty). Chapter 2 elucidated the specific role of premotor cortex (PMC) in speech perception: TMS to PMC disrupted phonological, but not semantic judgements. However, this region is part of a larger network contributing to both representation and control, and a natural question leading on from the confirmation of a domain specific response at a particular site is the interaction of domain and control. Therefore, this chapter will focus on phonological and semantic control across a wider network using fMRI (PMC, left inferior frontal gyrus (LIFG), posterior middle temporal gyrus (pMTG), and parietal cortex).

Premotor cortex

There has been some support for the motor theory of speech perception (Galantucci, et al., 2006) from neuroimaging and TMS studies showing PMC involvement for speech perception tasks (e.g.,Fadiga, et al., 2002; Liberman & Mattingly, 1985; Pulvermuller, et al., 2006; Uppenkamp, et al., 2006; Watkins & Paus, 2004; Watkins, et al., 2003; Wilson, et al., 2004). However, these tasks require participants to make metalinguistic judgements, which are not a naturalistic assessment of speech perception. Recent studies using ‘naturalistic’ listening/reading (comprehension) tasks, with no explicit task requirements, have reported activation in superior temporal sulcus (STS)/superior temporal gyrus (STG)/temporoparietal (TP) and anterior temporal lobe (ATL) regions, but *no activation* in areas previously shown to be active for tasks requiring control, such as PMC, LIFG and pMTG (Spitsyna, et al., 2006). Our TMS results (Chapter 2) support these findings demonstrating a role for PMC in non-natural speech perception tasks, but not access to meaning. Additionally, studies of patients with expressive aphasia have lesions to left frontal cortex and show marked impairment in language production. Contrary to the predictions of the motor theory of speech perception, these patients do not show deficits in global comprehension (e.g.,Miceli, et al., 1980), but *do* show impairment on explicit perceptual categorization tasks (i.e., identifying the acoustic boundary between two phonemes) that are not reflected in general comprehension (Basso, et al., 1977; Moineau, et al., 2005). Many studies in healthy populations provide evidence that corroborates these neuropsychological findings, such as studies showing premotor response to non-native speech sounds (i.e., ingressive clicks; Agnew, McGettigan, & Scott, 2011), syllable judgements but not passive listening (Zatorre, et al., 1992), segmentation of consonants not simple speech discrimination (Burton, et al., 2000), discerning phonetically ambiguous speech (Gow Jr & Segawa, 2009), as well as one study showing that simple phoneme discrimination does not necessitate PMC with recruitment only necessary for more challenging phoneme discrimination tasks (Sato, et al., 2009), and our finding that TMS to PMC disrupted phoneme, but not semantic decisions (Chapter 2); these findings all speak to a non-essential role for PMC in speech perception. This suggests that while motor areas may be recruited in some language tasks, they are not necessary for general comprehension of clear auditory input. While Chapter 2 provided evidence for a non essential role for PMC in general comprehension – the exact nature of the role of PMC remains unclear. For example, is PMC recruitment modulated by difficulty across linguistic tasks, or restricted to the phonological domain – if at all.

Left Inferior Frontal Gyrus

Many studies reporting PMC involvement in speech perception tasks also report activation spreading into pLIFG (Noonan, et al., submitted; Price, 2010; Vigneau, et al., 2006); and much research has investigated the contribution of LIFG to linguistic processing, with numerous studies exploring specialisation for different domains (e.g., phonology or semantics). Many studies report posterior recruitment of LIFG (BA 44) for tasks requiring phonological decisions (e.g., Blumstein, et al., 2005; Nixon, et al., 2004; Ojemann & Mateer, 1979; Poldrack, et al., 2001; Romero, et al., 2006), and anterior recruitment (BA 45/47) for tasks that are semantic in nature (e.g., Badre, et al., 2005; Devlin, et al., 2003; Wagner, et al., 2001; Whitney, Kirk, et al., 2011). As such, there is evidence to suggest a graded response along LIFG for phonological and semantic input; and some studies have directly compared the two domains in LIFG, in order to confirm this posterior-anterior phonological-semantic dissociation within the same experiment (e.g., Bokde, et al., 2001; Gough, et al., 2005; Koechlin & Jubault, 2006; Poldrack, et al., 1999). A theory that unites these studies is the idea that LIFG contributes to linguistic *control* (Fiez, 1997), which finds support in a recent meta-analysis which showed that phonological and semantic tasks activated the entire LIFG, but with subtle distinctions: specialisation in posterior IFG for phonology and anterior IFG for semantic control (Noonan, et al., submitted). However, very few studies have simultaneously manipulated domain (semantic vs. phonology) and difficulty/control demands.

There are, however, some studies that have attempted to manipulate control demands while also investigating domain specificity in LIFG. For example, Snyder et al. (2007) used a factorial design, with high and low conflict conditions for semantic similarity (global vs. specific) and vowel sound judgements. However, the high conflict phonological judgements required participants to inhibit semantic information, thereby confounding the direct comparison of phonological and semantic control in LIFG. Another study used challenging phonological and semantic tasks, but rather than comparing them to easy versions of the same task, they were compared to a baseline task, thus domain and difficulty (easy vs. hard) could not be directly compared (Gold, et al., 2005). Therefore, our study tried to assess the degree to which subdivisions of LIFG are modulated by domain, difficulty and the interaction of the two.

Posterior Middle Temporal Gyrus

While the role of LIFG in linguistic processing has been widely studied, the role of pMTG remains less certain. The neuropsychological literature indicates a role for this site in semantic control, as patients with lesions to temporoparietal cortex show marked impairments on tasks requiring controlled access to semantic representations (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006). Additionally, it has been shown to be involved in tasks requiring semantic control in both fMRI (Badre, et al., 2005; Noppeney, et al., 2004; Whitney, et al., submitted; Whitney, Jefferies, et al., 2011; Zempleni, et al., 2007) and TMS (Whitney, Kirk, et al., 2011; Whitney, et al., 2012); and in a recent meta-analysis it was the second largest cluster to result from a comparison of high – low semantic control (Noonan, et al., submitted). It has also been shown to respond to tool use (Kable, Kan, Wilson, Thompson-Schill, & Chatterjee, 2005) and actions/verbs (Kable, et al., 2005; Tranel, Martin, Damasio, Grabowski, & Hichwa, 2005), which may, as noted by Noonan et al. (submitted), indicate that this area is sensitive to changing context (many of these tasks require participants to generate a verb given a noun). This site has also been implicated in models of language as an interface between speech representations in superior temporal gyrus (STG) and conceptual representations in the anterior temporal lobes (ATL; Hickok & Poeppel, 2007). Moreover, connectivity studies have suggested that this site acts as a ‘cortical hub’, due to its rich structural and functional connectivity throughout the language network: this may indicate a role for this site in both semantic and phonological control, as it has up to six major pathways connecting with it. Therefore, our study was interested in investigating the degree to which pMTG is domain specific, given a recent meta-analysis that found this site to contribute exclusively to the semantic domain (specifically control; Noonan, et al., submitted), and as such also measure this sites contribution to control.

Parietal Cortex

Another area often implicated in the language network is angular gyrus (AG)/intraparietal sulcus (IPS): it has emerged as a key site activated by semantic material in numerous meta-analyses (Binder, et al., 2009; Noonan, et al., submitted; Vigneau, et al., 2006). This site has also been shown to be involved in a wide range of tasks such as semantic (Demonet, et al., 1992; Noonan, et al., submitted; Sharp, et al., 2010; Vigneau, et al., 2006), sentence comprehension (Mashal, Faust, Hendler, & Jung-Beeman, 2009; Obleser & Kotz, 2010), reading (Carreiras et al., 2009) visual search/attention (i.e., feature and conjunction search; Donner et al., 2000; Donner et al., 2002), number comparison tasks (Gobel, Walsh, & Rushworth, 2001), and, even, left/right decisions (Hirnstein, Bayer, Ellison, & Hausmann, 2011). Therefore it is not surprising that it has been implicated as part of the multi-demand network (Duncan, 2010). Likewise, Seghier et al. (2004) report that dorsal AG responded to both semantic and non-semantic material, consistent with the multi-demand network; while the response in other parts of AG, such as mid AG, was less domain general and was found to be specifically involved in word reading and semantic associations. Additionally, AG activation has been reported for semantic tasks, while meaningless tasks cause deactivation, further implicating it as a part of the semantic network (Binder et al., 1999; Noonan, et al., submitted; Seghier, et al., 2004). Despite activation in this area being reported across various task types (language and non-language tasks), there are few reports of phonological tasks eliciting AG activation (and AG is not reported in either of these meta-analyses for phonology: Noonan, et al., submitted; Vigneau, et al., 2006), with most studies reporting the activation in supramarginal gyrus (e.g., Noonan, et al., submitted; Vigneau, et al., 2006) or parietal operculum (e.g., Sharp, et al., 2010). This makes AG an interesting site to examine, as two recent investigations suggest graded functional specialisations across AG for semantic, domain general and default networks (Noonan, et al., submitted; Seghier, et al., 2004).

This study assesses the contribution of PMC, LIFG, pMTG and AG to phonological and semantic control, using fMRI, with a paradigm where task format is matched as well as manipulating difficulty across both language domains. Therefore, we could assess the increased activity in each of these brain areas for heightened difficulty which was both specific to and shared across domains. In line with the findings from Chapter 2, as well as other research suggesting a restricted role for PMC in speech perception (e.g., Lotto, Hickok, & Holt, 2009; Rogalsky, et al., 2011; Scott, et al., 2009), we hypothesised that activation in PMC would be restricted to resolving phonological, but not semantic, judgements. Additionally, the previous literature indicates a functional graded distinction along LIFG for phonological and semantic tasks (e.g., Gough, et al., 2005; Poldrack, et al., 1999; Vigneau, et al., 2006). Therefore, we predicted a heightened response in posterior LIFG (BA 44) for phonological tasks, potentially modulated by difficulty (i.e., additional recruitment for the phonological hard condition in comparison with the semantic hard, while possibly still resolving difficulty in both domains); the opposite effect was expected in anterior LIFG (BA 47). The specificity of BA 45 is less certain as it is often reported for both task types, and has in some cases been suggested as an integration zone for phonological and semantic material (Gough, et al., 2005; Hagoort, 2005; Ihara, et al., 2007), therefore it was predicted that this site may not show a specific preference for either task (i.e., domain general response). We predicted that pMTG would show a modulation with task difficulty for the semantic judgements, given previous studies showing its involvement in semantic control (Noonan, et al., submitted; Whitney, et al., submitted; Whitney, Jefferies, et al., 2011; Whitney, Kirk, et al., 2011; Whitney, et al., 2012). Additionally, pMTG recruitment for the phonological tasks was not predicted, as it did not emerge as a key site in the comparison of phonology > semantics in a recent meta-analysis, but did emerge in the reverse contrast (Noonan, et al., submitted). The last key area to be investigated was AG, where much research has shown a response to semantic tasks, but its contribution to phonological tasks is somewhat unclear. In line with the multi-demand network and other studies showing dAG/IPS activation for a range of tasks, we expected dAG/IPS to be activated by tasks requiring semantic control, as well as likely being activated by difficult phonological judgements. In mid AG, we expected activation for the semantic tasks as this site has been shown to be active for semantic associations (independent of stimulus input; Seghier, et al., 2004); it’s contribution to phonological tasks is less clear, however, the previous findings of mid AG involvement in word reading suggested that this site may also be activated by the phonological tasks as reading involves access to phonology.

Method

Design

A within subjects 2 x 2 factorial design was used for the behavioural tasks, with task (phonological, semantic verbal) and difficulty (hard/easy) as factors.

Participants

Twenty-three participants were examined in the study (16 males; mean age = 23.2, SD = 2.9). One participant was removed as their accuracy was too low (53%) and yielded too few trials to include in the analysis. All participants examined were right handed, native English speakers recruited from the University of York student population and the general York population, and were compensated £10 for their time. All participants were screened for MRI safety.

Tasks

Each task involved auditory presentation of a probe word and a target and two distracters presented on screen. A three alternative forced choice (3AFC) format was used for both tasks (see Table 1). The hard phonological task required participants to match a phoneme from the auditory probe word to the correct target, which had the relevant phoneme missing. Participants performed this task in mini-blocks in which they were instructed as to which phoneme to pay attention to (i.e., “match first”, “match last”). The task consisted of an auditory probe and three answer choices (for example, a “match last” trial would consist of an auditory probe “duck” and three on-screen choices (e.g., <u>tru_</u> - _gar - ga_), where matching “ck” to “tru” is the correct response (truck). The phonological easy task required participants to make rhyme judgements: they heard an auditory probe such as “duck” and were required to choose the appropriate rhyming word from three on-screen choices (e.g., “duck” – <u>truck</u> – cigar – game), which in this case would be “truck”. Eye-rhymes were also used to prevent participants from simply matching based on orthography. The semantic verbal hard and easy tasks involved making associative judgements to semantic stimuli, where probes and targets either share low (hard) or high (easy) semantic associations. For example, an easy association (highly associated words) would include an auditory probe, “duck”, and three answer choices such as <u>lake</u> – cigar – door, with lake being the correct response. A hard trial (lowly associated words), the association may be duck – gun, a less prevalent association for either word to the other (Table 3-1).

	Probe	**Target**	**Distractor 1**	**Distractor 2**
Phonological Easy	“duck”	truck	cigar	game
Phonological Hard	“duck”	tru_	_gar	ga_
Semantic Easy	“duck”	lake	cigar	door
Semantic Hard	“duck”	gun	cigar	door

Table 3-1: Task conditions.

Stimuli

Stimuli were auditory probes, and target and distractors appeared on a black screen in succession. Auditory probes were recorded by a male native English speaker, using Audacity (http://audacity.sourceforge.net/), in a sound-proof room. The stimuli were normalised for volume and power by digitally scaling them in Matlab (www.mathworks.co.uk/), producing a level of -25db root mean square. The MRI auditory stimulus system (MR Confon mkII+, www.mr-confon.de/en/products.html) presentation is calibrated to give a maximum level of 80-90 db. The same probes were used for hard and easy versions of the two tasks, and the same probes were used across semantic and phonological tasks (however, there were additional probes for the semantic condition, that did not appear in the phonological task, due to the experimental design in which another semantic task also occurred in the same scanning session[1]). Stimuli were acquired from the MRC psycholinguistic database (search criteria: concrete nouns, concreteness and imageability > 500; Coltheart, 1981; Wilson, 1988). Targets and distractors were developed using the MRC psycholinguistic database (phonological hard), two websites (www.rhymezone.com and www.rhymer.com) were used for the phonological easy task, and the Edinburgh Association Thesaurus (http://www.eat.rl.ac.uk/) for the semantic tasks. There were no significant differences for target words across task and condition for written frequency (F(3, 357) < 1) or word length (F(3, 357) = 1.087, *p* = .355). However, the semantic and phonological targets did differ on imageability (F(3, 282) = 10.656, *p* < .001). Additionally, there were no significant differences for imageability between hard and easy

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[1] Participants completed three tasks in the scanner: easy/hard phonological, easy/hard verbal semantic association judgements, and easy/hard picture semantic association judgements which will be discussed in chapter 4.

conditions of each task (phonological: t(116) = -1.395, *p* = .166; semantic: t(142) = -.532, *p* = .595).

Procedure

A PC running Presentation 13.1 software (Neurobehavioural Systems, www.neurobs.com) was used to present the tasks and record accuracy and RT. Responses were given with the left hand, with three buttons corresponding to the positions of the three response options on the screen. The tasks started with a fixation screen for a jittered amount of time (500 – 2000 ms) followed by the auditory probe and the on-screen target and distracters. Participants were required to make a response, which triggered the next trial, if no response was given after a maximum of 5 secs the experiment would move onto the next trial.

The experiment began with a practice prior to entering the MRI scanner, to familiarise participants with the tasks. The experimental task consisted of 45 experimental trials per task type and difficulty manipulation (phonological (hard/easy), semantic verbal (hard/easy), semantic picture (hard/easy)), with participants performing a total of 270 trials. The tasks were presented in mini blocks of 15 trials per block, with a total of 18 blocks (3 blocks per condition). Each mini-block was followed by 7 secs of rest, with a fixation cross on the screen. The order in which the trials occurred was pseudo-randomised and the order in which the tasks were presented was counterbalanced across participants. Each task block was preceded by a screen which informed participants of the new task type: the duration of this instruction screen was 1 sec. Participants also performed a picture semantic task, which was interleaved with the other tasks explained above: this task is discussed in the next chapter.

Image Acquisition

Data were acquired with a GE 3 Tesla HD Excite MRI scanner at the York Neuroimaging Centre (YNiC), in a single scanning session. A Magnex, 8 channel, gradient insert head coil with a birdcage, radio frequency coil tuned to 127.4MHz was used. A gradient-echo EPI sequence was used to collect data from 39 contiguous axial slices (TR 3s, TE = 25 ms, FOV 260 mm^2, matrix size = 128 x 128, slice thickness = 3.5 mm). Structural MRI images were acquired with a resolution of 1 mm x 1 mm x 1 mm. The functional data was co-registered onto structural T1-weighted images (TR = 8.03, TE = 3.07 ms, FOV 290 mm x

290 mm x 176 mm, matrix size 256 x 256 x 176, slice thickness = 1.13 mm x 1.13 mm x 1 mm). Functional data was additionally co-registered to T1 – weighted FLAIR images (5.6 mm x 5.6 mm x 3.5 mm), taken in the same plane as the EPI slices with interleaved slice acquisition.

Data Analysis

An event related design was used in which accurate responses only were used in the analysis. All first-level and higher-level analyses were run using FEAT (FMRI Expert Analysis Tool) Version 5.98, in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Prior to inferential statistical analysis the following pre-processing was applied: Individual brain extraction (BET) to remove non-brain material from images for co-registration of the functional data, MCFLIRT motion correction (using fMRIB's Linear Registration Tool), slice timing correction using Fourier-space time-series phase shifting (Sinc interpolation with a Hanning-windowing kernel), FWHM 6.0 mm spatial smoothing (Gaussian Kernel), high-pass temporal filtering (Gaussian – weighted least – squares straight line fitting, with sigma = 100 sec). We used FILM (FILM; FMRIB's Improved Linear Model) nonparametric estimation of time series autocorrelation to fit the model to the data, on all lower-level analyses. FSL's canonical gamma HRF was used to model the HRF response with a temporal derivative of 6 seconds. The first two volumes were removed to match the NFI presentation files and volumes collected by the scanner. To analyse the data at the group level, we entered lower level FEAT directories into a higher level FLAME (FMRIB'S Local Analysis of Mixed Effects) Bayesian mixed effects analysis (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $z > 2.3$ and a (corrected) cluster significance threshold of $p < .05$ (Worsley, 2001).

Each task and condition was modelled separately using event based explanatory variables (EV) which were convolved to the haemodynamic response function (gamma function). The haemodynamic response function was aligned to the beginning of each correct trial and lasted for the duration of the event. Incorrect/removed trials were modelled as a separate EV, therefore, any data not modelled was included as rest. Several contrasts were run (11 total): A contrast against rest/baseline was conducted for each task (phonological easy, phonological hard, semantic verbal easy, semantic verbal hard, semantic picture easy, semantic picture hard), the hard version of each task was also contrasted against the corresponding easy version (phonological hard – phonological easy, semantic verbal hard – semantic verbal easy, etc.), contrasts of semantic verbal – rhyme judgements and of semantic picture – semantic verbal were also included.

Region of Interest Analysis

Each region of interest was created using ALE maps (Figure 3-1) resulting from a high – low semantic control analysis in a recent meta-analysis investigating semantic control (Noonan, et al., submitted). These ALE maps were converted into MNI space using FLIRT (fMRIB's Linear Registration Tool) and the 'colin1.1.nii' (http://www.brainmap.org/ale/) and standard 'MNI152_T1_2mm_brain' (FSL-4.1) images were used to align the two coordinate spaces, in order to transform the Talairach ALE maps into MNI space maps. Each relevant ROI was created by using the 'draw tool' in FLSVIEW to remove/erase areas not needed for each individual ROI (e.g., for the AG ROI, LIFG activation was removed and vice-versa). The individual demarcations of LIFG (BA 44, 45, 47) were created by using the Harvard-Oxford Cortical Structural Atlas ROIs (thresholded at 25) and multiplying (using fslmaths) them by the LIFG mask from the ALE maps. BA 44 was created using 'Inferior Frontal Gyrus, pars opercularis' and BA 45 using 'Inferior Frontal Gyrus, pars triangularis'. BA 47 was created using 'Frontal Orbital Cortex' thresholded at 30 in order to avoid overlap with the posterior LIFG ROIs. Fslmaths was used to ensure that each ROI was unilateral and 'binarised' (containing only ones and zeroes). An additional concern was that while we were using ROIs that were known to be involved in linguistic control (i.e., the contrast between high – low control for semantic tasks within the Noonan et al., submitted, meta-analysis), we may be truncating activation specific to phonology at the extents of the ROIs used (particularly LIFG), therefore we supplemented our LIFG ROI with an ROI of PMC/BA44 from an ALE map of phonology > semantics and an aLIFG ROI from an analysis of semantics > phonology (Noonan, et al., submitted), to capture any truncated activation in the high > low semantic control ROI of LIFG (Figure 3-1b). The PMC and pSTG ROI were created using fslmaths to create spheres around the coordinates used in chapter 2. The pSTG sphere was 10mm in size to capture all of the coordinates which contributed to the mean TMS coordinate, and the PMC sphere was 9mm to capture all of the dorsal PMC coordinates in the TMS coordinate. The ROIs were analysed using the FSL FEAT tool, as in the whole brain analysis, but here we applied pre-threshold masking to constrain the search of activation to voxels within a given ROI. These Z (Gaussianised T/F) statistical images were voxel corrected for multiple comparisons within the ROI volume (*p* < .05; Worsley, 2001), as the voxel-based correction method has good localisation power and we were interested in the gradient of functional specialisation within our ROIS (in contrast, cluster size inference favours the detection of larger regions of activation). Additionally, the featquery tool was used to interrogate the FEAT results for each participant and extract mean parameter estimates (pe) for percent signal change of the voxels defined by each ROI for each task contrasted over rest. These values were converted to percent signal change, and were then subjected to ANOVA analysis.

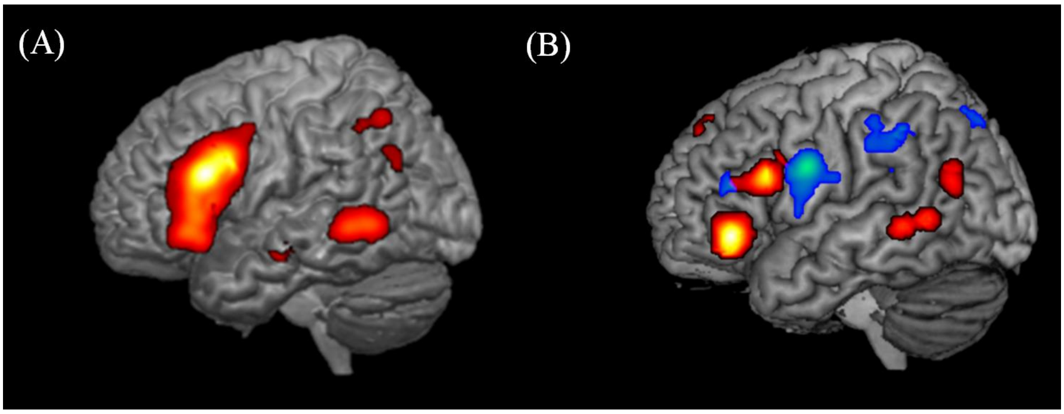

Figure 3-1. ALE maps resulting from contrasts of (A) high – low semantic control and (B) phonology > semantic (blue activation) and semantic > phonology (red activation).

Results

Behavioural Results

The assignment of semantic associations to easy or hard conditions was based on each participant's reaction time (RT) across all accurate trials. There were 90 verbal semantic and 90 phonological trials in total, and an RT was recorded for each trial. In order to maximise the difference between easy and hard trials, the fastest one third (of the total accurate trials) were taken for each participant for the easy semantic condition; as well as the slowest one third (of the total accurate trials) were taken for the semantic hard condition. The phonological tasks could not be collapsed in a parallel way because the easy and difficult phonological judgements were different: whereas the semantic tasks always involved the same instructions – find the associated word – and only the strength of the association changed, the phonological judgements involved two different types of decisions (easy rhyme vs hard segment – match). Therefore, the fastest 24 rhyme trials were taken and the fastest 24 segment (phonological hard) trials were taken, in order to keep the semantic and phonological hard/easy tasks well matched. 24 trials for each condition were taken because this was the average number of trials used for each semantic condition for each participant. We could not use the same criterion as in the semantic task, since using 1/3 of the trials would have resulted in a maximum of 15 usable trials (45/3 = 15) per condition. This method ensured that the effects we were modelling for easy and hard conditions were maximally distinct in terms of difficulty and not overlapping. This analysis was used because our original assignment of trials to easy and hard conditions revealed a large degree of overlap for the semantic conditions - also meaning the semantic and phonological tasks were not well matched on RT (Figure 3-2; also see Appendix 3.1 and Appendix 3.2 for the original RT analysis and fMRI results).

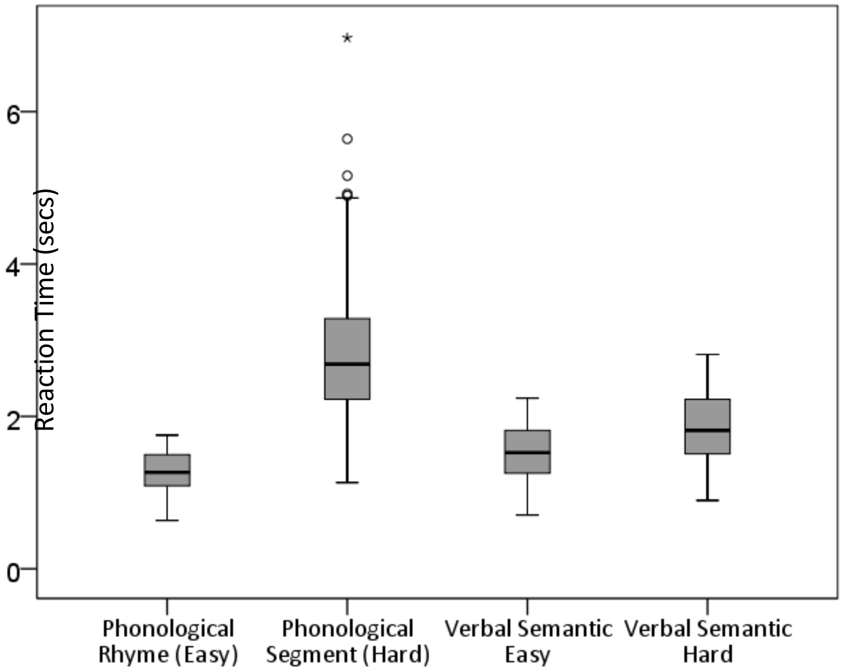

Figure 3-2. RTs for the original designation of easy and hard trials, where semantic RTs were highly overlapping for the hard and easy conditions, thus phonological hard and easy conditions did not align well in RT to semantic hard/easy RTs. Error bars indicate minimum and maximum RTs, circles (1.5 IQR) and stars (3 IQR) indicate outliers.

Analysis of RTs Used for the Event Related fMRI Analysis

A comparison of RTs, for correct responses only across both verbal tasks revealed no overall difference between the two task types (F(1, 21) = 2.279, *p* = .146), while the difficulty manipulation, unsurprisingly, was highly significant across both tasks (F(1, 21) =

1059.232, *p* < .001). Difficulty affected both tasks to the same degree, since there was no significant interaction of task by difficulty (F(1, 21) = 1.023, *p* = .323). This suggests that both tasks and difficulty manipulations were well matched at the behavioural level within our stimuli subset (Figure 3-3).

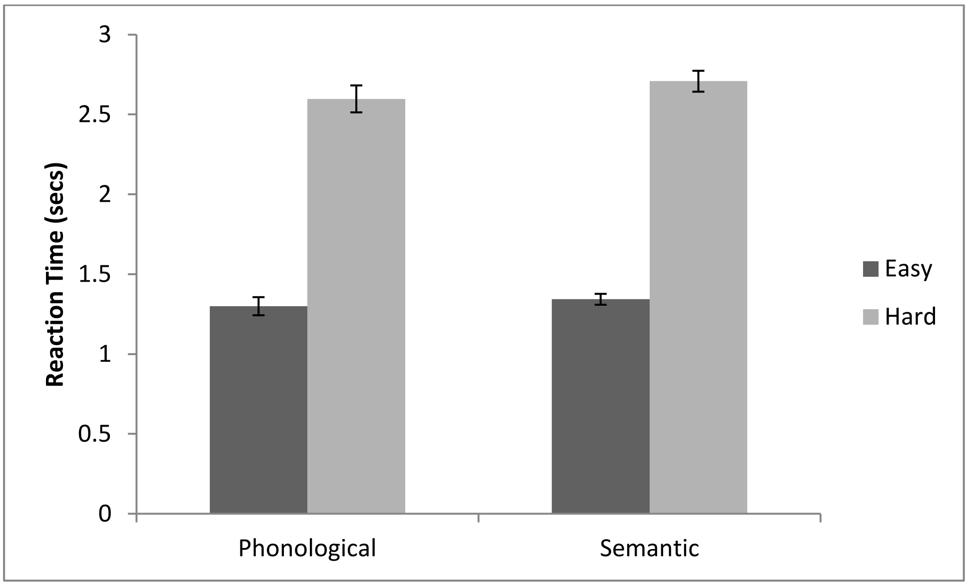

Figure 3-3. Behavioural reaction time for correct responses. Error bars indicate standard error of the mean.

Whole Brain Analyses

To investigate which areas were activated by the two domains (phonological and verbal semantic), a whole brain analysis was used to reveal which areas were active against rest for the hard versions of the tasks (cluster corrected, *p* < .05). This ensured that we were capturing activation for these tasks, without the risk of cancelling out mutual activity using contrasts (i.e., activity seen in both the hard and easy conditions, which would be cancelled out in a hard > easy contrast). This analysis revealed common activity throughout LIFG (BA 44, 45, 47), right posterior IFG, left and right parietal areas, left and right temporal areas and visual cortex (Figure 3-4). The semantic activation extended further into the left anterior temporal lobe. The phonological task showed additional recruitment across the cortex, especially within posterior parietal cortex (particularly in the right hemisphere). Furthermore, Figure 3-5 and Figure 3-6 reveal activations for each task separately to show areas of peak activation as ‘hotspots’ in each domain. In order to address the potential concern that the phonological hard and easy tasks may activate different areas, an additional figure has been included to demonstrate the large degree of overlap of the two phonological tasks, with some additional recruitment of right IFG and more extensive recruitment of LIFG for the difficult phonological task (Figure 3-7). Additionally, a contrast of semantic > phonological rhyme revealed activation throughout LIFG, AG, pMTG, anterior superior temporal gyrus, and visual cortex (Figure 3-8).

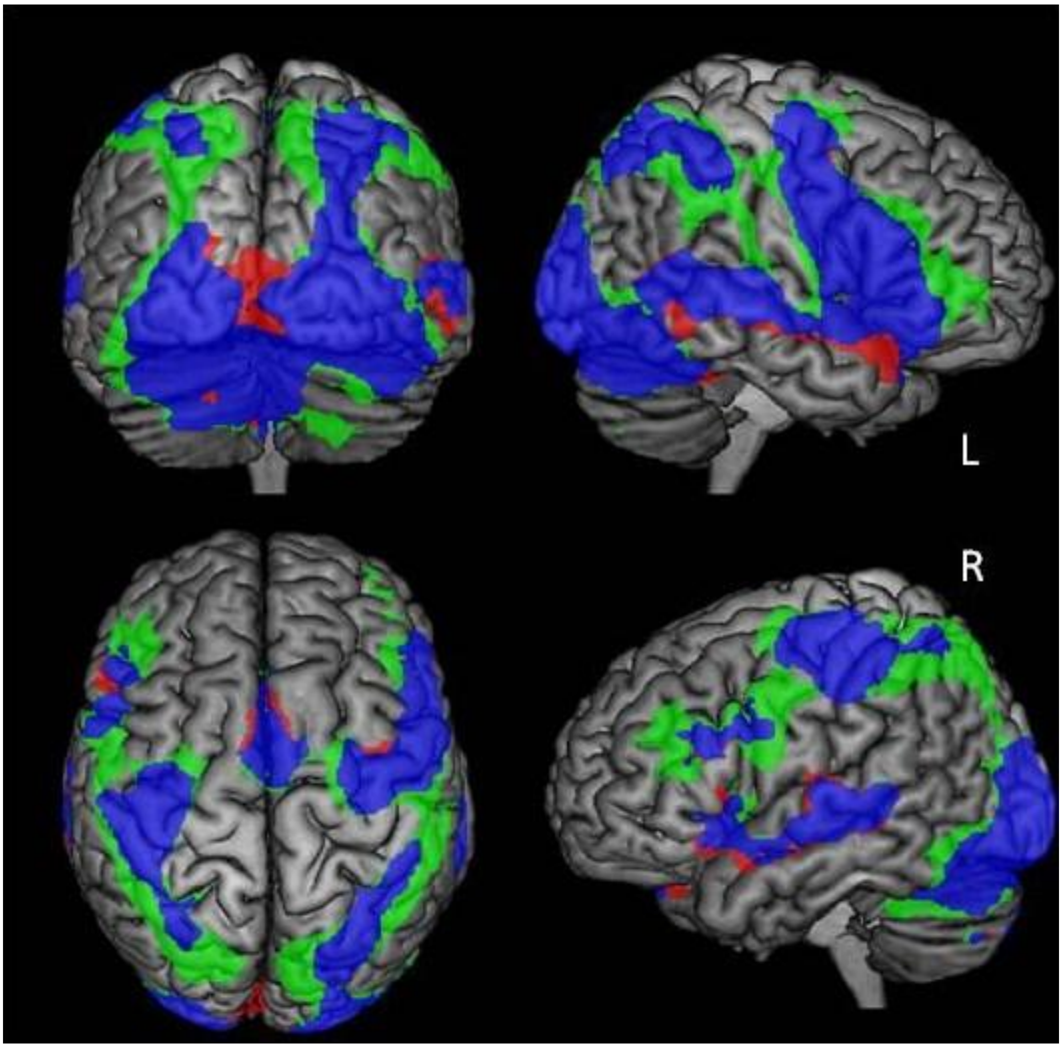

Figure 3-4: Whole brain analysis (cluster correction, $Z \geq 2.3$, $p < .05$). Phonological hard (green), verbal semantic hard (red) and mutual activity (blue). L = left, R = right hemisphere.

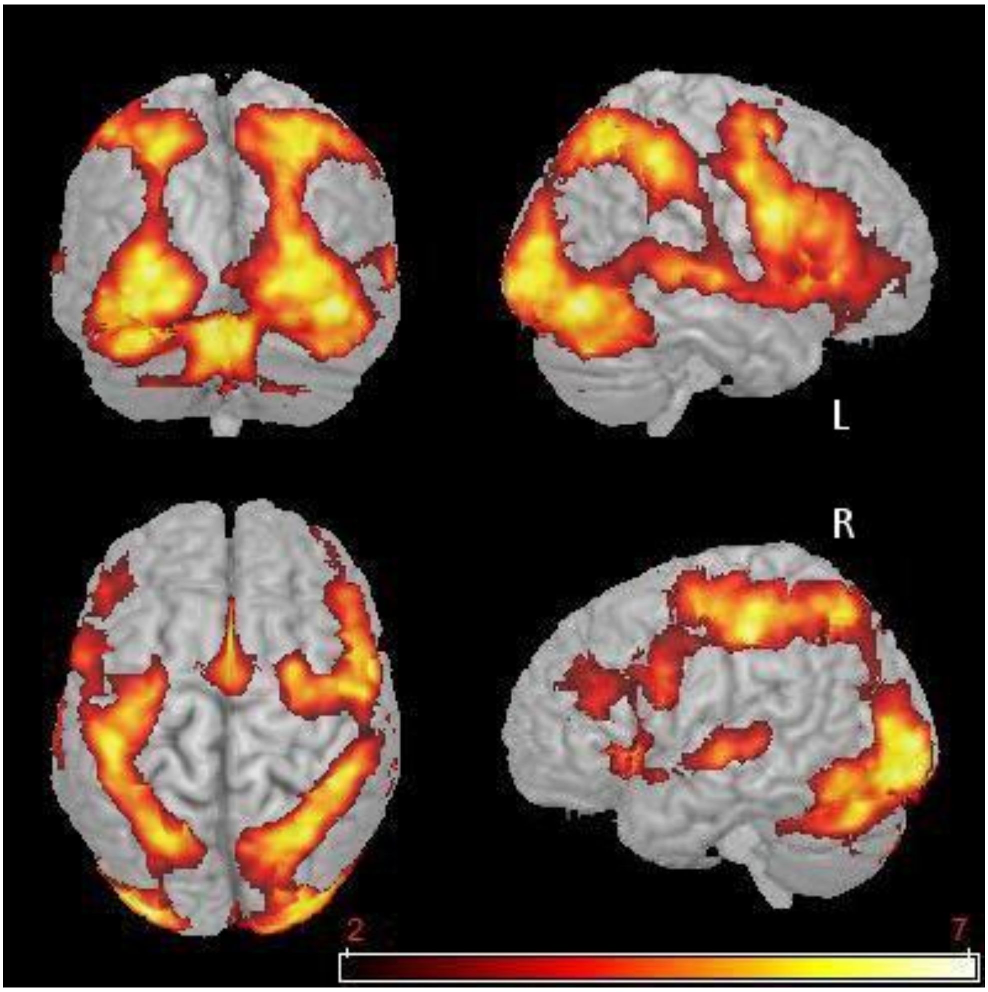

Figure 3-5. Cluster corrected whole brain analysis ($Z \geq 2.3$, $p < .05$) of phonological hard over rest. L = left, R = right hemisphere. *Z* values are indicated on the colour scale.

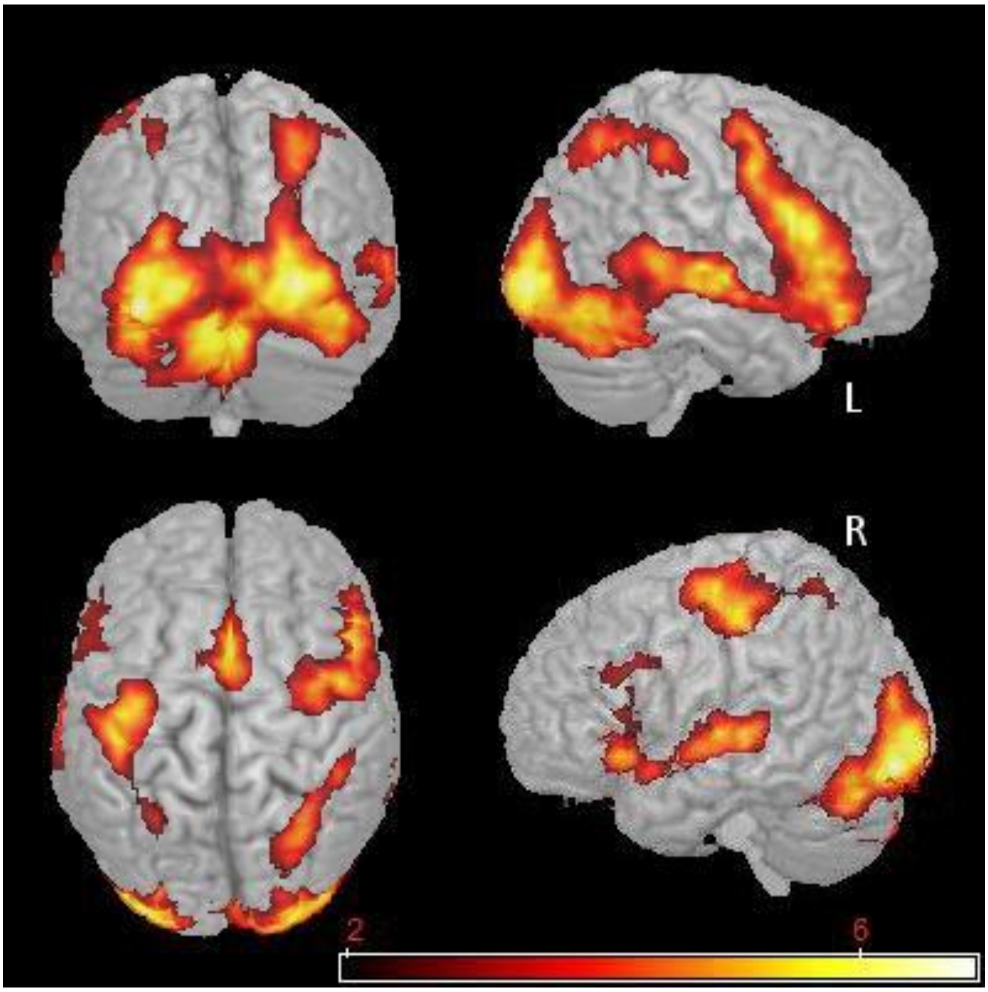

Figure 3-6. Cluster corrected whole brain analysis (*Z* ≥ 2.3, *p* < .05) of semantic verbal hard over rest. L = left, R = right hemisphere. *Z* values are indicated on the colour scale.

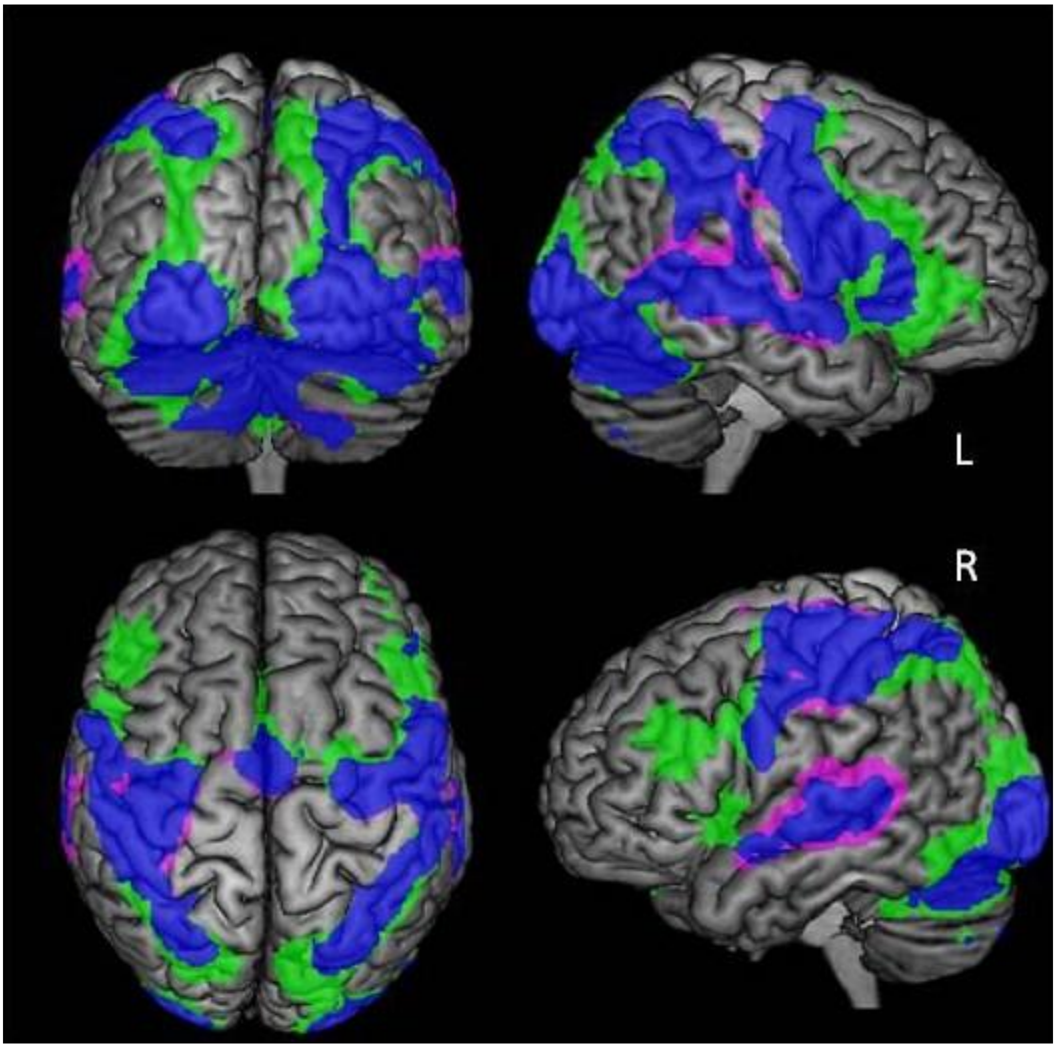

Figure 3-7. Whole brain analysis (cluster correction, *Z* ≥ 2.3, *p* < .05). Phonological hard (green), phonological easy rhyme (violet) and mutual activity (blue). L = left, R = right hemisphere.

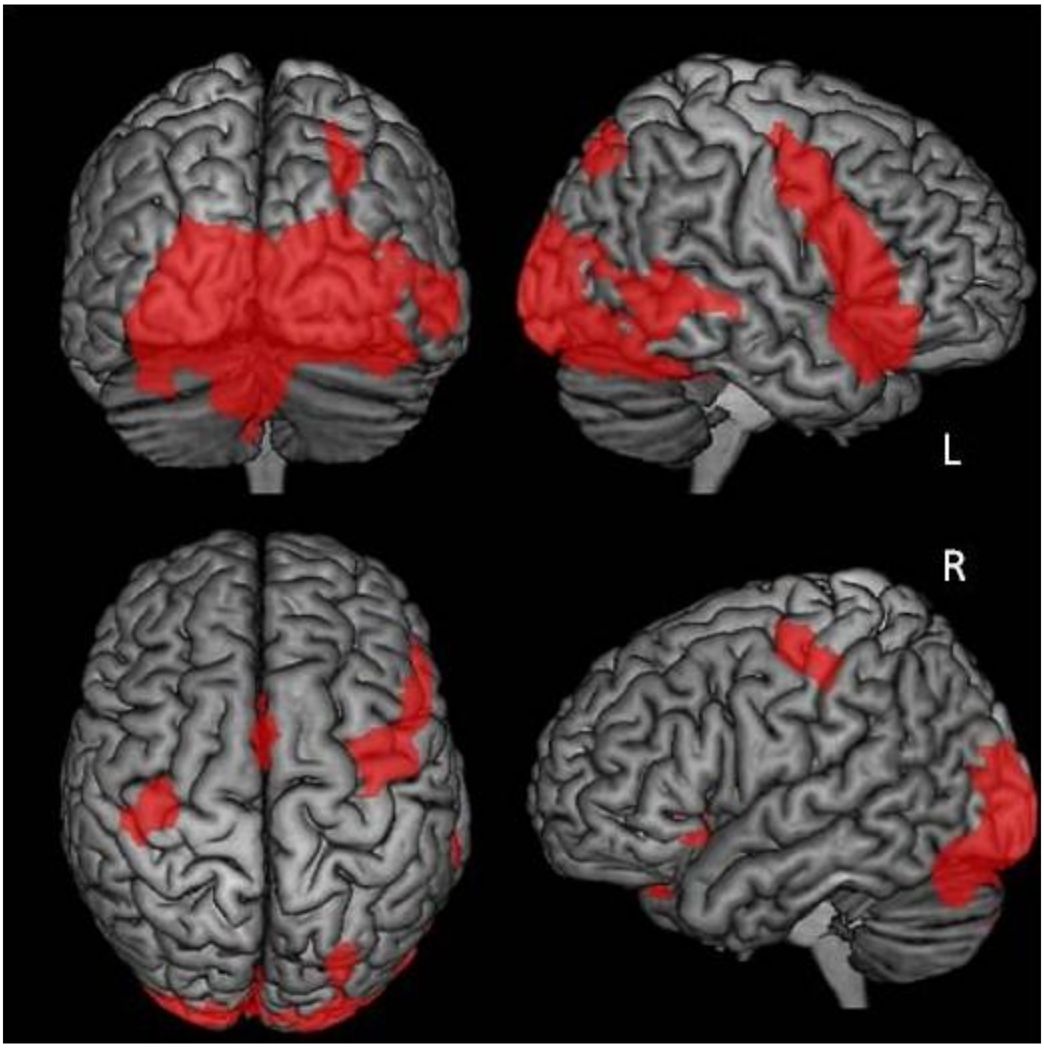

Figure 3-8. Whole brain analysis contrast of semantic over phonological rhyme judgements (cluster correction, $Z \geq 2.3$, $p < .05$). L = left, R = right hemisphere.

Contrasts were also used to investigate which areas showed additional recruitment when task demands increased. The contrasts for the hard > easy phonological task revealed activation in parietal cortex (superior parietal lobule, angular gyrus), paracingulate gyrus, frontal gyri (BA 6, 9, 44, 45, 46, 11), and posterior temporal gyri (occipital-temporal, fusiform and inferior temporal areas). These contrasts can be found in Table 3-2 and Figure 3-9, and only clusters showing significant activation after cluster correction ($Z = 2.3$) are reported. Names of brain areas reported are labelled according to the Harvard-Oxford Cortical Structural Atlas, Talairach Deamon and the Juelich Histological Atlas built into the FSL view software library. The contrast for the hard > easy semantic task revealed activation in paracingulate and anterior cingulate gyrus, superior frontal gyrus, parietal lobe (precuneus, superior parietal lobule; BA 7), anterior temporal gyrus, inferior frontal gyrus (BA 44, 45, 47), and superior and middle frontal gyri (BA 9, 10, 11). These contrasts can be found in Table 3-3 and Figure 3-9.

