Occipito-temporal Contributions to Reading

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I, Keith James Kawabata Duncan, 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.

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くみこへ、

頭は科学に捧ぐにせよ、心は貴女へ

Publications arising from this thesis

Duncan KJ, Pattamadilok C, Knierim I, Devlin JT (2009) Consistency and variability in functional localisers. NeuroImage 46: 1018-1026

Duncan KJ, Pattamadilok C, Devlin JT (2010) Investigating occipito-temporal contributions to reading with TMS. Journal of Cognitive Neuroscience 22: 739-750

"Mental faculties are notions used to designate extraordinarily involved complexes of elementary functions… One cannot think of their taking place in any other way than through an infinitely complex and involved interaction and cooperation of numerous elementary activities, with the simultaneous functioning of just as many cortical zones, and probably of the whole cortex and perhaps also including even subcortical centers. Thus, we are dealing with a physiological process extending widely over the whole cortical surface and not a localized function within a specific region. We must therefore reject as a quite impossible psychological concept the idea that an intellectual faculty or a mental event or a spatial or temporal quality or any other complex, higher psychic function should be represented in a single circumscribed cortical zone, whether one calls this an 'association centre' or 'thought organ' or anything else."

(Brodmann 1909 [translated and edited by Garey LJ. 1994. Brodmann's 'Localisation in the Cerebral Cortex.' London: Imperial College Press, pages 254-255].)

General Abstract

The debate regarding the role of ventral occipito-temporal cortex (vOTC) in visual word recognition arises in part from difficulty delineating the functional contributions of vOTC as separate from other areas of the reading network. Successful transcranial magnetic stimulation (TMS) of the area could provide a novel source of information regarding the area's function, by offering the possibility of temporarily, non-invasively perturbing its information processing and assessing the consequences on behaviour. However, the area is often considered too deep to successfully stimulate with TMS. Thus the initial step was the demonstration of the feasibility of stimulation, which I proved in the first series of experiments. The stimulation resulted in a disruption in visual word recognition that was stimulus- and site- specific. The second series of experiments further investigated the stimulus-specificity, demonstrating that the nature of this specificity was task-dependent. The final series of TMS experiments in the thesis utilised the high temporal resolution of TMS to map out the dynamics of processing in both left and right vOTC, revealing hemispheric asymmetries in the time course of ventral occipito-temporal processing consistent for both visual words and objects. To complete these experiments, I acquired a large amount of functional localiser data for neuronavigated TMS. This allowed the investigation of the effectiveness of fMRI localisation for TMS and in addition the investigation of the important issue of how consistent the functional regions of interest (fROI) produced by these scans are. The first of two experiments showed these fROIs may have surprisingly poor reliability while the second investigated how best they can be optimised, maximising reliability. In conclusion, my PhD has demonstrated the feasibility and potential of using TMS to investigate vOTC contributions to visual word and object recognition, providing a novel source of information capable of informing the ongoing debate concerning vOTC.

1 Introduction

1.1 Classical neurological model of reading

Though reading is a skill which requires many years of instruction to master, once learned it is accomplished with remarkable ease despite requiring the rapid coordination of visual, phonological, semantic and linguistic processes. Understanding how this is achieved is a major goal of cognitive neuroscience. The investigation of the neurology of reading dates back to the seminal work of Dejerine (1891; 1892). These early efforts, together with the work of Broca (1861), Wernicke (1874) and Lichtheim (1885), resulted in what is now referred to as the classical neurological model of reading (Geschwind 1965b; Geschwind 1965a). This model, shown in Figure 1-1, proposed that visual information arrives in visual cortex, and then proceeds to the left angular gyrus where it is linked to abstract visual word forms. These abstract visual word forms are then sent to Wernicke's area, where they are linked to appropriate auditory word forms. From there the auditory word forms link to motor word forms stored in Broca's area. This influential model has helped to shape research into the neuroscience of reading by identifying a set of key regions involved in visual word recognition and their functional interactions.

Figure 1-1: The classical neurological model of reading. Visual information arrives in visual cortex (light blue), and then proceeds to the angular gyrus (green) which stores abstract visual representations of words. These abstract visual word representations are then linked with corresponding auditory word forms in Wernicke's area (red) which then link to motor word forms in Broca's area (dark blue). Note the absence of ventral occipito-temporal cortex and that connections between the cortical centres are feedforward only. Adapted from Devlin (2008). Reproduced with kind permission of Springer Science+Business Media.

1.2 Ventral occipito-temporal involvement in reading

Over the decades since its development, it has become increasingly apparent that the classical model omits at least one key region involved in reading, namely left ventral occipito-temporal cortex (vOTC). vOTC encompasses the posterior aspect of the fusiform gyrus along with the adjacent occipito-temporal sulcus, and lies between posterior visual areas such as V4 and more anterior ventral temporal areas. Evidence for the involvement of this area in reading came initially from studies of patients with pure alexia and subsequently from neuroimaging studies of normal, healthy readers.

Pure alexia, also referred to as alexia-without-agraphia, is a type of reading impairment that can occur in previously skilled readers following brain injury. “Pure” refers to the fact that while writing along with production and comprehension of oral language are generally spared, word reading is severely impaired (Benson and Geschwind 1969). These patients often rely on an inefficient letter-by-letter reading strategy (reconstructing the word after identifying its constituent letters). This results in the word length effect that is characteristic of pure alexia: unlike skilled readers, the naming latencies of words increase dramatically as the number of letters increases. Pure alexia can occur in the absence of a visual field deficit but commonly is accompanied by a right homonymous hemianopia (Leff et al. 2001). The functional locus of the impairment that results in pure alexia remains a matter of some debate with hypotheses regarding the possible loci falling into two categories. The first suggests that the deficit is in a reading-specific component, such as letter recognition (Reuter-Lorenz and Brunn 1990; Arguin and Bub 1993) or orthographic form processing (Dejerine 1892; Warrington and Shallice 1980; Cohen et al. 2003), while the second proposes the impairment lies in low level perceptual processing (Kinsbourne and Warrington 1962; Kinsbourne and Warrington 1963; Friedman and Alexander 1984; Farah and Wallace 1991; Sekuler and Behrmann 1996; Behrmann et al. 1998a; Mycroft et al. 2009; Starrfelt et al. 2009; Starrfelt et al. 2010). By definition, a deficit in a reading-

specific component should only affect lexical processing. There are, however, a growing number of reports of subtle deficits in non-lexical stimuli, such as digits and visually presented objects, in patients with pure alexia that may not be detected when using standard clinical tests, suggesting that *pure* alexia may be somewhat of a misnomer (Kinsbourne and Warrington 1962; Friedman and Alexander 1984; Farah and Wallace 1991; Sekuler and Behrmann 1996; Behrmann et al. 1998a; Mycroft et al. 2009; Starrfelt et al. 2009; Starrfelt et al. 2010). As will be seen, this specificity debate is also present in the neuroimaging literature.

Leff and colleagues (2001) investigated the anatomical locus of pure alexia by comparing the site of the lesion in a patient with pure alexia (Figure 1-2a) to activity elicited by word reading in normals and patients with visual field defects but no reading deficit. They found that the activity associated with word reading in the unimpaired reading groups was within the boundaries of the pure alexic patient's left vOTC lesion, consistent with other reports of pure alexia following injury to the area (Dejerine 1892; Damasio and Damasio 1983; Binder and Mohr 1992; Beversdorf et al. 1997; Gaillard et al. 2006). This association provides strong evidence in favour of an important role for the area in reading.

The picture, however, is more complicated than a simple one-to-one mapping between lesion site and symptoms. First, lesions tend to be large and do not confine themselves to anatomically or functionally defined boundaries (Damasio and Damasio 1983), making it difficult to determine the critical site. Second, lesions to left vOTC do not always produce reading impairment. Hillis and colleagues (2005) found no association between damage to left vOTC and impaired written word comprehension or written lexical decision in 80 patients with acute left hemispheric stroke. Rather, damage to this area was associated with impaired picture naming and reading aloud. Finally, left inferior parietal lesions can also result in pure alexia (Warrington and Shallice 1980; Philipose et al. 2007). Taken

together, these findings suggest that successful reading requires a network of regions, including left vOTC, to be intact.

vOTC involvement in reading has been confirmed using neuroimaging in normal healthy readers. Petersen and colleagues (1988) used PET to identify the brain areas involved in single word reading. They found that silent reading of single words elicited activation in visual cortex extending as far forward as vOTC. Reading related activation in vOTC has since been replicated many times, using PET (Price et al. 1994; Price et al. 1996; Herbster et al. 1997; Rumsey et al. 1997), and more recently using fMRI (Figure 1-2b)(Cohen et al. 2000; Cohen et al. 2002; Kronbichler et al. 2004; Devlin et al. 2006). In addition, activity has been observed in scripts such as Chinese (Kuo et al. 2003) and Japanese (Sakurai et al. 2000; Ino et al. 2009), demonstrating that the activity is not limited to alphabetic scripts. Activity in the area can be observed using a number of baseline contrasts, such as fixation (Dehaene et al. 2002), checkerboards (Cohen et al. 2003), consonant strings (Cohen et al. 2002), and during a number of different tasks that engage word recognition, including lexical (Fiebach et al. 2002) and semantic (Chee et al. 2003b) decisions. The area activates even if it is not necessary for the task (Price et al. 1996). Intracranial recordings (Nobre et al. 1994) and magnetoencephalography (MEG) (Salmelin et al. 1996; Tarkiainen et al. 1999) have also demonstrated reading related activity in vOTC at approximately 170-200msec after a word is visible. In summary, although omitted from the classical model, there is strong support for vOTC making important contributions to reading.

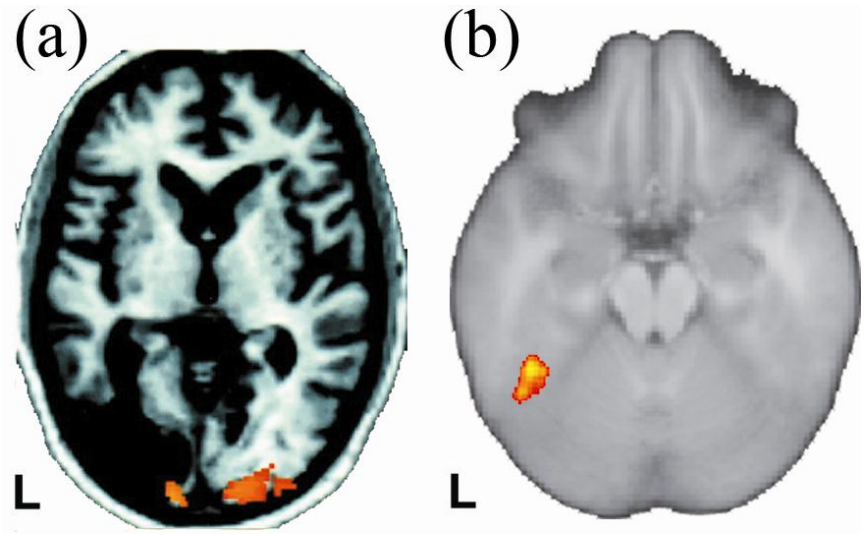


Figure 1-2: (a) A lesion to left ventral occipito-temporal cortex that resulted in pure alexia. Leff and colleagues (2001) Permission to reproduce this figure has been granted by Oxford University Press (b) fMRI activation in ventral occipito-temporal cortex during reading (Duncan et al. unpublished data)

1.3 Functional and anatomical interactivity in reading

Behavioural studies of reading suggest that unlike the purely feedforward processing shown in the classic neurological model of reading, there are considerable interactions between different levels of the functional architecture of reading. For example, when recognising letters in the context of a string of letters, performance is better when the letter is part of a real word compared to when it is presented in a nonword (i.e. a letter string that does not conform to the orthotactic rules of a language), a phenomenon referred to as the word superiority effect (WSE; Cattell 1886; Reicher 1969; Wheeler 1970). The WSE indicates that lexical knowledge influences the perception of words. The most widely accepted explanation is that this knowledge supports letter identification by way of feedback connections (McClelland and Rumelhart 1981; though see Norris et al. 2000). Furthermore, interactions are also thought to occur between visual word recognition and higher-order non-visual properties, such as phonology (Stone et al. 1997; Grainger and Ziegler 2008) and semantics (Reimer et al. 2008). For example, words that have rimes that may be spelt differently in different words (i.e. are inconsistent in the sound-to-spelling

direction, for example, *young*) require longer to read compared to words which have rimes that can only be spelt in one way (i.e. are consistent in the sound-to-spelling direction, for example, *probe*) (Stone et al. 1997; Grainger and Ziegler 2008). Furthermore, words are easier to recognise if they are preceded by a semantically related word (e.g. *toad* preceded by *frog*) (Reimer et al. 2008). These effects are difficult to account for within a purely feedforward framework, and strongly suggests that feedback information from phonology and semantics influence visual word recognition.

