The Role of the Left Inferior Parietal Lobule in Reading

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Declaration

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

Abstract

One of the regions that have consistently been included in the neurological models of reading is the left inferior parietal lobule (IPL), however, the precise functional and temporal contributions of this region to reading have not yet been fully established. There are three hypotheses concerning IPL contributions to visual word recognition. The first one claims that the IPL is the site of stored visual word forms although it remains unclear whether these are stored in supramarginal (SMG) or angular (ANG) fields of the IPL. The second hypothesis argues that the procedures for converting spelling-to-sound are a function of the IPL, but it is unclear whether these are specifically located in SMG or ANG, or both. Finally, a third hypothesis suggests that SMG and ANG preferentially contribute to phonological and semantic processing of written words, respectively. In this thesis, I empirically evaluated these hypotheses using repetitive transcranial magnetic stimulation (rTMS) to temporarily and selectively disrupt processing in left SMG and ANG during visual word recognition and measure the effect on reading behaviour. I also investigated the time course of SMG and ANG involvement to visual word recognition using double-pulse TMS. My research demonstrates that SMG contributes preferentially to phonological aspects of word processing and the processing begins early and over a sustained period of time (between 80 to 200 msec post-stimulus onset). ANG contributes preferentially to semantic aspects of word processing but the temporal dynamics of this contribution were not successfully revealed in this thesis and require further investigation.

In addition, I empirically evaluated the efficiency of using functional magnetic resonance (fMRI) and TMS to functionally localize a target site for TMS experiments. I demonstrated that both methods are similarly accurate in identifying stimulation site but neither of them is 100% accurate.

Presentation of Findings

The data from this thesis have been presented in the following papers:

Sliwinska, M. W., James, A., & Devlin, J. T. (2014). Inferior parietal lobule contributions to visual word recognition. *Journal of Cognitive Neuroscience*, 27(3), 593-604.

Sliwinska, M. W., Vitello, S., & Devlin, J. T. (2014). Transcranial magnetic stimulation for investigating causal brain-behavioral relationships and their time course. *Journal of Visualized Experiments*, 89: 51735.

Sliwinska, M. W., Khadilkar, M., Campbell-Ratcliffe, J., Quevenco, F., & Devlin, J. T. (2012). Early and sustained supramarginal gyrus contributions to phonological processing. *Frontiers in Psychology*, 3(161), 1-10.

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1. General Introduction

1.1 Origins of Reading

Reading is the ability to translate a visual symbol into its corresponding sound and meaning and it is a relatively new addition to the human communication repertoire that developed together with writing. The first known writing systems date back to approximately 3200 B.C. (Daniels, 1996), although historians distinguish at least three independent origins of writing systems in the ancient world. The earliest was cuneiform writing developed by the Sumerians in Mesopotamia. Chinese characters appear to have developed independently around 1200 B.C. and a third writing system was developed by the Olmecs or Zapotecs around 600 B.C. in Mexico (Boltz, 1996; Daniels, 1996). The original purpose of the writing systems was to create basic administrative, religious, and cultural records. Those included, for example, quantities of livestock, notes to gods, or calendar information written initially on clay (in Sumer), papyrus (in Egypt), bamboo or silk (in China). The majority of symbols in the early writing systems were pictographs where individual symbols represented whole words. For example, a drawing of a stalk of barley or wheat represented *grain* in Summer script (Michalowski, 1996). Consequently, those systems consisted of a very large number of symbols (Lyons, 2010).

The cultural diffusion, mainly due to trading, allowed a transmission of the first writing systems to other cultures which very often adopted the general concepts of writing and developed their own system. One such example is Egyptian script which is believed to develop from the Sumerian cuneiforms because of the conceptual similarities that exist between the two scripts (Daniels, 1996). In contrast to Sumerians, however, Egyptians created a system in which the hieroglyphs corresponded to phonetic symbols, rather than pictorial drawings. In fact, this was an exceptionally important transition in the history of writing since it gave a beginning to the first phonetic writing system. Even more importantly, the great

cultural influences of Egypt on the rest of the world shaped the majority of writing systems in a way that phonetic writing systems came to dominate across the world and are currently the most common among the world's writing systems. These include, for example, syllabic (e.g., Japanese Kana) or alphabetic (e.g., Greek, English, or Spanish) systems. It is also worth mentioning that the cultural diffusion of phonetic scripts did not affect the Chinese writing system which is still based on logographs where a symbol corresponds to a whole meaningful unit.

Reading and writing skills developed from the exclusive attribute of a privileged few into a necessity of life for all in many societies (Lyons, 2010). In the ancient societies, the complexity of the two processes confined reading and writing to political and clerical elites who had exclusive rights to them. It was only towards the end of the eighteenth century that those skills became widely popularized in many societies (Lyons, 2010). At present, from texts to twitter, e-mails to blogs, we live in a world that is dominated by written communication and reading is one of the crucial skills we need to learn in order to fully function in modern society. In the modern world, reading is fundamental since it is a gateway to information and knowledge. As a result it constitutes one of the most important skills taught in schools (Kucer, 2014). The ability to read has life-shaping consequences. Skilled reading provides individuals with the opportunity to be successful in their education and consequently in their employment and life prospects. According to the National Literacy Trust (for reviews see Dugdale & Clark, 2008; Morrisroe, 2014), individuals with low or very low literacy skills are more likely to be unemployed or in low-paid jobs with fewer chances for promotion or career choices. This lack of choices appears to negatively influence their self-development, family life, physical health, mental wellbeing, civic/cultural engagement, and general life satisfaction. Low literacy has also been strongly associated with increased levels of crime. Therefore it is very important to

understand skilled reading and critical for this aspect is learning how reading is achieved in the brain.

An understanding of how human brains produce reading is important for several reasons. First, reading is a language function and therefore one part of our cognitive inheritance that appears to be unique to the human species. A better understanding of reading in adults will also facilitate our understanding of reading disturbances (Bishop & Adams, 1990; Dyer, MacSweeney, Szczerbinski, Green, & Campbell, 2003). In addition, knowledge of the neural basis of reading will allow us to better assess cognitive models of reading (Coltheart, Curtis, Atkins, & Haller, 1993; McClelland & Rumelhart, 1981; Patterson & Shewell, 1987; Plaut, McClelland, Seidenberg, & Patterson, 1996; Seidenberg & McClelland, 1989).

In the ninetieth and twentieth centuries, understanding of reading in the brain rested mainly on investigations of patients with brain damage. Those studies localized reading functions in the brain by correlating areas of brain damage with impaired reading skills. Since the 1980s, the availability of neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) advanced our knowledge of functional anatomy of reading while the spatio-temporal dynamics of reading have been investigated with electromagnetic techniques such as magnetoencephalography (MEG) and electroencephalography (EEG). Although our understanding of the functional anatomy and temporal dynamics of reading have come a long way since the first neurological investigations, there are still important questions to be answered.

1.2 Classical Neurological Model of Reading

Joseph Jules Dejerine pioneered the neurology of reading. His primary investigations into the neural basis of reading date back to early 1890's and involved examination of patients with brain damage. Dejerine was the first to show that the syndrome of *word blindness,* known as alexia (i.e., inability to recognize written words), was the result of damage to the inferior parietal lobule, indicating the importance of this region in reading. Dejerine (1891) described the case of a 63 year old sailor who became unable to read or write (alexia with agraphia) due to damage to the left inferior parietal lobule. A dissection of the patient's brain after his death revealed an extensive lesion involving in particular the inferior three quarters of the left angular gyrus, an area located in the posterior part of the inferior parietal lobule. Dejerine reasoned that the patient's inability to recognize written words coupled with his writing difficulty indicated a central loss of *visual word images* (i.e., orthographic forms of entire words), which he argued were stored in the angular gyrus. In other words, because of damage to angular gyrus the patient had no access to the visual word forms to associate with incoming written words and therefore could not read. Similarly, he could not link his inner speech to these damaged visual word forms and therefore could not write. Additional support for the storage of visual word forms in the angular gyrus came from a second patient one year later. According to Dejerine's (1892) report, a 68 year old textile merchant initially lost the ability to read but his writing was intact (i.e., pure alexia or alexia without agraphia) until shortly before his death when he also experienced a sudden loss of writing skills. At post-mortem, two lesions were identified in his brain. The older infarct was found in the left occipital lobe and the splenium of the corpus callosum while the fresh infarct was found in the left angular gyrus. Dejerine concluded that the patient's inability to read was caused by the occipital lesion that disconnected the primary vision regions from the angular gyrus preventing the transfer of visual information from the occipital lobe

to the angular gyrus. In other words, he believed that in this case the visual centres of the occipital lobes were disconnected from the visual word forms in angular gyrus preventing reading. Because the visual word representations stored in the angular gyrus were initially intact in this patient, they could still be fed forward to the later stages of the language system enabling writing. The presence of a more recent lesion to angular gyrus explained the patient's later inability to write, confirming Dejerine's hypothesis that the angular gyrus was the visual word centre and the damage to this area resulted in alexia with agraphia.

In 1891, Dejerine adapted Lichtheim's (1885) neurological model of language to incorporate reading at the basic word level. Lichtheim's model was based on the seminal findings of Broca (1861) and Wernicke (1874). Broca described a patient with motor aphasia in which damage to the left posterior third frontal convolution (i.e., inferior frontal gyrus, now known as *Broca's area*) impaired speech production leaving speech comprehension intact. Broca argued that the faculty for speech articulation could be localized in the left ventro-lateral frontal lobe. In contrast, Wernicke described patients with a form of sensory aphasia in which lesions to the left posterior first temporal convolution (i.e., superior temporal gyrus, now known as *Wernicke's area*) caused speech comprehension impairments but left speech production intact. Based on these findings, Wernicke localized the faculty for speech recognition in the left superior temporal cortex. Wernicke also created a neurocognitive model of language (Figure 1-1) in which visual information was suggested to reach the speech production area (*b*) first and then was transferred to speech comprehension area (a_1) via the white matter tract known as the arcuate fasciculus. His additional, but purely theoretical prediction, was that damage to this specific pathway leads to conduction (or commissural) aphasia in which patients fail to transfer information from the comprehension to production areas due to their disconnection. According to Wernicke, this disconnection would result in fluent

although paraphasic speech and good speech comprehension since areas responsible for those functions remain intact but would result in impaired speech repetition because of disabled transfer of information between the speech production and comprehension areas.

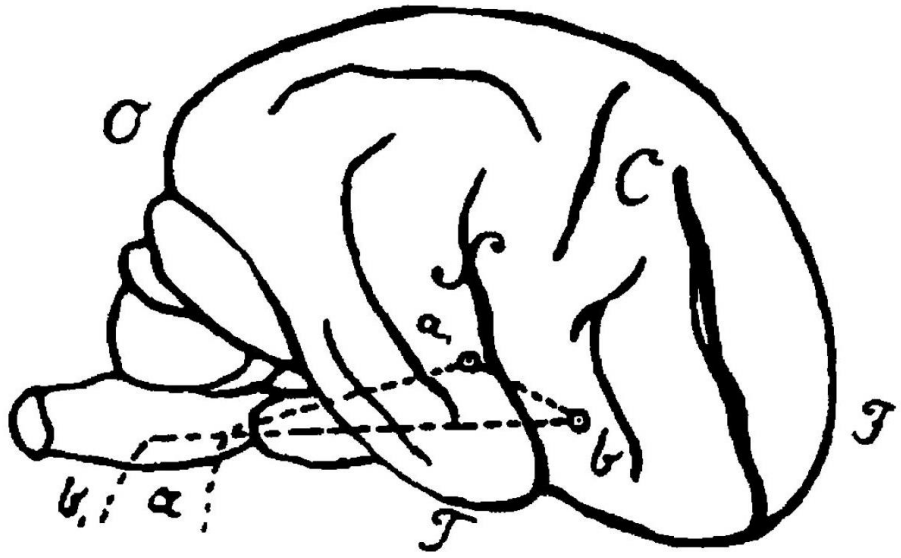

Figure 1-1: The Wernicke's (1874) classical neurocognitive model of language. The speech comprehension (Wernicke's) area is represented by a_1 and speech production (Broca's) area is represented by *b*. Both areas are connected via the a_1 – *b* pathway. Figure was taken form Wernicke (1874).

Lichtheim formalized Wernicke's (1874) preliminary language model in order to further explain brain functions required for normal language processing (Figure 1-2). He suggested that when we listen to speech, auditory information about words is passed to the auditory centre in Wernicke's area (A) where the *auditory images of words* (i.e., the phonological forms of words) are activated. These are then transmitted to the motor centre in Broca's area (B) where the *motor images of words* (i.e., articulatory forms of words) are accessed either directly via the arcuate

fasciculus or indirectly via the ideational centre (I) where the concepts of the words are elaborated prior to the motor forms of the words. The ideational centre did not have any specific location in the brain but it rather referred to the interconnected associational network suggested by Wernicke. When we speak, however, we activate the ideational centre for semantic information which in turn directly access articulatory forms of words in Broca's area. The direct route connecting the auditory and motor centres was supposed to be particularly important for speech repetition since this process relies on successful information transfer between the two centres. Lichtheim argued that any type of aphasia and its symptoms should be easily predicted by the model. In fact, his model managed to account not only for Wernicke's or Broca's aphasias followed by damage to the centre A or B, respectively, but also for a number of other types of aphasia which could result from either damage to the actual language centres or to the interconnecting pathways. For instance, Lichtheim's model successfully predicted transcortical motor aphasia characterized by good comprehension but non-fluent speech which Lichtheim associated with damage to the route connecting centres I and A as well as transcortical sensory aphasia characterized by the opposite pattern of symptoms which he associated with damage to the pathway connecting centres I and B. In addition, Lichtheim presented a patient who clearly showed the symptoms of conduction aphasia, predicted originally by Wernicke. Lichtheim's patient, a 46 year old labourer, exhibited speech repetition problems while his speech comprehension and fluent speech were preserved. His autopsy revealed specific damage to the arcuate fasciculus which supported Wernicke and Lichtheim's predictions regarding localization of this language impairment and the existence of two different routes connecting the auditory centre with the motor centre.

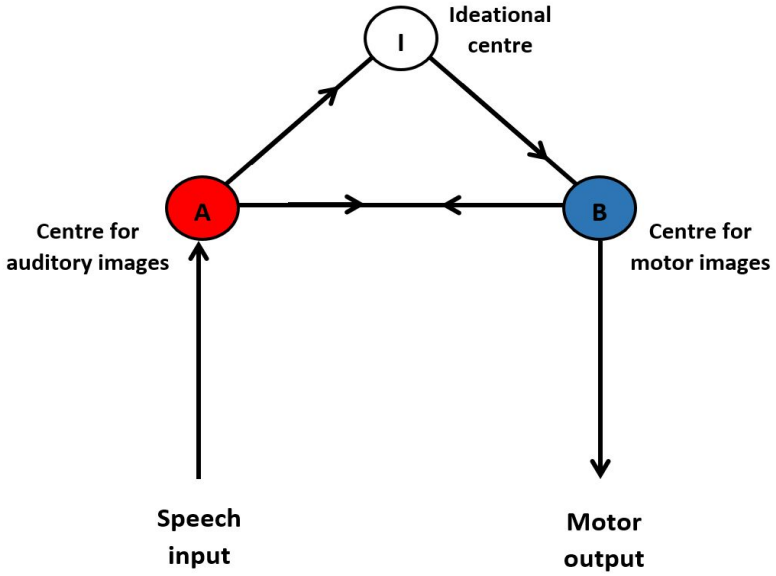

Figure 1-2: The Wernicke--Lichtheim's (1885) neurocognitive model of language. Auditory information is passed to the auditory centre (A) in Wernicke's area where the phonological forms of words are activated. These are then transmitted to the motor centre (B) in Broca's area where the articulatory forms of words are accessed either directly via the arcuate fasciculus or indirectly via the ideational centre (I) where the concepts of words are elaborated prior to the articulatory forms.

Dejerine elaborated on the Wernicke-Lichtheim's model by proposing a separate centre for visual word images located in the angular gyrus required for reading (Figure 1-3). He assumed that in order to read, a written word must be sent from the basic visual areas in occipital cortex to the centre for *visual word images* (V) in the left angular gyrus where the word activates its orthographical form. From there, the orthographic representation of the word gains simultaneous access to the corresponding *auditory word image* in Wernicke's area (A) and to the corresponding *motor word images* in Broca's area (B). Dejerine argued that auditory and motor images are closely related and that it is their union which constitutes *the idea of the*

word. Dejerine's argument was of a critical theoretical value since he was the first to acknowledge brain *interactivity* as an important dynamic necessary for word recognition. Dejerine also stressed the importance of phonology in reading and rejected the possibility of separate phonological and semantic routes because he believed that reading could not happen without accessing phonology. This is shown in the diagram where the visual centre (V) is not in direct communication with the ideational centre (I) but it is linked to it through the auditory (A) and motor (B) centres. Dejerine's argument in support of this claim was that even during silent reading we hear the words in our mind and we are aware of their articulation. It was also implicated in this model that there are brain regions dedicated only to reading which could be inferred from the assumption that damage to the centre for the visual images of words (i.e., the angular gyrus) leads to selective deficits for reading and writing.

A) **B)**

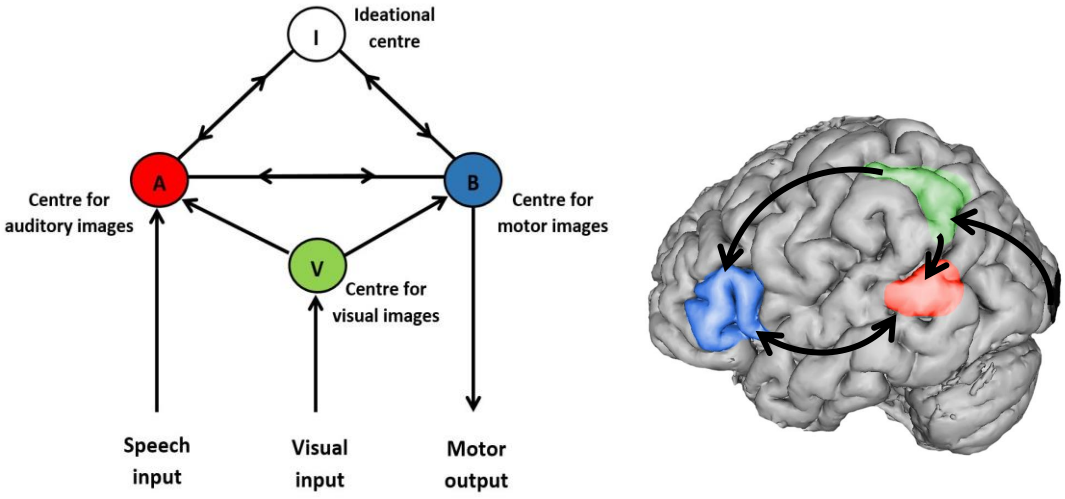

Figure 1-3: A) Dejerine's (1891) neurocognitive model of reading and B) its anatomical illustration: visual information reaches basic visual cortex (black), and then proceeds to angular gyrus (green) where abstract visual word representations are stored. These visual word forms are then simultaneously transferred to Wernicke's area (red) where they are linked to corresponding auditory word forms and to Broca's area (dark blue) where they are linked to appropriate motor word forms. Wernicke's and Broca's areas closely interact to allow recognition of the word.

The seminal work of Broca, Wernicke, Lichtheim and Dejerine resulted in the so-called *classical neurological model of reading* proposed by Geschwind (1965) (Figure 1-4). Similarly to the two theoretical models presented earlier, it included the motor centre located in Broca's area, the auditory centre located in Wernicke's area and the centre for visual images in the angular gyrus suggested by Dejerine. In contrast to the Dejerine's model of reading, however, visual information was transferred down a single route in a feed-forward manner. Dejerine's concept of interactivity between brain regions necessary for successful word recognition seems to be omitted by Geschwind for no obvious reason. Consequently, in the classical

model, reading proceeds in a purely serial, feedforward fashion with visual information about a written word first reaching visual cortex, then being sent to the left angular gyrus where its association with abstract visual word forms occurs. These abstract forms travel then to Wernicke's area where they are linked to appropriate auditory word forms and finally to their motor word forms in Broca's area.

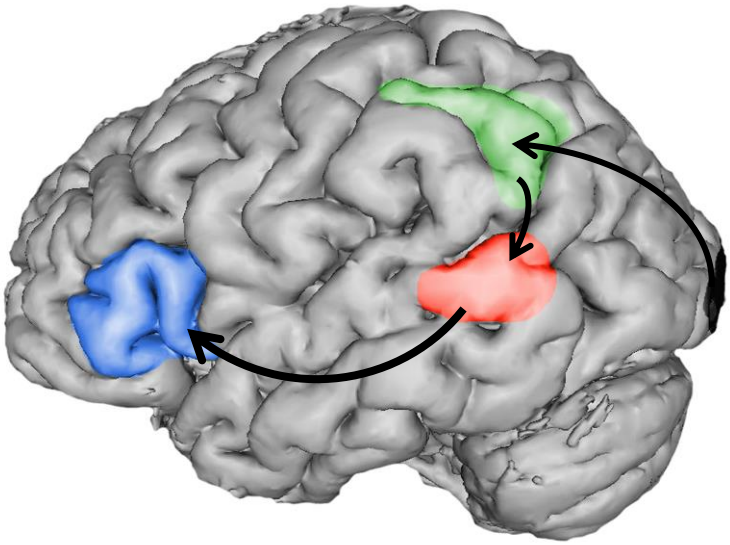

Figure 1-4: Geschwind's (1965) classical neurological model of reading: areas involved in reading and their function are the same as in Dejerine's model but information transfer is purely sequential with no interactions between regions.

The classical neurological model of reading emerged from the neurocognitive models proposed by Wernicke, Lichtheim, and Dejerine in the nineteenth century. At that time, all three aphasiologists were recognized as connectionists, also called *diagram makers*, whose goal was to create cognitive models of language corresponding to the actual brain anatomy (Finger, 1994; Levelt, 2013). Localization of cognitive functions to specific structures in the brain was the main feature that

distinguished their models from purely cognitive models of language. Models proposed by diagram makers were based on a one-to-one correspondence between the centres and pathways in the abstract diagrams to brain areas and fibre paths. The key example was localization of the motor or auditory centre in the left inferior frontal or superior temporal gyrus, respectively, and their interconnection through the arcuate fasciculus. The neurocognitive models were made from inferences based on observations of patients with brain lesions and were supposed to represent a theory of normal brain functions and predict pathological syndromes. Although the intentions were great, these models were strongly criticised.

1.3 Classical Criticism of the Diagram Makers

The classical neurological model of reading was developed based solely on neurological case studies in order to identify the functional centres (or faculties) required for normal reading and language processing together with their localization in the brain. By the end of the nineteenth century, however, there was considerable debate about the value of such models and even the fundamental methods that were used to create them (Finger, 1994; Levelt, 2013). Henry Head (1926) dismissed all the models and claimed that aphasiologists such as Wernicke or Lichtheim distorted their data in order to support their own diagrams. The main cause of this criticism was lack of mapping between what was predicted by the models and what was actually seen in patients. For instance, Finkelnburg (1870 translated in Duffy & Liles, 1979) pointed out that many scientists were unable to support Broca's precise location of articulatory language because there were patients who showed impaired articulation although their lesion did not affect the left posterior third frontal convolution. Similarly, Marie (1906 translated in Cole & Cole, 1971) noticed that in his stroke patients with lesions to the left posterior third frontal

convolution, only about half showed symptoms of Broca's aphasia. Marie argued that the diagram makers proposed strong claims from a very small number of clinical cases and as an example he referred to the most important work of Wernicke (1874) which was based on just 10 cases including only 4 backed by autopsy materials.

More theoretical concerns were raised by people like Freud (1891) who argued that equating a lost function in a brain damaged patient with a cortical faculty in an intact brain was a logical fallacy. Freud argued that one cannot assume that abnormal behaviour due to a lesion can simply reflect workings of a healthy brain. The same argument was made by many researchers in the subsequent years, including Gregory (1963) and Farah (1992). In his famous example, Gregory argued that one would never correctly understand the functional organization of a radio by observing that piercing whistles or deep growls were emitted after removing one of its components. Clearly the component's function is not a *growl suppressor* but rather it plays a complex role in the function of the entire system. Similarly, one cannot infer that a region functions as a *speech area* just because damage to the region results in a loss of speech. Instead it is necessary to understand the entire system in order to know how damage changes the functional abilities of the whole. Farah (1992) referred to this as the *transparency assumption* and claimed it led to incorrect conclusions about the functioning of the healthy brain.

As a result of these criticisms, the connectionist models fell out of favour and were largely ignored for decades. Investigations of the neural basis of language based on patient data were considered uninteresting. Instead, more attention was paid to characterizing language deficits following brain damage that included, for instance, the identification of different types of acquired dyslexia (e.g., Marshall & Newcombe, 1973). Only a few pioneering scientists continued to investigate the neural side of language. Most notable among these was Wilder Penfield, a neurosurgeon, who

developed awake neurosurgical methods for mapping language functions onto the surface of the exposed brain and in the process continued the tradition of early neurologists (Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950; Penfield & Roberts, 1959).

1.4 Evaluating the Classical Neurological Model of Reading

Interest in the work of the diagram makers was revived by Geschwind (1965) in his seminal paper that re-introduced the neurological model of language and reading to a modern audience (Figure 1-4). Fifty years on, however, it is clear that Geschwind's formulation of the classic neurological model of reading suffered from four main problems. First, a single route of processing could not explain different types of acquired dyslexia (i.e., loss of previous ability to read) identified by behavioural psychologists. Second, it was missing key brain regions involved in reading. Third, functions assigned to the brain regions in the model were inaccurate, and lastly, the model did not provide any information about neural dynamics of reading. Each of these will be considered in the following sections.

1.4.1 Multiple Routes of Processing

The first criticism of the Geschwind's model is that information transfer along a single processing route cannot account for different types of acquired dyslexia. In fact, patient studies on *surface*, *phonological*, and *deep* dyslexia provided invaluable evidence for multiple processing routes necessary for successful visual word recognition. Surface dyslexia was first defined by Marshall and Newcombe (1973) in their seminal paper on different types of reading disorders caused by brain damage. Two patients presented with missile wounds to the left temporo-parietal region both displayed letter-to-sound (i.e., grapheme-to-phoneme) conversion errors during

reading (e.g., reading *pint* to rhyme with *hint*). It was hypothesized that these *surface dyslexics* read via grapheme-to-phoneme mappings that were occasionally unsuccessful. A few years later, Beauvois and Derouesne (1979) described the first case of phonological dyslexia. Their patient had part of his left occipito-parietal cortex removed due to a tumor. After surgery, the patient showed the opposite symptoms to surface dyslexics. He was able to read all familiar words, but showed difficulties reading unfamiliar words or pronounceable nonwords (also called pseudowords: combinations of letters which do not have meaning but follow phonotactic rules of a language, e.g., *nurm*). It was hypothesized that phonological dyslexics read words as a whole but were unable to read by translating letters onto sounds (i.e., using grapheme-to-phoneme conversion rules).

In the two types of dyslexia described above, patients clearly show two opposite ways of reading. Surface dyslexics can only read using the rules of grapheme-to-phoneme conversion but they cannot recognize words in their entirety. In contrast, phonological dyslexics are able to read using the whole word method but are unable to read following rules of phonological translation. This double dissociation of symptoms indicates a need for two separate routes subserving reading, namely a lexical route linking the written form of whole words to their known pronunciation which was disabled in surface dyslexics and a sublexical route based on grapheme-to-phoneme conversion which was damaged in phonological dyslexics. Attempts to explain both of these acquired deficits were problematic for the classical model of reading because it proposed only a single route from visual to phonological information. That is, there was no place that a lesion could selectively affect either irregular words (surface dyslexia) or novel words (phonological dyslexia) without affecting the others as well. Despite the fact that Dejerine's model of reading included two separate paths linking the visual form center (the angular gyrus) to the articulation center (Broca's area), it was still unable to explain the two different types

of acquired dyslexia because neither path distinguished between whole word reading or reading via grapheme-to-phoneme conversion.

A third type of dyslexia, deep dyslexia, was also described by Marshal and Newcombe (1973). They observed two patients who experienced either a missile injury to the left temporo-parietal region or a gunshot to the left occipito-parietal region. The lesions led to lexico-semantic errors during reading aloud in those patients. In particular, their errors included semantic paralexias involving production of one word when another one is meant (e.g., *view* → *scene*; *large* → *big*; *defend* → *defence*). Marshall and Newcombe hypothesised that deep dyslexics have access to the semantic information about a written word but they cannot access its phonological association during reading. These cases suggest that there is a direct route to semantic information from print before reaching phonological information, in contrast to Geschwind's and Dejerine's models of reading; Geschwind's model simply did not include any centre for semantic information while Dejerine explicitly stated that phonology must be accessed prior to semantics during reading.

Evidence from surface, phonological, and deep dyslexia demonstrated that the visual information of a word gets associated with its phonological information via multiple, independent paths. One path allows for phonology to be accessed directly from the print while another path enables indirect access to phonology via semantics. Consequently, the classical neurological model of reading which suggests a single route from letters to sounds is unable to explain different cases of acquired dyslexia. The only type of acquired dyslexia that the model can account for is pure alexia, which is not surprising given that it was created based on the cases of pure alexics.

1.4.2 Brain Regions Involved in Reading

The second criticism of the classic neurological model is that it missed brain regions that are important to reading and indeed, recent patient and neuroimaging studies demonstrated that reading clearly involves areas outside the nineteenth century model. In fact, reading engages a widely distributed network of subcortical and cortical structures located in both hemispheres (Cattinelli, Borghese, Gallucci, & Paulesu, 2013; Fiez & Petersen, 1998; Joubert et al., 2004; Price, 2012; Turkeltaub, Eden, Jones, & Zeffiro, 2002). For instance, it has become clear that in addition to cortical territories, subcortical areas including the thalamus (Binder, Medler, Desai, Conant, & Liebenthal, 2005; Bohland & Guenther, 2006; Fiebach, Friederici, Müller, & Cramon, 2002; Price, Moore, Humphreys, & Wise, 1997; Rumsey, Horwitz, et al., 1997), basal ganglia (Booth, Wood, Lu, Houk, & Bitan, 2007; S. H. Chen & Desmond, 2005), and cerebellar regions (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 1995; Booth et al., 2007; S. H. Chen & Desmond, 2005; Fulbright et al., 1999; Herbster, Mintun, Nebes, & Becker, 1997; Price et al., 1994) also contribute to reading. Within the neocortex, the major regions involved in reading include occipito-temporal, parieto-temporal, and inferior frontal regions (Fiez & Petersen, 1998; Herbster et al., 1997; Pugh et al., 1996; S. E. Shaywitz et al., 1998). The classical model included Broca's area in the inferior frontal gyrus together with angular gyrus and Wernicke's area in the parieto-temporal area but it missed the entire occipito-temporal cortex as well as the supramarginal gyrus located in the anterior part of the inferior parietal cortex, two regions which have been shown to be crucial for reading. In addition, more recent studies have clearly demonstrated that within each of the three large brain areas there are distinct subdivisions that contribute differentially to reading and this information was also missing from the classical model.

Although all areas within occipito-temporal, parieto-temporal, and inferior frontal regions play important roles in reading, this section focuses specifically on two

areas, namely the left ventral occipito-temporal cortex and the left supramarginal gyrus. I present converging evidence for involvement of these two regions in reading from a wide range of studies including neurological and *virtual* patients as well as functional neuroimaging studies on healthy subjects. Of particular importance are data from transcranial magnetic stimulation (TMS) and neuroimaging studies that help to overcome the classical criticisms of diagram makers by investigating brain functions in healthy readers.

A large number of lesion-deficit studies demonstrated that ventral occipito-temporal lesions can cause severe reading impairments such as pure alexia (L. Cohen et al., 2004; Damasio, 1983; Leff et al., 2001; Leff, Spitsyna, Plant, & Wise, 2006; Pflugshaupt et al., 2009; Starrfelt, Habekost, & Leff, 2009). In addition, the importance of the area in reading has been demonstrated in patients who have undergone direct intracranial recordings prior to their neurosurgeries (Nobre, Allison, & McCarthy, 1994) or in patients with *virtual lesion* to the ventral occipito-temporal region created by means of TMS (Duncan, Pattamadilok, & Devlin, 2010; Pattamadilok et al., 2015). The involvement of the ventral occipito-temporal cortex in reading was also demonstrated in the very first neuroimaging study of a higher cognitive function (Petersen, Fox, Posner, Mintun, & Raichle, 1988). Petersen and colleagues used PET to identify brain areas involved in passive reading of single words by normal subjects. They found that silent reading of single words activated the left extrastriate cortex together with ventral occipito-temporal region. In their next PET study, Petersen and colleagues (Petersen, Fox, Posner, Mintun, & Raichle, 1989) confirmed the association of these areas with visual processing of single words. Since then, activation in the region has been consistently replicated in different reading experiments using PET (Herbster et al., 1997; Price, Wise, & Frackowiak, 1996; Price et al., 1994; Rumsey, Horwitz, et al., 1997), fMRI (L. Cohen et al., 2000; L. Cohen et al., 2002; Devlin, Jamison, Gonnerman, & Matthews, 2006;

Kronbichler et al., 2004), and MEG (Salmelin, Kiesilä, Uutela, Service, & Salonen, 1996; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999). Indeed this activation is not limited to alphabetic scripts but is also present in logographic orthographies such as Chinese (Kuo et al., 2003) and Japanese Kanji (Sakurai et al., 2000). Interestingly, it has been also demonstrated that even poor readers such as developmental dyslexics (Brunswick, McCrory, Price, Frith, & Frith, 1999; Richlan et al., 2010; B. A. Shaywitz et al., 2002; Van der Mark et al., 2009) or profoundly deaf readers (Aparicio, Gounot, Demont, & Metz-Lutz, 2007; Emmorey, Weisberg, McCullough, & Petrich, 2013; Waters et al., 2007) engage the ventral occipito-temporal cortex during reading, although often to a different extent than typically developing readers. In fact, an area within ventral occipito-temporal cortex has replaced the angular gyrus as the putative visual word form area (L. Cohen et al., 2000; L. Cohen et al., 2002) mainly because this region has been shown to be consistently activated in reading tasks across different orthographies (e.g., L. Cohen et al., 2002; Duncan et al., 2010; Fiebach et al., 2002; Herbster et al., 1997; Kronbichler et al., 2004; C. Liu et al., 2008; Nobre et al., 1994; Petersen et al., 1988; Price et al., 1994; Rumsey, Nace, et al., 1997; Salmelin et al., 1996); activation in the region is reduced in individuals with developmental reading disorders (S. E. Shaywitz & Shaywitz, 2008); and the spatial location of the ventral occipito-temporal cortex corresponds to a lesion site implicated in pure alexia (Binder & Mohr, 1992; Dejerine, 1892; Leff et al., 2001). Together this evidence led to a proposal that the ventral occipito-temporal cortex, rather than the angular gyrus, plays an important role in orthographic processing of words with some researchers even suggesting that the region should be regarded as the new *visual word form area* (L. Cohen et al., 2000; L. Cohen et al., 2002), although this is certainly contentious (Price & Devlin, 2003).

Another brain area that is important for reading but is missing from the classical neurological model is the supramarginal gyrus, one of the major subregions of the inferior parietal lobule. Like the angular gyrus, damage to this area can lead to reading impairments including pure alexia or alexia with agraphia (D. F. Benson & Ardila, 1996; Friedman, Ween, & Albert, 1993; Marin, 1980; Metter et al., 1990; Philipose et al., 2007; Sakurai, Asami, & Mannen, 2010; Warrington & Shallice, 1980). For instance, Warrington and Shallice (1980) described cases of two patients who become pure alexics due to a lesion selectively affecting different subregions of the left inferior parietal lobule. One of the two patients became a pure alexic following damage to the angular gyrus, similarly to Dejerine's (1891) original case. The second patient, however, was presented with pure alexia due to damage in the supramarginal gyrus that spared the angular gyrus, demonstrating that the entire inferior parietal lobule (i.e., not just the angular gyrus) is important for reading. Virtual lesions induced by both cortical electrostimulation in neurological patients during neurosurgery (Roux et al., 2012) and by TMS in healthy subjects (Hartwigsen, Baumgaertner, et al., 2010; L. Romero, Walsh, & Papagno, 2006) also indicate supramarginal gyrus involvement in reading tasks. In addition, neuroimaging studies on healthy readers tell a similar story. Petersen et al. (1989) demonstrated supramarginal gyrus activation in response to rhyme judgements performed on two visually presented words that placed explicit demands on phonological processing. Since the region showed no activation for listening to simple auditory stimuli such as clicks, tones, or noise bursts, the researchers associated it with phonological, as distinct from auditory, processing. Since then, numerous PET, fMRI, and MEG studies have shown increased activation in supramarginal gyrus for reading tasks (Bookheimer et al., 1995; Booth et al., 2004; Devlin, Matthews, & Rushworth, 2003; Law et al., 1991; Menard, Kosslyn, Thompson, Alpert, & Rauch, 1996; Mummery, Patterson, Hodges, & Price, 1998; Paulesu, Frith, & Frackowiak, 1993; Price et al., 1997; Roux, Lubrano, Lauwers-

Cances, Giussani, & Démonet, 2008; Salmelin et al., 1996; Seghier et al., 2004; Tarkiainen et al., 1999).

Altogether, there is strong evidence for the important roles of the ventral occipito-temporal region and supramarginal gyrus in reading even though these regions were not included in the classical model. The omission of the ventral occipito-temporal cortex, in particular, had an important impact on the interpretation of the functional roles of the remaining regions in the brain system underlying reading. In addition, the fact that not only the angular gyrus but also the supramarginal gyrus is involved in reading demonstrates that the entire inferior parietal lobule is important for reading and the region may be actually composed of different subregions which contribute to reading in distinct ways. The next section addressed both of these points in greater detail.

1.4.3 Functional Contribution of Regions Involved in Reading

The third criticism of the classical neurological model was that functions assigned to individual cortical regions were not accurate. For example, although Broca's area seems to be involved in some aspects of articulatory planning and execution (Price, 2010), it is also important for a range of other linguistic functions including phonological awareness (Demonet et al., 1992), syntax (Caplan, Alpert, & Waters, 1998), lexical decision making or semantic processing (Fiez, 1997; Kapur et al., 1994; Petersen et al., 1989) as well as non-linguistics functions including behavioural inhibition (Forstmann, Van den Wildenberg, & Ridderinkhof, 2008) or different executive processes that mediate working memory such as selective attention and task management (Baddeley, 2003; E. E. Smith & Jonides, 1999). Within linguistic functions, Broca's area is not a single unitary region; different functions seem to be associated with its different subregions. For instance, a posterior and dorsal part of the region has been suggested to contribute primarily to

syntactic and phonological processing while the anterior and ventral part is preferentially involved in semantic processing (Hartwigsen, Price, et al., 2010; S. D. Newman, Just, Keller, Roth, & Carpenter, 2003; Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004; Poldrack et al., 1999). Similarly, Wernicke's area has been hypothesized to have an important role in both linguistic and non-linguistic processes. Linguistic processes include phonological processing at a phoneme level (Hickok et al., 2000; Simos et al., 2000) in contrast to whole-word processes postulated by the classical model, conceptual matching of different types of stimuli (Hocking & Price, 2008), or integration of semantic and syntactic information (Friederici, Makuuchi, & Bahlmann, 2009). Apart from linguistic functions, Wernicke's area also participates in perception of action (Saxe, Xiao, Kovacs, Perrett, & Kanwisher, 2004) or processing of nonverbal auditory information (Binder et al., 2000; Saygın, Dick, Wilson, Dronkers, & Bates, 2003; S. K. Scott, Blank, Rosen, & Wise, 2000).