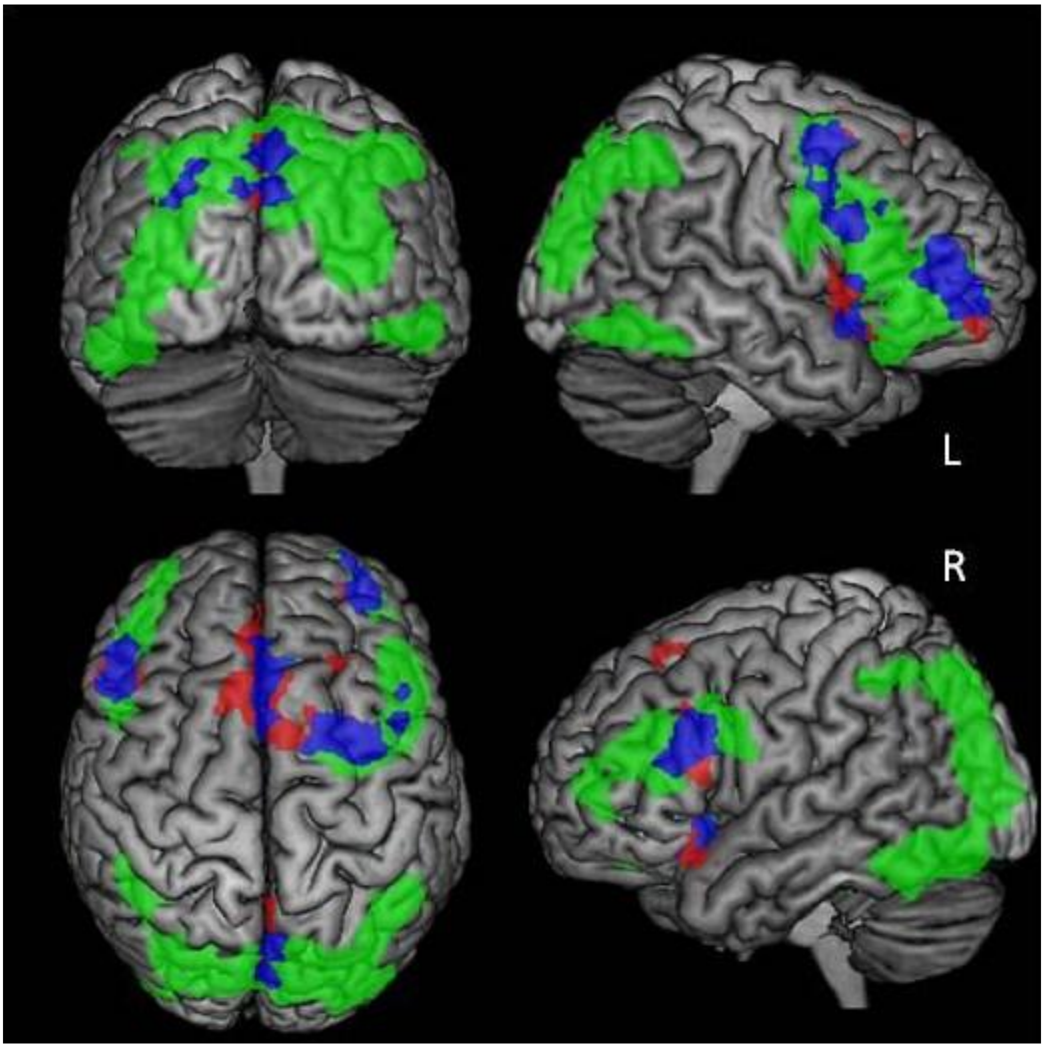

Figure 3-9. Whole brain analysis contrasts of hard over easy for phonological and semantic tasks (cluster correction, $Z \geq 2.3$, $p < .05$). Phonological hard > easy (green), verbal semantic hard > easy (red) and mutual activity (blue). L = left, R = right hemisphere.

Contrast of phonological hard > easy judgements

Brain Area	BA	Voxels	*Z*	*x*	*y*	*z*
Parietal Lobe		13406				
L Superior Parietal Lobule	7		5.61	-26	-70	34
R Superior Parietal Lobule/ Lateral Occipital Cortex	7		5.52	28	-70	40
R Parietal Lobe (Sub Gyral)			5.42	28	-70	32
L Angular Gyrus	40		5.15	-36	-58	40
L Superior Parietal Lobule/ Precuneus	7		5.09	-24	-76	44
L Superior Parietal Lobule/ Precuneus	7		5.01	-16	-74	48
Cingulate Gyrus/ Medial Frontal Areas		8307				
L Paracingulate Gyrus	32		5.53	-6	26	36
L Paracingulate Gyrus	32		5.46	-2	22	38
L Middle Frontal Gyrus / Premotor Cortex	~6		5.32	-28	0	46
L Inferior Frontal Gyrus	44/45		4.92	-48	22	20
L Precentral Gyrus/ Inferior Frontal Gyrus	44		4.91	-40	6	26
L Middle Frontal Gyrus/ Precentral Gyrus/ Inferior Frontal Gyrus	9/44		4.75	-44	8	32
Frontal Gyri		2713				
R Insula Cortex			4.61	32	22	-6
R Middle Frontal Gyrus / Inferior Frontal Gyrus	9/44		4.2	50	22	30
R Precentral Gyrus/ Inferior Frontal Gyrus	~9/44		4.18	42	6	28
R Inferior Frontal Gyrus	45		4.14	46	32	12
R Frontal Cortex	46		4.1	50	38	16
R Sub Gyral Frontal Cortex	11		3.63	22	40	-16

Table 3-2. Cluster corrected ($Z \geq 2.3$) contrast of hard > easy task difficulty for phonological judgements.

Temporal Gyri		1309				
L Temporal Occipital Fusiform Cortex / Fusiform Gyrus			4.44	-30	-52	-10
L Posterior Inferior Temporal Gyrus	37/20		4.36	-52	-58	-12
L Posterior Inferior Temporal Gyrus	37		4.32	-52	-62	-14
L Temporo-occipital Fusiform Cortex / Fusiform Gyrus	37		4.07	-24	-54	-10
L Posterior Inferior Temporal Gyrus	37		3.5	-52	-42	-14
L Occipital Fusiform Gyrus	18		2.77	-28	-72	-14

Table 3-2. Cluster corrected ($Z \geq 2.3$) contrast of hard > easy task difficulty for phonological judgements.

Contrast of semantic verbal hard > easy judgements

Brain Area	BA	Voxels	*Z*	*x*	*y*	*z*
Cingulate Gyrus/ Medial Frontal Areas		4412				
L Paracingulate Gyrus	32		4.6	-4	28	32
L Paracingulate Gyrus	32		4.59	-4	26	36
L Paracingulate Gyrus / Superior Frontal Gyrus			4.5	0	18	50
R Superior Frontal Gyrus	8		4.43	4	24	52
R Superior Frontal Gyrus	8		3.91	0	30	46
L Anterior Cingulate Gyrus	24		3.91	-6	28	22
Parietal Lobe		1504				
R Superior Parietal Lobule / Precuneus			3.49	2	-60	50
R Parietal Lobe / Precuneus	~31		3.49	16	-62	24
L Precuneus / Superior Parietal Lobule	7		3.44	-8	-68	34
L Precuneus / Superior Parietal Lobule	7		3.43	-4	-70	34
L Precuneus / Superior Parietal Lobule	7		3.42	-6	-64	50
L Precuneus / Superior Parietal Lobule	7		3.32	-6	-58	48
Temporal Gyri		957				
L Inferior Frontal Gyrus / L Anterior Temporal Gyrus	47/38		4.25	-34	22	-10
L Anterior Superior Temporal Gyrus/ L Inferior Frontal Gyrus	38/47		3.46	-46	14	-10
L Pallidium			3.45	-14	0	-4
L Anterior Superior Temporal Gyrus/ L Inferior Frontal Gyrus	38/47		3.39	-52	20	-12
L Inferior Frontal Gyrus	44/45		3.22	-48	20	2

Table 3-3. Cluster corrected ($Z \geq 2.3$) contrast of hard > easy task difficulty for semantic decisons.

L Caudate/Putamen			3.02	-16	18	-6
Frontal Gyri		748				
L Middle Frontal Gyrus	10		4.45	-32	48	6
L Superior Frontal Gyrus (Sub Gyral)	10		3.23	-22	48	4
L Superior Frontal Gyrus	10		3.14	-26	62	-10
L Superior Frontal Gyrus	10		3.13	-28	62	-6
L Middle Frontal Gyrus			3.04	-28	58	2
L Medial Frontal Gyrus	11		2.87	-16	58	-14
Frontal Gyri		697				
R Insula			3.9	32	20	-4
R Inferior Frontal Gyrus/ Insula	47		3.75	40	18	-12
R Inferior Frontal Gyrus	47		3.63	30	16	-18
R Inferior Frontal Gyrus/ Insula	47		3.22	42	20	-6
R Frontal Orbital Cortex			3.13	22	8	-24
R Frontal Orbital Cortex			2.95	22	8	-20
Frontal Gyri		565				
R Inferior Frontal Gyrus	44/45		4.08	54	24	18
R Inferior Frontal Gyrus	44		3.66	54	22	26
R Middle Frontal Gyrus	9		3.4	48	26	30
R Inferior Frontal Gyrus	45		3.19	60	24	12
R Sub Gyral	~45		2.8	36	20	16

Table 3-3. Cluster corrected ($Z \geq 2.3$) contrast of hard > easy task difficulty for semantic decisons.

Region of Interest Analyses (ROI)

Voxel corrected (*p* < .05) ROI analyses were used to further establish the relative contribution of brain areas that were the focus of our research questions to the phonological and verbal semantic material. The Featquery tool was also used to read out activation patterns (percent change) averaged across each ROI. An advantage of interrogating specific ROIs using both techniques is that the voxel corrected mask allows functional specialisations within an area to be revealed, while the featquery method allows interactions between difficulty, tasks, and regions to be easily investigated.

Premotor Cortex (PMC)

To assess the contribution of this site to the two language tasks, featquery was used to extract percent signal change within each condition. This yielded a significant main effect of task (F(1, 21) = 27.773, *p* < .001), reflecting the hypothesised higher response for phonological than semantic decisions, and a significant main effect of difficulty (F(1, 21) = 7.012, *p* = .015), as increased demands on difficulty yielded higher percent change values. There was an interaction of task by difficulty which approached significance (F(1, 21) = 3.013, *p* = .097). Bonferroni corrected paired-samples t-tests confirmed that premotor cortex showed significantly more activation for the hard condition compared to the easy condition for the phonological tasks (t(21) = -3.348, *p* = .006), but not the semantic tasks (t(21) = -.61, *p* = .696). This supports the hypothesis, and the results from Chapter 2, that dorsal premotor cortex is recruited for phonological decisions, but is not crucial to decisions based on access to semantic representations, even when these involve speech perception (Figure 3-10).

Posterior Superior Temporal Gyrus (pSTG)

In line with Chapter 2, we conducted an ROI analysis of pSTG using featquery. This analysis of pSTG revealed an unexpected pattern, with a significant main effect of task (F(1, 21) = 15.614, *p* < .001) due to a greater increase for the phonological task; and a significant main effect of difficulty (F(1, 21) = 64.820, *p* < .001) which reflected greater activation for the easier judgements, as well as a significant task by difficulty interaction (F(1, 21) = 14.793, $p \leq .001$) (Figure 3-10). A comparison of PMC and pSTG revealed no site by task interaction (F(1, 21) = 2.695, *p* = .116), but there was a highly significant site by difficulty interaction (F(1, 21) = 54.675, *p* < .001), as well as a significant three-way interaction of site by task by difficulty (F(1, 21) = 14.282, *p* = .001).

The main effect of task type for pSTG was unexpected, as both tasks required participants to process an auditory probe. Additionally, the decrease in activation for the difficult condition was unexpected, because pSTG is thought to be involved in processing auditory stimuli – a requirement which does not change for the difficult version of the tasks. However, the contrast between PMC and pSTG supports our conclusions from the previous chapter: PMC is engaged by more difficult phonological decisions, while pSTG is preferentially activated by simple tasks that involve activating meaning or phonological forms from auditory input.

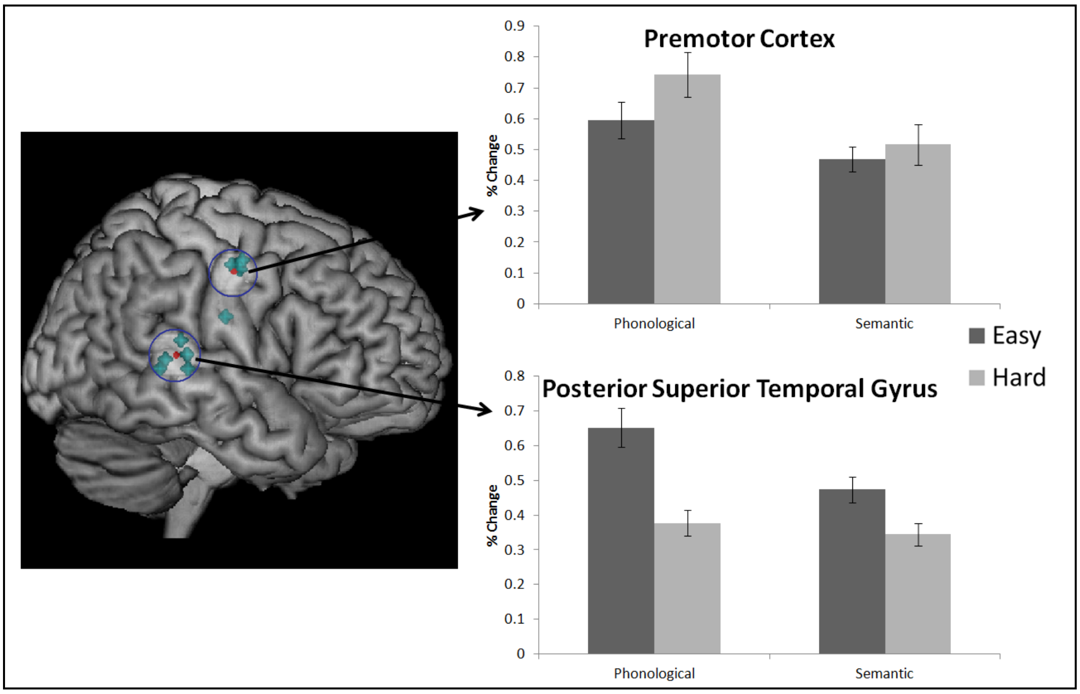

Figure 3-10. PMC and pSTG ROI results. Cyan points in each ROI represent the studies used for the average peak coordinate (peak shown in red) in the TMS study in Chapter 2, ROI outlined in blue. Error bars indicate standard error of the mean.

Left Inferior Frontal Gyrus (LIFG: BA 44, 45, 47)

In order to explore the functional subdivisions in LIFG for phonological and semantic material, we used an ROI to show where in LIFG the phonological and semantic tasks produced activation for both: 1) phonological hard > rest; and, 2) semantic hard > rest. When contrasted with rest, the phonological and semantic hard tasks revealed a pattern of activation consistent with a graded functional specialisation in LIFG, with activation for the phonological task through posterior parts of LIFG (PMC, BA 44, 45) and activity for the semantic hard task spreading more anteriorly into BA 47. Additionally, there was a large degree of overlap for the two domains in ventral parts of pLIFG (BA 44, 45): the activation for the semantic task was more constrained to ventral LIFG, while the phonological hard task activated both ventral and dorsal LIFG (Figure 3-11).

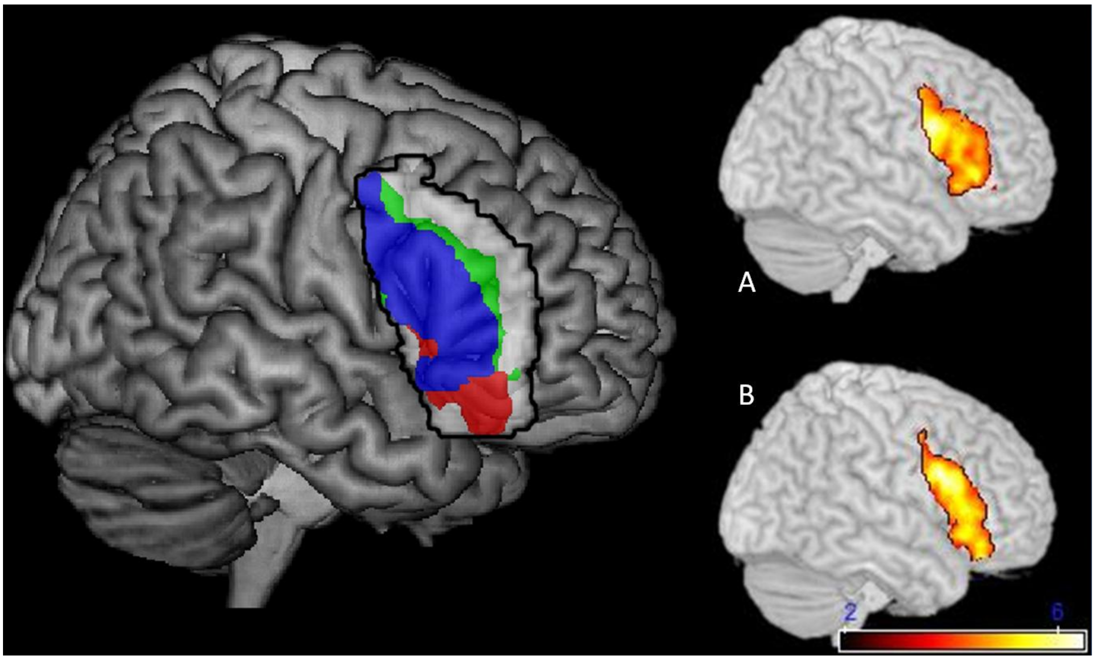

Figure 3-11. Voxel corrected ($p < .05$) ROI analysis of LIFG: The left-hand image shows the extent of activity for each task (green: phonological; red: semantic; blue: overlap). The right-hand images show the regions in which activation was strongest (A: phonological; B: semantic; *Z* values are indicated by the colour scale).

This large ROI was further interrogated by using the featquery tool to extract percent signal change within individual demarked subdivisions of LIFG (BA 44, 45, 47).

A direct comparison of the verbal tasks confirmed the hypothesis that BA 44 is recruited more for the phonological task than the verbal semantic task with a significant main effect of task (F(1, 21) = 5.346, $p = .031$). There was also a main effect of difficulty (F(1, 21) = 91.621, $p < .001$), and a marginal interaction of task by difficulty (F(1, 21) = 3.737, $p = .067$) indicating that BA 44 showed a greater response to difficulty within the phonological domain. Bonferroni t-tests comparing easy and hard conditions for both domains confirmed BA 44 recruitment for difficulty across domains (phonological: t(21) = -8.478, $p < .001$; verbal: t(21) = -6.013, $p < .001$). Overall, these results suggest that BA 44 is recruited for difficult tasks across domain, but shows additional activation for phonological tasks (Figure 3-12).

A comparison within BA 45 revealed a marginal main effect of task type (F(1, 21) = 3.127, *p* = .092), a significant effect of difficulty (F(1, 21) = 42.956, *p* < .001) and a significant interaction of task by difficulty (F(1, 21) = 6.018, *p* = .023). Bonferroni t-tests comparing easy and hard conditions for both domains showed increased BA 45 recruitment for difficult decisions in both domains (phonological: t(21) = -8.13, *p* < .001; verbal: t(21) = -3.595, *p* = .004). In summary, BA 45 shows a similar response profile to BA 44, as both domains recruited BA 45 to resolve the difficulty manipulation, however, unlike BA 44, there is no clear preference for the phonological domain given the marginal main effect for task (Figure 3-12).

For BA 47 there was no significant main effect of task (F(1, 21) = 1.559, *p* = .226), but there was a main effect of difficulty (F(1, 21) = 47.547, *p* < .001), which did not interact with task type (F(1, 21) < 1); this suggests that BA 47 does not show differential recruitment for the two domains. However, the ROI analysis of entire LIFG shows semantic hard activity spreading into aLIFG, but the phonological hard task does not extend into aLIFG. Combining the results from both ROI analyses, we can infer that BA 47 is significantly involved in accessing verbal semantic material when demands on semantic control are increased and also resolved difficulty for our phonological manipulations (Figure 3-12).

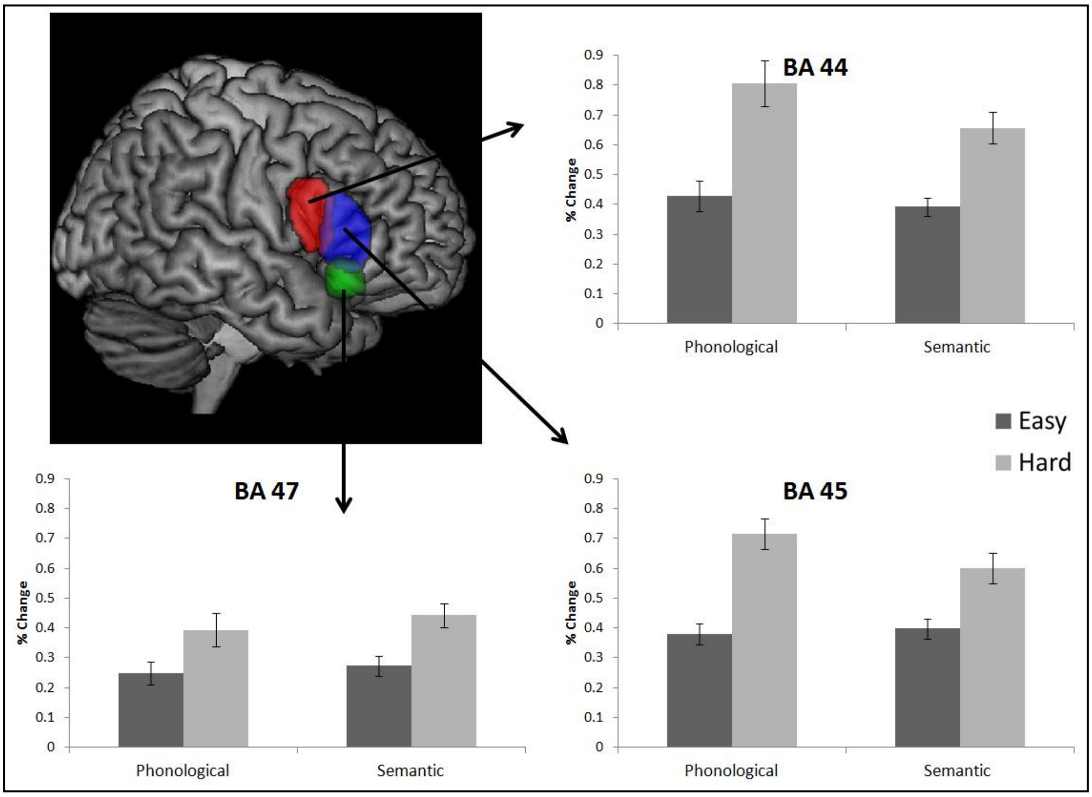

Figure 3-12. Left Inferior Frontal Gyrus percent signal change analysis results. Error bars indicate standard error of the mean.

To further investigate the graded distinction across LIFG for phonological and semantic decisions, a between sites ANOVA was used to explore differences between BA 44 and BA 47 in response to task and difficulty, since these regions have been previously shown to be recruited for phonological and semantic decisions, respectively. This revealed a significant interaction of site and task (F(1, 21) = 25.131, *p* < .001): BA 44 showed a stronger response to phonological decisions, while BA 47 showed greater activation to semantic tasks (Figure 3-13). There was also a significant site by difficulty interaction (F(1, 21) = 32.497, *p* < .001), with a greater response to the difficulty manipulations in BA 44 than BA 47 (Figure 3-13). This analysis also revealed a significant three-way interaction of site by task by difficulty (F(1, 21) = 7.573, *p* = .012), which further suggests that anterior and posterior LIFG responded to the domain and difficulty manipulations differently.

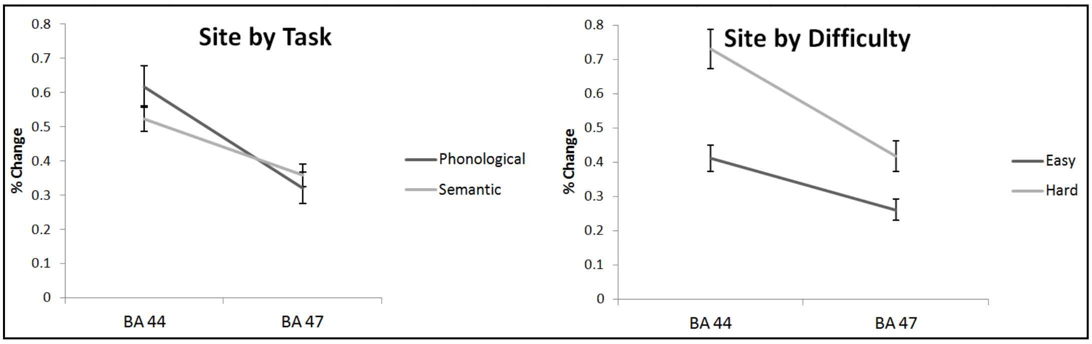

Figure 3-13. Interactions across BA 44 and BA 47 resulting from an investigation of the percent signal change at each site. Error bars indicate standard error of the mean.

These analyses show that LIFG is recruited for all three task types, with differential recruitment in subdivisions of LIFG. While all three subdivisions are recruited for both task types and show modulation with increased difficulty, these results point to a graded specialisation along LIFG for phonological and semantic material, with BA 44 showing greater recruitment for phonological material as well as resolving difficult semantic associations, BA 45 revealing less specialisation by domain, and ventral BA 47 showing preferential recruitment for semantic decisions (but, again, also resolving difficulty across linguistic tasks).

The use of ROIs defined by high over low semantic control is useful as it provides functionally defined regions that have been shown to be involved in linguistic control, and as such can be used to investigate 1) semantic control using our tasks and 2) phonological control (i.e., are these ROIs that have been identified in semantic control specific to the semantic domain, or is there a degree of linguistic domain generality). However, it is possible that in using these ROIs we are truncating activation for phonological tasks (for example, in Figure 3-11, the activation appears to be truncated at the boundary of the ROI). For this reason, we used two supplemental ROIS to explore the activation with regard to the functional specialisation in posterior and anterior LIFG. These ROIs were defined using ALE maps that resulted from contrasting phonology > semantic (posterior LIFG) and semantic > phonology (anterior LIFG), in a recent meta-analysis (Noonan, et al., submitted).

Posterior LIFG/PMC

There was a large degree of overlap for phonological and semantic hard tasks in the anterior and dorsal parts of this ROI, but the activation for the phonological task also extended further posteriorly and ventrally (Figure 3-14). Analysis of the percent signal change revealed a highly significant main effect of task (F(1, 21) = 43.549, *p* < .001) reflecting the increased activity for the phonological task. There was also a significant main effect of difficulty (F(1, 21) = 56.339, *p* < .001) and an interaction of task by difficulty (F(1, 21) = 10.378, *p* = .004). Bonferroni corrected paired sample t-tests confirm an increase across both domains for the difficult judgements (phonological: t(21) = -8.862, p < .001; semantic: t(21) = -3.685, *p* = .002; Figure 3-16).

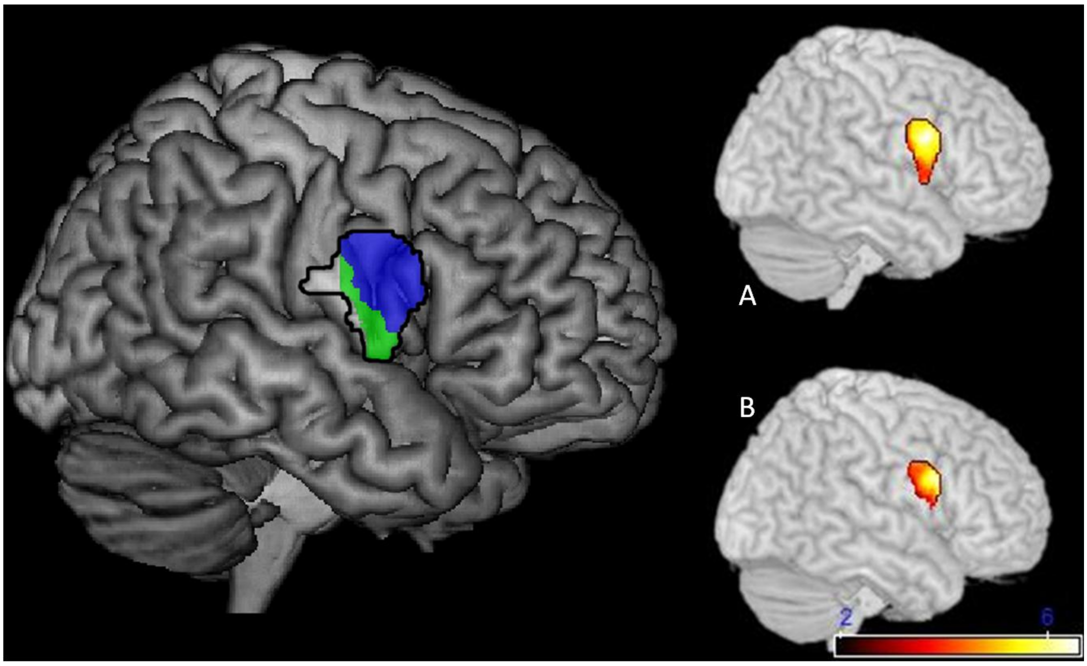

Figure 3-14. Voxel corrected (*p* < .05) ROI analysis of LIFG: The left-handed image shows the extent of activity for each task (green: phonological; blue: overlap). The right-hand images show the regions in which activation was strongest (A: phonological; B: semantic; *Z* values are indicated by the colour scale).

Anterior LIFG

Interrogation of anterior LIFG revealed a dorsal to ventral gradient for the phonological and semantic tasks, with overlap in the middle. More specifically, the semantic hard judgements elicited significant activation in the most ventral and anterior parts of this ROI, while the activity for the difficult phonological decisions was constrained to posterior and dorsal parts of this ROI (Figure 3-15). However, there was no main effect of task when comparing the percent signal change in this region (F(1, 21) = .279, p = .603), but there was a main effect of difficulty (F(1, 21) = 18.482, *p* < .001). There was also no interaction of task by difficulty (F(1, 21) < 1; Figure 3-16). These results indicate some degree of specialisation within aLIFG for semantic material in the most ventral parts of this ROI and phonology in the more posterior and dorsal parts of aLIFG.

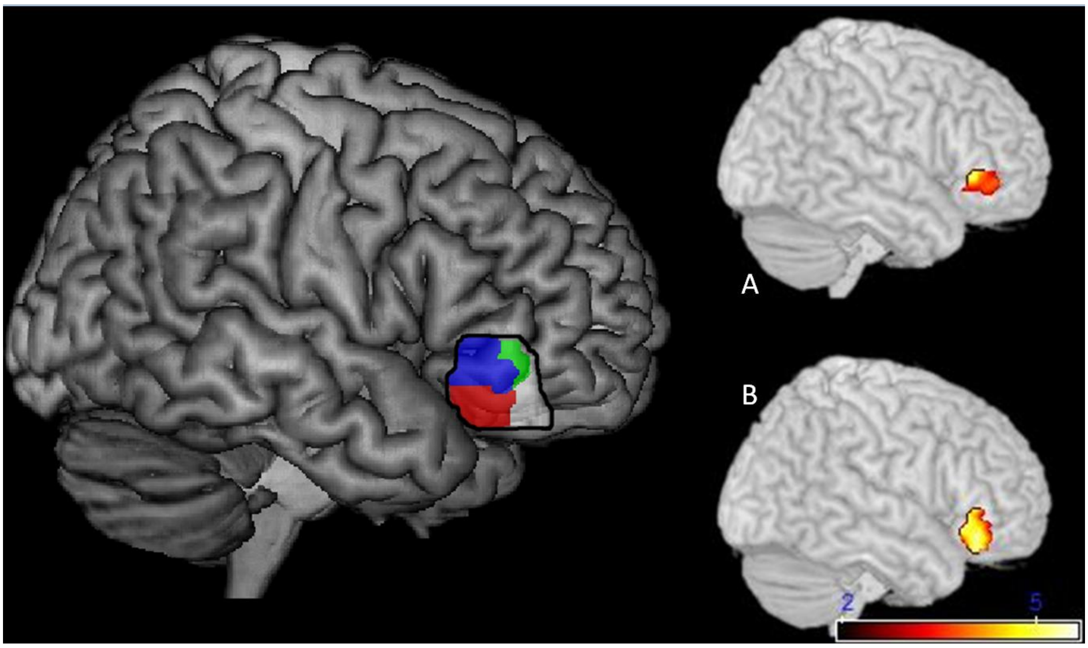

Figure 3-15. Voxel corrected ($p < .05$) ROI analysis of LIFG: The left-handed image shows the extent of activity for each task (green: phonological; red: semantic; blue: overlap). The right-hand images show the regions in which activation was strongest (A: phonological; B: semantic; *Z* values are indicated by the colour scale).

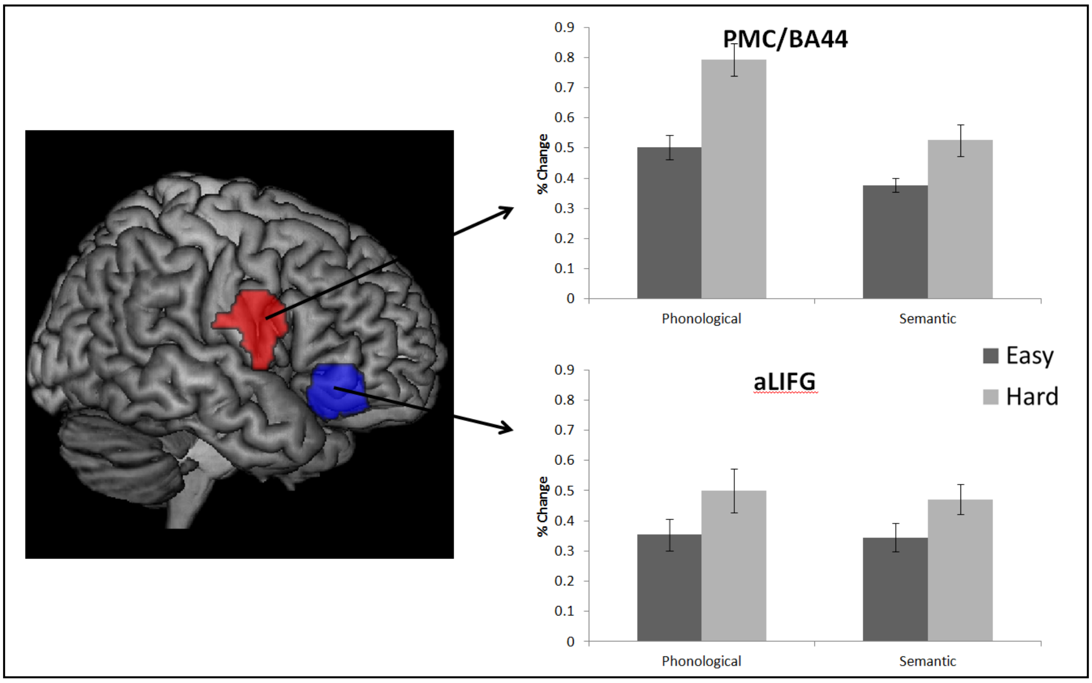

Figure 3-16. Percent signal change resulting from interrogation of premotor cortex (PMC)/BA44 and anterior left inferior frontal gyrus (aLIFG). Error bars indicate standard error of the mean.

PMC vs LIFG

To further investigate the relative role of PMC and LIFG to phonological and semantic control tasks, between sites ANOVAs were used to examine differences in response to task manipulations for PMC and BA 44, which have both been previously shown to be recruited for language tasks (e.g., Thompson-Schill, et al., 1997; Zatorre, et al., 1992; Zatorre, et al., 1996). This revealed a near – significant interaction of site by task (F(1, 21) = 4.127, *p* = .055), reflecting the greater involvement of PMC in phonological than semantic decisions. There was also a significant site by difficulty interaction (F(1, 21) = 26.446, *p* < .001), due to a smaller effect of difficulty in PMC, than BA 44 (Figure 3-17): BA 44 showed a strong response to difficulty across both tasks (also seen in the above analyses of LIFG). This suggests that PMC may not be recruited for *difficult* judgements even when these involve speech perception, rather, specifically for challenging *phonological* judgements (Figure 3-10: PMC shows difficulty effect for phonological domain only).

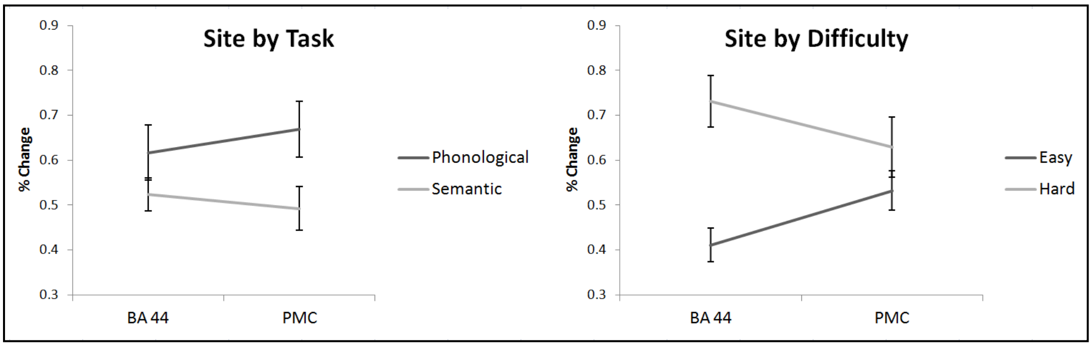

Figure 3-17. Site by task and site by difficulty interactions for PMC and pLIFG area BA 44. Error bars indicate standard error of the mean.

Posterior Middle Temporal Gyrus (pMTG).

In order to assess the contribution of pMTG to tasks requiring linguistic control, we used an ROI of pMTG resulting from a contrast of semantic high > low control in Noonan et al.'s meta-analysis (submitted). This analysis showed overlapping activation of the two tasks across the dorsal part of the ROI (Figure 3-18). Additionally, the percent signal change values revealed a significant main effect of task (F(1, 21) = 5.945, *p* = .024) reflecting higher values for the phonological tasks. There was no significant effect of difficulty (F(1, 21) = 2.519, p = .127) and no interaction (F(1, 21) = 1.368, *p* = .255; Figure 3-19).

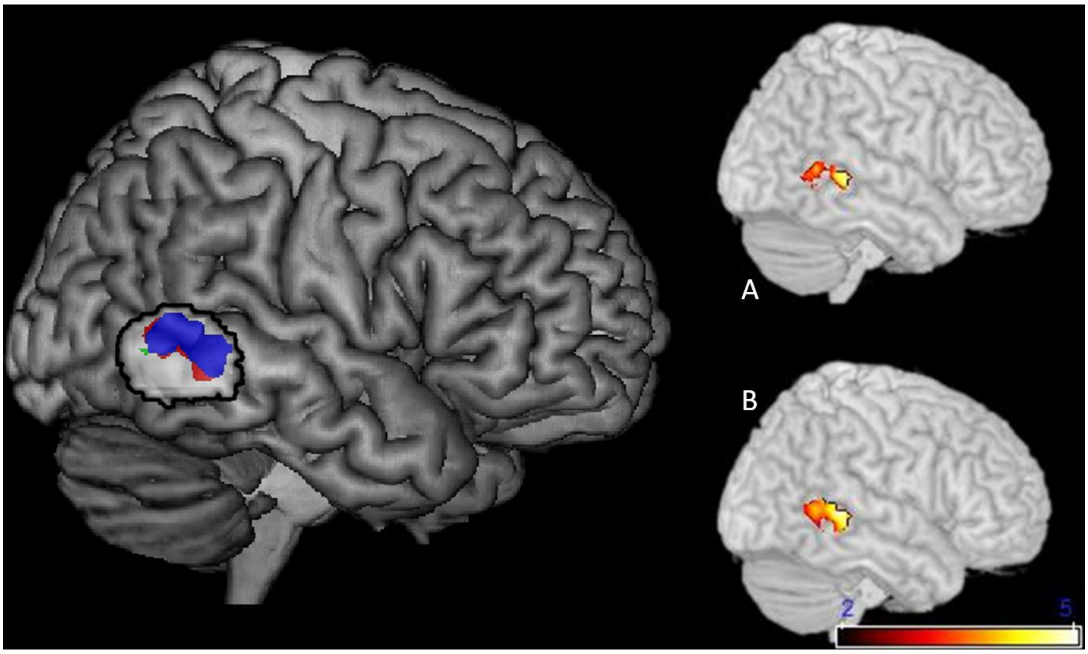

Figure 3-18. Voxel corrected ($p < .05$) ROI analysis of pMTG: The left-handed image shows the extent of activity for each task (green: phonological; red: semantic; blue: overlap). The right-hand images show the regions in which activation was strongest (A: phonological; B: semantic; *Z* values are indicated by the colour scale).

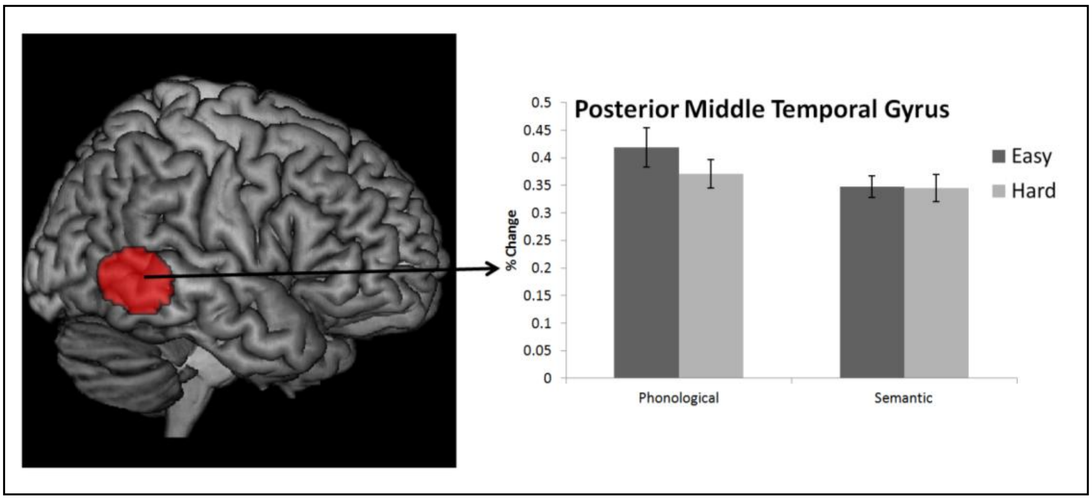

Figure 3-19. Percent signal change resulting from interrogation of posterior middle temporal gyrus. Error bars indicate standard error of the mean.

Left Angular Gyrus/Parietal Cortex: Dorsal/Intraparietal Sulcus (dAG/IPS) and mid Angular Gyrus (midAG)

We also used ROIs of dorsal and mid angular gyrus, resulting from the high over low semantic control ALE maps from Noonan et al. (submitted) to assess the degree of functional overlap for phonological and semantic hard tasks, given previous research indicating a role for these regions in semantic control (Noonan, et al., submitted; Seghier, et al., 2004; Sharp, et al., 2010). Additionally, we were interested to see if the contributions of these regions extended beyond semantic material to other domains such as phonology. The ROI analysis of dAG/IPS showed activation throughout dAG/IPS for the phonological hard task, but more constrained (and less significant) activity for the semantic hard task, which overlapped with the phonological hard task in the most anterior part of dAG/IPS (Figure 3-20).

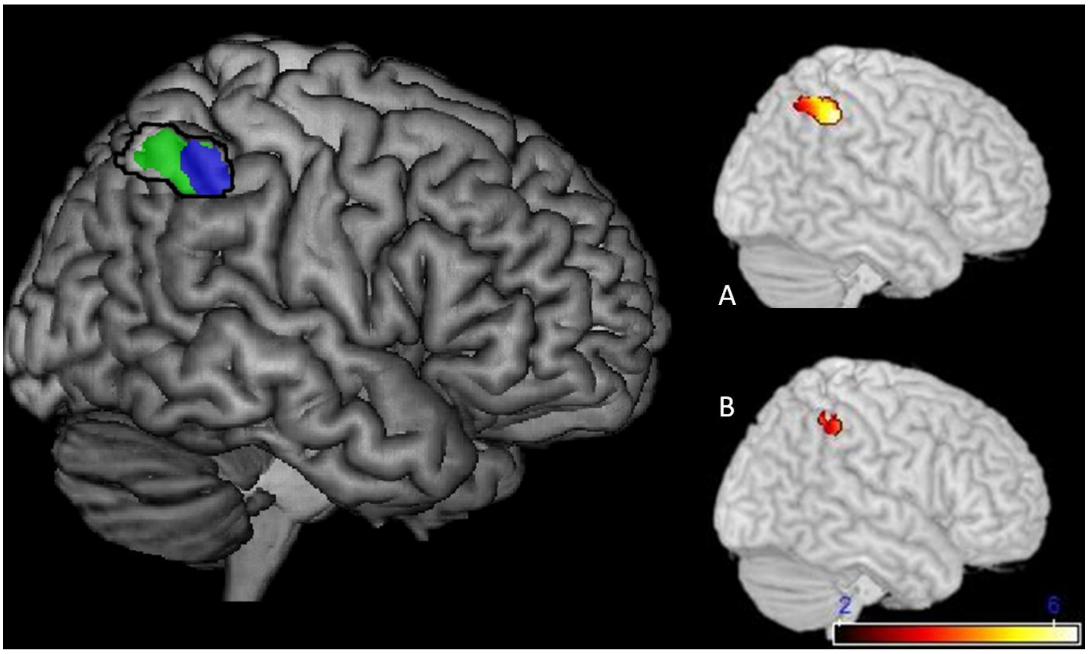

Figure 3-20. Voxel corrected (*p* < .05) ROI of dAG/IPS: The left-hand image shows the extent of activity for each task (green: phonological; red: semantic; blue: overlap). The right-hand images show the regions in which activation was strongest (A: phonological; B: semantic; *Z* values are indicated by the colour scale).

Additionally, analysis of the percent signal change in dAG/IPS revealed a significant main effect of task (F(1, 21) = 52.406, *p* < .001) corresponding a greater response for the phonological tasks, and a main effect of difficulty (F(1, 21) = 66.629, *p* < .001). There was also a significant interaction of task by difficulty (F(1, 21) = 27.329, *p* < .001). Bonferonni corrected paired sample t-tests demonstrated that dAG/IPS responded significantly more to the difficult phonological condition than the easy one (t(21) = -7.627, *p* < .001), but also responded to the semantic difficulty manipulation, to a lesser degree (t(21) = -2.374, *p* = .054). Overall, dAG/IPS was recruited for task difficulty across domain, but showed significantly more activation for the phonological tasks and phonological difficulty (Figure 3-22).

Similarly, in order to assess the degree of functional overlap in mid angular gyrus (mid AG) for phonological and semantic hard tasks, an ROI analysis was used which showed overlapping activation in the most dorsal part of mid AG for the phonological and semantic hard tasks (Figure 3-21).

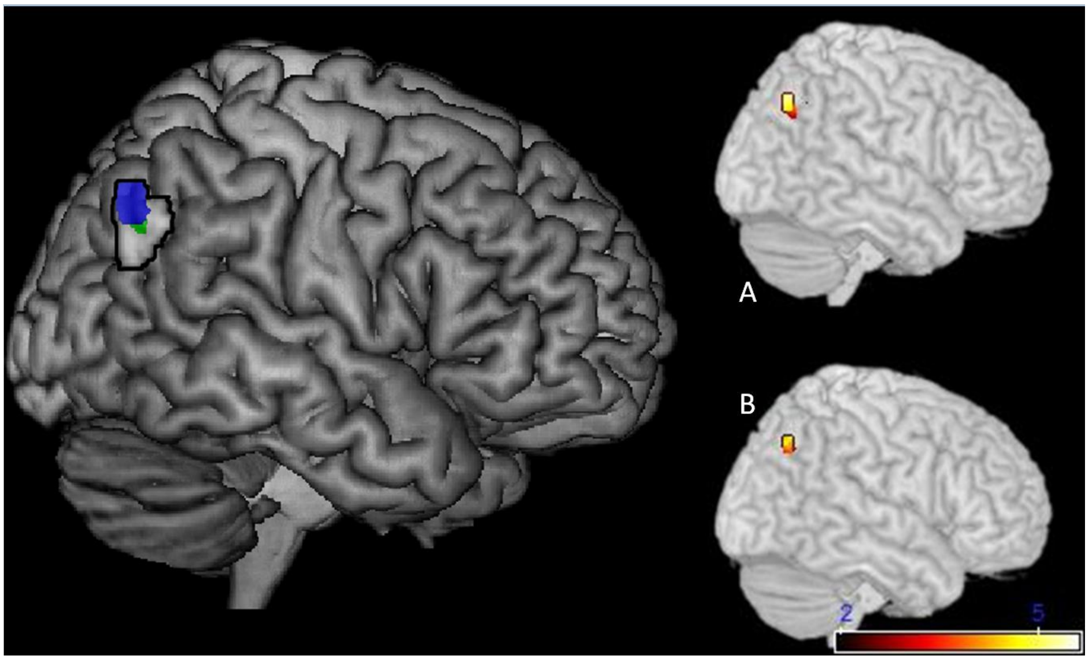

Figure 3-21. Voxel corrected (*p* < .05) ROI of midAG: The left-hand image shows the extent of activity for each task (green: phonological; red: semantic; blue: overlap). The right-hand images show the regions in which activation was strongest (A: phonological; B: semantic; *Z* values are indicated by the colour scale).