As a consequence, interactivity, i.e. the presence of feedforward *and* feedback connections between components within the functional architecture, is a practically ubiquitous feature of computational models of reading (Rumelhart and McClelland 1982; Plaut et al. 1996; Coltheart et al. 2001; Jacobs et al. 2003; Harm and Seidenberg 2004; Perry et al. 2007). Moreover, behavioural reports of interactivity, such as the WSE and the feedback consistency effect, highlight the importance of processing dynamics for a comprehensive understanding of the interactions in the reading network.

In contrast, the classical model lacks feedback connections between anatomical areas (Figure 1-1), making it difficult to see how it could support interactivity between different processing levels involved in reading. In fact, despite the ubiquity of interactivity in computational models, the assumption of feedforward processing is still common in neurological models, particularly regarding orthographic processing (for example, Pugh et al. 1996; Shaywitz et al. 2002; Dehaene et al. 2005). Feedback connections are on occasion mentioned but are typically excluded from comprehensive consideration (e.g. Dehaene et al. 2005), and are relegated to a peripheral role, such as when participants explicitly visualise words (Cohen et al. 2002).

1.4 Modern neurological models of reading

Figure 1-3 shows an updated neurological model which proposed that three left hemisphere regions subserve reading (Pugh et al. 1996; Shaywitz et al. 2002). When compared to the classical model (Figure 1-1), it is clear that there is some overlap with the updated model. However, there are also differences: First, the updated model now includes an occipito-temporal area, including vOTC, and suggests that the area automatically and rapidly decodes the visual form of whole words. Second, the functions ascribed to the remaining areas have changed. Phonological processing is now suggested to be subserved by both the parieto-temporal region and inferior frontal cortex, with the latter also involved in motor control of speech. As the regions posited by this model remain quite large, it is possible that they may contain many anatomical and functional subdivisions.

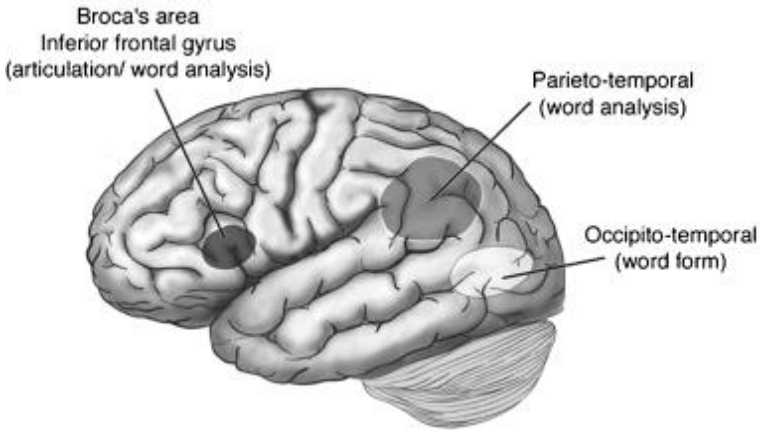


Figure 1-3: The Pugh and Shaywitz (1996; 2002) model proposed that three left hemisphere regions subserve reading. OTC decodes the visual word form, parieto-temporal areas are involved in phonological aspects of word form analysis along with inferior frontal gyrus which is also involved in articulation. Permission to reproduce this figure has been granted by Elsevier.

Following this model, considerable amounts of neuroimaging data have been acquired and the neurological models have become increasingly fine-grained (Price 2000; Price and Mechelli 2005; Frost et al. 2008). Like previous models, the model developed by Price and

colleagues (2000; 2005) and an evolution of the Pugh and Shaywitz model (Sandak et al. 2004; Frost et al. 2008) contain occipito-temporal, parieto-temporal and frontal areas, with the two models ascribing similar functions to the areas. However, where previously fairly large cortical areas were treated as homogenous zones, these models subdivide the regions and provide more description of what occurs within them. For example, the left occipito-temporal region is subdivided into three areas. The posterior region and vOTC are involved with the processing of higher order visual input, with the latter additionally acting as an interface between a visual stimulus and its higher order properties, while the anterior region is involved in semantic processing. The left inferior frontal area is now subdivided into two: pars opercularis (POp) and pars orbitalis (POr) / pars triangularis (PTr). Though both subdivisions are activated by tasks that require either phonological or semantic processing, a relative activation difference exists where POr and PTr are more active during tasks which load more on semantic processing relative to tasks loading on phonological processing (Buckner et al. 1995; Fiez 1997). The converse is true for POp, where activation is stronger for phonological processing demanding tasks relative to semantic tasks (Poldrack et al. 1999; Devlin et al. 2003b). Phonological processing is subdivided into sensorimotor integration and articulatory planning. The former is subserved by bilateral supramarginal gyrus and POp, while the latter by bilateral anterior insulae and frontal operculum. Semantic processing is suggested to occur over a number of areas distributed throughout the cortex, including the aforementioned left inferior frontal and anterior occipito-temporal areas, and also angular gyrus and middle temporal gyrus (Price 2000; Price and Mechelli 2005).

Although these more detailed models are in general agreement regarding the areas involved (including the fact that they essentially contain only left hemisphere components), the model proposed by Price and colleagues is unique in explicitly stating that none are dedicated to reading and in fact, some may not even be specific to language.

For example, vOTC is involved in object recognition (Malach et al. 1995; Grill-Spector et al. 1998; Farah 2004). In fact, theories of vOTC function can be grouped into two categories: those that suggest the area is specific to reading or contains reading-specific elements (Kronbichler et al. 2004; Dehaene et al. 2005; Bruno et al. 2008; Tsapkini and Rapp 2010) and those, like the Price model, that suggest that the area shares a common function for lexical and non-lexical stimuli (Nakamura et al. 2002; Hillis et al. 2005; Price and Friston 2005; Devlin et al. 2006; Xue et al. 2006; Cai et al. 2010)[1].

1.5 Reading-specific hypotheses – Visual word form areas

One of the most detailed and influential reading-specific accounts of vOTC function is the Local Combination Detector (LCD) model of visual word recognition (Dehaene et al. 2005; Vinckier et al. 2007). It is the first neurological model of reading to attempt the non-trivial matter of incorporating some of the wealth of information known about non-human primate visual cortex and relies heavily on the classical hierarchical model of the visual system. Neurons in the lower levels have small receptive fields and prefer simple stimuli but as one ascends the hierarchy, neurons have increasingly large and invariant receptive fields and a preference for increasingly complex visual stimuli. The output of a level is integrated and processed in turn by successive levels (Vogels and Orban 1985; Maunsell and Newsome 1987). The LCD model proposes that a similar hierarchical structure governs word recognition. Information proceeds in a serial, essentially feedforward fashion from simple feature detectors located in early visual cortex, to letter detectors in V4, to bigram detectors in vOTC, and then on to whole word detectors located anterior temporal lobe areas (Dehaene et al. 2005; Vinckier et al. 2007).

[1] Other models refer only to reading and word recognition but do not explicitly claim reading specificity or otherwise (for example, Frost et al. 2008).

To investigate the role of vOTC specifically, Cohen and colleagues (2000) used split-field presentation of word stimuli and investigated how visual field affected brain activity (indexed by both fMRI and ERP) in normal participants and split-brain patients. The key finding was that visual field was irrelevant for left vOTC activation for controls but only RVF stimuli elicited left vOTC activation in the two patients. No activation was found in right vOTC for either visual field in either group. This, Cohen and colleagues suggest, reveals the direct versus transcallosal routes to the "left-hemisphere reading system" that word stimuli presented in RVF and LVF respectively must take. As the latter route is unavailable in split-brain patients, only RVF word stimuli elicit left vOTC activation. In the controls, the latency of the ERP peak thought to originate from vOTC was approximately 170-200msec post-stimulus onset, consistent with the N170 component known to be sensitive to orthographic processing (Neville et al. 1992; Nobre et al. 1994; Salmelin et al. 1996; Bentin et al. 1999; Tarkiainen et al. 1999; McCandliss et al. 2003). This ERP component was hemifield independent, unlike the preceding components. Cohen and Dehaene suggest that these data indicate that vOTC is the cortical area where information regarding visually presented words from the two visual hemifields is combined. Subsequent studies from the same group demonstrated that the activation in the area is greater for visual words relative to consonant strings (Cohen et al. 2002) and independent of typographic case (Dehaene et al. 2001) and that the area is not responsive to auditory words (Dehaene et al. 2002). As a consequence of these imaging studies together with the association of damage to the area and reading impairment, Dehaene and colleagues proposed that this region is the neural equivalent of the visual word form area (VWFA), a component of some but not all cognitive models of reading (McCandliss et al. 2003; Cohen and Dehaene 2004; Dehaene et al. 2005). Furthermore, they propose that this area contains neurons that during the course of learning to read become 'recycled' from object-sensitive to reading-specific neurons.

In fact, there are now two VWFA hypotheses of vOTC function. The first hypothesis was proposed to account for the fact that vOTC shows activation to pseudowords, and in fact this pseudoword activation is frequently greater than activation to real words (Fiez et al. 1999; Hagoort et al. 1999; Xu et al. 2001; Mechelli et al. 2003; Binder et al. 2005a; Lee et al. 2010). Although pseudowords should not have entries in the hypothesised VWFA, they are composed of orthotactically legal letter pairs, leading Dehaene and colleagues (2004; 2005) to suggest that left vOTC contains abstract orthographic codes for these letter pairs, known as bigrams.

The second VWFA hypothesis of vOTC function suggests that the area is in fact a *lexical* VWFA and that the activation to pseudowords is a result of "several visual orthographic word representations [getting] partly activated or each letter or letter pattern may have to be processed separately resulting in higher activation" (Kronbichler et al. 2004). This account is supported by the inverse relationship between word frequency (i.e. how many times a particular word occurs in written text) and activation strength (Chee et al. 2003b; Kronbichler et al. 2004). Components sensitive only to prelexical features should be blind to properties, such as frequency, that emerge at the lexical level since these are not contained within its constituent parts (such as bigrams). Moreover, the left vOTC is activated during reading of Chinese (Kuo et al. 2003) and Japanese (Sakurai et al. 2000; Ino et al. 2009) logographs, consistent with the area containing whole word form representations but difficult to explain in terms of bigrams, which have no equivalent in these scripts.