Another important region in the neurological model of reading was the angular gyrus, which was hypothesized to be the site of the visual word form area. Dejerine (1891) found that lesion to this region resulted in alexia with agraphia and a number of later lesion studies also identified the angular gyrus as an area most important for accessing visual forms of words (D. F. Benson, 1979; Black & Behrmann, 1994; Hillis et al., 2005; Nielsen & Raney, 1938; Vanier & Caplan, 1985). Indeed, Geschwind (1965) imputed this function to the angular gyrus in his classical neurological model of reading. The involvement of this region in orthographic processing was, however, questioned due to inconsistent activation of this region across neuroimaging studies which used various reading tasks (Beauregard et al., 1997; Brunswick et al., 1999; Herbster et al., 1997; Kronbichler et al., 2004; Moore & Price, 1999; Petersen et al., 1988; Price, Wise, Warburton, et al., 1996; Rumsey, Horwitz, et al., 1997) as well as a number of more selective lesions to this region

which did not impair reading comprehension (Price & Friston, 2002). More recently, the ventral occipito-temporal region has become associated with stored visual word forms (Cohen, 2000; Cohen, 2002; but for a contrasting arguments see Price & Devlin, 2003; Price & Devlin 2011), taking over the putative functional role from the angular gyrus. As a consequence, other hypotheses have been proposed to explain inferior parietal involvement in reading.

One such hypothesis suggests that the left inferior parietal lobule, including the angular gyrus, contributes to sublexical processes involving conversion of graphemes into phonemes (Booth et al., 2003; Horwitz, Rumsey, & Donohue, 1998; Vigneau, Jobard, Mazoyer, & Tzourio-Mazoyer, 2005). The evidence supporting this hypothesis primarily comes from neuroimaging studies on healthy readers who showed increased activation in the inferior parietal lobule during tasks that required explicit grapheme-to-phoneme conversion such as reading pseudowords relative to familiar words (Vigneau et al., 2005) or low-frequency words (Horwitz et al., 1998). Additional evidence has been provided by neuroimaging studies of individuals with developmental reading disorders who revealed abnormal activation of the region in the tasks emphasizing grapheme-to-phoneme conversion (Booth et al., 2003).

A different hypothesis suggests a functional double dissociation within the left inferior parietal lobule with different subregions contributing to reading in distinct ways. More specifically, the supramarginal gyrus and angular gyrus are selectively involved in processing phonological or semantic aspects of written words, respectively (Price & Mechelli, 2005). This hypothesis derives from the neuroimaging studies which showed that phonologically demanding tasks increase activation in the supramarginal gyrus while semantically demanding tasks increase activation in the angular gyrus (Demonet, Price, Wise, & Frackowiak, 1994; McDermott, Petersen, Watson, & Ojemann, 2003; Paulesu et al., 1993; Price, Wise,

& Frackowiak, 1996). In fact, the primary theme of the current thesis is to test the three existing functional hypotheses of the left inferior parietal lobule contribution to reading and for this reason more detailed discussion of these two alternative hypotheses will be presented in Chapter 3.

In summary, there is a large amount of evidence suggesting that functions assigned to the brain regions in the classical neurological model of reading were not accurate. Broca's and Wernicke's areas are no longer associated with the store of articulatory or phonological forms of written words, respectively, but have been hypothesised to play important roles in a wide range of linguistic and non-linguistic tasks. Similarly, the role of the angular gyrus as a store of orthographic word forms has been dismissed and new hypotheses explaining the inferior parietal lobule function have been proposed.

1.4.4 Dynamics of Information Processing during Reading

The final criticism of the classical neurological model of reading is its lack of any information about temporal dynamics of reading. This is perhaps unfair given that the classical model was based solely on lesion-deficit data from which evidence about dynamics of information flow was not available. The data that were available to the researchers in the nineteenth century included only descriptions of behavioural deficits linked to post-mortem examinations. For this reason, the information flow in the classical models actually represents intuition and interpretation of the investigator rather than evidence and it is clear that different investigators had different intuitions. For example, the initial Wernicke-Lichtheim's model assumed a feedforward flow of information where a stimulus reached the periphery, was recognized, and then was processed. Dejerine's intuition was slightly more sophisticated and presaged more modern thinking. He assumed interactive processing dynamics, at least between Broca's and Wernicke's areas, and noted

that this interaction was critical for word recognition. For unknown reasons, this interactivity was lost in Geshwind's (1965) version of the model and thus the classical neurological model of reading became a purely serial and feedforward account. In this model, visual input arrives at the occipital pole before projecting to the angular gyrus where visual word forms are stored. These are then linked to the corresponding auditory word forms in Wernicke's area and from there to Broca's area to access articulatory motor patterns of words. This linear progression allowed a written word to be recognized, converted into sound and read aloud. It is perhaps unfair to criticize the classical model for its unsophisticated dynamics but there is no doubt that processing dynamics is an important aspect of any successful model and this information is now more readily available with techniques that were unavailable to the nineteenth-century neurologists.

Neuroimaging studies have begun to address this issue using MEG, EEG, and TMS. In contrast to PET and fMRI, these techniques are characterised by high-temporal resolution necessary for chronometric investigation of brain activity and decent spatial resolution (particularly MEG and TMS) required for associating temporal information with specific brain areas. The initial MEG/EEG studies focused on investigating spatio-temporal evolution of cortical activity for visual word recognition in the whole brain. For instance, Salmelin et al. (1996) demonstrated that posterior parts of the brain were predominantly active during the first 200 msec after stimulus presentation while later activation typically occurred in more anterior areas. More specifically, they recorded the earliest signals in occipital areas within the first 150 msec followed by activation in occipito-temporal areas around 200 msec, in temporo-parietal regions between 200-400 msec, and in frontal areas after 400 msec post-stimulus onset. Subsequent experiments tried to determine at what point in time the brain differentiated between word-like stimuli and non-linguistic stimuli. Tarkianen et al. (1999) found that around 100 msec the extrastriate cortex was

insensitive to the stimulus content suggesting its involvement in early visual analysis. In contrast, the area around inferior occipito-temporal region showed a preference for letter stimuli relative to non-linguistic symbols at approximately 150 msec. Similarly, Rossion et al. (2003) demonstrated that the occipito-temporal regions distinguished between words, faces and objects as early as 130 to 170 msec after stimulus presentation. In addition, Cohen et al. (2000) showed that initial processing of written stimuli is confined to early visual areas contralateral to the stimulated hemifield in the first 160 msec post-stimulus onset and then between 180-200 msec left-lateralized processing specific to real words is accessed within the ventral occipito-temporal cortex. Overall, these chronometric studies demonstrated that the earliest visual processing did not distinguish between words and nonword stimuli but soon afterwards (around 180-200 msec post-stimulus onset) information reached the ventral occipito-temporal cortex where the earliest signs of visual word recognition occurred. In other words, this appears to show a feedforward processing of information from primary visual areas into ventral occipito-temporal cortex, rather than into the angular gyrus as postulated in the classic neurological model.

Further evidence for serial processing came from studies investigating the time course of different linguistic processes using neuroimaging techniques. Bentin and colleagues (1999) showed that visual/orthographic processing elicited by a size detection task on orthographic and non-orthographic stimuli peaked around 170 msec within occipito-temporal areas with activation much stronger for orthographic stimuli than non-orthographic stimuli. Bentin at al. also demonstrated that phonological/phonetic processing elicited by rhyme judgements on words and pseudowords showed strongest activation around 320 msec within a region of middle temporal cortex near Wernicke's area. A lexical decision task which required phonological/lexical processing peaked at approximately 350 msec in the temporo-

parietal regions and overlapped with some areas that were present in the rhyme judgement task. Semantic processing was registered at around 450 msec within areas that overlapped with the lexical task in addition to frontal areas. Altogether, the results suggested an evolution of the linguistic processes involved in visual word recognition from early orthographic processes (around 170 msec) in the area of ventral occipito-temporal cortex to phonological processing (around 320 msec) in posterior middle temporal gyrus, to lexical (around 350 msec) and then semantic processing (around 450 msec) in temporo-parietal and frontal areas. To a large extent, these results are consistent with the feedforward flow of information proposed in the classic neurological model.

This conventional wisdom, however, has been challenged by a number of recent MEG studies that revealed very early co-activation of frontal and posterior brain regions (Cornelissen et al., 2009; Pammer et al., 2004; Salmelin, Schnitzler, Schmitz, & Freund, 2000). For example, Cornelissen et al. (2009) found strongly left-lateralized word-specific responses in the inferior frontal gyrus peaking as early as 130 msec post-stimulus onset, similar to the response at 140 msec in the left ventral occipito-temporal cortex. Even earlier responses in the left inferior frontal gyrus and precentral gyrus were recorded by Wheat et al. (2010) who found that their priming paradigm elicited activation in these two frontal regions within 100 msec of the presentation of a target word. Cornelissen and colleagues (Cornelissen et al., 2009; Pammer et al., 2004) have suggested that the first MEG studies of reading may have failed to identify this early frontal brain involvement due to a lack of sensitivity in both their experimental paradigms and their data analysis methods. If correct, these findings suggest very early interactions between anterior and posterior regions that would challenge the assumed dynamics within the classic neurological model of reading.

Additional evidence for interactions comes from a combination of TMS and fMRI studies of reading. For instance, Duncan et al. (2010) tested the temporal dynamics of the ventral occipito-temporal cortex during visual word recognition with chronometric TMS. Unlike many previous chronometric studies that showed a disruptive effect of TMS within a specific time window (e.g., Juan & Walsh, 2003; Pitcher, Walsh, Yovel, & Duchaine, 2007; Schluter, Rushworth, Passingham, & Mills, 1998), Duncan and colleagues found that stimulation delivered the ventral occipito-temporal cortex between 80 and 200 msec post-stimulus onset interfered with word recognition, potentially indicative of ongoing interactions between this area and other brain regions. An fMRI study by Twomey et al. (2011) found that during visual word recognition, top-down modulation of the ventral occipito-temporal cortex were driven by Broca's area, consistent with both the TMS (Duncan et al., 2010) and MEG (Pammer et al., 2004; Cornelissen et al., 2009) data. Woodhead et al. (2014) also found that Broca's area constrained early activity in the ventral occipito-temporal cortex. In their study, subjects viewed written words and false font stimuli during MEG scanning. The data were analysed with dynamic casual modelling and during the first 200 msec, Broca's area modulated activity in the ventral occipito-temporal cortex during the early stages of word processing, indicating functional interactions between the two regions during the first 200 msec. Overall, these findings demonstrate that both posterior regions such as the ventral occipito-temporal cortex and more anterior regions such as Broca's area are engaged in visual word processing from a very early stage (about 80-130 msec post-stimulus onset). In addition, they suggest that this processing is both sustained and interactive that is in direct contrast to the classical view of a serial processing sequence in reading. Evidence for neuronal interactivity is certainly consistent with behavioural studies that have also focused attention on its importance during reading.

In the behavioural literature, it is well-established that reading requires interactions between different levels of representations. A classic example is the word superiority effect where subjects are better able to recognise a letter presented in a real word than the same letter in a string of letters that has little resemblance to a real word (Cattell, 1886; Reicher, 1969; Wheeler, 1970). The word superiority effect was explained by McClelland and Rumelhart (1981) in their interactive activation model of visual word recognition (Figure 1-5). In their model, feedback projections from the word level support activation of letter nodes that form part of the word. For example, the word node *cart* supports the letter node *A* in the second position, increasing activation of the letter node more quickly than it would based solely on bottom-up visual features. In contrast, if *A* had appeared in the letter string *cakh* there would be no top-down support from the word level (because *cakh* is not a word). As a result, activation of *A* would be slower in *cakh* than in *cart* because it would be based solely on bottom-up information. In other words, the word superiority effect arises from interactivity between different levels of information processing and cannot be explained by a purely feedforward account.

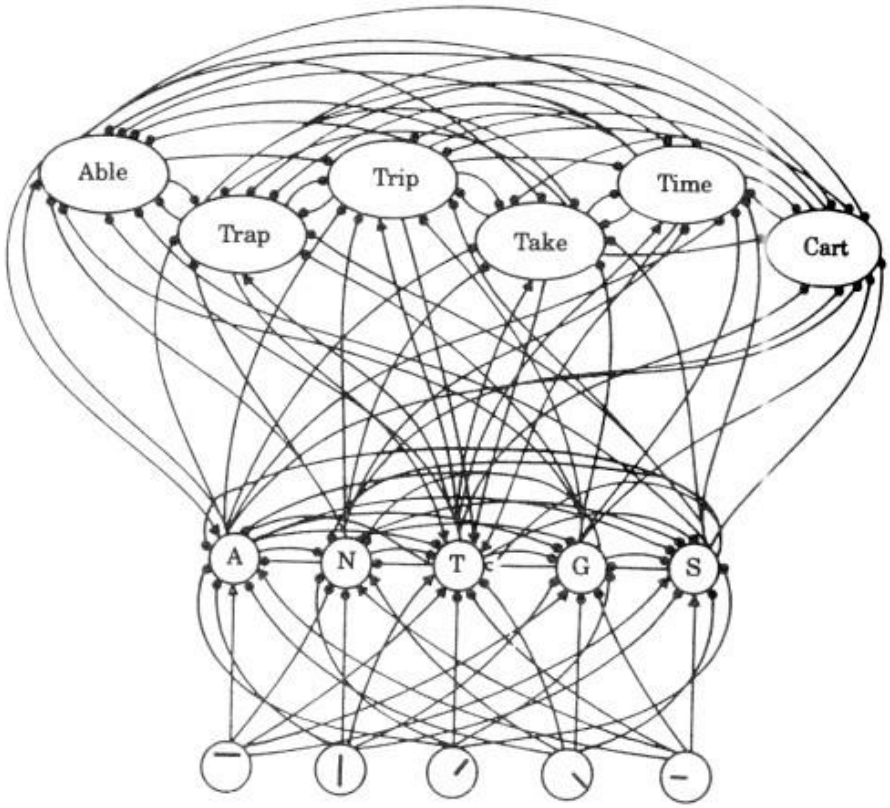

Figure 1-5: The interactive activation model of visual word recognition (McClelland & Rumelhart, 1981). The flow of information starts at the feature level where the basic visual feature of each letter in the word is detected. Excitatory activation (represented with an arrow at the end of connection) or inhibitory activation (represented with a circle at the end of connection) spreads then upwards to nodes representing a letter that contain or does not contain the feature, respectively. From the letter level, excitatory activation spreads upwards to nodes representing a word that contain the relevant letter in the right position while selection of other words is inhibited. Simultaneously, excitatory activation spreads downwards to the node containing the letter while inhibitory activation spreads downwards to other letters.

The pseudohomophone effect provides another example from the behavioural literature that illustrates the existence and importance of interactions between different levels of word recognition. A pseudohomophone constitutes a nonword which sounds like a real word (e.g., *bild*). The pseudohomophone effect is that subjects are slower to read and reject nonwords that are pseudohomophones in comparison to nonwords that do not sound like real words (e.g., *jate*) in a lexical decision task (e.g., McCann, Besner, & Davelaar, 1988). This effect can only be clearly explained by influences of higher-level phonological information that the letter strings in pseudohomophones become associated with.

In summary, the classical neurological model of reading assumes a serial feedforward flow of information which is perhaps surprising, given the importance that Dejerine (1891) placed on interactions. Even so, many modern neurological models of reading also assume a serial processing dynamic (e.g., L. Cohen et al., 2002; Dehaene, Cohen, Sigman, & Vinckier, 2005; Kronbichler et al., 2004) although such a way of information processing has been increasingly challenged by evidence of interactivity at both the neuronal and behavioural levels. The assumption of a serial processing dynamics in modern neurological models of reading is very surprising considering the fact that interactivity constitutes a fundamental feature of cognitive and computational models of reading (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Harm & Seidenberg, 2004; Jacobs, Graf, & Kinder, 2003; McClelland & Rumelhart, 1981; Perry, Ziegler, & Zorzi, 2007; Plaut et al., 1996).

Despite its criticisms, the classic neurological model of reading has played a vital role in developing a basic understanding of the neural underpinnings of reading. Its four main criticisms have highlighted important shortcomings of the model and led to revised neurological models that provide principled explanations for different types

of acquired dyslexia via additional functional-anatomical detail and a more thorough consideration of processing dynamics.

1.5 Modern Models of Reading

Pugh and Shaywitz (2000) proposed an updated neurological model of reading (Figure 1-6) based on neuroimaging studies testing healthy readers and developmental dyslexics. Their new model suggested that identification of words during fluent reading was related to the functional integrity of three regional systems located in the left hemisphere: an occipito-temporal (posterior ventral) system, a temporo-parietal (posterior dorsal) system, and an inferior frontal (anterior) system. The posterior ventral system included lateral and inferior occipito-temporal areas where functional imaging studies showed robust activation in many reading tasks (Fiez & Petersen, 1998; Henderson, 1986) and abnormally low activation in reading disability (Pugh et al., 2000; Salmelin et al., 1996; S. E. Shaywitz et al., 1998). This system was hypothesised to be involved in rapid and automatic memory-based word recognition. In other words, it served as a new ventral *visual word form system*. One of the main arguments supporting this claim was that the region showed increased activation to familiar words relative to unfamiliar words and nonwords (e.g., pseudowords) (Fiebach et al., 2002; Frackowiak, Friston, Frith, Dolan, & Mazziotta, 1997) indicating its response to well-learned orthographic word forms. The occipito-temporal area was suggested to be engaged in orthographic processing of words between 150-200 msec post-stimulus onset as this was a time window of its highest response to words relative to nonwords revealed by MEG recordings (Salmelin et al., 1996; Tarkiainen et al., 1999). The posterior dorsal system encompassed the angular gyrus, supramarginal gyrus and a posterior section of the superior temporal gyrus. These regions were associated with rule-based analysis of written words

required for integration of the orthographic, phonological and lexico-semantic information of words. This conclusion was based on findings that showed increased response of those regions in healthy readers and decreased response of those regions in developmental dyslexics to unfamiliar words (e.g., pseudowords and low frequency words) in contrast to familiar words indicating effortful decoding and rule-based phonological analysis (Horwitz et al., 1998; Pugh et al., 2000; Rumsey, Nace, et al., 1997; S. E. Shaywitz et al., 1998). This claim was further supported by studies which showed greater response of the posterior dorsal system to the tasks which place increased demands on phonological or semantic processes (e.g., rhyming) rather than to simple word identification tasks (Petersen et al., 1989). The posterior dorsal system was thought to contribute to its function later in time, at approximately 200-250 msec after word presentation (Salmelin et al., 1996; Tarkiainen et al., 1999). Finally, the anterior system was located in the inferior frontal cortex. This region was associated with articulation (i.e., output phonology) for its significantly higher levels of activation during word and pseudoword naming in relation to silent reading of the same stimuli (Hino & Lupker, 2000). Maximum involvement of this system was believed to be after 400 msec from stimulus onset (Salmelin et al., 1996; Tarkiainen et al., 1999).

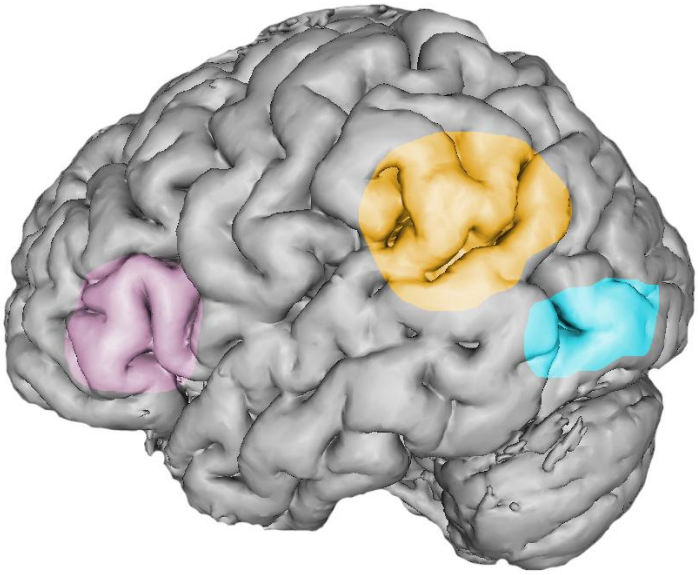

Figure 1-6: Pugh and Shaywitz's (2000) neurological model of reading: the posterior ventral region (shown in blue) is located in the occipito-temporal cortex and is involved in word identification. The posterior dorsal region (shown in orange) is located in the parieto-temporal cortex and is involved in word analysis. The anterior region (shown in pink) is located in the inferior frontal cortex and is involved in articulation. Pugh and Shaywitz did not describe the anatomical pathways for transferring information between these regions.

The Pugh and Shaywitz's model overlapped with the classical model but also showed substantial changes. The three key regions of the classical model, namely the angular gyrus, Wernicke's area, and Broca's area, were all present in Pugh and Shaywitz's model, although the first two were grouped into a single *posterior dorsal system*. The new model also included additional brain regions such as ventral occipito-temporal cortex and supramarginal gyrus. The three *systems* of the new model were assigned (mostly) new functional labels. The posterior ventral system was associated with orthographic processing; the posterior dorsal system was associated with rule-based word analysis which included grapheme-to-phoneme conversion processes; and the anterior system was still assumed to be involved in

articulatory processes. Like its predecessor, the new model assumed a linear information processing timeline, although it provided specific time windows for each function. Somewhat surprisingly, the new model lacked defined pathways linking the three systems and thus was difficult to relate to the different types of acquired dyslexia.

Over time, together with constantly increasing amount of data, models of reading have become more informative and fine-grained (Price, 2000; Price & Mechelli, 2005). The established language areas did not change but were subdivided into functionally distinct subregions. In the model created by Price and colleagues (2000; 2005), the left occipito-temporal region was subdivided into three distinct areas serving different functions. Its posterior part and ventral occipito-temporal cortex were involved in the processing of higher order visual input with the latter one integrating visual stimulus with its higher order properties. The anterior (fusiform) and middle (temporal) parts of the region were associated with semantic processing. In the parietal region, supramarginal and angular gyri were suggested to be preferentially involved in phonological or semantic processing, respectively. Similarly, a dissociation of activation for phonological and semantic tasks was suggested within the left inferior frontal region. The pars opercularis and premotor cortex (the posterior and dorsal part of the inferior frontal region) had their role assigned to the phonological processing while pars orbitalis and triangularis (the anterior and ventral part of the inferior frontal region) to semantic processing. This model accounted for multiple routes of processing visual words which at minimum included a dorsal route via the superior longitudinal fasciculus leading to Broca's area through angular and supramarginal gyri as well as ventral route via the inferior longitudinal fasciculus leading to Broca's area via the ventral occipito-temporal cortex. The model also postulated that all the routes are bi-directional enabling feedforward and feedback information flow between connected regions and highly

interactive fashion of information processing. The model was, however, still missing temporal information of regional involvement in reading processes.

In conclusion, the model proposed by Price and colleagues presents considerably more fine-grained description of neural basis of reading than Pugh and Shaywitz's model and responds to all four criticisms addressed to the classical neurological model of reading. It includes additional regions important to reading and updates their functional labelling. In addition, it distinguishes multiple routes that enable reading and introduces interactivity between brain regions as an important aspect of neural dynamics during reading. One of the striking differences between the two modern models of reading is how they define a functional contribution of the inferior parietal lobule to visual word recognition. Pugh and Shaywitz's model associates inferior parietal lobule with rule-based processes including grapheme-to-phoneme conversion which are restricted to reading while Price's model postulates anterior-posterior division of general phonological and semantic processing.

To summarize, a comparison of neurological models of reading created over decades of research illustrates gradual evolution of our understanding of neural basis of reading. The development of neurological models of reading would not be possible without novel techniques of investigation and novel findings since those made us realize that language functions are incredibly complex and are not localized in dedicated only to them brain regions. Overall, there has been convergent evidence that reading engages a bilaterally distributed set of brain regions contributing to visual word recognition in their own individual way. Those brain regions are part of more complicated circuits interacting between each other on multiple levels of reading processing.

1.6 Testing Hypotheses

The importance of the left inferior parietal lobule in reading was already recognized by the neurologists in the nineteenth century when Dejerine (1891) located a centre of visual word images in the angular gyrus. At the beginning of the second half of the twentieth century, Geschwind (1965) incorporated this finding into a model of reading that is known in the modern literature as the classical neurological model of reading. Together with the development of new methods for investigating brain functions, however, it became apparent that not only is the angular gyrus involved in reading but also another subregion of the inferior parietal lobule, namely the supramarginal gyrus. In addition, the functional role assigned by Dejerine to the inferior parietal lobule was questioned and new hypotheses suggested. One claims that the inferior parietal lobule performs the procedures necessary for grapheme-to-phoneme conversion although it remains unclear whether these are specifically located in the angular gyrus or supramarginal gyrus, or both. Another suggests that the angular and supramarginal fields of the inferior parietal lobule preferentially contribute to semantic and phonological processing of written words, respectively. In fact, each of the three hypotheses may be possible and each of them makes testable predictions. However, many techniques that can theoretically be used to investigate these hypotheses come with a number of serious limitations that make interpretation of data difficult. For example, although data from lesion studies can provide information regarding causal relationship between brain region and behaviour, lesions rarely are restricted to a particular brain region but tend to affect multiple anatomical areas together with adjacent white matter passages. This is particularly problematic for interpretation of functional contributions of distinct brain regions that are anatomically adjacent such as the supramarginal and angular gyri. In addition, the interpretation of data in lesion studies can be confounded by functional reorganization and compensation. Finally, lesion studies cannot provide

information about the dynamics of cognitive processes. Similarly, although fMRI or PET can be used to investigate brain functioning in healthy subjects with better spatial precision than lesion studies, they are unable to demonstrate causal inferences between brain activity and behaviour and these offer limited temporal resolution. As a result, TMS was used in this thesis as the primarily investigative tool.

TMS offers a non-invasive method of brain stimulation that can be used for drawing causal brain-behaviour inferences and for investigating the temporal dynamics of on-line neural information processing in both healthy adults and neurological patients (Paus, 2005; Sack, 2006). Unlike neuroimaging techniques that measure neural activity and correlate it with behaviour, TMS offers the opportunity to perturb neural information processing and measure its effects on behaviour. In this sense, it is more like traditional lesion-deficit analyses in patients with brain damage except that TMS is non-invasive and the effects are temporary and reversible. TMS also has several advantages over lesion studies. For instance, the effects of stimulation are generally more spatially precise than naturally occurring lesions. In addition, participants can be used as their own controls, thereby avoiding the issue of potential differences in pre-morbid abilities between patients and controls. Finally, there is insufficient time for functional reorganization to take place during TMS, meaning that recovery processes are unlikely to confound the results (Walsh & Cowey, 1998). In this thesis, TMS was used to characterize the contributions of the inferior parietal lobule to reading as well as the time course of their involvement in reading.

Chapter 2 introduces the TMS methodology I used in this thesis, reviewing the basic technique as well as the range of design decisions that are necessary in order to conduct the experiments reported here.

Chapter 3 tested the three main hypotheses concerning functional roles of the left inferior parietal lobule in visual word recognition. I used repetitive TMS to temporally disrupt neural information processing in the left supramarginal and angular gyri and observed the effects of stimulation on reading tasks that focused attention on either the sound or meaning of written words. Relative to no-TMS, stimulation of the supramarginal gyrus selectively slowed responses in the sound, but not meaning, task whereas stimulation of the angular gyrus affected responses in meaning, but not sound, task. These results demonstrated that supramarginal and angular gyri doubly dissociate in their contributions to visual word recognition and helps to refine the neurological model of reading.

Chapter 4 investigated the timing of supramarginal gyrus involvement in phonological processing of visually presented words with chronometric TMS. A different group of participants performed the tasks designed to focus on either the phonological, semantic, or visual aspects of written words while double pulses of TMS (delivered 40 msec apart) were used to temporarily interfere with neural information processing in the left supramarginal gyrus at five different time windows. Stimulation at 80/120, 120/160, and 160/200 msec post-stimulus onset significantly slowed subjects' reaction times in the phonological task, but not semantic or visual tasks. The fact that the effect began within 80-120 msec of the onset of the stimulus and continued for approximately 100 msec, indicates that phonological processing initiates early and is sustained over time. In addition, the fact that the inhibitory effect was specific to the phonological condition allows for replication of findings from the previous experiment which showed preferential contributions of supramarginal gyrus to sound processing over processing of meaning.

Chapter 5 investigated the timing of angular gyrus involvement in semantic processing of visually presented words using exactly the same experimental

procedures as were used in the previous experiment but during angular gyrus stimulation. Unlike the previous chapter, the results were less robust and indeed subsequent control experiments suggested the findings were most likely to be false positives. As a result, the findings did not reveal any information about the temporal dynamics of angular gyrus contribution to semantic processing. Possible explanations are discussed.

Chapter 6 draws general conclusions regarding functional contributions of the left inferior parietal lobule to reading and discusses all the findings in relation to the theories of its function as well as neurological models of reading.

2. Transcranial Magnetic Stimulation Methodology

2.1 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a method for non-invasive brain stimulation that allows one to draw causal brain-behaviour inferences and investigate the temporal dynamics of on-line neural information processing. Although it was originally developed for investigating the physiology of the motor system (Barker, Jalinous, & Freeston, 1985), it was quickly adopted as a valuable tool for cognitive neuroscience. One of its earliest uses was a *virtual lesion* technique to induce speech arrest by stimulating the left inferior frontal cortex (Epstein et al., 1999; Pascual-Leone, Gates, & Dhuna, 1991; Stewart, Walsh, Frith, & Rothwell, 2001). The results confirmed the importance of Broca's area for speech production and suggested a potential alternative to Wada testing used to determine language dominance subsequent to neurosurgical interventions (Pascual-Leone et al., 1991; Picht et al., 2013). TMS can also be used to investigate the time course of neural information processing by using very short bursts and varying the onset of stimulation during task performance (Walsh & Pascual-Leone, 2003). Typically this involves either a single- or double-pulse TMS delivered at different points of time within a trial. Some studies use TMS in both its virtual lesion mode and as a chronometric tool. For example, Pitcher and colleagues (2007) showed that repetitive TMS (rTMS) delivered to the occipital face area disrupted accurate facial discrimination and then used chronometric TMS to determine that this effect was only present when TMS was delivered at 60 and 100 msec post-stimulus onset, demonstrating that this particular brain region processes face-part information at an early stage of face recognition. In this example, chronometric TMS caused a virtual lesion at a specific point in time during the processing of face stimuli.

TMS relies on Faraday's principle of electromagnetic induction by using a rapidly changing electric current within a conducting coil to generate a strong, but relatively focal, magnetic field. When placed adjacent to the scalp, the magnetic field induces electrical activity in the underlying brain tissue, temporarily disrupting local cortical information processing. Such transient interference effectively creates a short-lasting virtual lesion (Pascual-Leone, 1999; Walsh & Rushworth, 1999). By selectively interfering with regionally-specific cortical processing, TMS can be used to draw causal links between brain regions and specific behaviours. That is, if stimulating a cortical area significantly affects task performance relative to appropriate control conditions, this indicates that the stimulated area is necessary to perform the task normally. Typically TMS induces either increased error rates or slower reaction times, both of which are taken as indicators of causal relations between brain and behaviour (Paus, 2005; Sack et al., 2009). This ability of TMS to induce a transient interruption of normal activity is used to test specific hypotheses about causal links between a brain region and a particular behaviour. It differs TMS from functional neuroimaging techniques such as fMRI, PET, EEG, or MEG that record brain activity and correlate it with behavioural events. Although these correlations provide valuable information about whole brain responses, unlike TMS they cannot indicate causal brain-behaviour relationships. It is important to note that under certain circumstances such as when a stimulated area is not required for the task or when a TMS pulse is administrated at an inappropriate time, TMS can have no effect on performance or even facilitate performance due to inter-sensory facilitation (Walsh & Rushworth, 1999). As a result, careful experiment design is crucial for producing robust, replicable and meaningful results. This chapter first describes the spatio-temporal properties of TMS before discussing a number of free parameters that must be chosen when creating a TMS protocol. These include the type of TMS (on-line vs. off-line), the shape of the stimulating pulse, coil shape, the frequency and duration of stimulation, and finally the intensity. The motivation for

selection of TMS parameters used in this thesis is provided in subsection. The second half of the chapter presents different functional localization methods and my motivation for the choice of localization used in this thesis.

Spatio-temporal Resolution

TMS offers a relatively high degree of both spatial and temporal resolution. Empirically, it has been demonstrated that the effective spatial resolution of TMS can be as precise as 5-10 mm (Brasil-Neto et al., 1992; Ravazzani, Ruohonen, Grandori, & Tognola, 1996; Thielscher & Kammer, 2002; Toschi, Welt, Guerrisi, & Keck, 2008). For instance, the first TMS studies showed that different upper limb muscles could be selectively stimulated by TMS applied to the areas in motor cortex that are only 5-10 mm away from each other (Brasil-Neto et al., 1992; Singh, Hamdy, Aziz, & Thompson, 1997; Wassermann, McShane, Hallett, & Cohen, 1992). Moreover, a number of TMS studies have successfully demonstrated a functional double dissociation in closely located brain regions (10-30 mm apart). Those include double dissociation of visual attention from saccades in the right superior parietal cortex (Ashbridge, Walsh, & Cowey, 1997), semantic processing from phonological processing in the left inferior frontal gyrus (Gough, Nobre, & Devlin, 2005) and triple dissociation of faces, bodies, and objects processing in three adjacent regions in the right extrastriate cortex (Pitcher, Charles, Devlin, Walsh, & Duchaine, 2009).

One potentially important limitation with respect to the spatial resolution is the extent to which the effects of TMS spread from the targeted region. A number of studies showed that the current induced by TMS spreads transsynaptically to affect distal, but anatomically connected, regions (Bestmann, 2008; Bohning et al., 1999; Esser, Hill, & Tononi, 2005; Fox et al., 1997; Ilmoniemi et al., 1997; Pascual-Leone et al., 1998; Paus et al., 1997). The amount of spreading depends on the intensity of the magnetic field but it can be easily observed in the brain areas located even several

centimetres away from the targeted site (Maccabee, Eberle, Amassian, Cracco, & Rudell, 1990). For instance, Paus et al. (1997) used PET to analyse the effects of TMS applied over the left frontal eye field. Stimulation resulted in increased regional cerebral blood flow at the targeted site as well as at several distant sites including the left and right superior parietal lobule, left medial occipito-parietal cortex, and right supplementary eye field located in the frontal lobe. This raises the question whether observed behavioural effects are the consequence of stimulating the target region or could arise from transsynaptic stimulation of distal sites. Although the full relationship between the extent of induced current and the anatomical specificity of effects is still not fully understood (Walsh & Rushworth, 1999), certain aspects are clear from biophysical modelling and empirical studies. Biophysical and animal models suggested that the external magnetic field is actually fairly focal and affects a cortical area of approximately 100-200 mm^2 (Toschi et al., 2008; Wagner et al., 2004), in line with spatial resolution described earlier (Ashbridge et al., 1997; Brasil-Neto et al., 1992; Duncan et al., 2010; Gough et al., 2005; Pitcher et al., 2009). Empirical studies clearly demonstrated that TMS can have remote behavioural effects as evidenced by stimulation of the primary motor cortex where stimulation affects neocortical pyramidal cells that synapse on α-motor neurons in the dorsal root of the spinal cord and causes a contraction of the first dorsal interosseous hand muscle. However, it was also suggested that the cortical connectivity between the two regions does not result in equivalent effects of their stimulation. For instance, stimulation to the dorsal premotor cortex does not have the same effect on the hand muscle as equivalent stimulation to the primary motor cortex although these regions are synaptically connected (Koch et al., 2007). This is further supported by studies which showed functional double dissociation between two interconnected cortical regions. For instance, stimulation to the pars opercularis (i.e., the posterior part of the left inferior frontal gyrus) selectively affected phonological but not semantic processing while stimulation to the pars triangularis (i.e., the anterior part of the left

inferior frontal gyrus) selectively affected semantic but not phonological processing (Gough et al., 2005). Considering these data, it can be concluded that the spread of stimulation should not have any behavioural consequences in the targeted area and it does not seem to be the case that the spread of stimulation limits spatial resolution of TMS.

A second spatial limitation of TMS is that of accessibility, specifically only certain brain regions are accessible to TMS. For instance, TMS has limited depth of stimulation because the strength of the magnetic field decreases rapidly with distance from the coil (Walsh & Cowey, 2000). Consequently, TMS is most effective at stimulating brain regions near scalp (approximately 2-3 cm from the coil) and is ineffective at stimulating deep brain structures (Roth, Saypol, Hallett, & Cohen, 1991; Zangen, Roth, Voller, & Hallett, 2005). As a result, the only regions directly accessible to TMS are limited to the cortical mantle, although differently shaped coils are being developed in an attempt to reach deeper regions such as the basal ganglia (Roth et al., 1991; Zangen et al., 2005).

TMS also has sufficient temporal resolution to investigate the time course of neural information processing. Various studies have demonstrated that single or double pulses of TMS can produce different behavioural effects at different time points separated as little as 10 to 40 msec (Amassian et al., 1989; Corthout, Uttl, Walsh, Hallett, & Cowey, 1999; Duncan et al., 2010; Juan & Walsh, 2003; Pitcher, Goldhaber, Duchaine, Walsh, & Kanwisher, 2012). For example, in their classic TMS study, Amassian et al. (1989) induced visual suppression of letters between 80-100 msec post-stimulus onset using single pulses of TMS applied in 20 msec increments over the occipital pole. Stimulation applied between 0-60 msec or between 120-200 msec had no effect on visual letter perception indicating a specific temporal window where occipital processing contributed to letter recognition. More

recently, Pitcher and colleagues (2012) applied double-pulse TMS with pulses separated by 10 msec to the right occipital face or extrastriate body areas during a face or body recognition task, respectively. TMS disrupted performance of these tasks at two distinct time periods, namely 40-50 msec and 100-110 msec post-stimulus onset, leaving processing at the remaining time windows unaffected. Because the effect of an individual TMS pulse occurs immediately and lasts somewhere between 10 and 40 msec (Amassian et al., 1989; Corthout et al., 1999; Esser et al., 2005; Ilmoniemi et al., 1997), this enables the researcher to map the temporal dynamics of regional neuronal activity including its onset, duration, and offset (Amassian et al., 1993; Pitcher et al., 2007).

The spatial and temporal resolution of TMS can be compared with other neuroscientific techniques (Figure 2-1). This figure from Walsh and Cowey (2000) shows spatial resolution on the x-axis, temporal resolution on the y-axis and correlation vs. causation on the z-axis. Note that the x- and y-axes use a logarithmic scale going from very fine grained (molecules, milliseconds) to large scale (brains, days). The z-axis is binary with correlative techniques coming out of the plane and causal methods going into the plane. It is clear from the diagram that neither TMS nor any other non-invasive technique has the spatial (cell level) and temporal (milliseconds) resolution of single cell recording and microstimulation, but these techniques are highly invasive and only used in humans in very restricted clinical settings (i.e., during awake neurosurgery). TMS offers comparable spatial resolution to fMRI and PET as well as only slightly poorer temporal resolution than EEG and MEG. The timings observed in chronometric TMS studies, however, tend to match those from invasive neurophysiological recordings better than those from EEG and MEG (Corthout et al., 1999; Duncan et al., 2010). Presumably this is because these electromagnetic imaging techniques measure large scale neuronal synchrony that lags behind the earliest onset of activity (Walsh & Cowey, 2000). In summary, TMS

provides reasonably good spatio-temporal resolution relative to other non-invasive techniques with the added benefit of being able to perturb regional information processing and measure its effect on behaviour, allowing the researcher to draw causal brain-behavioural inferences.