A direct comparison of the verbal tasks using percent signal change revealed only a marginal main effect of task (F(1, 21) = 3.07, *p* = .094), and a main effect of difficulty (F(1, 21) = 55.624, *p* < .001). There was also a significant interaction of task by difficulty (F(1, 21) = 7.103, *p* = .014). Bonferonni corrected paired sample t-tests, revealed that mid AG responded significantly more to the difficult phonological condition than the easy one (t(21) = -7.069, *p* < .001), and also significantly for the semantic hard compared to easy condition (t(21) = -5.014, *p* < .001). In summary, mid AG was recruited to resolve task difficulty across both domains (Figure 3-22).

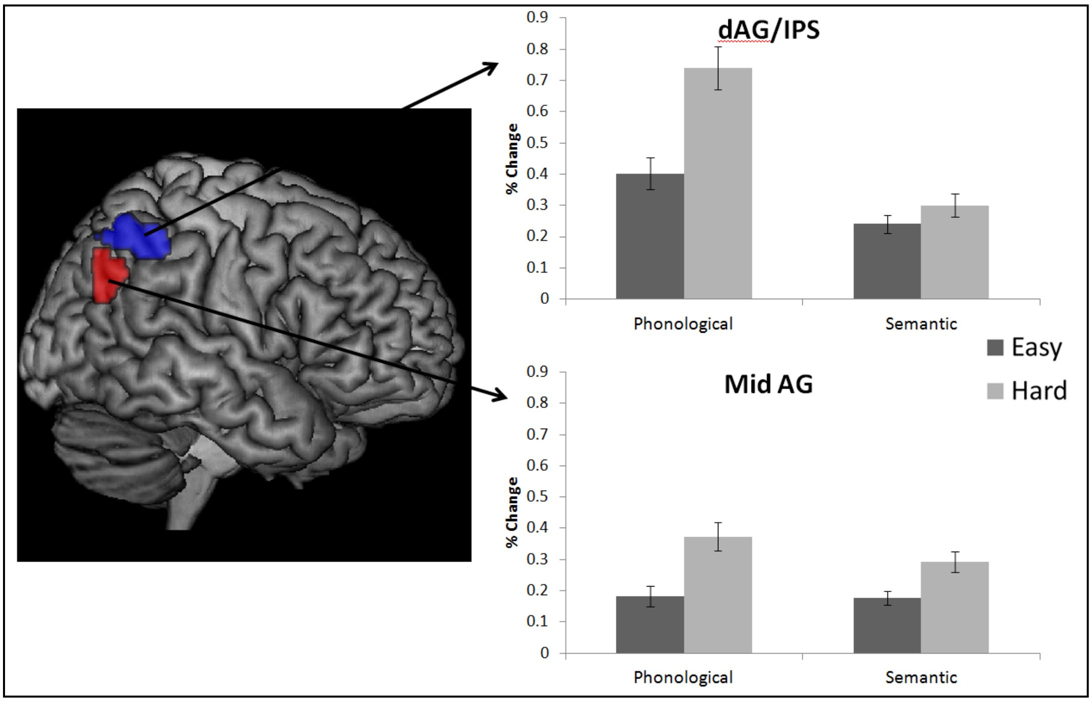

Figure 3-22. Percent signal change values for dorsal angular gyrus/intraparietal sulcus (dAG/IPS) and mid angular gyrus (mid AG). Error bars indicate standard error of the mean.

Discussion

This study examined phonological and semantic control with fMRI. Using semantic association judgements, phonological rhyme and phonological segmentation/matching tasks we manipulated difficulty in order to try to assess the relative contribution of areas in the language network (premotor cortex (PMC), left inferior frontal gyrus (LIFG), posterior middle temporal gyrus (pMTG), angular gyrus (AG)) to tasks tapping phonological and semantic control.

Premotor Cortex (PMC) and Posterior Superior Temporal Gyrus (pSTG)

One aim of this study was to elucidate the role of premotor cortex in speech perception tasks. Many studies have shown PMC to play a crucial role in speech perception, using fMRI (e.g., Pulvermuller, et al., 2006; Wilson & Iacoboni, 2006; Wilson, et al., 2004) and TMS paradigms (D'Ausilio, et al., 2009; Meister, et al., 2007; Mottonen & Watkins, 2009). However, many of these tasks require participants to make explicit judgements on the constituent sounds of a word, rather than perceiving the word as a whole. This demonstrates an advantage of the current study, where phonological and semantic judgements made to spoken words were compared directly. Our results suggest that the role of PMC in speech perception is restricted to phonological tasks and is thus not essential to perception of clear auditory input. More specifically, our whole brain analysis yielded a sub cluster in PMC for the phonological hard - easy contrast, but no such clusters in PMC for the semantic hard – easy contrast. Additionally, interrogation of a dorsal PMC ROI found a larger contribution of PMC to phonological judgement tasks than semantic association judgements, further implicating its role in tasks requiring meta-linguistic task performance, not general comprehension.

These findings are in line with the findings of the previous chapter, where TMS to PMC disrupted phonological but not semantic judgements (matched in task format). An additional strength of the current design is that the tasks are matched on both format and reaction time (reaction time was not matched in our TMS study). These results also align well with data from patients showing a discrimination/comprehension dissociation (e.g., Bishop et al., 1990; Rogalsky et al., 2011). For example, in one study patients with impaired speech production performed more poorly than controls on syllable discrimination (i.e., same or different? “boy”-“voy”), but crucially, not on picture-syllable matching (i.e., a picture of a boy, and asked “Is this a voy?” or “Is this a boy?”; Bishop et al., 1980). Our results sit comfortably with these studies showing that PMC is recruited specifically for meta-linguistic tasks, not general comprehension. This is also in line with fMRI studies showing PMC activation for tasks requiring syllable discrimination, but not passive listening (e.g., Burton, et al., 2000; Zatorre, et al., 1996). For example, Zatorre et al. (1992) reported premotor cortex activity for decisions on syllables, but not passive speech listening; additionally, Burton et al. (2000) reported PMC activity for segmenting consonants, but not for simple discrimination of CVC words, again speaking to the non-essential role of PMC in simple language perception, but rather, in solving meta-linguistic judgements.

An unexpected result was obtained for pSTG, which showed a decrease in activity for difficult judgements/associations. pSTG has been shown to be recruited during normal auditory processing (Buchsbaum, et al., 2001; Hickok & Poeppel, 2007; Scott, 2005; Scott & Johnsrude, 2003; Seghier, et al., 2004), and was thus expected to show similar activation across both tasks and difficulty manipulations. Meister et al. (2007) also reported an unexpected null effect following TMS stimulation of pSTG for their phonological discrimination task. One possible interpretation is that while the phonological easy task was immediately phonological, the phonological hard task required working memory and access to lexical representations, thus activation is allocated to other areas (i.e., PMC) for resolution of this task, while the phonological rhyme task required more auditory analysis. Support for this argument comes from other studies also reporting deactivation of STG when difficulty increased – for example, Sharp et al. (2010) found that when semantic difficulty increased, activity in STG decreased, and suggest, as we do, that this change may reflect reallocation of resources to other brain areas. Furthermore, Blumstein et al. (2005) found that STG was involved in early perceptual analysis, but was insensitive to difficulty (as measured by RT), in line with our finding that pSTG activation was lower for the difficult versions of the two tasks.

Premotor Cortex vs. Left Inferior Frontal Gyrus

What, then, is the relative contribution of PMC and LIFG to phonological and semantic control? The current study further implicates PMC in aspects of non-natural language tasks and not general speech perception of clear auditory input (as suggested by the motor theory of speech perception; Liberman & Mattingly, 1985): while BA 44 contributes to *both* domains (with some degree of specialisation), PMC is more specific to the phonological domain, as shown by the significant interaction of site and task type (phonological judgement/semantic association). It has been previously suggested that PMC may respond to an increase in the number of stimuli presented, while BA 44 is active for an increase in the number of required responses (Rajah, et al., 2008), but this is not the case in the current study, where stimuli and response number were the same across conditions. Another interesting finding arising from the comparison between PMC and BA 44 was that while BA 44 is recruited across domains to resolve difficult judgements, PMC only showed an increased response to resolving difficult phonological judgements. The factorial design of the current study allowed for comparison of difficulty across conditions, permitting us to clarify the contribution of PMC to 1) domain, 2) difficulty and 3) the interaction of domain and difficulty. This speaks, again, to the specific contribution of PMC to language perception: PMC recruitment is only necessitated by non-natural judgements on the *constituent sounds of a word*, but not required for judgements that require *access to meaning,* regardless of difficulty. While both the phonological and semantic tasks recruited BA 44, PMC was restricted to the phonological tasks.

The connections running from BA 44 to both phonological and semantic regions in posterior cortex align with this domain general function; and PMC is connected to temporal lobe areas sub serving phonological function, via the superior longitudinal fascicle (SLF) and

AF (Parker, et al., 2005; Saur, et al., 2008), but not semantic representation, further emphasizing the relative contribution of BA 44 and PMC to phonological and semantic control. While BA 44 has been consistently shown to be a part of the speech perception architecture, the specific role of PMC in speech perception is still unclear – our fMRI (and TMS) data help to elucidate the role of PMC, but its *exact* contribution remains unanswered. PMC has been shown to be recruited in a variety of tasks, involving phonetically ambiguous (Gow Jr & Segawa, 2009) and distorted speech (Devlin & Aydelott, 2009; Osnes, et al., 2011; Scott, et al., 2009), again, suggesting that the role of motor cortex is restricted to 1) non – natural language tasks, requiring explicit knowledge of phoneme segments (Hickok & Poeppel, 2000; Rogalsky, et al., 2011; Sato, et al., 2009) 2) distorted/degraded speech (Devlin & Aydelott, 2009; Osnes, et al., 2011; Scott, et al., 2009) and 3) repetition/learning new words (Burton, et al., 2000; Demonet, et al., 1992). However, whatever its exact role, it is clear that our data, and that of these studies, consistently show that PMC is *not necessary* for comprehension of clear auditory input.

Certain limitations should be considered, however. For example, while the phonological hard task required phonological segmentation, it may also have required access to lexical representations in order to match the given phoneme onto the target word. Future studies could examine the role of real vs. non-word phoneme matching has on the contribution of PMC and BA 44, given previous suggestions that lexicality matters (Kotz, et al., 2010; Roy, et al., 2008). In summary, these results combined with those from the previous chapter, further confirm the role of PMC for phonological judgements, but not semantic association judgements matched in task format and reaction time. While PMC may play a role in explicit phonological judgements, it does not appear to be a crucial part of the semantic network required for accessing semantic representations, even when control demands are maximised.

Left Inferior Frontal Gyrus (LIFG)

Another key aim of this study was to investigate the functional graded distinction along LIFG for phonological and semantic control. Previous studies have shown posterior LIFG involvement in phonological control and anterior recruitment for semantic control (Devlin, et al., 2003; Gold & Buckner, 2002; Gough, et al., 2005; Poldrack, et al., 1999; Sharp, et al., 2010; Vigneau, et al., 2006). A recent meta-analysis also confirmed this graded functional specialisation along LIFG, while noting that LIFG responds to control demands *across domains*, but to a varying degree (Noonan, et al., submitted). The results of the current study support these previous findings, showing a graded specialisation along LIFG, with greater recruitment of posterior LIFG (PMC, BA 44, 45) for challenging phonological judgements, and more anterior recruitment for difficult semantic associations (BA 45/47). These findings are in line with other studies which have also found a graded LIFG response across domains, with additional recruitment for specific task types in pLIFG and aLIFG (Gold, et al., 2005).

There has been some suggestion that the neural theme of control ties these inferior frontal regions together, with posterior LIFG for phonological control and aLIFG for semantic control (Fiez, 1997). The precise contribution of LIFG to linguistic control is still unclear: what might be the reason for this posterior to anterior gradient for phonological and semantic control? A hierarchical organisation of the frontal lobe has been previously suggested, whereby anterior recruitment is necessitated by increasingly abstract and complex information/rules (Badre & D'Esposito, 2009). Our data fit comfortably with this view, with more difficult semantic association judgements (which may require more abstraction, given the weak relationship between the target and the probe) activating the most anterior parts of LIFG. Additionally, the posterior to anterior gradient for the hard and easy tasks may reflect the increased demands on maintaining complex information in working memory in order to establish the correct target for the difficult phonological judgements. This gradient, from easy phonological rhyme judgements (where activity was constrained to the most posterior parts of our LIFG ROI), to phonological judgements requiring the maintenance of complex information/rules (for which activity spread from posterior LIFG to dorsal aLIFG) and finally to the most abstract judgements for the semantic associations (spreading into the most ventral and anterior parts of LIFG) reflect this posterior to anterior gradient for linguistic control. Moreover, there is some suggestion that this gradient exists beyond the linguistic domain (Badre & D'Esposito, 2009; Badre & Wagner, 2007; Wagner, et al., 1997), and this will be examined in the next chapter (Chapter 4), using non-linguistic materials to assess the extent to which LIFG contributes to amodal control.

The graded specialisation for phonological and semantic material along LIFG is also in line with various connectivity studies. For example, Anwander, Tittgemeyer, von Cramon, Friederici, and Knosche (2007) report similar connections for BA 44/45 along the Arcuate Fasciculus (AF) and the Superior Longitudinal Fascicle (SLF) to the parietal lobe and perisylvian areas, as well as dorsomedial prefrontal cortex and precentral gyrus; and to the ATL along the extreme capsule (EmC). Our findings are consistent with this as they show involvement of BA 44/45 in both phonological and semantic control, in line with the connections to STG (Petrides & Pandya, 2002), motor cortex for phonology, and ATL for accessing semantic representations. Additionally, Anwander and colleagues (2007) report that BA 44 is more strongly connected to STG/dorsomedial prefrontal cortex, while BA 45 is more strongly connected to the ATL via the EmC. Furthermore, BA 47 is strongly connected to ATL along EmC and the uncinate fascicle (UF), implicating its role in accessing semantic material. Friederici (2009) reports similar findings showing connections from BA 44/45 along the AF, which separates into two segments, one connecting to STG for lower level phonological processing; and the other to middle temporal gyrus for lexical/semantic retrieval. Saur et al. (2008) also report strong connections running from aLIFG (BA 47) to the temporal lobe along the EmC, again implicating its role in semantic control. Given the connections of LIFG to language areas sub serving both domains, our findings are in line with a functional graded specialisation along LIFG in accordance with the strength of connectivity to posterior association areas.

Posterior Middle Temporal Gyrus (pMTG)

The lack of difficulty effect for the verbal semantic task in pMTG was surprising given that the ROI came from an analysis of high over low semantic control. Moreover, this was the second biggest cluster resulting from the comparison of high > low semantic control (Noonan, et al., submitted). Despite many studies reporting equivalent recruitment of pMTG and LIFG for tasks manipulating semantic control using associative judgements, as we did (Whitney, et al., submitted; Whitney, Kirk, et al., 2011), and the largely equivalent deficits in semantic control seen in patients with semantic aphasia (SA), who have lesions in frontal or temporoparietal cortex (Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006; Noonan, et al., 2010), there is some indication that the two sites may differ. For example, a recent meta-analysis reported that pMTG differed from LIFG in that activation for this site was restricted to: 1) receptive/comprehension tasks; and 2) the semantic domain (not domain general executive control; Noonan, et al., submitted). Additionally, patients with SA, although presenting largely similar deficits across tasks, do dissociate on certain tasks requiring cyclical processing of stimuli (i.e., selection/inhibition) (Gardner, et al., 2012; Jefferies, et al., 2007). Therefore, differences between pMTG and LIFG are not unprecedented; in our study pMTG did not show modulation with task difficulty, but activation did spread across the dorsal aspect of this ROI when participants were making semantic judgements. These results are somewhat compatible with a recent double prime study, where participants were required to make a yes/no relatedness judgement on the third word presented. Neither pMTG nor LIFG were active for the unambiguous double-related condition (e.g., ‘lion – stripe – tiger’), as there was no need for semantic control. However, pMTG activation was seen across trials that required participants to recognize: 1) ambiguous double-related (game – dance – ball), 2) dominant one-related (game – pillow – ball), and 3) subordinate one-related (dance – clock – ball) targets. However, aLIFG (BA 45/47) only showed activation for the third type of double prime (subordinate, one-related). This is in line with our findings, where LIFG showed additional recruitment for more distantly related associations, while pMTG resolved associative judgements regardless of semantic distance.

In Noonan et al.’s (submitted) meta-analysis, pMTG emerged as a key site in both the semantic control and the semantic > phonological task contrasts. Therefore, our main effect of task (phonological > semantic) was not predicted, particularly as it has been postulated that this site contributes exclusively to semantic control (i.e., not general executive control; Noonan, et al., submitted). However, there is some indication that pMTG could contribute to other aspects of language processing, such as acting as an interface between speech and conceptual representations, as suggested by Hickok and Poeppel (2004, 2007). This also fits with the idea that pMTG may act as a ‘cortical hub’ for the comprehension network, as it has strong structural and functional connections to frontal, parietal, temporal and occipital regions (Turken & Dronkers, 2011), of particular relevance to our findings, pMTG is well connected to both BA 47 and STG, and may therefore respond to both of our language tasks. Additionally, resting state connectivity studies have shown that pMTG is correlated with both regions in the frontal parietal (PFC; IPS/dAG) and temporal (i.e., language representations) systems (Spreng, et al., 2010; Vincent, et al., 2008). We found pMTG to be significantly activated by both phonological and semantic tasks and these findings are in line with connectivity studies showing rich connections of pMTG to other parts of the language network (Catani, et al., 2005; Turken & Dronkers, 2011). pMTG activation has been shown to start around 90ms after auditory stimulus presentation, while prefrontal regions respond around 120ms, therefore it has been suggested that information flows from pMTG to prefrontal regions (Saur et al., 2010). This makes it an ideal candidate as an ‘integration’ zone for language comprehension, as it is well placed to receive input from temporal cortices (e.g., STG, ATL) and is connected to prefrontal regions allowing for maximal control over language representations.

Left Angular Gyrus/Parietal Cortex

The comparison of phonological and verbal semantic material in parietal cortex/angular gyrus (AG), revealed a dissociation between dorsal/intraparietal sulcus (dAG/IPS) and mid angular (mid AG) gyrus response profiles for the two domains. The dorsal AG/IPS site revealed a greater response to both phonological tasks and a far greater increase for the phonological difficulty manipulation than the semantic one; while mid AG showed a similar response to both domains. There is research to suggest a graded specialisation along AG, with dorsal AG/IPS involved in a variety of perceptual and semantic tasks (Noonan, et al., submitted; Seghier, et al., 2004; Whitney, et al., 2012). For example, tasks requiring participants to orient attention to specific features (both semantic and non-semantic) report dAG/IPS recruitment (Cristescu, Devlin, & Nobre, 2006; Donner, et al., 2002; Whitney, et al., 2012; Woolgar, Hampshire, Thompson, & Duncan, 2011), as do tasks requiring conjunction search (which necessitate integration of information) (Donner, et al., 2000, 2002). Our phonological hard task required participants to 1) attend to a particular phoneme segment and 2) match this onto three possible choices: thus dAG/IPS activation would be expected in light of previous studies demonstrating its involvement in feature selection/orienting attention to specific features and integrating this information to find the correct target. This is also in line with the strong connections reported by Xiang, Fonteijn, Norris, and Hagoort (2010) between BA 45 and dAG/IPL, with weaker connections of this region to BA 47; likewise, our study showed a stronger response of dAG/IPS to the phonological task, especially when it involved high-control decisions.

Meanwhile, mid AG has been suggested to be the point of overlap between the default and semantic networks: with *deactivations* for meaningless stimuli, but *activation* for demanding semantic tasks, word reading and non-stimulus driven semantic associations (Noonan, et al., submitted; Seghier, et al., 2010). However, our results show equivalent activation of phonological and semantic tasks in mid AG suggesting that it may be the point of overlap for the default and language networks more generally. This is in line with Binder et al.’s (2009) suggestion that mid AG plays a role in high level amodal integration, as it is well connected with various association areas, while receiving little/no direct input from sensory cortices. AG activation has often been reported when semantic load increases, while phonological activation is often reported in more anterior parts of parietal cortex (e.g., SMG). Sharp et al. (2010) report activation for semantic tasks within an area of AG that is ventral to the ROI's reported here, as well as activation for increased semantic difficulty (i.e., more distant featural semantic relationship) in an area just posterior to our mid AG ROI, while their phonological task elicited activity in parietal operculum (anterior to our AG ROIs). In line with a role for mid AG in tasks involving semantic material, Obleser and Kotz, (2010) report activation for sentences over spectrally rotated speech and suggest that this region is recruited for top-down activation of concepts. Also, Vigneau et al. (2006) suggest that mid AG is the "gateway that coordinates reciprocal interactions between the sensory representation of words or objects and the symbolic association that gives them meaning" (p. 1424), and is as such a multimodal integration area for conceptual knowledge. Strong functional connectivity between mid AG and BA 47 has also been reported, with weaker connections between mid AG and BA 44/45 (Xiang, et al., 2010): This would suggest the preference for phonological material should be reduced in mid AG, since BA 45 showed broadly equivalent activation for the two domains. This is largely consistent with our results, where mid AG, in comparison to dAG, shows a reduced response for phonology, while resolving difficulty across domain; accordingly, our results point to a domain general interpretation for mid AG, where both semantic and phonological material may be integrated. Our data also indicate a greater contribution of dAG/IPL to phonological, than semantic, control.

Conclusions

This study sought to investigate the role of PMC, LIFG, pMTG and AG in language control. We manipulated difficulty across phonological and semantic tasks, and confirmed dissociations previously seen in LIFG: i.e., more anterior recruitment for semantic material, contrasting with more posterior recruitment in the phonological task. We also add more data to the debate over PMC contribution to language perception by showing that PMC is recruited for tasks requiring meta-linguistic judgements. Our pMTG ROI revealed a domain general response that was not modulated by our manipulation of difficulty (despite prior studies indicating pMTG involvement for difficult semantic judgements; e.g., Whitney, et al., submitted; Whitney, Kirk, et al., 2011; Whitney, et al., 2012). Additionally, we showed dAG/IPL activity for phonological tasks, with a similar contribution to the two domains in mid AG.

Chapter 4: Amodal Contributions of Distributed Brain Areas to Semantic Control – An fMRI Investigation

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Introduction

Chapter 3 investigated the contribution of the language networks to both domain (phonological and semantic) and control, revealing a largely distributed and similar network across domain, with discrete differences. For example, we confirmed the posterior to anterior gradient for phonological and semantic control in LIFG, while also revealing some surprising findings such as the response of pMTG to both domains, with no modulation of difficulty. While Chapter 3 was restricted to the linguistic domain, Chapter 4 will focus on semantic control across picture and verbal modalities, thus further teasing apart the role of areas formerly shown to be involved in language.

Semantic cognition involves the combination of diverse representations of semantic knowledge, in many different forms such as words, pictures, sounds, objects, to name a few; as well as efficient access and use of these representations for the given context. For example, the word 'bank' has multiple meanings and retrieving the representation of a money-bank would be inappropriate when discussing a river. The various representations of this concept draw on the anterior temporal lobes (ATL; Jefferies & Lambon Ralph, 2006; Pobric, et al., 2007), as shown by semantic dementia patients, with atrophy in this area, who have degraded semantic knowledge and are insensitive to cueing (Jefferies & Lambon Ralph, 2006), as well as neuroimaging studies in healthy individuals confirming the ATL as a semantic store (Pobric, et al., 2007; Visser & Lambon Ralph, 2011). Additionally, the control processes required for the appropriate use of these representations are thought by some researchers to be distributed, drawing on a large-scale cortical network that includes both anterior and posterior brain areas (e.g., Noonan, et al., submitted). For example, patients with semantic aphasia (SA) show semantic control deficits following both anterior and posterior lesions, yet their representations are largely intact: they are sensitive to the effects of cueing – suggesting that efficient access to semantic representations is impaired (Jefferies & Lambon Ralph, 2006). This is consistent with a recent activation likelihood estimation meta-analysis of neuroimaging studies of semantic control, which revealed reliable activity in both LIFG and pMTG (Noonan et al., submitted). Furthermore, the control deficit in SA is amodal in nature, seen in a variety of modalities including environmental sounds, pictures, object use and verbal material (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Corbett, et al., 2011; Jefferies & Lambon Ralph, 2006). This suggests that semantic control processes are (at least partially) amodal in nature; however there has been relatively little investigation into semantic control in healthy populations employing non-verbal stimuli. This chapter will focus on the distributed network of semantic control areas including left inferior frontal gyrus (LIFG), right inferior frontal gyrus (RIFG), posterior middle temporal gyrus (pMTG), and angular gyrus/intraparietal sulcus (AG/IPS), using fMRI, with particular emphasis on exploring how the response of these regions does or does not vary with modality.

Left inferior frontal gyrus (LIFG: BA 44, 45, 47) has long been shown to be involved in varying aspects of language control. For example, LIFG has been implicated in phonological, semantic and syntactic language processing, with these functional differences corresponding to a graded distinction along LIFG (for reviews see Binder, et al., 2009; Bookheimer, 2002; Price, 2010; Vigneau, et al., 2006): Posterior LIFG (BA 44) has been widely implicated in phonological control (e.g., Demonet, et al., 1992; Démonet, et al., 1994; Gough, et al., 2005; Nixon, et al., 2004; see Chapter 3), but does also show increased activation for challenging semantic decisions (e.g., Badre, et al., 2005; Noonan, et al., submitted; Thompson-Schill, et al., 1997; Wagner, et al., 2001); BA 45 has been implicated in both syntactic processing (e.g., Bookheimer, 2002; Vigneau, et al., 2006; Xiang, et al., 2010) and several aspects of semantic control (e.g., selection amongst competing alternatives; e.g., Badre, et al., 2005; Whitney, Kirk, et al., 2011; Whitney, et al., 2012); and, the most anterior part of LIFG, BA 47, has been implicated in semantic control/abstract semantic judgements (Badre & D'Esposito, 2009; Devlin, et al., 2003; Gough, et al., 2005; Noonan, et al., submitted; Poldrack, et al., 1999; Vigneau, et al., 2006). The peak response reported in many semantic control tasks is in BA 45 and there is some debate over the role of this site in semantic control: For example, some argue that it plays a role in selection amongst competing alternatives (Thompson-Schill, et al., 1999), others in controlled semantic retrieval (Wagner, et al., 2001), while some argue for a hybrid of these two accounts with more anterior areas (BA 47) recruited for semantic retrieval and BA 45 for controlled selection of the retrieved items (Badre, et al., 2005). However, one study shows that the two processes interact, with no such BA 45 – 47 distinction according to selection and retrieval, with BA 45/47 recruitment in both instances (Snyder, et al., 2011).

While many of these tasks focus on verbal aspects of control, there has been relatively little investigation into the *amodal* nature of LIFG contribution to semantic control.

However, there are studies that investigate the LIFG's contribution to amodal semantic processing (with no manipulation of control) and they have often found activation for both picture and word semantic tasks. Many studies have reported activation in anterior LIFG (BA 45/47) for tasks using both picture and word judgements. For example, Vandenberghe, Price, Wise, Josephs, and Frackowiak (1996) report a common semantic network for pictures and words when participants were required to make associative or semantic size judgements across both modalities, with aLIFG activity (BA 45/47/11) across all task types and modalities. Similarly, Wagner et al. (1997) showed repetition priming effects for living/non-living and abstract/concrete semantic decisions in anterior LIFG (BA 45/47/46), for both verbal and picture modalities, however they do report that the picture task produced more 'modest' activity than the verbal task. While, Bright, Moss, and Tyler (2004a) report equal activation for both verbal and picture semantic categorisation tasks in anterior LIFG (BA 47). Other studies have used picture combinations to convey a meaningful or non-meaningful message, revealing activation for meaningful picture combinations in BA 45 (Tylen, Wallentin, & Roepstorff, 2009). There are also some studies which report more posterior recruitment of LIFG (BA 44/45) for tasks across semantic modalities. For example, Chee et al. (2000) report a common network for semantic tasks using Chinese characters, English words and pictures, including LIFG (BA 9/44/45). Another study which investigated the amodal contribution of LIFG beyond pictures by assessing activation for the subordinate meaning of words for both pictures and environmental sounds, reported posterior recruitment of LIFG (BA 6/8/44) (Adams & Janata, 2002). While these studies implicate a role for LIFG in amodal semantic processing, the relative contribution of the subdivisions along LIFG is not clear, nor is the specific contribution to semantic *control*.

The contribution of right inferior frontal gyrus (RIFG, i.e., right homologue of LIFG) to semantic control is interesting to explore, given a recent meta-analysis that showed reliable RIFG activation for semantic control (Noonan, et al., submitted). Many studies have reported bilateral IFG activation for tasks involving various aspects of semantic control (e.g., Bright, et al., 2004a; Shibata, Abe, Terao, & Miyamoto, 2007; Snyder, et al., 2011), especially processing (novel) metaphors (Ahrens et al., 2007; Eviatar & Just, 2006; Hoenig & Scheef, 2009; Lee & Dapretto, 2006); as well as studies reporting deficits in matching metaphors to pictures following right hemisphere lesions (Winner & Gardner, 1977). However, given the predominance of the left hemisphere in language, the role for RIFG in semantic control for verbal metaphors is likely to be quite constrained. For example, right hemisphere involvement may be necessitated by the relative salience of a given stimulus; for example, when a less conventional meaning of a word is required (Giora, 1997; Giora, Zaidel, Soroker, Batori, & Kasher, 2000). Similarly, Jung-Beeman (2005) suggests that right hemisphere activation is required for distant semantic relationships. This suggests that RIFG may act as a ‘back-up’ system for a more difficult/unconventional semantic relationship that the left hemisphere alone cannot resolve. Additionally, the right hemisphere has been shown to be involved in processing picture semantic material (Gazzaniga & Hillyard, 1971; Henke, Landis, & Markowitsch, 1993), as such RIFG may play a role in amodal/picture semantic control, as well as unconventional/metaphorical language.

There is also strong evidence to suggest that the semantic control network extends beyond IFG to posterior temporal and parietal areas. For example, patients with semantic aphasia (SA) who have lesions to LIFG (BA 44, 45, 47) and temporoparietal areas (TP: AG, pMTG) show similar deficits in semantic control (Noonan, et al., 2010), but have largely intact semantic representations (Jefferies & Lambon Ralph, 2006). The deficit is multimodal, extending to environmental sounds, action understanding, tool use, and pictures (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Corbett, et al., 2011). This is paralleled by a recent TMS study showing equivalent disruption of executively demanding semantic association judgements following TMS to pMTG and LIFG (Whitney, Kirk, et al., 2011). There is also extensive evidence from neuroimaging studies revealing pMTG involvement for tasks requiring varying aspects of semantic control (Badre, et al., 2005; Gold, et al., 2006; Noppeney, et al., 2004; Rodd, Davis, & Johnsrude, 2005; Thompson-Schill, et al., 1997; Whitney, Jefferies, et al., 2011; Zempleni, et al., 2007), and also from TMS studies (Whitney, et al., submitted; Whitney, Kirk, et al., 2011; Whitney, et al., 2012).

Furthermore, other posterior/parietal areas such as angular gyrus (AG, and intraparietal sulcus/IPL) have been implicated in semantic and domain general control (Noonan, et al., submitted; Seghier, et al., 2010). For example in a TMS study manipulating both semantic and non-semantic feature selection, TMS to pMTG disrupted the semantic decisions only, while TMS to AG/IPS disrupted both semantic and domain general feature selection. Recent investigations indicate a functional specialisation along AG for domain general and semantic tasks: for example, while dorsal AG may contribute to domain general and semantic control (as, indeed, our results from Chapter 3 confirm), more ventral areas may be preferentially recruited specifically for the semantic domain, and possibly activated irrespective of control demands (Binder, et al., 2009; Noonan, et al., submitted; Seghier, et al., 2004); however, our results in Chapter 3 suggest that there may be some modulation of activity in this area with increased demands on control across linguistic domain.

The current study uses verbal and picture semantic association judgements to assess the contribution of the semantic control network across the cortex. For example, while the graded distinction between phonology and semantics in LIFG has been widely investigated, the functional organisation of this area across picture and word semantic tasks is still relatively unknown. In line with the pattern of amodal semantic control deficits seen in SA, as well as some neuroimaging studies reporting similar activation for verbal and picture semantic tasks, we predicted that: 1) LIFG would be involved in both verbal and picture semantic control, with more anterior areas (BA 45/47) showing an amodal response due to their specialised involvement in semantic control; 2) a right hemisphere preference for picture stimuli, as well as for more unusual semantic judgements (e.g., Tylen, et al., 2009); 3) equivalent contribution of pMTG to verbal and picture semantic judgements; and, 4) an amodal response to verbal and picture semantic material in AG, given its role in both semantic and domain general control.

Method

The participants (N = 23), scanning parameters, procedure, and data analysis are the same as in Chapter 3.

Design

A within subjects 2 x 2 factorial design was used for the behavioural tasks, with task (semantic verbal, semantic picture) and difficulty (hard/easy) as factors.

Tasks

The probes were presented either auditorally (verbal task) or visually in picture format (picture task). Targets and distracters were presented either as written words (verbal task) or pictures (picture task). A three alternative forced choice (3AFC) format was used. The semantic verbal and picture tasks both involved making associative judgements on the *same* semantic stimuli, where probes and targets either shared low (hard) or high (easy) semantic associations. For example, “duck” with lake, cigar, or door; the only difference being the presentation modality of probes and answer choices (Table 4-1).

Condition	**Probe**	**Target**	**Distractor 1**	**Distractor 2**
Picture Easy				
Verbal Easy	Duck	Lake	Cigar	Door
Picture Hard				
Verbal Hard	Duck	Gun	Cigar	Door

Table 4-1. Task details.

Stimuli

The auditory probes were the same as in Chapter 3 (Method, p.54). Picture stimuli were coloured pictures all fitted to a standard 255 x 149 pixel size using GNU Image Manipulation Programme (GIMP http://www.gimp.org/), Adobe Photoshop 7.0 (www.adobe.com) and ImageMagick 6.3.7.9 (www.imagemagick.org/script/index.php). Stimuli were all concrete nouns acquired from the MRC psycholinguistic database (concreteness and imageability > 500; Coltheart, 1981; Wilson, 1988). Targets and distractors were developed using Edinburgh Association Thesaurus (www.eat.rl.ac.uk/). The same probe, distracters and associations were used across modalities (picture and verbal).

Region of Interest (ROI) Analysis

The ROIs for left inferior frontal gyrus, posterior middle temporal gyrus, dorsal angular gyrus/intraparietal sulcus, and mid angular gyrus were the same as those used in Chapter 3 (Method, p.54). An additional ROI of right inferior frontal gyrus (and the corresponding sub divisions, BA 44, 45, 47) was used in order to investigate the laterality of modality. These ROIs were created using ‘fslswapdim’ to ‘flip’ the ROIs to the right hemisphere.

Results

Behavioural Results

The assignment of semantic associations to easy or hard conditions was based on each participant’s reaction time (RT) across all accurate trials. There were 90 verbal semantic and 90 picture semantic trials, and an RT was recorded for each trial. In order to maximise the difference between easy and hard trials, the fastest one third (of the total accurate trials) were taken for each participant for the easy semantic condition; as well as the slowest one third (of total accurate trials) were taken for the semantic hard condition (the average number of trials selected per condition was 24). This method ensured that the effects we were modelling for easy and hard conditions were maximally distinct in terms of difficulty and not overlapping. This analysis was used because our original assignment of trials to easy and hard conditions revealed a large degree of overlap in RT (Figure 4-1; see Appendix 4.1 and Appendix 4.2 for the original RT analysis and fMRI results). Moreover, we noted that the assignment of items to difficulty conditions was potentially more problematic for pictures than words since free-association norms were used and these were based on verbal probes and responses. In contrast, the difficulty for picture trials depends on the specific choice of picture. By basing our assignment to conditions on RT we were able to match verbal and picture tasks for difficulty.

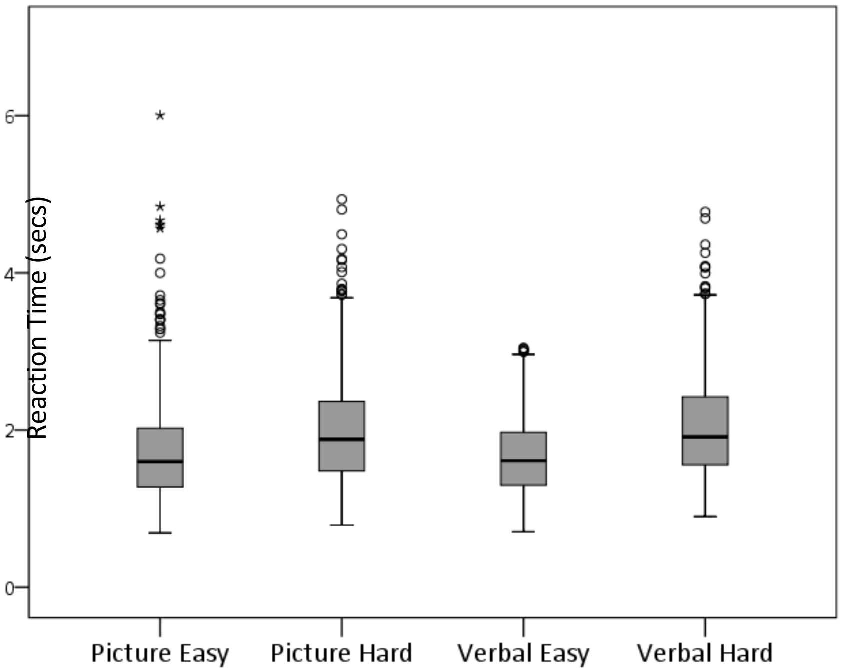

Figure 4-1. RTs for the original designation of easy and hard trials, where picture and verbal semantic RTs were highly overlapping for the hard and easy conditions. Error bars indicate minimum and maximum RTs, circles (1.5 IQR) and stars (3 IQR) indicate outliers.

Analysis of RTs Used for the Event Related fMRI Analysis

A comparison of RTs, for correct responses, across task modalities revealed no overall difference between the two tasks (F(1, 21) = 2.234, *p* = .150), while the difficulty manipulation, unsurprisingly, was highly significant across both tasks (F(1, 21) = 832.184, *p* < .001). Difficulty affected both tasks to the same degree, since there was no significant interaction of task by difficulty (F(2, 42) < 1). This suggests that the task and difficulty manipulation were well matched at the behavioural level within our stimuli subset (Figure 4-2).

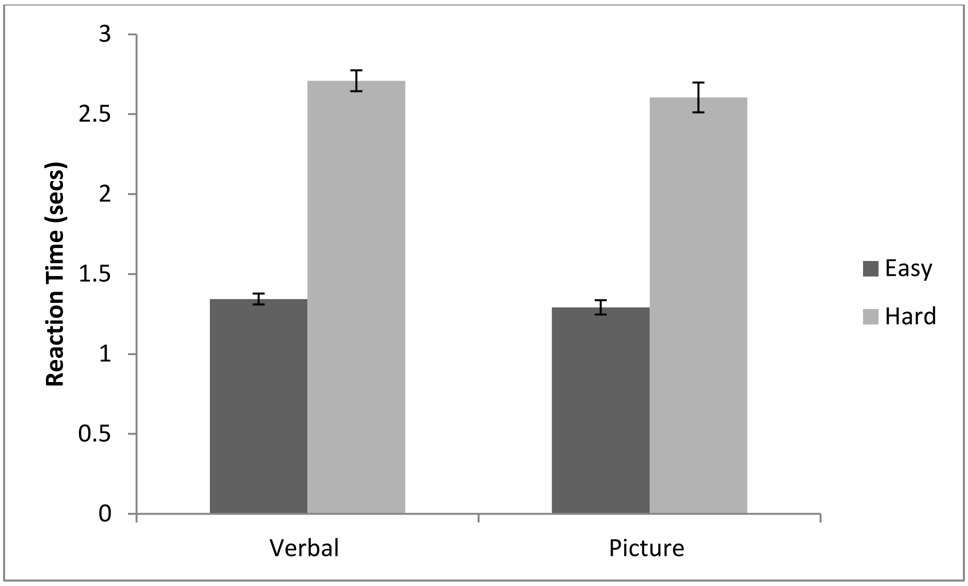

Figure 4-2. Behavioural reaction time for correct responses. Error bars indicate standard error of the mean.

Whole Brain Analysis

To investigate which areas were activated by the two modalities (verbal and picture semantic), whole brain analyses were used to reveal which areas were active against rest for the hard versions of the tasks. We used a cluster-based inference in FSL, with a cluster forming threshold of $Z = 2.3$, and corrected for multiple comparisons at $p = .05$. This ensured that we were capturing activation for these tasks, without the risk of cancelling out mutual activity using contrasts (i.e., activity seen in both the hard and easy conditions, which would be cancelled out in a hard > easy contrast). This analysis revealed common activity throughout LIFG (BA 44, 45, 47), left and right angular gyrus/IPL regions, right SMA and visual cortex. The verbal semantic task revealed activation of the temporal lobe bilaterally, extending into the temporal pole in the left hemisphere (Figure 4-3). Furthermore, Figure 4-4 and Figure 4-5 reveal activations for each task separately to show areas of peak activation as ‘hotspots’ in each modality.

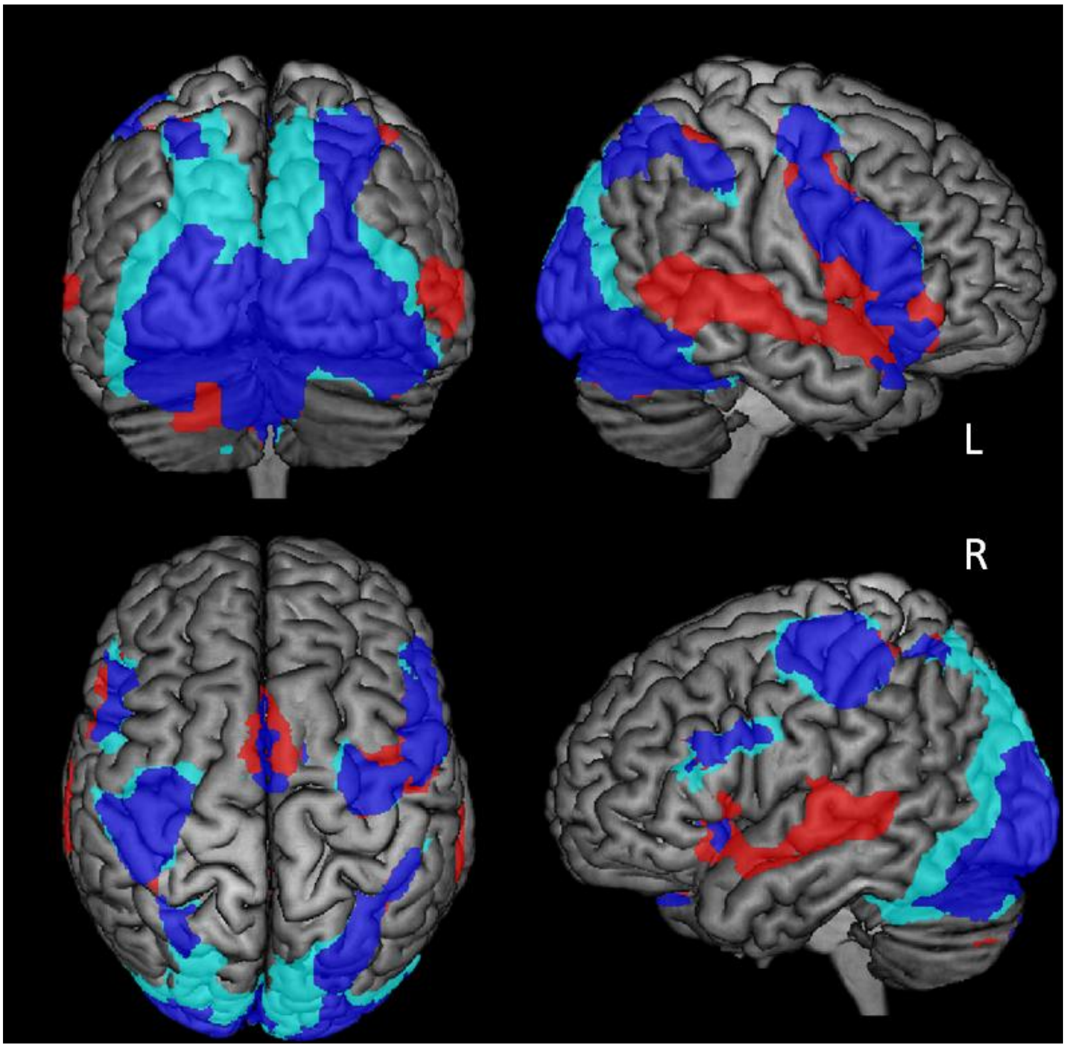

Figure 4-3. Whole brain analysis (cluster correction, $Z \geq 2.3$, $p < .05$). Semantic hard tasks over rest: verbal (red), picture (cyan) and overlapping activity (blue). L = left, R = right hemisphere.

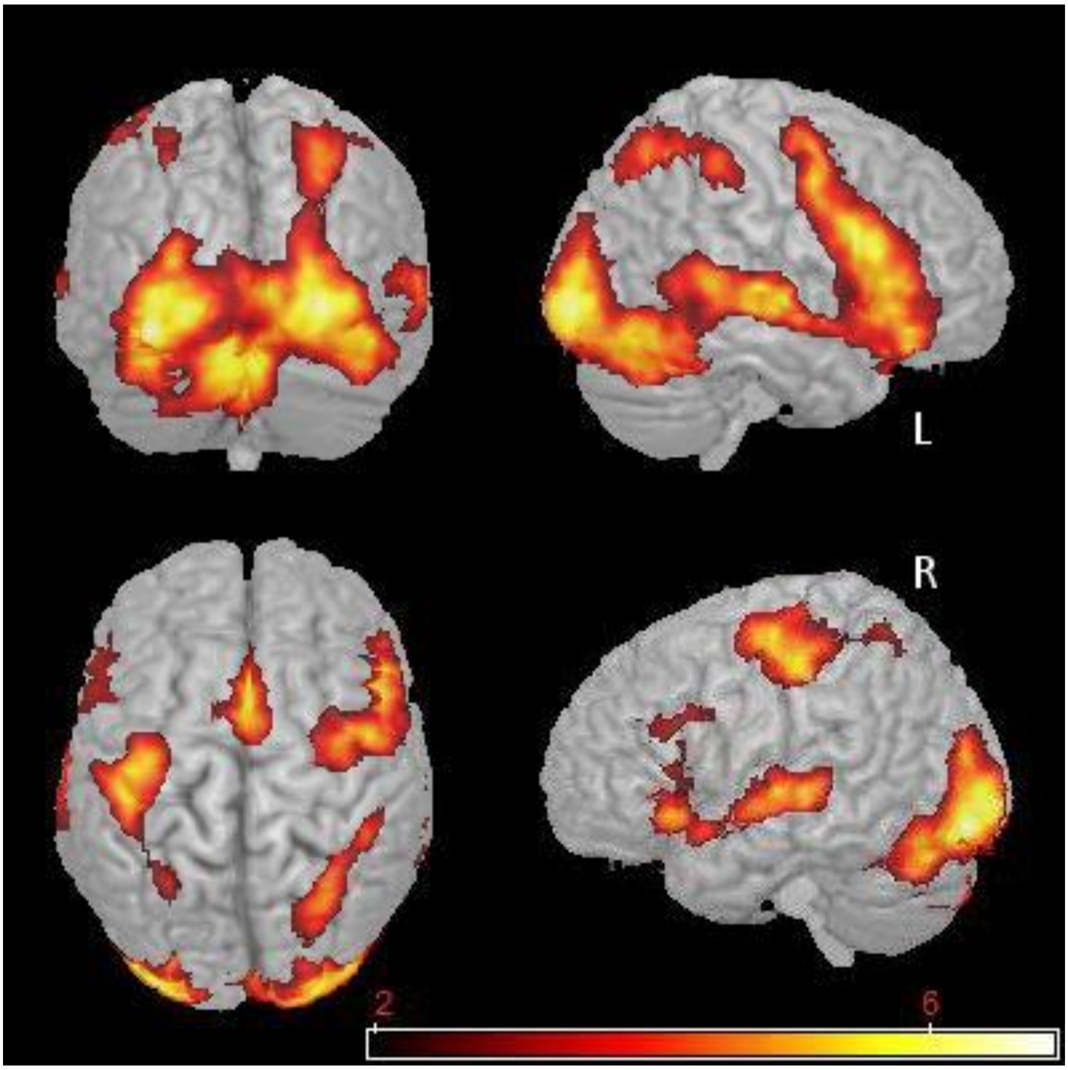

Figure 4-4. Cluster corrected whole brain analysis (*Z* ≥ 2.3, *p* < .05) of semantic verbal hard over rest. L = left, R = right hemisphere. *Z* values are indicated by the colour scale bar.