Despite the reading-specific nature of both visual word form accounts, viewing objects also activates the same area (Malach et al. 1995; Grill-Spector et al. 1998; Duncan et al. 2009), and neuroimaging has been unsuccessful in spatially dissociating the two stimulus categories within vOTC (Price et al. 2006; Ben-Shachar et al. 2007). In fact, objects typically elicit greater activation relative to words (Moore and Price 1999; Price et al. 2006). Of

course, objects are not words, neither do they have bigrams, so to account for the object related activation, the word form accounts suggest that there are distinct sub-populations of object- and word- specific neurons with vOTC (Dehaene et al. 2002; McCandliss et al. 2003). Indeed, findings consistent with this were obtained by Baker and colleagues (2007), who using high resolution fMRI found areas within vOTC which show greater activity for words relative to objects. Subsequent work, however, again using high resolution fMRI, revealed that these are unreliable, false positives and only present when using liberal statistical thresholds (Wright et al. 2008). Moreover, fMRI adaptation, which can theoretically determine if the same or distinct neuronal populations are involved in processing of two stimulus types (Naccache and Dehaene 2001), has also failed to provide any evidence of neuronal specialisation for words (Kherif et al. 2010).

1.6 The alternative to reading-specificity – The interface account

The interface hypothesis suggests that vOTC interacts with other regions, acting as an interface associating feedforward visual form information with feedback from higher order non-visual properties of the stimulus (Nakamura et al. 2002; Hillis et al. 2005; Price and Friston 2005; Devlin et al. 2006; Xue et al. 2006; Cai et al. 2010). These non-visual properties include meaning and sound but also properties not related to language such as manual affordances[2] associated with unnameable non-objects (Phillips et al. 2002). In contrast to the reading- and object- specific neurons of the word form accounts, the interface hypothesis posits that a single set of neurons makes the same contributions to any visual stimulus, and is therefore consistent with activation elicited in the area by words and objects (Malach et al. 1995; Grill-Spector et al. 1998; Moore and Price 1999; Price et al. 2006; Ben-Shachar et al. 2007; Wright et al. 2008; Duncan et al. 2009). Since the variability in the visual appearance of writing is considerably less than the variability in

[2] Such as whether something can be twisted or poured etc.

the appearance of objects, the visual form representations for writing (that are not specific to writing) likely constitute a subset of the more general purpose visual form representations. Therefore objects elicit more activity in left vOTC relative to words (Moore and Price 1999; Price et al. 2006) as viewing objects recruits more neurons, necessary to represent their richer visual form (relative to viewing words).

Since the area shares a common function for all visual stimuli, the interface hypothesis is also consistent with reports of subtle impairments in non-linguistic visual form processing that can accompany reading impairments following damage to left vOTC (Behrmann et al. 1998a; Mycroft et al. 2009; Starrfelt et al. 2009; Starrfelt et al. 2010). Furthermore, the interface hypothesis can explain the hemispheric asymmetry observed in both neuroimaging and neuropsychological literature. As the critical non-visual information required for reading tends to be left lateralised, activity in left vOTC is greater than its right homologue (Cai et al. 2010) and reading is sensitive to unilateral damage to left vOTC (Dejerine 1892; Damasio and Damasio 1983; Binder and Mohr 1992; Beversdorf et al. 1997; Leff et al. 2001; Gaillard et al. 2006). In contrast, object recognition relies on both hemispheres more equally and thus gross impairments in object processing generally require either bilateral vOTC damage (Sparr et al. 1991; Humphreys and Rumiati 1998; James et al. 2003; Kohler et al. 2004; Karnath et al. 2009) or extensive unilateral damage (Barton et al. 2004).

The interactivity inherent in the interface hypothesis is also consistent with the previously mentioned interactivity observed in behavioural studies of reading (Cattell 1886; Reicher 1969; Wheeler 1970). Feedback processing also explains why there are differential effects of lexicality and semantics on repetition priming within the area (Fiebach et al. 2005; Devlin et al. 2006), which are difficult to explain within the framework of the essentially feedforward only prelexical and lexical word form theories.

Although the interface hypothesis can explain the modulatory effect of lexicality (Mechelli et al. 2003) and lexical frequency (Chee et al. 2003b; Kronbichler et al. 2004) on left vOTC activity, in its current form it is underspecified. For example, the greater activity in vOTC reported for pseudowords relative to words may reflect the additional processing demands of the search, and since there is no meaning, eventual failure of integration. Conversely, because pseudowords do not have any meaning, the contribution of vOTC may be reduced since there is less to integrate. In this scenario, pseudowords should elicit less activation relative to real words. Similarly, all words regardless of frequency may require integration with their non-visual properties, suggesting that activity in left vOTC should not be modulated by lexical frequency, in contrast to the frequency effects reported in some neuroimaging studies. Alternatively, the increased processing demands required to recognise low frequency words (reflected in their longer reaction times) may necessitate more extensive integration and thus vOTC activity, consistent with the previously mentioned studies.

Since interactivity means information flow is both forward and backward it suggests that, if the hypothesis is correct, understanding the interactions of left vOTC with other brain regions is critical to understanding its function. It is clear, however, that additional work is required to fully specify this hypothesis of vOTC function.

1.7 Testing hypotheses

Both classes of vOTC function make testable predictions. However, many tests although theoretically possible, can be difficult to implement in practice due to the intrinsic limitations of particular methodologies. For example, although analysis of patient data can provide information regarding a brain area's causal influence over behaviour, there are a number of limitations that make interpretation of the data difficult. First, lesions that result in reading impairments such as pure alexia do not restrict themselves to particular

regions of interest and frequently result in damage to widespread areas of cortex and adjacent white matter. Secondly, the neural vasculature is such that cerebrovascular accidents do not occur with equal regularity over the whole brain, making it difficult to prove or disprove the causal involvement of particular areas. Thirdly, the neural organisation and behavioural performance of patients before their cerebrovascular accident is not known, thus potential premorbid differences confound the interpretation of post-lesion data. Finally, possible functional reorganisation in the weeks and months following the lesion can further cloud the interpretation of patient data (Pyun et al. 2007; Rosenberg et al. 2008). Similarly, although fMRI can be used to investigate normal functioning with high spatial precision, it is limited by a poor temporal resolution, making it difficult to investigate the temporal profile of a region. Moreover, it is unable to determine the causal influence of brain activity on behaviour, meaning it is not capable of differentiating essential from other co-activated areas (Price et al. 1999).

In contrast, transcranial magnetic stimulation (TMS) offers the possibility of testing causality, with good temporal resolution and reasonable spatial resolution in normal healthy subjects. The majority of this thesis focuses on characterising the contributions vOTC makes to reading using TMS. However, the location of vOTC on the ventral surface of the brain has lead to the assumption that it cannot be stimulated with TMS (for example, Simos et al. 2008).

Therefore Chapter 3 investigated the feasibility of using TMS to temporarily interfere with processing in ventral occipito-temporal cortex in order to explore its specific contributions to visual word recognition. This chapter demonstrated that vOTC can be selectively stimulated. Moreover, lexical status significantly affected vOTC processing, a finding difficult to reconcile with pre-lexical accounts of ventral occipito-temporal cortex function.

Chapter 4 investigated how lexical frequency affects processing within vOTC and demonstrates that activity within the area is both stimulus-specific and task-dependent. This suggests that feedback information from higher order areas modulates vOTC activity, emphasising the importance of the area's temporal dynamics.

Chapter 5 investigated the temporal dynamics of vOTC during word and object recognition in both hemispheres. The onset of activity within the area was considerably earlier than estimates suggested by ERP studies and the temporal profile suggested that activity within vOTC is both interactive and cascaded. In addition, the temporal profile differed between hemispheres but was consistent for words and objects.

In addition, in Chapter 6 I took the opportunity to investigate the reliability of functional localiser scans, as each participant in the TMS experiments completed an fMRI scan to localise the target site for stimulation. Although initial findings suggested that the reliability of these functional localisers can be poor, I provide guidelines detailing how the scans can be optimised and consequently achieve more acceptable levels of reliability.

Chapter 7 draws some general conclusions regarding the implications of the data presented in this thesis for theories of vOTC function and cognitive models of reading, as well as for TMS and fMRI.

2 General Methods

TMS was the primary method of investigation in the majority of this thesis. Consequently, the aim of the current chapter is to first provide background information about the technique and second to provide a general overview of the specific methods employed in during my doctoral research.

2.1 Overview of Transcranial Magnetic Stimulation

TMS is a non-invasive method that allows the investigation of the causal relevance of a cortical area when performing a particular task. TMS consists of essentially two pieces of hardware, the main unit – a capacitive high voltage, high current discharge system – and a stimulating coil. TMS relies on Faraday's principle of electromagnetic induction. During stimulation the main unit discharges a strong, brief current through the stimulation coil. This in turn induces a relatively brief (~100μs), focal and rapidly changing magnetic field, perpendicular to the plane of the coil. When the coil is held against the scalp, the magnetic field passes unimpeded through the scalp and skull. The time-varying magnetic field induces a weak and short-lived current, flowing in loops parallel to the orientation of the coil, at the site of stimulation that results in neuronal depolarisation or spiking (Ruohonen and Ilmoniemi 2002). The magnitude of the induced current is dependent on both the magnitude and rate of change of the current discharged through the coil.

2.1.1 Modes of TMS

In addition to being able to apply a single pulse of TMS, pulses can be applied in pairs or in trains, respectively referred to as *paired-pulse* and *repetitive TMS*. The protocol (i.e. the pattern and frequency of the pulse trains) of repetitive TMS (rTMS) can be classified as being *conventional* or *patterned* (Figure 2-1). Conventional rTMS can be further subdivided into low frequency (<1Hz) and high frequency rates (>1Hz) of stimulation, and also whether it is applied during or immediately after a subject performs a task (referred

to as *online* TMS) or whether the stimulation and task are separated in time (*offline* TMS). The success of online TMS relies on the pulse train altering neural activity during processing[3] while the success of offline TMS relies on the stimulation effects outlasting the stimulation period. Patterned TMS refers to protocols where short trains of pulses are separated by periods of no stimulation, and is only employed in an offline approach. The behavioural impact of TMS depends on the stimulation parameters used, though the neurophysiology of these differences remains unclear. Only single- and paired-pulse TMS and online conventional rTMS (10Hz) were used in this thesis.