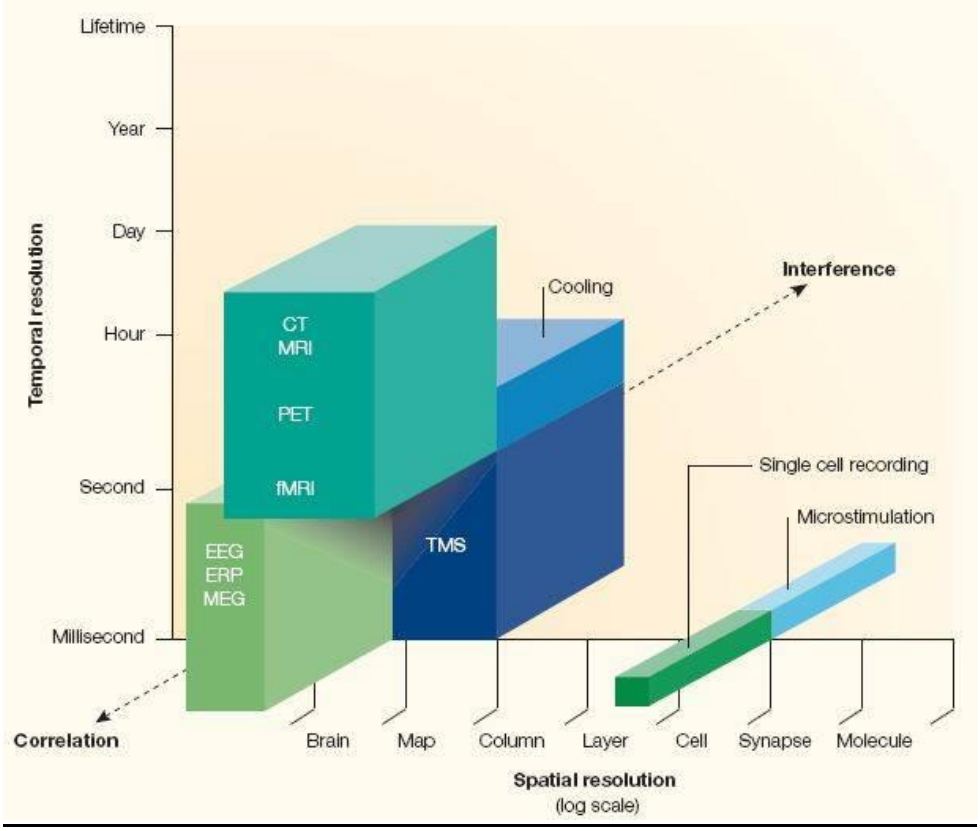

Figure 2-1: Spatial and temporal resolution of TMS in relation to other methods. Figure was taken from Walsh and Cowey (2000).

2.2 Creating TMS Protocol

TMS experiments have a large number of *free* parameters – that is, choices that are largely up to the experimenter and are not intrinsically *right* or *wrong*. These options include: i) whether stimulation will be applied during task performance (i.e., on-line)

or before performing the task (i.e., off-line); ii) the type of TMS pulse (monophasic or biphasic); iii) the shape of the stimulating coil; iv) a set of stimulation parameters such as frequency, duration and intensity of TMS; and v) a procedure for accurately targeting the stimulation site. Choosing the stimulation parameters from a large space of possibilities is critical to the success of the experiment. In most cases, there are clear constraints on the choices that help to limit the options and these include internationally agreed safety guidelines (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Wassermann, 1998). Even so, finding an optimal set of parameters for a particular paradigm is typically done empirically through extensive pilot testing to determine which options work best for a given experiment. The following section reviews the major parameter options and the constraints on these choices.

2.2.1 On-line vs. Off-line Stimulation

There are two ways of administering TMS. On-line TMS occurs during task performance so that the effects of TMS are immediate and short lived. That is, the effects last as long as the duration of stimulation (Duncan et al., 2010; Hartwigsen, Baumgaertner, et al., 2010; Pitcher et al., 2012; Sakai, Noguchi, Takeuchi, & Watanabe, 2002). As a result, TMS can be used on some trials but not others allowing a direct trial-by-trial comparison. This contrasts with off-line TMS which involves either long runs of low frequency stimulation (Pobric, Jefferies, & Lambon Ralph, 2010) or short bursts of patterned stimulation (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) that occur before starting a task. The effects last well beyond the duration of the TMS application itself such that subsequent behavioural tests can be run immediately afterwards without the distraction of TMS during individual trials. Consequently, the behavioural experiment is typically run once before TMS (control condition) and once after TMS (test condition) to compare the effects of stimulation on the task. Both on- and off-line TMS have their strengths and limitations.

The main strength of on-line TMS is that it can be used to induce robust virtual lesions with rTMS and it can also be used to investigate the timing of neural processing using temporally specific chronometric TMS. In fact, it is possible to use both types of on-line stimulation within a single study. For example, one can use rTMS to show that a particular area is necessary for normal task performance and then test when in time the same area is activated in the task using single- or double-pulse stimulation without worrying that the preceding rTMS has long-lasting effects on behaviour. Even so, on-line TMS has important limitations primarily due to concurrent sensory side effects that can influence task performance and lead to non-specific effects associated with stimulation. Most notably, each magnetic pulse is accompanied by an auditory click and a tapping sensation. These sensory cues can sometimes affect behaviour even without neuronal stimulation, particularly in experiments using auditory or somatosensory stimuli where the side effects interfere with task performance. It is worth noting that on-line TMS that included active control conditions to rule out non-specific confounds has been used successfully in some auditory experiments (Bestelmeyer, Belin, & Grosbras, 2011; Pattamadilok, Knierim, Kawabata Duncan, & Devlin, 2010). Another consideration is that the intensity of the sensory effects differs across head locations. For example, stimulation that is administered to a location close to the ear will sound louder than locations further away. Similarly, more ventral locations on the head produce greater muscle contraction than dorsal areas that may be more difficult to ignore (Deng, Lisanby, & Peterchev, 2013; Mennemeier et al., 2009). Apart from the sensory side effects produced by on-line TMS, anxiety that participants can feel towards stimulation may also have undesirable effect on their performance. In some cases, however, experimental limitations caused by on-line TMS can be overcome by using stimulation off-line.

One of the main advantages of off-line TMS is the absence of stimulation during task performance which eliminates non-specific behavioural and attentional confounds. This is particularly valuable for auditory experiments where the concurrent sound of the coil discharge can mask with auditory stimuli. The costs of off-line TMS include, however, an unknown time course for the effects of stimulation. The heuristic guideline is that 10-15 min of 1 Hz TMS produces effects that become maximal roughly 5 min after stimulation ends and last for 15-30 min (R. Chen et al., 1997; Muellbacher, Ziemann, Boroojerdi, & Hallett, 2000; J. R. Romero, Anschel, Sparing, Gangitano, & Pascual-Leone, 2002). It is currently unknown, however, whether these results measured with motor evoke potentials (MEPs) following the motor cortex stimulation generalize to other dependent measures and other cortical stimulation sites. So a disadvantage of off-line rTMS is the uncertainty associated with the time course of the effects.

2.2.2 Pulse Type and Coil Shape

Two properties of the TMS device, namely the pulse type and coil shape, need to be chosen before other aspects of the experiment can be determined. Pulse type refers to the nature of the current flow when brief electric pulses are discharged into the stimulating coil in order to enable neural stimulation. TMS stimulators are designed to produce one of two different types of pulses: monophasic or biphasic. Figure 2-2 illustrates the difference between them. At the beginning of any pulse all the current is stored in the charged capacitor and there is no voltage in the coil (light curve). As the capacitor discharges, the whole current is transferred into the coil. Neurons are most likely to be stimulated (i.e., depolarized) during induction of the highest voltage in the coil (shaded areas within the dark curve). In a monophasic pulse (Figure 2-2A), once the coil current reaches its maximum it decreases rapidly and most energy stored in the coil is dissipated in the form of heat, rather than returning into the capacitor. Only the initial phase of the current flow is high enough to depolarize

cell membranes and the capacitor must be completely recharged in order to send the next pulse. As a consequence, a monophasic stimulator is relatively slow and allows only a single pulse of TMS to be delivered. Monophasic pulses are most frequently used in neurophysiological studies to elicit MEPs where the inter-trial interval is less critical (Patuzzo, Fiaschi, & Manganotti, 2003; Watkins & Paus, 2004). In biphasic mode (Figure 2-2B), a larger portion of the coil's energy is returned to the capacitor, reducing its time required to recharge for the next pulse. Consequently, biphasic stimulators are faster, offering rapid trains of pulses (i.e., rTMS) necessary for creating robust virtual lesions. The main advantage of rapid stimulation is the possibility to cover a large time window of processing, especially important if temporal dynamics of regional activation is unknown.

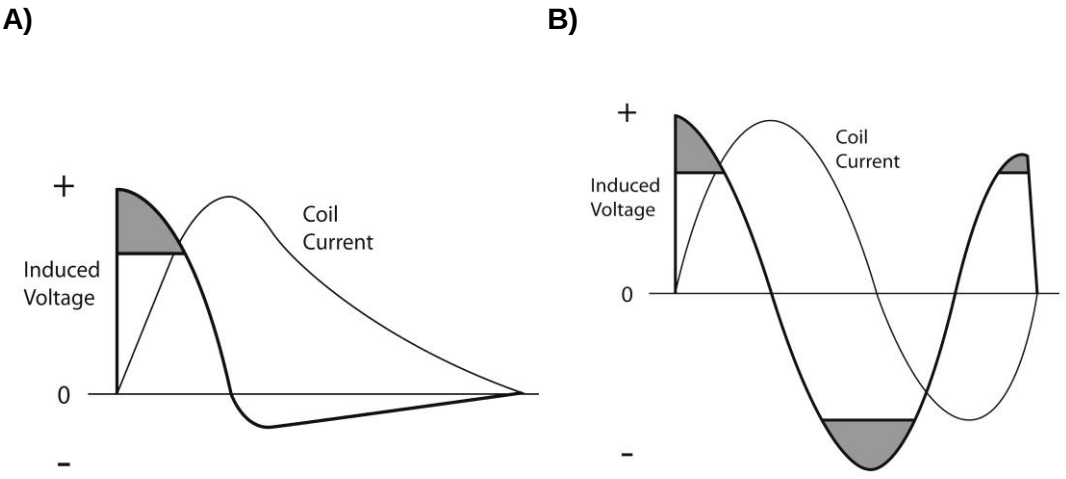

Figure 2-2: Current wave forms for A) monophasic TMS pulse and B) biphasic TMS pulse. The light curve corresponds to the current passing through the stimulating coil while dark curve represents the induced voltage in the brain. Shaded areas illustrate the highest induced voltage which is needed to cause neuronal depolarization. Figure was adapted from Epstein (2008).

The second property of the stimulator that needs to be chosen is the coil shape. Although there is a range of different coil morphologies to choose from, the two most commonly used coils are circular and figure-of-eight (also known as double or butterfly) coils. Circular coils are the simplest and were the first to be used because they are particularly effective in the stimulation of human hand motor cortex (Barker et al., 1985). The single circular coil does not, however, offer good spatial precision because the induced electric field is strongest under the wing of the coil. More specifically, the field is maximal under the mean diameter (dark red; Figure 2-3A) and minimal in the centre of the coil (dark blue). As a result, the stimulation is not very focal and instead affects a large cortical area, usually encompassing several distinct brain structures. In order to improve the spatial precision of stimulation, the figure-of-eight coil was designed (D. Cohen & Cuffin, 1991; Evans, 1991; Jalinous, 1991; Maccabee et al., 1990; Ueno, Tashiro, & Harada, 1988). A figure-of-eight coil is made up of two circular coils placed side-by-side. The coils carry current in opposite directions that leads to the flow of the current in the same direction at the intersection of the two coils. This results in the strongest induced electric field in the centre of the whole coil and much weaker current on its periphery (Figure 2-3B). A figure-of-eight coil therefore has the ability to predominantly stimulate neurons under the area where the two coils meet providing more focal stimulation than a circular coil (Jalinous, 1991). In addition, the outer parts of the coil are usually away from the scalp during stimulation and unlikely to induce effective currents in brain tissue (Walsh & Pascual-Leone, 2003). In many cases, the spatially limited area of stimulation also makes stimulation more comfortable for the subject.

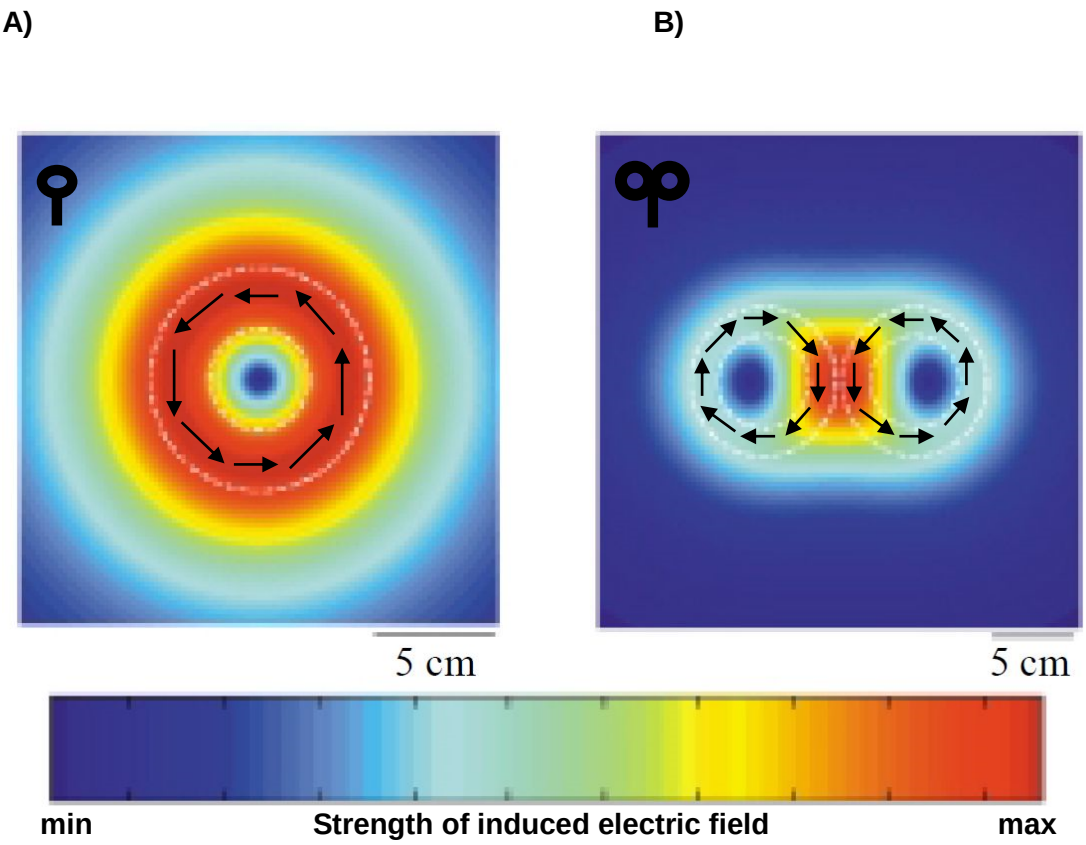

Figure 2-3: Distribution of the induced electric fields by A) circular coil and B) figure-of-eight coil. The shape of the coil is shown in the top left corner. The black arrows indicate direction of the current in the stimulating coil. The colours indicate the strength of induced electric field with dark red representing the strongest and dark blue the weakest electric field. Figure was adapted from Walsh and Pascual-Leone (2003).

2.2.3 Frequency, Duration and Intensity

When designing a stimulation protocol, the three parameters that are most important to the success of the experiment are the frequency, duration and intensity of stimulation. Frequency refers to the rate of stimulation in rTMS and is measured in pulses per second (i.e., Hz). Typically, frequencies at or below 1 Hz are considered to be *low frequencies* while those above 1 Hz are considered to be *high frequencies*.

Conventional wisdom suggests that low-frequency stimulation decreases cortical excitability while high-frequency stimulation increases cortical excitability. This classification of TMS frequencies can be clearly illustrated in the motor system where low-frequency rTMS delivered to primary motor cortex reduces the amplitude of MEP while high-frequency rTMS enhances MEP amplitude (Berardelli et al., 1999; R. Chen et al., 1997; Jennum, Winkel, & Fuglsang-Frederiksen, 1995; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Pascual-Leone, Valls-Solé, Wassermann, & Hallett, 1994; Rossi et al., 2000). For example, after Chen and colleagues (1997) used rTMS at 0.9 Hz for 15 min over hand motor cortex, MEPs decreased for another 15 min following stimulation. It is less clear, however, that these findings generalize to areas outside the motor cortex. For instance, to induce speech arrest, rTMS at high frequencies between 4-32 Hz has been used over the left prefrontal cortex (Epstein et al., 1996; Jennum, Friberg, Fuglsang-Frederiksen, & Dam, 1994; Pascual-Leone et al., 1991). Similarly, the majority of studies using either high- or low-frequency rTMS to areas involved in cognitive processes showed disruptive, rather than facilitatory, effects on behavioural measures such as reaction times or accuracy (Gough et al., 2005; Hartwigsen, Baumgaertner, et al., 2010; Pitcher et al., 2007; Pobric et al., 2010; L. Romero et al., 2006; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2010). Consequently, these results demonstrate that it may be somewhat simplistic to classify a stimulation protocol as inhibitory or facilitatory based solely on the frequency of stimulation. Moreover, choosing the *right* frequency for a TMS experiment is not a trivial task.

Choosing a specific frequency of stimulation is challenging because different values are likely to work equally well. There are, however, some heuristic guidelines that help to constrain the choice. Low-frequency rTMS is used in off-line TMS experiments where long-lasting stimulation is believed to have an inhibitory after-effect lasting from 30-60 min, depending on the duration and intensity of the

stimulation (Ridding & Rothwell, 2007). For example, Pobric and colleagues (2007) used rTMS of 1 Hz for 10 min over the anterior temporal lobe and found this increased decision times in picture naming and word comprehension tasks for approximately 20 min. On-line experiments, on the other hand, tend to use high-frequency rTMS. Many studies use 10 Hz stimulation during task performance to slow reaction times (Göbel, Walsh, & Rushworth, 2001) and/or induce errors (Hartwigsen, Baumgaertner, et al., 2010). In fact, a specific paradigm using on-line rTMS at frequency of 10 Hz for 500 msec has proven to be very effective and robust for producing virtual lesions across different cortical areas (Bjoertomt, Cowey, & Walsh, 2002; Duncan et al., 2010; Göbel et al., 2001; Hartwigsen, Price, et al., 2010; Lavidor & Walsh, 2003; Pitcher et al., 2007; Rushworth, Ellison, & Walsh, 2001). Because 10 Hz has been so commonly used in the literature, it has virtually become the *de facto* standard in cognitive neuroscience studies.

The choice of frequency has important implications for the participant's safety. Although the risk is small, there is always a possibility that TMS may induce a seizure in an otherwise healthy participant. Low-frequency stimulation is believed to decrease the risk of a seizure by reducing cortical excitability and thus minimizing the likelihood of kindling. In contrast, high-frequency stimulation is believed to increase cortical excitability, theoretically increasing the risk of inducing a seizure (but see above). The commonly chosen 10 Hz protocol has proven remarkably safe to date (Rossi et al., 2009). To minimize risks, there are internationally agreed upon safety guidelines that suggest safe stimulation frequencies, durations, intensities and inter-trial intervals that non-clinical studies are expected to adhere to. These guidelines also reduce the risk of less serious, but more common, side effects of TMS including transient headache, local pain and discomfort.

Another free parameter when designing a stimulation protocol is the duration of the rTMS. Duration refers to a time period during which a train of pulses is continuously delivered to the stimulation site. The choice of the *right* duration is equally important for both on- and off-line rTMS in inducing an effective virtual lesion although its implementation differs between the two. In on-line rTMS, the duration of a pulse train must be long enough to cover a critical time window of the neuronal activity related to the process of interest in order to cause its disruption. It is also important that a train of pulses is delivered during the critical time window since pulses delivered either too early or too late will not affect the process of interest. Protocols using 10 Hz pulse trains typically use durations of 400-500 msec, although longer train durations have also been used successfully (Rossi et al., 2009). In off-line rTMS, the duration of a train pulse is much longer than in on-line rTMS, usually in a range of 10 to 20 min. Usually, longer durations use lower stimulation intensities to meet safety requirements.

The final stimulation parameter when designing a stimulation protocol is intensity of stimulation. Intensity refers to the strength of the induced magnetic field and is determined by the amount of current released into the coil during stimulation; the larger the current, the larger the magnitude of the magnetic field. The *right* stimulation intensity is one that ensures the magnetic field affects neural processing in the target brain region. This is nearly impossible to determine *a priori* without knowing the current density needed to affect a particular cortical region, the position, orientation, and depth of this region as well as the inter-subject variability in functional-anatomy. It is clear that measurable effects of stimulation will not be achieved if intensities are too low because the proportion of affected neurons will not be large enough. It is not clear, though, how the effects change with increasing intensity. In other words, the curve of intensity dosage has not been determined. It seems likely that there is a minimal intensity required to produce an effect followed

by a range of intensity values that suffice. These may continue indefinitely but there is some evidence that effectiveness decreases as the magnitude of intensity increases beyond a certain point (Julkunen, Ruohonen, Saaskilahti, Saisanen, & Karhu, 2011). In other words there is probably a range in the intensity dosage curve where amounts of intensity are functionally equivalent. Intensity is typically expressed as a percentage of maximum stimulator output (e.g., 55% maximum intensity) but this figure crucially depends on the specific hardware being used. As a result, intensity values are often not comparable across studies, even when equipment from the same vendor is used.

It is possible to estimate current density induced in neural tissue by a given stimulation intensity and this provides a meaningful measure for reporting intensity (Hämäläinen & Ilmoniemi, 1994; Ilmoniemi, 1991). Unfortunately, the software to do this is only implemented in a few neuronavigation packages (Ruohonen & Karhu, 2010), limiting its accessibility. The estimation of the current density is primarily affected by the distance between the stimulating coil and the target area (Stokes et al., 2007; Stokes et al., 2005), but it is also affected by the location and orientation of the target tissue within the stimulating field. Therefore, if the target site has clear anatomical landmarks, then by using a high resolution structural scan of the participant's brain, one could in theory customize the stimulation intensity based on the estimated current density. Our knowledge of the functional representations for brain regions is however very limited. Even for well-defined anatomical landmark such as the *omega knob* in the precentral gyrus that identifies hand motor cortex (Boling, Olivier, Bittar, & Reutens, 1999; White et al., 1997; Yousry et al., 1997), there is considerable variability across individuals with respect to the specific cortical site where stimulation has its greatest effect. As a result, it is rarely feasible to determine the *right intensity* for stimulation a priori, making choosing intensity for a TMS experiment another difficult task.

At present there is no consensus on the optimum way to identify stimulation intensity for all TMS experiments. Many studies identify the intensity of stimulation necessary to produce a motor response when stimulating the hand area of primary motor cortex and use this to normalize intensity across participants (Duncan et al., 2010; Göbel et al., 2001; Meister, Wilson, Deblieck, Wu, & Iacoboni, 2007; Watkins & Paus, 2004; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2012). This measure, however, is not a reliable index of the optimal intensity for non-motor areas (Deblieck, Thompson, Iacoboni, & Wu, 2008; Stewart, Walsh, & Rothwell, 2001; Stokes et al., 2013). For example, Stewart and colleagues (2001b) found that the stimulation intensity necessary to induce an MEP when stimulating primary motor cortex were different from the intensity needed to induce phosphenes when stimulating visual cortex within the same individuals. Moreover, there was not even a consistent relationship between the intensities. Presumably, a major factor influencing this is the coil-to-cortex distance that may vary between brain areas (Stokes et al., 2013). Different distances from the coil to cortex increase variability in conductivity and permittivity of the tissue that the stimulation needs to go through before reaching the targeted area, leading to different effects across brain areas stimulated at the same intensity.

Another option for setting intensity is to use the same intensity for all participants (Bjoertomt et al., 2002; Gough et al., 2005; Pitcher et al., 2007; Stewart, Walsh, & Rothwell, 2001; Walsh, Ellison, Battelli, & Cowey, 1998). This approach, however, does not account for possible inter-subject variability of the minimum stimulation threshold that may lead to under- or over-stimulation in the region of interest for some subjects. On the other hand, if the range of equivalent intensity values is sufficiently broad, it may be feasible to choose intensity within that range that works across participants. At the moment, it is not clear which of these methods is optimal as both methods seem to produce reliable effects across published experiments.

All experiments in this thesis used on-line TMS. The main motivation for this choice was the intention to test both functional and temporal contributions of the inferior parietal lobule to visual word recognition. In addition, all experiments used biphasic pulses because they offer rapid trains of pulses which allow testing both functional and temporal contributions of the region with rTMS and chronometric TMS, respectively. A figure-of-eight shape coil was also used in all experiments because it allowed for precise and selective stimulation of supramarginal and angular gyri that was particularly important for distinguishing functional contributions of precise subregions within these regions. For all rTMS testing, high-frequency stimulation was chosen. To produce virtual lesions, I chose the most common protocol of 10 Hz in combination with a train of 5 pulses for 500 msec from onset of the stimulus which produced robust behavioural effects in pilot testing. For all chronometric TMS testing, double-pulse TMS with pulses separated 40 msec from each other at five different time windows was used. Finally, all the experiments used a set intensity of 55% of the maximum stimulator output for each participant. The fixed intensity of 55% of the maximum stimulator output was selected since it proved to be effective across a number pilot tests in producing robust TMS effects on language tasks in the inferior parietal lobule. This stimulation protocol was well within safety and comfort limits for all the participants and permitted easy comparisons with results of related studies in the literature.

2.3 Localization Methods for TMS

Successful TMS experiments require an effective and robust method of targeting the stimulation site. The spatial precision of TMS means that stimulation affects an area with a 5-10 mm radius, implying that small deviations in coil placement or orientation can dramatically influence the effects of stimulation. In addition, significant

differences in individual functional anatomy mean that the optimal stimulation site needs to be customized for each individual participant. Choosing a robust, accurate targeting procedure that accounts for individual differences in functional anatomy is therefore essential. Some brain regions can be functionally identified in an objective way using only single pulses of TMS. For instance, the primary motor and visual cortices can be localized by searching for optimal coil position that induces visible twitches of the contralateral hand muscle (Rossini et al., 1994) or visual phosphenes (Boyer, Harrison, & Ro, 2005), respectively. Similarly, the frontal eye fields can be localized by delays in saccadic eye movements produced by TMS applied approximately 1.5 cm anterior to the motor hand area (Müri, Hess, & Meienberg, 1991; Priori, Bertolasi, Rothwell, Day, & Marsden, 1993). The effect of TMS on the majority of brain areas, however, is not obvious. For these so-called *silent regions*, localization requires a different approach. There are a number of different methods that can be used for identifying a *silent* TMS target site including localization based on i) the International 10-20 EEG system; ii) standardized function guidelines; iii) individual anatomical brain landmarks; iv) standard space coordinates from group imaging studies; and v) functional localization in individual participants based on either fMRI or TMS.

The International 10-20 EEG electrode scalp positioning system (Jasper, 1958) constitutes a very basic approach for TMS localization. In this system, external locations on the skull represent underlying cortical areas. Before testing, the electrodes are placed at fixed distances from the head registration points in steps of 10 or 20% which takes into consideration individual differences in head sizes. This method has been used by a number of TMS studies where TMS coil was positioned, for example, over Wernicke's area, operationally defined as the tissue underlying the CP5 electrode (Knecht et al., 2002) or over left posterior parietal cortex,

operationally defined as the tissue beneath the P3 electrode (Kessels, d'Alfonso, Postma, & de Haan, 2000).

The second approach uses previously identified spatial relationships between a brain region and an easily localized function. For example, Pascaul-Leone and colleagues (1996) targeted dorsolateral prefrontal cortex by first finding a participant's hand area of primary motor cortex (identified by a visible hand twitch) and then moving the coil 5 cm anterior on a line parallel to the midsagittal line following the Talairach atlas.

A third localization option is to mark a target site based on anatomical landmarks visible in the participant's MRI scan. Broca's area, for instance, was marked as the crest of the left pars opercularis approximately 1 cm below the inferior frontal sulcus (Carreiras, Pattamadilok, Meseguer, Barber, & Devlin, 2012); an anterior temporal lobe site was defined as the region 10 mm posterior to the tip of the temporal pole along the middle temporal gyrus (Pobric, Jefferies, & Lambon Ralph, 2007); while the primary visual area V1 was identified as the most posterior part of the calcarine sulcus in the occipital pole (Camprodon, Zohary, Brodbeck, & Pascual-Leone, 2010).

A fourth approach is to choose standardized space (e.g., MNI152) coordinates associated with a particular function and mark that location on each participant's structural scan for stimulation. For the most part, researchers tend to use coordinates from functional neuroimaging studies that show specific brain regions activated during performance of a relevant task. For example, Pitcher and colleagues (2007) chose coordinates for the occipital face area from an fMRI study of face processing (Rossion, Caldara, et al., 2003) and used these to stimulate the region in their participants. In another example, coordinates for a region of left inferior parietal lobule involved in processing semantic categories (Kellenbach, Brett,

& Patterson, 2003; Noppeney, Price, Penny, & Friston, 2006) were used to stimulate that region in order to determine its role in semantic cognition (Pobric et al., 2010).

Finally, it is possible to functionally localize a stimulation site in each participant using either functional neuroimaging or TMS. In the former approach, it is typical to collect fMRI or PET data from each of the prospective TMS participants and use their peak activation within a region as the target stimulation site. This has been done, for example, using fMRI to identify two regions within left occipito-temporal cortex sensitive to either written words or visual objects (Duncan et al., 2010) or using PET to identify a region within left inferior frontal gyrus involved in verb generation (Thiel et al., 2005). Similarly, functional localization can also be done using TMS. This technique was initially employed in localizing the hand area within primary motor cortex (Barker et al., 1985) by placing a grid of targets covering the area and testing each until a motor *hot spot* (i.e., area showing the strongest and most reliable muscle contraction) is identified. Although localization of motor hand area relies on obvious behavioural TMS effects, it has been also used successfully on *silent* brain regions. In such regions, TMS-based localization can be done by marking several potential stimulation sites within the brain region and then testing each with a short localizer task that taps into the cognitive function of interest and has measurable behaviour (e.g., reaction times, accuracy, eye-movements). TMS-based functional localization has been used, for example, to identify the frontal eye fields involved in overt eye movements (Taylor, Nobre, & Rushworth, 2007). In a TMS study which investigated temporal contribution of anterior inferior prefrontal cortex to semantic processing, Devlin and colleagues (2003) used rTMS of 10 Hz for 300 msec during a short semantic task to determine a site involved in semantic processing. If TMS did not produce slower reaction times than no stimulation at the first site, then a new site located approximately 1 cm away was tested. The procedure was repeated until a stimulation site was successfully established.

Clearly, there are numerous ways to identify a stimulation site and all of them can be effective. The question then becomes: what are strengths and weaknesses of these different approaches? The main advantages of using the International 10-20 system or scalp-based measurements are their ease and low costs but neither methods offers good anatomical precision nor any consideration for anatomical and functional variation across participant. In fact, Herwig and colleagues (2003) found considerable variability in the anatomical regions underlying electrodes across participants. In contrast, localization based on MRI-guided anatomical landmarks or group functional coordinates accounts for inter-individual differences in anatomical brain structure since the target sites are marked in respect to brain structure of each individual. The need for structural brain scans for all participants, however, introduces significant expenses in both time and cost. In addition, these methods still do not account for individual differences in functional anatomy. The primary advantage to fMRI- and TMS-based functional localization is the ability to account for inter-subject differences in functional anatomy. fMRI-based functional localization is the most resource intensive method of identifying stimulation sites and may not be feasible in many cases. TMS-based localization is much less expensive but involves additional runs of TMS used to identify a *hot spot* which may lead to additional discomfort (depending on the stimulated region) or introduce safety concerns given the extra stimulation required (Rossi et al., 2009). There are numerous examples of each of these methods being used successfully so choosing one primarily involves weighing their relative pros and cons.

Sack and colleagues (2009) conducted an empirical, systematic comparison of different localization approaches commonly used in TMS experiments. Their investigation involved an evaluation of TMS effect strength and sample size for one TMS study on parietal cortex which was performed using four different localization methods: i) 10-20 EEG position P4; ii) individual MRI-guided TMS; iii) group

functional Talairach coordinates; or iv) individual functional coordinates. The results suggested that the methods did not differ qualitatively in their TMS-induced effects but rather in the magnitude of their respective effect sizes and the sample size required to observe statistically significant behavioural effects. The strongest TMS effect was revealed (Cohen's d = 1.13) when using individual fMRI-based localization, followed by the MRI-guided approach (Cohen's d = 0.82), group Talairach coordinates (Cohen's d = 0.67), and finally 10-20 EEG approach (Cohen's d = 0.34). A power analysis revealed that the number of participants sufficient to find a significant effect was the smallest for the experiment with fMRI-based localization (n = 5), followed by MRI-guided neuronavigation (n = 9), group Talairach coordinates (n = 13), and finally 10-20 EEG system (n = 47). In other words, although all four methods sufficed to identify a stimulation target, fMRI-based functional localization was the most sensitive method inducing the largest effects and requiring the fewest participants to be successful. Localization based on 10-20 EEG system was least effective, producing the smallest effects and thus requiring the largest sample for success. These results are in line with those obtained by Sparing et al. (2008) who also found the largest behavioural effects using fMRI-based localization and the smallest effects using 10-20 EEG system in a TMS study of primary motor cortex. Even stronger findings have been reported by Feredoes et al. (2007) who demonstrated that significant TMS effects in their experiment were only obtained using fMRI-based localization in individuals but not using group coordinates. It can be concluded that methods that customize stimulation sites based on functional localization in individuals lead to more effective TMS results.

So is fMRI-based functional localization the best way to identify target stimulation sites? There are two reasons why it may not be. First, the method targets a peak coordinate within the region-of-interest despite the fact that these have been shown to be highly variable within an individual (Berman et al., 2010; Duncan,

Pattamadilok, Knierim, & Devlin, 2009; Kung, Peissig, & Tarr, 2007). For instance, Duncan and colleagues (2009) used two runs of fMRI to functionally localize written word- and object-sensitive regions within extrastriate visual cortex in a set of 45 subjects. They found that on average, the peak voxels across the two runs within an individual were 8 mm apart, which is right at the limit of the spatial resolution of TMS. Twenty-seven % of the participants had peaks 12 mm or more apart, which would clearly be outside the resolution of TMS. In other words, the inconsistency in fMRI-based functional localization of peak coordinates can lead to different target locations for stimulation. A second concern is that fMRI and TMS are subject to different spatial biases. Specifically, the changes in blood oxygenation arising from local brain activity measured in fMRI propagate downstream in veins and can give rise to spurious activation at sites remote from neuronal activity (Turner, 2002). In contrast, the effects of TMS are mediated by the specific gyral and sulcal morphology with stimulation preferentially affecting axons that curve within the magnetic field (Rotem et al., 2014). These spatial biases are illustrated in Figure 2-4. Differences in spatial biases are problematic since they may lead to different localization of the same neural generator across the two techniques. TMS-based functional localisation avoids the twin problems of variability in peak voxel location as well as the differential spatial bias between fMRI and TMS, thus offering a more accurate targeting method than fMRI.

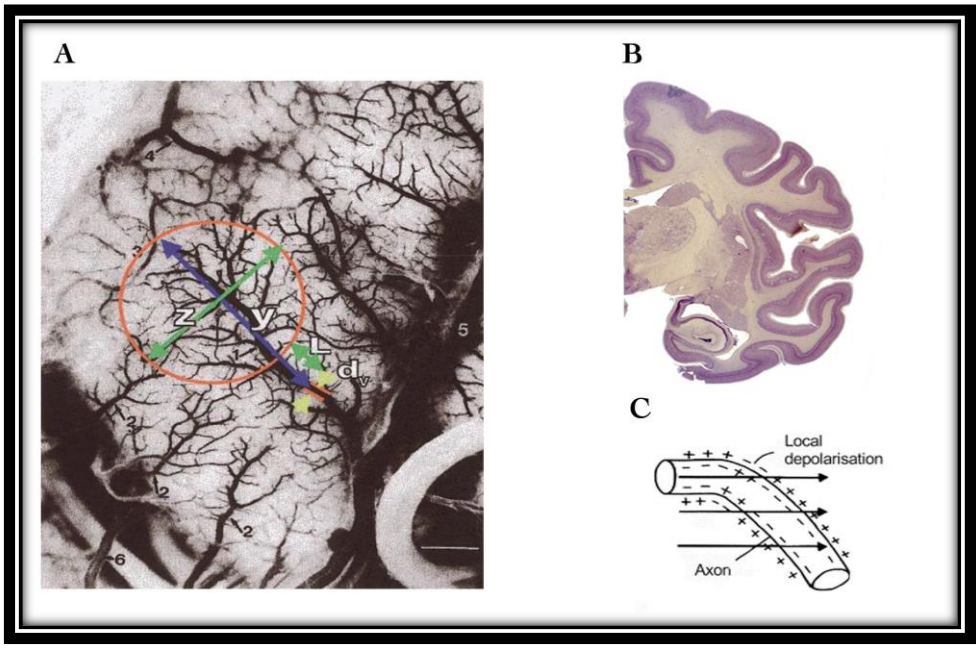

Figure 2-4: A) All veins within the red circled area drain towards the main vein (blue arrow) producing the strongest signal in the centre (Turner, 2002). B) A coronal slice through a single hemisphere together with a typical orientation of the intracranial electric current (black arrow) induced by TMS. As schematically shown in (C) the largest TMS effects are produced in axons bent closer to the stimulation site (Maccabee, Amassian, Eberle, & Cracco, 1993; Walsh & Pascual-Leone, 2003).

To empirically evaluate the efficacy of using fMRI to functionally localize stimulation sites within individuals, I examined four experiments previously run in my lab (refs). I calculated the percentage of participants who showed a TMS-induced effect on measured behaviour following fMRI-based localization (Duncan et al., 2010; Kawabata Duncan, 2010; Pattamadilok et al., 2010). Each of those experiments used fMRI to identify an area within ventral occipito-temporal cortex sensitive to visual words in individual participants in order to test its involvement in visual word recognition with TMS. There were a number of notable outcomes from this examination. First, fMRI-based functional localization was successful in identifying

stimulation targets which produced highly significant group results in the main TMS experiments despite relatively small sample sizes (range: 13-18). This is consistent with the idea that functional localization performed for each subject individually leads to high success rates in producing robust effects in TMS experiments (Sack et al., 2009; Sparing et al., 2008). In other words, by taking into account inter-subject variability in functional anatomy, one maximizes the experimental sensitivity. Interestingly however, although the method produced significant effects on a group level, there were always participants who did not show a TMS effect despite *successful* functional localization. Only 46 (out of 60) participants (77%) showed a TMS-induced slowdown despite the fact that fMRI identified a clear stimulation site in each participant. This pattern was seen in each of the four experiments with success rates ranging from 61-88%. Failure to produce stimulation effects in some individuals could result from difference in spatial biases between TMS and fMRI (Maccabee et al., 1990; Turner, 2002).

All experiments in this thesis used individual TMS-based functional localization (see Chapter 3) in order to account for variability in functional anatomy across individuals and to maintain identical spatial biases across localization and the main experiment in order to optimize the likelihood of stimulating the *correct* target site. In addition, TMS-based localization is cheaper in time and resources than fMRI-based localization and can be typically done with the main testing within a single session, minimizing the risk of functional variability of time (Penfield & Boldrey, 1937). Finally, TMS to angular or supramarginal gyrus are easily accessible for stimulation and stimulation of those regions usually does not cause any discomfort or pain to the participant.

3. *Experiment 1: Functional Contributions of the Left Inferior Parietal Lobule to Reading*

3.1 Introduction

In this chapter, I present a TMS study designed to evaluate three competing hypotheses concerning the functional contributions of the left inferior parietal lobule (IPL) to visual word recognition. The first hypothesis suggests that IPL stores visual forms of written words. The second hypothesis argues that IPL is involved in processes required for grapheme-to-phoneme conversion which are characteristic to the sublexical visual word processing. In contrast, the third hypothesis associates the two major subregions of IPL, namely supramarginal gyrus (SMG) and angular gyrus (ANG), with specific language functions used during reading. According to the third hypothesis is involved in processing phonology while ANG processes semantics. The third hypothesis also leads to the question whether IPL can fulfil multiple, distinct functions during reading as a result of its anatomically subdivided structure. Clearly, there are substantial differences between the three hypotheses in respect to the functions they propose. As it stands all of the suggested functions are plausible and the question to be asked is which of them is correct. Validation of these three hypotheses is especially important for assigning correct functional labels to IPL and further improvement of the neurological model of reading.

The first hypothesis claims that IPL is the site of stored visual word forms. This derives from the seminal work of Joseph Jules Dejerine (1891) who described the cases of two patients unable to read or write due to lesions of the left posterior IPL, more specifically the left ANG. Dejerine reasoned that the patients' inability to recognize visual words coupled with their writing difficulty indicated a central loss of visual word forms, which he argued must be stored in ANG. Subsequent studies of patients with acquired reading deficits have confirmed the importance of IPL for reading, but have introduced uncertainty regarding the specific anatomical fields. For instance, Warrington and Shallice (1980) reported two patients with profound

reading impairments subsequent to lesions predominantly affecting either the anterior (SMG) or posterior (ANG) fields of IPL. Similarly, Philipose and colleagues (2007) found that reading deficits were more commonly due to SMG, rather than ANG, lesions. The evidence shows, therefore, that IPL is important for storing visual word forms but there is uncertainty regarding localization of this function to the specific anatomical field within the region.