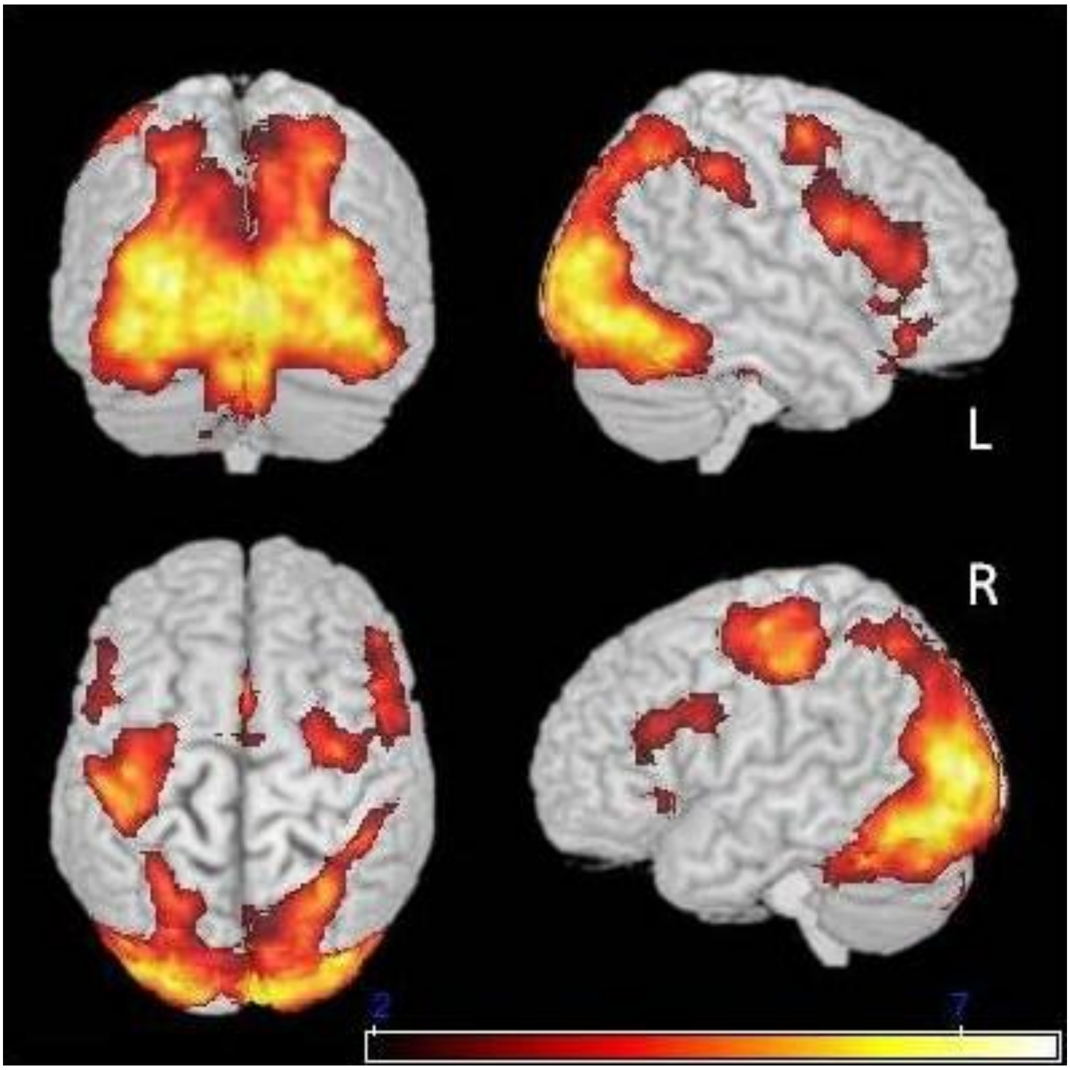

Figure 4-5. Cluster corrected whole brain analysis (*Z* ≥ 2.3, *p* < .05) of semantic picture hard over rest. L = left, R = right hemisphere. *Z* values are indicated by the colour scale bar.

Contrasts were also used to investigate which areas show additional recruitment when task demands increased. The contrast for the hard > easy verbal semantic task revealed activation in para and anterior cingulate gyrus, superior frontal gyrus, parietal lobe (precuneus, superior parietal lobule (BA 7)), anterior temporal gyrus, inferior frontal gyrus (BA 44, 45, 47), and superior and middle frontal gyri (BA 9, 10, 11). These contrasts can be found in Table 4-2 and Figure 4-6, and only clusters showing significant activation after cluster correction (*Z* = 2.3) are reported. Names of brain areas reported are labelled according to the Harvard-Oxford Cortical Structural Atlas, Talairach Deamon and the Juelich Histological Atlas built into the FSL view software library. The contrasts for the hard > easy picture semantic task revealed activation in paracingulate gyrus, middle frontal and superior frontal gyri (BA 10), left inferior frontal gyrus (BA 44), left angular gyrus (BA 39), left posterior middle temporal gyrus, posterior supramarginal gyrus (BA 40) and the parietal lobe (precuneus). These contrasts can be found in Table 4-3 and Figure 4-6.

Contrast of semantic verbal hard > easy judgements

Brain Area	BA	Voxels	*Z*	*x*	*y*	*z*
Cingulate Gyrus/ Medial Frontal Areas		4412				
L Paracingulate Gyrus	32		4.6	-4	28	32
L Paracingulate Gyrus	32		4.59	-4	26	36
L Paracingulate Gyrus / Superior Frontal Gyrus			4.5	0	18	50
R Superior Frontal Gyrus	8		4.43	4	24	52
R Superior Frontal Gyrus	8		3.91	0	30	46
L Anterior Cingulate Gyrus	24		3.91	-6	28	22
Parietal Lobe		1504				
R Superior Parietal Lobule / Precuneus			3.49	2	-60	50
R Parietal Lobe / Precuneus	~31		3.49	16	-62	24
L Precuneus / Superior Parietal Lobule	7		3.44	-8	-68	34
L Precuneus / Superior Parietal Lobule	7		3.43	-4	-70	34
L Precuneus / Superior Parietal Lobule	7		3.42	-6	-64	50
L Precuneus / Superior Parietal Lobule	7		3.32	-6	-58	48
Temporal Gyri		957				
L Inferior Frontal Gyrus / L Anterior Temporal Gyrus	47/38		4.25	-34	22	-10
L Anterior Superior Temporal Gyrus/ L Inferior Frontal Gyrus	38/47		3.46	-46	14	-10
L Pallidium			3.45	-14	0	-4
L Anterior Superior Temporal Gyrus/ L Inferior Frontal Gyrus	38/47		3.39	-52	20	-12
L Inferior Frontal Gyrus	44/45		3.22	-48	20	2
L Caudate/Putamen			3.02	-16	18	-6
Frontal Gyri		748				
L Middle Frontal Gyrus	10		4.45	-32	48	6
L Superior Frontal Gyrus (Sub Gyral)	10		3.23	-22	48	4

Table 4-2. Cluster corrected ($Z \geq 2.3$) contrast of hard > easy task difficulty for verbal judgements.

L Superior Frontal Gyrus	10		3.14	-26	62	-10
L Superior Frontal Gyrus	10		3.13	-28	62	-6
L Middle Frontal Gyrus			3.04	-28	58	2
L Medial Frontal Gyrus	11		2.87	-16	58	-14
Frontal Gyri		697				
R Insula			3.9	32	20	-4
R Inferior Frontal Gyrus/ Insula	47		3.75	40	18	-12
R Inferior Frontal Gyrus	47		3.63	30	16	-18
R Inferior Frontal Gyrus/ Insula	47		3.22	42	20	-6
R Frontal Orbital Cortex			3.13	22	8	-24
R Frontal Orbital Cortex			2.95	22	8	-20
Frontal Gyri		565				
R Inferior Frontal Gyrus	44/45		4.08	54	24	18
R Inferior Frontal Gyrus	44		3.66	54	22	26
R Middle Frontal Gyrus	9		3.4	48	26	30
R Inferior Frontal Gyrus	45		3.19	60	24	12
R Sub Gyral	~45		2.8	36	20	16

Table 4-2. Cluster corrected ($Z \geq 2.3$) contrast of hard > easy task difficulty for verbal judgements.

Contrast of semantic picture hard > easy judgements

Brain Area	BA	Voxels	*Z*	*x*	*y*	*z*
Cingulate Gyrus/ Medial Frontal Areas		13938				
L Middle Frontal Gyrus (Sub Gyral)	10		5.14	-30	50	4
R Paracingulate Gyrus/ Medial Frontal Gyrus	32		4.88	4	34	28
R Paracingulate Gyrus	32		4.86	2	34	32
R Paracingulate Gyrus/ Superior Frontal Gyrus	32/8		4.82	0	20	48
R Superior Frontal Gyrus (Sub Gyral)	10		4.78	32	50	8
L Inferior Frontal Gyrus	44		4.52	-52	14	10
Temporal Gyri		1976				
L Angular Gyrus	39		4.47	-56	-60	26
L Posterior Middle Temporal Gyrus			3.77	-56	-44	6
Lateral Occipital Cortex			3.68	-34	-80	40
L Posterior Middle Temporal Gyrus			3.67	-62	-40	-4
L Posterior Middle Temporal Gyrus			3.42	-58	-40	-8
L Posterior Supramarginal Gyrus	40		3.22	-62	-50	34
Parietal Lobe		925				
L Cingulate Gyrus/ Precuneus	31		3.6	-4	-48	40
L Precuneus			3.49	-6	-64	44
L Precuneus			3.43	-4	-54	42
L Cingulate Gyrus/ Precuneus	31		3.4	-12	-50	34
L Precuneus			3.23	-12	-64	26
L Precuneus			3.06	-4	-68	38

Table 4-3. Cluster corrected ($Z \geq 2.3$) contrast of hard > easy task difficulty for picture judgements.

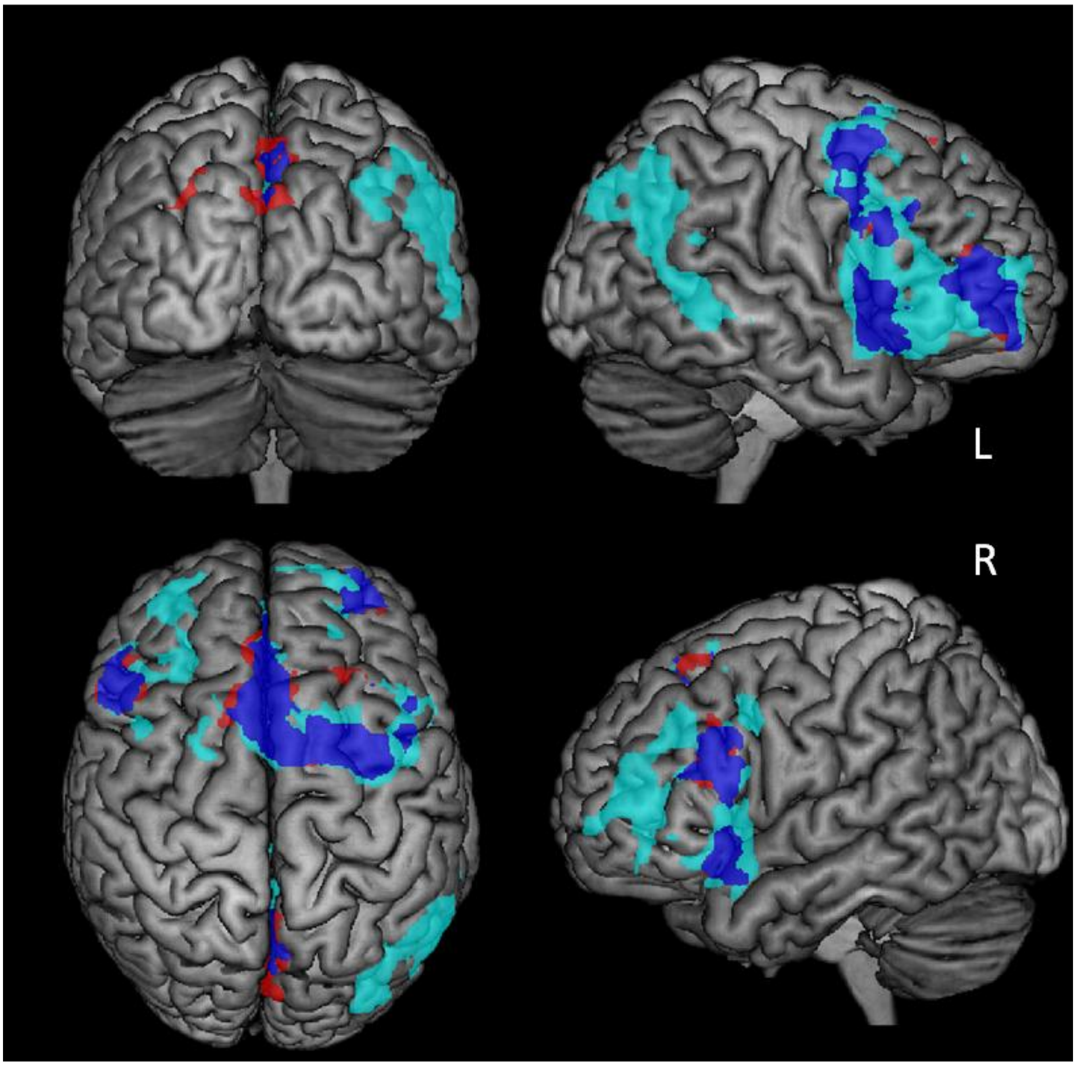

Figure 4-6. Whole brain analysis contrast of semantic hard > easy judgements (cluster correction, $Z \geq 2.3$, $p < .05$): Verbal (red), picture (cyan) and overlapping activity (blue). L = left hemisphere, R = right hemisphere.

Region of Interest Analyses (ROI)

Voxel corrected ($p < .05$) ROI analyses were used to further establish the relative contribution of brain areas that were the focus of our research questions to the verbal and picture semantic material. Featquery results were also used to investigate activation patterns (percent change) for each ROI. An advantage of interrogating specific ROIs using both techniques is that the voxel corrected mask allows functional specialisations within an area to be revealed, while the featquery method allows interactions between difficulty, task (modality), and regions to be easily investigated.

Left Inferior Frontal Gyrus (LIFG)

In order to explore the functional specialisation of LIFG for verbal and picture semantic material, we used an ROI to show where our tasks produced activation for 1) verbal hard > rest, and 2) picture hard > rest. There was a large degree of overlap in posterior to mid LIFG for the two modalities. Additionally, the verbal semantic hard task elicited more activation throughout this ROI extending into the most anterior and ventral parts of LIFG; however, the picture task activation was restricted to more posterior LIFG, with two small clusters in aLIFG (Figure 4-7).

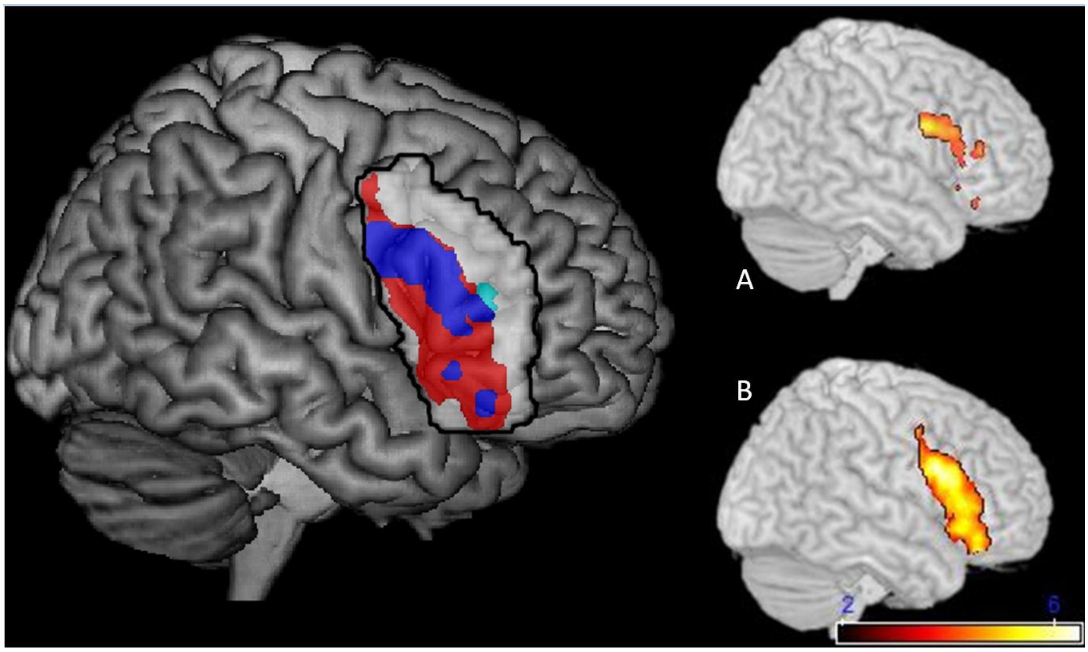

Figure 4-7. Voxel corrected ($p < .05$) ROI analysis of LIFG: The left-hand image shows the extent of activity for each task (red: verbal; cyan: picture; blue: overlap). The right-hand images show the regions in which activation was strongest (A: picture; B: verbal; *Z* values are indicated by the colour scale).

This large ROI was further investigated using the featquery tool in FSL to interrogate individual demarked subdivisions of LIFG (BA 44, 45, 47).

A direct comparison of the semantic tasks revealed that BA 44 responded more to the verbal than the picture modality ($F(1, 21) = 18.546$, $p < .001$). There was also a significant main effect of difficulty ($F(1, 21) = 64.663$, $p < .001$), with no interaction of task by difficulty ($F(1, 21) = 1.163$, $p = .293$). Overall, these results suggest that BA 44 is recruited for difficult tasks across modality, but shows additional activation for tasks in the verbal modality, in this case verbal semantic material (Figure 4-8).

A comparison within BA 45 revealed no main effect of task (F(1, 21) < 1), but there was a significant main effect of difficulty (F(1, 21) = 31.538, *p* < .001), with no interaction (F(1, 21) < 1). In summary, BA 45 is equally recruited by both semantic tasks, and helps to resolve difficulty across both modalities (Figure 4-8).

For BA 47 there was a significant effect of task type (F(1, 21) = 23.589, *p* < .001) and a significant effect of difficulty (F(1, 21) = 35.979, *p* < .001), but no interaction of the two (F(1, 21) < 1). We can infer that BA 47 is significantly involved in accessing verbal and picture semantic material when demands on semantic control are increased, while also showing a preference for verbal semantic material overall (Figure 4-8).

These analyses suggest that LIFG is recruited for both modalities, with differential recruitment in subdivisions of LIFG (verbal > picture, except in BA 45 which responds equally to both). These results provide some evidence towards a graded specialisation along LIFG with picture semantic material activating posterior IFG, with minimal activation in aLIFG, while the verbal semantic material activates the entire LIFG into the most anterior parts of BA 47; however the entire LIFG helped resolve difficulty for both tasks/modalities.

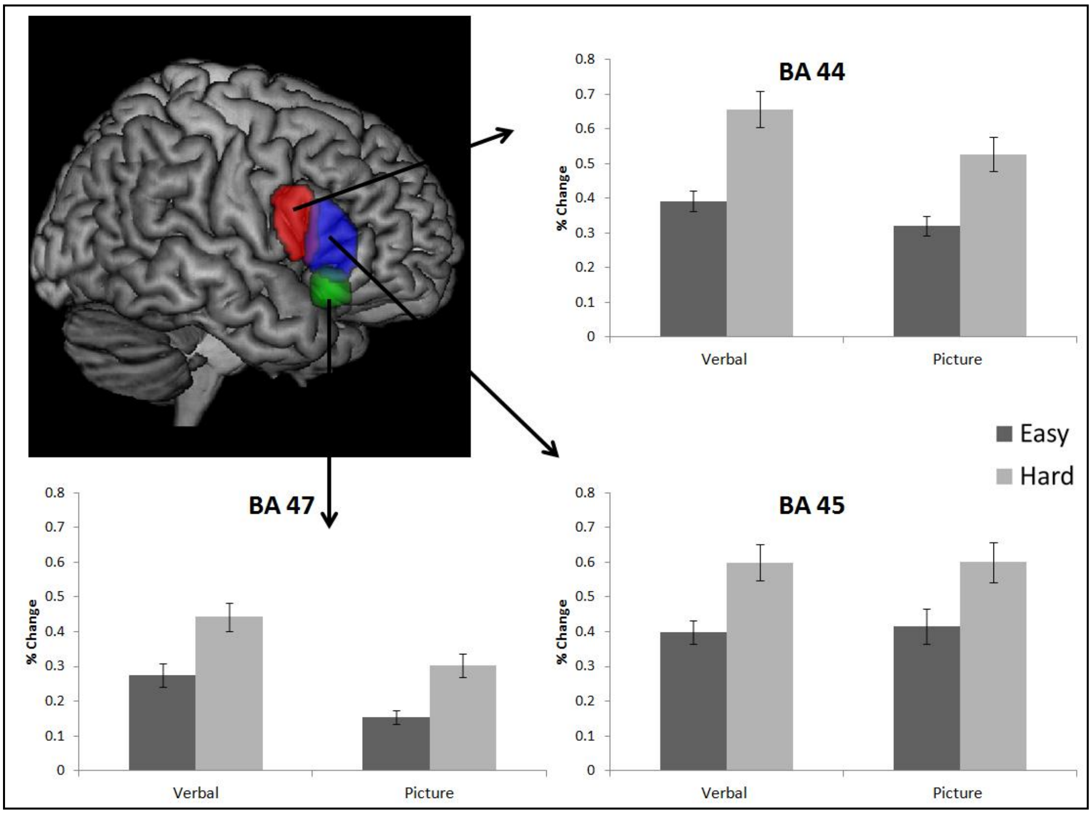

Figure 4-8. Left Inferior Frontal Gyrus percent signal change results. Error bars indicate standard error of the mean.

To further investigate any possible graded distinction across LIFG for semantic modality, between sites ANOVAs were used to reveal any between sites differences in response to modality and difficulty: BA 44 and BA 47 may be comparatively selective for verbal material, while BA 45 did not show modality specificity. A between sites ANOVA of BA 44 and BA 45 confirmed this difference (Table 4-4, Figure 4-9), with a significant site by task interaction (p = .027). Moreover, a comparison between BA 45 and BA 47 (Table 4-4, Figure 4-9) further confirms the amodal nature of BA 45 with a significant site by task interaction (p = .013). In contrast, a direct comparison of BA 44 and BA 47 (Table 4-4) revealed no significant site by task interactions (p = .361), but did reveal a significant site by difficulty interaction (p = .003), with the increase in activation for the difficulty manipulation in BA 47 being less than that in BA 44 (Figure 4-10). These between sites ANOVAs confirm the functional distinctions, predicted by our within sites ANOVAs, along LIFG: BA 44 and BA 47 were more activate for verbal than picture semantic material, and BA 45 responded in an amodal fashion to both verbal and picture semantic material.

Between Sites Comparisons

	BA 44 vs. BA 45	*BA 45 vs. BA 47*	*BA 44 vs. BA 47*
df	1, 21	1, 21	1, 21
Site x Task	5.68*	13.27**	< 1
Site x Difficulty	1.89	1.27	11.35**
Site x Task x Difficulty	≤ 1	< 1	< 1

Notes: **p* < .05, ***p* < .01, ****p* < .001

Table 4-4**.** F values for between (LIFG) site ANOVAs.

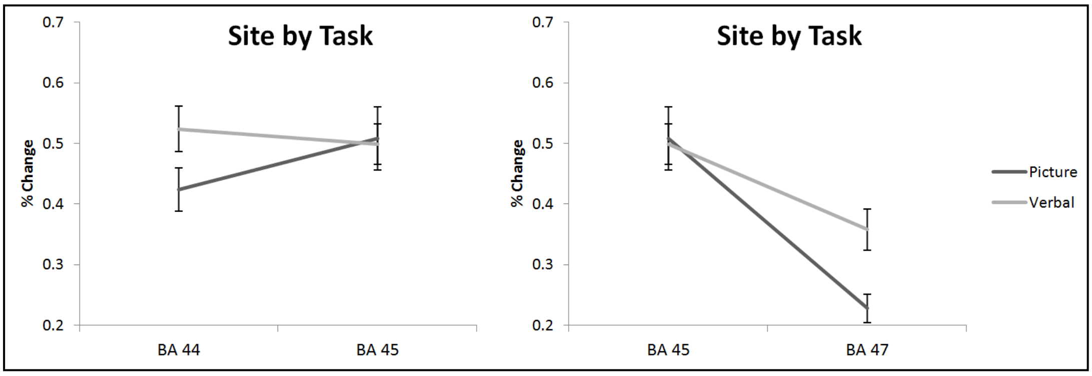

Figure 4-9. Interactions of site by task resulting from an investigation of percent signal change in LIFG sub-regions. Error bars indicate standard error of the mean.

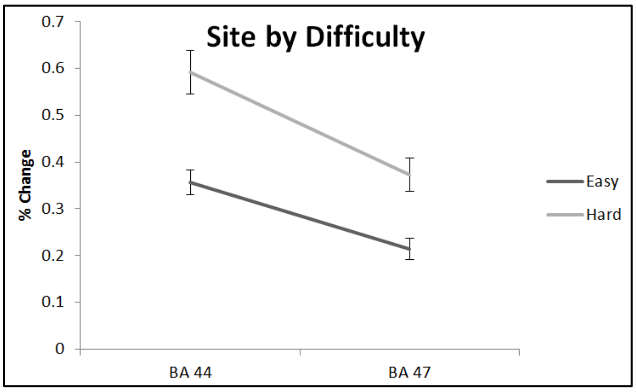

Figure 4-10. Interactions of site by difficulty resulting from an investigation of percent signal change in LIFG sub-regions. Error bars indicate standard error of the mean.

Right Inferior Frontal Gyrus (RIFG)

An ROI analysis of entire RIFG revealed constrained activation for both modalities, with the activation for the picture task in posterior LIFG (BA 44) and for the verbal task in anterior LIFG (BA 47). This large ROI was further interrogated using featquery of individual demarked subdivisions of RIFG (BA 44, 45, 47) (i.e., homologues of LIFG BA 44, 45, 47).

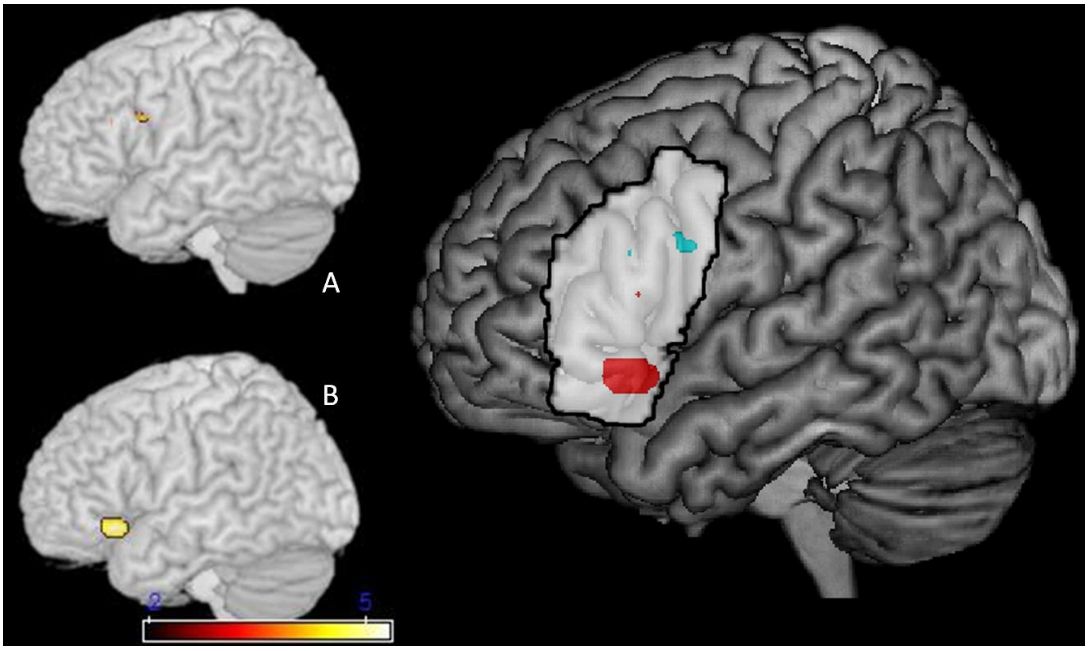

Figure 4-11. Voxel corrected ($p < .05$) ROI of RIFG: The right-hand image shows the extent of activity for each task (red: verbal; cyan: picture). The left-hand images show the regions in which activation was strongest (A: picture; B: verbal; Z values are indicated by the colour scale).

Right BA 44 revealed a significant main effect of task (F(1, 21) = 13.237 p = .002), corresponding to higher activation for the picture task. There was also a significant main effect of difficulty (F(1, 21) = 66.923, p < .001) but no interaction of task by difficulty (F(1, 21) < 1).

Interrogation of right BA 45 revealed a significant effect of modality, with a stronger response, again, for the picture task (F(1, 21) = 4.280, p = .05), and stronger activation for more difficult trials (F(1, 21) = 18.753, p < .001), with no interaction of task and difficulty (F(1, 21) < 1).

A comparison of the semantic tasks in right BA 47 revealed a significant difference between the two modalities (F(1, 21) = 8.508, p = .008) reflected by a higher response to the verbal modality. There was a significant main effect of difficulty (F(1, 21) = 20.766, p < .001), with no interaction of task by difficulty (F(1, 21) < 1).

The results show an increased response to picture stimuli in BA 44 and BA 45, whereas BA 47 retained its verbal modality preference.

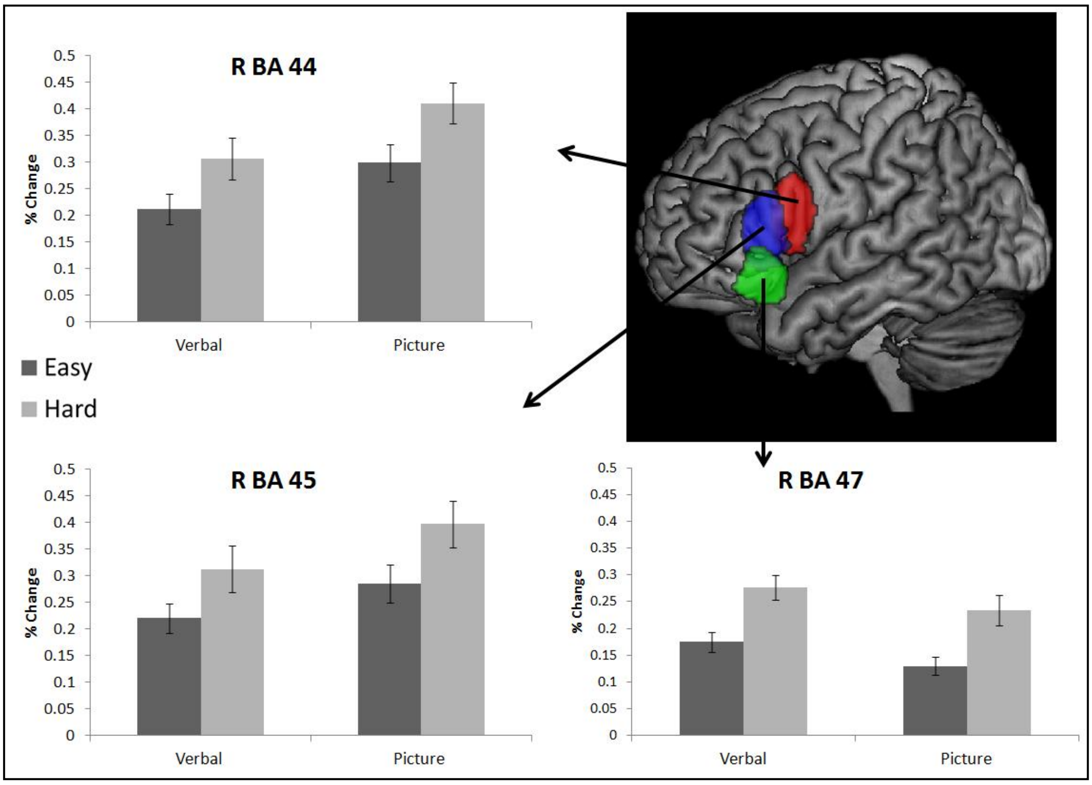

Figure 4-12. Right inferior frontal gyrus percent signal change analysis results. Error bars indicate standard error of the mean.

To further investigate any possible functional specialisation across RIFG for modality, between sites ANOVAs were used to reveal any differences in response to modality and difficulty between the subdivisions of RIFG. The within sites ANOVAs for right BA 44 and BA 45 suggest that the two sites are similar in their contribution to the semantic tasks, with a preference for the picture modality. A between sites ANOVA of the two sites (BA 44, 45) confirmed this similarity, with no interactions (F(1, 21) < 1). Comparisons with BA 47 confirmed that this site responded differently with significant site by task interactions when compared with both BA 45 (F(1, 21) = 9.41, *p* = .006; Figure 4-13) and BA 44 (F(1, 21) = 24.82 *p* < .001; Figure 4-13). There were no site by difficulty interactions (F(1, 21) < 1) and no three-way interactions (F1, 21) < 1) for any of the site comparisons. These between sites ANOVAs suggest functional distinctions along RIFG with BA 44 and BA 45 activated more by picture semantic material than verbal semantic material, and right BA 47 more responsive to verbal semantic material.

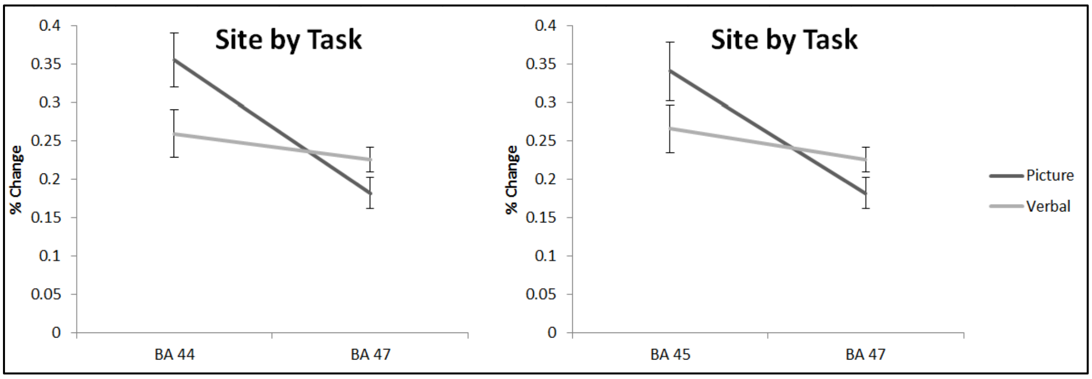

Figure 4-13. Interactions of site by difficulty in RIFG, resulting from interrogation of percent signal change. Error bars indicate standard error of the mean.

Comparisons Between Left and Right Inferior Frontal Gyrus

The within sites ANOVAs for left and right BA 44 suggest that left BA 44 is more responsive to verbal semantic material and right BA 44 shows a stronger response to picture semantic material. This was confirmed with a direct comparison of left and right BA 44, which revealed a significant hemisphere by modality interaction (F(1, 21) = 33.386, *p* < .001; Figure 4-15), and a hemisphere by difficulty interaction (F(1, 21) = 19.471, *p* < .001; Figure 4-14), due to a more modest increase in activity for the difficulty manipulation in right BA 44. This hemisphere by difficulty interaction was replicated in the comparisons of left and right BA 45 (F(1, 21) = 6.402, *p* = .019; Figure 4-14) and left and right BA 47 (F(1, 21) = 6.962, *p* = .015; Figure 4-14). There was no significant site by modality interaction for the comparison of left and right BA 45 (Figure 4-15). However, there was a significant site by modality interaction for left and right BA 47 (F(1, 21) = 18.976, *p* < .001; Figure 4-15), due to less dramatic difference between verbal and picture material in the right hemisphere. These results suggest that posterior and anterior IFG show greatest selectivity for modality, while BA 45 is activated equivalently by words and pictures across both hemispheres.

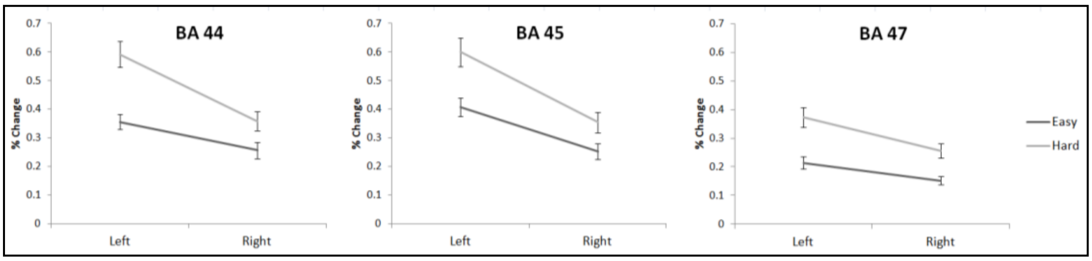

Figure 4-14. Hemisphere by difficulty interactions for BA 44, BA 45, BA 47, resulting from percent signal change ANOVAs. Error bars indicate standard error of the mean.

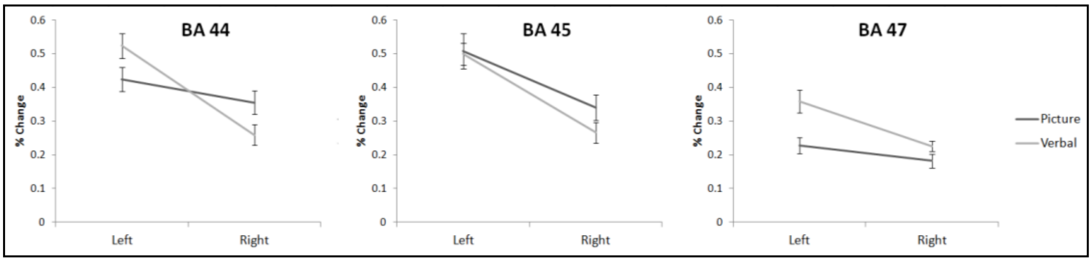

Figure 4-15. Hemisphere by modality interactions for BA 44, BA 45, and BA 47, resulting from a featquery interrogation of each ROI. Error bars indicate standard error of the mean.

Posterior Middle Temporal Gyrus (pMTG)

We used the contrast of high > low semantic control demands in Noonan et al.'s (submitted) meta-analysis to delineate a ROI in pMTG, allowing us to further investigate the amodal contribution of this site to semantic control. Only the verbal semantic task (hard > rest) revealed activation for this site (Figure 4-16). This was confirmed by a direct comparison of the two semantic tasks using featquery which revealed a significant main effect of task on percent signal change (F(1, 21) = 33.159, *p* < .001). There was also a main effect of difficulty (F(1,2 1) = 4.186, *p* = .054), and a significant interaction of task by difficulty (F(1, 21) = 6.207, *p* = .021). These effects were due to a greater overall response to the verbal semantic task, which showed no effect of difficulty (t(21) < 1), and in contrast an effect of difficulty for the picture semantic task (t(21) = -4.581, *p* < .001) was seen (Figure 4-17).

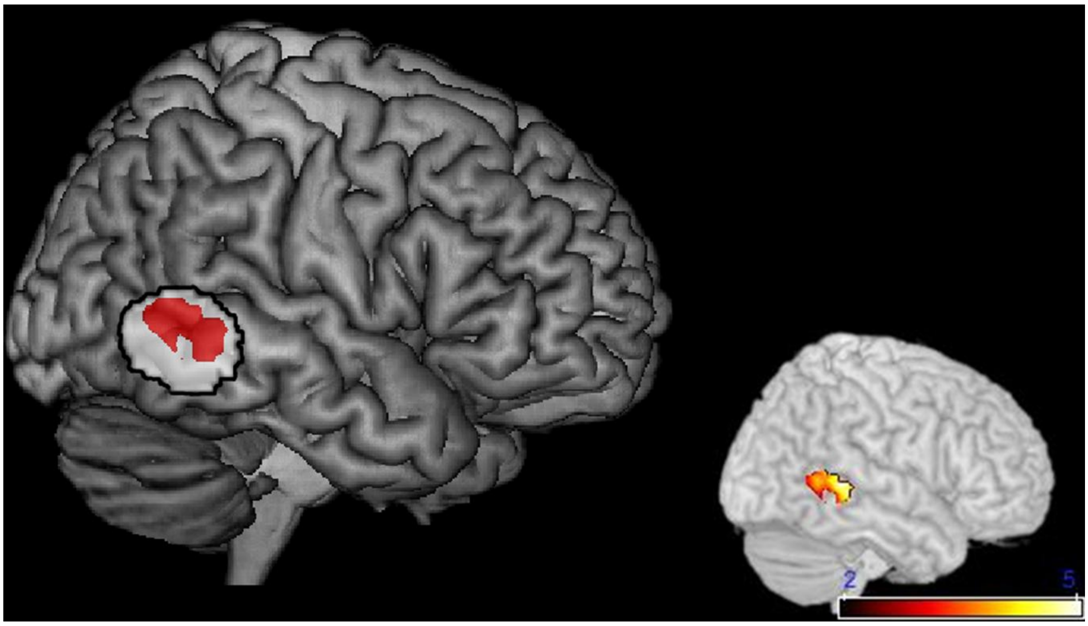

Figure 4-16. Voxel corrected (p < .05) ROI analysis of pMTG: the left-hand image shows the extent of activity for verbal semantic hard > easy task. There was no activity for the picture hard task. The right-hand image shows where the verbal hard activation was the strongest (*Z* values are indicated by the colour scale).

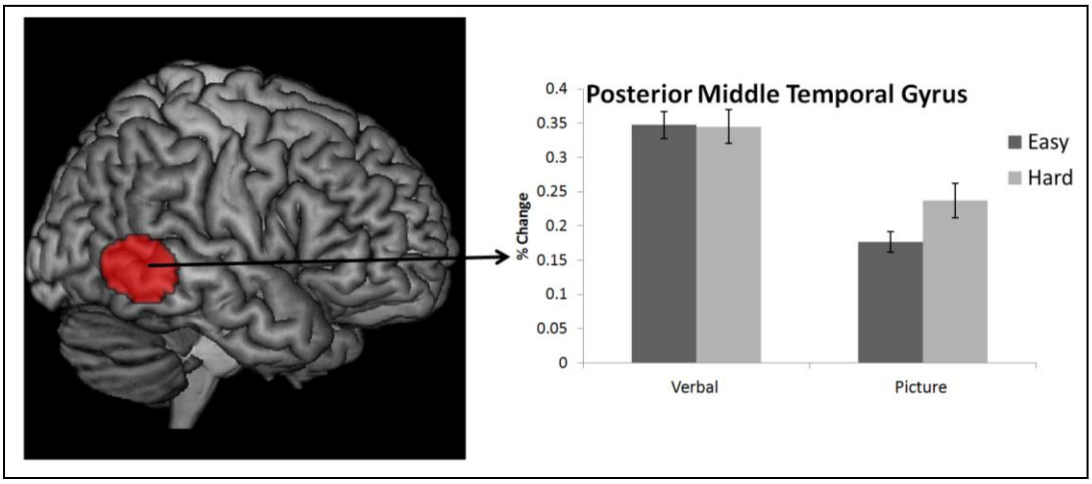

Figure 4-17. Percent signal change resulting from featquery interrogation of posterior middle temporal gyrus. Error bars indicate standard error of the mean.

Left Angular Gyrus: Dorsal/Intraparietal Sulcus (dAG/IPS) and mid Angular Gyrus (mid AG)

We used ROIs of dorsal angular gyrus/intraparietal sulcus (dAG/IPS) and mid angular gyrus (mid AG), resulting from a contrast of high > low semantic control in Noonan et al.'s (submitted) meta-analysis, to assess the degree to which these areas are specialised by modality. The ROI of dorsal angular gyrus/intraparietal sulcus (dAG/IPS) revealed overlapping activation in the anterior part of the ROI for both modalities (Figure 4-18).

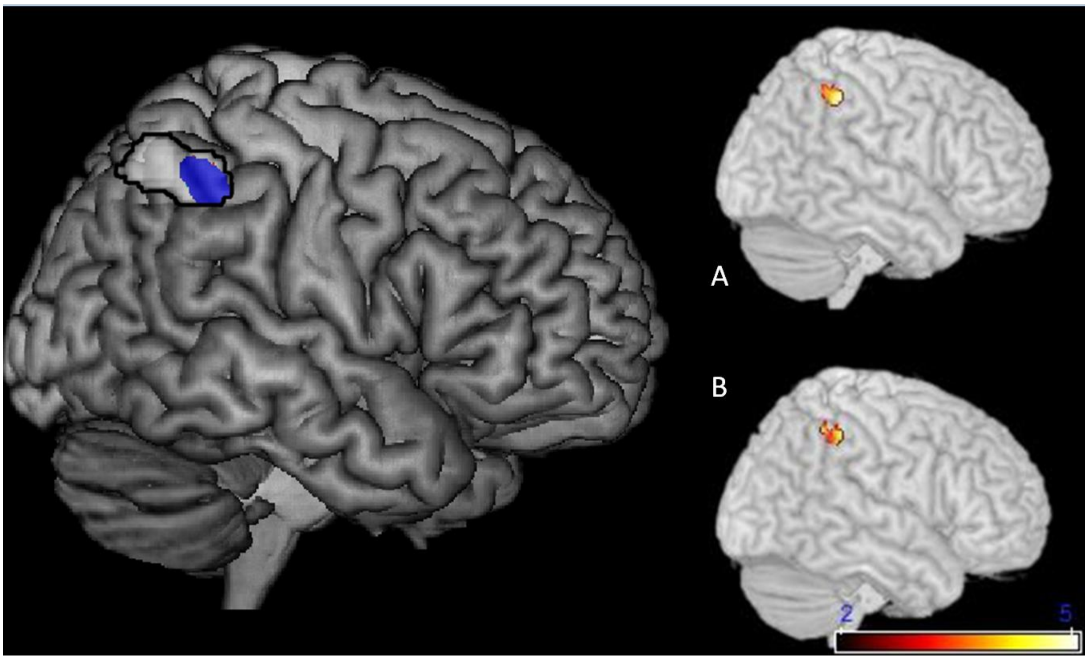

Figure 4-18. Voxel corrected (p < .05) ROI analysis of dorsal angular gyrus: The left-hand image shows the large degree of overlap for both modalities (blue). The right-hand images show the extent of the activation (A: picture; B: verbal; *Z* values are indicated by the colour bar).

Additionally, a direct comparison of the two modalities using featquery revealed no significant main effect of task (F(1, 21) < 1), but there was a main effect of difficulty (F(1, 21) = 14.769, $p \leq .001$) with no interaction of task and difficulty (F(1, 21) < 1; Figure 4-20). This suggests that a subregion in dAG shows greater activation for more difficult tasks, with no preference for either modality.

An ROI of mid angular gyrus (mid AG) showed overlapping activation in the most dorsal part of the ROI, with no further activation seen for either task in more ventral parts of the ROI (Figure 4-19).

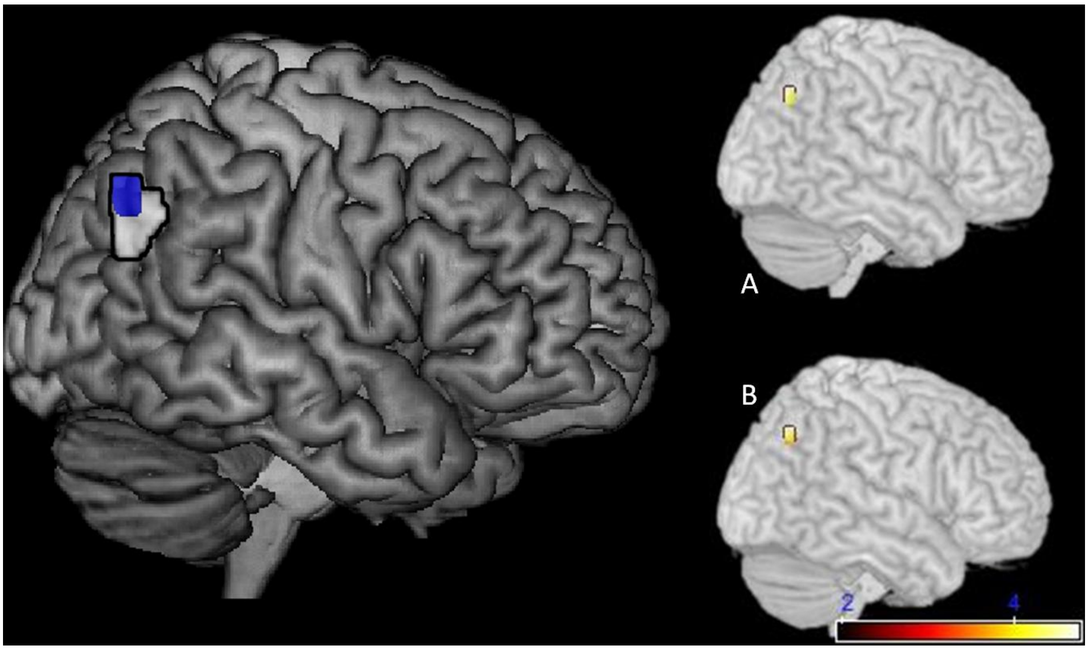

Figure 4-19. Voxel corrected (p < .05) ROI analysis of dorsal angular gyrus: The left-hand image shows the overlap of the two modalities in this site (blue). The right-hand images show the extent of the activation (A: picture; B: verbal; *Z* values are indicated by the colour bar).