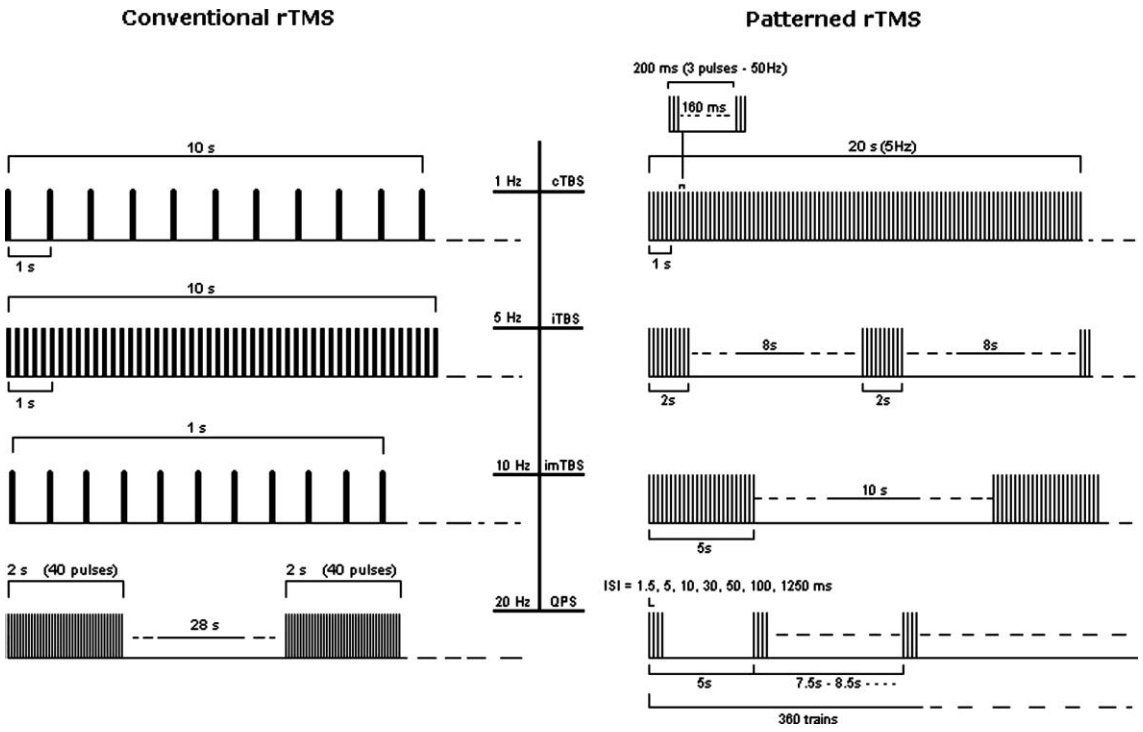


Figure 2-1: Types of rTMS. rTMS can be grouped into two main categories conventional TMS (left) and patterned TMS (right). Conventional rTMS (10Hz) was used in this thesis alongside single-pulse and paired-pulse TMS. From (Rossi et al. 2009). Permission to reproduce this figure has been granted by Elsevier.

[3] The disruption must be short-lived as the rTMS pulse trains are delivered during an experiment that often contains no TMS trials randomly intermixed with TMS trials.

Although the effects of conventional TMS in primary motor cortex can be measured objectively by recording motor evoked potentials (Barker and Jalinous 1985), the effect of TMS on the majority of brain areas has no visible outcome thus must be indexed by either changes in accuracy or response times (or both) in an appropriate task. If the stimulated area is causally involved in processing of a task (Pascual-Leone et al. 1999; Walsh and Rushworth 1999), and the TMS is administered at an appropriate time (Amassian et al. 1989), then TMS temporarily affects task performance (e.g. decreases in accuracy or increases in RTs). Consequently, online TMS is sometimes referred to as using TMS in 'virtual lesion' mode (Pascual-Leone et al. 1999; Pascual-Leone et al. 2000). Under certain circumstances TMS can improve task performance, for example if the target area is not required for the task or the TMS pulse is administered at an inappropriate time, then the TMS either has no effect or can facilitate task performance, the latter effect consistent with intersensory facilitation (Terao et al. 1997). Unlike offline TMS (conventional or patterned), the effects of online rTMS appear to be short lived. This allows the investigation of when an area is causally involved in a cognitive function and is often referred to as using TMS in neurochronometric mode (Pascual-Leone et al. 2000).

Using TMS to create virtual lesions offers multiple advantages over actual patient studies and can address a number of the difficulties of neuropsychological studies detailed in Chapter 1. In contrast to actual brain lesions which tend to be fairly large, involving cells within the grey matter but also severing the white matter that lie below the grey matter, TMS affects a relatively focal area of cortex without affecting white matter connections. Moreover, comparing trials with TMS to trials without TMS allow subjects to serve as their own controls, negating the possible effect of premorbid differences that can confound lesion studies. The transient nature of the online TMS impairment rules out any functional reorganisation (Walsh and Cowey 1998), which can render the interpretation of lesion studies problematic.

2.1.2 How does TMS work?

TMS is often conceptualised as suppressing activity or adding noise to a cortical area. Suppressing neural activity is likely to impair behavioural performance. Likewise an increase in noise in a system generally disrupts processing, impairing behavioural performance, though under certain circumstances (i.e. depending on the state of the system) the added noise may facilitate behavioural performance (Silvanto et al. 2008; Siebner et al. 2009).

A number of methodologies have been employed to develop these conceptualisations, including phantom head models (Cohen et al. 1990; Roth et al. 2007; Salinas et al. 2009), invasive studies on animals (Moliadze et al. 2003; Hayashi et al. 2004; Moliadze et al. 2005; Valero-Cabré et al. 2005; Aydin-Abidin et al. 2006; Allen et al. 2007; Aydin-Abidin et al. 2008; Pasley et al. 2009; Trippe et al. 2009; Yue et al. 2009), *in vitro* neuron studies (Rotem and Moses 2008; Tokay et al. 2009) and 3D head model simulations (Mouchawar et al. 1993; Liu and Ueno 1998; Wagner et al. 2004; Chen and Mogul 2009; Salinas et al. 2009). However, the majority of the physiological research has focused primarily on understanding the effect of stimulation of primary cortices, frequently using very long trains of pulses (though see Moliadze et al. 2003; Moliadze et al. 2005). It is not clear how this relates to either pairs of pulses of short trains of pulses delivered online to higher order cortex used in this thesis.

Given the fact that TMS induces a current in the brain, one might reasonably might ask *where* is this current induced, i.e. where is the locus of excitation? Considering that magnetic field strength decreases rapidly with the square of the distance, it seems reasonable to expect that elements in the cortical mantle are preferentially affected, with minimal impact on sub-adjacent white matter. Indeed, this backed up by evidence from simulations of the effects of TMS on increasingly realistic whole heads (Wagner et al.

2004; Salinas et al. 2009) and somewhat less realistic phantom heads (containers filled with physiological saline solution) (Roth et al. 2007). Within the gray matter, mathematical modelling and empirical evidence suggest that excitation is most likely to occur at axonal bends, terminals and hillocks (where the cell body joins the axon), that is locations where the spatial derivative of the induced voltage exceeds a particular negative value (Tranchina and Nicholson 1986; Maccabee et al. 1993; Nagarajan and Durand 1995; Nagarajan and Durand 1996). Neurons with lower thresholds activate first and can propagate the excitation along the axons and therefore to connected regions (Rotem and Moses 2008).

In order to understand what effect this excitation has on both the stimulated tissue and local and distant networked neurons, a small, but growing number of invasive animal studies have been conducted. The most common animal used in studies of TMS neurophysiology is the cat (Moliadze et al. 2003; Moliadze et al. 2005; Valero-Cabré et al. 2005; Aydin-Abidin et al. 2006; Allen et al. 2007; Pasley et al. 2009). Following single, paired or rTMS stimulation of an area of cat cortex there is an early period of enhanced (but not necessarily coherent) activity (up until ~500msecs post-stimulation) and a later offline period of altered activity (from ~500msecs to a few seconds) (Moliadze et al. 2003; Moliadze et al. 2005; Valero-Cabré et al. 2005). For single- and paired- pulse TMS, there is decreased activity in this latter period while for rTMS the characteristics of this latter period are dependent on the stimulation frequency, with high and low frequency stimulation increasing and decreasing activity, respectively (Valero-Cabré et al. 2005). Furthermore, the timing of neuronal spiking in the area becomes decoupled from the ongoing oscillatory activity (Allen et al. 2007), and the spectral coherence and phase locking of the local field potentials are altered (Pasley et al. 2009). In other words, the temporal dynamics of neural activity are severely disordered, and these effects can persist for several minutes following termination of stimulation. Alterations in temporal dynamics

following stimulation have also been reported in humans using simultaneous TMS and EEG (Paus et al. 2001; Van Der Werf and Paus 2006), with the duration of the effect lasting from minutes to approximately one hour in the case of long trains of conventional or patterned TMS (Thut and Pascual-Leone 2010). The prolonged TMS induced change in neural activity, is suggestive of synaptic plasticity, and has also been reported in monkeys where long trains of conventional rTMS induced changes in cerebral glucose metabolism that lasted for a remarkable eight days (Hayashi et al. 2004). In addition, a number of studies have investigated the effect of TMS on rat brains both *in vitro* (Tokay et al. 2009) and *in vivo* (Aydin-Abidin et al. 2008; Trippe et al. 2009; Yue et al. 2009), showing that rTMS can induce long-term changes in expression of proteins intimately linked with neurotransmission and associated with synaptic plasticity.

The short- and long-term effects of TMS are not limited to the target site. It is known that TMS effects from even single pulses can spread via anatomical connections beyond the site of stimulation (Fox et al. 1997; Ilmoniemi et al. 1997; Paus et al. 1997; Bestmann et al. 2004; Hayashi et al. 2004; Denslow et al. 2005). The clearest example of this is that despite being separated by at least two synapses, a single suprathreshold pulse to the hand area of primary motor cortex (M1) produces a visible twitch in the muscles of the hand. By altering the activity in the target site, TMS may also have knock-on effects on other areas of the network.

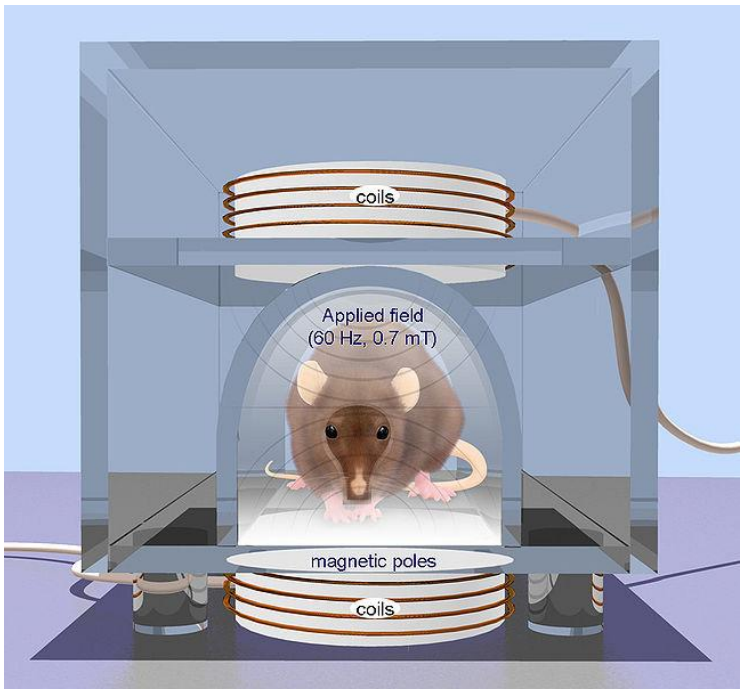


Figure 2-2: The problem of the ratio of coil size to head size in animal TMS studies. Due to the limitations in coil design, coils used to stimulate animal brains are disproportionately large relative to human coils. From Arias-Carrion (2008), reprinted under the terms of the Creative Commons Attribution License.

In summary, rTMS appears to induce complex changes in both the directly stimulated target area and the connected network, which may include long term changes in synaptic plasticity. It is important to note however, that these studies are typically investigating the effect of a large number of pulses of rTMS, with only two studies examining the effect of single and paired pulse TMS (Moliadze et al. 2003; Moliadze et al. 2005). Thus the protocols used correspond best to offline TMS – i.e. TMS that is specifically intended to induce medium and long term effects. In part this may reflect the urgent need to investigate how rTMS can be applied in clinical settings where long term effects are necessary for effective treatment. It remains to be seen whether these effects can occur during short trains of pulses that are commonly used in online TMS studies in humans and all experiments in this thesis. Furthermore, translating information derived from *in vitro* cell culture and *in vivo* animal studies to humans is highly problematic. For example, due

to constraints in coil design, the ratio of brain to coil size relative to that in humans differs considerably for cats, rats and even monkeys, leading to a serious loss of stimulation focality. Indeed, in the case of rat stimulation, the magnetic field may affect part of the rat's body, in addition to the whole brain (Figure 2-2). Moreover, the animals are anaesthetised, and it is unclear how this may interact with stimulation. Finally, it should also be noted that as yet the design and safety requirements of experimental human studies are empirically determined (Wassermann 1998; Rossi et al. 2009) and as yet information from animal studies is only rarely incorporated.