The second hypothesis claims that IPL is required for grapheme-to-phoneme (i.e., letter-to-sound) conversion during reading. The foundations of this hypothesis need a few words of explanation. Reading involves a series of cognitive processes that include, among other things, conversion of spelling (orthography) into sound (phonology). However, the way that orthography is mapped into phonology is still a matter of debate. The dual-route model proposed that there are two procedures for conversion of orthography into phonology: an assembled procedure based on grapheme-to-phoneme conversion rules and an addressed procedure based on a whole-word orthographic form (Coltheart et al., 1993; Paap & Noel, 1991). Phonological assembly relies on accessing phonology of the written word by mapping its individual graphemes onto corresponding phonemes thanks to grapheme-to-phoneme correspondence rules that are specific to the sublexical route of word processing. In contrast, the addressed procedure for accessing phonology of the written word relies on direct retrieval of the phonological word form from the orthography of the whole word via a lexical route. The sublexical route is particularly important for reading new words that can be sounded out from their spelling (i.e., regular words) such as *bench* or *ten* as well as pronounceable pseudowords such as *nawk* since whole-word pronunciation patterns of such words have not been memorised and need to be generated using grapheme-to-phoneme conversion rules. Words that do not obey traditional grapheme-to-phoneme correspondence rules (i.e., irregular words) such as *pint* or *yacht*, however, require a different

mechanism to be read successfully. According to dual-route theories, such words use a lexical route where their pronunciation patterns have been memorised and can be accessed directly from memory. Evidence for separate sublexical and lexical routes originated from observations of patients with acquired surface and phonological dyslexia, respectively. Phonological dyslexics (Beauvois & Derouesne, 1979) show more difficulty reading nonwords in relation to real words while surface dyslexics (Marshall & Newcombe, 1973; Patterson, Marshall, & Coltheart, 1985) experience problems reading irregular words in relation to regular words. Unlike the classic neurological model of reading, the dual-route model was purely cognitive and described mechanisms for grapheme-to-phoneme conversion without any reference to neuroanatomy. More recently, however, researchers have tried to establish neural correlates of the lexical and sublexical processes underlying grapheme-to-phoneme conversion using neuroimaging methods and a number have suggested that IPL constitutes a crucial region involved in this process (Booth et al., 2004; Y. Chen, Fu, Iversen, Smith, & Matthews, 2002; Das, Padakannaya, Pugh, & Singh, 2011; Horwitz et al., 1998; Kronbichler et al., 2006; Law et al., 1991; Pugh et al., 2000; Roux et al., 2012; S. E. Shaywitz et al., 1998; Simos et al., 2002).

By manipulating tasks and stimuli that putatively require grapheme-to-phoneme conversion, investigators sought to identify brain activity directly related to phonological assembly. In the first instance, functional imaging studies compared activation for reading pseudowords relative to familiar words with the expectation that reading pseudowords would increase activation in areas involved in sublexical grapheme-to-phoneme conversion. This contrast revealed increased SMG activation for pseudoword reading in a number of studies (Abutalebi et al., 2007; Henson, Price, Rugg, Turner, & Friston, 2002; Price, Wise, & Frackowiak, 1996; Thompson et al., 2007; Vigneau et al., 2005; Xu et al., 2001). The results are in line with those obtained by Roux et al. (2012) who performed cortical electrostimulation mapping on

neurosurgical patients to investigate brain regions required for conversion of graphemes into phonemes using a pseudoword reading task. Roux and colleagues demonstrated that interference specific to pseudoword reading was concentrated in a restricted inferior and anterior subpart of SMG. A similar manipulation by Horwitz et al. (1998), however, associated grapheme-to-phoneme conversion with ANG rather than SMG. The researchers investigated brain regions involved in grapheme-to-phoneme conversion by comparing regional cerebral blood flow specific to pseudoword relative to low-frequency word reading. Like to familiar words, low-frequency words were believed to involve areas required for lexical reading without involvement of sublexical processes necessary for grapheme-to-phoneme conversions. Horwitz and colleagues found a strong positive correlation between the left ANG and other brain areas during pseudoword reading which they claimed made the region a perfect candidate for a main role in grapheme-phoneme transformations.

Another approach used to investigate neural correlates of grapheme-to-phoneme conversion was to compare reading in orthographies that require grapheme-to-phoneme conversion to those which do not. For instance, Law et al. (1991) used PET to compare reading in two different Japanese writing systems, namely Kanji and Kana. Kanji script was derived from the ancient Chinese and has maintained a logographic orthography where each symbol corresponds to a whole word. In contrast, Kana characters represent syllables and as a result, reading Kana strongly relies on phonological assembly. This study showed significant SMG and ANG activation for Kana relative to Kanji reading. Similarly, Chen et al. (2002) contrasted neuronal activation elicited by reading alphabetic to non-alphabetic Chinese scripts in their fMRI study. As the alphabetic Chinese script, the researchers used Pinyin developed from English letters as sound symbols for Chinese characters. Pinyin was contrasted with the logographic Chinese script as reading Pinyin requires

grapheme-to-phoneme mapping. Reading Pinyin relative to Chinese logographs led to greater activation in both SMG and ANG. In addition, Das et al. (2011) compared brain activation for reading words in two languages with considerably different degrees of the orthographic transparency. Their task involved reading Hindi versus English words. Das et al. assumed that Hindi words, which are characterised by transparent orthography, would rely on grapheme-to-phoneme conversion more than English words where there is a less consistent orthography. Das and colleagues showed that in contrast to monolingual English readers, monolingual readers of Hindi primarily elicited activation in SMG and they argued that the results reflect its involvement in sound assembly.

In developmental studies, Booth and colleagues (2003, 2004) also argued that the left IPL is involved in the process of grapheme-to-phoneme conversion. In one of their studies, Booth et al. (2003) used fMRI to determine whether performance on tasks that required explicit translation of graphemes to phonemes (e.g., rhyme judgements to visually presented words) was correlated with cerebral activation patterns. They found that in this task, better performance was associated with greater SMG and ANG activation in adults. This led them to a prediction that children are likely to show less activation in these regions performing the same task since they are less skilled in phonological assembly than adults. Therefore, in their following study, Booth et al. (2004), examined developmental differences in the neurocognitive networks in children and adults. As predicted, adults showed greater activation for rhymes in ANG than children. On the basis of the results from both studies, the researchers argued that the left IPL must be involved in grapheme-to-phoneme conversion.

Additional evidence for the left IPL involvement in conversion of letters to sounds comes from neuroimaging studies of readers with developmental dyslexia. Dyslexics

have a persistent difficulty in acquiring reading skills, often associated with a lack of phonemic awareness leading to problems with phonological assembly (Bruck, 1992; Fletcher et al., 1994; Rieben & Perfetti, 2013; Shankweiler et al., 1995; Stanovich & Siegel, 1994). This indicates that dyslexic readers struggle reading words and nonwords which require efficient grapheme-to-phoneme conversions. Neuroimaging techniques have been used to assess brain activation patterns characteristic for developmental dyslexics in attempt to identify brain structures involved in grapheme-to-phoneme conversion by comparing brain activation in dyslexics to normal readers during reading tasks which explicitly engage phonological decoding (e.g., pseudoword reading). A number of studies have shown severe activation abnormalities in IPL for developmental dyslexics (Habib, 2000; McCandliss & Noble, 2003; Pugh et al., 2000; Sandak, Mencl, Frost, & Pugh, 2004; S. E. Shaywitz & Shaywitz, 2005). Activation in SMG and ANG was negatively correlated with reading skill in developmental dyslexics during tasks involving, for example, single word reading (Rumsey, Nace, et al., 1997), rhyme judgements (Hoeft et al., 2006; Rumsey et al., 1992; B. A. Shaywitz et al., 2002; S. E. Shaywitz et al., 1998) or sentence reading in a language with consistent grapheme-to-phoneme conversions (Kronbichler et al., 2006). In addition, Simos et al. (2002) demonstrated that dyslexic children showed a significant increase in reading skills along with increased activation in both IPL subregions after an intervention that was designed to improve child's awareness of phonological structure and its relation to the alphabetic principle. Altogether, studies on developmental dyslexics provide additional evidence for involvement of the left IPL in grapheme-to-phoneme conversion.

Additional claims of SMG association with grapheme-to-phoneme conversion can be found in studies on readers with phonological agraphia which is characterized by an impairment of spelling pronounceable pseudowords and unfamiliar words relative to spelling familiar words (Roeltgen & Heilman, 1985; Shallice, 1981). Many

researchers share the assumption that reading and spelling share common cognitive processes (A. S. Brown, 1990; Rapcsak et al., 2009). Like reading therefore, spelling unfamiliar words and pseudowords is achieved through a sublexical route based on grapheme-to-phoneme conversion (Ellis, 1982). Phonological agraphia is most strongly associated with damage to the anterior SMG (Bub & Kertesz, 1982; Penniello et al., 1995; Rapcsak, Arthur, & Rubens, 1988; Roeltgen & Heilman, 1985; Roeltgen, Sevush, & Heilman, 1983; Tanaka, Yamadori, & Murata, 1987). Consequently, the inability to create phoneme-grapheme relationships in phonological agraphia is argued to indicate that SMG plays a vital role in phonological assembly.

Taken together these studies argue for an important role of the left IPL in grapheme-to-phoneme conversion. The evidence supporting this claim comes from various neuroimaging studies on healthy readers who showed increased activation in this part of the brain for tasks that require explicit conversion of graphemes into phonemes as well as readers with disturbed reading conditions who showed abnormal involvement of the region during this process. However, there are problems with this hypothesis. First, the increased activation for pseudowords relative to regular words in IPL has not been consistent. A considerable number of studies demonstrating no difference in activation for pseudowords relative to words (Fiez, Balota, Raichle, & Petersen, 1999; Herbster et al., 1997; Mechelli, Gorno-Tempini, & Price, 2003; Osipowicz et al., 2011; Paulesu et al., 2000; Woollams, Silani, Okada, Patterson, & Price, 2011) or greater activation for regular words than pseudowords (Mechelli et al., 2003; Vigneau et al., 2005). Second, clearly the strongest contrast for dissociating sublexical and lexical processes would be a comparison of reading pseudowords (sublexical route) relative to irregular (lexical route) words, however, there are no reports of greater activation for pseudowords relative to irregular words in IPL. By definition, pseudowords have no lexical

representations and the only way to pronounce them is via grapheme-to-phoneme rules represented in the sublexical route. This is in contrast to reading irregular words that cannot be read successfully following grapheme-to-phoneme rules but require mapping of the whole-word orthographic representation onto a whole word phonological pattern via the lexical route. Rumsey et al. (1997) directly compared pseudowords to irregular words and showed essentially identical patterns of activation for the two types of stimuli with no regions showing differences between sublexical and lexical routes. Instead, both types of stimuli activated SMG and ANG to the same extent. Finally, even if IPL plays some role in grapheme-to-phoneme conversion, there is no consensus regarding the specific anatomical locus of this function with some studies focusing on SMG (Das et al., 2011; Henson et al., 2002; Hoeft et al., 2006; B. A. Shaywitz et al., 2002; Thompson et al., 2007; Vigneau et al., 2005; Xu et al., 2001), others on ANG (Booth et al., 2004; Horwitz et al., 1998; Pugh et al., 2000; Rumsey et al., 1992; S. E. Shaywitz et al., 1998) and still others arguing that both fields are important for this process (Booth et al., 2003; Y. Chen et al., 2002; Law et al., 1991; Simos et al., 2002).

The third hypothesis about IPL involvement in visual word recognition suggests that the supramarginal and angular fields of IPL have different functions during word reading. By this account, SMG contributes to sound processing while ANG is involved in processing meaning (Demonet et al., 1994; Graves, Desai, Humphries, Seidenberg, & Binder, 2010; Paulesu et al., 1993; Price & Mechelli, 2005; Price et al., 1997). This hypothesis derives from functional imaging studies which consistently showed increased activation in SMG or ANG for reading tasks that place demands on phonological or semantic processing, respectively. For instance, greater activation in SMG was revealed during rhyme judgements in relation to perceptual categorization of meaningless Greek letter strings (Seghier et al., 2004); rhyme judgements in relation to semantic relatedness judgements (McDermott et al.,

2003); passive word viewing in relation to passive picture viewing (Menard et al., 1996); viewing words in relation to viewing objects and false fonts (Moore & Price, 1999); reading unfamiliar pseudowords in relation to familiar words (Price, Wise, & Frackowiak, 1996); or reading Japanese Kana in relation to Kanji (Law et al., 1991). In contrast, ANG was demonstrated to have greater activation during semantic category decisions in relation to perceptual categorization of meaningless Greek letter strings (Seghier et al., 2004); reading words in relation to nonwords (Binder et al., 2003); semantic category judgements in relation to nonword rhyming and letter case judgements (Pugh et al., 1996); and contrasting semantically related words with semantically unrelated words (Mechelli et al., 2007). Several neuroimaging studies have also confirmed a double dissociation within IPL in directly contrasting phonological and semantic tasks (Devlin et al., 2003; Mummery et al., 1998; Price et al., 1997; Vigneau et al., 2006). For instance, Devlin and colleagues (2003) demonstrated enhanced activation in the dorsal SMG for a phonological task in which participants decided whether the word consisted of two syllables relative to a semantic task in which the participants were asked to judge whether the word presented to them was a man-made (e.g., *radio*) or natural item (e.g., *cloud*). In contrast, the opposite comparison (semantic vs. phonological task) revealed activation in the posterior inferior ANG. In their PET study, Mummery et al., (1998) found similar results. SMG was activated when subjects decided which of two response words had the same number of syllables (i.e., phonological similarity judgments) relative to decisions on which of two response words was more similar in color to the target word or which of two response words was typically found in the same location as the target word (i.e., semantic similarity judgments). In contrast, judgments on semantic similarity increased activity in ANG when compared to judgments on phonological similarity. The same functional double dissociation of semantic and phonological processing was revealed by the comparison of decisions on living/non-living objects vs. number of syllables (Price at al., 1997) or specific

phoneme detection vs. specific noun detection (Demonet et al., 1994). This third hypothesis builds on the findings that the SMG is important for phonological processes associated with verbal working memory (Buchsbaum & D'Esposito, 2008) while ANG is considered a key node in the cortical semantic system (Binder, Desai, Graves, & Conant, 2009).

It is worth noting that according to this account, the SMG and ANG contribution to processing of sound and meaning, respectively, is not limited to written words but true for all types of stimuli. For instance, SMG is also involved in processing speech and non-speech sounds during auditory tasks (R. R. Benson et al., 2001; Burton, Small, & Blumstein, 2000; Callan, Jones, Callan, & Akahane-Yamada, 2004; Celsis et al., 1999; Demonet et al., 1992; Heim, Opitz, Müller, & Friederici, 2003; Jacquemot, Pallier, LeBihan, Dehaene, & Dupoux, 2003; Jäncke, Wüstenberg, Scheich, & Heinze, 2002; Pattamadilok et al., 2010; Prabhakaran, Blumstein, Myers, Hutchison, & Britton, 2006; Raizada & Poldrack, 2007; Zatorre, Evans, Meyer, & Gjedde, 1992; Zevin & McCandliss, 2005). As suggested by a number of researchers (Awh, Smith, & Jonides, 1995; Buchsbaum & D'Esposito, 2008; Burton et al., 2000; Jonides et al., 1998; Koelsch et al., 2009; Paulesu et al., 1993; L. Romero et al., 2006), this could reflect SMG role in phonological working memory where the region is used for temporal store of phonological patterns. The idea is especially plausible considering the fact that SMG shows activation in more demanding phonological tasks which involve maintaining sound patterns in memory, but not in simple speech comprehension tasks (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009). Similarly, ANG shows involvement in semantic processing that does not only involve visual word reading. It is also implicated in semantic processing during tactile reading of Braille words in blind subjects (Büchel, Price, Frackowiak, & Friston, 1998) or during semantic decisions on pictures (Seghier, Fagan, & Price, 2010; Vandenberghe, Price, Wise, Josephs, &

Frackowiak, 1996) and spoken words (Awad, Warren, Scott, Turkheimer, & Wise, 2007; Brownsett & Wise, 2010; Mashal, Faust, Hendler, & Jung-Beeman, 2007; Obleser & Kotz, 2009; Warburton et al., 1996). These findings provide strong evidence associating ANG with the distributed semantic system that is shared by various types of stimuli. Overall, the third hypothesis not only proposes specific functional roles for the supramarginal and angular gyri but also argues that their roles are more general language processing roles that contribute to reading but are not specific to reading. This is in contrast to the first two hypotheses which assign IPL to functions that are specific to reading.

The functional double dissociation of phonological and semantic processing within IPL is also supported by the anatomy of this region. SMG and ANG differ in both their cytoarchitectonic structure and connectivity profiles, consistent with separate functional properties. The two areas essentially correspond to Brodman's (1909) areas 40 and 39 (Figure 3-1A), or Von Economo and Koskinas' (1925) areas PF and PG (Figure 3-1B), respectively (Caspers et al., 2008; Caspers et al., 2006). Critically, the two regions have distinct patterns of connectivity and thus participate in separable functional circuits (Caspers et al., 2011; Göbel, Rushworth, & Walsh, 2006). Specifically, SMG has strong reciprocal connections with pars opercularis and ventral premotor cortex via the third branch of the superior longitudinal fasciculus (Makris et al., 2005; Martino et al., 2013). This fronto-parietal circuit plays a key role in verbal working memory (Buchsbaum & D'Esposito, 2008; L. Romero et al., 2006) and in phonological processing more generally (Demonet et al., 1994; Devlin et al., 2003; Mummery et al., 1998; Price et al., 1997). In contrast, ANG sits at the posterior end of the middle longitudinal fasciculus, linking it with middle and anterior temporal lobe regions involved in semantic memory (Binder et al., 2009; Makris et al., 2009; Price, 2010). These cortico-cortico connectivity patterns

presumably explain the observed double dissociation between phonological processing in SMG and semantic processing in ANG.

A) **B)**

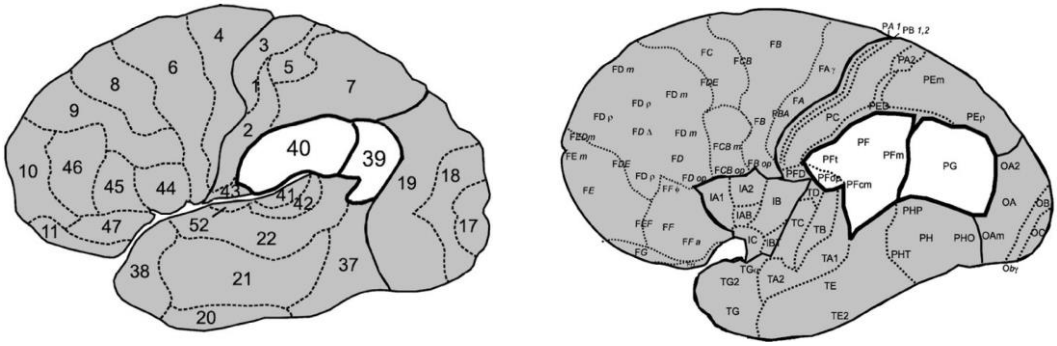

Figure 3-1: Schematic representation of the brain maps created by A) Brodmann (1909) where SMG and ANG correspond to areas BA40 and BA39, respectively and B) Von Economo and Koskinas (1925) where SMG and ANG correspond to area PF and PG, respectively. The SMG and ANG areas are highlighted in white. Figure was taken from Caspers et al. (2006).

In summary, there are three hypotheses concerning IPL contributions to visual word recognition. The first claim is that IPL is the site of stored visual forms of written words although it remains unclear precisely where within the IPL these are stored. The second hypothesis argues that the procedures for converting letters-to-sounds are a function of the IPL but it is also unclear whether these are specifically located in ANG or SMG, or both. Finally, the third hypothesis suggests that the angular and supramarginal fields of the IPL preferentially contribute to semantic and phonological processing of written words, respectively. It is unclear, however, whether the differential contribution of ANG and SMG to semantic and phonological processing is *necessary* because of the nature of the neuroimaging techniques

which can only indicate correlations between brain and behaviour, but do not allow causal relations to be drawn. Moreover, in patients with IPL lesions this double dissociation is not readily apparent, in part because focal lesions selectively affecting either ANG or SMG are rare. The aim of the current study was to evaluate these three hypotheses using repetitive transcranial magnetic stimulation (rTMS) to temporarily and selectively disrupt processing in left ANG and SMG during visual word recognition and measure its effect on reading behaviour.

3.2 Methods

Participants

Seventeen people volunteered for this study and 12 (7F, 5M; aged 18-42, mean = 26) participated in the main experiment. One of the five excluded participants experienced right hand twitching during SMG stimulation that interfered with making a button press response and therefore could not participate in the experiment. In the other four, functional localization failed to identify an appropriate ANG (2) or SMG (2) testing site. All of the remaining participants were right-handed, monolingual native English speakers with normal or corrected to normal vision. They reported having no neurological conditions and no form of dyslexia. Each person provided informed consent after the experimental procedures were explained and was paid for their participation. The experiment was approved by the University College London Research Ethics Committee.

Experimental Procedures

The experiment consisted of three separate testing sessions for each participant. The first lasted approximately 30 minutes and involved acquisition of a T1-weighted magnetic resonance imaging (MRI) scan [FLASH sequence, repetition time (TR) = 12 ms, echotime (TE) = 5.6 ms, flip angle = 19°, resolution = 1 mm × 1 mm × 1 mm] at the Birkbeck-UCL Centre for Neuroimaging (BUCNI). The structural images were used for anatomical identification of left ANG and SMG in each participant. Scanning was followed by two TMS sessions in which either ANG or SMG were tested, with the order counterbalanced over participants. The TMS sessions were separated by at least two days and lasted approximately one hour each. Each testing session consisted of a TMS-guided functional localization and then the main experiment. The aim of the localization procedure was to identify specific testing sites within ANG and SMG. In other words, the testing sites used in the main experiment were determined using a TMS-based functional localization procedure (Ellison, Lane, & Schenk, 2007; Pattamadilok et al., 2010; Taylor et al., 2007), similar to "functional localizer" scans commonly used in fMRI experiments (Kanwisher, McDermott, & Chun, 1997; Kraft et al., 2005). The aim of this functional localization procedure was to customize the stimulation site in each individual taking into account inter-subject functional-anatomical variability.

In order to identify appropriate testing sites we chose localization tasks that optimized the constraints placed by the three hypotheses under investigation. According to the first hypothesis, left IPL stores visual word forms and therefore the only constraint was that the task used real words (i.e., as opposed to pseudowords). The second hypothesis suggests that IPL is involved in grapheme-to-phoneme conversion. In this case localization required a task that involved mapping of letters onto sounds, a procedure that is thought to occur automatically in virtually all reading tasks (Coltheart et al., 2001; R. Frost, 1998; Plaut et al., 1996). Finally, the third hypothesis claims that SMG and ANG are required in phonological and

semantic processing of written words, respectively, and thus localization required separate tasks that were either phonologically or semantically demanding. As a result, a visual rhyme judgement task was used to localize stimulation site within SMG while a semantic category judgement task was used for ANG. Rhyme judgments focused the participant's attention on the sounds of words by forcing them to decide whether two visually presented words rhymed (e.g., *queen* – *green*) or not (e.g., *slug* – *muck*). Semantic category judgments focused the participant's attention on the meaning of the words by forcing them to decide whether the two visually presented words came from the same semantic category (e.g., *inch* – *mile*) or not (e.g., *skirt* – *hero*). The stimuli were designed such that half of the words in rhyme trials had different spellings (e.g., *razor* – *laser*) while half of the non-rhyming pairs had similar spellings (e.g., *farm* – *warm*). This prevented participants adopting a purely orthographic strategy.

Note that I purposely did not localize both phonological and semantic processing within a single region because none of the three possible outcomes were relevant here. The neuroimaging evidence suggests that the most likely outcome would be an inability to localize phonological processing within ANG and an inability to localize semantic processing within SMG. That finding, however, would be a null result and therefore not informative due to the potential that I inaccurately delivered stimulation, incorrectly selected stimulation sites, inappropriately chose localization tasks, or any number of other experimental failures. In other words, it would needlessly expose participants to an extra 160 trials with rTMS to no purpose because a lack of evidence could not logically be used as evidence for a lack of phonological or semantic processing in ANG or SMG, respectively. A more interesting possibility would be if both types of processing were localized at different locations within an anatomical region (e.g., within SMG). Although informative, it would answer a different question than the one I investigated here. The final

possibility would be that both the phonological and semantic localizer tasks would identify the same location within each anatomical region – a possibility I explicitly test in the main experiment (see below). As a result, it was only necessary to localize phonological processing in SMG and semantic processing in ANG. Critically, though, both localization tasks required recognizing visual word forms and converting graphemes-to-phonemes so were equally appropriate for localizing stimulation sites relevant for all three hypotheses, thereby avoiding the potential for circularity in the results.

Prior to the TMS session, three potential stimulation targets were anatomically marked within each region on an individual's MRI scan using the Brainsight frameless stereotaxy system (Rogue Research, Montreal, Canada). For ANG, three potential stimulation sites were marked using standard space coordinates based on a study by Seghier et al. (2010) who identified three functionally distinct subregions within ANG. These were located within dorsal ANG at [–30 –66 42], middle ANG at [–48 –68 28], and ventral ANG at [–48 –68 20] (see Figure 3-2). For SMG, a different method of marking potential stimulation sites was applied. Instead of using standard space coordinates, sites were marked anatomically within the anterior part of the left SMG since this area has been shown to be most consistently involved in visual word recognition across a number of neuroimaging studies (Devlin et al., 2003; Petersen et al., 1988; Price, 2000; Price et al., 1997; Roux et al., 2012; Seghier et al., 2004). The three sites were located: i) just superior to the termination of the posterior ascending ramus of the Sylvian fissure; ii) at the ventral end of the anterior SMG, superior to the Sylvian fissure, posterior to the postcentral sulcus, and anterior to the posterior ascending ramus of the Sylvian fissure; and iii) approximately halfway between these sites and approximately 10-15 mm from the other two (see Figure 3-2). This resulted in different standard space coordinates for each potential stimulation site across individuals. Each site within ANG and SMG

was then tested to functionally localize the specific target site where stimulation interfered with a semantic or a phonological task, respectively.

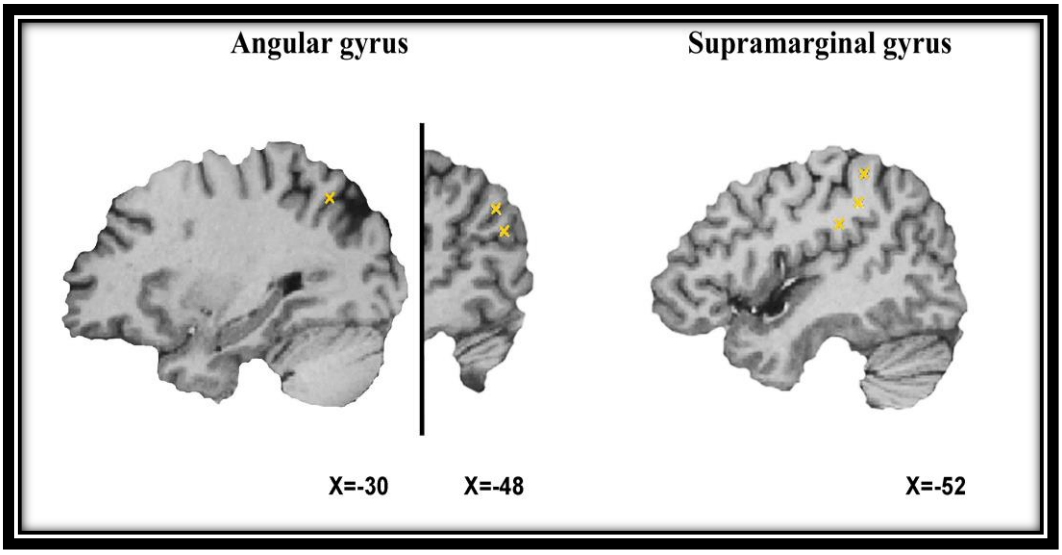

Figure 3-2: Stimulation sites in ANG and SMG. Three possible stimulation targets marked within each participant's left ANG (left panel) and left SMG (right panel) are indicated with yellow crosses.

TMS-based Functional Localization

A TMS session began with functional localization. For localization in ANG, participants performed a visual semantic categorization task that focused their attention on the meaning of the words. They were asked, "Do these two words belong to the same semantic category?" For localization in SMG, participants performed a visual rhyme judgement task designed to focus their attention on the sounds of the words. Subjects were asked, "Do these two words rhyme?" Participants were seated approximately 60 cm in front of computer display and responded using the keyboard. At the beginning of each trial, a white fixation cross

was centrally presented on the black screen for 1000 msec immediately followed by two words presented in 32pt white Helvetica font that appeared simultaneously above and below the cross and remained there for 500 msec. Participants had to make their response during a 2500 msec inter-trial interval by pressing the appropriate button using their left and right index fingers. The pairing of yes/no responses with fingers was counter-balanced across participants. All stimuli presentation and response recording was performed using MATLAB 2010 (Mathworks Inc.) and COGENT 2000 toolbox (www.vislab.ucl.ac.uk/cogent/index.html).

Each run consisted of 34 trials and lasted 1 min 35 sec. There were five different stimuli lists for each localization task. In both tasks, word stimuli (n = 160 plus 10 dummy trials in each task) ranged in length from three to eight letters and were divided into five separate lists, matched for concreteness, familiarity, written word frequency, number of letters, and number of syllables [one-way ANOVA, all $F(1, 158) < 1.7$, $p > 0.14$ for both tasks]. Concreteness and familiarity ratings were taken from the MRC Psycholinguistic database (Coltheart, 1981) while British English word frequencies came from the Celex database (Baayen & Pipenbrook, 1995). In addition, within each list trials were divided into TMS and no-TMS items equally distributed between yes and no trials and also matched across these five factors [all $t(30) < 1.8$, $p > 0.1$ for both tasks]. rTMS (10 Hz, 500 msec) was delivered on half of the trials with trial order pseudorandomized within each run. Stimulation involved five pulses starting from the onset of the stimulus and separated by 100 msec. The data from the first two trials in each run were discarded to allow participants to get past anticipating the first stimulation trials.

At the beginning of the localization procedure, the participant performed a practice run without stimulation to become familiarized with the task and to ensure that it was understood correctly. The next step was to introduce the participant to the sensation

of rTMS at the first testing site by placing the coil on the scalp such that the line of maximum magnetic flux intersected the target site. Once familiarized with the sensation, each subject went through one more practice run with concurrent rTMS. Localization then began at the first testing site using one of the five matched stimulus sets. When rTMS facilitated (i.e., shortened) RTs relative to non-TMS trials, the next site was tested. When rTMS increased RTs, the site was re-tested in order to determine whether stimulation produced consistent slowdowns at this site. All three sites were tested but only a site that produced two or more RT slowdowns during the localizer task was used as a stimulation site in the main experiment. Any numeric increase in RTs, including a few milliseconds, was qualitatively distinct from the facilitation effects typically observed at incorrect sites and therefore considered a slowdown. The important criterion here was reproducibility of the direction of the effect, rather than its magnitude. The order of testing the target sites was counter-balanced across participants. If after 10 runs, no site resulted in consistent TMS-induced slowdowns, then the experiment terminated and the participant was not tested in the main experiment.

In order to identify testing sites in terms of standard space coordinates, each participant's structural scan was registered to the Montreal Neurological Institute-152 template using an affine registration (Jenkinson & Smith, 2001). Note that all stimulation was done in native anatomical space – the standard space coordinates were computed solely for reporting purposes. In addition, for illustrative purposes a group mean structural scan was created in standard space and used as a background image when presenting the stimulation sites in order to accurately reflect the anatomical variability across subjects (Devlin & Poldrack, 2007).

Main Experiment

The main experiment included three different visual tasks: i) a synonym judgement task where participants were asked, "Do the two words mean the same thing?" (e.g.,

student – *pupil* or *soap* – *cream*); ii) a homophone judgement task where participants were asked "Do the two words sound the same?" (e.g., *brake* – *break* or *circle* – *circus*); and iii) a control task where participants were asked, "Are the two letter strings identical?" (e.g., *wrdmb* – *wrdmb* or *bxgwf* – *bnpvf*). The first two tasks were conceptually similar to the localisation tasks and shared all aspects of visual word recognition in order to provide an unbiased test of the three hypotheses. Critically, these tasks were not identical to those used in the localization procedure to avoid circularity. Rhyme and homophone judgements both focused attention on phonological aspects of written words but in different ways. The former required matching the final syllables while the latter involved matching the phonological forms of the whole words. In addition, both tasks required processing of visual word forms (hypothesis I) and grapheme-to-phoneme conversion (hypothesis II), therefore the task tested all three hypotheses. Similarly, category and synonym judgements draw participants' attention to semantic aspects of written words but required searching for either semantically related or identical pairs of words, respectively. Once again, these tasks required visual word form processing and by many accounts, also involve grapheme-to-phoneme conversion (Coltheart et al., 2001; R. Frost, 1998; Plaut et al., 1996; Van Orden, Johnston, & Hale, 1988), thereby testing all three hypotheses. In other words, both the localization and main experimental tasks were designed to be unbiased with respect to the three hypotheses. The third task served as a control condition that included orthographic processing but none of the hypothesized processes expected to engage IPL. Consonant letter strings are often used as a low level control in reading studies because they convey orthographic information but are immediately recognized as non-lexical items (Howard et al., 1992; Joubert et al., 2004; Mayall, Humphreys, Mechelli, Olson, & Price, 2001; Petersen, Fox, Snyder, & Raichle, 1990; Price et al., 1994; Pugh et al., 1996). I chose a visual matching task because it was intuitively similar to phonological matching (homophone decisions) and semantic matching (synonym decisions) and

it controlled for processes unrelated to reading including sustained attention, decision making and response selection. Across tasks, the number of *yes* and *no* responses was equal in all cases.

There were four versions of the experiment. The stimuli from each task were first divided in half creating two sets of different items to avoid repetition across the two testing sessions. Then within each set, items were divided in half again and TMS was assigned to one half of the items for one version and other half in the other version, ensuring that any effects of TMS were not simply due to item differences. The word stimuli used in the main task (96 trials plus 6 dummy trials in each task) ranged in length from 3 to 10 letters and were fully matched between TMS and no-TMS items for concreteness [$F(3, 178) = 0.71$, $p = 0.55$], familiarity [$F(3,180) = 1$, $p = 0.37$], imageability [$F(3,179) = 1.4$, $p = 0.24$], written word frequency [$F(3,186) = 0.54$, $p = 0.66$], number of letters [$F(3,188) = 0.29$, $p = 0.83$], and number of syllables [$F(3,188) = 1.6$, $p = 0.18$]. In other words, items in the phonological and semantic tasks were matched across the four versions as well as within the two versions of each task. In addition, consonant strings were matched in length to the lexical stimuli. These consisted of five letter strings that were either identical (e.g., *msxqr – msxqr*) or differed only in the middle letters (e.g., *bztgj – bwrcj*) so that matching could not rely solely on the initial or final letter. The order of the tasks within each version was counter-balanced across subjects. The order of the testing sites was counter-balanced across participants.

The experiment was presented in 12 blocks (6 per session) of 24 trials each to minimize task-switching costs. Each session was divided into two runs of three blocks with each run lasting approximately 3 min 40 sec. In between runs, subjects took a self-paced break. Each block started with a short instruction screen to remind the participant of the task. An extra *dummy* item was used for the first trial in each

block and discarded from the analysis to avoid the RT cost of switching tasks. The remaining 24 items in the block constituted the data used for further analysis. A trial began with a fixation cross displayed for 500 msec and then stimuli presentation for another 500 msec. A blank screen was then presented for a random interval between 1300 and 2300 msec, giving an average duration of 2500 msec per trial. The stimulus presentation characteristics and button press responses were identical to those used during localization. Testing started with a practise run without TMS to familiarize participants with the task requirements. It included all three tasks and provided practice in switching between them. Each word was only used once in the experiment. RTs were recorded from the onset of the stimuli and only correct responses were analysed. In all statistical analysis, median RTs were used to minimize the effects of outliers (Ulrich & Miller, 1994).

Predictions

The three hypotheses associated with IPL contributions to visual word recognition make different predictions regarding the effects of TMS. If one or both fields of the IPL store orthographic word forms then TMS to that region should affect both lexical tasks equally because both use highly familiar words. Similarly, if stimulation affects both tasks but the effect is exaggerated in the phonological task, it would indicate that the IPL plays an important role in converting orthographic into phonological information. In contrast, if ANG and SMG contribute to semantic and phonological processing, respectively, I would expect to observe a three-way interaction where rTMS to ANG affects semantic but not phonological judgements and rTMS to SMG affects phonological but not semantic judgements.

TMS

Stimulation was performed using a Magstim Rapid^2 stimulator (Magstim, Carmarthenshire, UK) and 70-mm diameter figure-of-eight coil. The stimulation

intensity was set to 55% of the maximum stimulator output and held constant for all subjects. During the localizer and main tasks, trains of five pulses (i.e., 10 Hz for 500 msec) were delivered with the first pulse administrated at the onset of the stimulus presentation and the additional pulses occurring at 100, 200, 300, and 400 msec post-stimulus onset in half of all trials. TMS and non-TMS trials were pseudorandomly ordered. The TMS frequency, intensity, and duration were well within established international safety limits (Rossi et al., 2009; Wassermann, 1998). During testing, a Polaris Vicra infrared camera (Northern Digital, Waterloo, ON, Canada) was used in conjunction with the Brainsight frameless stereotaxy system (Rogue Research, Montreal, Canada) to register the participant's head to their own MRI scan in order to accurately target stimulation throughout the experiment. All participants used an earplug in their left ear to attenuate the sound of the coil discharge and avoid damage to their hearing (Counter, Borg, & Lofqvist, 1991).

3.3 Results

Functional Localization

For each localizer task, median RTs to TMS and no-TMS conditions were compared between the main testing site and non-localized sites. In 12 out of 16 participants, TMS led to successful identification of the main testing site within both ANG and SMG. There was no single ANG or SMG site where stimulation consistently interfered with semantic or phonological processing, respectively. Instead, it varied across individuals as illustrated in Figure 3-3. Within ANG, the most common stimulation site was Seghier et al.'s (2010) dorsal ANG [7 participants], followed by ventral ANG [3 participants], and then medial ANG [2 participants]. These three locations are marked with white circles and labelled with the number of subjects

slowed by TMS at each site. The right panel shows the spread of SMG stimulation sites – individual testing sites are shown as white filled circles. The mean coordinate in standard space was [–52 –34 30] and is shown as a black filled circle.

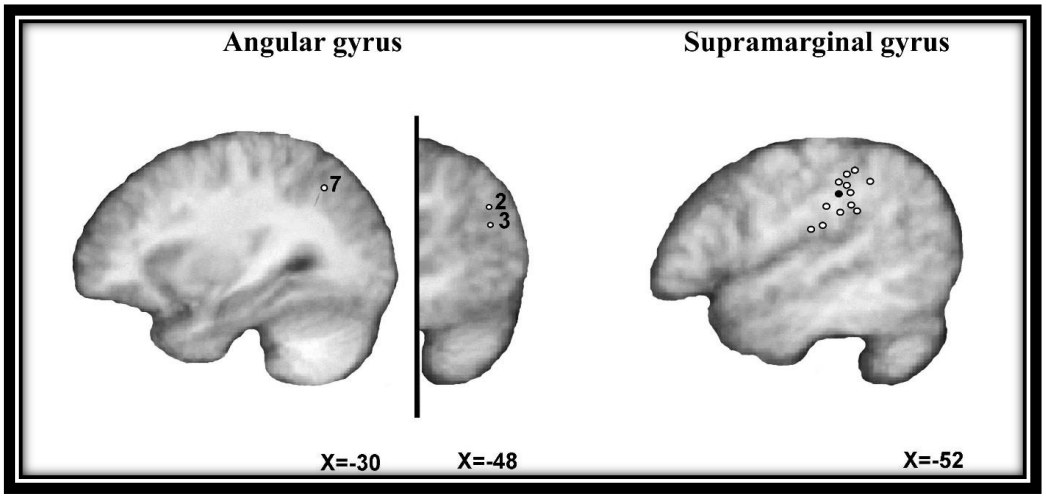

Figure 3-3: The three ANG testing sites (left panel) on the same averaged brain. 7 participants had stimulation to dorsal, 3 to ventral, and 2 to medial ANG. The final SMG testing sites for all 12 participants (right panel) in white filled circles and the mean group location in black filled circle on the averaged brain of all participants shown on a parasagittal plane. Note that three ANG testing sites had exactly the same coordinates in each participant so they are represented only by three circles.