The featquery interrogation of mid AG also suggests that this site does not respond preferentially to either semantic modality, with no main effect of task (F(1, 21) < 1). There was a main effect of difficulty (F(1, 21) = 49.681, *p* < .001), which did not interact with modality (F(1, 21) < 1; Figure 4-20).

The analysis of AG (dorsal/IPS and mid) shows similar recruitment across modalities, for both sites. There were no significant interactions between the two sites (site by task, site by difficulty, and site by task by difficulty: F(1, 21) < 2.4, *p* > .14).

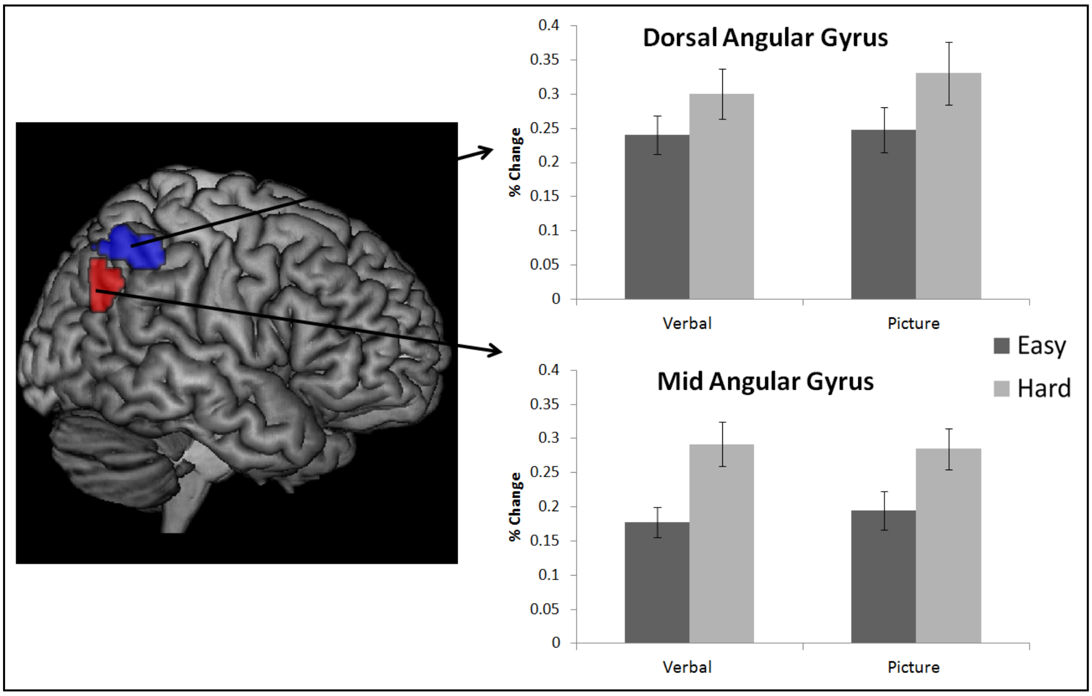

Figure 4-20. Percent signal change values for dorsal and mid angular gyrus. Error bars indicate standard error of the mean.

Discussion

This study aimed to address the relative contribution, across the cortex, of areas involved in *amodal* semantic control. Patients with semantic aphasia (SA) have semantic control deficits which are amodal in nature as they extend across a variety of stimulus types (e.g., words, pictures, sounds, objects; Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009). However there is a relative paucity of neuroimaging studies manipulating modality and semantic control demands simultaneously. While there is evidence to suggest a similar distribution of picture (and other modalities) and verbal semantic material across the cortex (e.g., Adams & Janata, 2002; Bright, et al., 2004a; Vandenberghe, et al., 1996; Wagner, et al., 1997), the question still remains as to how varying semantic control demands effects processing of semantic associations that are matched for items used (i.e., the same association for both verbal and picture tasks); given that almost all studies of semantic control have employed verbal materials and there appears to be only partial overlap between the network underpinning verbal semantic control and the domain-general multimodal network (Duncan, 2010). Our study reveals a highly similar distribution of picture and word semantic control across the network, with discrete differences. Given the number of regions investigated, each region will be discussed separately.

Left Inferior Frontal Gyrus

We used an ROI approach to investigate the graded distinctions often seen within LIFG, in accordance with its subdivisions. This approach allowed us to investigate discrete changes according to both modality and semantic control demands. Broadly, our findings confirm previous literature showing involvement of LIFG in verbal semantic control (Badre, et al., 2005; Thompson-Schill, et al., 1997; Whitney, et al., 2009; Whitney, Kirk, et al., 2011), while also revealing LIFG contribution to nonverbal (picture) semantic control (i.e., more challenging association judgements). We found that both BA 44 and BA 47, while showing increased activation for heightened difficulty across modalities, were preferentially recruited for *verbal* semantic material, while BA 45 responded to both modalities to an equal extent.

The finding that BA 47 responds to both modalities, but shows a stronger preference for the verbal semantic material is a novel finding, as some previous studies have found a similar contribution to the two modalities (Bright, et al., 2004a; Vandenberghe, et al., 1996; Wagner, et al., 1997), even without any manipulation of difficulty/semantic control. Our results are consistent with these studies as we saw significant activation throughout IFG into aLIFG when the tasks were contrasted against rest. However, our data highlight the discrete differences in the response seen in BA 47 to the two modalities: 1) there is a preference for verbal semantic material, but 2) the additional recruitment/activity for resolving difficult semantic associations is equivalent across both modalities. The lesser recruitment of BA 47 for picture semantic material may be explained by previous research implicating this area in abstract semantic control (Badre & D'Esposito, 2009). While the picture semantic judgements used the same associations (as the verbal judgements), the items are more concrete, as there can be no ambiguity as to which meaning of a word is to be associated. Not only this, but pictures also afford faster access to semantic representations than words (Potter & Faulconer, 1975; Wagner, et al., 1997). The verbal domain provides fewer constraints on semantic activation, making it a more abstract task, and BA 47 activity has previously been reported to be stronger for abstract/concrete judgements (in comparison to living/non-living) for both pictures and words (Wagner, et al., 1997), suggesting that this site may be modulated by ‘abstractness’

(Badre & D'Esposito, 2009). Taken together, BA 47 may be recruited for efficient access to semantic material in both the picture and verbal modalities, and is more likely to be recruited when the nature of the association is less concrete (i.e., when the demands on semantic control are heightened).

Additionally, the equivalent activation seen in BA 45 for the verbal and picture semantic material highlights this site's amodal contribution to semantic control. This site has been implicated in a wide variety of semantic tasks including semantic priming (Wagner, et al., 2000), word generation (Peterson, et al., 1988; Thompson-Schill, et al., 1997; Thompson-Schill, et al., 1999), selection (Thompson-Schill, et al., 1997), heightened response to novel over repeated semantic stimuli (Thompson-Schill, et al., 1999), resolving semantic ambiguity (Rodd, et al., 2005), and semantic knowledge violations (Hagoort, Hald, Bastiaansen, & Petersson, 2004). A role that often emerges for this site is that of selection amongst competing alternatives (Badre, et al., 2005; Nagel, Schumacher, Goebel, & D'Esposito, 2008; Thompson-Schill, et al., 1997), possibly because at the point at which selection is necessary, the relevant 'abstract' representation of a word has already been established (possibly via BA 47), along with any words associated with this representation, and thus selection of the relevant association becomes necessary. While there is still some debate over the exact contribution of BA 45 to semantic control, it is clear that its contribution is significant as well as amodal, as demonstrated by our results. Some studies have also suggested that BA 45 may contribute to domain general executive control (Duncan & Owen, 2000; Gold, et al., 2005; Thompson-Schill, 2003). However, Nagel et al. (2008) attempted to disambiguate semantic selection from response selection, and found that both BA 45 and 47 responded exclusively to *semantic* selection, while dorsolateral prefrontal cortex (BA 9/46) was recruited for *response* selection. Recent TMS studies also support a specific role for BA 45 in semantic/linguistic control, where TMS to BA 45 disrupted semantic judgement tasks, but not executively demanding non-semantic tasks (Whitney, Kirk, et al., 2011; Whitney, et al., 2012). This is corroborated by other findings showing that activation in LIFG is driven by semantic selection, not competition alone, in both implicit (Bilenko, Grindrod, Myers, & Blumstein, 2009; Grindrod, Bilenko, Myers, & Blumstein, 2008) and explicit tasks (Kan & Thompson-Schill, 2004a, 2004b; Thompson-Schill, et al., 1997; Thompson-Schill, et al., 1999; Thompson-Schill et al., 2002; Thompson-Schill et al., 1998; as cited in, Gindrod et al., 2008). While our results do not elucidate the role of this site beyond language control; they do show BA 45 recruitment for both phonological (Chapter 3) and amodal semantic control, suggesting that this site plays a crucial role in amodal language control.

Our results indicate that BA 44 shows greater recruitment for verbal semantic than picture semantic tasks. However, this site does play a role in amodal control as shown by the equivalent degree of *additional* recruitment for the difficult semantic association judgements across modality. While many studies have demonstrated domain general executive processing in BA 44, many are exclusive to the verbal domain (e.g., Gold, et al., 2005; Snyder, et al., 2007). One possible explanation for the verbal modality preference is that BA 44 has stronger connections with STG via the Arcuate Fasciculus (Anwander, et al., 2007; Petrides & Pandya, 2002), as such verbal material benefits from privileged access to BA 44 for resolving task difficulty, with a more incidental role in picture semantic difficulty due to connections to BA 45 (Petrides & Pandya 2002, as cited in Gough, et al., 2005; Hagoort, 2005; Ihara, et al., 2007).

The current study reveals modality specific dissociations along LIFG for semantic *control*. While LIFG responds to both semantic modalities, there are subtle distinctions, with the most anterior and posterior regions showing additional recruitment for verbal material, while BA 45 recruitment is equivalent across modalities. In light of the previous chapter, this dissociation can be further clarified highlighting further distinctions with modality preference. BA 44 appears to be recruited for linguistic control, with a specific preference for phonological material despite also being activated by tasks requiring amodal semantic control. This site is functionally and anatomically strongly connected with pSTG (Anwander, et al., 2007; Xiang, et al., 2010), while also less strongly connected to areas such as pMTG (Friederici, 2009; Xiang, et al., 2010) thus facilitating its ‘secondary’ role in semantic control. Like BA 44, BA 45 has functional connections to pSTG, pMTG, and inferior temporal cortex (Xiang, et al., 2010) and has thus been implicated in a wide range of tasks as discussed above. Some anatomical connectivity studies have shown that BA 45 is more strongly connected to semantic areas (ATL, via the external/extreme capsule (EmC)) than phonological areas (e.g., pSTG; Anwander, et al., 2007); however we did not see a clear preference for semantic material, instead we saw a domain and modality invariant response with an increase for difficulty across tasks. BA 47 is strongly connected to the ATL (and inferior occipitofrontal and inferior longitudinal fascicle) via the EmC, with an additional pathway along the uncinate fascicle (UF) into the ATL (Anwander, et al., 2007). These connections are in line with a role for BA 47 in semantic control, however our results indicate that while this site did help resolve difficulty across both modalities there was a preference for verbal semantic material.

Right Inferior Frontal Gyrus (RIFG)

Investigation of right IFG yielded a preference for the picture modality across both BA 44 and BA 45, however BA 47 remained preferentially recruited for the verbal modality. This confirms previous research reporting right hemisphere activation for semantic tasks using picture stimuli. For example, Kelley et al. (1998) required participants to encode words, pictures (line drawings of objects) or faces for a later memory test, and found RIFG to be more activate for the two picture conditions than the one relying strictly on the verbal modality alone. Similarly, Adams and Janata (2002) report an amodal response in right BA 44/45 when participants were required to match visually presented verbal subordinate items to pictures or environmental sounds. RIFG has also been reported in a variety of executive control tasks including auditory working memory (e.g., pitch, Zatorre, Evans, & Meyer, 1994), visual-spatial working memory (Wagner, 1999), and inhibition across modalities (Aron, Robbins, & Poldrack, 2004; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). While these studies indicate more domain general contribution of posterior RIFG (BA 44/45) to picture (and verbal) semantic control, R BA 47 appears to play a more specialised role in semantic control. Snyder, et al. (2011) report R BA 47 activation for tasks tapping selection and retrieval of verbal semantic material, as well as Bright, et al. (2004a) who report R BA 47 activation for picture semantic material. This is in line with our findings, where R BA 47 showed a clear preference for verbal material, but activation was still modulated by difficulty for picture semantic material. This adds more data to the suggestion that IFG may be hierarchically organised with more ‘abstract’/complex information activating the most anterior parts of IFG (Badre & D'Esposito, 2009), in our case, bilaterally.

Additionally, the relative contribution of left and right IFG is of considerable interest. We found a dissociation between left and right BA 44, with a clear leftward asymmetry for the verbal material, and a right sided preference for the picture modality. Meanwhile, left and right BA 45 did not differ greatly in response to modality. In contrast, BA 47 showed a clear preference for verbal material across hemispheres. Amunts et al. (1999) report a greater leftward asymmetry for left BA 44, but not 45, consistent with our results, where BA 44 shows greater asymmetry with respect to modality than more anterior parts of IFG. Additionally, the left IFG shows a greater relative increase for resolving difficulty than RIFG (across all three subdivisions). One possible explanation for this finding is the relative contribution of left and right IFG to different aspects of competition/difficulty. For example, RIFG has been implicated in inhibition of responses across domains/modalities (Aron, et al., 2004; Chikazoe, et al., 2007; Hampshire, et al., 2010). It may be the case that resolution of the difficult semantic associations in our tasks does not require strong inhibition, but rather strategic retrieval or selection. For example, our distractor items were not specifically designed to create increased demand for inhibition (i.e., no distractor items/information needed to be inhibited in order to allow for accurate target identification as in some tasks, where certain aspects of a semantic item/association must be attended to (e.g., feature selection; Whitney, et al., 2012)). Additionally, damage to RIFG has not been shown to have serious consequences for semantic control (Thompson & Jefferies, in prep), and thus suggests that RIFG is not a core part of the semantic network; but rather may act as a possible ‘back up’ for tasks requiring additional resources (e.g., Giora, et al., 2000; Jung-Beeman, 2005). For example, some studies implicate RIFG in metaphor understanding (e.g., Ahrens, et al., 2007; Eviatar & Just, 2006; Winner & Gardner, 1977), and accessing unconventional meanings of words or pictures (Tylen, et al., 2009); however Lee and Dapretto (2006) suggest that this role is not exclusive to RIFG as they report bilateral activation of IFG in their tasks which use non-literal words. As is seen in our study, LIFG is more heavily recruited than RIFG in resolving difficulty, but the dissociation between left and right IFG speaks to the widely distributed nature of semantic control, suggesting that both have a role to play.

Posterior Middle Temporal Gyrus (pMTG)

Posterior middle temporal gyrus (pMTG) has been implicated as a key part of the semantic network across many disciplines. For example, patients with semantic aphasia (SA) with temporoparietal infarcts have impairments on tasks requiring semantic control in both the verbal and non-verbal domain, but have intact semantic representations (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006). Additionally, neuroimaging studies have consistently shown pMTG activation for semantic retrieval/selection (Badre, et al., 2005; Bedny, et al., 2008; Copland et al., 2003; Gold, et al., 2006; Noppeney, et al., 2004; Noppeney & Price, 2004; Raposo, Moss, Stamatakis, & Tyler, 2006; Ruff, Blumstein, Myers, & Hutchison, 2008; Thompson-Schill, et al., 1997; Wagner, et al., 2001) and semantic ambiguity resolution (Gennari, MacDonald, Postle, & Seidenberg, 2007; Rodd, et al., 2005; Whitney, Jefferies, et al., 2011). Therefore, the results of the pMTG ROI analysis are both surprising and interesting. Firstly, the verbal modality preference which emerged is interesting as patients with damage to this area show multimodal deficits (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009), however it should be noted that their lesions are large and thus could incorporate areas, other than pMTG, involved in picture semantic cognition. Secondly, the finding that pMTG was modulated by picture semantic difficulty, but not verbal difficulty, is a surprising finding; it does, however, show that while the verbal modality elicited significant activity overall with no modulation for difficulty, pMTG was modulated by demands on picture semantic control as shown by the increase in activation for more challenging picture semantic associations. What might account for the lack of increased activity for the difficult verbal semantic associations when many studies report pMTG involvement in resolving competition? For example, TMS studies have shown pMTG recruitment for semantic associations in both the verbal and non-verbal modality (Hoffman, Pobric, Drakesmith, & Lambon Ralph, 2011), and have also shown disruption of the difficult, but not easy, verbal semantic associations following TMS to pMTG (Whitney, Kirk, et al., 2011). Perhaps most strikingly, pMTG was the second biggest cluster reported in a recent meta-analysis, comparing high and low semantic control (high > low) (Noonan, et al., submitted), thereby providing clear support for this site in semantic control. Noonan et al. (submitted) suggest that pMTG may have a specific role in capturing the context for which a given meaning of a word must be extracted. In the current study, using associative judgements, the demands on context may be constant across verbal difficulty manipulations, where the meaning of a word is less readily apparent than for picture semantic associations where there is less ambiguity as to the meaning of the word (as it is revealed by the picture). Turken and Dronkers (2011) report that five of the six major language pathways connect with MTG, connecting it with frontal (more specifically BA 47 along the IOFF), parietal (along the AF) and temporal areas (via the MdLF), as well as the right hemisphere (via the tapetum). This strong interconnectivity strongly supports the idea that pMTG plays a crucial role in the semantic control network, namely as the so-called “neural epicentre” or “convergence zone” for contextualizing semantic material.

Angular Gyrus/Intraparietal Sulcus

The comparison of picture and verbal semantic material in angular gyrus (AG), revealed a very similar response profile across both dorsal AG/intraparietal sulcus (IPS) and mid AG regions for both modalities. Neither site showed a preference for either modality and responded to the difficulty manipulation to an equal degree across modalities. This is in line with Binder, et al.'s (2009) suggestion that AG plays a role in high level amodal integration, as it is well connected with various association areas, while receiving little/no direct input from sensory cortices. Despite its equal contribution to the two semantic modalities, AG is unlikely to serve the semantic domain exclusively. For example, Nagel, et al. (2008) found LIFG (BA 45/47) to be specifically engaged by semantic selection, while AG (BA 7/40) was engaged by response selection (e.g., domain general selection). This is also corroborated by the findings from the previous chapter, where AG was engaged by both phonological and semantic tasks. More specifically, there is research to suggest a graded distinction along AG, with dAG/IPS involved in a variety of tasks such as perceptual, semantic, and phonological decisions (Chapter 3; Noonan, et al., submitted; Seghier, et al., 2004; Whitney, et al., 2012); and mid AG implicated more specifically in semantic tasks (Hoenig & Scheef, 2009; Noonan, et al., submitted; Seghier, et al., 2010), although our results from Chapter 3 indicate a more domain general interpretation for this site. Furthermore, mid AG may be the point at which the default and semantic networks overlap, as it shows *deactivations* for meaningless stimuli, but *activation* for demanding semantic tasks, word reading and non-stimulus driven semantic associations (Noonan, et al., submitted; Seghier, et al., 2004), as is the case in our study where a significant increase is seen for difficult semantic association judgements across modalities.

Furthermore, when combined with the results of Chapter 3, our data are in line with a role of dAG/IPS in feature selection (Cristescu, et al., 2006; Donner, et al., 2002; Whitney, et al., 2012; Woolgar, et al., 2011), as shown by the significantly greater contribution of this site to the phonological hard task (which required participants to attend to specific phonemes, as well as matching to other incomplete words), while perhaps it's role in amodal semantic control is incidental due to weak functional connections with BA 47 (Xiang, et al., 2010). Mid AG showed equivalent activation for both verbal domains in Chapter 3 and across both semantic modalities here. Therefore, this site may play a role in amodal integration across domains, as previously suggested by Binder et al. (2009).

Conclusions

This study sought to assess the contributions of the semantic control network to verbal and picture semantic associative judgements. Our results are compatible with the idea that semantic control is amodal and found consistent responses to both modalities across the network. However, small differences did emerge with regard to specialisation. Posterior and anterior LIFG may be recruited for verbal more than picture language tasks, while continuing to resolve difficulty across modalities. Meanwhile BA 45, which may act as a 'convergence zone' (Hagoort, 2005; Ihara, et al., 2007) was amodal and domain-free (Chapter 3) in nature. Additionally, a functional dissociation was found between left BA 44 and right BA 44, with left BA 44 predominance for verbal material and right for picture material. In contrast, BA 47 showed a preference for more abstract verbal semantic judgements bilaterally. Additionally, difficulty modulated activity in LIFG to a greater degree than RIFG; these findings are in line with the suggestion that RIFG acts as a 'back up' system for unusual/less salient semantic associations. The role of pMTG is less clear, but this site may play a role in contextualizing information, a requirement not always necessitated by picture semantic tasks. Lastly, AG also shows graded distinctions across domains (Chapter 3), but was amodal in its contributions to our semantic control tasks.

Chapter 5: A Transcranial Magnetic Stimulation Investigation of Phonological and Semantic Control in Left Inferior Frontal Gyrus and Posterior Middle Temporal Gyrus

Introduction

In Chapters 3 and 4 we investigated the contribution of various parts of the language network to domain (phonology vs. semantics), modality (picture vs. verbal) and control (ease with which the relevant target can be identified). Here, we focus the question on three specific areas: posterior left inferior frontal gyrus (LIFG; BA 44), anterior LIFG (BA 47) and posterior middle temporal gyrus (pMTG) in an attempt to tease apart and confirm functional specialisation using a technique that allows for focal, transient, 'virtual lesions': transcranial magnetic stimulation (TMS).

TMS is a useful tool for investigating language, as it allows for focal stimulation of brain areas purportedly involved in a certain cognitive function. This can be particularly helpful because language tasks can create large swathes of activation across the cortex, and as such TMS can go some way in helping to indicate which areas are necessary for a given function; particularly when the role of an area is contentious. For example, a majority of studies report overlap of phonological and semantic material in LIFG across a variety of tasks in fMRI, with some degree of posterior to anterior functional specialisation by domain (e.g., Amunts et al., 2004; Hagoort, 2005; Heim, Eickhoff, & Amunts, 2008; Noonan, et al., submitted; Poldrack, et al., 1999; Roskies, Fiez, Balota, Raichle, & Petersen, 2001; Vigneau, et al., 2006). Our results from Chapter 3 also support this assertion, as we found LIFG to be activated across phonological and semantic tasks, but with some degree of functional specialisation for phonology in posterior and semantics in anterior parts of LIFG. However, the extent of overlap can sometimes be so great that no differences are found in LIFG for phonological and semantic tasks, with the functional specialisation revealing itself via differential coactivation with posterior brain areas specialised by domain. For example, Gold and Buckner (2002) report coactivation of LIFG with pMTG for semantic tasks and LIFG with BA 6 and parietal cortex (40) for phonological tasks. Therefore, TMS can be a useful technique for investigating fine grained functional distinctions as it allows focal stimulation of areas purportedly involved in language control. Devlin, Matthews, and Rushworth (2003) used a combined fMRI and TMS approach, and stimulated BA 47 to disrupt semantic, but not phonological decisions, confirming the functional dissociation reported in their fMRI study. Similarly, Nixon, Lazarova, Hodinott-Hill, Gough, and Passingham (2004) stimulated posterior and anterior LIFG and disrupted phonological, but not a visual control task for the posterior site only (similar findings: Aziz-Zadeh, Cattaneo, Rochat, & Rizzolatti, 2005). One study directly contrasted stimulation of anterior and posterior LIFG with tasks in both domains (Gough, et al., 2005), and disrupted homophone judgements following stimulation of BA 44, and semantic synonym judgement tasks following BA 47 stimulation, demonstrating a functional dissociation within the same experimental paradigm.

While the functional dissociation in LIFG for phonological and semantic material has received some attention in the TMS literature, no studies have *simultaneously* investigated the effect of LIFG stimulation on control/difficulty across domains and modalities. There are two TMS literatures, one on domain across LIFG (e.g., Devlin, et al., 2003; Gough, et al., 2005; Nixon, et al., 2004) and one on control in BA 45 (e.g., Whitney, et al., submitted; Whitney, Kirk, et al., 2011; Whitney, et al., 2012), therefore this study was designed to integrate these investigations. TMS to LIFG (BA 45) has been shown to produce disruption of demanding *verbal* semantic association judgments, but not executively demanding non-semantic judgements matched in task format (Whitney, Kirk, et al., 2011; Whitney, et al., 2012). TMS can also be a useful tool when combined with data from the neuropsychological literature. For example, one study used TMS on healthy individuals to confirm their finding that patients with semantic aphasia who had damage encompassing LIFG, were impaired on abstract, but not concrete semantic judgements. These results are particularly powerful as they combine data from patients with brain lesions encompassing LIFG and data from the ‘virtual lesion’ method in healthy participants (Hoffman, Jefferies, & Lambon Ralph, 2010). One study used picture stimuli and slowed naming of simple line drawings when a TMS pulse to LIFG was applied 300 ms after picture presentation (but not at 150, 225, 400, 525 ms), but with no requirement of semantic control to complete the task (Schuhmann, Schiller, Goebel, & Sack, 2009). Taken together with Whitney et al.’s (Whitney, et al., submitted; Whitney, Kirk, et al., 2011; Whitney, et al., 2012) TMS data, this suggests that stimulation of LIFG may cause disruption of both verbal and picture tasks that place demands on semantic control. These studies highlight TMS as a useful tool for confirming/disambiguating our fMRI data (Chapter 3 & 4) where BA 44 and 47 showed preferential activation for the verbal modality (with subtle specialisation by domain – phonological/semantic), while still being modulated by difficulty across modality *and* domain.

Our ROI of pMTG in Chapter 3 and 4 contradicted our initial predictions about this site’s contribution to language: we did not find an effect for verbal semantic control, nor equivalent contribution to the semantic and phonological domains. Instead there was an effect of both domain and modality, though pMTG did show a significant response to both verbal semantic and phonological tasks, and a significant modulation of activity for picture semantic control. This site has, however, been implicated in semantic control across a number of disciplines (neuropsychology, fMRI, TMS; Corbett, et al., 2011; Jefferies & Lambon Ralph, 2006; Noonan, et al., 2010; Noonan, et al., submitted; Whitney, et al., submitted; Whitney, Jefferies, et al., 2011; Whitney, Kirk, et al., 2011; Whitney, et al., 2012), as such our tasks may not have captured the specific nature of pMTG’s role in semantic control (e.g., context integration; Noonan, et al., submitted). Nonetheless, TMS is a useful technique for clarifying the functional role of pMTG in language processing. TMS has previously been used to confirm the role of pMTG in verbal semantic control and revealed equivalent TMS disruption of semantic association judgements following stimulation of pMTG and LIFG (Whitney, Kirk, et al., 2011; Whitney, et al., 2012). There is a paucity of TMS studies confirming the role of pMTG in amodal semantic control, but one TMS study did slow both word and picture associative judgements following TMS to pMTG, but without the explicit manipulation of control/difficulty (Hoffman, et al., 2011), providing evidence for pMTG recruitment in both verbal and non-verbal semantic cognition. Therefore, stimulation of pMTG was of particular interest using our tasks, given our fMRI data did not strongly confirm the role of pMTG in semantic control across modalities, while these previous TMS studies have confirmed the role of this site in (amodal) semantic control.

The current study was designed to complement the fMRI findings in Chapters 3 and 4, therefore the same task manipulations were used for phonological, verbal and picture semantic material. Stimulation of BA 44 was expected to disrupt difficult phonological judgements, while TMS to BA 47 was expected to slow verbal semantic judgements (in line with other studies showing this dissociation; e.g., Devlin, et al., 2003; Gough, et al., 2005). Our fMRI results indicate that stimulation of LIFG may cause disruption of all demanding tasks, as we saw significant modulation of all three LIFG sites with difficulty. However, we also saw a verbal modality preference across BA 44 and BA 47 (Chapter 4), therefore stimulation of these sites may result specifically in verbal semantic disruption. Based on the literature which indicates a domain specific contribution of pMTG to semantic control

(Noonan, et al., submitted; Whitney, Jefferies, et al., 2011; Whitney, et al., 2012; Zempleni, et al., 2007), we predicted slowing of both verbal and picture semantic, but not phonological, judgments following stimulation of this site; however, our predictions were somewhat exploratory due to our unexpected main effect of domain (phonological > semantic verbal) and modality (verbal > picture) in Chapters 3 and 4. We also made use of a control site (as in Chapter 2), occipital pole, to confirm that any effects seen were site specific, and not due to general non-specific effects of TMS stimulation; as such no TMS effects were predicted at this site.

Method

Design

A within subjects 2 x 3 x 2 x 4 factorial design was used, with TMS (no stimulation vs. stimulation), task (phonological, verbal semantic, picture semantic), difficulty (hard vs. easy) and site (BA 44, BA 47, pMTG, OP) as factors. This study used the rTMS virtual lesion method, delivering a train of rTMS pulses offline; participants then performed the task immediately after stimulation, allowing us to rule out the possibility that the loud clicks associated with each pulse, jaw contractions, or eye blinks following peripheral nerve stimulation disrupted performance on the behavioural tasks. The order in which participants performed the task was counterbalanced, such that half of the participants performed the baseline (without TMS) behavioural task before TMS stimulation and the other half performed the baseline 30 mins or more post TMS stimulation, by which time the effects are believed to have washed out (Pobric, et al., 2007).

The stimuli and tasks used in this experiment are the same as in Chapter 3 (Method, p. 54) and 4 (Method, p. 98). Table 5-1 provides an example of each task.

Condition	Probe	Target	Distractor 1	Distractor 2
Phonological Easy	"duck"	truck	cigar	game
Phonological Hard	"duck"	tru_	_gar	ga_
Picture Semantic Easy				
Verbal Semantic Easy	duck	lake	cigar	door
Picture Semantic Hard				
Verbal Semantic Hard	duck	gun	cigar	door

Table 5-1. Examples of phonological, verbal and picture semantic trial manipulations.

Participants

Twenty-two participants were examined in this study (16 males; mean age = 23, SD = 2.3). All participants were right-handed, native English speakers recruited from the University of York student population and the general York population, and were compensated £40 for their time (£10 per TMS session). All participants were screened for TMS and MRI safety and were thus free from any history of neurological disease or mental illness and were not taking any prohibited medication.

Procedure

A PC running E-Prime software was used to present the tasks and record accuracy and RT. Responses were given with the right hand, using the first three fingers, corresponding to the positions of the three response options on the screen. The tasks started with a fixation screen for 400ms followed by the presentation of the auditory or picture stimulus along with the target and two distractor items, these remained on the screen until the participant made a response, triggering the next trial.

Participants performed practice trials before the experimental conditions began, in order to re-familiarise participants with the tasks. There were 30 experimental trials per task type and difficulty manipulation: phonological (hard/easy), semantic verbal (hard/easy), semantic picture (hard/easy); with participants performing a total of 180 trials per TMS condition (baseline, post-TMS). No trials were repeated within a session (the same trials were used for the semantic verbal and semantic picture tasks, but they never occurred in the same testing session: for example "bridge" – water might be presented as a verbal trial in week one, and a picture trial in week two). The order in which the trials occurred was randomised. Each task block was preceded by a screen which informed participants of the new task type, and participants pressed the space bar to continue. The majority of participants performed two baselines either before TMS or one before TMS and one 30 minutes post TMS stimulation – only one baseline was used for data analysis and we attempted to counterbalance this across trials.

Selection of TMS Site

Structural T1-weighted MRI scans were used to identify sites for stimulation in each participant's brain. For sixteen of the participants, the stimulation sites were identified from each participant's individual peak activations within the test-sites of interest (using Brainsight 2): we used the functional peak for the phonological task that fell within anatomically constrained area BA 44, and the semantic verbal tasks within BA 47 and pMTG. The average coordinate across participants for each site was as follows: BA 44: -52, -42, 2; BA 47: -46, 25, -2; pMTG: -45, 9, 13; and the occipital pole was measured as 20mm superior and 10 mm left of the inion, as in previous TMS studies (e.g., Ishibashi, et al., 2011). For the remaining six participants, the group average coordinate from the initial sixteen participants was used to identify the stimulation site, since we did not acquire functional MRI data for these six participants.

Brainsight 2 (Rogue Research, Montreal Canada, www.rogue-research.com/) was used to co-register participant brains and to identify stimulation sites prior to rTMS administration. Four landmarks were used for co-registering the participants head to their brain image (tip of the nose, bridge of the nose, left/right tragus).

Stimulation Parameters

Before TMS testing began, individual motor threshold was determined in each testing session. This was determined by the lowest stimulation intensity required to elicit contraction of the first dorsal interosseous (FDI) muscle in the contralateral hand. Motor thresholds ranged between 40% and 65%, with an average of 58% of maximum stimulator output. A 50 mm figure of eight coil, attached to a MagStim Rapid2 stimulator was used for repetitive magnetic pulses. Repetitive trains of TMS were delivered at 1 Hz for 15 mins; participants were stimulated at 120% of their motor threshold.

Data Analysis

We used a similar approach to data analysis as in Chapters 3 and 4, where participant reaction time was used as a measure of difficulty. Here, we used baseline data across all participants to create an average RT for each item, and used this to create sets of fast and slow semantic trials. For the semantic tasks, all 60 trials were collapsed and the fastest 25 items were assigned to the easy condition, the slowest 25 to the hard condition and the middle 10 items were discarded. For the phonological task, the fastest 25 rhyme trials (of 30) were used for the easy phonological condition, and the fastest 25 (of 30) phonological segment trials for the hard phonological task. We used the fastest trials for the phonological segment condition because this task was particularly challenging, therefore the average RT for trials for this task was higher than that of the other hard tasks; therefore in an attempt to match RT we selected the fastest trials. This new assignment of trials/items to hard and easy conditions was then applied to all of the baseline and post TMS data for each participant.

TMS disruption was expected to manifest itself in delayed RT, rather than a decline in accuracy (Walsh & Cowey, 2000), therefore, our primary dependent variable was RT for correct responses. Accuracy data can be found in Appendix 5.1: mean accuracy was lower for the hard versions of all three tasks; TMS effects emerged at site BA 44 for the picture and verbal hard tasks, and BA 47 for the phonological easy task. A composite score analysis that accounts for RT and accuracy can be found in Appendix 5.3. The data was screened for any RTs lying outside of 3 standard deviations of the participants mean for each task (phonological, semantic verbal, semantic picture), difficulty (hard/easy) and TMS condition (TMS/baseline), for that testing session.

Within subjects ANOVAs were used to analyze the effect of TMS on each condition, for each individual site (e.g., to establish an interaction of TMS by task by difficulty in BA 44). Additionally, effects emerging from ANOVAs were explored using paired sample t-tests. We did not correct our t-tests for multiple comparisons as the TMS effects were relatively weak and, in most cases, would not have survived the correction. As such, our results can only be interpreted tentatively, but are nevertheless interesting in light of the fMRI findings in Chapters 3 and 4.

Results

Posterior LIFG (BA 44)

Statistical tests for this site were used to test the functional specialisation of BA 44 for phonological material, and for verbal as opposed to picture semantic tasks.

Phonological and Verbal Semantic Comparisons

There was no significant effect of TMS (F(1, 21) < 1), and no interactions between TMS and task (F(1, 21) < 1), or TMS and difficulty (F(1, 21) = 2.405, *p* = .136). There was, however, a significant three-way interaction of TMS by task by difficulty (F(1, 21) = 6.558, *p* = .018). Paired-tests revealed significant disruption of the easy verbal semantic condition (*p* = .026), but no other significant TMS effects (Table 5-2). The significant three-way interaction therefore appears to reflect an absence of TMS effects for the phonological task, in the context of facilitation for demanding semantic decisions (Figure 5-1).

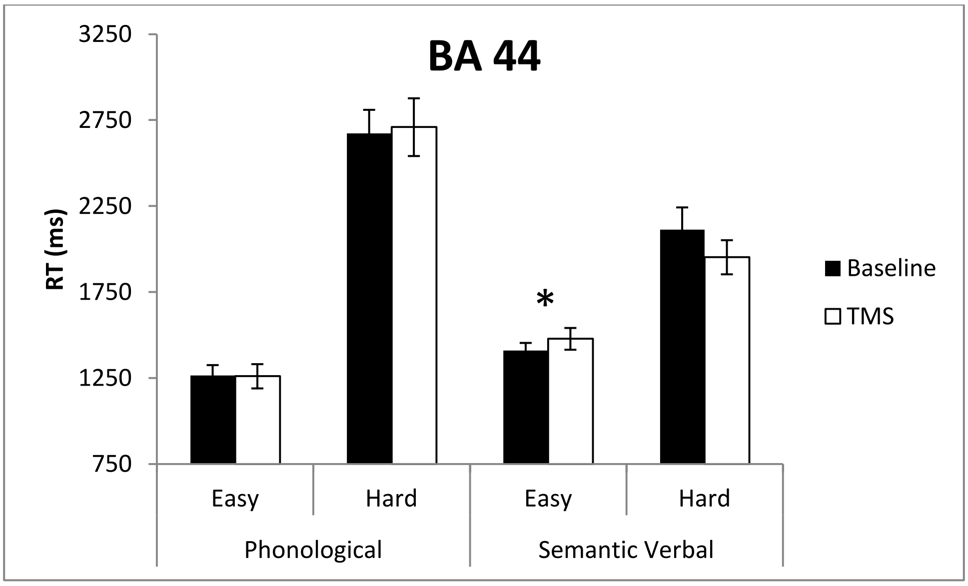

Figure 5-1. Baseline and TMS RTs for phonological and semantic tasks following TMS to BA 44. Error bars indicate standard error of the mean.

Verbal and Picture Semantic Comparisons

There was a marginal effect of TMS (F(1, 21) = 3.002, *p* = .098), and a significant interaction of TMS and difficulty (F(1, 21) = 15.375, *p* = .001), but no interaction of TMS and task (F(1, 21) < 1), and no three-way interaction of TMS by task by difficulty (F(1, 21) < 1). Paired t-tests for the picture semantic tasks revealed significant facilitation for the hard picture condition (*p* = .021; Table 5-2), that resembled the facilitation seen for the hard verbal semantic condition. The significant TMS by difficulty interaction therefore reflected the increase in RT for the easy versions of the tasks and the decrease in RT for the hard versions of the tasks following TMS (Figure 5-2).

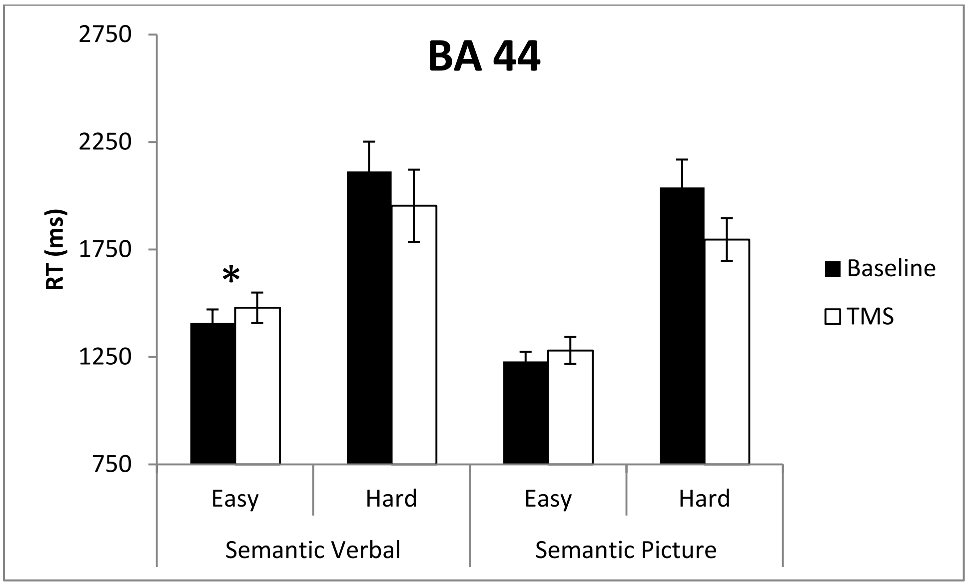

Figure 5-2. Baseline and TMS RTs for verbal and picture semantic tasks following TMS to BA 44. Error bars indicate standard error of the mean.

Anterior LIFG (BA 47)

Statistical tests for this site examined the hypothesis that BA 47 shows functional specialisation for semantic, over phonological, material. Additionally, we wanted to explore whether this site is recruited when participants are required to identify semantic associations for pictures as well as words.

Phonological and Verbal Semantic Comparisons

There was no significant effect of TMS (F(1, 21) < 1), and no interactions between TMS and task (F(1, 21) < 1). There was a significant interaction of TMS and difficulty (F(1,

21) = 13.574, *p* = .001), but no three-way interaction of TMS by task by difficulty (F(1, 21) < 1). Paired-tests revealed a significant inhibitory effect of TMS for the easy verbal semantic association judgements (*p* = .016), and significant facilitation for the phonological hard task (*p* = .048), but no other significant TMS effects (Table 5-2). The significant TMS by difficulty interaction is likely to be the result of the facilitation seen for both hard tasks following TMS. The significant slowing of the easy verbal semantic judgements shows some overlap with our fMRI results where BA 47 was preferentially involved in verbal semantic judgements (Figure 5-3).

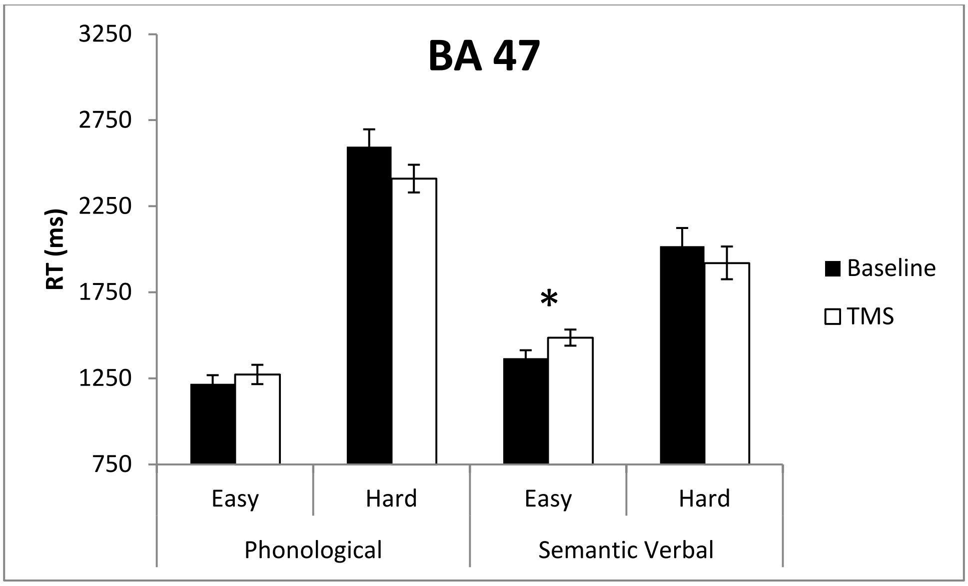

Figure 5-3. Baseline and TMS RTs for phonological and semantic tasks following TMS to BA 47. Error bars indicate standard error of the mean.

Verbal and Picture Semantic Comparisons

There was no effect of TMS (F(1, 21) < 1), and no significant interaction of TMS by task (F(1, 21) < 1), but there was a significant interaction of TMS and difficulty (F(1, 21) = 6.356, *p* = .020). The three-way interaction of TMS by task by difficulty was not significant (F(1, 21) < 1). Paired-tests revealed no significant TMS effects for the picture tasks (Table 5-2). The significant TMS by difficulty interaction is therefore likely to be a result of the facilitation seen for both hard tasks following TMS (Figure 5-4).

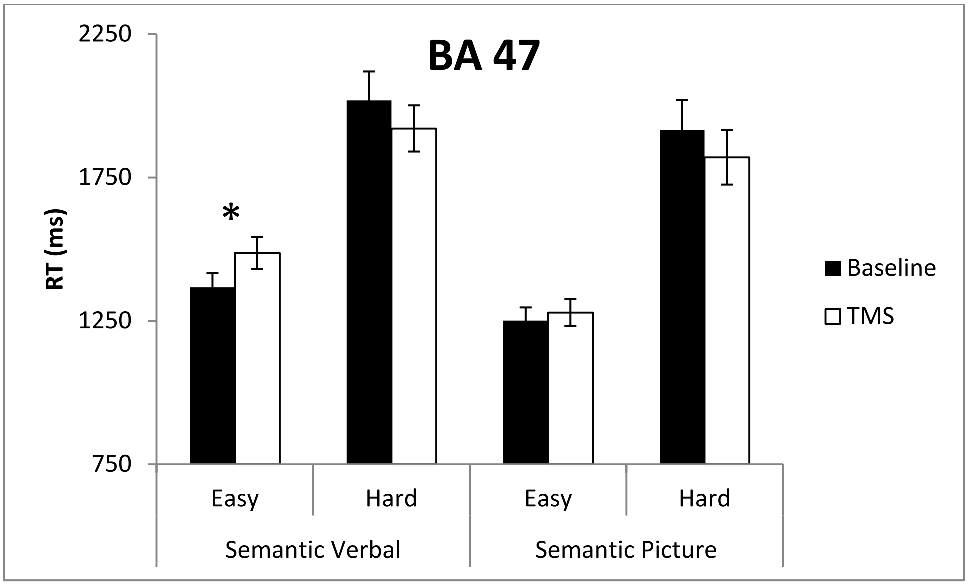

Figure 5-4. Baseline and TMS RTs for verbal and picture semantic tasks following TMS to BA 47. Error bars indicate standard error of the mean.

Posterior Middle Temporal Gyrus (pMTG)

Statistical tests for this site were used to explore the role of pMTG in both verbal and non-verbal semantic control.

Phonological and Verbal Semantic Comparisons

There was no significant effect of TMS (F(1, 21) < 1), and there were no significant interactions involving TMS (TMS by task, TMS by difficulty, TMS by task by difficulty: F(1, 21) $\leq$ 2.6, $p \geq .12$). As there were no significant effects, no further statistical tests were performed (Figure 5-5).

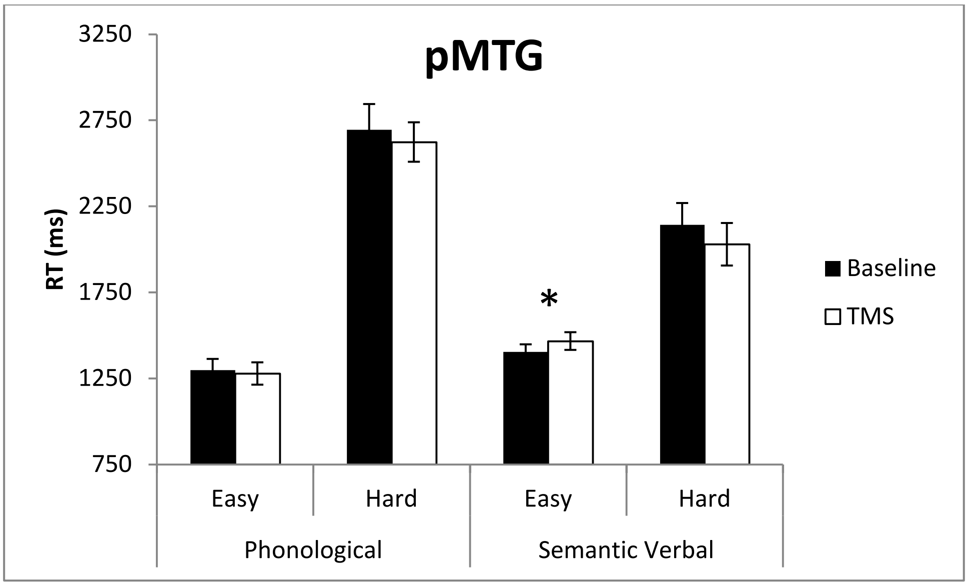

Figure 5-5. Baseline and TMS RTs for phonological and semantic tasks following TMS to pMTG. Error bars indicate standard error of the mean.

Verbal and Picture Semantic Comparisons

There was no effect of TMS (F(1, 21) < 1), and no significant interaction of TMS by task (F(1, 21) < 1), but there was a significant interaction of TMS and difficulty (F(1, 21) = 11.659, *p* = .003). The three-way interaction of TMS by task by difficulty was not significant (F(1, 21) < 1). Paired-tests revealed significant slowing of the easy picture condition (*p* < .001), and the easy verbal judgements (*p* = .053), as well as significant facilitation for the hard picture task (*p* = .021; Table 5-2; Figure 5-6). The significant TMS by difficulty interaction is likely to be a result of the facilitation seen for both hard tasks, while there was slowing for both easy semantic tasks, following TMS to this site. The finding that the semantic picture associations were slowed following TMS to pMTG is consistent with the significant increase in pMTG activity for hard relative to easy picture judgements (despite this task not producing significant activation over rest).