2.1.3 Magnetic fields and distance

The strength of a magnetic field decreases exponentially with distance (Bohning et al. 1997), which together with studies examining field distribution in phantom brains suggests that direct stimulation of cortical structures greater than a few centimetres from the scalp is not possible (structures other than the apices of gyri) (Roth et al. 2007). However, the strength of the magnetic field is not the only parameter that influences the effect on the stimulated tissue: The shape of the magnetic field, the total area of stimulated cortex and that area's local connectivity area likely all have some influence on the effect TMS has. Indeed, empirical studies have failed to demonstrate the expected exponential drop-off in magnetic field strength (Stokes et al. 2005; Stokes et al. 2007; Cukic et al. 2009). Newer coil designs, such as H-coils, may allow for deeper stimulation (Roth et al. 2002; Zangen et al. 2005) but as yet have not been extensively used.

2.1.4 Stimulation intensities and motor thresholds

As the magnetic field intensity decays rapidly with distance, successful stimulation of a target tissue depends on choosing an appropriate stimulation intensity. However, at present there is no consensus on the optimum way to do this. Some researchers use a set

intensity for all subjects in a study (e.g. Pitcher et al. 2007); however, given that there are likely to be intersubject differences in factors such as the depth of the target (McConnell et al. 2001) and the target area's local connectivity the minimum stimulation threshold is likely to vary across individuals and thus the choice of an arbitrary fixed stimulation intensity may lead to subjects being under- or over-stimulated. If the targeted area is under-stimulated, the probability that the TMS-induced current will affect processing is reduced. Over-stimulation increases the area of cortex being stimulated (Roth et al. 1991) and increases transynaptic current spread (Paus et al. 1997), potentially confounding interpretation of results. Furthermore, overstimulation increases the likelihood of adverse reactions to TMS, such as peripheral nerve stimulation and importantly increasing the possibility of seizure (Wassermann 1998).

The alternative is to attempt to adjust the stimulation intensity for each participant in an experiment, most commonly by calibrating the stimulation intensity to a percentage of each participant's motor threshold (MT). When TMS is applied over primary motor cortex (M1), the induced currents depolarise neurons in the corticospinal tract. If the intensity of stimulation is high enough, this results in a motor evoked potential (MEP) or a visible twitch in the muscle corresponding to the stimulated cortical area. The MT is often defined as the minimum TMS intensity that elicits a response (either MEP or twitch) in the contralateral thumb (abductor pollicis brevis) or index finger (first dorsal interosseous muscle) in at least 50% of the trials. MT is lowered by voluntarily contracting the muscle (active motor threshold) relative to the resting motor threshold (Devanne et al. 1997). Initial studies found no relationship between a subject's MT and their phosphene threshold (the minimum intensity required to elicit phosphenes on 50% of trials of visual cortex stimulation), calling into the question the suitability of using MT as a means of calibrating intensity for areas outside M1 (Stewart et al. 2001; Antal et al. 2003; Gerwig et al. 2003). However, more recent work has shown that thresholds for motor and visual

cortices are correlated when the thresholding procedure is the same across sites (Deblieck et al. 2008), providing a validation of the use of MT-calibrated stimulation intensities in non-motor areas. An alternative approach, where the MT is scaled according to the difference in depth between M1 and the cortical site of interest, is also promising (Stokes et al. 2005; Stokes et al. 2007) though awaits empirical testing.

2.1.5 Spatial resolution

The focality of the induced current is affected by the shape of the stimulating coil, and while a circular coil generates the strongest magnetic field, the most commonly used coil is the figure-of-8 design (Ueno et al. 1988; Cohen et al. 1990; also referred to as double or butterfly coil). In the latter, the induced electric field under the intersection of the 8, sometimes referred to as the 'hot spot', is double the magnitude as that induced at the wings. For certain target sites and coil orientations, the wings may be sufficiently distant from the scalp that the magnetic field produced by them may be discounted. However, this may not always be the case and the field produced by the wings may be sufficient to induce unwanted current in peripheral muscles, nerves or possibly neural tissue[4]. Approximations of the actual extent of induced neural current can be obtained from mathematical three dimensional head models (Wagner et al. 2004) and phantom head simulations however these estimates do not provide information regarding the physiologically effective spatial resolution, i.e. the distance between two points where stimulation produces different responses. For example, though the area that experiences at least 90% of the maximum induced current is thought to be greater than 1cm^2, using

[4] Indeed, stimulation of the neck muscles was sometimes experienced in the experiments in this thesis as the position and orientation of the coil meant that one wing was near the neck. When the coil was too close to the neck there was peripheral enervation of sternocleidomastoid and / or trapezius, which can be quite uncomfortable.

single pulse TMS it is possible to resolve sites less than 1cm apart in motor and premotor cortex (Brasil-Neto et al. 1992; Wilson et al. 1993; Schluter et al. 1999). It is likely that the effective spatial resolution will be affected by the stimulation intensity and protocol, with higher intensities and increasing number of pulses decreasing the resolving power. Nonetheless, sites as close as 2cm have been effectively resolved using short pulses of high frequency rTMS (Pitcher et al. 2007). The effective spatial resolution will also be affected by properties of the stimulated tissue, including the orientation of neurons, the areas local and distant connectivity, as well as the pre-existing activation state of the network, though to what extent is unknown.

2.1.6 Temporal resolution

It is important to do distinguish between the time that the neural effects persist from the time that the behavioural effects persist. As discussed above, invasive animal studies suggest that changes in neural activity induced by single, paired or repetitive TMS may persist for greater than 500msecs, however, the effect on behaviour in humans is considerably shorter than this. For example, using single and paired pulse TMS it is possible to show disruption in a task (for example increased RTs) during a particular time window much smaller than half a second. For example, a single pulse TMS significantly impairs semantic processing when it is delivered at 250msec post-stimulus onset, but not 200msec or before nor 300msec and onwards (Devlin et al. 2003a). Paired pulse TMS to the frontal eye fields impairs stimulus discriminability when the pair of pulses occurs at 40 and 80msec, but not at 0 and 40 or 80 and 120msec onwards (O'Shea et al. 2004). These

studies suggest that the effective temporal resolution of TMS is approximately 40-50msec[5], though this is likely to be dependent on the stimulation parameters and properties of the stimulated tissue.

2.1.7 Unwanted effects of TMS and Safety

In addition to the desired neural effects, TMS also has ancillary effects including somatosensory stimulation of the scalp under the coil, an audible 'click' noise and the possibility of peripheral muscle involvement (which all increase with stimulation intensity). Any or all of these may influence the participant's behavioural, confounding interpretation of the results (Walsh and Rushworth 1999). A major disadvantage of TMS is the lack of a truly effective sham-TMS technique, though sham-coils that attempt to replicate the ancillary effects have been developed (Rossi et al. 2007; Hoeft et al. 2008; Jeffrey et al. 2008) but are not yet in general use and may never be able to replicate the ancillary effects of TMS without the magnetic field. However, various strategies are employed to minimise the ancillary effects. First, ear-protection can minimise the effect of the clicking sound (and in doing so, provide valuable ear protection, especially if the coil is near the subject's ear). Second, researchers commonly use a number of different control conditions. A control site, such as the vertex, can help demonstrate that the effects of interest are specific to a given site and not a general property of TMS delivered anywhere on the head, while control tasks can be used to prove that the TMS effect is selective and not just a general impairment or facilitation in performance. Timing controls, that is,

[5] As noted above, invasive animal studies have reported altered neural function for a period of minutes to even days (Moliadze et al. 2003; Hayashi et al. 2004; Moliadze et al. 2005; Valero-Cabre et al. 2005; Allen et al. 2007; Pasley et al. 2009) that appears at odds to the reports of effective temporal resolution in the tens of milliseconds. However, these prolonged changes in neural activity may at least in part be explained by the considerable difference in the ratio of coil size to brain size, the use of anaesthetic and the large number of pulses delivered.

showing that a TMS effect is specific to a point in time are possibly the most convincing TMS controls, since the location (and thus subjective experience) and task (and thus difficulty) remain constant.

As long as correct screening and safety procedures are followed, TMS is considered to be safe (Wassermann 1998; Rossi et al. 2009) and generally involves only minimal discomfort. However, on occasion, particularly at higher intensities or when stimulating an area in proximity to muscles or peripheral nerves, TMS can cause discomfort or pain. Screening and safety procedures aim to minimise the risk that an adverse reaction to TMS occurring but in the event that a problem arises, stimulation must be terminated immediately followed by an assessment of the situation and possible contacting of first aiders or emergency services, as laid down by the laboratory guidelines.

2.2 General procedures used in this thesis

All TMS experiments in this thesis tested ventral occipito-temporal cortex (vOTC) and used a common set of basic procedures. Rather than detail these procedures repeatedly in every chapter, they are described below. Each chapter therefore describes only the methodological components specific to the experiment being presented.

In all experiments after Chapter 3, Experiment 1, participants were invited to attend a short TMS 'pre-test', where they received a short introduction to TMS, were able to ask any questions they had and were able to experience rTMS over both vertex and ventral occipito-temporal sites (Lambon Ralph, M., Personal communication, 2009). This helped allay anxiety and identified subjects who experience considerable muscle involvement before they participated in the fMRI session. Before receiving any TMS, all subjects had the opportunity to read information sheets about TMS and fMRI (see Appendix A). If they were happy to participate, they completed screening forms that ensured that there were

no contraindications for TMS or fMRI (see Appendix B), for example, the possibility of metal in the body, any personal or family history or seizures etc.

A Magstim Rapid^2 stimulator (Magstim, Whitland, UK) with a 70mm figure-of-eight coil was used to deliver the stimulation in every TMS experiment in this thesis. In addition, a frameless stereotaxy system (Brainsight software, Rogue Research, Montreal, Canada) was used with a Polaris Vicra infrared camera (Northern Digital, Waterloo, Ontario, Canada) to accurately target stimulation. In all experiments and for all sites, the coil was positioned and held in place by hand, while the trajectory of the magnetic field was monitored continuously using Brainsight. All stimulation intensities were individually calibrated based on the participant's motor threshold (MT). The stimulation intensity in Chapter 3, Experiment 1 was 110% of MT and 100% of MT in all other experiments. MT was defined as the intensity necessary to produce a visible twitch in the muscles of the right hand in 5 trials out of 10 during primary motor cortex (M1) stimulation. The hand area of motor cortex was identified anatomically according to the method of Yousry et al (1997) and verified by finding the location which produced a twitch in the right hand.

There is considerable inter-subject variability in the location of reading- and object-induced activity within the visual stream (Wright et al. 2008; Duncan et al. 2009). Consequently, although there are a number of options for choosing the target for stimulation, methods that do not take this variability into account, such as using standard space coordinates from published imaging studies, or using heuristic methods such as the 10-20 system, are suboptimal and require higher stimulation intensities and / or larger numbers of subjects (Sparing et al. 2008; Sack et al. 2009). There are two methods that can be used to functionally localise target sites in individuals. The first, TMS localisation, involves using short TMS experiments, stimulating a series of sites within an anatomical region of interest using an independent but related task. The site that shows a consistent impairment in performance is chosen as the target for the main experiment (Devlin et al.