Stimulation at each individual's ANG testing site produced a significant mean inhibitory effect of 47 msec relative to no-TMS trials [paired t-test; $t(11) = 6.4$, $p < 0.001$]. This represented a 7% slowdown after normalizing for between-subject variance in RTs (Loftus & Masson, 1994). In contrast, stimulation of the other ANG sites resulted in a non-significant 7 msec facilitation effect [paired t-test; $t(11) = 0.65$, $p = 0.53$]. To test whether this apparent difference was statistically reliable, I

conducted a 2 × 2 repeated-measures ANOVA with TMS (TMS vs. no-TMS) and Site (main testing site vs. the non-testing sites) as within-subject factors. A significant TMS × Site interaction ($F(1,11) = 21.6$, $p < 0.001$) indicated that the effect of TMS on the non-localized sites was reliably different from the main testing site. A similar pattern of localization was observed in SMG, where stimulation led to a significant 35 msec increase of RTs in the localized site [paired t-test; $t(11) = 6.5$, $p < 0.001$] and represented a 5% slowdown in RTs. In the remaining sites, stimulation produced a non-significant 4 msec decrease of RTs [paired t-test; $t(11) = 0.37$, $p = 0.72$], that was reliably different from the main testing site [TMS × Site interaction, $F(1,11) = 8.9$, $p = 0.01$]. In other words, in these 12 participants, the inhibitory effects of rTMS were highly localized with clearly different effects on the final testing site than on adjacent stimulated regions located as little as 1 cm away. Figure 3-4 illustrates this in each participant. Sites where TMS consistently slowed performance relative to no-TMS trials are marked with red crosses (i.e., the final stimulation sites) and sites that showed either faster responses or no effect of TMS are marked with yellow crosses. The standard space coordinates for all SMG testing sites are presented in Table 3-1 but because there were only three ANG coordinates and these were provided in the main text, they are not repeated here.

In the remaining 4 participants, functional localization only succeeded in one of the two regions (2 in ANG, 2 in SMG). Without a testing site in both regions, however, I was unable to continue testing these participants in the main experiment.

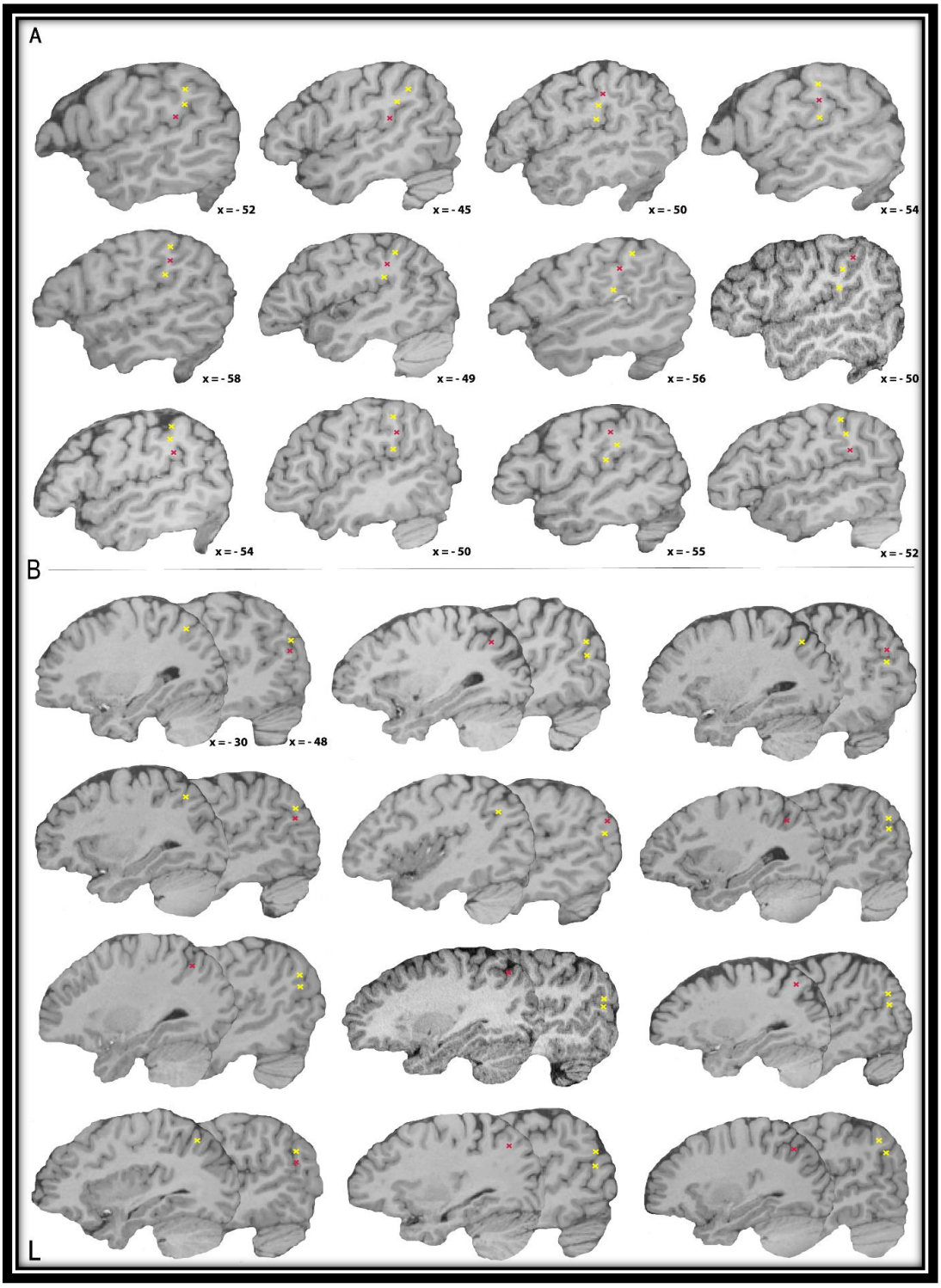

Figure 3-4: Pattern of TMS effects in A) SMG and B) ANG. A red cross corresponds to the final testing site and the two yellow crosses correspond to unsuccessfully localized sites presented on the individual brain images for each participant.

Table 3-1: The coordinates for the final testing sites and non-testing sites in the anterior SMG for each participant. The location coordinates correspond to the standard MNI 152 space.

Participant	Final testing site				Non-tested sites			
	location	coordinates			location	coordinates		
		x	y	z		x	y	z
1.	vSMG	–52	–25	18	mSMG dSMG	–52 –52	–39 –40	27 38
2.	vSMG	–45	–31	19	mSMG dSMG	–45 –45	–38 –42	28 38
3.	dSMG	–50	–30	36	mSMG vSMG	–50 –50	–26 –25	28 18
4.	mSMG	–54	–27	28	vSMG dSMG	–54 –54	–28 –27	15 39
5.	mSMG	–58	–37	33	vSMG dSMG	–58 –58	–34 –38	23 44
6.	mSMG	–49	–43	35	vSMG dSMG	–49 –49	–39 –47	25 45
7.	mSMG	–56	–32	29	vSMG dSMG	–56 –56	–27 –39	17 42
8.	dSMG	–50	–38	43	vSMG mSMG	–50 –50	–31 –32	24 34
9.	vSMG	–54	–40	25	mSMG dSMG	–54 –54	–39 –38	39 47
10.	mSMG	–50	–34	30	vSMG dSMG	–50 –50	–38 –40	21 44
11.	dSMG	–55	–34	39	mSMG vSMG	–55 –55	–33 –25	31 21
12.	vSMG	–52	–42	24	mSMG dSMG	–52 –52	–40 –37	35 46

Main Experiment

The mean accuracy across the tasks was relatively high (89%) suggesting that participants did not encounter any difficulties performing the tasks. Accuracy data were analyzed with a 2 × 3 × 2 repeated measures ANOVA with Site (ANG and SMG), Task (Semantic, Phonological, and Visual), and Stimulation (TMS and no-TMS) as independent factors. There was a significant main effect of Task [$F(2, 22) = 13.02$; $p < 0.01$], indicating that the semantic task (85%) was significantly more difficult than either phonological (92%; paired t-test, $t(47) = 4.7$, $p < 0.001$) or visual (89%; paired t-test, $t(47) = 2.7$, $p < 0.01$) tasks. However, there was no evidence that accuracy in any of the three tasks was affected by TMS since neither the main effect of TMS [$F(1,11) = 0.04$, $p = 0.85$] nor its interaction with Task [$F(2,22) = 0.2$, $p = 0.82$] was significant. No other main effects or interactions were significant (all $F < 1$).

To investigate the effects of TMS on RTs, the median RTs of each participant were also analysed with a 2 × 3 × 2 repeated measures ANOVA and the results are presented in Figure 3-5. The analysis revealed a main effect of Task [$F(2,22) = 29.3$, $p < 0.001$], indicating that responses on the semantic task (777 msec) were significantly slower than on the phonological task (723 msec; $t(47) = 5.3$, $p < 0.001$) and the visual task (636 msec; $t(47) = 10.7$, $p < 0.001$). The main effect of TMS also reached significance [$F(1,11) = 5.6$, $p = 0.04$] indicating that RTs in TMS condition (745 msec) were significantly slower than response times in no-TMS condition (734 msec). This was, however, qualified by a highly significant three way interaction [$F(2,22) = 15.8$, $p < 0.001$], indicating that TMS affected the semantic, phonological, and visual tasks differently depending on the stimulation site.

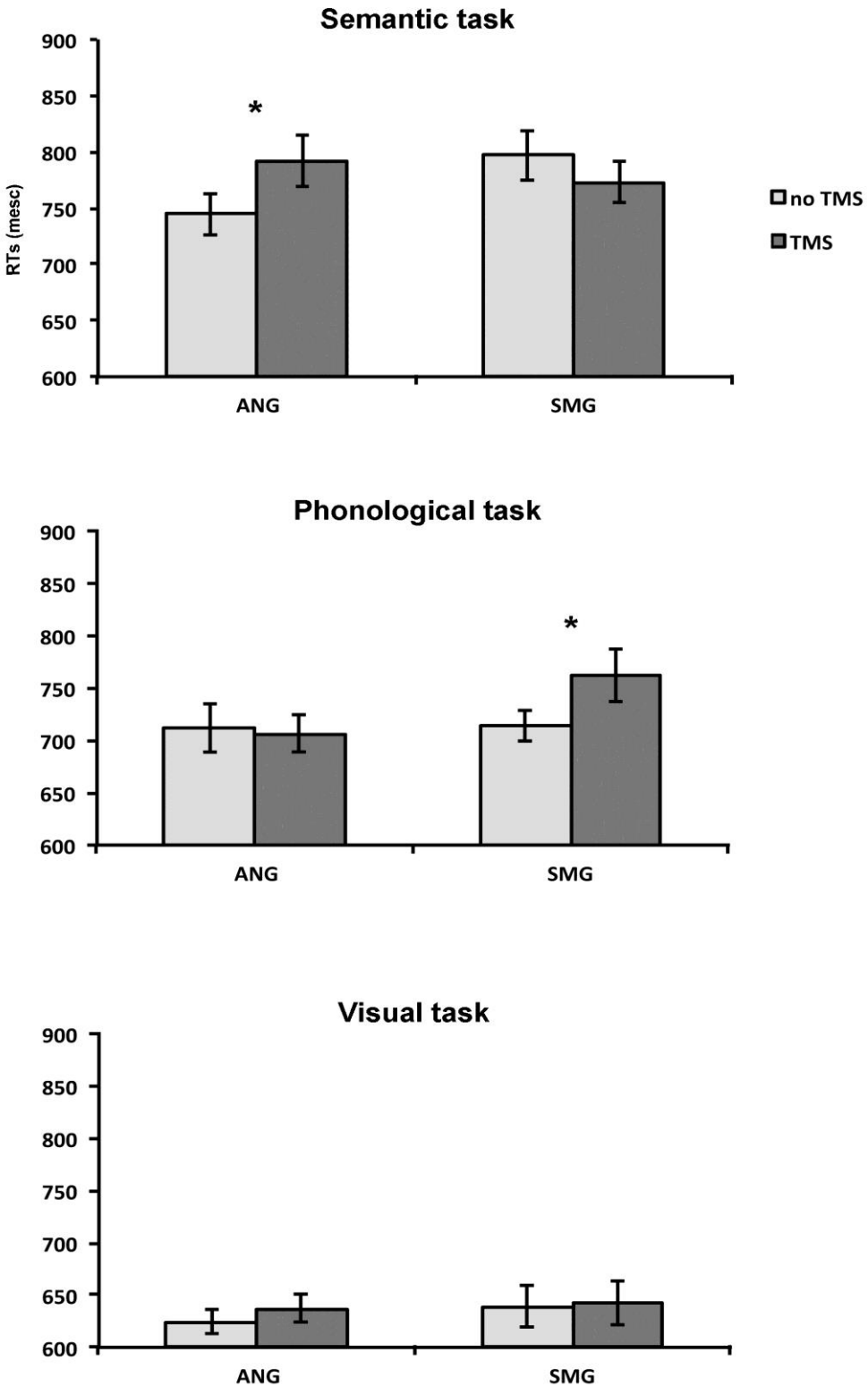

Figure 3-5: Group mean RTs for each of the three tasks in the main experiment. Error bars indicate SEM adjusted to reflect the within-subject design (Loftus & Masson, 1994). * p<0.05.

To characterize the interaction further, a 2 × 2 repeated measures ANOVA was conducted for each task with Site (ANG and SMG) and Stimulation (TMS and no-TMS) as independent factors. For the semantic task, the main effects of Site and TMS were not significant (both $F(1,11) < 1$). There was, however, a reliable interaction ($F(1,11) = 18$, $p < 0.001$) indicating that TMS had differential effects depending on the stimulation site (Figure 3-5). Specifically, stimulation to ANG slowed responses by 48 msec (paired t-test, $t(11) = 3.1$, $p = 0.01$) whereas SMG stimulation speeded responses by 24 msec (paired t-test, $t(11) = 1.8$, $p = 0.096$). The opposite pattern was observed in the phonological task where stimulation of SMG selectively slowed responses by 47 msec ($t(11) = 2.7$, $p = 0.02$) while ANG stimulation speeded responses by an average of 5 msec ($t(11) = 0.5$, $p = 0.64$). This difference was confirmed statistically by a significant Site × TMS interaction ($F(1,11) = 7.8$, $p = 0.017$) in the absence of a significant main effect for either Site ($F(1,11) = 0.8$, $p = 0.35$) or TMS ($F(1,11) = 3.9$, $p = 0.073$). Finally, TMS had no significant effects on the visual task; neither the main effects nor interaction (all $F(1,11) < 1.8$, $p > 0.2$) were significant.

3.4 Discussion

The current findings show that stimulation to the left ANG slowed semantic, but not phonological, judgements whereas stimulation to the left SMG showed the opposite pattern, selectively affecting responses in the phonological, but not semantic task. Moreover, the visual task was not significantly affected by stimulation, confirming that the effects of TMS were specific to these semantic and phonological processes. These results demonstrate a functional double dissociation within the left IPL and additionally provide evidence for a causal link between ANG and semantic processing, on the one hand, and between SMG and phonological processing, on

the other. These findings are consistent with previous studies that found TMS of SMG increased response times across a range of phonological tasks including initial sound similarity, stress assignment in multi-syllable words, and digit span (L. Romero et al., 2006), syllable counting with visually and auditorily presented words (Hartwigsen, Baumgaertner, et al., 2010), and auditory lexical decisions (Pattamadilok et al., 2010). In contrast, evidence that TMS to ANG influences semantic processing is less common. For instance, Hartwigsten et al. (2010) asked participant to judge the animacy of auditory and written words (e.g., *zebra*) and did not observe any significant effects of ANG stimulation. Other studies have used TMS to map eloquent cortex in preparation for neurosurgical intervention and reported small effects of ANG stimulation on picture naming abilities (Krieg et al., 2014; Lioumis et al., 2012; Picht et al., 2013) that may be due to semantic disruption. Thus the current findings are the first to demonstrate a clear effect of ANG stimulation on semantic processing. More generally, this double dissociation between different cortical fields of the IPL is largely inconsistent with claims that the region stores the visual forms of words or that the region is responsible for converting orthographic information into phonological codes, but was predicted by the third hypothesis.

According to the original Dejerine (1891) hypothesis, stimulation of ANG should interfere with both the semantic and phonological tasks by temporarily disrupting the ability to match visual input with the stored images of words. Instead, ANG stimulation selectively affected the semantic task without significantly affecting the phonological task. Clearly, these results are not compatible with this hypothesis even if SMG, rather than ANG, was the site of stored visual word forms.

The relation between the data and the second hypothesis is less clear, in part because the interpretation is theory-dependent. Many theories of visual word

recognition assume that access to a word's meaning is only possible by first accessing its phonology (R. Frost, 1998; Van Orden et al., 1988). If correct, then the current results are incompatible with this hypothesis because both tasks required grapheme-to-phoneme conversion. Alternately, some theories suggest that semantic information is available directly from the written word without accessing phonology (Seidenberg & McClelland, 1989; Ziegler, Benraïss, & Besson, 1999), although they acknowledge that in normal, healthy adults semantic and phonological information would be accessed in parallel and moreover, that these processes interact. According to these accounts, the phonological task would *require* grapheme-to-phoneme conversion but even the semantic task would involve converting spelling-to-sound and consequently disruption of this process should still have an impact on reaction times. If these procedures were associated with the SMG (Jobard, Crivello, & Tzourio-Mazoyer, 2003; Law et al., 1991; Roux et al., 2012), this would be consistent with the fact that TMS to SMG significantly slowed responses in the phonological task but inconsistent with the finding that TMS actually facilitated responses in the semantic task, albeit non-significantly. It is also worth noting that this hypothesis would only explain one half of the double dissociation seen here.

A wide range of neuroimaging studies implicate SMG in phonological processing (Booth et al., 2004; Petersen et al., 1988; Raizada & Poldrack, 2007; Seghier et al., 2004; Yoncheva, Zevin, Maurer, & McCandliss, 2010; Zevin & McCandliss, 2005), consistent with the current TMS findings. By this account, reading tasks that engage SMG do so because they require some form of phonological processing, not because grapheme-to-phoneme conversion procedures are stored here. Precisely what aspects of phonological processing are being computed in SMG are, however, open to debate. Studies of speech comprehension, for instance, typically do not show SMG activation (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009), even

though phonology plays a central role in speech perception. Instead, the region seems to be engaged by more demanding phonological tasks such as rhyme (Petersen et al., 1988; Yoncheva et al., 2010), syllable (Devlin et al., 2003; Price et al., 1997), or phoneme judgments (Raizada & Poldrack, 2007; Zevin & McCandliss, 2005). More specifically the SMG may be important for covertly articulating and monitoring inner speech (Pattamadilok et al., 2010; Price, 2012). This ability is a core component of verbal working memory (Baddeley, 2003) and strongly associated with SMG (Buchsbaum & D'Esposito, 2008; Paulesu et al., 1993). The SMG is anatomically well situated for this role. Given its proximity to the caudal parabelt fields of the auditory cortex (Hackett, Preuss, & Kaas, 2001; Sweet, Dorph-Petersen, & Lewis, 2005), SMG is likely to encode some form of higher order auditory information. In addition, there are reciprocal connections that link SMG to ventral premotor cortex and pars opercularis (Catani, Howard, Pajevic, & Jones, 2002; Catani & Jones, 2005; Makris et al., 2009; Martino et al., 2013; Petrides & Pandya, 2009; Rushworth, Behrens, & Johansen-Berg, 2006), two regions involved in articulatory motor planning (Price, 2010). In particular, neurons in ventral premotor cortex control oro-facial movements of the lips, tongue and larynx, playing an important role in articulation (Petrides, Cadoret, & Mackey, 2005; M. I. Sereno & Dick, 2008). These reciprocal connections between ventral premotor cortex/pars opercularis and SMG may form a processing loop for acting on reproducible sound patterns that would provide a simple resonance circuit for temporarily storing these patterns (Botvinick & Plaut, 2006; McClelland & Elman, 1986). Indeed, studies of verbal working memory commonly implicate these regions (Buchsbaum & D'Esposito, 2008; Koelsch et al., 2009; Paulesu et al., 1993) and TMS to either region has a disruptive effect on phonological judgements that require some form of monitoring internal speech (Gough et al., 2005; Hartwigsen, Baumgaertner, et al., 2010; Nixon et al., 2004; Pattamadilok et al., 2010). This hypothesis is also consistent with a very recent TMS experiment in which Deschamps et al. (2014)

demonstrated that contributions of the anterior SMG to phonological processing are more specific to verbal working memory than phonological encoding. In their experiments, rTMS had no effect on the phonological task that minimized working memory demands (i.e., same/different sonority judgements) but it significantly affected performance on the phonological task that required verbal working memory (i.e., sonority n-back task), although in both tasks phonological complexity was manipulated. The authors argued that their findings were consistent with the claim that SMG is involved in storing phonological representations rather than processing phonological features of words. Consequently, I suggest the most likely explanation for the current SMG findings is that stimulation interfered with participants' ability to covertly articulate and monitor their inner speech, which was critical for the phonological tasks and irrelevant to the semantic tasks.

A different explanation is necessary to account for the fact that ANG stimulation selectively affected synonym judgements presumably by interfering with some aspect of semantic processing. Functional neuroimaging studies consistently demonstrate ANG involvement in semantic processing (Binder et al., 2009; Bonner, Peelle, Cook, & Grossman, 2013; S. J. Frost et al., 2005; Mummery et al., 1998; Noonan, Jefferies, Visser, & Lambon Ralph, 2013; Seghier et al., 2010; Vandenberghe et al., 1996), although there is a debate regarding its specific contribution. One account suggests that ANG's role in the anatomically distributed semantic system is to guide the selection of relevant semantic information (Jefferies & Lambon Ralph, 2006). Jefferies and Lambon Ralph argue that this function constitutes a component of semantic cognition that requires a combination of semantic representations and executive control processes to direct activation in a task- and time-appropriate fashion. Their investigation of patients with semantic dementia caused by gradual tissue degradation and post-stroke semantic aphasia led them to associate semantic *representations* with the bilateral anterior temporal

lobe and executive *control processes* with a number of distributed brain regions within the left hemisphere which encompass ANG but exclude the anterior temporal lobe. This regional dissociation of semantic processes became apparent after a direct comparison of semantic and stroke dementia patients on a battery of semantic tasks (Jefferies & Lambon Ralph, 2006; Jefferies, Patterson, & Lambon Ralph, 2008; Jefferies, Sage, & Lambon Ralph, 2007). The results reflected degraded knowledge in case of semantic dementia and deregulated semantic control in case of patients with stroke-induced aphasia. Although, the two groups of patients showed a similar degree of impairment on the same range of verbal and nonverbal semantic tasks, their impairments were qualitatively different for a number of reasons. First, in contrast to semantic dementia patients, patients with semantic aphasia showed significant consistency in their performance within different versions of the same task (e.g., semantic association judgements for words and pictures) while their performance was considerably inconsistent between tasks posing different semantic control demands (e.g., semantic association judgements vs. word-picture matching). In other words, aphasic patients were unable to consistently retrieve information about a particular concept. The lack of consistent performance across tasks was interpreted as a result of impaired executive processes rather than a loss of amodal semantic knowledge. Second, patients with semantic dementia showed familiarity/frequency effects on their performance supporting the idea that these effects are characteristic to semantic dementia in a way that highly familiar/frequent words are less sensitive to degradation than the low familiarity/frequency words (Rogers, Lambon Ralph, Hodges, & Patterson, 2004). Such effects were not present in patients with semantic aphasia supporting the fact that their deficit is of a different nature than degradation of semantic information. Instead, the ability of patients with semantic aphasia to make semantic associations was based on how readily the relevant associative dimension could be discerned and competitors rejected. For instance, only patients with semantic aphasia made

associative errors during picture naming (e.g., providing the word *nut* for a picture of a squirrel). The occurrences of such errors suggested that the semantic information is preserved in those individuals but cannot be appropriately selected in the context. Finally, picture naming was improved by phonemic cues in semantic aphasics which indicated that they retained semantic knowledge but could not retrieve it easily because of their difficulties in selection of the relevant information. The positive effects of cueing seemed to enhance self-generated semantic control. Overall, data from the direct comparison of semantic abilities in semantic dementia and semantic aphasia led to the conclusion that regions such as ANG are involved in the cognitive control of semantic knowledge, rather than a store of this knowledge per se. This has been further supported by studies which experimentally manipulated the nature and the degree of the semantic control demands of various verbal and nonverbal conceptual tasks (Corbett, Jefferies, & Lambon Ralph, 2011; Noonan, Garrard, Jefferies, Eshan, & Lambon Ralph, 2013; Noonan, Jefferies, Corbett, & Lambon Ralph, 2010).

In contrast, another account claims that ANG is specifically involved in representational aspects of semantic memory (Binder & Desai, 2011), rather than aspects of semantic control. This account is based on theories which propose that semantic memory requires two different types of brain regions. The first type includes different sensory and motor areas of the brain where modality-specific feature representations of semantic concepts are grounded. The second type includes heteromodal association regions where the semantic information from modality-specific areas converges during conceptual tasks (Barsalou, 2008; Damasio, 1989; Martin, 2007). Binder and Desai proposed that ANG constitutes one of the higher-level heteromodal association regions where semantic information is integrated. The main argument supporting this hypothesis is that ANG has been consistently shown to be involved in semantic processing regardless of task type

and in fact, it has been identified as the most commonly reported region in semantic memory studies in recent meta-analysis reviews (Binder et al., 2009; Vigneau et al., 2006). In addition, Binder and Desai argued that the level of activation in ANG seems to reflect the amount of semantic information that is successfully retrieved from the stimuli. This indicates that semantically richer stimuli evoke larger activations in ANG than stimuli with a smaller amount of semantic information. For example, functional neuroimaging studies have shown stronger ANG responses to words than to matched pseudowords (Binder et al., 2009), to high-frequency relative to low-frequency words (Graves et al., 2010), to concrete relative to abstract words (Binder, Westbury, McKiernan, Possing, & Medler, 2005) and to meaningful relative to meaningless sentences (Humphries, Binder, Medler, & Liebenthal, 2007). In line with the claim that ANG is involved in heteromodal conceptual processing is a recent fMRI study done by Bonner and colleagues (2013) who examined the processing of concepts in four semantic categories that varied on their sensory-motor feature associations (sight, sound, manipulation, and abstract). They found that ANG, as a locus of integrated concept representations, was activated across all categories regardless of their modality-specific features. Overall, these findings support the claim that semantic memory relies on a distributed system that involves a heteromodal component located in ANG and modality-specific feature representations in sensory and motor areas. To be even more specific, Binder and Desai hypothesized that ANG is most likely involved in representation of event concepts (e.g., *birthday party*) which refer to temporal and spatial interaction of concrete semantic representations (e.g., *cake*, *presents*, *lighting candles*, *eating*), rather than their individual entities per se. This hypothesis was formulated considering the cortical neighbourhood of ANG which makes the region a plausible candidate for such role. For instance, ANG has been shown to be bounded by dorsal attention networks that are important for spatial cognition, anterior parietal regions associated with representation of action and posterior temporal regions

contributing to movement perception (Kravitz, Saleem, Baker, & Mishkin, 2011). In addition, this hypothesis is consistent with the recent evidence showing involvement of ANG in retrieval of episodic memories and in understanding theory-of-mind stories which leads to the hypothesis that the region has a function in retrieving event memories through the mental construction of the scenes (Van Overwalle, 2009).

It is important to note that phonological or semantic processing is only one of several functions that SMG or ANG contributes to, respectively. For instance, SMG is also involved in making visually guided hand actions (Binkofski, Buccino, Zilles, & Fink, 2004; Price, 2010; Rushworth, Krams, & Passingham, 2001) and in spatially localizing auditory stimuli (Lewald & Ehrenstein, 2001; Renier et al., 2009) while ANG is also involved in number processing (Göbel et al., 2001; Grabner et al., 2009) and in visuospatial navigation (Spreng, Mar, & Kim, 2009). In other words, the apparent functional specificity of the SMG for phonological processing and ANG for semantic processing is limited to a very restricted context – namely when processing linguistic information.

It is also worth introducing a word of caution here regarding the anatomical specificity of the current findings. Although I have discussed them in terms of the two major subdivisions of the IPL, namely SMG and ANG, the results are actually more focal than that. A great advantage of using TMS as an investigative tool is its spatial precision, which is approximately 5-10 mm (Brasil-Neto et al., 1992; Ravazzani et al., 1996; Thielscher & Kammer, 2002; Toschi et al., 2008). In other words, although the basic pattern of SMG stimulation slowing phonological, but not semantic, processing while ANG stimulation slowed semantic, but not phonological, processing the specific stimulation sites varied between participants. Moreover, within a participant, different sites within a region responded differently during

localization (see Figure 3-4). As a result, I cannot rule out the prospect that within a region it may be possible to find two different sites that show this same pattern. Instead, all I can conclude is that the current findings are consistent with functional and structural neuroimaging studies that suggest these two regions broadly serve different functions (Göbel et al., 2001; Nelson et al., 2010; Rushworth, Johansen-Berg, Göbel, & Devlin, 2003) by virtue of participating in separable neuronal circuits (Caspers et al., 2011; Rushworth et al., 2006).

Finally, the results show considerable variability in the exact localization of testing sites within ANG and SMG across participants. Although Seghier et al. (2010) identified three separable regions within ANG involved in distinguishable semantic processes (i.e., semantic associations, search for semantics, and conceptual identification), these appear to be trends present in groups of participants rather than predictive of individuals. I observed considerable inter-subject variability in the precise location within ANG where TMS disrupted semantic processing and also within SMG where it affected phonological processing, similar to variability in the localization of language functions described by Ojemann et al. (1989) in neurosurgical patients. In both the neurosurgical work and the current study, the disruptive effects of stimulation were very focal (≤ 1 cm) and certainly did not extend to cover a significant portion of a macro-anatomical region (e.g., SMG), suggesting that large activations in functional neuroimaging studies can be somewhat misleading. Clearly they demonstrate a reliable overall pattern of activation at a fairly large scale (centimetres) but these hide considerable inter-subject variability in terms of the precise anatomical fields. In other words, it is important to recognize that the results of group imaging studies represent a spatial averaging that may not be predictive in individuals. This, presumably, is why using published *peak coordinates* to guide TMS studies can be problematic and require larger numbers of participants than using an individualized functional localization method (Sack et al.,

2009). More generally, it means that descriptions linking function to macro-anatomical labels may be broadly correct on aggregate, but not in detail.

To conclude, this chapter showed that the two main subdivisions of the left IPL make distinct functional contributions to visual word recognition. On average, ANG plays crucial role in semantic processing while SMG is necessary for phonological processing during reading. It is worth stressing, however, that my results apply to only specific parts of these large anatomical regions and moreover, that the precise location varies somewhat from person to person. Nevertheless, the findings are consistent with the pattern seen in functional neuroimaging studies and help to demonstrate that these activations appear to be causally linked to semantic and phonological processing in ANG and SMG, respectively.

In addition, the current experiment demonstrated that TMS-based functional localization was successful in identifying an appropriate stimulation sites as demonstrated by a significant group slowdown of 47 msec in SMG and 48 msec in ANG for the main task. However, these slowdowns were only present in 9 out of 12 (75%) participants in SMG and 11 out of 12 (92%) participants in ANG (mean: 83%). In comparison to the number of participants showing TMS effect in the main experiment following fMRI-based functional localization presented in Chapter 2, it is apparent that neither fMRI- (77%) or TMS- (83%) based localization methods were 100% successful in producing TMS effects. Moreover, a comparison of the success rates did not show any significant differences between the two methods ($\chi^2 = 0.053$, df = 1, p = 0.82) indicating comparable degree of efficiency/effectiveness.

It is a novel finding that highly effective individual customization of localization is not only possible with fMRI but also with TMS. Previous comparisons of localization methods (Sack et al., 2009; Sparing et al., 2008) did not test TMS-based functional localization even though this approach also accounts for variability in functional

anatomy across individuals. Interestingly, however, there were no significant differences in efficacy between fMRI- and TMS-based localizations. Success rates were relatively high for both methods although there were always participants who did not show a TMS effect despite *successful* functional localization. Failure in producing stimulation effects was expected to be more prevalent in experiments that used fMRI-based localization since TMS and fMRI have different spatial biases. Obviously, this should not be an issue when TMS is used for localization since the spatial bias is identical across localization and testing. While fMRI was slightly less successful than TMS (77 vs. 83%), the difference was not significant. This may indicate that the fMRI spatial biases are relatively modest and within the spatial resolution of TMS in the majority of participants.

Perhaps surprisingly, though, neither fMRI nor TMS were 100% effective despite the fact that only successfully localized sites were tested. There are a number of possible explanations for this. For fMRI, differences in spatial biases between fMRI and TMS may be partially to blame (Maccabee et al., 1990; Turner, 2002). These, however, cannot explain why TMS-based functional localization occasionally failed to produce robust effects of TMS in the main experiments. There are a number of potential methodological reasons for lack of TMS effect in the main experiment. One obvious possibility is inaccurate coil placement due to a change in registration between localization and testing. Once the registration is performed with neuronavigation system, it assumes that the registration stays unchanged throughout the duration of testing. Accidental bumps or adjustments, however, can occur without being noticed and have undesirable effects on the registration and thus the results. Similarly, small movements of the coil during testing that affect either its location or orientation can also adversely impact the results. For example, if the coil placement and/or orientation differed between the localization and main task in some participants, this could easily result in a failure to produce a TMS effect

in the main task. A final methodological issue is the use of two different stimulating coils in a testing session. To avoid coil overheating, it was necessary to occasionally replace one coil with a fresh (i.e., cool) coil in between localization and testing. Although they were always the same type (i.e., 70-mm figure-of-eight coils made by MagStim), it may not be correct to assume that they were completely identical. This is because the coils are handmade and thus subtle differences in their internal structure may lead to slight differences in the actual peak intensity or its spatial distribution despite an accurate registration. In addition to these methodological issues, there is also a potential theoretical explanation of the cases in which TMS did not show effects in the localized site.

A critical assumption necessary for successful TMS-based functional localization is that the localizer task taps into the same processing demands as the main task. For instance, rhyme and homophone judgments both required some form of phonological processing which was assumed to consistently engage the anterior SMG. Indeed, in aggregate this assumption appears to be borne out by the results. It is possible, however, that individual participants may not have used precisely the same phonological strategies for both tasks. If so, then TMS may impact rhyme judgements during localization without affecting homophone judgements in the main task.

Overall, these results showed that both fMRI and TMS localizations performed on individuals lead to a high success rates in producing robust TMS effects. The two methods offered comparable level of effectiveness, although neither reached 100% in any of the cases. Clearly, either method is preferable to localization procedures that follow a *one-size-fits-all* approach (e.g., the 10-20 system, scalp coordinates, or standard space coordinates). By taking into account between-subject variability in functional anatomy, both fMRI- and TMS-based functional localization optimize the

likelihood of stimulating the *correct* target site to find an effect of TMS. Given that neither method is fully accurate, the optimum choice of localization procedure depends on additional constraints posed by each TMS experiment. TMS-based localization is cheaper in time and resources than fMRI; it maintains the same spatial bias between localization and testing; and can be typically done in a single testing session, minimizing the risk of functional variability of time (Penfield & Boldrey, 1937). Even so, fMRI-based localization may be a better option in certain circumstances. For instance, when localization information is available as a result of an fMRI experiment run for a different reason, it makes sense to use that information and avoid exposing participants to unnecessary additional TMS. Similarly, fMRI can be a good solution when rTMS to a target area results in discomfort or pain due to unavoidable stimulation of peripheral nerves or muscles. In such a case, the additional stimulation necessary to localize the site may preclude participants from successfully finishing the entire experiment. Finally, if there is very little prior information available to constrain the anatomical search space during TMS-based localization, fMRI may be a more suitable option. If there was no prior information about what part of ANG was involved in semantic processing, then searching the entire region with TMS during localization would exceed the safety guidelines for stimulation during a single session, even without running the main experiment (Rossi et al., 2009). It is clear, then, that practical considerations such as resources, comfort and safety help to determine which method is most appropriate for any given TMS experiment.

4. Experiment 2: Temporal Dynamics of Supramarginal Gyrus Involvement in Phonological Processing during Reading

4.1 Introduction

The previous chapter demonstrated that the supramarginal gyrus (SMG) makes a necessary contribution to phonological processing during normal reading. This finding complemented previous neuroimaging findings suggesting preferential SMG involvement in phonological processing based on observations of selectively increased activation in this region for phonologically demanding reading tasks. To further improve our understanding of SMG's role in reading, we need to establish the timing of its involvement. EEG and MEG constitute the most commonly used methods to measure the time course of neural processing because of their outstanding temporal resolution. In fact, a vast number of EEG and MEG studies have been conducted to assess the time course of phonological processing in the brain during visual word recognition (Ashby & Martin, 2008; Ashby, Sanders, & Kingston, 2009; Barber, Vergara, & Carreiras, 2004; Barnea & Breznitz, 1998; Bentin et al., 1999; Braun, Hutzler, Ziegler, Dambacher, & Jacobs, 2009; Carreiras, Vergara, & Barber, 2005; Grainger, Kiyonaga, & Holcomb, 2006; Hutzler et al., 2004; Kramer & Donchin, 1987; R. L. Newman & Connolly, 2004; Niznikiewicz & Squires, 1996; Polich, McCarthy, Wang, & Donchin, 1983; Proverbio, Vecchi, & Zani, 2004; Rugg, 1984b; Rugg & Barrett, 1987; Salmelin et al., 1996; Simon, Bernard, Largy, Lalonde, & Rebai, 2004; Wheat et al., 2010). EEG and MEG studies have not, however, led to a clear conclusion about the time window during which phonology is activated. Instead, a range of different time windows has been suggested with some suggesting early (e.g., Ashby et al., 2009; Braun et al., 2009; Wheat et al., 2010) while others suggest late onset of phonological activation (e.g., Bentin et al., 1999; R. L. Newman & Connolly, 2004; Polich et al., 1983; Rugg & Barrett, 1987). In addition, the temporal activation of phonological processing has been rather poorly localized by the EEG and MEG studies. The majority associated timing information to extensive parts of the brain (e.g., Braun et al., 2009; Grainger

et al., 2006; Rugg, 1984b), rather than localizing it to particular brain regions. This leaves the question about the dynamics of SMG's contribution to phonology unanswered and awaiting investigation using techniques such as chronometric TMS that provide a combination of a good spatial and temporal resolution.

Studies that mapped the spatio-temporal evolution of cortical activity during passive word reading suggest that SMG activity begins around 200 msec after the onset of the word and lasts for approximately another 200 msec. For instance, a study by Pammer and colleagues (2004) using MEG found activation in SMG from 200 to 400 msec post-stimulus onset that was accompanied by co-activation of other brain regions such as ANG or posterior middle temporal gyrus. Similarly, Salmelin and colleagues (1996) demonstrated that activation during passive word viewing spreads throughout the temporo-parietal cortex after 200 to 400 msec post-stimulus onset. This activation, however, was only observed in healthy readers but not in dyslexics, leading the authors to associate temporo-parietal activation with phonological processing. Although this is one plausible interpretation of activity in SMG, it certainly does not provide a strong evidence of phonological processing.