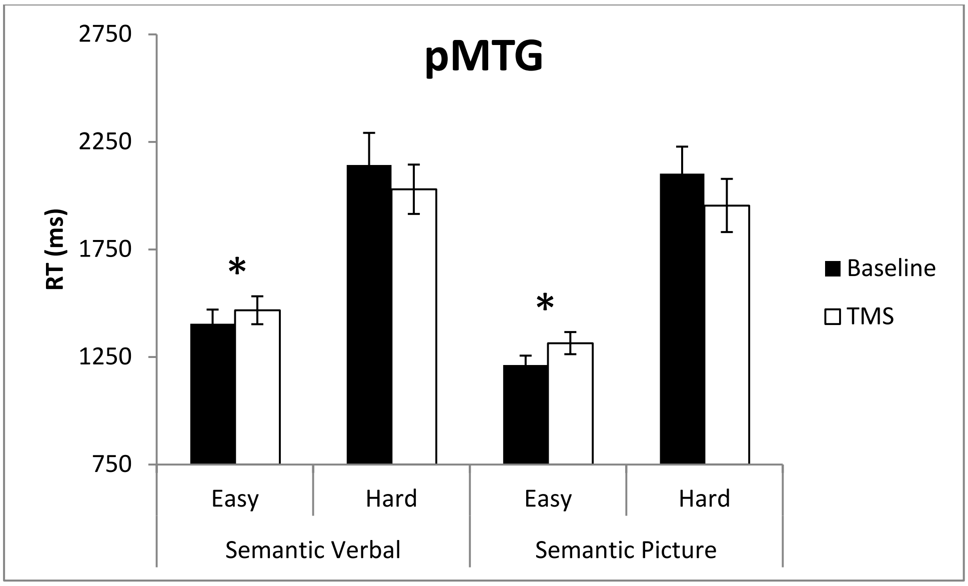

Figure 5-6. Baseline and TMS RTs for verbal and picture semantic tasks following TMS to pMTG. Error bars indicate standard error of the mean.

Occipital Pole (OP)

OP was used as a control site; therefore statistical tests were used to capture any non-specific effects of TMS (typically behavioural facilitation; Lambon Ralph, et al., 2009; Whitney, Kirk, et al., 2011).

Phonological and Verbal Semantic Comparisons

There was no significant effect of TMS (F(1, 21) < 1), and no interactions between TMS and task (F(1, 21) = 1.119, *p* = .302), and TMS and difficulty (F(1, 21) < 1), but there was a three-way interaction of TMS by task by difficulty (F(1, 21) = 7.135, *p* = .014). This three-way interaction was investigated using paired-tests and these revealed no significant TMS effects (Table 5-2, Figure 5-7). The interaction may have resulted from the facilitation seen for the verbal semantic hard task and not other tasks.

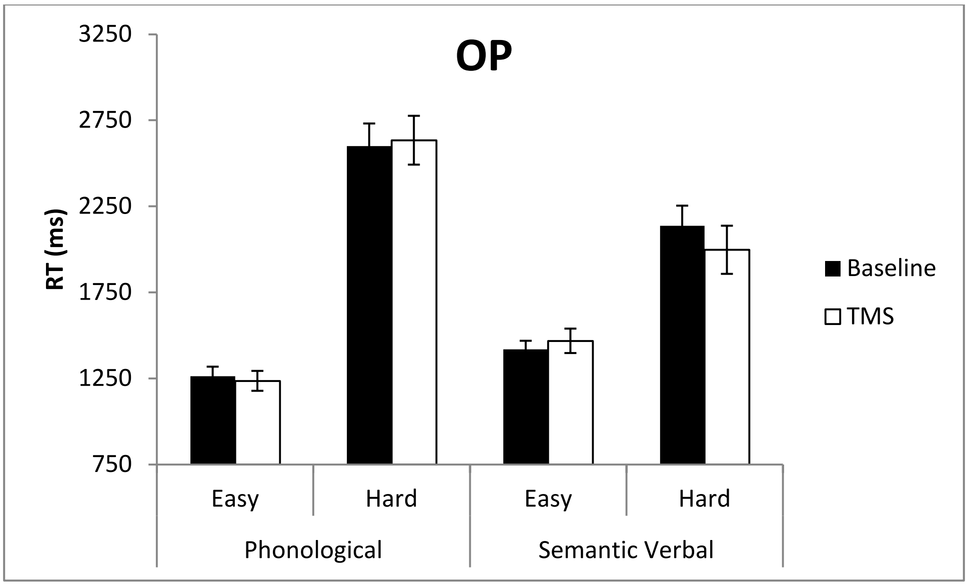

Figure 5-7. Baseline and TMS RTs for phonological and semantic tasks following TMS to OP. Error bars indicate standard error of the mean.

Verbal and Picture Semantic Comparisons

There was no significant effect of TMS (F(1, 21) = 1.831, *p* = .190), and no significant TMS interactions (TMS by task, TMS by difficulty, TMS by task by difficulty: F(1, 21) < 1). As there were no significant effects, no further statistical tests were performed (Figure 5-8).

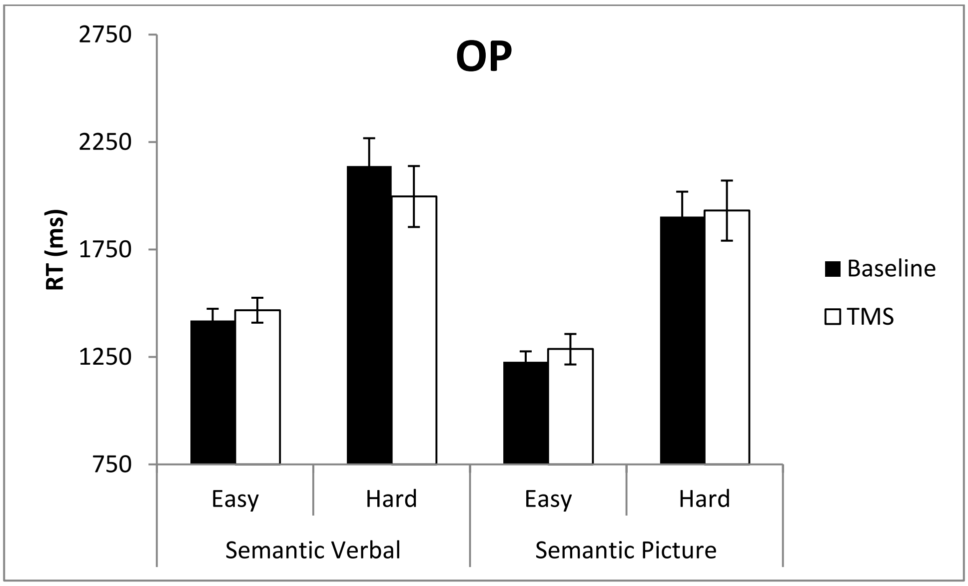

Figure 5-8. Baseline and TMS RTs for verbal and picture semantic tasks following TMS to OP. Error bars indicate standard error of the mean.

Table 5-2**.** T-tests comparing RTs for baseline and post TMS performance at each site

	Phonological		*Verbal*		*Picture*	
	Easy	*Hard*	*Easy*	*Hard*	*Easy*	*Hard*
df	21	21	21	21	21	21
BA 44						
t	0.13	-0.34	-2.07	1.99	-1.5	2.49
p	0.9	0.741	0.026*[a]	0.059[†]	0.075[a]	0.021[†]
BA 47						
t	-1.54	2.1	-2.32	0.87	-1.11	1.33
p	0.138	0.048[†]	0.016*[a]	0.395	0.28	0.2
pMTG						
t	0.76	.763	-1.69	1.06	-4.55	2.49
p	0.456	.454	0.053*[a]	0.3	.000***	.021[†]
OP						
t	1.03	-0.5	-1.52	1.221	-1.19	-.306
p	0.316	0.62	0.144	0.236	0.247	.762

Table 5-2. Paired sample t-tests. *Notes*: pMTG = posterior middle temporal gyrus, OP = Occipital Pole; *p < .05, ***p < .001, all comparisons are two-tailed; * denotes significant disruption; †denotes significant facilitation; [a]one-tailed t-test

Summary of Findings

The hard versions of each task did not show significant slowing following TMS for any of the sites. Participant RTs may have been at ceiling performance and therefore insensitive to the disruptive effects of TMS. Thus it may be the case that stimulation produces either no effect at all, or has an alerting effect on performance (for a graphical representation, see Appendix 5.2). Therefore, the TMS effects for the ‘easy’ versions of each task have been plotted in order to help summarise the TMS disruption for each task at each site. We found that TMS significantly disrupted verbal semantic judgements following stimulation of BA 44 and BA 47, with perhaps some indication that picture semantic judgments were slowed following TMS to BA 44 (non-significant) and that stimulation of pMTG resulted in significant slowing of picture and verbal semantic association judgments, but not phonological tasks.

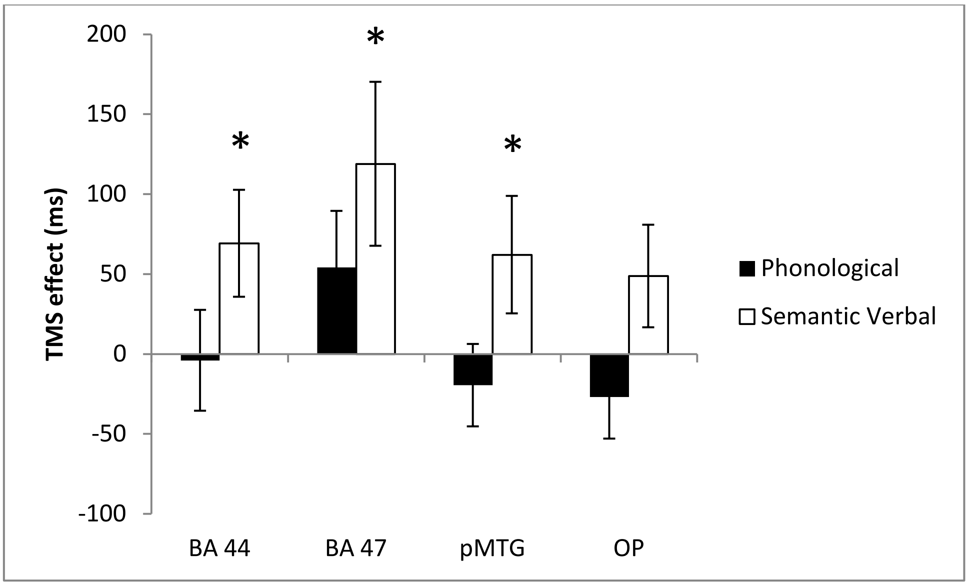

Figure 5-9. TMS effects. Difference in RT between TMS and baseline performance (TMS – no TMS) for each site. Positive values indicate a decline in performance following TMS. Error bars indicate standard error of the mean, *indicates a significant effect of TMS relative to baseline, *p* ≤ .05.

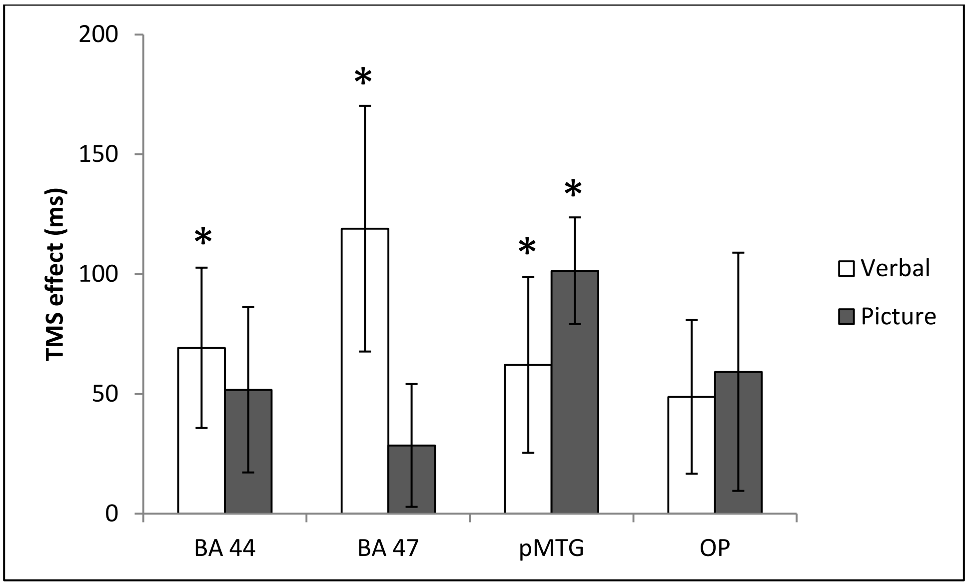

Figure 5-10. TMS effects. Difference in RT between TMS and baseline performance (TMS – no TMS) for each site. Positive values indicate a decline in performance following TMS. Error bars indicate standard error of the mean, *indicates a significant effect of TMS relative to baseline, *p* ≤ .05.

An additional analysis using composite scores can be found in Appendix 5.3.

Discussion

This study sought to confirm the functional dissociations within the language control network seen in both the literature and our own data (Chapters 3 and 4) by using TMS to disrupt performance in three test sites, BA 44, BA 47 and pMTG on tasks spanning domain and modality. We attempted to manipulate difficulty, but this manipulation proved insensitive to TMS: baseline performance for our ‘difficult’ tasks was so slow that if any TMS effects were seen, they resulted in generic facilitation. Thus in order to answer questions as to 1) specialisation by domain and 2) modality, the difficulty manipulation was discarded, and we focused our interpretation on the ‘easy’ version of each task only. Given the long RTs for the easy condition, these tasks may be better classed as challenging phonological rhyme, verbal and picture semantic decisions. In comparison to many other studies, our ‘easy’ RTs are long: For example, Gough et al. (2005) report RTs under 1,000 ms, even after TMS, across both their phonological and semantic tasks (as did: Devlin, et al., 2003; Nixon, et al., 2004), whereas our RTs exceed 1,200 ms on the ‘easy’ trials even without TMS. Using the ‘easy’ only trials we found: 1) disruption of verbal semantic judgements following stimulation of BA 44 that exceeded the effects for the phonological task; 2) significant slowing of verbal semantic judgements following TMS to BA 47 that exceeded the effects for the picture task; 3) TMS to pMTG resulted in slowing of semantic, not phonological, judgements, including a highly significant effect for picture semantic judgements, and slowing of the verbal semantic judgments; and 4) no effects of stimulation for occipital pole (OP).

The disruption of the verbal semantic judgements following stimulation of BA 44 partially confirms our fMRI findings (Chapter 4), where a preferential response to verbal semantic material was seen. Additionally, BA 44 showed significant activity for the picture semantic judgments which was also modulated by difficulty, despite being preferentially activated by verbal material overall (Chapter 4); similarly, stimulation of BA 44 showed slight (marginally significant) slowing of picture semantic judgments in our TMS study. However, the greater fMRI response in BA 44 to the phonological tasks (Chapter 3) was not confirmed by our TMS results, possibly because the phonological tasks were insensitive to TMS (as we did not see disruption for either phonological task following stimulation of any of our sites). However, significant disruption of phonological tasks following TMS to BA 44 has previously been shown (with less than half our N: Gough, et al., 2005; Nixon, et al., 2004): both of our phonological tasks had longer RTs than those in these studies which may have reduced the capacity for TMS to lengthen RTs. The verbal semantic disruption is in line with previous fMRI studies reporting BA 44 activation in tasks requiring selection from amongst competing semantic alternatives (Badre, et al., 2005; Thompson-Schill, et al., 1997). Furthermore, many studies shown posterior LIFG activation for tasks requiring both phonological and semantic control (Gabrieli, et al., 1998; Gold, et al., 2005; Noonan, et al., submitted; Snyder, et al., 2007). Our TMS data therefore add to the literature suggesting that BA 44 may contribute to linguistic (and possibly non-linguistic) control across modalities/tasks.

TMS to anterior BA 47 disrupted verbal, but not picture semantic judgements, which is in line with our findings in Chapter 4, where BA 47 showed preferential activation for verbal semantic material. Our results are also in accordance with previous TMS studies reporting disruption of semantic tasks in anterior LIFG (Devlin, et al., 2003; Gough, et al., 2005; Hoffman, et al., 2010; Whitney, Kirk, et al., 2011; Whitney, et al., 2012), while adding that stimulation of BA 47 does not affect picture semantic judgements, which is contrary to some fMRI studies reporting equivalent activation of verbal and picture semantic material (Wagner, et al., 1997; Wright, et al., 2011). This provides more evidence to suggest that aIFG is reserved for more abstract semantic judgments, whereby LIFG shows a gradient of specificity with tasks requiring use of abstract information necessitating recruitment of BA 47 (Badre & D'Esposito, 2009). Additionally, the lack of TMS effect for the phonological task agrees with both fMRI (Roskies, et al., 2001) and TMS studies (Devlin, et al., 2003; Gough, et al., 2005) reporting anterior IFG to be specific to the semantic domain. The combined fMRI and TMS study conducted by Devlin and colleagues (2003) speaks to our data: they found activation throughout LIFG for phonological *and* semantic tasks, and used TMS to show that despite the activation of anterior IFG areas for phonological tasks, stimulation of this site only disrupted the semantic task (with no disruption of their phonological task). This is similar to our data, as we found BA 47 to be active in fMRI for both phonological and semantic decisions (although upon further inspection, our ROI also highlighted a degree of domain specificity from dorsal to ventral BA 47) (Barde & Thompson-Schill, 2002; Gold & Buckner, 2002), but there was no effect of TMS at BA 47 for the phonological tasks. It is helpful to discuss our findings in light of other studies, as we did not manage to disrupt the phonological task at any of our stimulation sites, therefore the lack of effect cannot be taken as strong evidence against a role for BA 47 in phonology. However, other studies have confirmed this functional dissociation using TMS, and thus are helpful in drawing conclusions with regard to our own data.

Interestingly, while our picture semantic tasks did not elicit significant activation in pMTG, stimulation of pMTG was the only site which showed disruption of the picture semantic task. This finding is in line with another TMS study which disrupted picture semantic judgements following TMS to pMTG, while also disrupting verbal semantic tasks (Hoffman, et al., 2011). Previous TMS studies have shown that TMS to this site *does* significantly affect RTs for verbal semantic tasks (Hoffman, et al., 2011; Whitney, Kirk, et al., 2011; Whitney, et al., 2012); in fact stimulation of pMTG has disrupted numerous semantic task types involving both associative and feature selection judgements (Whitney, et al., 2012). Our TMS results showing significant slowing for picture semantic judgements have parallels with the neuropsychological literature where patients with semantic aphasia, who have lesions to temporoparietal regions, have been shown to have deficits in *amodal semantic control* (Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009), and this demonstrates an advantage of combining techniques (neuropsychology, fMRI, TMS). We also found no disruption of the phonological task following TMS to pMTG, in line with other studies suggesting a specific role for this site in semantic control (Noonan, et al., submitted), but our TMS results cannot confirm the involvement (or not) of this site in phonological tasks, as there is no evidence our phonological tasks were sensitive to the effects of TMS.

While our results show some similarities to both our fMRI data (Chapters 3 & 4) and previous findings in the literature, they also highlight some of the difficulties associated with using TMS. For example, while we used functional peaks from the fMRI data for sixteen of our twenty-two participants, the selection of TMS site was anatomically constrained, and as such we may not have been stimulating a site of maximal functional relevance. Previous TMS studies have stimulated BA 45 for their investigations of semantic control (Whitney, et al., submitted; Whitney, Kirk, et al., 2011; Whitney, et al., 2012), however our TMS sites were restricted to peaks falling within BA 44 and BA 47, and therefore may have reduced the likelihood of producing large TMS effects. Moreover, the facilitation seen for the majority of the hard conditions (Appendix 5.2, Figure 1 & 2) demonstrates the importance of creating tasks that are sensitive to the effects of TMS. Other studies have also reported general arousal following TMS to both control tasks and sites (Hoffman, et al., 2011; Lambon Ralph, et al., 2009; Pobric, Jefferies, & Ralph, 2010;

Whitney, Kirk, et al., 2011; Whitney, et al., 2012), and in some cases the experimental tasks as well (Drager, Breitenstein, Helmke, Kamping, & Knecht, 2004). While no strong conclusions can be drawn based on our TMS data, they do align well with our fMRI findings, and as such, are informative in that they: 1) tentatively confirm BA 44 and BA 47 preference for verbal over picture semantic material, and 2) cautiously implicate a role for pMTG in semantic associative judgements across modality (i.e., verbal and picture).

Chapter 6: A Study of Retrieval and Selection Processes in Left Inferior Frontal Gyrus and Posterior Middle Temporal Gyrus Using Cyclical Picture Naming

Introduction

We have shown that a distributed network of brain areas contributes to amodal semantic control (Chapters 4, 5), and in this chapter we turn to the contribution of, two areas within this network, left inferior frontal gyrus (LIFG) and posterior middle temporal gyrus (pMTG) to different aspects of semantic control. Patients with semantic aphasia (SA) who manifest deregulated semantic control provide an opportunity to investigate deficits across the semantic network, as they have lesions in both frontal (encompassing LIFG) and temporoparietal (TP; encompassing pMTG) brain areas. These patients have been shown to have deficits in semantic control across a wide variety of tasks and across modalities (e.g., environmental sounds, pictures, object use, verbal material; Corbett, Jefferies, Ehsan, et al., 2009; Corbett, Jefferies, & Lambon Ralph, 2009; Corbett, et al., 2011; Jefferies, et al., 2007; Noonan, et al., 2010). Additionally, a large body of neuroimaging and TMS literature implicate the two areas in semantic control (e.g., Gold, et al., 2005; Gold & Buckner, 2002; Hoenig & Scheef, 2009; Hoffman, et al., 2010; Noonan, et al., submitted; Noppeney, et al., 2004; Price, 2010; Whitney, et al., submitted; Whitney, Jefferies, et al., 2011; Whitney, et al., 2012).

The left inferior frontal gyrus (LIFG) has been extensively studied with regard to its contribution to semantic control, with some debate over the exact mechanisms (selection and retrieval) involved in recovering context-appropriate semantic information. Some research has shown LIFG recruitment for semantic tasks in which competing representations vie for *selection*: Thompson-Schill, D'Esposito, Aguirre and Farah (1997) found consistent increased activity in BA44/45 for selection from amongst competing semantic alternatives, across three different semantic tasks (generation, classification and comparison). This is corroborated by other research which has also found activation throughout LIFG (BA 47, 45, 46) when selection demands are increased (Badre, et al., 2005; Moss, et al., 2005). However, LIFG has also been shown to be recruited when automatic processes are insufficient, so top-down processes guide controlled retrieval of task relevant information (i.e., in tasks with increased difficulty or ambiguity; Wagner, et al., 2001). For example, a study which manipulated retrieval demands by requiring participants to make decisions on strong or weak associations, with either two or four possible targets, demonstrated that even when selection demands were held constant, BA 47 showed increased activation for heightened demands on *retrieval* (Wagner et al., 2001; see also, Buckner, et al., 1996; Demb, et al., 1995; Fiez, 1997; Gabrieli, et al., 1998; Kapur, et al., 1994; Peterson, et al., 1988; Wagner, et al., 2000). As such, retrieval guides semantic activation when cue-target associations are weak, regardless of competition (i.e., selection).

Furthermore, Badre, Poldrack, Pare-Blagoev, Insler, and Wagner (2005) suggest a dissociation between retrieval and selection, within the semantic control network. They demonstrated that manipulations of retrieval *and* selection increased activation in BA 45, while only retrieval selectively activated BA 47. This shows, they argue, a graded distinction within LIFG for different aspects of semantic control, with aLIFG (BA 47) recruited for semantic retrieval (Bedny, et al., 2008; Wagner, et al., 2001; Whitney, et al., 2009) and pLIFG (BA 45) for selection (Gold, et al., 2006). Despite the attempt to tease apart selection and retrieval, it may be more accurate to say that these tasks load these two components differently (i.e., load more heavily on selection or retrieval; Snyder, et al., 2011; Whitney, Kirk, et al., 2011). Snyder, Banich and Munakata (2011) suggest that aLIFG (BA 47) and pLIFG (BA 45) play a role in *both* selection and retrieval. Using verb generation tasks, they manipulated difficulty for retrieval and selection demands using competition (selection) and associative strength (retrieval). They revealed very similar activation across the tasks for both BA 45 and BA 47, suggesting that selection and retrieval interact in LIFG.

Similar to BA 47, pMTG has often been implicated in retrieval, not selection (Badre, et al., 2005; Gold, et al., 2006; Noppeney, et al., 2004). For example, Badre et al. (2005) ascribe a role to pMTG in controlled semantic retrieval, showing increased activity for low semantic associations and increased target number, but not for increases in selection difficulty (i.e., insensitive to manipulations of judgement specificity and congruency), implicating a possibly exclusive role for this area in retrieval but not selection. However, other studies have reported pMTG recruitment across a range of semantic control tasks (i.e., not exclusive to retrieval; e.g., Bedny, et al., 2008; Eviatar & Just, 2006; Gennari, et al., 2007; Thompson-Schill, et al., 1997; Whitney, et al., submitted; Zempleni, et al., 2007). For example, Whitney et al. (2012) used tasks that manipulated either retrieval (associative strength) or selection (semantic feature selection) and disrupted performance on both manipulations following TMS to LIFG *and* pMTG. Therefore, it is clear that pMTG is recruited for tasks that place increased demands on semantic control, but the exact contribution of this site is unclear.

Therefore, developing tasks that manage to tease apart retrieval and selection processes is crucial to understanding the role of LIFG and pMTG in semantic control. A task often used when assessing semantic control deficits in patients with SA is the cyclical naming task (with versions across modalities, e.g., cyclical word to picture matching), which these patients perform poorly on. In cyclical naming/matching tasks, the same set of semantically related items is presented repeatedly, in cycles, such that targets become distractors on the next cycle. Performance on related items is compared to unrelated sets of items which are made up of those presented in the related blocks (i.e., carrot from a related set of vegetables occurs in the unrelated sets along with items such as car (from a related set of cars), football (related balls set), shoe (related clothing set), and so on). This repetition of semantically related items is thought to increase competition amongst related items (possibly due to spreading activation, and the task requires selection of concepts that have just been inhibited), making naming (or matching) the appropriate item more challenging (i.e., having to inhibit previously relevant semantic items of the same category; Belke, Meyer, & Damian, 2005; Campanella & Shallice, 2010; Gardner, et al., 2012; Jefferies, et al., 2007). An advantage of this task is that, in healthy participants, retrieval and selection can be assessed separately. Participants are slow to identify the first cycle of items (both related and unrelated), as each one must be *retrieved* for the first time, however, the sharp decrease in latencies from cycle one to two indicates that retrieval is no longer challenging. It is from cycle two onwards that the selection demands are seen, where semantically related sets of items are slower to be named/identified than unrelated items (as there is no within category competition).

Gotts and Plaut (2002) have provided a model to explain why repetition of semantically related items increases control demands. They suggest that there is an increase in pre-synaptic depression, which reduces the efficiency with which new stimuli can be dealt with, resulting in a ‘refractory period’ in which errors occur. According to this model, the cyclical naming/matching task offers a measure of neuromodulatory control over intact semantic representations: In semantically related sets – where more units are shared, synaptic depression builds up (because transmitter release is no longer suppressed, which allows synaptic depression to build up amongst related items as they share the same active units) therefore more errors are made than for unrelated sets (where synaptic depression is lower because items do not share active units). Alternatively, the blocking effect may not result from inhibition ('hyper-inhibition', as in the Gotts and Plaut (2002) model), but rather from 'hyper-facilitation' in which the concepts remain abnormally active interfering with subsequent trials (Campanella & Shallice, 2010). As such, the blocking effect occurs when semantically related items are presented at a fast rate, and there is little time for the activated items to de-activate causing the entire set of related items to be co-active, resulting in strong competition between the semantically related 'distractors' and the 'target' (i.e., 'hyper-facilitation') . This is supported by cases in which participants make more perseverations, suggesting that the previous item remains abnormally active (Campanella & Shallice, 2010).

Patients with SA show impaired performance for both naming and matching versions of these cyclical tasks as competition amongst related items builds up across cycles – causing more errors/perseverations; while patients with SD do not show a build-up of competition with item repetition across cycles (Jefferies, et al., 2007; Warrington & Shallice, 1984). Furthermore, not all patients with SA struggle on this task: patients with temporoparietal infarcts (TP; encompassing pMTG) show weaker blocking effects than patients with frontal lesions, on all versions of these cyclical semantic tasks (Gardner, et al., 2012; Jefferies, et al., 2007; Schnur, Schwartz, Brecher, & Hodgson, 2006; Schnur et al., 2009). A direct comparison of SA patients with frontal and TP lesions on comprehension versions of the cyclical matching task, reveals that patients with posterior lesions do not show an 'abnormal' blocking profile, despite being similar to the left frontal SA patients on other assessments of semantic and non-semantic control (Gardner, et al., 2012). This dissociation has also been demonstrated using cyclical naming tasks, where a correlation is seen between the size of LIFG damage, but not left temporal damage, and the size of the blocking effect (i.e., lesion size and location predicted the size of the blocking effect; Schnur, et al., 2006).

Furthermore, Schnur et al. (2009), using healthy participants, found that LIFG was significantly more active during semantically blocked naming compared to unrelated naming, as well as eliciting more activity than temporal cortex for semantically related naming: this replicates, in healthy individuals, the trend seen in patients with frontal/posterior lesions (e.g., Gardner, et al., 2012; Jefferies, et al., 2007; Schnur, et al., 2006). More specifically, they found a relationship between the number of errors produced and signal difference for LIFG, but not for left temporal cortex (left superior and middle temporal gyri). This suggests that LIFG is sensitive to competition arising in semantically related naming (i.e., difficulty selecting the appropriate name, when several others of the same semantic category ‘node’ are active), as measured by selection difficulty during blocked naming. Taken together, these results suggest that LIFG is recruited for the resolution of the type of competition (e.g., selection difficulty) that arises through cyclical naming of semantic items, as evidenced by this complementary fMRI and patient data. Additionally, a recent meta-analysis of neuroimaging work has also found a difference between LIFG and pMTG in their contribution to semantic control, namely a lesser involvement of pMTG in tasks requiring production (such as those in the Schnur et al. (2009) task in which pMTG activation is not seen; Noonan, et al., submitted). Taken together, this suggests that there may be fine distinctions in the semantic control network with regard to the specific contributions of LIFG and pMTG.

The current study uses rTMS to modify performance on the cyclical naming task (picture naming), with related and unrelated sets. The 1 Hz paradigm is used to induce “virtual lesions” in LIFG and pMTG. Our aim is to further clarify the role of these regions in semantic control, more specifically, using a task in which selection and retrieval demands are manipulated using the same stimuli. This is the first study, to our knowledge, that disrupts the cyclical naming task using TMS, exploring the relationship of selection and retrieval. Repetitive trains of TMS were delivered to transiently disrupt the neural processing of the underlying tissue, manifested in the concurrent behavioural disruption of tasks reliant on this area. Given that LIFG and pMTG have been widely shown to be a crucial part of the semantic control network (Badre, et al., 2005; Whitney, et al., submitted; Whitney, Jefferies, et al., 2011; Whitney, Kirk, et al., 2011; Whitney, et al., 2012), this study uses rTMS to provide insight into how these two key areas may be differentially recruited in semantic control. TMS is a useful tool for investigating this dissociation, as it can be used on healthy subjects and with much greater control over the ‘lesion’ size and location. Studies investigating deficits in SA have already provided useful information as to tasks in which LIFG and pMTG are differentially recruited, namely the cyclical naming task. In line with these findings from temporoparietal SA (Gardner, et al., 2012; Jefferies, et al., 2007; Schnur, et al., 2006), stimulation of pMTG was not expected to affect task performance, making it a useful ‘control’ site, while stimulation of LIFG was expected to show behavioural disruption on subsequent naming. More specifically, in line with the behavioural blocking effect, in which healthy participants show a reaction time detriment in later cycles, rTMS disruption of LIFG may manifest itself as longer reaction times on later cycles of semantically related sets (where selection demands increase). As such, rTMS disruption is measured using related and unrelated sets in the cyclical naming paradigm after stimulation of pMTG and LIFG.

Method

Design

A within subjects 2 x 2 x 3 x 2 factorial design was used, with TMS (no stimulation vs. stimulation), condition (related, unrelated), cycle (1+2, 3+4 or 5+6) and site (LIFG, pMTG) as factors. This study used the rTMS virtual lesion method, delivering a train of rTMS pulses offline; participants then performed the task immediately after stimulation, allowing us to rule out the possibility that the loud clicks, jaw contractions, or eye blinks associated with each pulse disrupted performance on the behavioural tasks. The order of the baseline and TMS tasks was counterbalanced, such that half of the participant behavioural performance without TMS (i.e., “baseline performance”) was measured before TMS stimulation and the other half was measured 30 mins or more post TMS stimulation, by which time the effects have washed out (Pobric, et al., 2007).

Participants

Thirteen participants were examined in the study (9 females; mean age = 20.15, SD = 1.72). One participant who showed blanket facilitation across both sites for both conditions (related/unrelated) was excluded from the analysis, as well as one other participant who spoke Singaporean English. All participants examined were right handed, native British English speakers recruited from the University of York student population, and were compensated £38 for their time. All participants were screened for TMS and MRI safety and were thus free from any history of neurological disease or mental illness and were not taking any prohibited medication.

Stimuli

All stimuli were colour pictures, which appeared on a white screen in succession in either related blocks or unrelated blocks. The categories for these sets were as follows: balls, balls 2, baked goods, birds, boats, cars, cartoons, cartoons 2, cereals, clothing, computer goods, dogs, drinks, evening wear, flowers, fruits, garden tools, hats, herbs/spices, instruments, instruments 2, jewellery, kitchen goods, kitchen goods 2, kitchen goods 3, pastries, pets, puddings, sea creatures, transport, tools, vegetables,

vegetables 2, winter gear, zoo animals, zoo animals 2. For a full list of items in each of these categories see Appendix 6.1.

Tasks

Picture probes were presented individually on a computer screen and participants named each picture as it appeared. The naming sets alternated between related and unrelated sets. In each set, five items were named in cycles, with six cycles per set, with a ready screen between sets, which was self-paced. Therefore TMS effects are cycle specific, and cannot be attributed to TMS effects being stronger or weaker at any cycle, given that all cycles are presented for a particular set, after which the next set of items (and cycles) begins, thus the TMS effects cannot be stronger on cycle one or wear off for the last cycle, because the last cycle occurs every six cycles (over a total of 72 cycles per condition).

Procedure

A PC running E-Prime software allowed for presentation and recording of response times. Responses were given verbally into a microphone which was connected to a Serial Response (SR) Box (Psychology Software Tools). Each trial started with a fixation screen for 50 ms followed by the presentation of the probe to which participants were required to make a verbal response (i.e., name the picture). The participant response triggered a blank screen (550ms) for the participant’s verbal response to end after which the next trial began. Each block was preceded by a “ready?” screen to which participants gave a button response, on the SR box, to move onto the next block (see Figure 6-1).

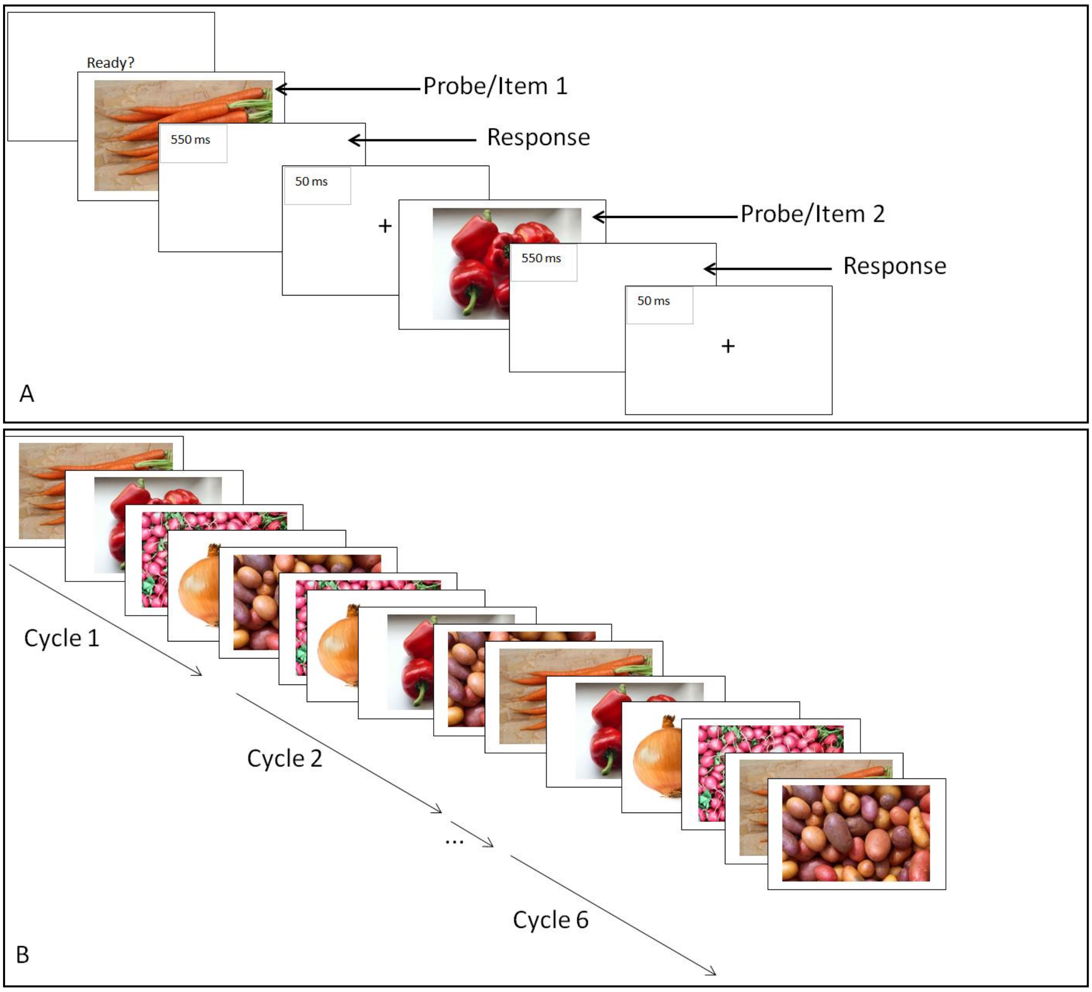

Figure 6-1: Experimental task procedure. Figure 6-1A provides a schematic of the trial structure; Figure 6-1B shows the repetition of cycles (related sets example).

Participants were familiarized with the stimuli before the experiment: participants were presented with each stimulus with its name on screen and could proceed at their own pace. They went through the stimuli twice before beginning the task. This familiarisation ensured that participants knew all the items so that we could examine the effects of task context (related/unrelated and cycle) on retrieval and selection.

We attempted to reduce/eliminate any task learning effects (that could potentially interfere with behavioural TMS effects), by requiring participants to practice the behavioural task the day prior to each TMS experimental session. This practice session required participants to practice the task two times (different items in each practice task), with a total of 12 related blocks and 12 unrelated blocks (6 per practice task). No practice items were used for the experiment.

The TMS experimental session began with a practice block, which included 6 related blocks and 6 unrelated blocks. There were 6 blocks per condition (related/unrelated), with participants performing a total of 12 blocks (360 trials) per experimental condition (baseline, post-TMS). Participants performed the baseline task once before TMS and once post TMS, but only one baseline was used for data analysis per participant, and this once counterbalanced across subjects and sites. Each block contained 5 items repeated 6 times randomly, but with no item occurring twice in a row (i.e., radish, carrot, potato, onion, pepper, onion). Related and unrelated blocks were alternated, such that participants performed a set of related items, followed by unrelated, followed by related and so on (or vice-versa, with an unrelated block first). No trials were repeated within a session, or across sessions (i.e., one week later). The order that categories were presented in was counterbalanced across participants (e.g., participant A: clothing in week one, dogs in week two; and vice versa for participant B: dogs in week one, clothing in week two), as was whether the task started with a related or an unrelated set (e.g., participant A: related-unrelated; participant B: unrelated-related) , as well as the order in which each site was tested (i.e., LIFG-pMTG, pMTG-LIFG).

Selection of TMS Site

Structural T1-weighted MRI scans were used to identify sites for stimulation in each participant's brain. These stimulation sites were identified from a neuroimaging meta-analysis examining semantic control, by way of a semantic high > low control contrast, with the two strongest clusters being LIFG and pMTG (Noonan, et al., submitted). The coordinates (x, y, z) for the LIFG site were -45, 19, 18 (MNI), and for pMTG were -54, -49, -2 (MNI). Brainsight 2 (Rogue Research, Montreal Canada, www.rogue-research.com/) was used to co-register participant scalps to their MRI structural image and to identify stimulation sites prior to rTMS administration. Four landmarks were used for co-registering the participants head to their brain image (tip of the nose, bridge of the nose, left/right tragus).

Stimulation Parameters

Before TMS testing began, individual motor threshold was determined in each testing session. This was determined by the lowest stimulation intensity required to elicit contraction of the first dorsal interosseous (FDI) muscle in the contralateral hand. Motor thresholds ranged between 39% and 65%, with an average of 49% of maximum stimulator output. A 70 mm figure of eight coil, attached to a MagStim Rapid2 stimulator was used for repetitive magnetic pulses. Repetitive trains of TMS were delivered at 1 Hz for 10 mins; participants were stimulated at 120% of their motor threshold.

Data Analysis

TMS disruption was expected to manifest itself in delayed reaction time (RT), rather than a decline in accuracy (Walsh & Cowey, 2000), therefore, RT data for correct responses only was used for all analyses (the accuracy data can be found in Appendix 6.2). The data was screened for any reaction times lying outside 2 standard deviations of the participant's mean for each cycle (1, 2, 3, 4, 5, 6), condition (related/unrelated) and TMS condition (TMS/baseline), for that testing session. We collapsed the six cycles into three for the purpose of analysis: 1) cycles 1 and 2; 2) cycles 3 and 4; 3) cycles 5 and 6. An analysis across all six cycles, yielding very similar results, can be found in Appendix 6.3.

Repeated measures ANOVAs were used to analyze the effect of TMS on each condition, for each individual site (to establish an interaction of TMS x condition x cycle in LIFG). Additionally, effects emerging from ANOVAs were confirmed using Bonferroni-corrected two-tailed paired sample t-tests (to confirm at which cycles TMS affected naming RT). Additionally, an omnibus ANOVA was used to compare effects across sites: The behavioural effects emerged as expected with a significant effect of condition (F(1, 12) = 54.768, p < .001), a significant effect of cycle (F(2, 24) = 98.158, p < .001) and an interaction of the two (F(2, 24) = 90.613, p < .001). This is seen in other cyclical naming studies in healthy populations, where there is a decrease in initial reaction time between the first two cycles and a relative increase for the related sets compared to the unrelated sets as the cycles progress (Belke, et al., 2005).

Results

Left Inferior Frontal Gyrus

Statistical tests for this site examined the hypothesis that TMS to LIFG would differentially disrupt retrieval of semantically related items and to examine if these effects interact with cycle. A within participants (2 x 2 x 3) ANOVA revealed a significant three-way interaction of TMS by condition by cycle (F(2, 24) = 4.98, p = .016). This interaction reflects, in part, the difference in response to the related and unrelated sets. The unrelated sets show priming after cycle one, so the RT decreases across cycles, whereas there is strong competition in the related sets therefore there is no facilitation of RTs in subsequent cycles. Therefore, the TMS by condition by cycle interaction is expected to be driven by a significant TMS effect for the related items where competition is greater.

A further 2 x 3 repeated measures ANOVA, investigating the effects of TMS and cycle, for each condition (related, unrelated) was used to investigate this three-way interaction. The ANOVA for related sets revealed a significant interaction of TMS by cycle (F(2, 24) = 3.85, p = .036). TMS to LIFG produced significant slowing at cycles 1+2, as evidenced by Bonferonni corrected paired t-tests (adjusted alpha of .0125 per test (.05/4)). There was a significant difference between cycle 1+2 and cycle 3+4 post TMS (t(12) = 3.15, p < .05), but no difference between cycles 1+2 and 3+4 in the no TMS condition (t(12) = -.14, p = .890). There were no significant differences between cycles 3+4 and 5+6 for TMS or baseline (t(12) < 1). TMS did not produce slowing of later cycles, where selection demands might be highest, but instead earlier cycles were differentially affected, when retrieval demands were highest (Figure 6-2).

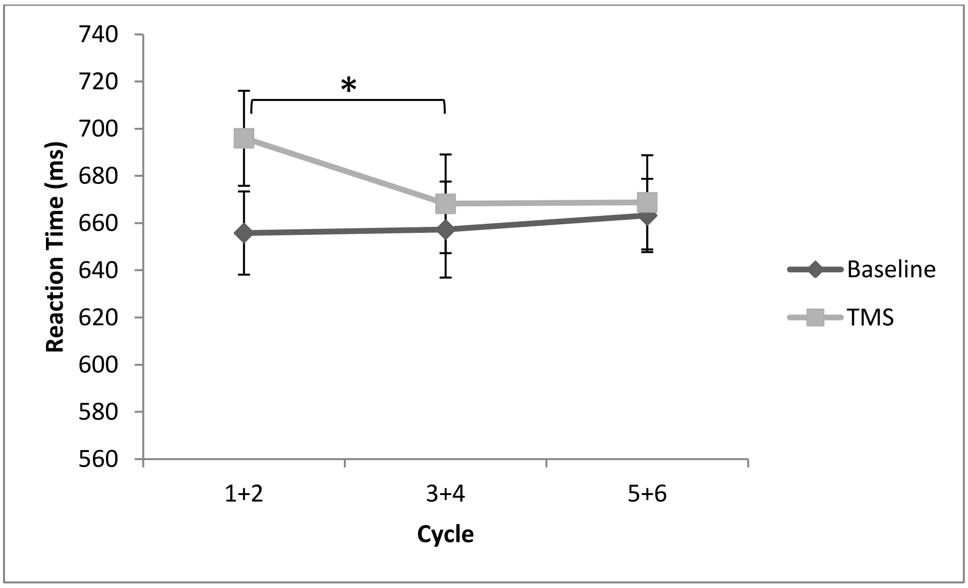

Figure 6-2: Left Inferior Frontal Gyrus: Related Sets. TMS to LIFG significantly increased the difference in RTs for cycles one and two of the semantically related sets but not the no TMS baseline. Error bars represent standard error of the mean. Asterisk represents significant change in RT (p < .05).

The ANOVA for unrelated sets showed a trend towards an effect of TMS (F(1, 12) = 3.704, p = .078), but no significant interaction of TMS x cycle (F(2, 24) = 1.394, p = .267; Figure 6-3).

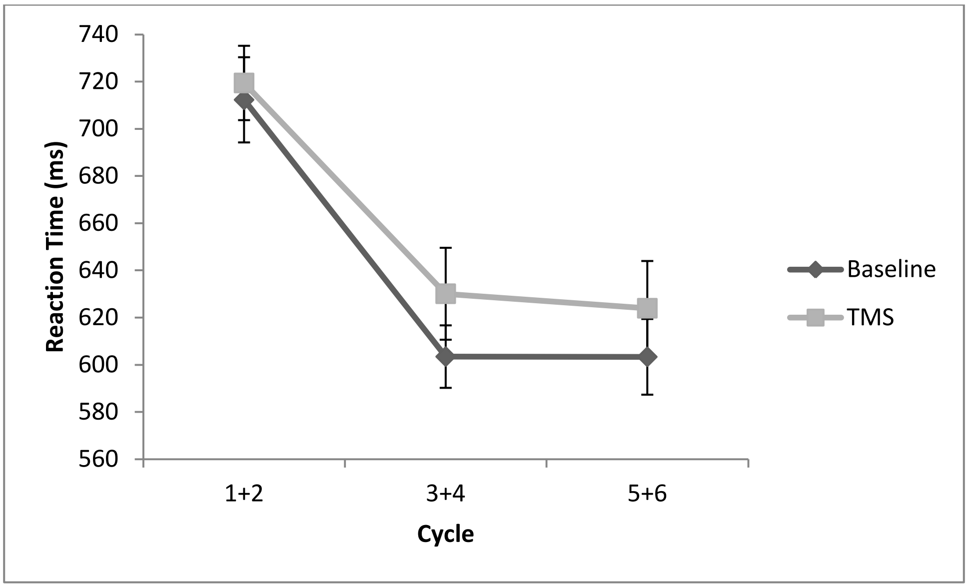

Figure 6-3: Left Inferior Frontal Gyrus: Unrelated Sets. TMS to LIFG did not slow RTs for semantically unrelated sets relative to the no TMS baseline. Error bars represent standard error of the mean.

TMS to LIFG only slowed naming on early cycles of naming related sets, with no such slowing for unrelated sets. If TMS were to disrupt retrieval, then this slowing should have been seen for cycle 1+2 of the unrelated sets, but this was not the case, suggesting that LIFG plays a crucial role when retrieval *and* selection demands are high due to the competition between related items.