2003a; Gough et al. 2005; Ellison et al. 2007; Taylor et al. 2007; Pattamadilok et al. 2010). The second, fMRI localisation, involves using a short fMRI experiment to localise the target in each participant. Although TMS localisation has a number of advantages, including cost-effectiveness and time efficiency, it involves additional stimulation. If the site being stimulated is prone to muscle involvement, for example, ventral sites, additional stimulation can be undesirable. For these target sites, fMRI localisation is the optimal solution.

Consequently, in all experiments in this thesis, fMRI was used to functionally localise reading- and object- sensitive areas in the ventral visual stream. All of the TMS subjects participated in a single fMRI session that involved visual word recognition in order to functionally localise left vOTC. A lateral region sensitive to visual objects, often called lateral occipital complex (LOC) (Malach et al. 1995; Grill-Spector et al. 1999) was localised in participants in Chapter 3 and right vOTC was localised in participants in Chapter 5. Two tasks were used to this end: The majority of subjects completed a one-back task with four categories of visual stimuli: written words, pictures of common objects, scrambled pictures of the same objects, and consonant strings / faces[6]. The remaining subjects completed a lexical decision task as part of a separate fMRI study of reading. In both cases, we collected approximately 20 minutes of imaging data, spread over two equal length runs. Both groups were scanned on a Siemens 1.5 Tesla MR scanner at the Birkbeck-UCL Centre for Neuroimaging (BUCNI) in London. The functional data were acquired with a gradient-echo EPI sequence (TR = 3sec; TE = 50msec, FOV = 192 × 192, matrix = 64 × 64) giving a notional resolution of 3 × 3 × 3mm. In addition, a high-resolution anatomical scan

[6] Note that consonant strings were originally intended to serve as a baseline condition for words analogous to scrambled pictures for objects. However, this contrast did not result in reliable activation in individuals. Consonant strings were replaced by faces as part of the investigation of functional localisers reported in Chapter 7.

was acquired (T1-weighted FLASH, TR = 12msec; TE = 5.6msec; 1mm^3 resolution) for anatomically localising activations in individuals.

Image processing was carried out using FSL 4.0 (www.fmrib.ox.ac.uk/fsl). To allow for T1 equilibrium, the initial two images of each run were discarded. The data were then realigned to remove small head movements (Jenkinson et al. 2002), smoothed with a 6mm FWHM Gaussian kernel and pre-whitened to remove temporal auto-correlation (Woolrich et al. 2001b). The resulting images were entered into a general linear model with either four conditions of interest (corresponding to the four categories of visual stimuli) in the one-back task or two conditions (words and pseudowords) in the lexical decision task. Trials were convolved with a double gamma "canonical" hemodynamic response function (Glover 1999) to generate the main regressors. In addition, the estimated motion parameters were entered as covariates of no interest to reduce structured noise due to minor head motion. The linear contrast of [Words > Fixation] identified reading-sensitive areas for both tasks, while that of [Objects > Scrambled objects] identified LOC. First level results were registered to the MNI-152 template using a 12-DOF affine transformation (Jenkinson and Smith 2001) and a subsequent second level, fixed-effects model combined the two first level runs into a single, subject-specific analysis. This was then transformed into the participant's native structural space. For each contrast, the peak voxel in the region of interest was used as the target for TMS. The regions of interest corresponded to grey matter of the posterior portion of fusiform gyrus (FG), occipito-temporal sulcus (OTS), and medial parts of the inferior temporal gyrus (ITG) for vOTC (Price et al. 1994; Price et al. 1996; Herbster et al. 1997; Rumsey et al. 1997; Fiez and Petersen 1998; Fiez et al. 1999; Shaywitz et al. 2004) and lateral posterior FG, posterior OTS and lateral parts of posterior ITG (Malach et al. 1995; Grill-Spector et al. 1999) for LOC. During stimulation of vOTC and LOC, the coil was held behind the participant's ear with the handle parallel to the ground and pointing posteriorly. As the coil was in close

proximity to the ear, all participants used an earplug to attenuate the noise of the TMS discharge. If stimulation resulted in unacceptable levels of muscle involvement, it was often possible to alter the coil position and orientation such that the relevant site was still being accurately targeted but muscle involvement was reduced. Typically, this involved ensuring that the lower wing of the coil was not in contact with the neck, as this results in peripheral enervation of the neck muscles, sternocleidomastoid and / or trapezius. In addition, due to the curvature of the head, it is also possible to move the coil in the anterior-posterior axis while still stimulating the same target. However, when it was not possible to accurately stimulate the target without unacceptable muscle involvement the session was stopped.

The vertex was defined anatomically using Brainsight as the highest midline point on the scalp. During stimulation of vertex, the coil was held flat on the participant's head with the handle pointing posterior. Vertex stimulation was almost universally tolerated however, there were a small number of occasions where a peripheral nerve was stimulated. In these cases, the coil was repositioned such that the nerve was not affected.

3 Feasibility and specificity of ventral occipito-temporal cortex stimulation

3.1 Introduction

A region in ventral occipito-temporal cortex (vOTC), encompassing mid-fusiform and the adjacent occipito-temporal sulcus (OTS), has become the focus of considerable debate. The uncertainty regarding the area's contribution to visual word recognition highlights the need for a method to temporarily and non-invasively perturb the information processing in this area to investigate the causal relations between activation and reading. Transcranial magnetic stimulation (TMS) would seem to offer such a tool (Barker and Jalinous 1985; Pascual-Leone et al. 1999; Sack 2006), but is frequently assumed that vOTC's location on the ventral surface of the brain makes it inaccessible to TMS (for example, Simos et al. 2008). There are, however, reasons to doubt this assumption: First, although the majority of the fusiform lies on the ventral surface, the portion within the ventral occipito-temporal area lies more laterally, closer to the skull. In fact, occipito-temporal sulcus (OTS), which separates the gyrus from inferior temporal gyrus (ITG), frequently merges with inferior temporal sulcus, exposing the lateral aspect of the fusiform gyrus (Figure 3-1). Secondly, TMS is capable of penetrating to a greater depth than is frequently thought. For instance, there is no doubt that the hand area of primary motor cortex can stimulated as it is possible to witness the resulting contraction in the hand and record the TMS evoked motor evoked potential (Barker and Jalinous 1985; Pascual-Leone et al. 1994; Rothwell 1997). Previous work has suggested that the depth of M1 ranges from 15mm to greater than 25mm (McConnell et al. 2001; Stokes et al. 2005; Herbsman et al. 2009). However these measurements are from the scalp to the cortical surface but the hand area of M1 is not on the crest of the gyrus but on the posterior bank of the pre-central sulcus, and thus is deeper than commonly assumed (Yousry et al. 1997). In other words, TMS has an effective depth of 2-3cm and since the critical region of vOTC is relatively close to the scalp, the possibility of stimulating vOTC is worth exploring.

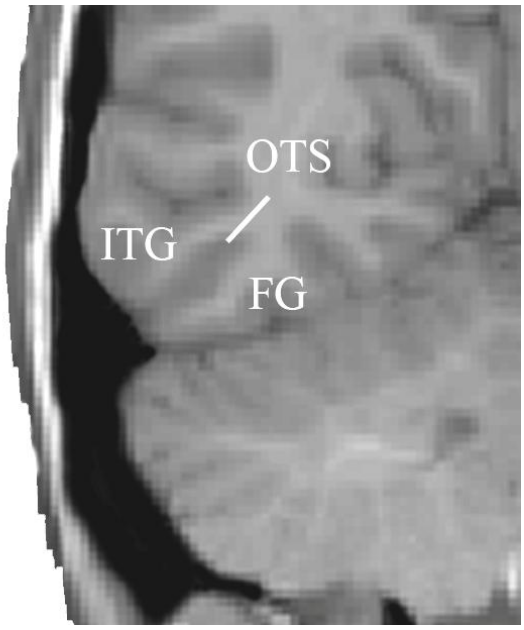


Figure 3-1: Anatomy of ventral occipito-temporal cortex. Note that in this subject, the fusiform gyrus and occipito-temporal sulcus are exposed. ITG = inferior temporal gyrus, OTS = occipito-temporal sulcus, FG = fusiform gyrus. Permission to reproduce this figure has been granted by Elsevier.

In order to convincingly demonstrate vOTC stimulation, any effect of TMS must be robust and specific. Robustness implies an observable and reliable effect present in the majority of participants. However, unlike motor cortex, where TMS elicits a visible response, stimulation of most brain areas produces no overt effect and therefore requires a task that produces a suitable dependent measure, changes in which can index the effect of stimulation. When rTMS is used, successful stimulation typically results in an impairment in behavioural performance, and although rTMS induced decreases in accuracy have been observed (e.g. Pitcher et al. 2007), stimulation most commonly elicits an increase in RTs (Göbel et al. 2001; Rushworth et al. 2001; Gough et al. 2005; Manenti et al. 2008; Sandrini et al. 2008). Therefore the experiment aimed to test the feasibility of ventral occipito-temporal stimulation during a visual lexical decision task. Although there are a number of tasks that involve visual word recognition and engage vOTC, the lexical decision was chosen because it is most frequently used in cognitive studies of visual word recognition.

Although accuracy on this task tends to be near ceiling levels and is therefore not typically affected by experimental manipulations, it is easy to elicit robust reaction time (RT) effects.

In addition, in order to attribute the observed effect to successful disruption of ventral occipito-temporal processing any effects must be both stimulus- and site- specific, that is not a general non-specific effect such as intersensory facilitation (Terao et al. 1997). To demonstrate this specificity, control stimuli and control sites were included. Successful stimulation is demonstrated by showing a behavioural impairment in responses to the experimental conditions during ventral occipito-temporal stimulation but crucially not in responses to the control condition or during stimulation of the control site.

The stimuli consisted of lexical and non-lexical items. For lexical items, low and high frequency words were treated separately because some imaging studies have shown greater vOTC activation for low than high frequency words (Chee et al. 2003b; Kronbichler et al. 2004), suggesting that the effect of stimulation may be modulated by frequency. Non-lexical items included both pronounceable pseudowords and consonant strings. Pseudowords were included to ensure that the subjects genuinely read the stimuli rather than performing the task based on sub-lexical properties (such as the presence of orthotactically illegal consonant clusters or absence of vowels). As pseudowords elicit robust activation in the area (Fiez et al. 1999; Hagoort et al. 1999; Xu et al. 2001; Fiebach et al. 2002; Bellgowan et al. 2003; Binder et al. 2003; Mechelli et al. 2003; Binder et al. 2005a; Binder et al. 2005b; Lee et al. 2010), I anticipated that TMS might also interfere with pseudoword responses. Consequently, consonant strings were included as an additional control condition because they elicit minimal vOTC activation (Cohen et al. 2002) and were not expected to be affected by stimulation. Testing such a wide range of stimuli maximises the possibility of detecting an effect. This is important because no TMS effect would be observed if vOTC is not causally involved in the processing of a particular stimulus, even in the event of successful stimulation (Postle et al. 2006).