The first event-related potential (ERP) analyses of EEG data designed to investigate the timing of phonological processing demonstrated relatively late onsets during reading (e.g., Bentin et al., 1999; R. L. Newman & Connolly, 2004; Polich et al., 1983; Rugg, 1984b; Rugg & Barrett, 1987). Those studies were most commonly performed on the recordings of the electric brain signals during the rhyme judgments performed on two visually presented words or nonwords (e.g., Polich et al., 1983; Rugg & Barrett, 1987) with the majority reporting phonological effects between 300 and 500 msec after the appearance of the visual stimuli. More recent studies using different task manipulations designed to distinguish phonological processing from other language processes have also shown phonological effects between 300 and

500 msec (e.g., Bentin et al., 1999; R. L. Newman & Connolly, 2004). For example, Newman and Connolly (2004) measured the timing of phonological processing during a silent reading task in which participants read sentences with highly predictable endings (e.g., *The gambler had a streak of bad luck*). By manipulating the phonological and semantic appropriateness of final item, phonological effects were isolated from semantic and orthographic effects and were identified as occurring approximately 400 msec after presentation of the target word. The anatomical location of the effect, however, was not provided. In another example, Bentin and colleagues (1999) designed a study in which they measured the neural electrical activity while participants read lists of words and pseudowords. Phonological processing induced two distinct ERP peaks. One was recorded at latency around 320 msec post-target onset and was bilaterally distributed over the temporo-parietal electrodes while the second occurred around 350 msec over left fronto-temporal electrodes. In this study, localization of the phonological effect was provided but included very extensive areas across different lobes. Overall, these studies demonstrated that phonological processing occurs between 300-400 msec after the onset of the visual word but anatomical location of the temporal effect remained unclear.

Other ERP and MEG studies have suggested that phonological processing may in fact begin earlier than 300 msec post-target onset (Ashby & Martin, 2008; Ashby et al., 2009; Barber et al., 2004; Barnea & Breznitz, 1998; Braun et al., 2009; Carreiras et al., 2005; Grainger et al., 2006; Hutzler et al., 2004; Kramer & Donchin, 1987; Niznikiewicz & Squires, 1996; Proverbio et al., 2004; Salmelin et al., 1996; Simon et al., 2004; Wheat et al., 2010). One of the first studies to suggest an early onset of phonological processing was Karmer and Donchin (1987) who reported an EEG study in which phonological differences between word pairs elicited an ERP component that peaked within 260 msec from the stimulus onset with the strongest

signal recorded over posterior-central electrodes. Similar results were obtained by a number of subsequent studies. For example, Grainger and colleagues (2006) measured ERPs to examine the time course of phonological priming in a masked priming paradigm and observed that phonological priming started to affect ERP components around 250 msec post-target onset with the effect lasting approximately another 200 msec. The phonological effect was initially significant only at frontal sites but gradually spread across the scalp to include frontal, middle and posterior sets of electrodes. Niznikiewicz and Squires (1996) demonstrated even earlier phonological effects, around 200 msec post-target onset, elicited by incorrect relative to correct homophones presented at the end of a sentence. A few studies have also found that processing of information about the initial syllable of a word during visual word recognition begins earlier than 300 msec. For instance, Barber et al. (2004) and Hutzler et al. (2004) observed syllable frequency effects starting around 190-200 msec post-target onset. Ashby and Martin (2008) observed syllable congruency effects that began around 250 msec post-target onset while Carreiras and colleagues (2005) reported syllable congruency effects beginning even earlier, around 180 msec post-target onset. These early syllable effects were mainly recorded over the frontal areas of the brain in all these studies.

A final set of ERP and MEG studies have demonstrated phonological effects occurring as early as 100 msec after stimulus onset. Using a visual lexical decision task, Braun et al. (2009) showed that ERPs to pseudohomophones (e.g., *roze*) differed from well-matched spelling controls (e.g., *rofe*) as early as 150 msec after stimulus onset. The highest activity for pseudohomophones was recorded in the right fronto-temporal area and the left temporo-parietal area. Similarly, Wheat et al. (2010) used MEG to investigate the spatio-temporal pattern of brain responses induced by a masked pseudohomophone priming task. They found that phonological processing induced activation in left inferior frontal gyrus and precentral gyrus within

100 msec after the onset of the target word. In addition, Ashby et al. (2009) found that sub-phonemic features of visual words are activated within 80 msec post-stimulus onset in their masked priming experiments (ERP/MEG). Sereno and colleagues (1998; 2003) have argued compellingly that lexical processing, which includes phonological and semantic processing, must happen rapidly within the first 100-150 msec given that the average duration of an eye fixation on a single word during natural reading is around 250 msec. Consequently, studies which suggest the timing of phonological processing is around 300-500 msec may be inaccurate given that during reading the eyes have already moved onto the next word by 400 msec.

To conclude, the majority of ERP research has located phonological processing between 300-500 msec (Bentin et al., 1999; R. L. Newman & Connolly, 2004; Polich et al., 1983; Rugg, 1984b; Rugg & Barrett, 1987) although there is increasing evidence that it begins earlier than 300 msec (Ashby et al., 2009; Braun et al., 2009; Kramer & Donchin, 1987; Niznikiewicz & Squires, 1996). Still others argue that phonological processing must, in fact, be completed within 200 msec (S. C. Sereno & Rayner, 2003; S. C. Sereno et al., 1998). There is a possibility that the timing of phonological processing is related to the choice of task in those ERP experiments. It appears that ERP studies which showed that phonological processing happens between 300-500 msec used explicit tasks while those studies which showed phonological processing occurring earlier than 300 msec used implicit tasks. Considering however the evidence from the eye-tracking experiments which show that fixation on a single word lasts only about 250 msec during natural reading (Rayner, 1993; Rayner, Slowiaczek, Clifton, & Bertera, 1983), it seems plausible that phonological processing occurs much earlier than the majority of ERP and MEG studies indicate. In addition, neither the ERP nor MEG studies have provided any reliable evidence for the temporal contribution of SMG to phonological processing.

The majority of ERP and EEG studies have not specified the cortical generators of the phonological signals (e.g., Ashby et al., 2009; Niznikiewicz & Squires, 1996; Polich et al., 1983) or they have simply described very broad brain areas as a locus of the signal (e.g., Braun et al., 2009; Grainger et al., 2006; Rugg, 1984a). Consequently, the current experiment used chronometric TMS delivered to the SMG to investigate the time course of SMG involvement during phonological processing of written words.

4.2 Methods

Participants

Forty right-handed, monolingual native English speakers volunteered to participate in this study, and of these thirty two (19F, 13M; aged 18-41, mean = 25) were included in the main experiment. For the other eight the functional location procedure failed to identify a region of SMG for testing in the main experiment. All participants were neurologically normal, with no personal or family history of epilepsy. In addition, none had any form of dyslexia according to self-reports. Each person provided informed consent after the experimental procedures were explained and subjects were paid for their participation. The experiment was approved by the University College London Research Ethics Committee.

Experimental Procedures

Like the previous experiment, there were two testing sessions. The first involved a 30 minute visit to BUCNI in order to acquire a T1-weighted structural MRI scan used to anatomically identify the left SMG in each participant. The second session occurred two to ten days later and involved TMS-based functional localization and the main chronometric experiment which together lasted approximately one hour.

Functional localization used the same stimuli and procedures to identify stimulation sites in SMG as described previously (Chapter 3). The main chronometric experiment used the same tasks as those used in the rTMS experiment presented in Chapter 3 but there were important differences in both stimuli matching and in the delivery of TMS.

The three tasks were homophone judgments (phonological), synonym judgments (semantic) and consonant letter string matching (visual). There were 105 trials per task. The tasks were presented in blocks of 22 trials to minimize task-switching costs. Following a short instruction screen to remind the participant of the task, the first two trials in each block were dummy items and discarded from the analyses to exclude the RT cost of switching tasks. The remaining 20 items in the block constituted the data used for further analysis. A trial commenced with a fixation cross displayed for 500 msec, followed by two letter strings presented above and below the fixation cross for another 250 msec. A blank screen was then presented for a random interval between 1300 and 2300 msec, giving an average duration of 2500 msec per trial. The experiment was divided into three runs of five blocks, each lasting approximately 5 min. In between runs, subjects took a self-paced break. The order of tasks was counter-balanced across participants. The word stimuli (200 trials plus 10 dummy trials) ranged in length from three to ten letters and were matched across the homophone and synonym tasks for concreteness, familiarity, written word frequency, number of letters, and number of syllables (all $t(198) < 1.66$, $p > 0.11$). In addition, the consonant strings in the non-lexical task were matched in length to the lexical stimuli. Within each task, the items were divided into five lists, again matched for all factors (all $F(4,95) < 2.1$, $p > 0.1$). Then, the lists were paired with each of the five time windows such that the lists occurred with equal frequency within each time window across participants.

A double pulse of TMS was delivered on every trial, at one of five different timing conditions. Pulses occurred at either 40 and 80 msec, 80 and 120 msec, 120 and 160 msec, 160 and 200 msec, or 200 and 240 msec post-stimulus onset. All the time windows were chosen before 250 msec post-stimulus onset in order to successfully identify the onset of phonological processing, especially considering findings of Sereno and her colleagues (S. C. Sereno & Rayner, 2003; S. C. Sereno et al., 1998) who convincingly demonstrated that phonological processing must begin early and be completed within 250 msec after word presentation. The TMS timings were not randomly distributed; instead, they were ordered in either an ascending or descending staircase in sets of four trials (Figure 4-1). For instance, the first four trials might have pulses delivered at 40/80 msec, while the next four were at 80/120, etc. such that all 20 trials in the block had TMS delivered at one of the five timing conditions. For the following block (i.e., the next task), the timing went in the opposite direction (i.e., 4 × 200/240 followed by 4 × 160/200, etc). The aim of this procedure was to avoid any late stimulation trials (e.g., 160/200) randomly following early trials (40/80), because during pilot studies there was some concern that participants were implicitly waiting for the TMS pulse before responding, and thus artificially inflating RTs on those trials. With the current staircase method there was no evidence that participants waited for the TMS before responding. Indeed, subjects reported that they were not aware that stimulation onsets differed. In contrast, when chronometric timings are delivered randomly subjects are typically aware of the different timings.

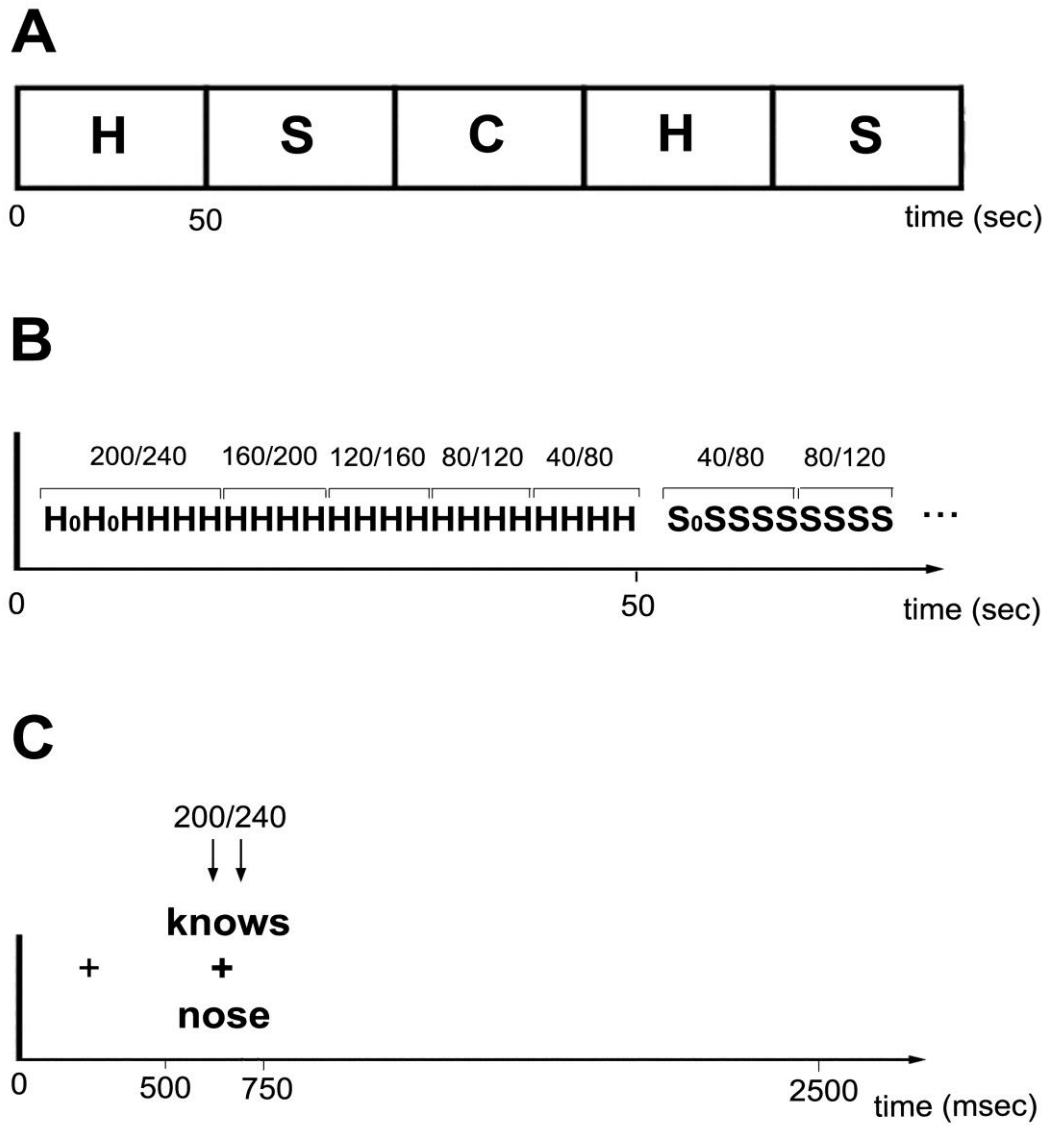

Figure 4-1: A) Within a run, homophones (H), synonyms (S), and consonant strings (C) alternated in 50 sec blocks. B) Each block consisted of 20 trials plus a dummy trial at the beginning. The first block in each run began with two dummy trials. Pulses occurred at either 40/80, 80/120, 120/160, 160/240, or 200/240 msec post-stimulus onset. TMS timings were ordered in either an ascending or descending staircase in sets of four trials. H_0 and S_0 indicate dummy trials. C) Each trial began with a fixation cross presented for 500 msec. A stimulus was then presented for 250 msec, followed by a blank screen displayed for random interval between 1300-2300 msec. Stimulation occurred at one of five time windows.

Analyses

For the main task the earliest timing window (i.e., pulses delivered at 40/80 msec) was considered the baseline condition as previous ERP, MEG, and TMS findings (e.g., Khateb et al., 1999; Pammer et al., 2004; Stoeckel, Gough, Watkins, & Devlin, 2009) indicate that this is too early for TMS to have an effect on SMG during phonological processing. As a result, within each of the three tasks, each of the four later time windows was compared to the baseline, using two-tailed, planned paired t-tests.

In order to identify testing sites in terms of standard space coordinates, each participant's structural scan was registered to the Montreal Neurological Institute-152 template using an affine registration (Jenkinson & Smith, 2001). Note that all stimulation was done in native anatomical space – the standard space coordinates were computed solely for reporting purposes. In addition, for illustrative purposes a group mean structural scan was created in standard space and used as a background image when presenting the stimulation sites in order to accurately reflect the anatomical variability across subjects (Devlin & Poldrack, 2007).

4.3 Results

Functional Localization

In eight out of 40 participants, the functional localization process failed and testing ceased after ten runs. In the remaining 32 participants, an average of five localizer runs per subject (range: 2-10, mean = 6) were required to successfully identify the main SMG testing site. In these participants, rTMS produced a significant inhibitory effect of 44 msec relative to the no-TMS trials (paired t-test; $t(31) = 9.8$, $p < 0.001$). When normalized to reflect between-subject variability in overall RT, this equated to

a 6% slowdown in individuals. In contrast, stimulation of the other SMG sites produced a significant facilitation effect of 32 msec (paired t-test; $t(31) = 4.9$, $p < 0.001$). When normalized, this constituted a 4% speedup in RTs. In other words, there was a clear difference between the final test site and other locations, even though they were only 1-2 cms apart and still within anterior SMG. The precise location where stimulation interfered with phonological processing varied across individuals and is illustrated in Figure 4-2. Here, white filled circles show where stimulation led to a slowdown for rhyme judgments in each participant. The mean coordinate in standard space was [–52, –37, +32] and is shown with a black circle, a region previously implicated in phonological processing (Devlin et al., 2003; Price et al., 1997; Raizada & Poldrack, 2007; Seghier et al., 2004; Zevin & McCandliss, 2005).

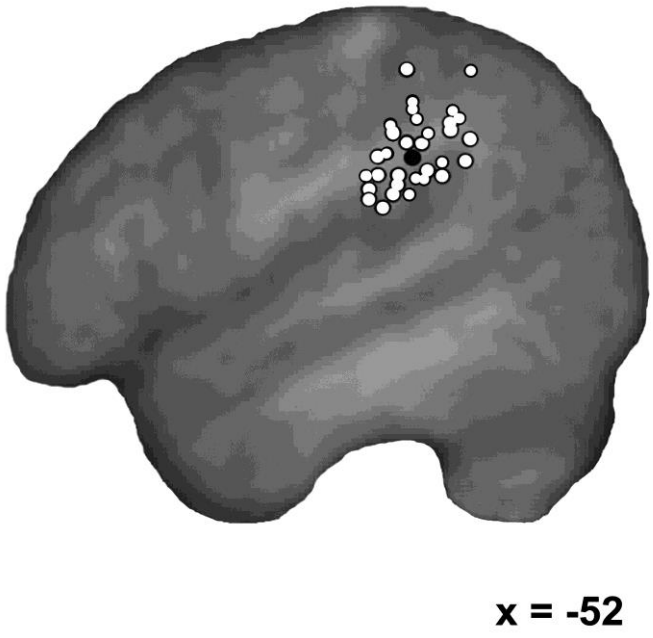

Figure 4-2: The final testing sites for all 32 participants (white filled circles) and the mean group location (black filled circle) on the averaged brain of all participants normalized to the standard MNI152 space with an affine registration (Jenkinson & Smith, 2001) shown on a parasagittal plane.

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Overall accuracy levels were reasonably high (88%) indicating that participants did not have any difficulty performing the tasks. When accuracy was analyzed with an omnibus 3 × 5 ANOVA with Task (Phonological, Semantic, Visual) and TMS (40/80, 80/120, 120/160, 160/200, 200/240) as independent factors, it revealed a significant main effect of Task ($F(2,63) = 30.4$, $p < 0.001$) indicating that the semantic task (83%) was significantly more difficult than either the phonological task (90%) or the visual task (91%). Neither the main effect of TMS nor its interaction with Task were significant (both $F<1$). In other words, there was no evidence that TMS affected accuracy in performing any of the three tasks.

The RT results are shown in Figure 4-3. From the figure, it is apparent that there was a main effect of Task ($F(2, 62) = 98$, $p < 0.001$), with slowest responses on the semantic task (893 msec), followed by the phonological task (803 msec) and then the visual task (665 msec), each of which was significant different from the others (all $p < 0.001$, after Bonferonni correction for multiple comparisons). Neither the main effect of TMS ($F(4, 124) = 1.2$, $p = 0.31$) nor the Task × TMS interaction reached significance ($F(8, 248) = 1.26$, $p = 0.27$) in the omnibus ANOVA. Even so, a set of planned comparisons were performed to specifically evaluate whether TMS modified RTs in the phonological and/or semantic task.

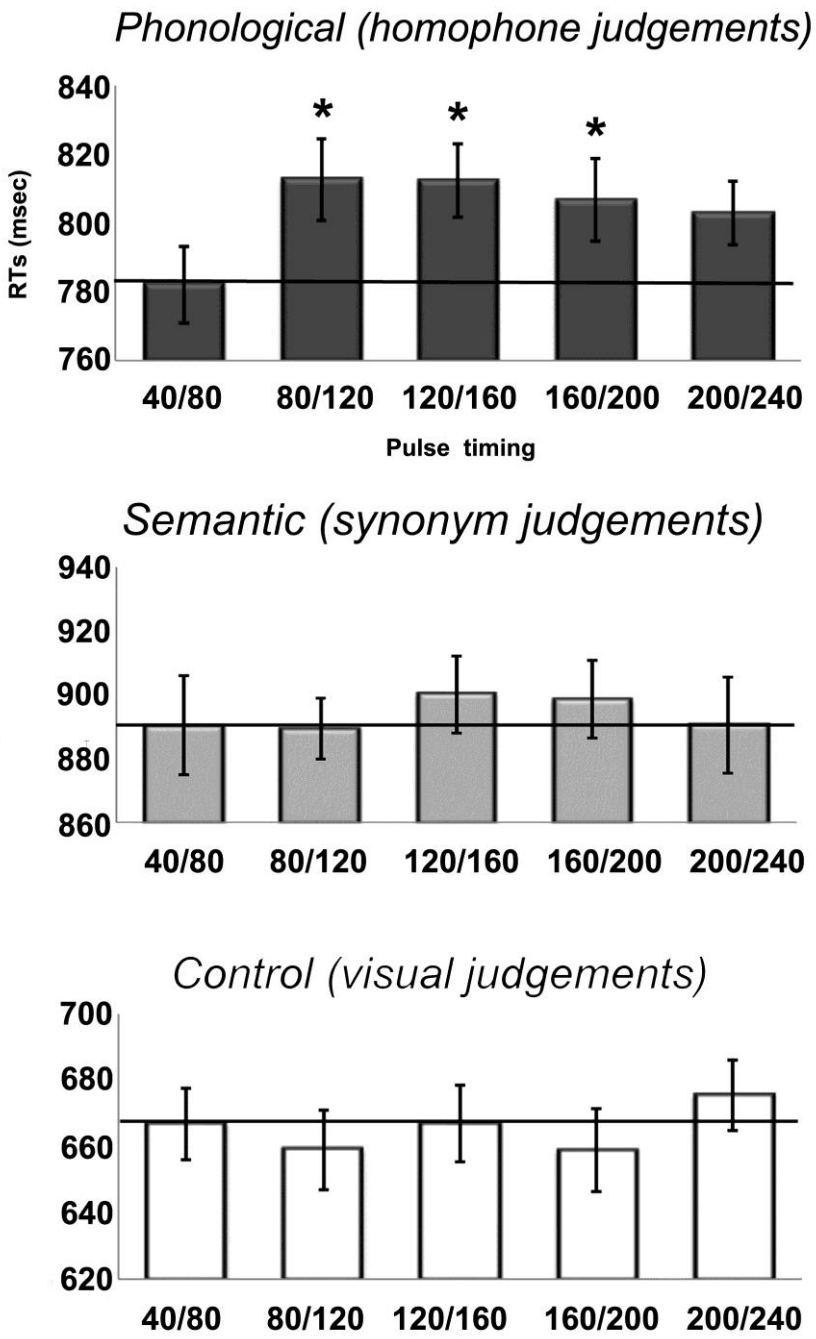

Figure 4-3: RTs from the onset of the visual stimulus for each of the five stimulation timings for all three tasks in the main experiment. Note the scales of the y-axes are not identical due to different RTs across the three tasks with visual < phonological < semantic. The solid line represents the baseline RTs. Error bars reflect standard error of the mean adjusted to correctly reflect the variance in the within-subject design (Loftus & Masson, 1994). *p < 0.05.

For the phonological task, a comparison of each time condition to the baseline condition (40/80 msec) indicated inhibitory effects at all four time windows relative to the baseline (plotted in Figure 4-3). I observed RT increases of 30, 30, 25 and 21 msec, although only the first three were significant (80/120: $t(31) = 3.9$, $p = 0.001$; 120/160: $t(31) = 2.4$, $p = 0.02$; 160/200: $t(31) = 2.3$, $p = 0.03$; 200/240: $t(31) = 1.6$, $p = 0.11$). Despite a similar size inhibitory effect, the final time window did not reach statistical significance because of greater inter-subject variability. Specifically, only 20 out of 32 participants were slowed by TMS during the 200/240 time window. In contrast, 26 subjects showed a slowdown in the 80/120 window, 22 subjects in 120/160 window and 24 subjects in the 160/200 window. In summary, double pulses of TMS delivered to the same site that slowed performance in the rhyme judgment localizer task resulted in significantly longer RTs between 80-200 msec post-stimulus onset.

In contrast, SMG stimulation had no significant effect on either the semantic or visual judgment task. For the semantic task, there were net slowdowns in each of the time windows relative to the baseline condition (40/80 msec), but none of these were significant (all $t(31) < 0.96$, $p > 0.34$). This was due to considerable inter-subject variability. Specifically, only 18, 15, 19, and 14 participants (out of 32) showed increased RTs in the four respective time windows. For the visual judgment control task, the effects of TMS were variable and none were significant (all $t(31) < 1.1$, $p > 0.3$).

To investigate the functional specificity of the slowdowns observed in the phonological test, I compared them to the TMS-effects in the semantic and visual tasks. Figure 4-4 illustrates the difference between RTs for each time window relative to its baseline condition (i.e., 40/80) across all three tasks. Dark grey, light grey and white bars show TMS-effects for phonological, semantic and visual tasks,

respectively. It is clear from the figure that slowdown in the phonological task was significantly greater than both the semantic (paired t-test: $t(31) = 2$, $p = 0.03$) and visual task ($t(31) = 3.1$, $p = 0.002$) in the 80/120 time window. In the later time window, however, the phonological TMS-effect did not differ statistically from the semantic TMS-effect, despite the fact that there were significant slowdowns relative to baseline in the phonological, but not the semantic, task. Relative to the TMS-effects in the visual task, TMS produced significantly larger slowdowns in the phonological task in the 120/160 ($t(31) = 2.2$, $p = 0.02$) and 160/200 ($t(31) = 2.6$, $p = 0.01$) time windows. Finally, there were no significant differences between the TMS-effects in the semantic and visual tasks in any time windows (all $t(31) < 0.83$, $p > 0.41$).

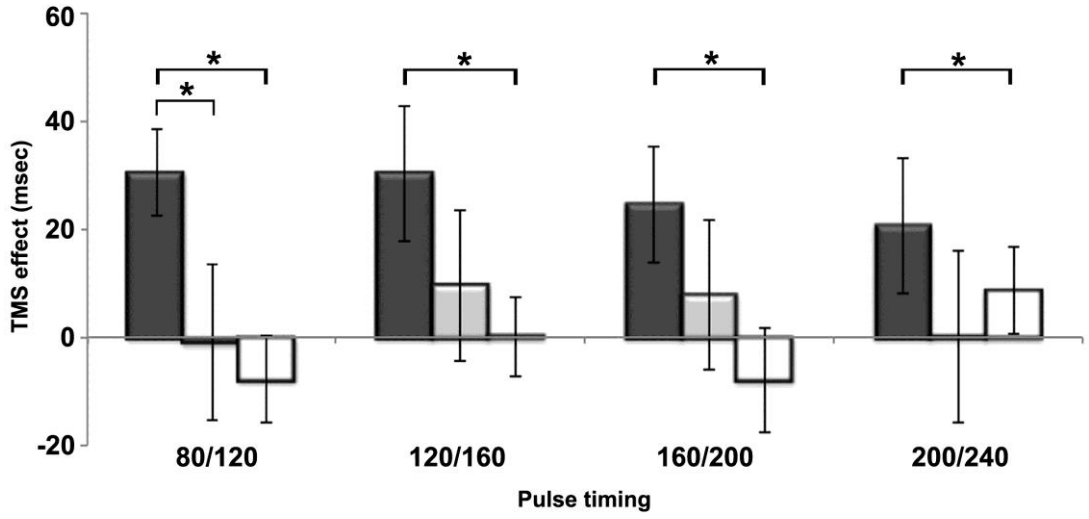

Figure 4-4: The difference between RTs for each time window relative to its baseline condition (i.e., the 40/80 time window) plotted for all three tasks. Dark grey bars represent the phonological task, light grey the semantic task and white the visual control task. **p < 0.05*.

4.4 Discussion

In the present study TMS was used to investigate the timing of phonological processing within the left SMG during reading. The main finding was that the inhibitory effects of TMS were apparent as early as 80-120 msec following stimulus presentation and were sustained for approximately another 100 msec. In addition, like the previous experiment, the effects of SMG stimulation were present for phonological judgments but were not observed for either semantic or visual judgments, confirming preferential involvement of SMG in phonological processing. Moreover, the effect of TMS was significantly greater for phonological judgments than either semantic or visual judgments in the 80/120 time window. Both findings are discussed as they pertain to the neural information processing underlying visual word recognition.

The main aim of this study was to investigate the temporal dynamics of SMG contributions to phonological task by disrupting processing at different time intervals during the first 250 msec of stimulus processing. In this task, a TMS-induced inhibitory effect was present from 80/120 msec post-stimulus onset. Although the detailed mechanisms of TMS action on the cerebral cortex remain unknown (Wagner, Rushmore, Eden, & Valero-Cabre, 2009), it is clear that TMS induces ionic currents in a percentage of neurons in all cortical layers within the stimulated area, leading to inhibitory and excitatory currents within local microcircuits (Esser et al., 2005). These can cause spiking of pyramidal neurons that in turn send a volley of spikes to distal, but anatomically connected regions. Affected neurons then enter a brief refractory state, such that the local physiological effect of a single TMS pulse within the stimulated area lasts approximately 10 milliseconds (Esser et al., 2005), although the distal effects may last for tens of milliseconds. Indeed, chronometric TMS experiments have shown functionally distinct effects of TMS for pulses

separated by as little as 40 msec (Amassian et al., 1993; Corthout et al., 1999; Juan & Walsh, 2003; Pitcher et al., 2007). Consequently, it is reasonable to assume that the inhibitory effects of 80/120 stimulation did not last beyond 160 msec post-stimulus onset. The effects of TMS on phonological processing were recorded earlier than could be expected based on many ERP findings which reported phonological effects in the 200-300 msec time range (Grainger et al., 2006; Kramer & Donchin, 1987; Niznikiewicz & Squires, 1996) or even later ranging from 300 to 500 msec (Bentin et al., 1999; R. L. Newman & Connolly, 2004; Rugg, 1984a). In other words, many studies indicate that the time course of phonological processing in word recognition begins roughly 100 msec later than reported here.

One possible explanation for this apparent discrepancy may have to do with the nature of the different methodologies. ERP and MEG signals reflect the aggregate electromagnetic activity of synchronous neuronal firing and as a result may be less sensitive to the earliest processing dynamics within a region before synchrony has time to develop (Schroeder, Mehta, & Givre, 1998). In contrast, the effect of TMS occurs immediately with the stimulation pulse and can interfere with neuronal activity that contributes to the build-up of the ERP/MEG signal (Walsh & Cowey, 2000). As a result, TMS effects tend to precede those seen in ERP/MEG and correspond more closely to the timings seen in intracellular recording studies (Corthout, Uttl, Walsh, Hallet, & Cowey, 2000; Duncan et al., 2010; Schuhmann, Schiller, Goebel, & Sack, 2012). In other words, despite its poorer temporal resolution (tens of milliseconds as opposed to milliseconds), TMS may provide more precise information regarding the onset of regional neuronal activity.

Another possible explanation for the relatively late ERP recordings is that the ERP components such as the N250 or N400 index processes based on recurrent feedback rather than the initial information passing through the system (S. C.

Sereno & Rayner, 2003). When reading text, the eyes fixate on a word for an average of 250-300 msec (Just & Carpenter, 1980; Rayner, Sereno, & Raney, 1996), indicating that lexical processing must be underway well before the next saccade. Indeed, Sereno and colleagues (1998) found that during reading, early ERP components such as the P1 and N1 are influenced by factors such as lexicality and frequency, demonstrating that higher order properties of the word are accessed as early as 100-200 msec post-stimulus onset (see also Hauk & Pulvermüller, 2004). In other words, there is growing evidence that nonvisual properties of a word become available as early as 100-200 msec from the onset of the visual word (Ashby et al., 2009; Braun et al., 2009; Hauk, Coutout, Holden, & Chen, 2012; Reichle, Tokowicz, Liu, & Perfetti, 2011; Wheat et al., 2010).

In addition to this rapid onset, I observed that the effects of TMS were sustained through the 160/200 msec time windows. In contrast, most previous chronometric TMS studies of visual processing have demonstrated separate early and late effects of stimulation, suggesting temporally distinct feedforward and feedback phases of processing (e.g., Corthout et al., 1999). In my data, however, TMS to each of the time windows between 80/120 and 160/200 msec significantly slowed responses, suggesting ongoing phonological processing, presumably due to dynamic interactions with regions processing other aspects of the word including visual and semantic information (Cao, Bitan, & Booth, 2008; Carreiras, Perea, Vergara, & Pollatsek, 2009; Frye et al., 2011). Indeed, the same temporal pattern of disruption was observed in a chronometric TMS study of left ventral occpito-temporal cortex – a region critically involved in processing the visual forms of words (Duncan et al., 2010). Taken together, the results suggest continuous and simultaneous communication between ventral occpito-temporal cortex and SMG occurring between approximately 100-200 msec after the presentation of a visual word. This type of interactive processing (as opposed to strictly feedforward processing) is a

fundamental principle of virtually all computationally explicit cognitive accounts of visual word recognition (Coltheart et al., 2001; Harm & Seidenberg, 2004; Jacobs et al., 2003; McClelland & Rumelhart, 1981; Perry et al., 2007; Plaut et al., 1996; Seidenberg & McClelland, 1989) and is increasingly important for neuro-anatomical models of reading as well (Price & Devlin, 2011; T Twomey et al., 2011; Wang, Yang, Shu, & Zevin, 2011; Woodhead, Brownsett, Dhanjal, Beckmann, & Wise, 2011). In other words, these data are not only consistent with accounts of visual word recognition that suggest parallel processing of orthographic, phonological (and presumably semantic) information over time and their integration as a result of constant regional interaction in order to achieve stable word representations, but they also provide a tentative time frame for this processing (i.e., 80-200 msec), consistent with estimates of the time available based on both eye movement and ERP data (S. C. Sereno & Rayner, 2003).

This study is consistent with the findings from Chapter 3 that SMG is necessary for phonological processing during visual word recognition and is in line with the previous functional imaging studies which suggested preferential engagement of SMG in phonological processing, rather than semantic processing (Demonet et al., 1994; Devlin et al., 2003; McDermott et al., 2003; Mummery et al., 1998; Price et al., 1997). SMG stimulation increased response latencies in the phonological task but not in the semantic or visual control tasks. Indeed, at the earliest time window (80/120) the effect of TMS on the phonological task (+30 msec) was significantly greater than in the semantic (–1 msec) or the visual (–8 msec) task, suggesting a degree of functional specificity for phonology early in the time course of processing visual words. Moreover, the results imply that the region is not necessary for other types of linguistic processing such as visual word recognition or semantic processing, nor for more domain-general processes such as sustained attention, decision making, action selection and initiation, etc.

5. *Experiment 3: Temporal Dynamics of Angular Gyrus Involvement in Semantic Processing during Reading*

5.1 Introduction

In Experiment 1, I demonstrated that ANG contributes to semantic processing during visual word recognition, in line with previous neuroimaging studies. The aim of this chapter is therefore to establish the time course of ANG involvement to semantic processing. To my knowledge, no previous studies have focused directly on investigating the timing of ANG to this process. Instead, EEG has primarily been used to establish a time line of semantic processing across the whole brain but without precise cortical localization because of insufficiently good spatial resolution.

According to the traditional view, the timing of semantic processing is reflected in a negative-going ERP component, known as the N400, commonly associated with the processing of semantic information (for review, see Kutas, Van Petten, & Kluender, 2006). A strong link between the N400 and semantic processing was originally established by Kutas and her colleagues (Kutas & Hillyard, 1980a, 1980b, 1980c) who investigated the role of the semantic context of a sentence on word recognition during reading. Kutas and colleagues were first to demonstrate that a semantic priming effect in sentential context can be detected by ERPs. In a series of studies, researchers asked their participants to read sentences presented one word at a time. They found that at the point of final word recognition, sentences with semantically anomalous endings (e.g., *I take my coffee with cream and dog*) led to larger negative ERP potential than sentences with semantically appropriate endings (e.g., *I take my coffee with cream and sugar*). This negative potential had a broad scalp distribution and lasted between 200-500 msec post-stimulus onset with a maximum negativity at about 400 msec over the centro-parietal electrode sites. It was also shown that deviation of the physical structure of terminal words (Kutas & Hillyard, 1980a) or grammatical structure of the sentence (Kutas & Hillyard, 1982, 1983) that did not involve semantic violations did not have any effect on the N400

component, strengthening its relation to semantic processing. A number of more recent ERP studies have also shown that the N400 amplitude can be modulated by semantically incongruent terminal words not only during passive sentence reading but also during semantic decisions performed on sentences (e.g., Halgren, 1990; Halgren et al., 2002; Helenius, Salmelin, & Connolly, 1999; Holcomb & Kounios, 1990). For example, Holcomb and Kounios (Holcomb & Kounios, 1990; Kounios & Holcomb, 1992) demonstrated that the N400 amplitude for sentence final words was inversely proportional to the semantic relationship between the subject of the sentence and the final word in the sentence verification task.

Other studies have revealed that modulation of the N400 amplitude can be achieved not only by sentences but also when a single word provides the semantic context (Bentin, 1987; Bentin, McCarthy, & Wood, 1985; Bentin et al., 1999; C. M. Brown & Hagoort, 1993; Franklin, Dien, Neely, Huber, & Waterson, 2007; Holcomb & Neville, 1990; Kutas & Hillyard, 1989; Rugg, 1985; Stuss, Picton, & Cerri, 1988). In these lexical priming studies, a prime word was presented prior to a target word and the degree and nature of the semantic overlap between the prime and the target word were manipulated. The maximal amplitude of the N400 component has been shown to be larger when a target word is preceded by semantically unrelated than related word (e.g., *cat* – *pan* vs. *cat* – *dog*). The difference in amplitude between unrelated and related pairs of words was usually largest at fronto-central electrode sites. The amplitude of N400 can be modulated by different types of semantic relations between the prime and target words including semantic category (Heinze, Muente, & Kutas, 1998; Kiefer, 2001), function (Bach, Gunter, Knoblich, Prinz, & Friederici, 2009), synonymy (Kutas & Iragui, 1998; Y. Liu, Perfetti, & Hart, 2003), association (Franklin et al., 2007) or general knowledge (Hagoort, Hald, Bastiaansen, & Petersson, 2004). Similar findings were obtained in MEG study by Vartiainen and colleagues (2009) who recorded the strongest priming effects between 300-450

msec over the superior temporal regions in a semantic relatedness task which required participants to judge whether a target word was semantically related or unrelated to three preceding words.

Apart from priming effects on the N400, a number of electrophysiological studies demonstrated effects of word concreteness (Kounios & Holcomb, 1994) or frequency (C. M. Brown, Hagoort, & Keurs, 1999; Polich & Donchin, 1988; Pulvermüller, Assadollahi, & Elbert, 2001; Rugg, 1990; Van Petten & Kutas, 1990) on this component and used them as markers for semantic processing. Investigations of the word frequency effects have been of particularly great importance since they are believed to affect recordings after semantic representations of words have been activated and therefore can be used to determine the upper limit for the latency of semantic processing (S. C. Sereno et al., 1998). Studies mentioned above detected word frequency effects between 200-500 msec which corresponded to the N400 component. According to the general pattern of results, less frequent words produced larger N400 amplitude than more frequent words.

In addition, the N400 was demonstrated to reflect semantic processing of words not only during reading but also during listening. For example, listening to semantically anomalous words placed in the final sentence position modulated the N400 in the same way as reading anomalous words at the end of a sentence (McCallum, Farmer, & Pocock, 1984). The N400 context effect has been also reported for nonverbal but meaningful stimuli. For example, the meaningful line drawings (Ganis, Kutas, & Sereno, 1996; Holcomb & McPherson, 1994), photographs (Kutas et al., 2006) or interpretable environmental sounds (e.g., horse hooves on pavement) (Plante, Van Petten, & Senkfor, 2000; Van Petten & Rheinfelder, 1995) also elicited central negativities similar to the linguistic N400 that was modulated by semantic

context. The meaningful nonverbal stimuli differed only slightly from the verbal stimuli in scalp distribution of the N400 potential which suggested engagement of similar neuronal populations in processing meaning. In contrast, stimuli that could not be mapped onto existing semantic information such as novel geometric shapes or unpronounceable nonwords did not produce the N400-like component (M. E. Smith & Halgren, 1986; Van Petten & Senkfor, 1996). Similarly, incongruent endings of well-known melodies did not elicit the N400 component (Besson & Macar, 1987).