Posterior Middle Temporal Gyrus (pMTG)

Statistical tests for this site examined the hypothesis that TMS to pMTG may not slow naming of the cyclical naming task. A within participants (2 x 2 x 3) ANOVA revealed no significant effects of TMS at this site (F(1, 12) < 1) and no three-way interaction between these factors (F(2, 24) = 2.008, p = .156; Figure 6-4). Given that no TMS effects or interactions emerged, no further analyses were conducted for this site, as TMS to pMTG does not appear to affect behavioural performance of the cyclical naming task.

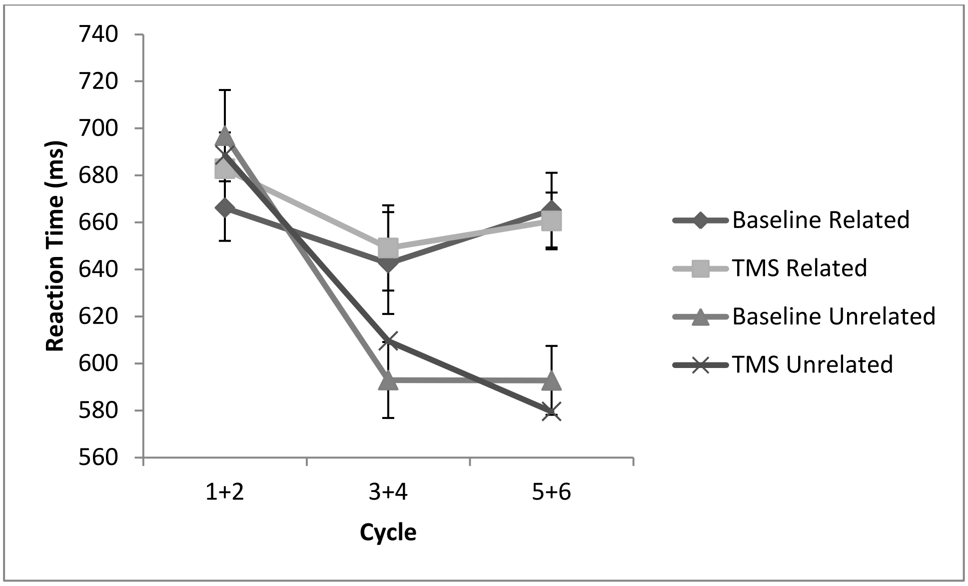

Figure 6-4: Posterior Middle Temporal Gyrus : TMS to pMTG had no effect on naming for either semantically related or unrelated sets, relative to baseline. Error bars represent standard error of the mean.

Between Sites

An omnibus ANOVA did not reveal a significant main effect of site but there was a site by condition interaction. There was also a significant interaction of TMS by condition by cycle (*p* = .008), possibly driven by the significant slowing of naming for the LIFG site, but there was no four way interaction of site by TMS by condition by cycle (F(2, 24) < 1; Table 6-1). The data presented above suggests that the two sites show different patterns, with effects of TMS at early cycles of related naming for LIFG, but not for pMTG; however, the omnibus ANOVA does not provide conclusive evidence for this difference.

Between Sites	*df*	*F*	*p*
Site	1, 12	1.363	.266
TMS	1, 12	1.972	.186
Site x TMS	1, 12	2.132	.170
Site x Condition	1, 12	5.626	.035*
TMS x Condition	1, 12	< 1	.396
Site x TMS x Condition	1, 12	< 1	.486
Site x Cycle	2, 24	< 1	.853
TMS x Cycle	2, 24	2.318	.120
Site x TMS x Cycle	2, 24	< 1	.530
Site x Condition x Cycle	2, 24	2.49	.104
TMS x Condition x Cycle	2, 24	5.883	.008**
Site x TMS x Condition x Cycle	5, 60	<1	.434

Table 6-1. F and p Values for between sites omnibus ANOVA; **p < . 001, *p < .05.

Discussion

This study sought to confirm the role of LIFG and pMTG in semantic control, namely retrieval and selection processes, using the cyclical naming task, with rTMS. Studies of patients with semantic aphasia (SA) have previously indicated that there may be a difference between LIFG and pMTG in their contribution to semantic control (Gardner, et al., 2012; Jefferies, et al., 2007; Schnur, et al., 2006), despite many studies showing similar involvement of the two areas in many control demanding tasks (Noppeney, et al., 2004; Whitney, Jefferies, et al., 2011; Whitney, Kirk, et al., 2011; Whitney, et al., 2012; Wright, et al., 2011). This study confirms that there is a dissociation, with TMS to LIFG causing disruption of performance on a naming version of the cyclical naming task, but no such disruption following TMS to pMTG. More specifically, this disruption manifests itself as a significant and specific slowing of naming latencies, relative to baseline, in the first cycles of repeated cyclical naming of semantically related items. Meanwhile, TMS to pMTG caused no change in naming latencies for either condition of the task – confirming, in healthy participants, the pattern seen in temporoparietal SA. This is in contrast to previous TMS studies showing parallel TMS effects after stimulation of LIFG and pMTG for semantic association tasks (Whitney, Kirk, et al., 2011; Whitney, et al., 2012); and therefore helps to elucidate the discrete specialisations within semantic control for these two sites.

Lexical vs. Semantic Access

LIFG is associated with speech production/lexical selection, as well as semantic selection, and our task involved both. Some studies propose that the effects seen in the cyclical naming task occur at the ‘lemma’ level of speech production, both in patients and with healthy participants (Belke, et al., 2005; Maess, Friederici, Damian, Meyer, & Levelt, 2002; Schnur, et al., 2006), and therefore effects for cyclical tasks would only be predicted for tasks requiring production. However, Jefferies et al. (2007) directly compared production and word-picture matching versions of the cyclical semantic task and revealed that patients with lesions encompassing LIFG showed a decline in performance on both tasks, suggesting that the competition occurs prior to lexical selection (see also: Gardner, et al., 2012). If the blocking effect occurs at ‘lemma selection’, then the effect should be specific to picture naming and not generalize to other versions of the task that do not require naming, such as word-picture matching tasks. However, the effect *is* seen in such tasks, thus the cyclical naming/matching task likely loads on some aspect of semantic control. Similarly, Campanella and Shallice (2010) found impaired recognition of items across serial presentations on a word to picture matching task, for healthy participants. The authors argue that the most compatible explanation with their findings is that competition occurs within the semantic system (also formerly proposed by Levelt, Roelofs, and Meyer (1999), and compatible with findings from Mahon, Costa, Peterson, Vargas, and Caramazza (2007)), as the competition can only occur after the concepts have been elicited by the pictures (there is no need for activation of post-semantic lexical representations).

Additionally, there is some debate as to the cause of this blocking effect: Campanella and Shallice (2010) claim that their results are due to hyper-facilitation, as participants made a greater number of perseverations – suggesting that the previous target is still ‘abnormally’ active; alternatively, the items might suffer from ‘hyper-habituation’, where items become inhibited after their initial activation due to increased synaptic depression (Campanella & Shallice, 2010; Gotts & Plaut, 2002). Low frequency TMS is thought to induce synaptic depression (Reithler, Peters, & Sack, 2011), which according to Gotts and Plaut (2002), results in more errors (in patients). This could be one possible explanation as to why we see TMS effects on early cycles, where TMS may have caused a decrease in post synaptic activity – which would usually result from repetitions of the same stimuli (Gotts & Plaut, 2002).

Left Inferior Frontal Gyrus

A recent study specifically investigated the role of retrieval and selection in LIFG using verb generation tasks to manipulate the difficulty of retrieval (associative strength) and selection (increased competition; Snyder, et al., 2011). They found that when retrieval demands were low, selection modulated activity in BA 45/47, whereas when retrieval demands were high (more difficult/lower associative strength), there was no further modulation of activity for selection (activation was constant for both low/high selection within the high retrieval condition) – this suggests that it may be difficult to see an effect of selection when retrieval demands are high. Our study demonstrates an interaction of the two processes in LIFG where on cycle one the demands on retrieval and selection are high: cycle one requires a) initial retrieval of each item and b) selection from amongst competing semantically related items. In contrast, on the second cycle of semantically related naming, the demands on retrieval are considerably reduced (due to repetition and within category facilitation), whereas the demands on selection remain, however TMS did not impact selection of the target item. Thus, stimulation of LIFG interfered with naming at the point when the requirement for retrieval *and* selection peaked, producing a cycle specific effect of TMS for the related sets on initial cycles.

The TMS effects emerge in our study at the point at which the demands on retrieval and selection are at their highest. This is in contrast to the pattern seen in SA, where the effects of competition emerge on later cycles of cyclical naming (or indeed, matching). It is possible that TMS to LIFG increases the difficulty of retrieving/selecting items at cycle one, but healthy participants manage to overcome this difficulty across multiple presentations, as such the TMS effect only manifests itself on the first cycle of each semantic set. More difficult tasks are often thought of as more vulnerable to TMS effects (Devlin & Watkins, 2007), as such, disrupting LIFG using TMS could make the most challenging part of the task more difficult which in this study would be the time at which the demands on retrieval and selection are at their highest (cycle one). It is important to note that this is not a result of the TMS effects wearing off across cycles, as all cycles are presented for a particular set, after which the next set of items (and cycles) begins, thus the TMS effects cannot wear off for the last cycle, because the last cycle occurs every six cycles (over a total of 72 cycles per condition).

Similarly, TMS has previously been shown to disrupt selection and retrieval processes in LIFG. For example, Whitney et al. (2012) used semantic associative judgments (to assess retrieval) and semantic feature selection tasks (to assess selection) and found equal disruption of tasks following TMS to either LIFG or pMTG; this suggests that LIFG is recruited for both executively demanding processes (retrieval and selection), as there was no disruption for the easy conditions of either task. Furthermore, Hoffman, Jefferies, and Lambon Ralph (2010) slowed abstract (synonym) judgments that were preceded by an irrelevant contextual cue (making the executive demands higher), but not abstract word judgments preceded by a relevant cue (lowering executive demands), following rTMS to LIFG. This task places demands on selection and retrieval: it requires participants to retrieve a word based on a cue, but to also select from amongst three alternatives. The current study complements these previous TMS findings with disruption of LIFG for tasks that load on both selection and retrieval (i.e., early cycles of the naming tasks where selection and retrieval are hard to tease apart), while also demonstrating a dissociation between LIFG and pMTG.

Posterior Middle Temporal Gyrus

Another key question motivating this study was the relative contribution of pMTG and LIFG to semantic control. Previous studies have found the two sites to be very similar in their contribution to tasks purportedly loading on selection and retrieval (Noppeney, et al., 2004; Whitney, Jefferies, et al., 2011; Whitney, Kirk, et al., 2011; Wright, et al., 2011). Some studies report pMTG activation for tasks purportedly loading on semantic retrieval, while LIFG activation has been reported for semantic selection (Badre, et al., 2005; Bedny, et al., 2008; Gold, et al., 2006). This framework would predict a double dissociation such that TMS to pMTG should slow naming for the first cycle of naming (for either the related or unrelated sets[2]) where the demands on retrieval are high, and in contrast, stimulation of LIFG should leave the first cycle of naming unaffected, with disruption at later cycles (i.e., when retrieval demands are low, but selection peaks). However, we found no disruption of naming following stimulation of pMTG, which suggests that the role of this site in semantic control lies beyond retrieval. One possibility is that the items presented at cycle one were no longer novel (i.e., no need for controlled retrieval), due to the familiarisation phase prior to testing (in which participants were exposed to the with-in semantic category items over

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[2] In fact, the demands on retrieval are highest for the first cycle of unrelated naming, where there is no within category facilitation, but even here, stimulation of pMTG showed no disruption.

two cycles). Campanella and Shallice (2010) found that when participants were familiarised with stimuli prior to testing, they were faster (and more accurate) at identifying items on the first cycle, than in cycles two and three. However, this is unlikely to be the sole explanation because although the participants in our study were familiarised with the items prior to testing, which may have reduced the initial facilitation normally seen from cycle one to two, they were still slower on the initial cycle of naming than later cycles, indicating that there was an initial retrieval stage. Therefore, the lack of TMS effect in pMTG is likely to reflect the role of this site beyond retrieval in semantic control.

Indeed, our data from Chapters 3, 4, and 5 also indicate differential involvement of LIFG and pMTG in semantic control, as well as other studies reporting differences for the two sites (Gardner, et al., 2012; Gennari, et al., 2007; Noonan, et al., submitted; Price, 2010). Two recent meta-analyses have noted that pMTG recruitment appears to be confined to the receptive domain, predominantly activated for comprehension, but not production, tasks (Noonan, et al., submitted; Price, 2010; Turken & Dronkers, 2011). However, this account may be too simplistic with regard to the cyclical naming task, because temporoparietal patients do not show performance outside the normal range for other versions of the cyclical semantic task, such as matching (non-production; Gardner, et al., 2012), suggesting that the cyclical naming/matching task may recruit other aspects of semantic control (e.g., selection difficulty) not specifically engaged by pMTG. The predominance of pMTG activation reported for receptive tasks may, however, reflect its role in semantic control, which has been suggested to lie in the domain of context-integration (Noonan, et al., submitted; Price, 2010) and therefore may not be recruited in traditional production tasks. A fruitful avenue for further investigation would be use a version of the cyclical matching task that does not require overt production (i.e., word-picture matching), post TMS to LIFG and pMTG would be a good starting point to establish whether the difference between these two sites is due to a production/comprehension dichotomy, or whether it is something more integral to the type of semantic control which is recruited by this task.

Conclusions

The cyclical naming tasks provides a unique opportunity to separate retrieval (cycle one, particularly unrelated sets) and selection (later cycles of related naming) processes, as well as the interaction of the two (cycle one of related naming). We show that neither pMTG nor LIFG were recruited for retrieval or selection alone, but that LIFG was crucially involved when the demands on selection *and* retrieval peaked. In summary, this study confirms, using rTMS, the dissociation of LIFG and pMTG in cyclical naming tasks previously seen in SA and neuroimaging studies. More specifically, we demonstrated that 1) LIFG is recruited by executive demands on selection *and* retrieval and 2) that pMTG recruitment may lie beyond the domain of semantic retrieval/selection.

Chapter 7: Thesis Summary and Discussion

This thesis sought to investigate the neural basis of language processing. While research has uncovered the broad organisation of language and semantic processing in the brain, this thesis focused on using TMS and fMRI to explore controversial issues such as overlap between different aspects of language processing (phonological/semantic; verbal vs. non-verbal). The empirical work investigates which regions within distributed language/semantic networks are critical for processing irrespective of context, and which regions show a response profile consistent with a contribution to executive linguistic and/or semantic processing. Moreover, the use of TMS allows us to explore hypotheses that have emerged from other methods (neuroimaging, neuropsychology) in a causal manner. Therefore, we interrogated specialisations within language networks with regard to three major themes:

Themes

i. Domain (phonological/semantic) and Modality (verbal/picture)

We were interested in elucidating how particular parts of the language network contribute to domain general and domain specific processing. A key question was whether areas previously implicated in language processing were specialised by domain: for example, more responsive to making decisions on the individual constituents of a word (i.e., phonology), than the meaning of the word (i.e., semantics) and vice-versa. This is an important distinction, for several reasons: (1) Many studies have used phonological tasks to indicate an essential role for motor areas in speech perception (e.g., Fadiga, et al., 2002; Meister, et al., 2007; Wilson, et al., 2004); however, without the requirement of access to meaning these tasks cannot speak to other aspects of language processing such as comprehension of auditory input, arguably the goal of speech perception. By examining this distinction between speech perception tasks requiring semantic judgements and explicit phonological awareness, we can test divergent theoretical accounts that alternatively suggest that (i) articulatory representations within premotor cortex (PMC) are critical for speech perception in general or (ii) that PMC is only required for phonological tasks that require production and/or the harnessing of subvocal articulation for challenging explicit phonological decisions (Chapter 2). (2) Within semantic tasks, the issue of modality also remains controversial. An amodal semantic network, activated by semantic decisions to both words and pictures, has been revealed in bilateral anterior temporal lobes (ATL; Pobric, et al., 2010; Visser, Jefferies, & Lambon Ralph, 2009; Visser & Lambon Ralph, 2011), left inferior frontal gyrus (LIFG; Bright, Moss, & Tyler, 2004b; Chee, et al., 2000; Vandenberghe, et al., 1996; Wagner, et al., 1997) and posterior middle temporal gyrus (pMTG; Chee, et al., 2000; Hoffman, et al., 2011; Vandenberghe, et al., 1996). However, these sites are hypothesised to differ in terms of their contribution to semantic representation and executive control processes, which bring task-relevant semantic features to the fore. ATL is thought to form amodal semantic representations, while the anterior parts of LIFG are thought to contribute specifically to semantic control (as opposed to domain and modality-free executive processes). The contribution of pMTG is also unclear, with some accounts (e.g., Hickok & Poeppel, 2007) emphasising its role in linguistic processing, for the mapping from words to meanings, others suggesting it represents specific semantic features (e.g., action knowledge) and a third literature primarily based on neuropsychological studies suggesting it contributes to semantic control in conjunction with LIFG. Chapters 4-6 report TMS and fMRI investigations designed to clarify the contribution of LIFG and pMTG to semantic processing for semantic decisions to words and pictures, and the mapping between meanings and words in the context of picture naming.

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ii. Control

We also investigated how domain specific and domain general areas responded to increased demands on controlled use of language and semantic knowledge (both pictures and words). In order to do this, we manipulated the difficulty with which the relevant target/information was accessible, for example, in the phonological tasks we used in Chapters 3 and 5, rhyme judgments were made quickly and with high accuracy, whereas judgments based on segmenting auditory stimuli for a matching task were slower and less accurate, and therefore required greater ‘control’. Within the domain of semantic cognition, control refers to the executive processes that are engaged to direct activation of the semantic store in a task relevant and time sensitive manner (e.g., when semantic distance increases between two words, making the relationship less apparent). We wanted to investigate specific contributions of language areas to control within and across domain in order to assess whether there are functional dissociations by domain (phonological/semantic) that interact with controlled use of language. The literature to date has often focussed on one of these aspects (i.e., domain *or* control), but given that areas such as LIFG have been shown to be specialised by domain and also recruited when the demands on control increase (e.g., large swathes of activation throughout LIFG for increased semantic control; Noonan, et al., submitted), a factorial design that interrogates the interaction between domain and control helps tie the two literatures together. We also wanted to assess any differential contributions within the semantic control network to modality (e.g., picture semantic control), as previous studies have shown similar networks recruited for picture and verbal semantic material, but not assessed their contribution to control across modality (e.g., Bright, et al., 2004a; Wagner, et al., 1997). Therefore, while it has been shown that the ATL store semantic knowledge amodally (e.g., Visser, et al., 2009), it may be the case that the way in which the brain accesses this material may differ according to modality. For example, while LIFG has often been shown to be recruited when the demands on linguistic/verbal semantic control increase, do areas within LIFG play the same role in accessing picture semantic material when automatic retrieval processes are insufficient to guide selection of concepts stored in ATL? Additionally, the umbrella term ‘semantic control’ can refer to any number of processes (e.g., retrieval, selection, context integration) and some studies have previously attempted to disambiguate two of these processes, namely retrieval and selection, and have reported differential recruitment across the semantic control network for these two processes (Badre, et al., 2005; Badre & Wagner, 2007; Thompson-Schill, et al., 1997; Wagner, et al., 2001). In Chapter 6, we attempted to further separate retrieval and selection within a cyclical picture naming task in order to assess the role of brain areas within the semantic control network (LIFG; pMTG) to these varying aspects of semantic control, given previous suggestions that there may be differential involvement across the network for the two processes (Badre, et al., 2005; Gold, et al., 2006; Noonan, et al., submitted; Noppeney, et al., 2004; Wagner, et al., 2001).

iii. Distributed network

Language is a complex process, with a diverse network of brain areas contributing to the apparent ease with which we use it. We were interested in investigating the way in which this diverse network interacts with both domain/modality (theme i) and control (theme ii), often by way of dissociations along these dimensions. For example, the semantic control network implicated in a recent meta-analysis suggests a diverse number of brain areas for semantic control – such as LIFG, pMTG and divisions of AG, however it is likely that these areas have differential contributions within the network. We also investigated the partial overlap between networks of brain regions specifically implicated in semantic control and those that contribute to domain-general executive processing (Duncan, 2010; Spreng & Schacter, 2012; Spreng, et al., 2010; Vincent, et al., 2008). LIFG has often emerged as a domain general control region across many language studies (Duncan, 2010; Duncan & Owen, 2000; Gold, et al., 2005; Gold & Buckner, 2002; Rajah, et al., 2008; Snyder, et al., 2007; Thompson-Schill, 2003), however, there is some evidence to suggest that dissociable parts of LIFG may be less domain general: anterior LIFG has often been implicated exclusively in semantic control (Badre, et al., 2005; Noonan, et al., submitted; Poldrack, et al., 1999). Additionally other areas such as pMTG have in some cases emerged as exclusive to the semantic domain (Noonan, et al., submitted), while other posterior areas within and around AG are often activated by a wide range of tasks, including phonological and semantic (e.g., Carreiras, et al., 2009; Seghier, et al., 2010; Sharp, et al., 2010). AG has been predominantly reported for semantic tasks, while SMG has been widely implicated in the phonological domain (e.g., Sharp, et al., 2010; Vigneau, et al., 2006). Furthermore, within AG there has been some suggestion that there are specialisations such that dorsal AG may be domain general, and mid AG may be more specific to control demanding semantic tasks (e.g., Noonan, et al., submitted; Seghier, et al., 2010). Our tasks were well placed to assess contributions throughout the network across language domain, modality and control processes (e.g., retrieval/selection).

Main Findings

1. Chapter 2 used TMS to establish the contribution of premotor cortex (PMC) to speech perception, using a phonological task that required explicit phoneme judgments and a semantic task requiring participants to identify the category membership of the stimulus. We showed that this site is recruited for non-natural, explicit phoneme judgments, but not mapping sound to meaning (theme i). Therefore, it is unlikely that PMC participates in general speech comprehension, but rather its role is reserved for other aspects of speech perception, such as these explicit phoneme judgment tasks.
2. Chapter 3 focussed on a larger network of brain areas (theme iii) in order to understand the specialisation by domain (theme i) and control (theme ii) of areas previously implicated in language processing. This study used phonological and semantic tasks, and we manipulated the demands on control by creating hard and easy versions of each task type (phonology: rhyme (easy), segment (hard); verbal semantic: high (easy), low (hard) semantic association strength). We were particularly interested in assessing the interaction of domain and control in areas such as left inferior frontal gyrus (LIFG), posterior middle temporal gyrus (pMTG) and inferior parietal cortex (i.e., dorsal angular gyrus/intraparietal sulcus (dAG/IPS) and mid AG), because each of these regions has previously been implicated in either domain specificity (e.g., pLIFG: phonological; aLIFG: semantic), control (e.g., pMTG, LIFG) or a combination of the two (e.g., semantic control in pMTG), but a *direct comparison* of both domain and control (i.e., domain by control) has not previously been made. Our key findings were that:
    a. Although LIFG was activated by linguistic control across phonological and semantic domains, there was some degree of graded specialisation along the posterior to anterior gradient: with posterior/dorsal recruitment of LIFG for phonological judgements, and specific recruitment of the most anterior/ventral parts of LIFG for verbal semantic judgements – showing that while there is a large degree of overlap across this site for the two domains, the extreme 'ends' show some specialisation by domain (theme i).
    b. There was no effect of difficulty/control in pMTG for either the phonological or the verbal semantic task (theme ii), despite previous indications predicting that this site would respond to our manipulation of

semantic control (e.g., its emergence as the second largest cluster in an analysis of high > low semantic control; Noonan, et al., submitted). There was, however, a significant main effect of domain with more activation for phonological than semantic tasks (theme i).

c. Our investigation of parietal cortex (dAG/IPS and mid AG) showed that this site was both modulated by our difficulty manipulation (theme ii) and showed specialisation by domain (theme i). We found a greater response of dAG/IPS to phonological than semantic material, with no such specialisation by domain in mid AG – while both sites were recruited for increased demands on control (theme ii) across domain.

This chapter showed functional specialisations by domain along LIFG, with PMC and posterior LIFG showing greater specialisation for phonology, while the most anterior part of LIFG was more specialised for verbal semantic judgments. This finding is similar to the specialisation previously reported in the literature (e.g., Devlin, et al., 2003; Gough, et al., 2005), but also demonstrates the subtle nature of this gradation, with LIFG modulation for difficulty across domains. Furthermore, there was a gradient into anterior LIFG such that the difficult phonological judgments activated dorsal aLIFG, but only the verbal semantic associative judgments activated the most anterior part of LIFG, and this maps onto the rostro-caudal gradient put forth by Badre and D'Esposito (2009), where more complex and abstract information is processed along a gradient into anterior IFG. That pMTG was not modulated by difficulty was unexpected, but the significant activation of this site across both tasks provides further support for its role in language processing, particularly as a cortical hub due to its rich connections with other areas in the network (Turken & Dronkers, 2011). Furthermore, the greater contribution of dAG/IPS to phonology, whilst still resolving difficulty across domains is in line with previous suggestions that dAG/IPS plays a domain general function in language control (Seghier, et al., 2010), while the finding that mid AG contributed equivalently to the two domains is somewhat surprising given other studies indicating greater activation for the semantic than the phonological domain at this site (Binder, et al., 1999).

3. fMRI was used to investigate the network of areas previously shown to be involved in semantic control (theme iii) in Chapter 4 in order to assess each regions contribution to both modality (theme i) and any interactions with control (theme

ii). We used verbal and picture semantic tasks where the probe and target shared either high (easy) or low (hard) association strength, allowing for manipulation of the demands on semantic control. Previous studies indicate that there should be some degree of overlap for the two modalities (e.g., Bright, et al., 2004a; Corbett, Jefferies, Ehsan, et al., 2009; Hoffman, et al., 2011; Wagner, et al., 1997), however there has been a relative paucity of studies investigating *amodal semantic control* with healthy participants. We found:

a. More extensive and more significant recruitment of LIFG for verbal, than picture semantic control, as well as specialisation by modality, such that more anterior LIFG (i.e., BA 47) was recruited for verbal semantic judgements, with minimal recruitment for picture semantic associations.
b. A dissociation between left and right IFG, with greater recruitment of posterior right IFG for pictures than words, but anterior IFG was specialised to the verbal domain across hemispheres.
c. Significant activation of pMTG for verbal, but not, picture semantic material. However, interestingly, the picture semantic task was the only one where the difficulty manipulation significantly modulated activity for this site.
d. Equivalent recruitment of dAG/IPS and mid AG across semantic modality for resolving difficulty arising from increased need for semantic control.

These findings corroborate our assertion in Chapter 3 that the pattern of activation seen in aIFG may reflect its role in processing abstract semantic information: there was bilateral activation for the verbal associations, and less recruitment for the picture semantic associative judgments, as they may be more concrete in nature (i.e., meaning is constrained by the picture). Furthermore, the significant modulation of pMTG activity for increased picture semantic difficulty is in line with the literature suggestive of a role for this site in semantic control (e.g., Whitney, Jefferies, et al., 2011; Whitney, Kirk, et al., 2011). It has previously been suggested that pMTG may be recruited for context integration (e.g., Noonan, et al., submitted; Price, 2010), as such we may not have seen modulation by difficulty for our verbal semantic judgments because they did not change in their requirement for context. Hard picture semantic tasks may have placed a greater strain on context integration, than the easy picture associations where the context is readily available due to the constraints offered by presenting semantic material in picture format; however the verbal semantic task may have required context across easy and hard trials, where context is not constrained as words are inherently more ambiguous than pictures. The equivalent recruitment of dAG/IPS and mid AG to control demanding associative judgments for the two modalities is in line with previous studies suggesting a role for these sites in semantic processing (Binder, et al., 2009; Noonan, et al., submitted; Seghier, et al., 2010; Sharp, et al., 2010).

4. We narrowed our investigation to focus on pLIFG (BA 44), aLIFG (BA 47) and pMTG in the TMS study in Chapter 5, with the intention of confirming the involvement of these areas in phonological, and amodal semantic (pictures and words) processing, using the same tasks as in Chapters 3 and 4. . We found:
    a. A disruption of verbal semantic judgements following stimulation of both LIFG sites, but no effect of stimulation for the phonological or picture semantic tasks.
    b. Highly significant picture semantic disruption, as well as some verbal semantic disruption, but no TMS effects for phonological decisions, following stimulation of pMTG.

These data helped to confirm the findings in Chapters 3 and 4 where both posterior and anterior LIFG manifested a preference for the verbal semantic modality. Moreover, the significant disruption of picture semantic judgments following stimulation of pMTG is in line with a recent TMS study showing disruption of picture semantic judgments following TMS to pMTG (Hoffman, et al., 2011), and the results are also useful in view of our fMRI findings, where pMTG only showed modulation by difficulty for the picture semantic tasks.

5. In Chapter 6 we conducted a TMS study that focussed specifically on semantic control (theme ii) using a cyclical naming paradigm. We required participants to name sets of semantically related or unrelated items across cycles, and this allowed us to disambiguate retrieval and selection processes: early cycles of unrelated naming place high demands on retrieval, while later cycles of related naming load on selection. We found that:
    a. TMS to LIFG disrupted performance on this task when the demands on selection and retrieval were maximal.

b. pMTG was not recruited to resolve competition over the course of the cyclical naming task, even when the demands on selection and retrieval were separated (i.e., no involvement of pMTG for retrieval, selection or an interaction of the two).

These results add data to the debate over retrieval and selection, and are in line with a recent paper suggesting that the two processes interact in LIFG (Snyder, et al., 2011).

Linking Data to Theory

Premotor Cortex

The motor theory of speech perception regained momentum with the discovery of mirror neurons in monkeys as well as various fMRI and TMS studies reporting involvement of this area in speech perception tasks (e.g., Meister, et al., 2007; Rizzolatti, 2004; Wilson, et al., 2004). However, these tasks often require participants to make metalinguistic judgments on the constituent sounds of a word, and not the word as a whole. Therefore, we were interested in investigating the specific contribution of this site and our data suggest a *revision of the motor theory*: we found that PMC was recruited for tasks that required phonological, but not semantic judgments (based on access to meaning), both in fMRI using hard and easy phonological and verbal semantic tasks (Chapter 3) and with TMS through explicit phoneme and semantic judgments to the same stimuli (Chapter 2). Therefore, the role of PMC as an essential part of the speech perception architecture falls into question as it was not shown to be essential for accessing word meaning in either of our studies (Chapter 2 & 3). Thus, in view of the previous literature and our findings, the role for PMC is likely restricted to 1) non – natural language tasks (e.g., identifying individual phonemes, not whole words for meaning; Burton, et al., 2000; Hickok & Poeppel, 2000; Rogalsky, et al., 2011; Sato, et al., 2009; Zatorre, et al., 1992), 2) distorted/degraded speech (e.g., as a ‘back up’ mechanism when perception is challenging; Devlin & Aydelott, 2009; Gow Jr & Segawa, 2009; Osnes, et al., 2011; Scott, et al., 2009) or 3) for repetition of and learning new words (e.g., Burton, et al., 2000; Demonet, et al., 1992; and results showing PMC recruitment for new/rare words: Kotz, et al., 2010; Roy, et al., 2008).

Inferior Frontal Gyrus

While the functional specialisation of LIFG by domain has received attention in previous studies (e.g., Devlin, et al., 2003; Gold & Buckner, 2002; Gough, et al., 2005; Nixon, et al., 2004), very few studies have manipulated domain (theme i) and difficulty (theme ii) simultaneously. While LIFG responded to the difficulty manipulation (theme ii) for all of our tasks across domain and modality (theme i), there was still a gradient such that pLIFG was specialised to phonology, and also presented a verbal modality preference; mid LIFG (BA 45) was domain and modality invariant; and perhaps most strikingly, the most anterior part of aIFG was most significantly activated by the verbal semantic tasks (bilaterally; Figure 7-1); corroborated by TMS stimulation of aLIFG disrupting only the verbal semantic judgments). These findings are consistent with the theory put forth by Badre and D'Esposito (2009), which suggests that IFG is hierarchically organised along a rostro-caudal gradient, with greater recruitment in anterior IFG for more abstract/complex information. Control-demanding semantic tasks are likely to require abstract processing to establish which possible semantic relationship is relevant: this may be especially true for verbal as opposed to picture association tasks, as the presence of a picture may help to highlight the relevant relationship being probed.

Furthermore, we demonstrated that LIFG recruitment is necessitated by high demands on *both* retrieval and selection, similar to one other study demonstrating an interaction between these two processes in aLIFG (Snyder, et al., 2011). We did not see TMS disruption of naming when the demands on these factors occurred in isolation (e.g., only retrieval; only selection) over the course of the cyclical naming paradigm we used in Chapter 6 (Finding 5a,b). More specifically, if LIFG recruitment were necessitated by retrieval alone, then we should have seen a specific slowing of cycle one of the unrelated sets, where the need for retrieval is high since there is no within category facilitation of items (e.g., no category ‘node’ can be activated as each item is unrelated; Belke, et al., 2005). Similarly, if LIFG recruitment occurred only when the demands on selection peaked, then we should have seen disruption of naming across later cycles: these have high selection yet low retrieval requirements (owing to both within category facilitation and familiarity with the items over repeated cycles). However, we saw a cycle specific slowing when the demands on both processes were maximised, suggesting that while previous studies have attempted to disambiguate the two processes (e.g., Badre, et al., 2005; Thompson-Schill, et al., 1997; Wagner, et al., 2001), it may be more accurate to say that the two processes interact and are resolved in LIFG (BA 45/47). As such, retrieval processes are engaged to activate representations (which have strong and weak synaptic weights), and selection works to increase “the difference in activation levels between the most active representation and its competitors” through lateral inhibition in order for one “winning” item to be selected (Snyder, et al., 2011, p. 3479).

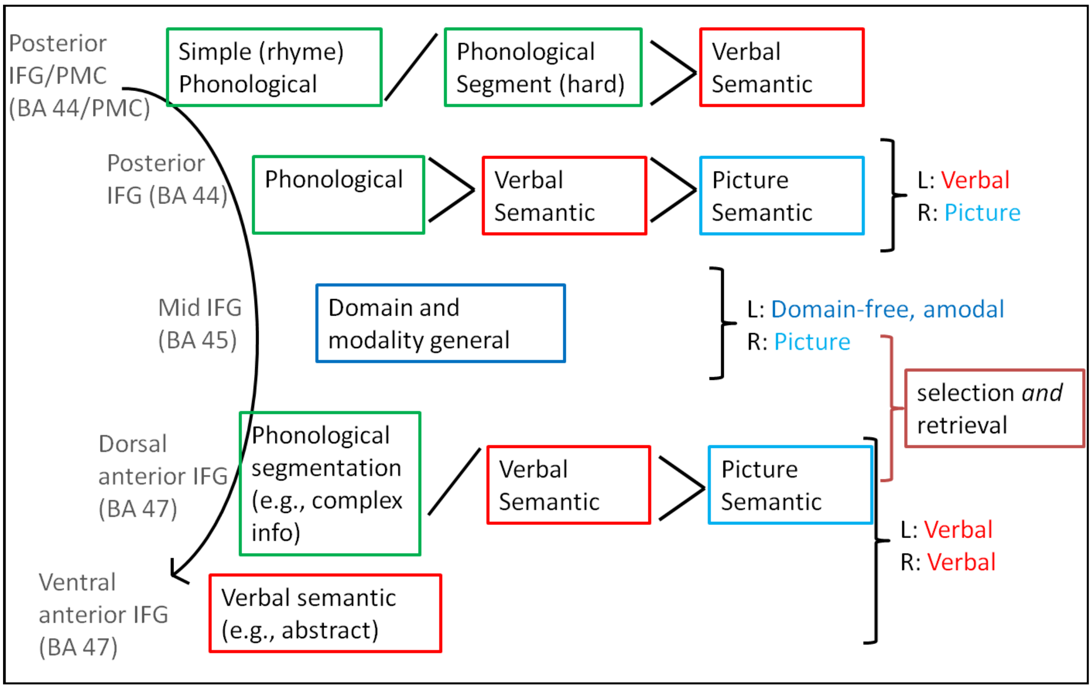


Figure 7-1. This image is used to illustrate the gradient of specialisation in LIFG based on our data (Chapters 3, 4 and 6) with regard to the suggestion put forth by Badre and D’Esposito (2009). Coloured boxes/text are used to denote the domain of specialisation (as in Chapters 3 and 4): red is used for verbal semantic, green for phonology, cyan for picture semantic, and blue for domain/modality general contributions. The symbols are used as follows: “>” denotes preferences within each LIFG subdivision (for example phonological > verbal semantic represents greater preference for phonological than verbal semantic material, yet still significantly activated for both task types); “/” denotes overlap of activation in specific ROIs (e.g., phonological segmentation / verbal semantic represents overlap of the two), “}” is used to group information (e.g., grouping dorsal and ventral anterior IFG to summarise its overall modality preference across hemispheres).

Posterior Middle Temporal Gyrus

The role of pMTG in language processing is less clear, and our results go some way in helping to elucidate the role of this site. For example, we confirmed the finding from patients with semantic aphasia (SA) who have lesions in temporoparietal cortex and are impaired on most tests of semantic control, but do not perform poorly on cyclical semantic tasks (Gardner, et al., 2012; Jefferies, et al., 2007), suggesting that this site has a *specific* role to play in semantic cognition that is not captured by cyclical tasks. While our results from the cyclical naming study (Chapter 6) cannot confirm what the specific role is, they can speak to prior suggestions that this site plays a specific role in semantic retrieval (Badre, et al., 2005; Wagner, et al., 2001), as our results suggest that the role for pMTG may lie beyond retrieval. If pMTG were involved in retrieval, we should have seen a specific disruption of naming for the first cycle; particularly for the unrelated sets where retrieval is most challenging due to the lack of within category facilitation afforded by related naming. We also did not see any slowing of naming following TMS for cycles where selection amongst semantically competing alternatives was necessary, therefore, the role of pMTG may lie beyond both retrieval and selection processes.

Additionally, in Chapters 3 and 4 we saw that for verbal semantic tasks which were designed to increase the need for semantic control (using RT to index difficulty), there was no modulation of activity in pMTG, rather this site showed an equivalent response to our hard and easy verbal semantic tasks. This further suggests that while pMTG is involved in semantic control (as shown by tasks that have found a necessary role for pMTG in semantic control; e.g., Noppeney, et al., 2004; Whitney, et al., submitted; Whitney, Jefferies, et al., 2011; Whitney, Kirk, et al., 2011), its exact role is still somewhat unclear. There is some suggestion that this site may play a specific role in context integration (Noonan, et al., submitted; Price, 2010), therefore activation of pMTG for the picture semantic associations may not be expected/necessitated, because the need for context integration is greatly reduced with the semantic relationship readily available as it has been constrained by the pictures (e.g., words are often more ambiguous, therefore more context integration may be needed). Further support comes from the significant modulation of pMTG activity for the difficult picture semantic tasks, presumably because the need for context is greater when the semantic relationship is less readily available. This hypothesis gains further support from studies that used semantically plausible and implausible sentences and found pMTG activation for the plausible sentences only (Adank & Devlin, 2010; Mashal, et al., 2009), and another study in which pMTG activation was seen for context integration for verbs rather than nouns (Gennari, et al., 2007). Other studies have found pMTG to be active when participants combine information provided by spoken input and hand gestures in an attempt to extract meaning (Dick, Goldin-Meadow, Hasson, Skipper, & Small, 2009; Holle, Obleser, Rueschemeyer, & Gunter, 2010; Kircher et al., 2009), making it a good candidate as a context integration ‘zone’. Additionally, the pMTG recruitment seen for tasks requiring feature selection may also reflect context integration as the ‘context’ may be driven by the relevant feature to attend to (i.e., liquid consistency – rather than association – in order to match custard with oil; Whitney, et al., 2012).

However, we also found significant activation of the phonological tasks in pMTG, contrary to a recent meta-analysis which found this site to be semantic specific (Noonan, et al., submitted). Hickok and Poeppel (2000, 2007) suggest that this site is an interface between speech representations in STG and ATL, however, this interpretation is not compatible with our findings as we did see a significant modulation of difficulty for the picture semantic tasks, and when taken in conjunction with other studies that have shown involvement of pMTG for picture semantic tasks, this explanation, which is restricted to the linguistic domain, is unlikely to be the case. Perhaps the most helpful framework within which to assess the role of pMTG in language processing, given our findings, is that of a cortical hub, as suggested by Turken and Dronkers (2011), due to the wealth of connections this area has to other parts of the network. Therefore it may show some characteristics of both representation and control because it may be essential to the interaction of these two networks, and thus pMTG would be crucial for contextualising information, as well as possibly for integrating phonological and semantic information in order to comprehend spoken input.

Angular Gyrus/Parietal Cortex

Angular gyrus has often been implicated in semantic cognition, and recent evidence suggests that there are several functional specialisations within this large area. dAG/IPS has been shown to be involved in tasks spanning several domains (e.g., reading, visuospatial search and 'number line' tasks, left/right discrimination; Carreiras, et al., 2009; Gobel, et al., 2001; Hirnstein, et al., 2011), including semantic processing (e.g., Noonan, et al., submitted; Price, 2010; Seghier, et al., 2004; Sharp, et al., 2010; Vigneau, et al., 2006). We found a greater response to phonological than semantic material (theme i); however, this site on the boundary of IPS, AG and SMG was still significantly activated for resolving difficulty across semantic modalities (theme i and ii) – corroborating previous findings that this site is involved in domain general cognitive control (theme ii). Our finding that this site showed the strongest response to the phonological hard task may relate to its role in feature selection and integration (e.g., Donner, et al., 2000; Friedman-Hill, Robertson, & Treisman, 1995). A recent TMS study showed that stimulation of this site caused disruption of feature selection tasks (across domain), but not verbal associative semantic judgments (Whitney, et al., 2012); we found a greater contribution of this site to the phonological segmentation than the semantic association tasks, and it is possible that the phonological segmentation task captured some aspect of feature selection and integration. One could speculate that if our semantic tasks had required feature selection we might have seen an equivalent response for phonological segmentation and semantic feature selection. However, despite the greater response for the phonological tasks, dAG/IPS was significantly activated by our semantic tasks, and showed a significant modulation of activity when demands on semantic control increased, corroborating previous studies that have reported activation at this site for tasks requiring some aspect of semantic control (e.g., Bedny, et al., 2008; Hirshorn & Thompson-Schill, 2006; Lee & Dapretto, 2006; Noonan, et al., submitted).

Additionally, our results align with other studies implicating mid AG as a part of the semantic control network (e.g., Hoenig & Scheef, 2009; Noonan, et al., submitted; Seghier, et al., 2004; Sharp, et al., 2010): we found an amodal response in this area to semantic association judgements, that was modulated by difficulty. It is therefore unlikely that this site acts as a ‘second’ cortical hub for storage of semantic representations, as the significant modulation of activity for the *difficulty* manipulation seen at this site for both semantic modalities does not align with this suggestion. There has been some suggestion that mid AG acts as a multimodal integration area for conceptual knowledge, and our results could reflect this role, where mid AG “coordinates reciprocal interactions between the sensory representation of words and objects and the symbolic association that gives them meaning” (Vigneau, et al., 2006, p. 1424), reflected in the amodal response of this area to our semantic judgements . Additionally, if mid AG were a semantic hub it should respond exclusively to the semantic domain, and we would not predict a significant response for our phonological tasks, however, mid AG *was* also significantly activated by the phonological domain. The equivalent response to the phonological and semantic domains may reflect previous findings that this site is involved in reading (e.g., Carreiras, et al., 2009) – which requires access to phonology. This indicates a slight revision of existing theories that postulate a specific role of mid AG in semantic cognition, as it may be better conceptualised as an interface for language across domains, due to its connections to various association areas (Binder, et al., 2009).

Distributed Network (Figure 7-2)

We present a complex network of brain areas that are often both domain/modality (theme i) invariant and sensitive to changing demands on control (theme ii). Combining the data in this thesis with the literature suggests that while some areas may show specialisation by domain, they often still help to resolve difficulty across other language domains. Our data suggest that the control processes in frontal and posterior cortices may be distinguishable such that frontal cortex may be more involved in retrieval/selection and posterior cortex in integrating information. We found LIFG to be essential to retrieval/selection processes and suggest that the most anterior aspect of IFG is most likely recruited for abstract semantic processing. The role for information integration in posterior cortices may fall along the following gradient: feature selection in dAG/IPS (via the allocation of attention to internal representations); domain general (language) integration in mid AG, e.g., for reading which requires accessing both phonology and semantics; and context integration in pMTG, due to its rich connections across the cortex (Gennari, et al., 2007; Noonan, et al., submitted; Price, 2010; Turken & Dronkers, 2011). Therefore, frontal and posterior cortices interact in order to select and use language in a time sensitive and appropriate manner. The anatomical and functional connections between frontal and posterior brain areas support this assertion (Catani, et al., 2005; Parker, et al., 2005; Spreng & Schacter, 2012; Turken & Dronkers, 2011; Xiang, et al., 2010), as well as a recent combined TMS and fMRI study demonstrating that pMTG and LIFG may work together via reciprocal connections in order to disambiguate the given semantic context, as shown by increased activation in pMTG following ‘virtual lesion’ stimulation of LIFG (i.e., compensatory activation; Whitney, et al., submitted). Additionally, the literature suggests that BA 44 and PMC may work together in resolving phonological tasks, with a possible modulation of PMC by BA 44 (Watkins & Paus, 2004), for instance when motor articulatory simulation is required, such as when rare/pseudowords are encountered (Kotz, et al., 2010).

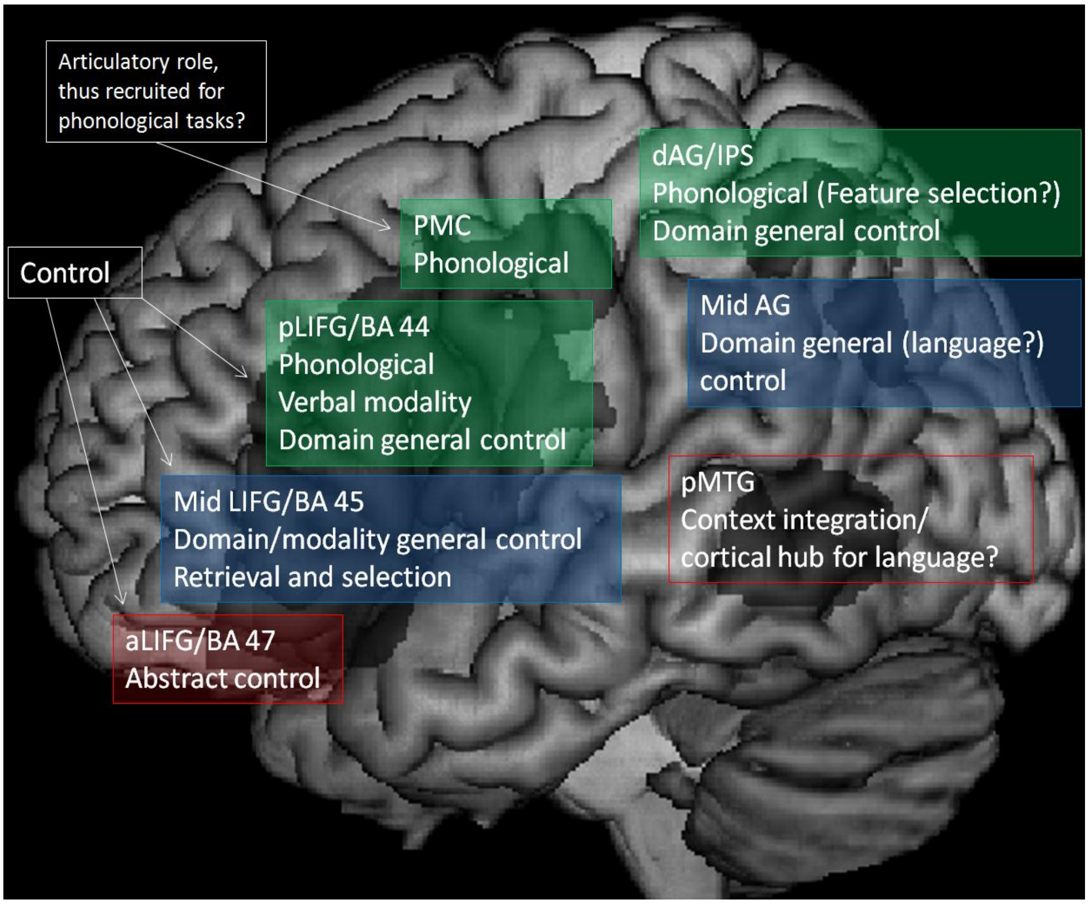


Figure 7-2. Distributed network of areas investigated in this thesis. Areas found to be preferential for phonology in green, semantic in red, and domain general in blue.