Two control sites were used: the vertex and the lateral occipital complex (LOC). The vertex is far removed from reading-related brain areas and stimulation in this region is easily tolerated by all participants. Consequently stimulation was not expected to result in impairments in performance in any condition in the lexical decision. However, due to the arrangement of scalp muscles, the subjective experience of stimulation of the vertex is likely to be noticeably different from that of vOTC where stimulation can produce peripheral enervation of the temporalis muscle. Therefore disruption of responses during vOTC but not vertex, may be the result of the phenomenological experience of ventral TMS. In other words, slowdowns at vOTC may be a consequence of distraction due to peripheral muscle stimulation. Unlike the vertex, stimulation of LOC, which is located on the lateral surface of occipito-temporal cortex (Malach et al. 1995; Kanwisher et al. 1996; Grill-Spector et al. 1998; Grill-Spector et al. 1999), is expected to produce comparable peripheral muscle stimulation, meaning that the subjective experience of stimulation of the area is likely to be similar to that of vOTC. Consequently, disruption during vOTC but not LOC stimulation would be strongly suggestive of site-specificity, ruling out the possibility that the effect is driven by peripheral stimulation effects. On the other hand, visually presented words activate LOC (Price et al. 2006; Wright et al. 2008; Duncan et al. 2009), although unlike vOTC, the region does not appear to be sensitive to the lexical status or frequency of a letter string (Hagoort et al. 1999; Fiebach et al. 2002; Binder et al. 2003; Kuo et al. 2003; Mechelli et al. 2003; Kronbichler et al. 2004; Lee et al. 2004; Binder et al. 2005a; Binder et al. 2005b; Carreiras et al. 2006; Hauk et al. 2008) and lesions to the area are not associated with reading impairment (Philipose et al. 2007). As such, its suitability as a control site is unclear because LOC stimulation may (or may not) affect visual word recognition.

In summary, Experiment 1 examined the feasibility of ventral occipito-temporal stimulation. Stimulation was delivered during a visual lexical decision involving high and

low frequency words, pseudowords and consonant strings. If ventral occipito-temporal stimulation is successful, the neuroimaging data suggests that the resulting disruption will slow the responses to high and low- frequency words and pseudowords without affecting responses to consonant strings. These impairments in performance will not occur during stimulation of vertex, where I expect no TMS effect or a non-specific intersensory facilitatory effect that is not stimulus-specific.

3.2 Experiment 1

3.2.1 Methods

Participants. 14 participants (7M, 7F, aged 19 to 38, mean = 25) took part. All were right handed, native English speakers with normal or corrected to normal vision. None had any form of dyslexia, a personal history of neurological disease, or a family history of epilepsy according to self-reports. Each gave informed consent after the experimental procedures were explained. The experiments were approved by the Berkshire NHS Research Ethics Committee.

Functional imaging. All participants completed a 1-back task during fMRI scanning in order to localise the precise region of vOTC and LOC to target with TMS in each individual (Table 3-1). The details of the fMRI scans are given in Chapter 2.

Table 3-1: Peak coordinates for the contrasts [Words > Fixation] and [Objects > Scrambled Objects] in vOTC (left) and LOC (right) respectively, in MNI space. Each individual's peak was used as their target for TMS.

Subject	*vOTC*					*LOC*			
	MNI Coordinates			*Z*-score		MNI Coordinates			*Z*-score
	x	*y*	*z*			*x*	*y*	*z*	
1	-44	-49	-27	10.6		-49	-74	-2	7.5
2	-44	-73	-16	7.1		-47	-77	-4	7.2
3	-40	-55	-17	4.6		-52	-77	-1	6.6
4	-41	-57	-22	4.2		-43	-80	-6	7.5
5	-39	-55	-17	11.1		-38	-76	-8	4.1
6	-37	-57	-16	2.1		-40	-70	-10	2.0
7	-46	-59	-12	6.3		-46	-73	-2	8.7
8	-43	-68	-11	9.5		-45	-80	-9	7.5
9	-45	-69	-12	12.2		-44	-85	-5	10.1
10	-37	-58	-14	10.9		-45	-83	-7	12.1
11	-47	-67	-5	10.9		-49	-77	-8	6.0
12	-49	-60	-14	5.2		-43	-81	-3	6.2
13	-41	-66	-18	9.4		-41	-80	-10	12.4
Mean	-43	-61	-15	8.1		-45	-78	-6	7.5
SEM	1.0	1.9	3.4	0.9		1.1	1.2	0.9	0.8

Task and stimuli. Participants performed a visual lexical decision task while rTMS was delivered to one of three target sites. The lexical decision consisted of four conditions, each comprising 100 items: low frequency words (1-10 occurrences per million), high frequency words (20-650 occurrences per million), pronounceable pseudowords (e.g. "glats") and unpronounceable consonant letter strings (e.g. "btfj"). Table 3-2 shows that the two lexical conditions differ significant in frequency and also in familiarity, which is

unsurprising given that the two properties are highly correlated (Noble 1954; Smith and Dixon 1971). Importantly, however, the stimuli were well matched across conditions in prelexical properties which crucially included bigram frequency. Word frequency values were obtained from the Celex database of British written English (Baayen et al. 1993), while bigram frequencies and familiarity values were obtained from N-Watch (Davis 2005).

Table 3-2: Experiment 1. Mean psycholinguistic properties per condition with standard error in parenthesis. HF = high frequency words, LF = low frequency words.

	HF Words	LF Words	Pseudo words	Consonants	*t / F*	*p*
Frequency	107 (12.5)	5 (0.3)	-	-	8.11	<0.001
Familiarity	546 (4.3)	484 (6.6)	-	-	9.21	<0.001
Bigram frequency	1344 (100)	1213 (92)	1397 (99)	-	0.84	0.435
No. of syllables	1.5 (0.1)	1.5 (0.1)	1.5 (0.1)	-	0.37	0.693
No. of Letters	5.2 (0.1)	5.1 (0.1)	5.1 (0.1)	5.1 (0.1)	0.26	0.853

To avoid repeating stimuli within a testing session, five versions of the lexical decision were created (each comprising 20 items per condition) and matched for written word frequency (overall and separately for both low and high frequency items), rated familiarity, letter length, number of syllables and bigram frequency. The order of the versions was balanced across subjects and stimulation sites. In addition, an independent set of items was used for practice.

The details of the TMS apparatus and the method used to localise target sites were reported in the General Methods. Repetitive TMS was pseudorandomly delivered on half of all trials. Pulses were delivered at 100, 200, 300, 400 and 500msec post-stimulus onset (i.e., 10Hz for 500msec). The intensity was set to 110% of the subject's motor threshold as measured by a visible twitch of the hand. This measure consistently results in higher estimates than motor thresholds measured with motor evoked potentials and therefore is

a very conservative measure in the sense that it ensured sufficient intensity to stimulate motor cortex (Conforto et al. 2004). This value was increased by an additional 10% in the main experiment to ensure sufficient intensity to reach vOTC. Even so, this was well within established safety limits (Wassermann 1998; Rossi et al. 2009). This general protocol has been widely used to temporarily interfere with processing in relatively focal cortical zones (Göbel et al. 2001; Rushworth et al. 2001; Gough et al. 2005; Skarratt and Lavidor 2006; Manenti et al. 2008; Pitcher et al. 2008; Sandrini et al. 2008). In summary, then, the experiment used a within-subject design with Site (vOTC, vertex, LOC), Stimulus (high frequency words, low frequency words, pseudowords, consonant strings), and TMS (none, rTMS) as independent factors.

Procedure. Each trial began with a fixation cross displayed for 500msec, followed by a visual letter string for 200msec and then a blank screen for 2300msec, giving a total duration of 3sec. Subjects indicated whether the letter string formed a real word in English or not by pressing a button using either their right or left index finger. Responses were fully counter-balanced for response hand across subjects. Accuracy and RTs were recorded.

The three stimulation sites were tested sequentially in a single session with their order counter-balanced across subjects. A session began by measuring the participant's motor threshold. The participant then performed a practice session of the lexical decision experiment without any TMS to familiarise them with the task. Next, one of the three testing sites was chosen and the participant was introduced to the sensation of rTMS at that site. After familiarisation with the sensation, the participant performed a practice session with rTMS pseudorandomly delivered on half of the trials to get used to performing the task with concurrent rTMS. Stimulation of vOTC and LOC was associated with stimulation of the temporalis and / or sternocleidomastoid muscles and in addition, often produced a unilateral facial twitch. When asked afterwards, participants were

unable to distinguish the sensation of stimulation from the two temporal lobe sites. In contrast, stimulation of the vertex did not produce any muscle twitches and was easily distinguished. After familiarisation with the sensation, the participant performed a practice lexical decision run with rTMS to get used to performing the task with concurrent rTMS. Finally, they completed the lexical decision experiment for the given site using one of the five stimulus versions. The procedure was then repeated for the other two testing sites using different stimulus versions. At each location, including finding motor threshold, the location and orientation of the coil was recorded for later analyses. Finally, the distance from the scalp to these three targets was measured for each subject to evaluate differences relating to accessibility. In each case, the distance between the target and the scalp was measured using Brainsight along the trajectory of stimulation.

Analyses. RTs were measured from the onset of the target. Responses times shorter than 300msec were considered too fast to represent genuine responses but rather anticipatory responses or delayed responses from the previous trial. Consequently these were trimmed, amounting to 0.2% of the data. To minimise the effect of outliers in the RT data, median RTs for correct responses per condition per subject were used in the statistical analyses (Ulrich and Miller 1994). Analyses of variance (ANOVA) were used to test for effects of interest, and post-hoc comparisons used two-tailed paired *t*-tests were used with Bonferroni corrections for multiple comparisons.

The disruption induced by the 10Hz, 500msec protocol is typically specific to a particular subset of conditions (i.e. not the control stimuli, or site). So when large inhibitory TMS effects are present across conditions, these are likely to result from the non-specific effects of TMS such as: i) anxiety about the stimulation, ii) a priori “knowledge” that TMS slows responses, or iii) strong peripheral muscle stimulation that the participant finds impossible to ignore. In all three cases, the effect size and distribution across conditions is clearly different from the normal pattern and is easily identified and excluded. The data

from one participant fitted these criteria for physiologically implausible TMS effects as their RT effects for vOTC stimulation were on average 173msec slower than no TMS trials across all conditions. This was more than double the next largest effect, over 100msec outside the range of the other participants, and present across conditions, suggesting they were primarily due to peripheral, rather than central, effects of TMS. Consequently these data were excluded from further analyses.

3.2.2 Results

Because vOTC is generally regarded as inaccessible to TMS due to its depth, I began by explicitly measuring the distance from the scalp to the most highly activated voxels within vOTC and LOC used to target the stimulation. The distance was measured along the trajectory of the magnetic field and therefore reflects the distance between the coil and the stimulated region of cortex (Figure 3-2). The distance to the hand area of primary motor cortex was measured as a comparison. Because we did not functionally localise this using fMRI, the "omega knob" was marked independently by myself and my supervisor using anatomical criteria (Yousry et al. 1997) and the mid-point of these voxels was used to compute the distance from the scalp along the stimulation trajectory. The results for all subjects are shown in Table 3-3. On average, the depth of vOTC was 26.3mm which was not significantly different from the M1 hand area at 27.2mm ($t(13)= 1.0$, $p = 0.684$), suggesting the two are equally accessible to TMS. LOC, on the other hand, was significantly closer to the scalp than M1 with an average depth of only 20.5mm ($t(13) = 5.2$, $p < 0.001$), confirming its accessibility. It is worth noting, however, that because M1 was localised anatomically while vOTC and LOC were localised with fMRI, the depth measurements are not fully compatible. Even so, the results suggest that the depth of vOTC is roughly equal to that of hand area of M1.