Overall, the evidence presented so far suggests that semantic processing of any meaningful stimuli is reflected by the N400 potential occurring approximately between 200-500 msec. However, the interpretation of the N400 potential in terms of semantic processing has been challenged by those who found potentials similar to N400 in tasks with no obvious semantic component. For example, Stuss and colleagues (1983) reported N400-like potential elicited by mental rotation of geometrical figures while Rugg (1984a, b) found that the N400 was not only sensitive only to semantic, but also phonological manipulations. In addition, the description of the N400 component lacks spatial precision in indicating temporal involvement of fine-grained cortical structures in semantic processing. The N400 has been rather associated with an extended network of neural generators including broad regions of temporal, temporo-parietal, and frontal cortex. Moreover, the description of the N400 scalp distribution seems to vary depending on the task used for testing. For instance, the N400 elicited by semantic incongruities in sentences is largest over the centro-parietal regions (Kutas & Hillyard, 1982; Kutas, Hillyard, & Gazzaniga, 1988) while the N400 elicited by single words is largest over fronto-central sites (Bentin, 1987; Bentin et al., 1985; McCarthy & Nobre, 1993) or even the anterior medial temporal lobe (McCarthy, Nobre, Bentin, & Spencer, 1995).

Another group of electrophysiological studies have demonstrated that semantic processing of a visual word occurs earlier than the N400 would suggest (Assadollahi & Pulvermüller, 2001a, 2001b, 2003; Dambacher, Kliegl, Hofmann, & Jacobs, 2006; Dien, Frishkoff, Cerbone, & Tucker, 2003; Hauk et al., 2012; Hauk, Davis, Ford, Pulvermüller, & Marslen-Wilson, 2006; Hauk, Patterson, et al., 2006; Hauk & Pulvermüller, 2004; Palazova, Mantwill, Sommer, & Schacht, 2011; Penolazzi, Hauk, & Pulvermüller, 2007; Pulvermüller et al., 2001; Rabovsky, Sommer, & Rahman, 2012; G. G. Scott, O'Donnell, Leuthold, & Sereno, 2008; S. C. Sereno & Rayner, 2003; S. C. Sereno et al., 1998; Skrandies, 1998). For example, Dien and colleagues (2003) analysed ERP responses to congruous and incongruous sentence endings with respect to meaningfulness and expectedness of the final word (i.e., how much sense the sentence makes including the target word vs. how strongly the participant expect this word given the preceding context). The earliest effects of both variables were recorded around 200 msec after final word onset suggesting that semantic information about the word and the context in which it occurred was already available at this latency. A number of other studies found word frequency effects occurring earlier than 200 msec post-stimulus onset (Assadollahi & Pulvermüller, 2001a, 2001b, 2003; Dambacher et al., 2006; Hauk, Davis, et al., 2006; Hauk, Patterson, et al., 2006; Hauk & Pulvermüller, 2004; Palazova et al., 2011; Penolazzi et al., 2007; S. C. Sereno & Rayner, 2003). Sereno and colleagues (1998; 2003) first demonstrated frequency effects on the N1 component as early as 132 msec post-stimulus onset in a lexical decision experiment. Subsequent studies reported early frequency effects around 120 msec (Assadollahi & Pulvermüller, 2001a, 2001b), 150 msec (Hauk & Pulvermüller, 2004), or 170 msec (Dambacher et al., 2006). Hauk and colleagues (2006) revealed even earlier effect of word frequency around 110 msec while Scott and colleagues (2008) found an interaction between word frequency effects and emotional quality of words around 100 msec. Interestingly, many of these studies (C. M. Brown et al., 1999; Hauk & Pulvermüller,

2004; S. C. Sereno et al., 1998) did not find any significant effects at later time windows or could not replicate them (Assadollahi & Pulvermüller, 2001a, 2001b).

Researchers have suggested that semantic processing begins early based on evidence from other linguistic manipulations as well. One (perhaps surprising) variable that potentially can reveal the timing of semantic processing is orthographic neighbourhood size (Coltheart, Davelaar, Jonasson, & Besner, 1977). Although this variable indicates the *orthographic* relations of words stored in memory, its effects have been also interpreted in terms of semantic competition processes (Andrews, 1997; Grainger & Jacobs, 1996; Holcomb, Grainger, & O'Rourke, 2002) or even post-lexical processing (Fiebach, Ricker, Friederici, & Jacobs, 2007) – both of which happen after semantic information about words is activated. Hauk and colleagues (2009) found neurophysiological effects of orthographic neighbourhood size around 100 msec after word onset in a lexical decision task. The ERP amplitude of the P1 component increased with orthographic neighbourhood size and was largest within left perisylvian regions. Another important way for investigating the time course of semantic processing during reading relies on the effects of semantic richness which indicates the number of semantic features (McRae, Cree, Seidenberg, & McNorgan, 2005). Rabovsky and colleagues (2012) investigated the time course of semantic richness effects on ERPs during a visual lexical decision task and found that this variable modulated ERP amplitudes at central sites starting about 190 msec post-stimulus onset indicating fast initial access to semantic representations. Other ERP and MEG studies have also reported early physiological differences between semantic word categories (e.g., animals vs. flowers) that began to appear around 100 msec (Skrandies, 1998) or lexical categories (e.g., nouns vs. verbs) that started around 100 msec (Pulvermüller et al., 2001). In addition, Hauk and colleagues (2012) used a multimodal approach in which they combined ERPs as a source of fast behavioural measures with EEG/MEG measures of cortical signal localization in

order to investigate the latencies of earliest semantic information retrieval in a visual word recognition task. In their experiment, participants performed a semantic Go/NoGo task in which they responded by eye-blink, instead of traditional button press, since the eye-blink method was believed to provide a faster and less variable dependent measures of behaviour. Hauk et al. (2012) found that the earliest differences between Go and NoGo conditions occurred around 160 msec in the left anterior middle temporal lobe which provided evidence for an early onset of semantic processing in the brain.

These studies provide evidence for the modulation of early electrophysiological brain responses revealing the time course of semantic processing. This is in line with the behavioural evidence presented by Sereno and her colleagues (1998; 2003) who demonstrated that eyes of a skilled reader usually rest on a word for about 250 msec before they move on to the next word during passive text reading. Following this behavioural finding, Sereno and colleagues argued that single word recognition must be accomplished within 250 msec and therefore any higher order processes, including semantic processing, must take place between 100-200 msec.

To conclude, a number of ERP and MEG studies demonstrated that semantic processing happens in the brain relatively late, around 400 msec (N400), while a number of other ERP and MEG studies demonstrated that semantic processing occurs between 100-200 msec and must be completed within 250 msec after word presentation. None of these studies, however, revealed timing of semantic processing specific to ANG, a brain region playing an important role in this process. Instead the majority of neurophysiological studies associated semantic information processing with broad areas of the brain, including frontal and temporo-parietal regions. It has been argued that the physiological effects on the early topographically specific, short-lived components are much more difficult to detect

than the widely distributed, long-lasting late effect such as those related to the N400 (Pulvermüller, 1999). Considering the fact that my previous TMS experiment found very early latency for phonological processing in SMG, it seems plausible that semantic processing in ANG also occurs much earlier than indicated by the N400. In addition, it seems that chronometric TMS is a strong candidate to investigate these effects. In the current experiment, a double-pulse TMS (delivered 40 msec apart) was applied at five different time windows during semantic, phonological and visual control tasks in order to map the temporal window of ANG contributions to semantic processing during visual word recognition within the first 250 msec of a word presentation. All the time windows were chosen before 250 msec post-stimulus onset in order to successfully identify the onset of semantic processing, especially considering findings of Sereno and her colleagues (S. C. Sereno & Rayner, 2003; S. C. Sereno et al., 1998) who convincingly demonstrated that semantic processing must begin early and be completed within 250 msec after word presentation.

5.2 Methods

Participants

Twenty three right-handed, monolingual native English speakers volunteered to participate in this study, and of these twenty (10F, 10M; aged 19-43, mean = 27) were included in the main experiment. For the other three the functional localization procedure failed to identify a region of ANG for testing in the main experiment. All participants were neurologically normal, with no personal or family history of epilepsy. In addition, none had any form of dyslexia according to self-reports. Each person provided informed consent after the experimental procedures were explained and subjects were paid for their participation. The experiment was approved by the University College London Research Ethics Committee.

Experimental Procedures

Similar to the previous experiments, this experiment consisted of two testing sessions. The first involved a 30 minute visit to BUCNI in order to acquire a T1-weighted structural MRI scan used to anatomically identify the left ANG in each participant. The second session occurred two to ten days later and involved the TMS-based functional localization and the main chronometric experiment which together lasted approximately one hour. The full details of the TMS-based functional localization for ANG were presented in Chapter 2. The main chronometric experiment used identical procedures and materials to the ones used in the main experiment described in the previous chapter.

Analyses

For the main task the earliest timing window (i.e., pulses delivered at 40/80 msec) was considered the baseline condition as previous ERP and MEG findings (e.g., Hauk, Davis, et al., 2006; Kutas & Hillyard, 1980c; Rabovsky et al., 2012; S. C. Sereno et al., 1998) indicate that this is too early for TMS to have an effect on ANG during semantic processing. As a result, within each of the three tasks, the four later time windows were compared to the baseline, using two-tailed, planned paired t-tests.

5.3 Results

Functional Localization

In three out of 23 participants, the functional localization procedure failed to find a consistent region within ANG where rTMS disrupted semantic processing. As a result, testing ceased after ten runs and these participants were not included in the main experiment. In the remaining 20 participants, an average of seven localizer

runs per subject (range: 6-10, mean = 8) were required to successfully identify the main ANG testing site. In these participants, rTMS produced a significant inhibitory effect of 38 msec relative to the no-TMS trials (paired t-test; $t(19) = 4.9$, $p < 0.001$). When normalized to reflect between-subject variability in overall RT, this equated to a 5% slowdown in individuals. In contrast, stimulation of the other ANG sites produced an insignificant inhibitory effect of 11 msec (paired t-test; $t(19) = 0.8$, $p = 0.45$). When normalized, this constituted a 2% slowdown in RTs. In other words, there was a clear difference between the final testing site and other locations within ANG. There was no single site which consistently produced slowdowns across participants. Dorsal ANG was localized in 8 participants, medial ANG in 6 participants and ventral ANG in another 6 participants.

Chronometric Experiment

Overall accuracy levels were reasonably high (88%) indicating that participants did not have any difficulty performing the tasks. When accuracy was analyzed with an omnibus 3×5 ANOVA with Task (Semantic, Phonological, Visual) and TMS (40/80, 80/120, 120/160, 160/200, 200/240) as independent factors, it revealed a significant main effect of Task ($F(2,38) = 20.5$, $p < 0.001$) indicating that the semantic task (83%) was significantly more difficult than either the phonological task (91%) or the visual task (91%). Neither the main effect of TMS nor its interaction with Task were significant (both $F < 1$). In other words, there was no evidence that TMS affected accuracy in performing any of the three tasks.

The RT results are shown in Figure 5-1. An omnibus 3×5 ANOVA revealed a main effect of Task ($F(2, 38) = 50.1$, $p < 0.001$). It is clear from the figure that the slowest responses were produced in the semantic task (855 msec), followed by the phonological task (771 msec) and then the visual task (674 msec), each of which was significant different from the others (all $p < 0.001$, after Bonferonni correction for multiple comparisons). There was also a main effect of TMS ($F(4, 76) = 3.1$, $p =$

0.02) but its correction for multiple comparisons revealed significant difference only between mean RTs in the baseline (753 msec) and 160/200 (769 msec) time windows ($p = 0.048$). No significant Task $\times$ TMS interaction ($F(8, 152) = 0.85$, $p = 0.56$) was obtained. A set of planned comparisons were performed to specifically evaluate how TMS modified RTs in the three tasks.

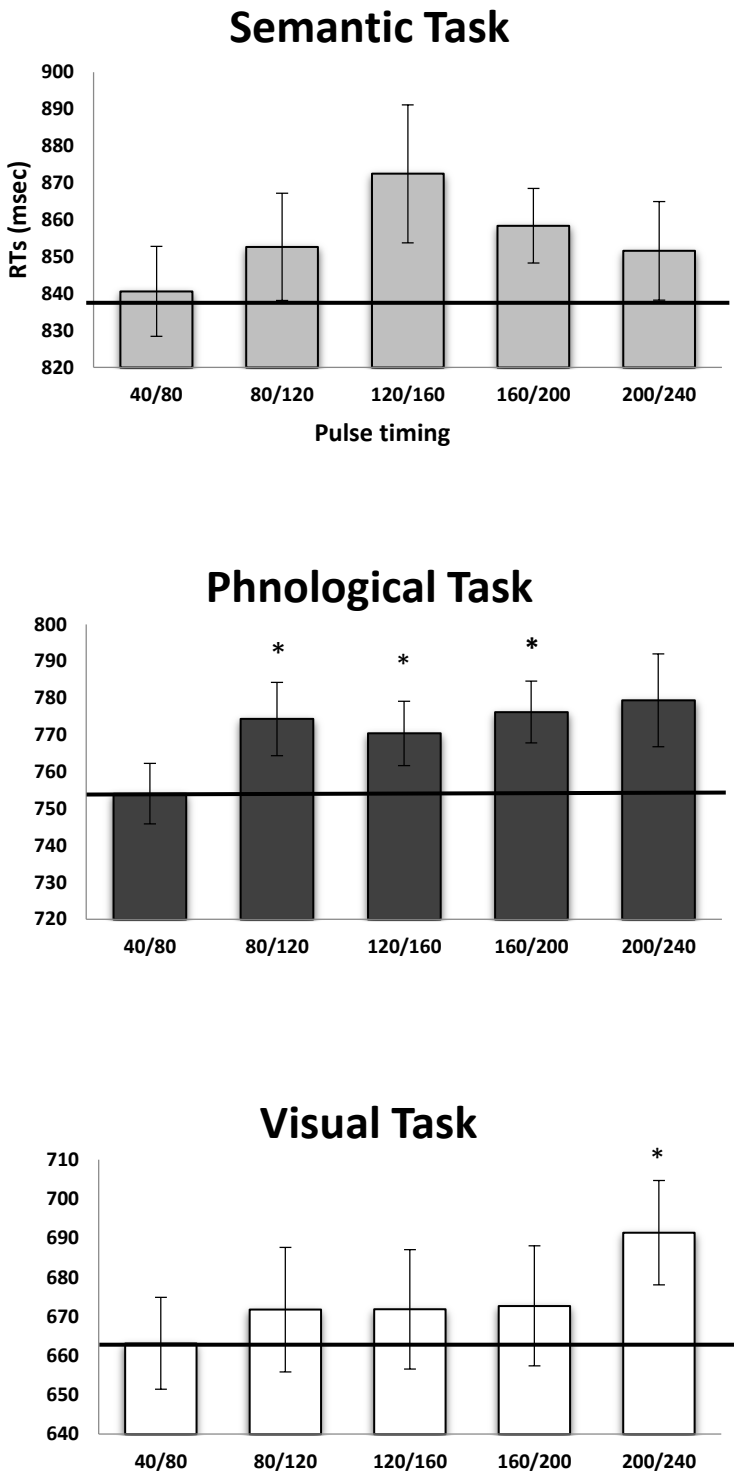

Figure 5-1: RTs from the onset of the visual stimulus for each of the five stimulation timings for all three tasks in the main experiment. Note the scales of the y-axes are not identical due to different RTs across the three tasks with visual < phonological < semantic. The solid line represents the baseline RTs. Error bars reflect standard error of the mean adjusted to correctly reflect the variance in the within-subject design (Loftus & Masson, 1994). * *p < 0.05*.

Figure 5-1 presents the difference between RTs for each time window relative to its baseline condition (40/80 msec) for all three tasks. It is clear from the figure that the later time windows were numerically slower than the baselines within each task. For the semantic task, observed RT increases were of 12, 32, 18 and 11 msec, although none of them was significantly different from the baseline RT (80/120: $t(19) = 0.79$, $p = 0.44$; 120/160: $t(19) = 1.8$, $p = 0.09$; 160/200: $t(19) = 1.4$, $p = 0.2$; 200/240: $t(19) = 0.8$, $p = 0.44$). In contrast, for the phonological task, stimulation produced RT slowdowns of 20, 16, 22 and 25 msec, which were significant in the first three time windows (80/120: $t(19) = 2.43$, $p = 0.03$; 120/160: $t(19) = 2.12$, $p = 0.05$; 160/200: $t(19) = 3.01$, $p = 0.01$). Here, 13 subjects showed a slowdown in the 80/120 window, 14 subjects in 120/160 window, and 16 subjects in the 160/200 window. Despite the fact that the inhibitory effect in the final time window was the largest in the size, it did not reach statistical significance (200/240: $t(19) = 2$, $p = 0.06$). For the visual task, TMS slowdowns were of 9, 9, 10, and 28 msec and only the RT increase in the final time window was significant (200/240: $t(19) = 3.49$, $p < 0.001$). In this time window, 13 subjects showed increased response times.

To investigate whether any of the slowdowns observed in the phonological or visual tests were functionally specific, I compared them to the TMS-effects in other tasks. Figure 5-2 illustrates the difference between RTs for each time window relative to its baseline condition (i.e., 40/80) across all three tasks. Light grey, dark grey and white bars show TMS-effects for semantic, phonological and visual tasks, respectively. It is clear from the figure that the phonological TMS-effects in the 80/120, 120/140, and 140/160 time windows were not statistically different from TMS-effects in the semantic and visual tasks (all $t(19) < 1.2$, $p > 0.25$). There were also no significant differences between the visual TMS-effect in 200/240 time window when compared to the semantic and phonological TMS-effects in this time window (all $t(19) < 1.2$, $p > 0.25$).

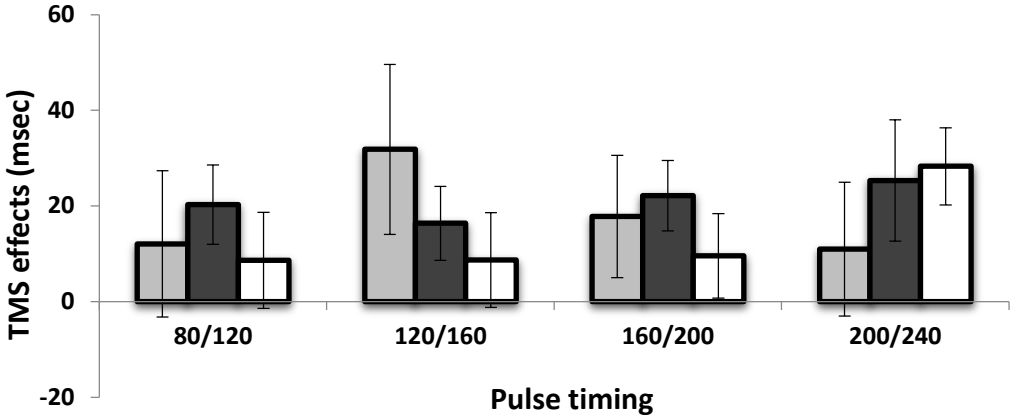

Figure 5-2: The difference between RTs for each time window relative to its baseline condition (i.e., the 40/80 time window) is plotted for all three tasks. Light grey bars represent the semantic task, dark grey bars the phonological task, and white the visual control task.

5.4 Interim Discussion

The results from this experiment were highly surprising. Considering the results from my previous rTMS experiment (Experiment 1), I expected to see effects of double-pulse TMS on the performance in the semantic task, but not the phonological or control visual tasks. In contrast, double-pulse TMS delivered to the same ANG site that slowed performance during the semantic localization task did not lead to significantly longer responses in any of the time windows in the main semantic task. Instead, the results showed significantly longer responses between 80 and 200 msec post-stimulus onset in the phonological task and between 200 and 240 msec in the visual control task. This is contrary to my previous findings that showed no effects of rTMS to ANG in the same phonological and control visual tasks. In addition, the fact that double-pulse TMS significantly affected the first three time windows in the phonological task in this and previously presented Experiment 2

raised concerns that either the stimuli or the stimulation may have produced artifactual slowdowns in these two experiments. To investigate whether the stimuli used in the main task induced any non-specific TMS effects, I tested a separate group of participants on the main chronometric task without concurrent TMS (Experiment 3a). To test whether stimulation affected the performance in the main phonological task in any undesirable way, I tested a third group of participants on the main chronometric task with stimulation delivered only to the Vertex (Experiment 3b).

5.5 Experiment 3a

5.5.1 Methods

Participants

Twelve monolingual native English speakers (8F, 4M; aged 18-32, mean = 26) volunteered to participate in this study. Out of those, 9 participated in the chronometric experiment performed in ANG. The sample size was smaller than in the original experiment since this was an exploratory experiment to assess the effects of stimuli choice and its matching on RTs in the three main tasks. None of the participants had any form of reading disorder according to self-reports.

Experimental procedures

Participants performed the main chronometric experiment. Stimuli and procedures were identical to those described earlier, with the only difference being that there was no TMS applied during the task performance. Even so, the data were analyzed as if there were separate TMS time windows, exactly like the original experiment.

5.5.2 Results

Overall accuracy levels were reasonably high (90%) indicating that participants did not have any difficulty performing the tasks. When accuracy was analyzed with an omnibus 3 $\times$ 5 ANOVA with Task (Semantic, Phonological, Visual) and time windows (40/80, 80/120, 120/160, 160/200, 200/240) as independent factors, it revealed a significant main effect of Task ($F(2,22) = 13.8$, $p < 0.001$) indicating that the semantic task (86%) was significantly more difficult than either the phonological task (94%) or the visual task (91%). Neither the main effect of TMS nor its interaction with Task were significant (both $F < 1$). The accuracy levels across the tasks were consistent with the accuracy levels in the TMS chronometric experiment performed in ANG.

The RT results are shown in Figure 5-3. An omnibus 3 $\times$ 5 ANOVA revealed a main effect of Task ($F(2, 22) = 23.3$, $p < 0.001$). It is clear from the figure that the slowest responses were produced in the semantic task (812 msec), followed by the phonological task (738 msec) and then the visual task (648 msec), each of which was significant different from the others (all $p < 0.001$, after Bonferonni correction for multiple comparisons). There was no significant main effect of TMS ($F(4, 44) = 0.45$, $p = 0.77$) or significant Task $\times$ TMS interaction ($F(8, 88) = 1.05$, $p = 0.41$). A comparison of RTs in later time windows to the RTs in baseline condition (40/80 msec) for each task indicated no inhibitory effects of TMS (all $t(11) < 1.5$, $p > 0.15$).

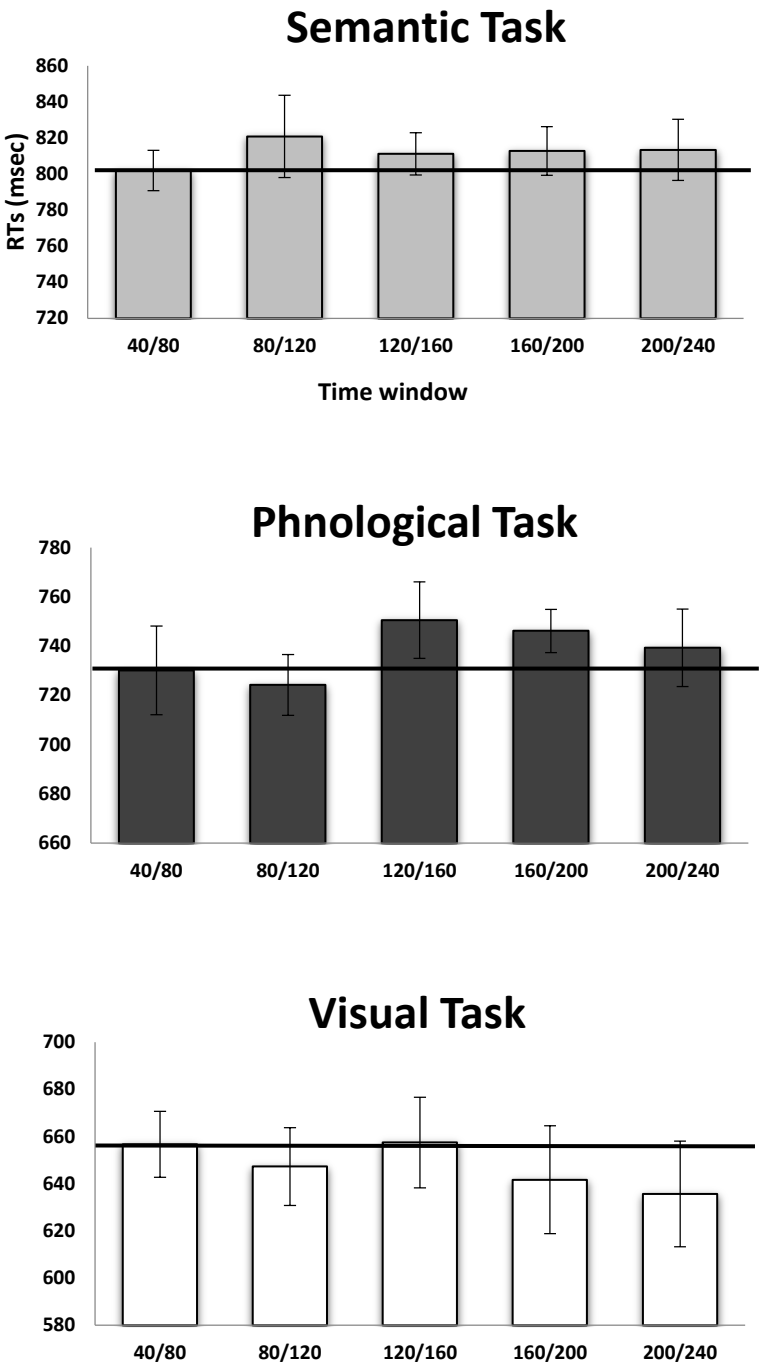

Figure 5-3: RTs from the onset of the visual stimulus for each of the five time windows for all three tasks in the main experiment performed without TMS. Note the scales of the y-axes are not identical due to different RTs across the three tasks with visual < phonological < semantic. The solid line represents the baseline RTs. Error bars reflect standard error of the mean adjusted to correctly reflect the variance in the within-subject design (Loftus & Masson, 1994).

In addition, to investigate whether RTs obtained in this experiment (mean = 733 msec) differed from the RTs obtained in the TMS chronometric experiment performed in ANG (mean = 767 msec), a repeated measures 3 × 5 ANOVA with 2 groups as a between-subjects factor was conducted. The analysis revealed no significant difference in RTs between the two experiments ($F(1, 30) = 0.74$, $p = 0.4$).

5.6 Experiment 3b

5.6.1 Methods

Participants

Fifteen monolingual native English speakers (9F, 6M; aged 20-31, mean = 26) volunteered to participate in this study. None of those participants was tested in the two previous experiments. The sample size was smaller than in the original experiment since this was an exploratory experiment to assess the effects of double- pulse TMS on the three main tasks used in the original experiment. None of the participants had any form of reading disorder according to self-reports.

Experimental Procedures

Participants performed only the main chronometric experiment – no effort was made to functionally localize the vertex to keep procedures parallel. Instead, the vertex was localized on each participant as the highest midline point between the nasion and the inion. Stimuli and procedures were identical to those described in the original experiment, with the only difference being that the stimulation was delivered to the vertex. The vertex was chosen as a control stimulation site because it is far from the reading-related brain areas and its stimulation would not be expected to affect performance on any of the main tasks. In addition, the vertex is commonly used in the TMS literature as a control site for the non-specific effects of TMS

caused by clicking sounds and the tapping sensation on the scalp since TMS to this site induces auditory and sensory artifacts such in a similar way it does during stimulation to other sites (Bestmann, Thilo, Sauner, Siebner, & Rothwell, 2002; Duncan et al., 2010; Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008).

5.6.2 Results

Overall accuracy levels were reasonably high (90%) indicating that participants did not have any difficulty performing the tasks. When accuracy was analyzed with an omnibus 3 $\times$ 5 ANOVA with Task (Semantic, Phonological, Visual) and TMS (40/80, 80/120, 120/160, 160/200, 200/240) as independent factors, it revealed a significant main effect of Task ($F(2, 28) = 18.8$, $p < 0.001$) indicating that the semantic task (86%) was significantly more difficult than either the phonological task (93%) or the visual task (92%). Neither the main effect of TMS nor its interaction with Task were significant (both $F < 1$). In other words, there was no evidence that TMS affected accuracy in performing any of the three tasks.

The RT results are shown in Figure 5-4. An omnibus 3 $\times$ 5 ANOVA revealed a main effect of Task ($F(2, 28) = 46.8$, $p < 0.001$). It is clear from the figure that the slowest responses were produced in the semantic task (899 msec), followed by the phonological task (784 msec) and then the visual task (650 msec), each of which was significant different from the others (all $p < 0.001$, after Bonferonni correction for multiple comparisons). There was also a main effect of TMS ($F(4, 56) = 3.2$, $p = 0.02$) but its correction for multiple comparisons revealed significant difference only between mean RTs in the baseline (759 msec) and 160/240 (790 msec) time windows ($p = 0.004$). No significant Task $\times$ TMS interaction ($F(8, 112) = 1.2$, $p = 0.32$) was found. A set of planned comparisons were performed to specifically evaluate how TMS modified RTs in the three tasks.

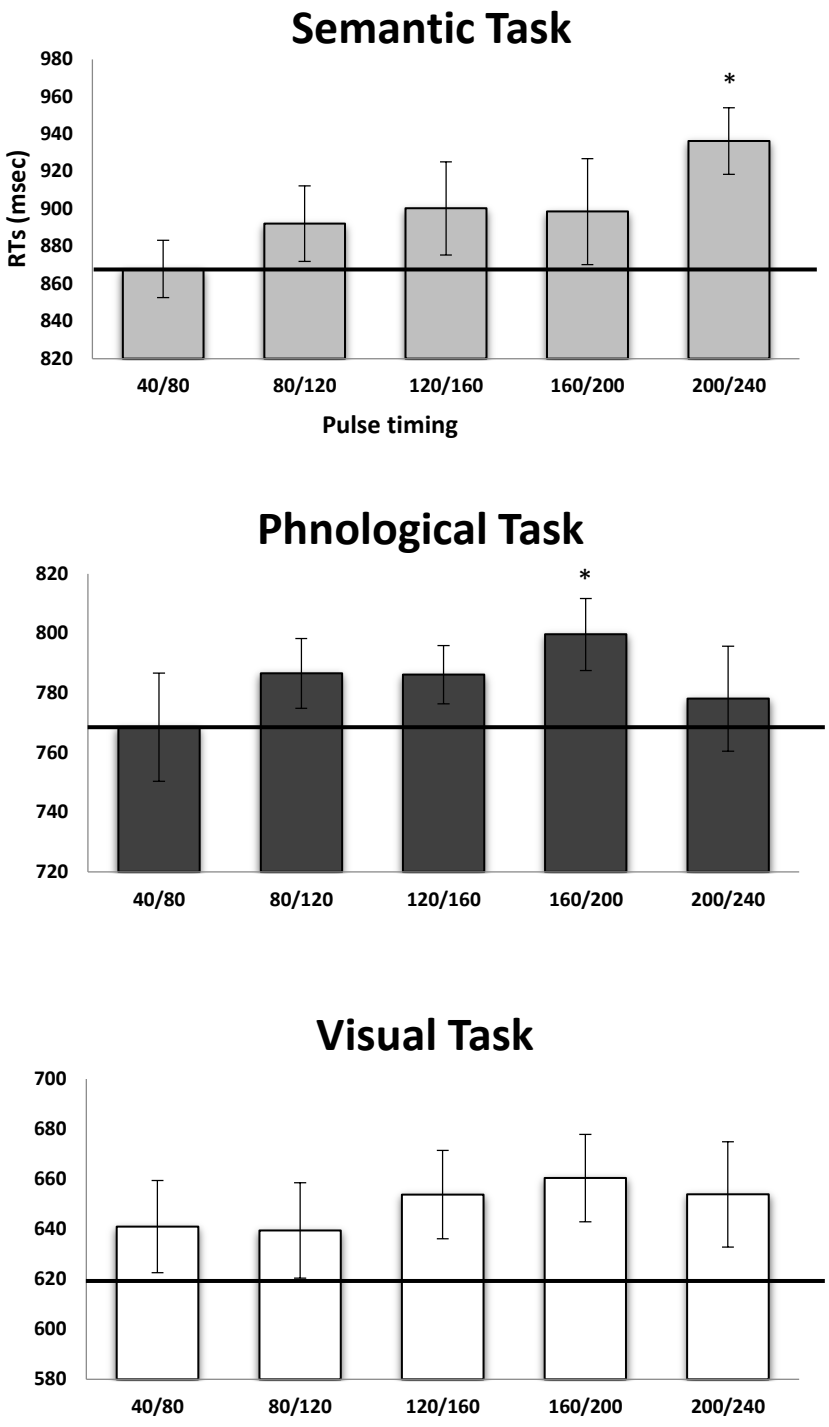

Figure 5-4: RTs from the onset of the visual stimulus for each of the five time windows for all three tasks in the main experiment. Note the scales of the y-axes are not identical due to different RTs across the three tasks with visual < phonological < semantic. The solid line represents the baseline RTs. Error bars reflect standard error of the mean adjusted to correctly reflect the variance in the within-subject design (Loftus & Masson, 1994). * *p* < *0.05*.

Overall, the data showed that TMS did not lead to significantly different RTs relative to the baseline condition (i.e., 40/80) in any time window except for 200/240 in the semantic task (+68 msec; paired t-test; $t(14) = 3.7$, $p = 0.003$) and 160/200 in the phonological task (+31 msec; paired t-test; $t(14) = 2.4$, $p = 0.03$).

To investigate whether the slowdowns observed in the semantic and phonological tasks were functionally specific, I compared them to the TMS-effects in the other tasks. Figure 5-5 illustrates the difference between RTs for each time window relative to its baseline condition (i.e., 40/80) across all three tasks. Light grey, dark grey and white bars show TMS-effects for semantic, phonological and visual tasks, respectively. The semantic TMS-effect in the 200/240 time window was significantly different from the phonological ($t(14) = 2.7$, $p = 0.02$) but not visual ($t(14) = 2$, $p = 0.07$) TMS-effects. There was no significant difference between the phonological TMS-effect in the 160/200 time window when compared to TMS-effect in the semantic task ($t(14) = 0.02$, $p = 0.99$) or the visual task ($t(14) = 0.62$, $p = 0.55$).

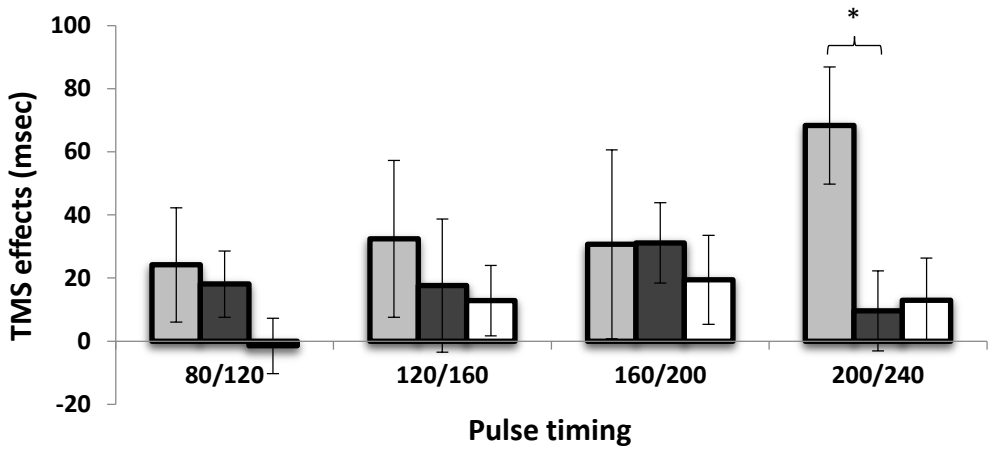

Figure 5-5: The difference between reaction times for each time window relative to its baseline condition (i.e., the 40/80 time window) is plotted for all three tasks. Light grey bars represent the semantic task, dark grey bars the phonological task, and white the visual control task.

5.7 Discussion

The aim of this study was to investigate the temporal dynamics of ANG contributions to semantic processing using double-pulse TMS at different time intervals during the first 240 msec of visual word processing. There were two main, although very surprising, findings: i) a main effect of TMS across tasks and ii) TMS-induced slowdowns in the phonological and visual tasks. It is possible that these are genuine findings or findings that resulted from either experimental error or noise. I can rule out the first possibility since the results are inconsistent with Experiment 1 (Chapter 3). Experiments 3a-b (Chapter 4) also rule out the second possibility. I will argue that lack of consistency in findings suggests they are false positives.

It was surprising to see a main effect of TMS across tasks when the experimental procedures were identical to the procedures that were used in the previous chapter where no such a main effect was observed and the area of stimulation (ANG vs SMG) was the only aspect of the design that differed between the studies. The post-hoc analysis showed that the main effect of TMS was caused by significantly slower responses in the 160/200 time window relative to the baseline time window (i.e., 40/80). Indeed, RTs from each of the three tasks were numerically slower in this time window but their increase reached statistical significance only in the phonological task. Nevertheless, this effect did not replicate in the two control experiments that I additionally performed. In the purely behavioural experiment (Experiment 3a), no main effect of TMS was found. In the vertex experiment (Experiment 3b) there was a main effect of TMS but it was not found in the 160/200 but 200/240 time window. In theory, unspecified interaction between the behavioural experiment and non-specific stimulation effects could produce a main effect of TMS but lack of replicability of the 160/200 effect in the vertex rules out this possibility. Altogether, the results suggest that the main effect of TMS observed in Experiment 3 constitutes a false positive.

The second surprising result was the fact that the tests of simple effects showed slowdowns in the phonological task (80/120 - 160/200) and also in the visual control task (200/240). ANG stimulation was not expected to produce effects in the phonological and visual tasks based on the results from the previous rTMS experiment (Experiment 1) in which no effects of TMS were found in these tasks despite using a more robust stimulation paradigm. According to the chronometric results presented here, TMS delivered at 80/120, 120/160, and 160/200 msec post-stimulus onset increased RTs of the phonological decisions which is similar to the results previously reported for SMG stimulation (Experiment 2). This raised the possibility that the chronometric findings are somehow artifactual which could be

due to inadequate stimulus matching across time windows and/or a non-specific interaction between the timings of the TMS delivery and the task. The control experiments reported in the current chapter, however, rule out both of these possibilities. The first re-run of the experiment without any stimulation aimed to check whether the results were endemic to the basic design of the experiment. As one would expect, there were no significant effects of time window nor interactions, indicating that without TMS participants responded equally quickly across stimuli sets. It is also worth noting that stimuli sets were counter-balanced across participants so that no set of stimuli occurred solely in one time window. The second control experiment used chronometric TMS but delivered to the vertex, a midline region of superior parietal cortex not involved in visual word recognition. This experiment was conducted to determine whether non-specific aspects of TMS interacted with the task to produce slowdowns in the phonological task. Again, as expected, this was not the case since no effects of TMS in the phonological task were found. In addition, the effect of TMS in the 200/240 time window that were observed in the visual task were also not replicated in the control vertex experiment. In other words, the two control experiments provided results consistent with the rTMS findings presented in Experiment 1 which suggest that the current findings from the main experiment were actually false positives. This is further supported by the fact that none of the current results survived correction for multiple comparisons.

Neither Experiment 3a nor Experiment 3b revealed the same pattern of effects as seen in the actual chronometric experiments. This showed that the obtained pattern is not systematic for the experiment because otherwise it would have been replicated by the two additional experiments. I conclude that the pattern of the effects in the current experiment is simply a result of noise which by chance happened to produce a similar pattern of the results to the one observed in the previous chronometric experiment. The reason that I am confident in reliability of the

chronometric results in SMG is that these results are consistent with the rTMS results presented in Experiment 1. In contrast, the chronometric results in ANG are not in line with my previous results but match rather the idea of noise. To test this assumption further I ran Monte Carlo simulations to assess a likelihood of obtaining the pattern of TMS effects in which the first three time windows in the phonological tasks and the final time window in the visual control task are affected without TMS signal but by chance in a noisy set data. The simulations were based on assigning random mean RTs from a normal distribution for each of the five time windows within the three tasks for 20 participants. The simulation involved also a comparison of the random mean RTs in late time windows to the random mean RTs in the baseline time window using paired t-tests. The whole procedure was repeated 100 000 times (see Appendix for the code performing the sampling and calculations). It was demonstrated that the pattern of interest showed up randomly 8 out of 100 000 times. Overall, the simulation demonstrated that it is possible to obtain the pattern as a false positive by chance.