Future Directions

This thesis provides evidence for a distributed network of brain areas contributing to both domain general and domain specific control over language representations. Naturally, there are questions which remain to be answered in view of the findings presented here. An important first step might be to replicate our findings from Chapter 2, using different tasks. For example, using a task that better mimics ‘natural’ speech perception, such as hearing degraded speech with or without context to test whether PMC is necessitated when phonetic ambiguity cannot be resolved based on context. Also, our data go some way in clarifying the role of LIFG in language processing across domain and modality; but future studies may wish to clarify the degree to which aIFG is activated by abstract picture semantic associations, by specifically creating picture semantic associative questions designed to vary in degree of ‘abstractness’. Our study used verbal ratings of ‘associativeness’ to create the picture semantic tasks, however, these ratings may be less ‘accurate’ for the picture modality; a more tightly constrained task would help to identify this sites role in *amodal* abstract semantic processing. Therefore, collecting independent ratings of the semantic associative relationship for the picture trials would help to elucidate the degree to which the picture semantic associative relationship accurately captures the 'assumed' association strength based on previous verbal ratings. Furthermore, a picture metaphor task might better capture 'abstract' picture semantic processing, whereby metaphors could be presented across verbal and picture domains in order to assess the contribution across the network of verbal and picture semantic 'abstract' processing, and with specific ROI's in aIFG bilaterally to assess activation to amodal 'abstractness'. Additionally, our verbal semantic tasks were not expressly designed to be abstract, therefore a study which uses judgments that have been specifically designed to vary in degree of 'abstractness' (e.g., perhaps by using a continuum from concrete – abstract and using this as a regressor in the model) would help confirm the role of aIFG in *abstract* semantic control. We also confirmed the role of mid LIFG (BA 45) in *both* retrieval and selection processes, and Snyder et al. (2011) suggest that the response in anterior LIFG is the same. Our result that aIFG showed greater specialisation for verbal, and thus possibly more abstract judgments, is in line with their finding where low association strength showed the greatest response, regardless of added competition. Therefore, a worthwhile advance would be to disambiguate the need for abstract semantic processing from competition and retrieval. For example, a possible avenue for exploration could be using tasks such as cyclical spoken word-to-written word matching where retrieval and selection processes can be separated across related and unrelated conditions and cycles – but with abstract and concrete groupings (e.g., concrete: apple – banana – pear - orange; abstract: democracy – freedom – politics – republic, but matched for frequency; Crutch, Ridha, & Warrington, 2006). This could be done using fMRI as a first step, in a factorial design (site: BA 47/ BA 45/ pMTG; by condition: related/unrelated; by concreteness: abstract/concrete; by cycle: one – three) where anterior IFG may show a greater response when retrieval and selection interact for abstract, but not concrete words; BA 45 when the demands on retrieval and selection are maximal across both abstract and concrete words; and pMTG may show a maximal response across cycles for the abstract condition, as these words may often require greater 'context' integration.

One major line of investigation is the role of pMTG in language processing. The results presented in this thesis suggest that the role of this site may have only been partially captured by the tasks we used. For example, future studies could investigate the contribution of pMTG to context integration, a role previously suggested in the literature (Gennari, et al., 2007; Noonan, et al., submitted; Price, 2010); our tasks were not designed to assess context integration, and therefore may not have been well placed to identify the specific role of this site. Therefore, designing tasks that require context integration and possibly comparing these with traditional tasks (e.g., semantic association judgments) may be a good starting point. Additionally, a recent meta-analysis found that the majority of studies reporting pMTG activation lay in the receptive domain (Noonan, et al., submitted), and we too did not find any involvement of pMTG for our production tasks (Chapter 6), however these results cannot confirm a role for pMTG in comprehension, but not production, because we did not have a comprehension task for comparison and it could therefore be the task requirements, not the domain, that we failed to disrupt with TMS. Future studies directly comparing pMTG involvement across speech modalities would be invaluable in further elucidating the role of this site in semantic cognition. A natural starting point may be a TMS study using comprehension versions of the cyclical semantic task we used in Chapter 6 to confirm pMTG recruitment (or lack thereof) across cyclical tasks types, and therefore helping to elucidate the role for this site in either/both 1) production/comprehension and 2) control processes engaged by cyclical tasks. Furthermore, tasks that required context integration across production and comprehension domains would help to assess the contribution of pMTG to both context and comprehension/production; pMTG recruitment may thus far only have been seen for comprehension tasks, because these have required more context integration than production tasks. Additionally, the exact contribution of this site to phonological and semantic processing is unclear given the tension between our results indicating a role for this site in phonological processing and other studies suggesting that this site is exclusive to the semantic domain (Noonan, et al., submitted). Other models of language have included a role for pMTG as an interface between the two domains (Hickok & Poeppel, 2000, 2007); it would, therefore, be interesting to clarify the role of this site in language processing in order to discover the specific role pMTG has to play: our ROI may have encompassed some of pSTG as it was fairly large and not anatomically defined for each participant. Therefore, studies using more precise functional and anatomical localisers may better elucidate the role of pMTG in phonological and semantic processing. For example, it would be useful to use a semantic task which has previously been shown to modulate activity in pMTG according to the difficulty/control manipulation, and contrast this with a phonological task. In this case, the data could reveal a functional dissociation, such that the phonological activation lies closer to/within STG, and semantic control within pMTG (e.g., ventral to STG); particularly if a functional localiser is used to identify these areas on a participant by participant basis.

Further elucidating the role of angular gyrus would also be a beneficial avenue for investigation, given that it has been implicated in a variety of task types. We found a significantly greater response to the phonological than the semantic domain in dAG/IPS, therefore it would be useful to investigate the specific role of this site in tasks requiring phonological segmentation and feature selection across domains (i.e., phonological, semantic, visual) to investigate whether the response is domain specific or due to a role for this site in domain-free feature selection/conjunction tasks. Additionally, mid AG would benefit from further study as the role of this site is still largely under debate and has been reported as an area of overlap between default and semantic networks (Seghier, et al., 2010), with some studies reporting greater activation for semantic than phonological tasks (Binder, et al., 2009; Binder, et al., 1999); but our results indicate a domain general function for this site. Therefore, further clarification is needed using non-language tasks to compare the response of this region directly with tasks such as ours which investigated controlled access to language representations (phonological, verbal, picture semantic), to firstly establish if this site is indeed specific to language. Then, further studies could investigate the role for this site as a language interface with tasks designed to force integration of language domains and asses mid AG activity in resolving these tasks.

Conclusions

This thesis sought to investigate the neural basis of linguistic and semantic processing within established brain networks by using convergent methods of fMRI and TMS. Much of the empirical work in this thesis takes inspiration from the neuropsychological literature which has helped to form our hypothesis as to specialisations by both domain/modality and control. We found that PMC was not recruited for meaning extraction, but rather for meta-linguistic tasks, possibly due to its role in articulation. Moreover, our data suggest a gradient of processing from PMC to anterior LIFG, such that PMC and more posterior parts of LIFG (BA 44) preferentially process phonological material, with domain and modality free processing in mid LIFG (BA 45), and the most anterior aspects of LIFG processing abstract semantic material. Furthermore, we confirmed the role of aLIFG (BA 45/47) in semantic control, and revealed that the retrieval and selection processes required for controlled access to semantic representations interact in LIFG.

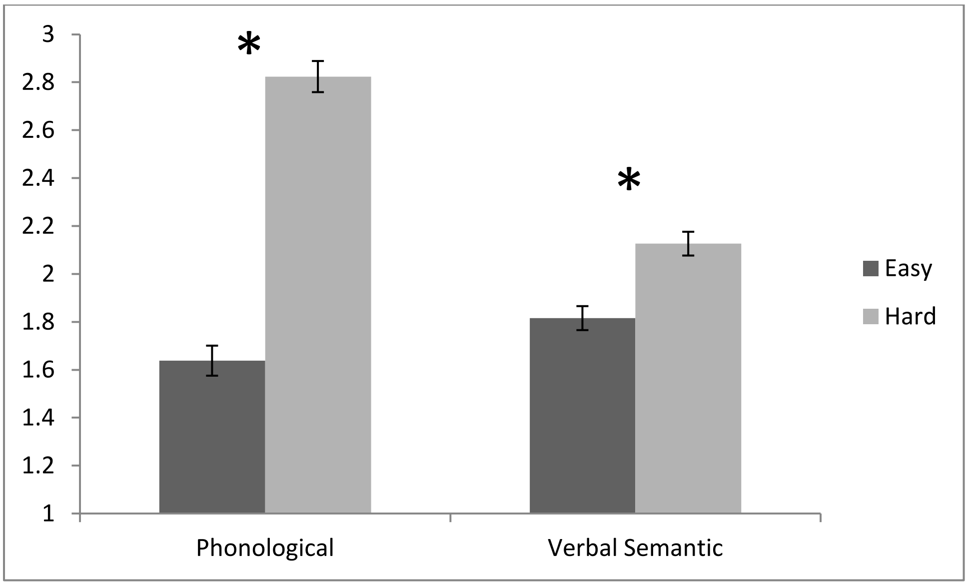
Appendices

Appendix 3.1

Behavioural Results

	Phonological vs. Verbal Semantic
Task	
df	1, 21
F	46.98
p	< .001
Difficulty	
F	590.53
p	< .001
Task x Difficulty	
F	330.25
p	< .001

F and p values for within subject ANOVAs comparing phonological and verbal semantic tasks.



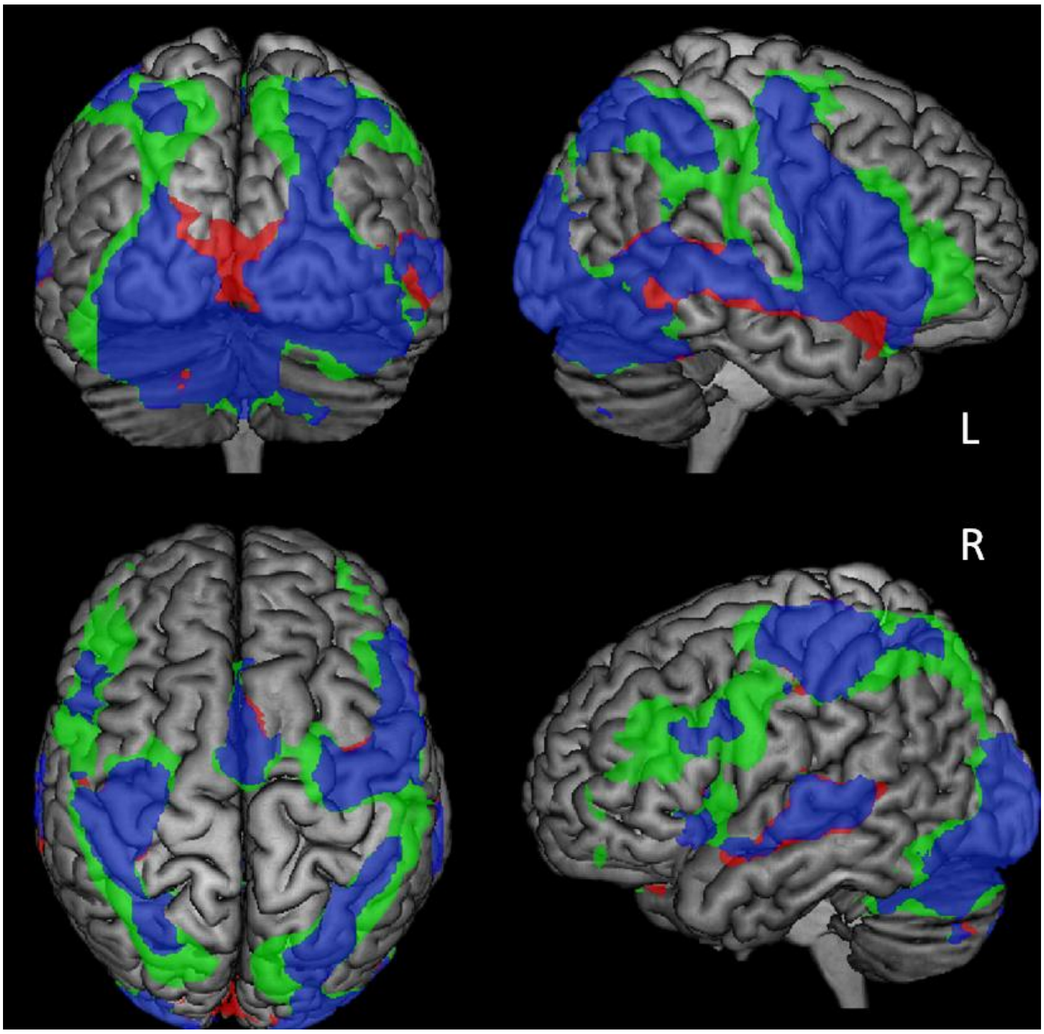
Behavioural performance across the phonological and verbal semantic experimental tasks. Error bars represent standard error of the mean. Asterisks represent significant differences in RT for difficulty manipulations ($p \leq .001$).

	Phonological	*Verbal Semantic*
df	1, 21	1, 21
t	-26.67***	-9.47***

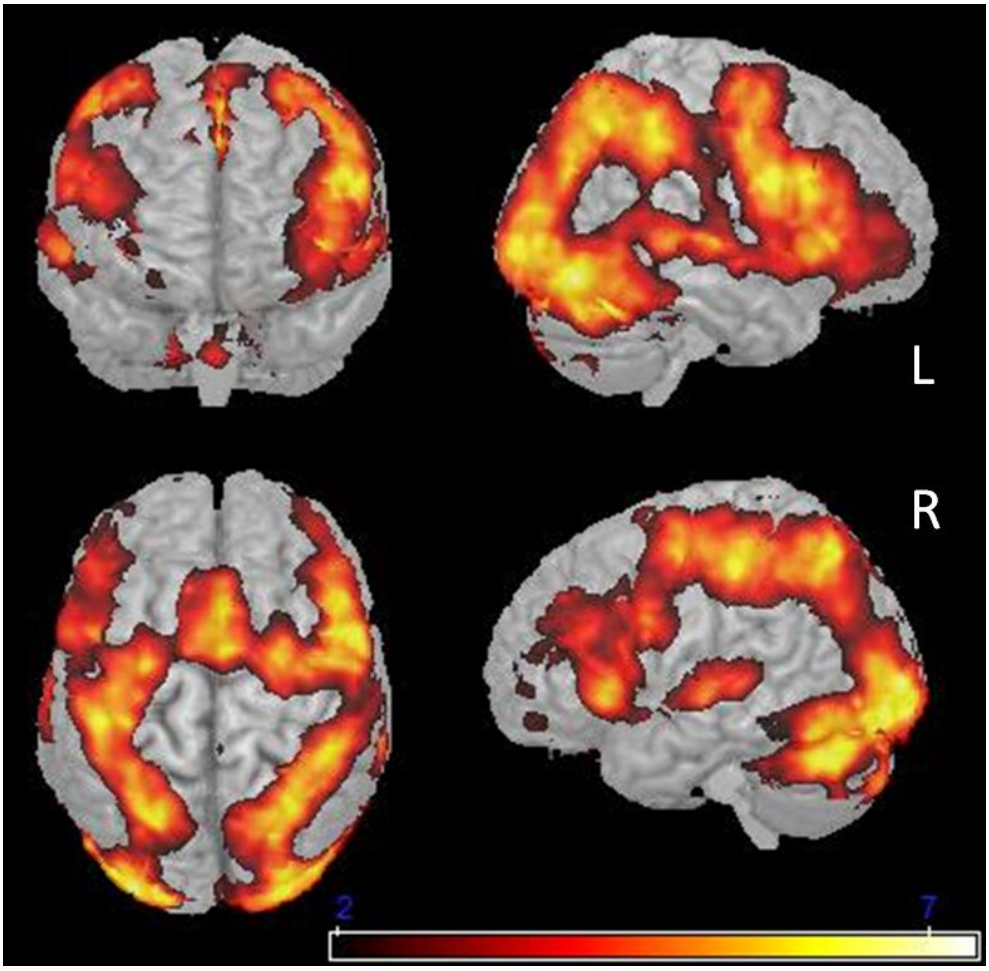
T-tests comparing RTs for easy and hard conditions for each task type.

Appendix 3.2

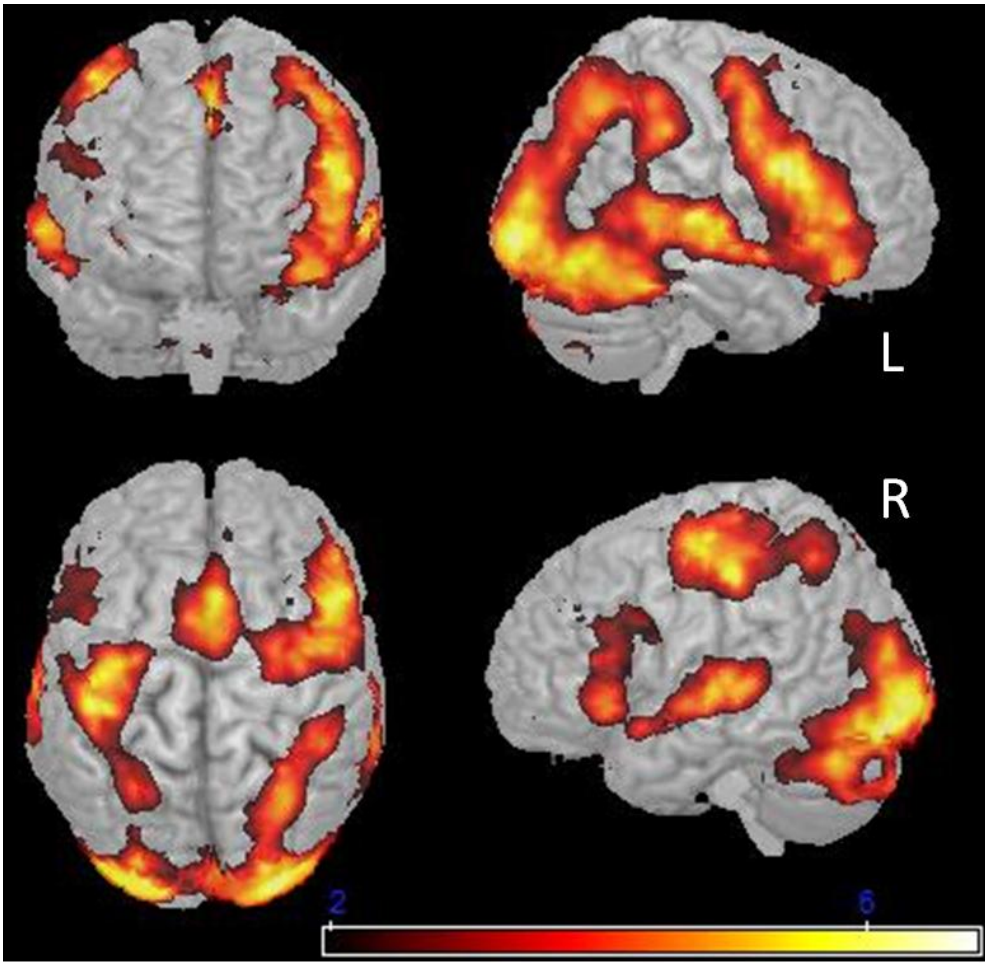
fMRI Results



Whole brain analysis (cluster correction, $Z \geq 2.3$, $p < .05$). Phonological hard (green), verbal semantic hard (red) and mutual activity (blue). L = left, R = right hemisphere.



Cluster corrected whole brain analysis (*Z* ≥ 2.3, *p* < .05) of phonological hard over rest. L = left, R = right hemisphere. *Z* values are indicated on the colour scale.



Cluster corrected whole brain analysis (*Z* ≥ 2.3, *p* < .05) of semantic verbal hard over rest. L = left, R = right hemisphere. *Z* values are indicated on the colour scale.

Contrast of phonological hard > easy judgements

					Voxel (MNI)		
	Brain Area	BA	Voxels	*Z*	*x*	*y*	*z*
R	Parietal Lobe, Precuneus	7	9375	5.75	28	-72	38
L	Middle Frontal Gyrus	~6	8038	5.05	-30	2	46
R	Fusiform Gyrus	37	1136	5.11	50	-62	-18
L	Inferior Temporal Gyrus		525	4.72	-54	-62	-14
R	Middle Frontal Gyrus	8	426	4.17	28	8	46
L	Fusiform Gyrus	19	387	4.06	-24	-54	-12
R	Fusiform Gyrus	37	364	3.6	32	-50	-12
L	Brainstem		109	3.6	-2	-24	-28
R	Fusiform Gyrus	36	98	3.1	42	-36	-26
R	Anterior Cingulate	25	80	3.63	8	4	-4
L	Inferior Temporal Gyrus	37	67	3	-52	-38	-20
R	Middle Frontal Gyrus	11	48	3.03	22	40	-16
R	Cerebellum		45	2.94	34	-68	-36
L	Posterior Cingulate	29	44	2.79	-8	-42	6
L	Posterior Cingulate	23	32	3.02	-6	-34	24
L	Occipital Lobe	18	31	2.69	-16	-100	8
R	Caudate		27	2.93	20	-24	26
L	Occipital Lobe	17	19	3	-10	-100	-4
L	Precentral Gyrus	~3	18	2.93	-38	-16	28
L	Orbitofrontal	~47	16	2.62	-28	32	-26
R	Lingual Gyrus	18	13	2.92	6	-94	-18
L	Sub Gyral	~45	12	2.69	-20	32	6
R	Posterior Cingulate		10	2.61	10	-34	22
L	Rectal Gyrus	11	10	2.74	-4	16	-22

Cluster corrected ($Z \geq 2.3$) contrast of hard > easy task difficulty for phonological judgements.

Contrast of semantic verbal hard > easy judgements

					Voxel (MNI)		
	Brain Area	BA	Voxels	*Z*	*x*	*y*	*z*
L	IPL	40	698	3.8	-38	-58	44
	Sub peak			3.35	-42	-44	34
L/R	Cingulate Gyrus	32	290	3.58	2	20	40
L	IFG	45/46	384	3.43	-48	32	18
	Sub peak; BA 9/44			3.28	-40	6	24
L	MFG	8	150	3.25	-30	14	48
L	MFG	10	146	3.16	-38	52	6
L	Posterior Inferior Temporal Gyrus	37	57	3.1	-50	-62	-14
L	MFG	11	29	2.77	-34	54	-10
L	IFG	45	13	2.73	-48	38	2
L	Superior Frontal Gyrus	8	28	2.67	-8	20	56
L	IFG	47	12	2.61	-30	20	-6
L	Ventral Angular Gyrus		25	2.6	-24	-74	30
L	Parietal Lobe	7	15	2.5	-18	-70	38
R	Cerebellum		200	3.54	32	-70	-36
R	Superior Parietal Lobule	7	113	3.39	28	-66	50
R	IFG	44/9	62	3.14	46	8	26
R	IFG	47	26	2.88	32	20	-4
R	pITG	37	25	2.69	48	-56	-12
R	Cingulate Gyrus	2	14	2.69	26	-24	32
R	IFG	45	15	2.56	44	24	18

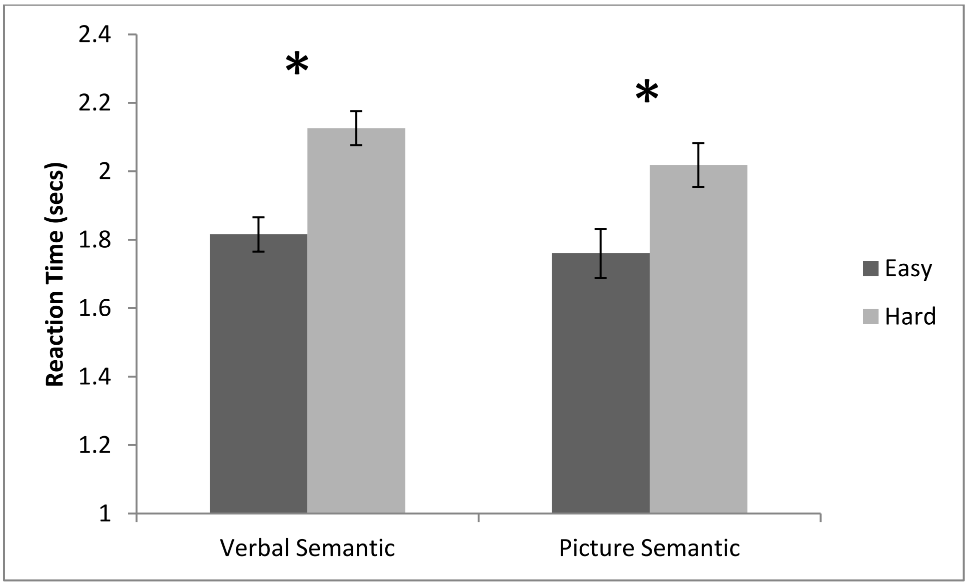
Cluster corrected ($Z \geq 2.3$) contrast of hard > easy task difficulty for semantic decisions.

Appendix 4.1

Behavioural Results

	Verbal vs. Picture Semantic
Task	
df	1, 21
F	2.51
p	0.13
Difficulty	
F	109.97
p	< .001
Task x Difficulty	
F	1.06
p	0.32

F and p values for within subject ANOVAs comparing verbal and picture semantic tasks.



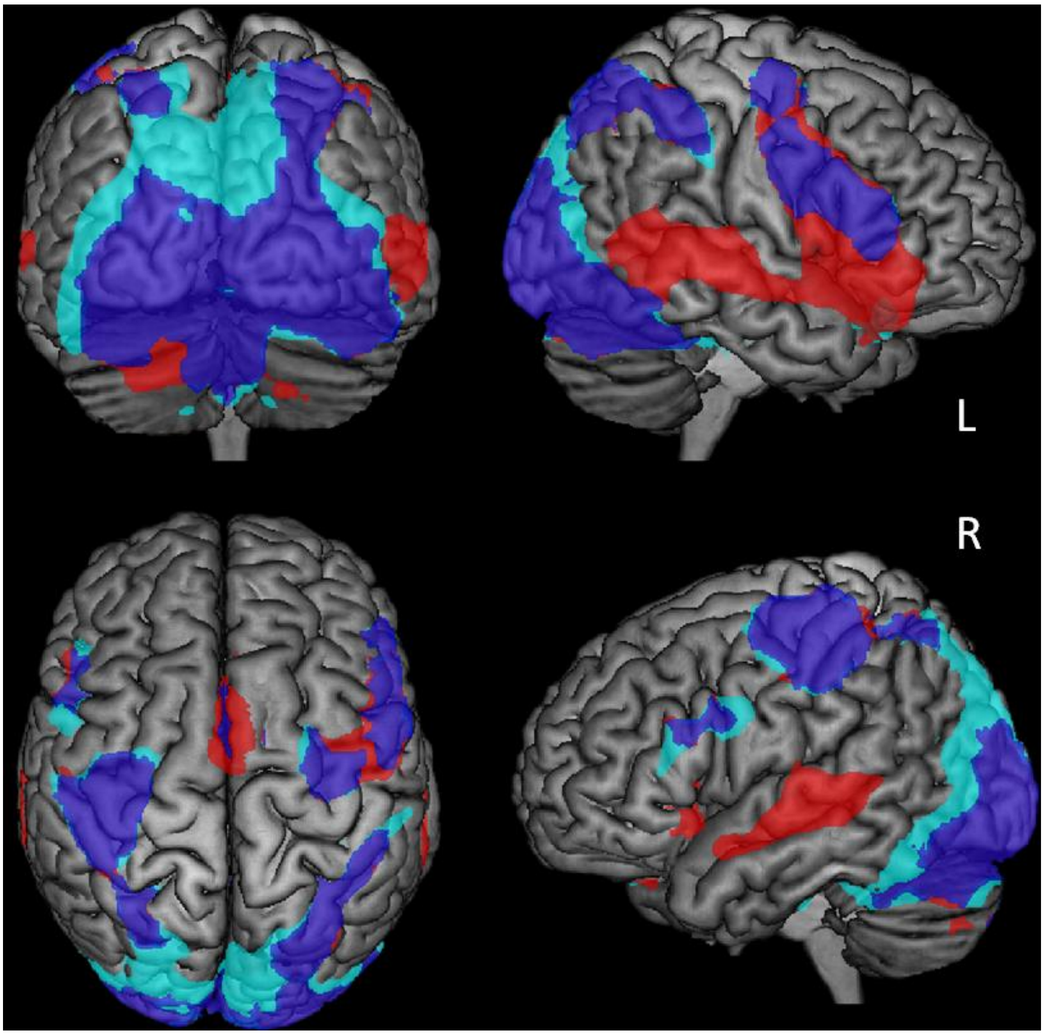
Behavioural performance across the verbal and picture semantic experimental tasks. Error bars represent standard error of the mean. Asterisks represent significant differences in RT for difficulty manipulations (*p* ≤ .001).

	Verbal Semantic	*Picture Semantic*
df	1, 21	1, 21
t	-9.47***	-6.26***

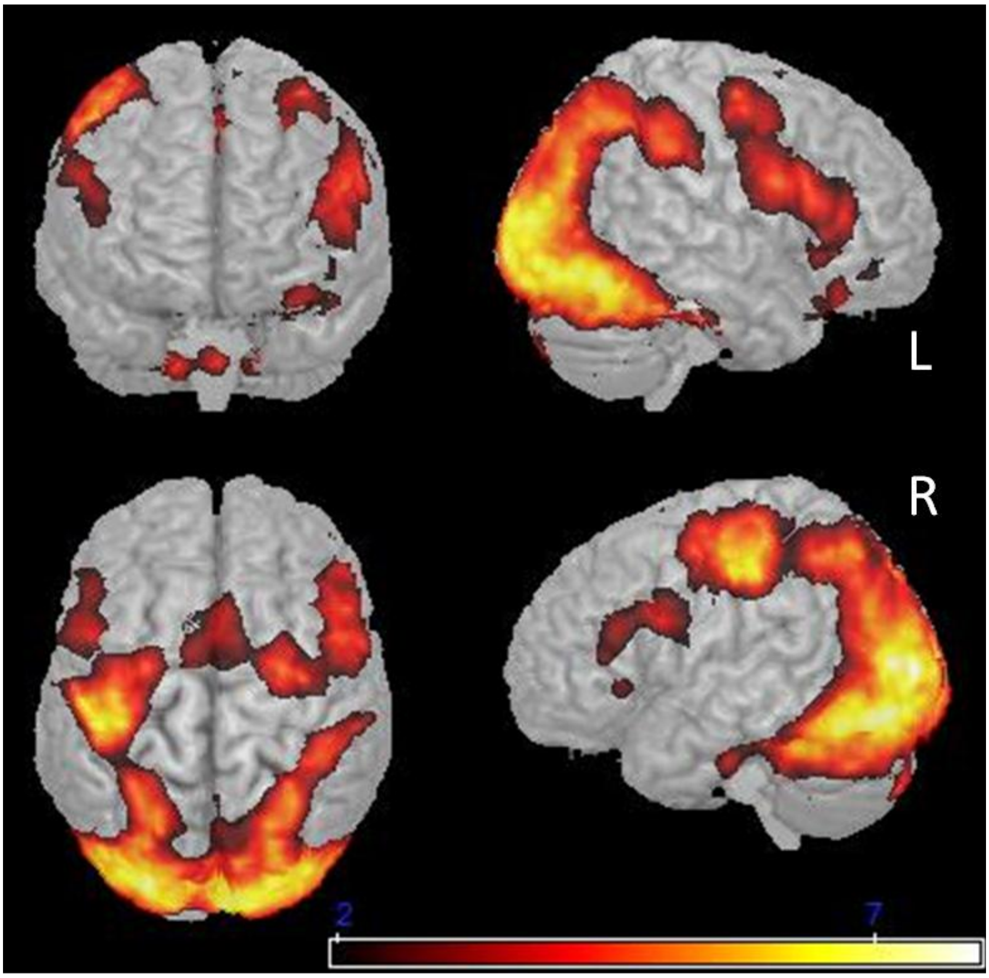
T-tests comparing RTs for easy and hard conditions for each task type.

Appendix 4.2

fMRI Results



Whole brain analysis (cluster correction, *Z* > 2.3, *p* < .05). Semantic hard tasks over rest: verbal (red), picture (cyan) and overlapping activity (blue). L = left, R = right hemisphere.



Cluster corrected whole brain analysis (*Z* = 2.3, *p* < .05) of semantic picture hard over rest. L = left, R = right hemisphere. *Z* values are indicated by the colour scale bar.

Contrast of semantic picture hard > easy judgements

					Voxel (MNI)		
	Brain Area	BA	Voxels	*Z*	*x*	*y*	*z*
L	Mid Occipital Gyrus	18	361	3.4	-30	-94	-6
R	Brainstem		74	3.18	10	-22	-24
R	Mid Occipital Gyrus	19	33	3.09	46	-84	0
R	Occipital Lobe	18	134	2.79	28	-100	-8
R	Temporal Lobe	28/38	11	2.76	32	12	-24
R	Temporal Lobe	20	13	2.72	44	-18	-24
R	IFG	47	14	2.66	54	22	-6
R	Posterior ITG/MTG	21	10	2.64	66	-42	-14

Cluster corrected (*Z* = 2.3) contrast of hard > easy task difficulty for picture judgements.

Appendix 5.1

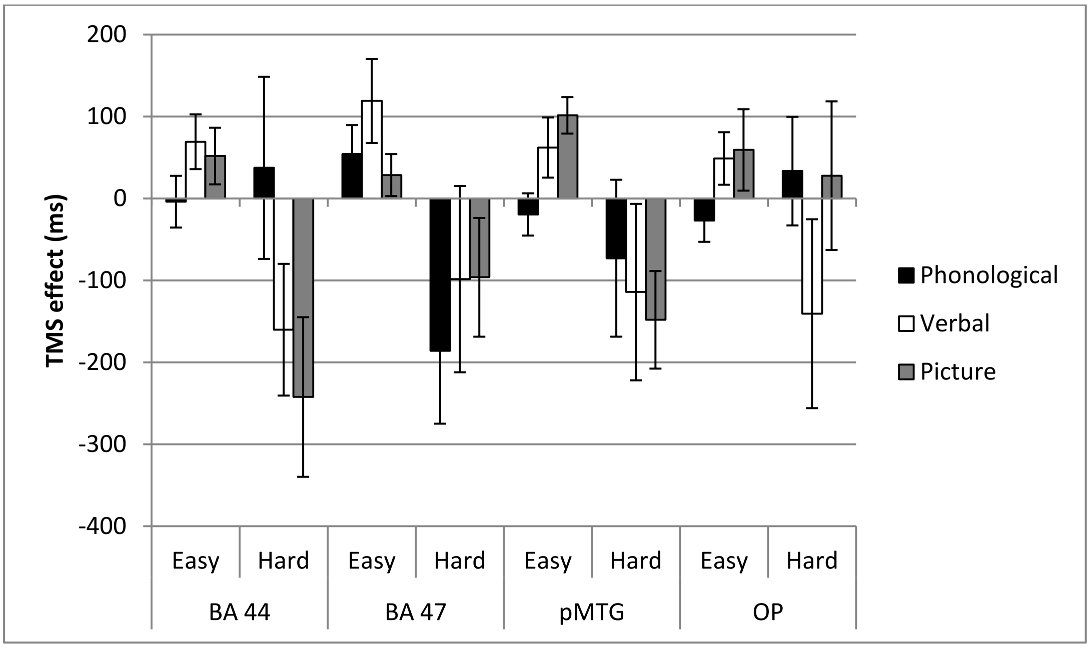
Accuracy Data.

	Phonological				Semantic Picture				Semantic Verbal			
	Easy		Hard		Easy		Hard		Easy		Hard	
BA 44												
Baseline	0.97	(0.01)	0.89	(0.02)	0.99	(0)	0.89	(0.01)	0.95	(0.01)	0.9	(0.02)
TMS	0.98	(0.01)	0.91	(0.02)	0.98	(0.01)	0.84*	(0.02)	0.95	(0.01)	0.86*	(0.02)
BA 47												
Baseline	0.98	(0.01)	0.93	(0.01)	0.96	(0.01)	0.84	(0.02)	0.97	(0.01)	0.88	(0.02)
TMS	0.97*	(0.01)	0.87	(0.02)	0.97	(0.01)	0.85	(0.02)	0.96	(0.01)	0.89	(0.01)
pMTG												
Baseline	0.97	(0.01)	0.9	(0.01)	0.98	(0.01)	0.86	(0.02)	0.97	(0.01)	0.87	(0.02)
TMS	0.98	(0.01)	0.9	(0.01)	0.98	(0.01)	0.87	(0.02)	0.97	(0.01)	0.89	(0.02)
OP												
Baseline	0.98	(0.01)	0.92	(0.01)	0.98	(0.01)	0.84	(0.02)	0.95	(0.01)	0.89	(0.02)
TMS	0.98	(0.01)	0.93	(0.02)	0.98	(0.01)	0.83	(0.02)	0.95	(0.01)	0.87	(0.02)

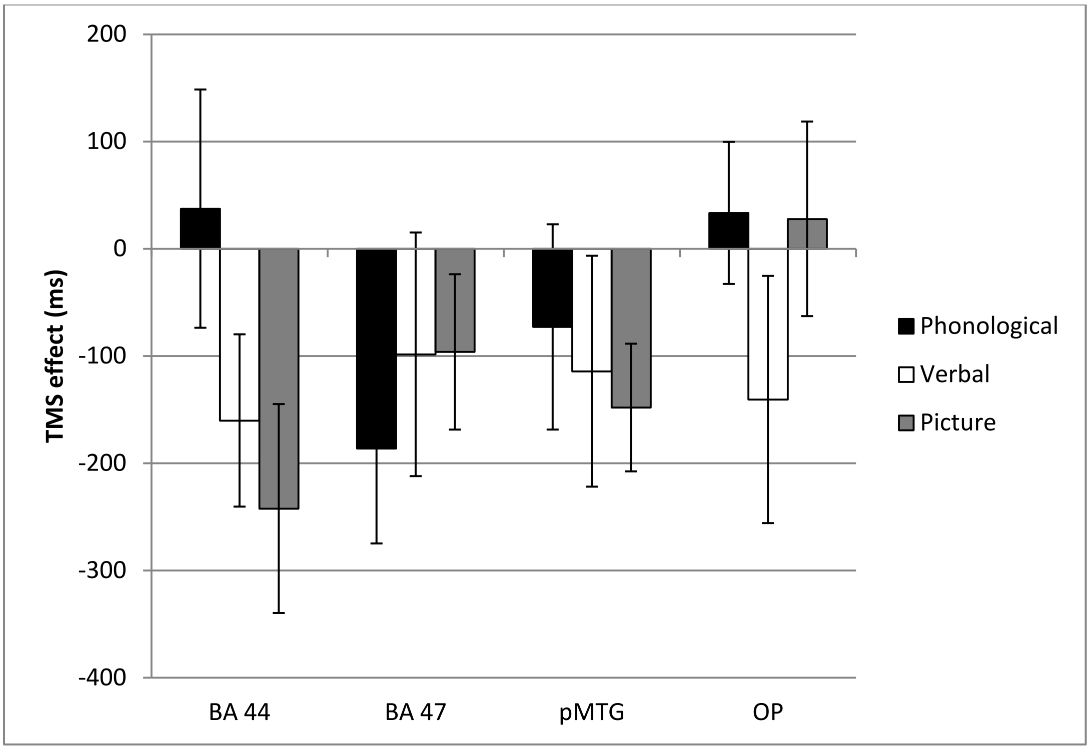
Accuracy data for baseline and TMS data. pMTG = posterior middle temporal gyrus, OP = occipital pole. Asterisks indicate any uncorrected, two-tailed, paired planned comparisons that were significant for the comparison between baseline and post TMS performance; standard error in parentheses.

Appendix 5.2

TMS effects to demonstrate facilitation for hard tasks.



TMS effects. Difference in RT between TMS and baseline performance (TMS – no TMS) for each site. Positive values indicate a decline in performance following TMS. Error bars indicate standard error of the mean.



Hard only: TMS effects. Difference in RT between TMS and baseline performance (TMS – no TMS) for each site. Positive values indicate a decline in performance following TMS. Error bars indicate standard error of the mean.

Appendix 5.3

Composite Scores

Average RT

	Phonological				Semantic Picture				Semantic Verbal			
	Easy		Hard		Easy		Hard		Easy		Hard	
BA 44												
Baseline	1317	(56)	3267	(252)	1259	(45)	2404	(141)	1516	(44)	2479	(133)
TMS	1307	(69)	3156	(208)	1330	(63)	2432	(136)	1607	(68)	2489	(121)
BA 47												
Baseline	1267	(51)	2837	(110)	1320	(44)	2386	(108)	1425	(44)	2423	(159)
TMS	1332	(59)	2995	(187)	1361	(49)	2340	(87)	1587	(65)	2273	(92)
pMTG												
Baseline	1369	(73)	3113	(187)	1259	(48)	2509	(141)	1482	(47)	2616	(140)
TMS	1356	(76)	3090	(175)	1388	(53)	2313	(116)	1552	(69)	2468	(155)
OP												
Baseline	1305	(59)	2894	(142)	1270	(51)	2436	(133)	1515	(46)	2472	(137)
TMS	1286	(57)	2959	(172)	1340	(75)	2580	(147)	1602	(58)	2475	(187)

Composite Score Average RTs. Reaction time given in ms, standard error of the mean in parentheses.

	TMS	*TMS x Task*	*TMS x Diff*	*TMS x Task x Diff*
df	1, 21	1, 21	1, 21	1, 21
BA 44				
F	0.013	1.483	1.146	0.015
p	0.909	0.237	0.297	0.905
BA 47				
F	0.802	1.249	1.925	3.14
p	0.381	0.276	0.18	0.091
pMTG				
F	0.434	0.055	1.921	1.244
p	0.517	0.817	0.18	0.277
OP				
F	0.467	0.075	0	0.999
p	0.502	0.787	0.999	0.329

F and p values for phonological vs semantic verbal tasks. pMTG = Posterior Middle Temporal Gyrus, OP = Occipital Pole.

	TMS	*TMS x Task*	*TMS x Diff*	*TMS x Task x Diff*
df	1, 21	1, 21	1, 21	1, 21
BA 44				
F	0.798	0	0.442	0.083
p	0.382	0.992	0.513	0.776
BA 47				
F	0.001	0.017	4.961	2.854
p	0.971	0.898	0.037*	0.106
pMTG				
F	0.714	0.012	10.814	0.824
p	0.408	0.915	.004**	0.374
OP				
F	1.831	0.778	0.003	0.763
p	0.19	0.388	0.958	0.392

F and p values for verbal and picture semantic tasks. pMTG = Posterior Middle Temporal Gyrus, OP = Occipital Pole ***p < .001, **p < .005 *p < .01.

	Phonological		*Verbal*		*Picture*	
	Easy	*Hard*	*Easy*	*Hard*	*Easy*	*Hard*
df	21	21	21	21	21	21
BA 44						
t	.344	.890	-1.764	-.091	-1.88	-.214
p	.734	.384	.046*[a]	.929	.037*[a]	.833
BA 47						
t	-1.608	-.970	-2.668	1.28	-1.282	.509
p	.123	.343	.007*[a]	.214	.214	.616
pMTG						
t	.436	.165	-1.774	1.438	-4.021	2.370
p	.667	.870	.046*[a]	.165	.0005*[a]	.027[†]
OP						
t	.728	-.553	-2.512	-.024	-1.338	-1.226
p	.475	.586	.020*	.981	.195	.219

T-tests comparing RTs for baseline and post TMS performance at each site. pMTG = posterior middle temporal gyrus, OP = Occipital Pole; *p < .05, ***p < .001, all comparisons are two-tailed. * denotes significant disruption; †denotes significant facilitation; [a]one-tailed t-test

Appendix 6.1

balls	**balls 2**	**baked goods**	**birds**	**boats**	**cars**
boomerang	rugby ball	cookie	dove	speed-boat	taxi
shuttlecock	basketball ball	Gingerbread	pigeon	submarine	beetle / bug
tennis ball	beachball	croissant	seagull	rowboat	smartcar
golf ball	bowling ball	muffin	robin	cruise-ship	mini
frisbee	football ball	waffles	magpie	sailboat	limo
cartoons	**cartoons 2**	**cereals**	**clothing**	**computer goods**	**dogs**
pinocchio	snow white	muesli	jeans	mouse	chihuahua
dumbo	homer	cornflakes	leggings	laptop	dalmatian
eeyore	cheshire cat	porridge	dungarees	printer	labrador
mickey mouse	bugs bunny	shreddies	skirt	scanner	terrier
piglet	shrek	weetabix	shorts	keyboard	poodle
drinks	**evening wear**	**flowers**	**fruits**	**garden tools**	**hats**
coffee	ballgown	rose	apricot	shears	cowboy-hat
coke	bowtie	poppy	grapes	shovel	baseball-cap
water	cufflinks	daffodil	kiwi	fork	hard-hat
orange juice	waistcoat	tulip	strawberry	spade	helmet
tea	tuxedo	dandelion	plum	trowel	chef-hat
herbs/spices	**instruments**	**instruments 2**	**jewelry**	**kitchen goods**	**kitchen goods 2**
garlic	recorder	violin	locket	jug	coffee machine
salt	flute	piano	bracelet	Kettle	kettle
herbs	saxophone	cello	Earrings	bottle	fridge
chillies	bagpipes	guitar	necklace	teapot	microwave
pepper	drums	xylophone	ring	mug	toaster
kitchen goods 3	**pastries**	**pets**	**puddings**	**sea creatures**	**transport**
grater	cornish pasty	tortoise	christmas pudding	jellyfish	Bus
kitchenknife	pie	goldfish	trifle	seahorse	train
ladle	sausage roll	snake	donut	starfish	tube
peeler	yorkshire pudding	hamster	cake	octopus	taxi
spatula	quiche	rabbit	cheesecake	stingray	tram
tools	**vegetables**	**vegetables 2**	**wintergear**	**zoo animals**	**zoo animals 2**
axe	cauliflower	Radish	gloves	koala	giraffe
screw driver	bean	carrot	coat	camel	rhinocerous
chainsaw	broccoli	potato	hat	kangaroo	elephant
cordless drill	cabbage	onion	scarf	panda	gorilla
saw	peas	pepper	mittens	monkey	polar bear

Appendix 6.2

Accuracy Data

	LIFG				pMTG			
	Baseline		TMS		Baseline		TMS	
Related								
Cycle 1	94.1	(1.776)	94.62	(1.336)	94.87	(1.628)	93.08	(1.622)
Cycle 2	94.36	(1.328)	97.18	(0.913)	95.64	(1.528)	93.08	(1.867)
Cycle 3	94.87	(1.628)	93.59	(2.15)	94.1	(1.563)	94.36	(1.786)
Cycle 4	94.1	(1.776)	96.15	(1.057)	93.59	(2.083)	92.56	(1.893)
Cycle 5	94.1	(1.261)	92.56	(1.93)	95.13	(1.755)	93.33	(1.688)
Cycle 6	93.08	(2.083)	94.36	(1.618)	93.59	(2.279)	94.36	(1.939)
Unrelated								
Cycle 1	92.56	(1.893)	93.85	(1.919)	94.36	(0.954)	94.62	(1.389)
Cycle 2	94.36	(1.574)	96.41	(1.098)	96.92	(1.098)	94.87	(1.17)
Cycle 3	97.18	(0.913)	96.15	(1.123)	98.21	(0.894)	96.15	(1.502)
Cycle 4	97.44	(0.936)	95.9	(1.736)	97.95	(0.804)	98.21	(0.61)
Cycle 5	97.44	(0.936)	95.9	(1.009)	95.13	(1.947)	97.18	(0.913)
Cycle 6	95.13	(2.789)	97.95	(0.71)	97.95	(0.804)	97.18	(0.74)

Accuracy Data. LIFG = left inferior frontal gyrus, pMTG = posterior superior temporal gyrus. Average Accuracy, standard error in parentheses. No paired comparisons (Baseline - TMS) reached significance.

Appendix 6.3

Six Cycle Refractory Data

	df	*F*	*p*
Condition	1, 12	54.768	.000**
Cycle	5, 60	55.712	.000**
Condition x Cycle	5, 60	67.805	.000**
Site	1, 12	1.266	.092
TMS	1, 12	1.972	.186
TMS x Condition	1, 12	5.626	.035*
TMS x Condition x Cycle	5, 60	3.363	.010*
Site x TMS x Condition x Cycle	5, 60	<1	.738

F and p Values for between sites ANOVA; ***p* < . 001, **p* < .05

	TMS x Condition x Cycle
df	5, 60
LIFG	
F	2.416
p	.046*
pMTG	
F	1.45
p	.220

F and p values for ANOVA at each site for to assess TMS by condition by cycle interaction; **p* < .05.

	Related		Unrelated	
	TMS	*TMS x Cycle*	*TMS*	*TMS x Cycle*
df	1, 12	5, 60	1, 12	5, 60
F	1.677	2.172	3.704	2.416
p	.220	.069	.078	< 1

F and p values for LIFG ANOVAs of related and unrelated sets.

TMS	*df*	*t*	*p*
Cycles 1-2	12	3.578	.004*
Cycles 2-3	12	1.176	.263
Cycles 3 - 4	12	-2.049	.063
Cycles 4 - 5	12	0.593	.564
Cycles 5 - 6	12	0.727	.481

Baseline	*df*	*t*	*p*
Cycles 1-2	12	2.994	.011
Cycles 2-3	12	-1.371	.196
Cycles 3 - 4	12	-0.503	.624
Cycles 4 - 5	12	-0.289	.778
Cycles 5 - 6	12	0.183	.858

Bonferroni corrected two-tailed T-tests (adjusted alpha of .01 (.05/5) per test) for LIFG comparing RTs between cycles, for TMS and baseline performance; **p* < .05.

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