Finally, the lack of an effect in the semantic task was very surprising given that I previously showed that rTMS to ANG affected semantic processing in the same semantic task. The lack of TMS effects in the semantic task between 40-240 msec came as a surprise considering a large body of behavioural and electrophysiological evidence suggesting that semantic processing happens within the first 200 msec after word presentation (e.g., Assadollahi & Pulvermüller, 2001a, 2001b; Dambacher et al., 2006; Dien et al., 2003; Hauk et al., 2012; Hauk, Patterson, et al., 2006; Hauk et al., 2009; Rabovsky et al., 2012; G. G. Scott et al., 2008; S. C. Sereno & Rayner, 2003; S. C. Sereno et al., 1998; Skrandies, 1998). It is, however, possible that semantic processing was missed in this experiment because it starts later than 200-240 msec. This explanation of the null results is possible given that a large number of electrophysiological studies have associated semantic processing with the late

N400 component (e.g., Bentin, 1987; Franklin et al., 2007; Helenius et al., 1999; Holcomb & Kounios, 1990; Kutas & Hillyard, 1980a, 1980b, 1980c; Polich & Donchin, 1988; Van Petten & Kutas, 1990; Vartiainen et al., 2009). In addition, the localization data indicated that ANG contributes to the semantic task within the first 500 msec. In combination with the main results this may suggest that semantic processing occurs in the second half of stimulus presentation. To test this possibility, a chronometric TMS experiment that provides stimulation between 240-500 msec would be required.

The null results of ANG stimulation on the semantic task within the first 240 msec could also result from ineffective stimulation rather than its mistiming. From a methodological point of view, chronometric TMS is less robust than rTMS. It is clear from the Experiment 1 that high-frequency rTMS proved to be a robust method for reliable disruption of the semantic processing in both semantic category and synonym judgements. rTMS, however, encompasses a larger temporal window and most likely affected a larger ANG area due to intra-cortical spreading of stimulation (Pascual-Leone, 1999) than double-pulse stimulation. It could be therefore the case that double-pulse TMS was not strong enough to disrupt performance of the semantic tasks in ANG. In fact, the TMS literature has demonstrated that disrupting semantic processing in ANG is challenging even using more robust TMS paradigms. For example, Hartwigsen and colleagues (2010) did not manage to reliably disturb semantic processing in ANG using high-frequency on-line rTMS directly. The only way they managed to impair semantic processing involved a combination of low-frequency off-line rTMS to ANG combined with high-frequency on-line rTMS to the anterior inferior frontal gyrus (Hartwigsen et al., in revision). This is in contrast to disrupting phonological processing in SMG which seems to be achievable much easier and has been reported by a number of different research groups (Hartwigsen, Baumgaertner, et al., 2010; Pattamadilok et al., 2010; L. Romero et al., 2006).

Difficulties in achieving robust semantic effects with TMS may result from the complexity of semantic processing which, in contrast to other language processes, involves a widely distributed neural system consisting of a large number of regions supporting each other in order to solve semantic problems in an intact way (Binder et al., 2009). A focal disruption of processing in one of those regions can be a particularly challenging task unless stimulation robustly affects a larger part of the system (e.g., Hartwigsen et al., in review; Pobric et al., 2010).

In summary, my investigation of semantic timing in ANG remains inconclusive. The current experiment did not show any TMS effects on the semantic processing in ANG. This could result from stimulating the region before its involvement in the process or ineffective stimulation that failed to affect the semantic decisions between 40-240 msec post-stimulus onset.

6. General Discussion

6.1 Theoretical Contributions of the Thesis and their Implications

The first major contribution of my thesis is the finding that both SMG and ANG, two main IPL subregions, play important but distinct roles during reading. SMG appears to be involved in processing phonological aspects of words while ANG is involved in semantic processing. Moreover, SMG involvement happens relatively early and continues for a sustained period of time after the onset of the word. These findings have important theoretical implications for neurological models of reading.

SMG was missing from the classical neurological model of reading (Geschwind, 1965) although modern versions of the model (Price, 2000; Price & Mechelli, 2005; Pugh et al., 2000) recognize it as an important component of the reading network. Experiment 1 demonstrated the importance SMG in reading tasks that emphasize phonological processing, providing additional support for including this region in the neural circuitry of reading. In terms of its function, my work shows that SMG contributes to phonological processing, in accordance with the claims by Price and colleagues (Price, 2000; Price et al., 2003; Price & Mechelli, 2005; Price et al., 1997) who associated the region with the store of universal phonological information. More specifically, SMG stimulation could interfere with processes required by verbal working memory such as covert articulation and inner speech monitoring. I hypothesize that SMG, together with pars opercularis and ventral premotor cortex, participates in a phono-articulatory loop that is critical for verbal working memory and plays an important role in visual word recognition. The current findings do not support the claim that SMG stores grapheme-to-phoneme conversion rules as suggested by Pugh and Shaywitz (Pugh et al., 2000).

My findings also reveal additional information about the temporal dynamics of SMG processing that can be used to further refine neurological models of reading. In general, information about the time course of regional information processing is essential for our complete understanding of a neuro-computational account of

reading. Unfortunately, such information has been missing from the majority of neurological models of reading. In defence of the classical neurological model, temporal information was impossible to obtain from lesion-deficit studies. Modern models, however, have access to temporal information from a variety of non-invasive sources but even so, they tend to stress anatomy over timing. Exceptionally, Pugh and colleagues (2000) used ERP and MEG findings to describe the timing of information flow in their model. They argued that the "posterior circuit," which encompasses SMG together with ANG and Wernicke's area, is active between 200-400 msec post-word presentation (Salmelin et al., 1996; Tarkiainen et al., 1999). The results from Experiment 2, however, appear inconsistent with this claim, at least for SMG. My chronometric TMS study showed that SMG contributions to phonological processing began within 80-120 msec following the word presentation and lasted for approximately 100 msec – much earlier than the timing proposed by Pugh and colleagues. This may be a result of systematic timing differences between ERP and chronometric TMS (Corthout et al., 1999; Duncan et al., 2010; Walsh & Pascual-Leone, 2003) and/or reflection of more precisely localized temporal investigation.

The information about temporal involvement of SMG to reading in combination with available data on temporal dynamics of other brain regions involved in the reading network and their anatomical connections can help us to understand the functional relationships between SMG and those regions. For instance, activation of regions during the same time window can be indicative of their functional connection and inter-regional interactivity during task performance. Considering my findings which showed SMG involvement to reading between 80-200 msec and findings which showed that the ventral occipito-temporal (Duncan et al., 2010) or inferior frontal regions (Wheat et al., 2010) contribute to reading during approximately the same time window, it can be speculated that SMG is functionally linked to these regions.

In fact, a number of studies have revealed functional connections between SMG and ventral occipito-temporal cortex (Kawabata Duncan et al., 2013; Van der Mark et al., 2011) as well as the inferior frontal cortex (Bokde, Tagamets, Friedman, & Horwitz, 2001; Paulesu et al., 1993; Zatorre et al., 1992). These were further supported by the anatomical connections existing between these regions (Catani et al., 2002; Catani & Jones, 2005; Martino et al., 2013; Tae Twomey, 2013). Overall, there is an increasing amount of evidence suggesting that the key brain regions involved in reading show an early and sustained activation during visual word recognition. In addition, they are activated around the same time window that suggests interactive fashion of processing between different brain areas and different levels of processing.

The information about temporal dynamics of reading that I have presented above challenges the conventional view of a serial feedforward processing sequence for visual word recognition (e.g., L. Cohen et al., 2002; Dehaene et al., 2005; Geschwind, 1965; Kronbichler et al., 2004; Pugh et al., 2000). Instead of a simple progression from decoding letter forms to linking them with their phonological representations and then accessing semantic representations, these findings suggest that visual word recognition is a dynamic and highly interactive process, consistent with cognitive and computational models of reading (Coltheart et al., 2001; Harm & Seidenberg, 2004; Jacobs et al., 2003; McClelland & Rumelhart, 1981; Perry et al., 2007; Plaut et al., 1996).

Experiment 1 also demonstrated the importance of ANG in visual word recognition, although Experiment 3 failed to replicate this finding with chronometric TMS. Both the classical and modern versions of neurological reading models include ANG in the reading network. My results suggest that ANG function is related to semantic processing of written words rather than to visual word form storage or to grapheme-to-phoneme conversion. I speculate that the exact nature of ANG involvement in

semantics may be explained by two recently proposed accounts. One of them suggests that ANG is involved in semantic control mechanisms where it guides selection of relevant semantic information (Jefferies & Lambon Ralph, 2006) while the other one suggests that ANG is a heteromodal association region which integrates various types of semantic information together (Binder & Desai, 2011). The results in this thesis, however, did not distinguish between these different accounts and therefore cannot provide particular support for any of them.

A Revised Neurological Model of Reading

My findings help to further develop a neurological model of reading. Figure 6-1 presents an updated version of the neural reading circuit. The model includes not only the key brain regions which are involved in reading but also the anatomical connections between regions and timing of regional involvement during reading. Regions involved in processing phonological or semantic information are shown in yellow and red, respectively. The orange area is a visual extrastriate region involved in the processing of visual form. In the model, visual information proceeds from the middle occipital gyrus (MOG) dorsally to SMG and ANG via the superior longitudinal fasciculus (SLF) and ventrally to the ventral occipito-temporal cortex (vOT) via the inferior longitudinal fasciculus (ILF). MOG projects to SMG and vOT in parallel and serves as an indirect functional connection between the two regions. The third branch of the SLF also links SMG to pars opercularis (POp) and ventral premotor cortex (PMv) and provides the anatomical substrates for phonological processing of written words. ANG, on the other hand, is directly connected to vOT via the vertical occipital fasciculus (VOF) and indirectly to pars orbitalis (POr) through the anterior temporal lobe (ATL) via the middle longitudinal fasciculus (MLF) and the uncinate fasciculus (UF). These regions contribute to the semantic processing of written words. All of this cortico-cortical information flow is bi-directional enabling inter-

regional interactivity of information processing and is illustrated by the large overlap of regional time-windows during their involvement in reading.

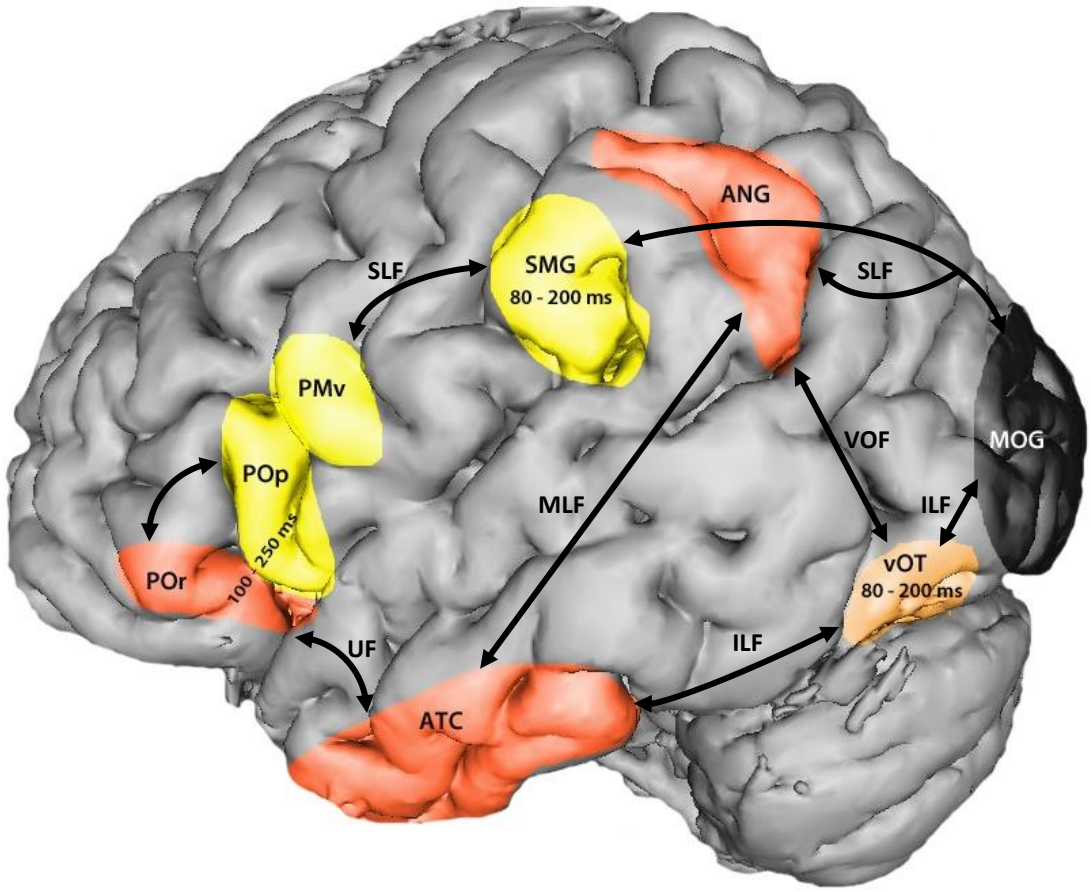

Figure 6-1: Revised neurological model of reading. Anatomical pathways are shown in with solid black lines. Double arrowheads indicate bi-directional information flow. Abbreviations of the brain regions: MOG = middle occipital gyrus; ANG = angular gyrus; SMG = supramarginal gyrus; PMv = ventral premotor cortex; POp = pars opercularis; POr = pars orbitalis; vOT = ventral occipito-temporal region; ATC = anterior temporal cortex. Abbreviations of the anatomical pathways: SLF = superior longitudinal fasciculus; MLF = middle longitudinal fasciculus; VOF = vertical occipital fasciculus; ILF = inferior longitudinal fasciculus; UF = uncinate fasciculus.

6.2 Methodological Contributions of the Thesis and their Implications

The second major contribution of this thesis is a better understanding of the efficacy of fMRI-based and TMS-based functional localization for TMS. My work demonstrates that fMRI is not the only viable method for functional localization; TMS can be equally successful in identifying stimulation targets that produce robust results. Indeed, both methods provide the same level of effectiveness – and neither is 100%. These findings have very important implications. Functional localization of TMS testing sites is an important component of successful TMS experiments because by accounting for individual differences in functional anatomy one gains improvements in statistical sensitivity, efficient designs, and increased safety.

It is clear that one-size-fits-all approaches to TMS targeting may be successful at a group level, but only on average with a significant portion of individuals not showing the group effect (Sack et al., 2009). In other words, there is a considerable variability between subjects resulting in reduced statistical power for finding an effect of TMS. An fMRI- or TMS-based localization procedure reduces inter-subject variability by significantly increasing the number of participants who show an effect of TMS and dramatically increasing statistical sensitivity. A consequence of this increased sensitivity is that smaller sample sizes are needed to gain statistically significant results than experiments that localize based on the 10-20 electrode system, standard space stereotactic coordinates, or even individual MRI-based anatomy. By reducing inter-subject variability, it is possible to maintain statistical sensitivity with smaller number of participants resulting in more efficient designs. This has the added benefit of increasing safety since it automatically decreases the likelihood of an adverse reaction to TMS within the experiment.

Contrary to the popular view that fMRI-based localization is the *gold-standard* for accurate functional localization, my results show that there is a choice of highly accurate methods; fMRI is just one option. fMRI is resource-intensive both in terms

of the financial costs of scanner time and the person-hours required to acquire and analyse the data. TMS-based functional localization provides a cheaper alternative with comparable effectiveness. This information is particularly important for researchers who plan cognitive tests with TMS but do not have access to an MRI scanner. The current findings demonstrate that an entire TMS experiment may be performed efficiently using just one TMS machine.

Finally, using the same method (i.e., TMS) throughout the experiment reduces safety risks. For instance, using fMRI as a localization method provides an additional and different set of safety factors that must be account for. Participants who are safe to receive TMS do not have to be excluded because they do not meet MRI safety requirements. In summary, the demonstration that both fMRI- and TMS-based functional localization produce comparable accuracy for targeting TMS offers a number of practical advantages when designing and implementing future TMS experiments.

6.3 Future Directions

This work has provided novel information that helps to refine and develop the neurological model of reading. Nevertheless, the criticisms of the classical model still apply. For instance, current models (including Figure 6-1) remain focused on the left hemisphere and largely ignore the fact that the right hemisphere also contributes to reading (Demonet et al., 1994; Hartwigsen, Baumgaertner, et al., 2010; Hartwigsen, Price, et al., 2010; Kinsbourne & Warrington, 1962; Mion et al., 2010; Ornstein, Herron, Johnstone, & Swencionis, 1979; Price et al., 1997). In addition, subcortical brain structures are missing from these models despite their undoubted contributions (Binder, Medler, et al., 2005; Bookheimer et al., 1995; Booth et al., 2007; S. H. Chen & Desmond, 2005; Herbster et al., 1997; Price et al., 1997). Our

understanding of the functional contributions of individual regions lacks neuro-computational sophistication and we still need more information about the temporal dynamics of individual regional contributions in order to understand the dynamic distribution of processing throughout the system. Continuing from my work, the following investigations could inform the model further.

First of all, establishing the temporal dynamics of ANG contributions to reading would be of a great value. This information would complete our understanding of a temporal relationship between phonological and semantic processing within the left IPL and also would provide more insight into functional associations between ANG and other brain regions involved in semantic processing. To investigate the timing of ANG involvement in semantic processing, revised versions of my chronometric TMS experiment could be created. If it is the case that semantic processing is happening later than 200-240 msec post-word presentation, then application of double-pulse TMS in time windows between 240-500 msec should reveal the time of semantic activity in ANG. If, however, double-pulse TMS lacked in power to affect semantic processing in ANG between 40-240 msec then potentially re-running this experiment with increased stimulation intensity or sample size and/or using an easier semantic task could be a way to achieve meaningful results in the first 240 msec of word processing. In addition, since there is some evidence that the right SMG also contributes to reading (Hartwigsen, Baumgaertner, et al., 2010), it would be worth using my paradigms to test whether the right SMG and ANG contribute to reading in the same way as their homologues in the left hemisphere and if so, what is the temporal dynamics of this contribution? A systematic investigation of the right IPL would not only allow us to recognize some regions in the right hemisphere that should be included in the reading model but also it would improve our understanding of the functional dynamics between the two hemispheres during reading.

Another step could involve a systematic investigation of temporal involvement of Broca's area to phonological and semantic processing during visual word recognition with chronometric TMS. Previously, Gough and colleagues (2005) demonstrated that TMS to anterior (i.e., POr) and posterior (i.e., POp) portions of this region selectively interfered with semantic and phonological processing, respectively. Devlin and colleagues (2003) used single-pulse TMS in pars triangularis to show that this region was involved in semantic processing at 250 msec post-stimulus onset but this information needs to be replicated especially in light of more recent evidence that activation in Broca's area during reading tasks starts much earlier than 250 msec (Cornelissen et al., 2009; Pammer et al., 2004; Wheat et al., 2010). A chronometric TMS experiment, similar to mine, could be used to selectively test the temporal dynamics of POr and POp contributions to reading. These tests with TMS could be also performed in the right hemisphere homologue to Broca's area.

In addition, the pattern of functional division within the left Broca's area during visual word recognition appears to be similar to the division of labour that I found in the left IPL. It seems, therefore, very likely that Broca's area and IPL are part of the same neural circuitry that would be essential for a fuller understanding of the reading process. First, establishing whether there are distinct anatomical pathways linking the anterior and posterior parts of Broca's area to ANG and SMG, respectively, would be valuable. Existing DTI tractography studies (Binney, Parker, & Lambon Ralph, 2012; Catani & Jones, 2005; Frey, Campbell, Pike, & Petrides, 2008; Parker et al., 2005; Rilling et al., 2008; Saur et al., 2008) suggest this is probably the case but they are not entirely convincing because they lack evidence of functional relevance. A combination of rTMS and PET (e.g., Fox et al., 1997; Paus et al., 1997), however, would help to establish this anatomical and functional connectivity more firmly.

Finally, it would be useful to investigate physiological connectivity between the regions using the paired-pulse TMS technique pioneered by (Civardi, Cantello, Asselman, & Rothwell, 2001). Although successfully applied in the motor system, this approach has not yet been used for cognitive tasks. There is, however, no obvious reason why this technique could not be used in cognitive neuroscience. In brief, paired-pulse TMS could provide a direct measure of physiological connectivity between regions by demonstrating that a conditioning pulse delivered to a distant, but connected region, changes the effects of the test pulse delivered to a putatively connected region. Such investigation would provide more insight into functional physiology of regions involved in reading.

6.4 Summary

In summary, my findings contribute to our understanding of neuroanatomy of reading in two different ways. First, they help to clarify the functional contributions of two major subregions of IPL, namely SMG and ANG, to reading. Second, they introduce novel temporal information about SMG processing dynamics. Both these findings can be used to refine the neurological model of reading. In addition, my findings also provide a significant methodological contribution which will help to design the future TMS experiment and improve their safety.

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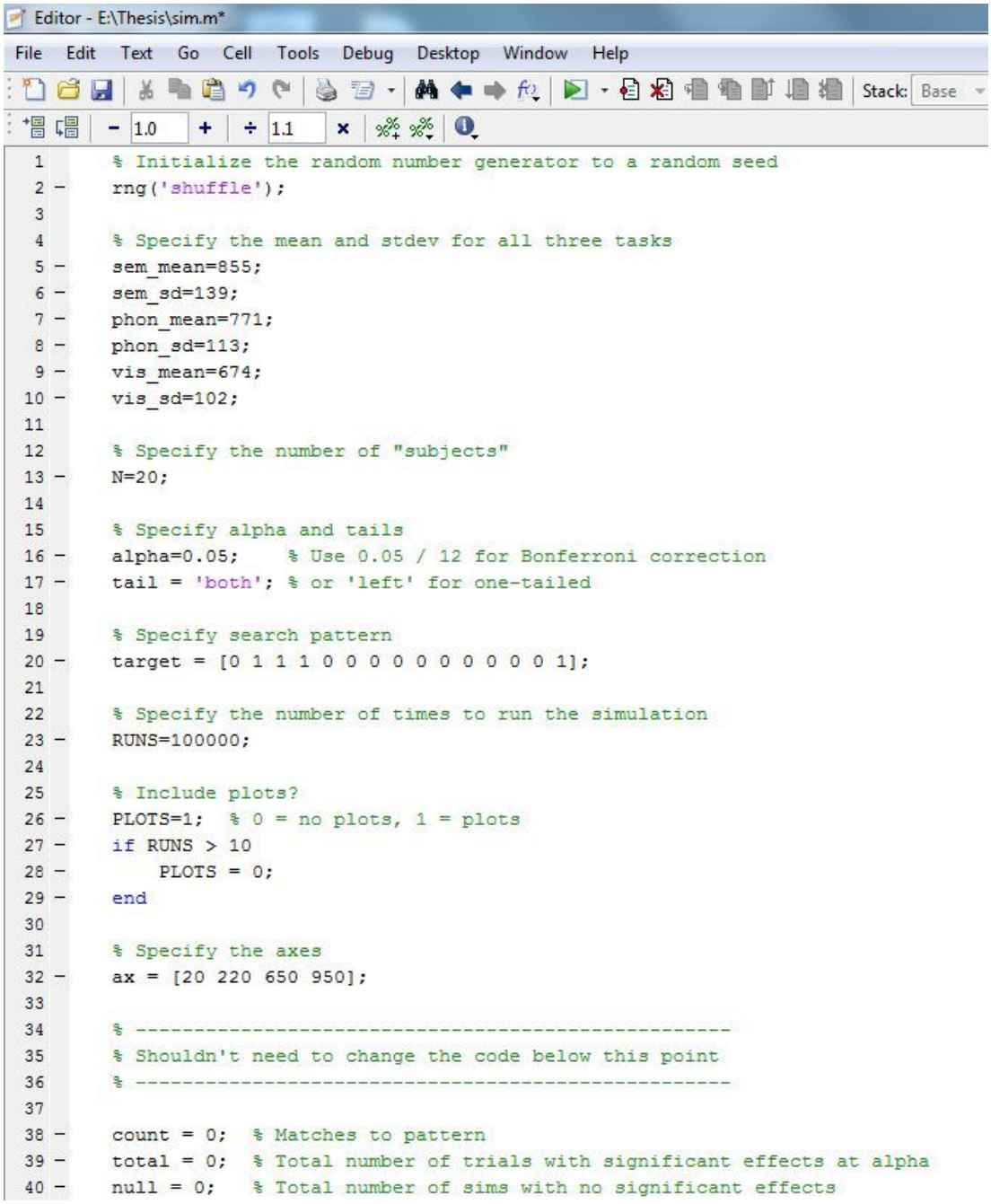
Appendix 1

1. Script performing Monte Carlo simulations.




```
% Initialize the random number generator to a random seed
rng('shuffle');

% Specify the mean and stdev for all three tasks
sem_mean=855;
sem_sd=139;
phon_mean=771;
phon_sd=113;
vis_mean=674;
vis_sd=102;

% Specify the number of "subjects"
N=20;

% Specify alpha and tails
alpha=0.05;    % Use 0.05 / 12 for Bonferroni correction
tail = 'both'; % or 'left' for one-tailed

% Specify search pattern
target = [0 1 1 1 0 0 0 0 0 0 0 0 0 0 1];

% Specify the number of times to run the simulation
RUNS=100000;

% Include plots?
PLOTS=1;  % 0 = no plots, 1 = plots
if RUNS > 10
    PLOTS = 0;
end

% Specify the axes
ax = [20 220 650 950];

% ------------------------------------------------------
% Shouldn't need to change the code below this point
% ------------------------------------------------------

count = 0;  % Matches to pattern
total = 0;  % Total number of trials with significant effects at alpha
null = 0;   % Total number of sims with no significant effects
```

```
41
42 -  for x=1:RUNS
43       % Generate random RTs from a normal distribution using the above values
44 -     SEM=round(sem_mean + sem_sd * randn(N,5));
45 -     PHON=round(phon_mean + phon_sd * randn(N,5));
46 -     VIS=round(vis_mean + vis_sd * randn(N,5));
47 -     DATA=[PHON SEM VIS];
48 -     [r, c] = size(DATA);
49
50       % Compute the means per condition and compare them to the baseline
51 -     means = round(mean(DATA));
52 -     sems = std(DATA) ./ sqrt(N);
53 -     effects = zeros(1,c);
54
55       % Generate a figure illustrating the "results"
56 -     if PLOTS
57 -         figure
58 -         x=[40:40:200];
59 -     end
60
61       % Phonology
62 -     if PLOTS
63 -         subplot(1,3,1);
64 -         b=bar(x, means(1:5), 'r');
65 -         axis(ax);
66 -         xlabel('Phon');
67 -         b.LineWidth = 2;
68 -         b.EdgeColor = 'black';
69 -         hold on
70 -         plot([20:20:220], [means(1)*ones(11)], '--k', 'LineWidth', 2);
71 -     end
72 -     for i=2:5
73 -         h = ttest(PHON(:,1), PHON(:,i), 'alpha', alpha, 'tail', tail);
74 -         if h
75 -             if PLOTS
76 -                 text(x(i), means(i)+10, '*', 'FontSize', 24)
77 -             end
78 -             effects(i)=h;
79 -         end
80 -     end
81
82       % Semantics
83 -     if PLOTS
84 -         subplot(1,3,2);
85 -         b=bar(x, means(6:10), 'b');
86 -         axis(ax);
87 -         xlabel('Sem');
88 -         b.LineWidth = 2;
89 -         b.EdgeColor = 'black';
```

```
90 -            hold on
91 -            plot([20:20:220], [means(6)*ones(11)], '--k', 'LineWidth', 2);
92 -        end
93 -        for i=2:5
94 -            h = ttest(SEM(:,1), SEM(:,i), 'alpha', alpha, 'tail', tail);
95 -            if h
96 -                if PLOTS
97 -                    text(x(i), means(5+i)+10, '*', 'FontSize', 24);
98 -                end
99 -                effects(5+i)=h;
100 -           end
101 -       end
102
103         % Visual
104 -       if PLOTS
105 -           subplot(1,3,3);
106 -           b=bar(x, means(11:15), 'g');
107 -           axis(ax);
108 -           xlabel('Vis');
109 -           b.LineWidth = 2;
110 -           b.EdgeColor = 'black';
111 -           hold on
112 -           plot([20:20:220], [means(11)*ones(11)], '--k', 'LineWidth', 2);
113 -       end
114 -       for i=2:5
115 -           h = ttest(VIS(:,1), VIS(:,i), 'alpha', alpha, 'tail', tail);
116 -           if h
117 -               if PLOTS
118 -                  text(x(i), means(10+i)+10, '*', 'FontSize', 24);
119 -               end
120 -               effects(10+i)=h;
121 -           end
122 -       end
123
124 -       if sum(effects) > 0
125 -           total = total + 1;  % Sims with significant effects
126 -       else
127 -           null = null + 1;    % Sims with no significant effects
128 -       end
129 -       if effects == target
130 -           count = count + 1;
131 -       end
132 -   end
133
134 -   str=sprintf('Out of %d trials: %d had significant effects ', RUNS, total);
135 -   disp(str);
136 -   str=sprintf('                  %d had no significant effects.', null);
137 -   disp(str);
138 -   str=sprintf('                  %d matched the ANG pattern.\n', count);
```

Appendix 2

Table 1: Word pairs used in the rhyme judgement task.

YES Trials	NO Trials
theme - beam	pocket - wrong
spade - aid	warn - barn
guitar - cigar	tree - bite
harp - carp	relax - relapse
take - snake	snort - well
queen - green	core - seen
door - shore	cow - snow
flower - hour	skull - full
sphere - near	pest - peat
pistol - crystal	phone - boar
tie - cry	glass - born
blue - who	play - grape
table - stable	gown - own
hair - where	said - raid
flute - fruit	dancer - long
walk - chalk	have - grave
late - weight	slug - muck
broom - tomb	paper - water
put - soot	move - love
right - night	height - eight
style - pile	farm - warm
pot - yacht	bee - hope
wheat - treat	sour - your

dial - tile	dusk - copper
turn - learn	fountain - curtain
lace - case	hunter - jumper
hear - year	wash - flash
apple - chapel	work - pork
cope - soap	angle - angel
write - might	egg - pen
smear - pier	folder - elder
grass - pass	dart - quart
term - germ	mare - game
shed - bread	tap - fuse
grate - bait	vow - tow
rope - pope	sue - whip
clock - rock	one - bright
freight - plate	heart - cover
made - blade	cold - colt
place - race	pint - hint
razor - laser	peach - leg
shears - ears	chin - kit
raw - saw	load - voice
sword - hoard	couch - touch
toast - most	citadel - citation
doll - fall	rocket - lung
bleach - speech	wand - sand
cake - break	bear - rear
spoon - prune	ease - lease
home - foam	cost - post
wall - call	puddle - hood

sun - none	tray - slat
slide - guide	shoot - tape
knee - sea	down - known
reap - heap	bowl - silk
flannel - panel	crew - lane
lone - stone	soil - foal
glue - zoo	futon - button
kite - white	earn - dip
board - lord	wool - tool
hose - clothes	before - beware
pane - vein	dove - stove
priest - beast	trim - show
note - moat	pail - fray
loan - zone	border - organ
thief - brief	veal - base
wire - tyre	vain - role
tooth - booth	cast - cart
smoke - joke	filter - fault
fair - glare	south - youth
crawl - hall	rain - used
chain - plane	worm - storm
noun - town	ink - mint
lice - nice	shown - crown
teeth - sheath	clamp - rant
coat - vote	baton - matter
laugh - calf	wrap - sing
would - good	jute - fluke

ladle - cradle lard - card	salon - melon stack - ramp

Table 2: Word pairs used in the semantic category judgement task.

YES Trials	NO Trials
hoe - rake	blouse - needle
tulip - daisy	fleet - pearl
ankle - elbow	powder - branch
square - triangle	steam - valley
moon - planet	collar - wheel
steel - brass	balloon - protest
funeral - corpse	blanket - channel
referee - match	autumn - soccer
dirt - dust	history - canteen
team - coach	wife - book
dinner - lunch	iron - horn
clam - oyster	seat - yard
whisky - brandy	maple - spray
lamb - chicken	spot - dark
haddock - herring	eagle - mayor
morning - evening	brother - sneeze
sight - taste	corridor - doughnut
beach - coast	contract - umbrella
painter - portrait	cells - frame
mist - fog	army - bird
cube - square	barrel - jelly
milk - cheese	lemon - sleeve
went - go	store - clown
summer - winter	drug - ring

skirt - shirt	walnut - bullet
west - east	soldier - pudding
five - nine	machine - mustard
boss - leader	veil - deck
pot - pan	ribbon - china
teacher - school	medal - nurse
light - dark	rusty - shell
chop - slice	wolf - coil
foxtrot - waltz	fan - jar
robin - pigeon	tailor - cheek
drums - piano	trash - lunch
slow - quick	cottage - weather
magician - wizard	magnet - carpet
boat - ferry	flood - floor
bracelet - necklace	sponge - closet
tornado - typhoon	banker - spider
pestle - mortar	envelope - library
ash - flame	shovel - shower
tennis - hockey	factory - sparrow
lace - sole	desk - straw
verb - adverb	napkin - ticket
hospital - patient	window - camera
lung - liver	spear - spark
tale - story	drizzle - passage
boy - man	riddle - anchor
nail - bolt	train - duck
inch - mile	grocer - monkey
paint - draw	helmet - mirror

onion - carrot	office - officer
stool - chair	jam - bin
dog - cat	purse - graph
carbon - oxygen	cancer - island
boots - sandals	hotel - driver
lime - lemon	vehicle - toaster
pillow - sheet	test - frog
elm - oak	tribe - waist
pencil - ruler	money - aisle
beans - peas	poetry - wallet
tiger - leopard	juice - nerve
lettuce - spinach	parade - rubber
birch - willow	empire - injury
cent - penny	nest - band
hat - cap	master - market
linen - velvet	economy - bacteria
judge - court	shepherd - platform
comedy - horror	earth - woman
yellow - red	belt - face
mosque - church	saint - blind
music - sound	wreck - glove
thief - robber	drum - aunt
vodka - beer	string - resort
minute - second	engine - temple
pond - ocean	essay - metal
cherry - apricot	stain - arrow
fuel - coal	tourist - slipper

wheat - maize	atom - club

Table 3: Word pairs used in the homophone judgement task.

YES Trials	NO Trials
bear - bare	seed - soot
tyre - tire	accordion - accordance
ode - owed	lad - lid
road - rode	petal - pebble
rote - wrote	butter - button
berry - bury	blood - blush
cue - queue	prince - print
bite - byte	liar - lair
raise - rays	mother - mutter
rain - reign	please - pliers
muscle - mussel	sausage - sauces
wrap - rap	cleaver - clover
hour - our	moose - mouse
great - grate	trombone - trumpet
foul - fowl	pillow - plough
sweet - suite	buckle - bubble
mode - mowed	poster - plaster
heel - heal	sentiment - sensitive
fair - fare	navel - novel
sew - sow	mall - mole
hear - here	kitten - knitting
jeans - genes	building - bullring
allowed - aloud	vision - villain
ware - wear	map - mop

ate - eight	hammer - hamster
way - weigh	pound - pounce
rye - wry	pint - pine
would - wood	border - bother
doe - dough	liquid - liquor
sail - sale	miner - mile
beach - beech	honey - hunter
board - bored	forest - frost
sole - soul	console - council
pray - prey	shot - shop
pain - pane	goddess - goodness
him - hymn	lather - leather
knows - nose	garden - guarded
ceiling - sealing	banana - banner
nay - neigh	pole - polo
key - quay	soup - supper
baize - bays	diary - dairy
brake - break	jury - duty
draft - draught	coffee - coffin
beet - beat	ask - axe
cereal - serial	projector - projectile
links - lynx	circle - circus
throne - thrown	filter - fillet
ail - ale	weed - weir
guise - guys	harbour - harvest
toe - tow	bottle - battle

Table 4: Word pairs used in the synonym judgement task.

YES Trials	NO Trials
king - monarch	coin - gold
certain - sure	canal - stream
menace - threat	sheep - wool
cargo - freight	garlic - sage
lobby - foyer	file - nail
visitor - guest	key - door
holiday - vacation	fence - gate
snake - serpent	comb - razor
absent - missing	moth - fly
physician - doctor	socket - plug
champion - hero	cigar - pipe
hint - clue	college - vow
child - kid	beef - pork
bucket - pail	spoon - fork
choir - chorus	satin - silk
belly - abdomen	copper - lead
films - movies	bone - joint
stairs - steps	otter - seal
gift - present	sugar - salt
punishment - penalty	mail - letter
dwelling - abode	pen - ink
country - nation	gravel - sand
prison - jail	text - journal
wrath - anger	candle - grave

staff - personnel	cloud - sky
identical - same	cake - pie
cry - weep	bulb - lamp
poison - venom	cliff - cave
brawl - quarrel	bank - note
enemy - foe	ice - drink
criminal - felon	tree - bush
task - job	reply - answer
enigma - mystery	river - bridge
baby - infant	jug - bottle
pony - mule	orange - apple
car - automobile	wall - brick
dress - frock	leg - foot
couch - sofa	stove - kettle
student - pupil	soap - cream
writer - author	meadow - hay
outcome - effect	luck - hope
bomb - explosive	wine - grape
biscuit - cookie	wax - candle
imitate - copy	cup - plate
fabric - cloth	pride - boast
devil - demon	stem - leaf
trip - journey	mug - saucer
lift - elevator	vase - urn
satchel - bag	boxes - jars
lawyer - attorney	fairy - ghost

Table 5: Word pairs used in the consonant letter string matching task.

YES Trials	NO Trials
zkjdf - zkjdf	zxhqt - zsdyt
brdqf - brdqf	brzcw - bdfhw
ghjkl - ghjkl	sdyxk - snmqk
cmxdy - cmxdy	gvncl - grwhl
spnkl - spnkl	vklcb - vwtsb
jbnhc - jbnhc	lrpgy - lcbfy
pgvcz - pgvcz	ydqvt - ycsjt
slmdf - slmdf	gzchn - gxdvn
tcbfr - tcbfr	fljyt - fwrpt
dwgly - dwgly	tdfhv - tjrqv
plfsk - plfsk	zdwqb - zvknb
jqzfc - jqzfc	fdnsc - fmrlc
qlgpk - qlgpk	zqlpm - zvswm
svwrb - svwrb	scjyw - shlqw
xzymd - xzymd	mzscv - mxwpv
sjwzb - sjwzb	ncsjx - npkhx
dxstw - dxstw	bnqft - bxhjt
msxqr - msxqr	qxlmj - qdgbj
lbmkp - lbmkp	pjrqg - pszcg
nctbv - nctbv	lvkpj - lznyj
brwhc - brwhc	lmqwn - lbxpn
jpmzf - jpmzf	ytcsd - yspmd
jxmrg - jxmrg	xhjyh - xlfsh
wrgxp - wrgxp	chrzd - cnlqd

mxjyt - mxjyt	tcgpk - thplk
fglqn - fglqn	jydmb - jbrwb
tdkyt - tdkyt	xwpdv - xlkgv
dvpxy - dvpxy	kxtmq - kfwtq
khgjp - khgjp	vsknc - vjdlc
cpyxk - cpyxk	zhlqd - zcjyd
nlhjd - nlhjd	cplhj - cyxkj
fxdvc - fxdvc	bztgj - bwrcj
ywqzv - ywqzv	nmbsh - nbylh
jlxjd - jlxjd	kbylx - kmhbx
vfzpl - vfzpl	zpjft - zpgtt
pdzct - pdzct	rctgp - rhqkp
ryqxp - ryqxp	nswpm - nbmkm
rszdw - rszdw	zbxpm - zmqwm
bjklp - bjklp	fmvrt - fhgjt
xtvkn - xtvkn	rqvfw - rjxmw
shqwy - shqwy	splqn - scgpn
zqpty - zqpty	vswkb - vdngb
vgbgx - vgbgx	ednhj - evpxj
dsfwq - dsfwq	lkgmn - lrqvn
fwtsp - fwtsp	dngtr - dzqlr
wrdmb - wrdmb	wyznq - wrysq
nzbgl - nzbgl	bxgwf - bnwvf
htrcv - htrcv	dsvcz - dhplz
fmbvc - fmbvc	mfrqp - mwcrd
wcthz - wcthz	kgbch - kcrpt