Table 3-3: Distances (in mm) from scalp to target stimulation site

Region	Participant														Mean (SEM)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
vOTC	24	32	29	26	28	25	31	22	30	26	25	21	21	28	**26.3 (0.9)**
M1	25	33	29	25	28	26	31	21	30	25	25	29	30	24	**27.3 (0.9)**
LOC	23	26	17	29	21	21	28	23	17	13	21	16	19	23	**21.3 (1.1)**

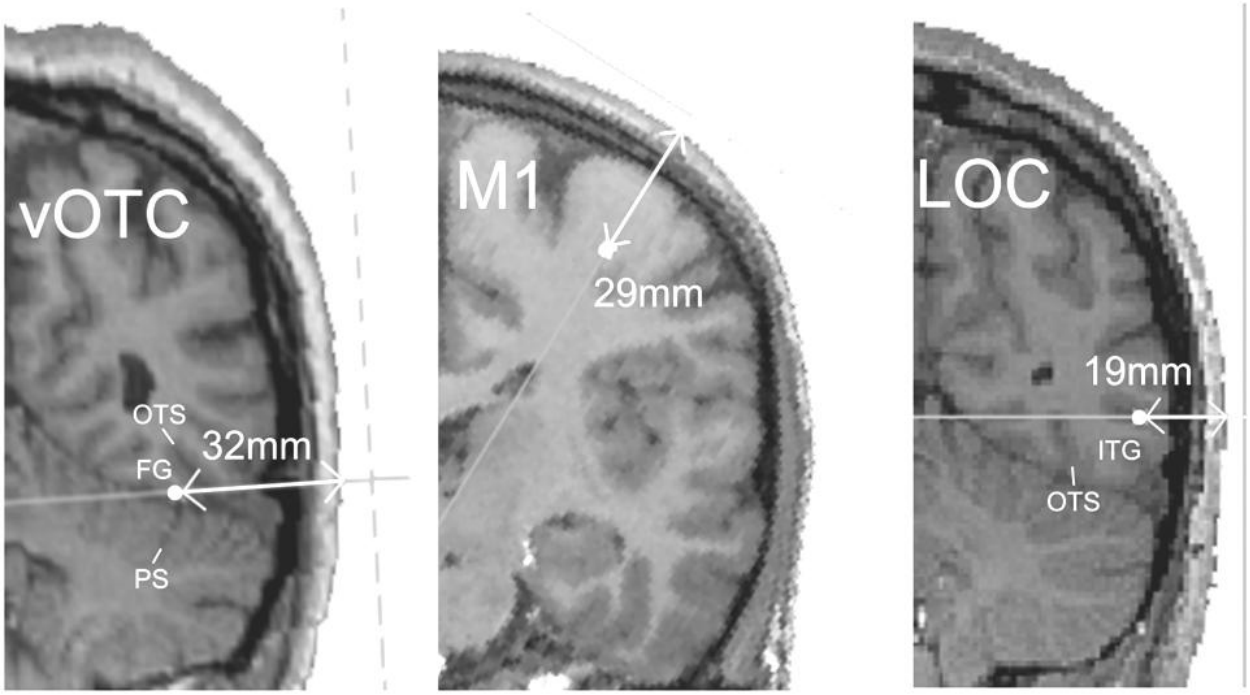


Figure 3-2: Sites and trajectories of TMS stimulation. Because the trajectories do not necessarily correspond to canonical orientations, these slices were chosen from three different participants as they were closest to coronal views and thus, most familiar. On each slice, the target voxel is marked with a filled circle along the trajectory (grey line) of maximum stimulation. A second gray line outside of the head indicates the orientation of the coil. The depth (in mm) measured from the scalp to the stimulation target is marked with an arrow. In addition, a number of anatomical landmarks are labelled: FG = fusiform gyrus, OTS = occipito-temporal sulcus; PS = principle sulcus of the cerebellum; and ITG = inferior temporal gyrus. Note the trajectory of stimulation for ventral occipito-temporal cortex involves minimal cerebellar and inferior temporal gyrus stimulation. Images are not to scale. Permission to reproduce this figure has been granted by Elsevier.

In the main lexical decision experiment, overall accuracy levels were 95%, indicating that subjects had no difficulty performing the task. Accuracy scores (Figure 3-3) were entered into a $3 \times 4 \times 2$ repeated-measures ANOVA examining the effects of Site (vOTC, vertex, LOC), Condition (consonant strings, pseudowords, low frequency words, high frequency words) and TMS (none, rTMS). The only significant main effect was for Condition ($F(3,39) = 14.0$, $p < 0.001$), indicating that subjects were significantly less accurate for pseudowords (91%) than high frequency words (97%; $t(13) = 6.0$, $p = 0.01$) and consonant strings (98%; $t(13) = 7.4$, $p = 0.003$) but only numerically less for low frequency words (93%; $t(13) = 2.6$, $p = 0.478$). There was no main effect of TMS and no significant interactions, indicating the presence of TMS did not significantly affect accuracy.

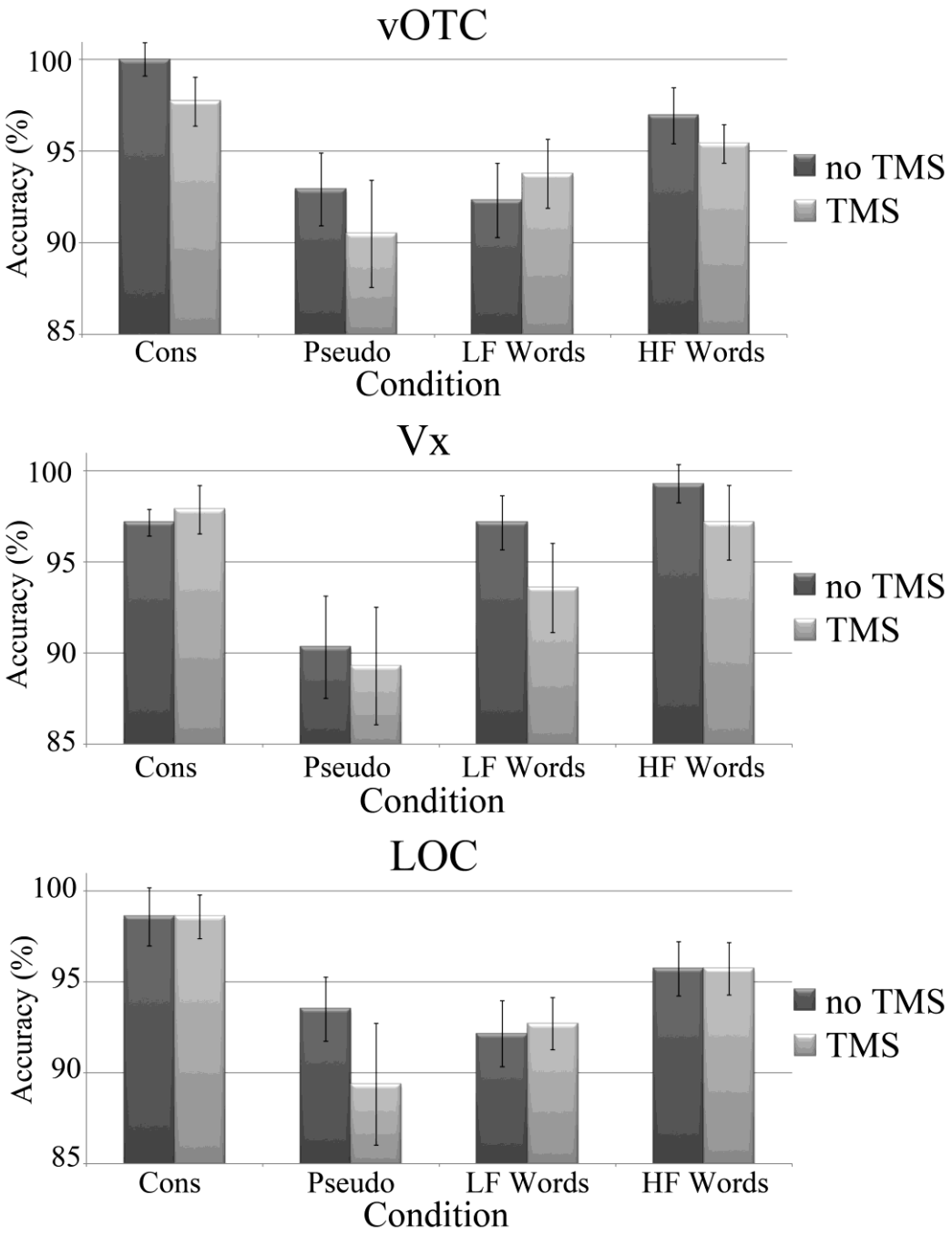


Figure 3-3: Mean accuracy (%) for rTMS to ventral occipito-temporal cortex (top), vertex (middle), and LOC (bottom) across the four stimulus conditions in Experiment 1 for no TMS (dark bars) and TMS (light bars). Cons = consonant letter strings, Pseudo = pronounceable pseudowords, LF = low frequency words, HF = high frequency words, vOTC = ventral occipito-temporal cortex, and LOC = lateral occipital complex. Error bars represent standard error of the mean, adjusted to accurately reflect the variance in a repeated-measures design (Loftus and Masson 1994).

The RT results are shown in Figure 3-4 and were analysed with the same omnibus ANOVA. There was a main effect of Condition ($F(3,39) = 51.1$, $p < 0.001$) indicating that as expected, the four types of stimuli differed in difficulty, with consonant letters strings the easiest (471msec), followed by high frequency words (517msec), low frequency words (550msec), and then pseudowords (624msec). In addition, there was a significant Condition $\times$ TMS interaction ($F(3,39) = 5.5$, $p = 0.003$) demonstrating that on average, rTMS decreased RTs across stimulation sites for pseudowords (634 vs. 613msecs) but increased RTs for low frequency words (543 vs. 558msecs). Interestingly, the facilitation effect on pseudowords was consistent for all three sites, whereas TMS interfered with low frequency words at the vOTC and LOC sites but facilitated responses at the vertex. Surprisingly, the three-way interaction was not significant, probably due to insufficient power given the complexity of the design (i.e. four stimulus conditions and three testing sites). Even so, Figure 3-4 shows that the response profiles to TMS were different across sites and consequently, I chose to investigate these further.

In order to investigate these difference response profiles, I conducted a 2-way repeated measures ANOVA for each site. The main effect of Condition was present for all sites. For the vOTC site, there was no main effect of TMS ($F(1,13) = 0.6$, $p = 0.449$) but a significant Condition $\times$ TMS interaction ($F(3,39) = 3.7$, $p = 0.021$). Planned comparisons revealed that TMS selectively slowed responses to low frequency words (+34msecs, $t(13) = 2.8$, $p = 0.017$) without significantly affecting the other conditions. The response profile for stimulation of the vertex, on the other hand, looked very different. Here, there was a significant main effect of TMS ($F(1,13) = 6.2$, $p = 0.027$) but no significant interaction ($F(3,39) = 1.8$, $p = 0.160$). Planned comparisons showed a significant TMS-induced speed-up for both pseudowords (–34msecs, $t(13) = 2.7$, $p = 0.018$) and high frequency words (–24msecs, $t(13) = 2.9$, $p = 0.012$), although both low frequency words and consonants were numerically faster as well. In other words, TMS of the vertex appeared to have a non-

specific, inter-sensory facilitation effect (Terao et al. 1997). Finally, stimulation at LOC produced neither a significant main effect of TMS ($F(1,13) = 0.6$, $p = 0.458$) nor an interaction ($F(3,39) = 1.5$, $p = 0.217$), although low frequency words showed a non-significant slowdown of +14msec ($t(13)=1.0$, $p = 0.327$) similar to that seen in vOTC.

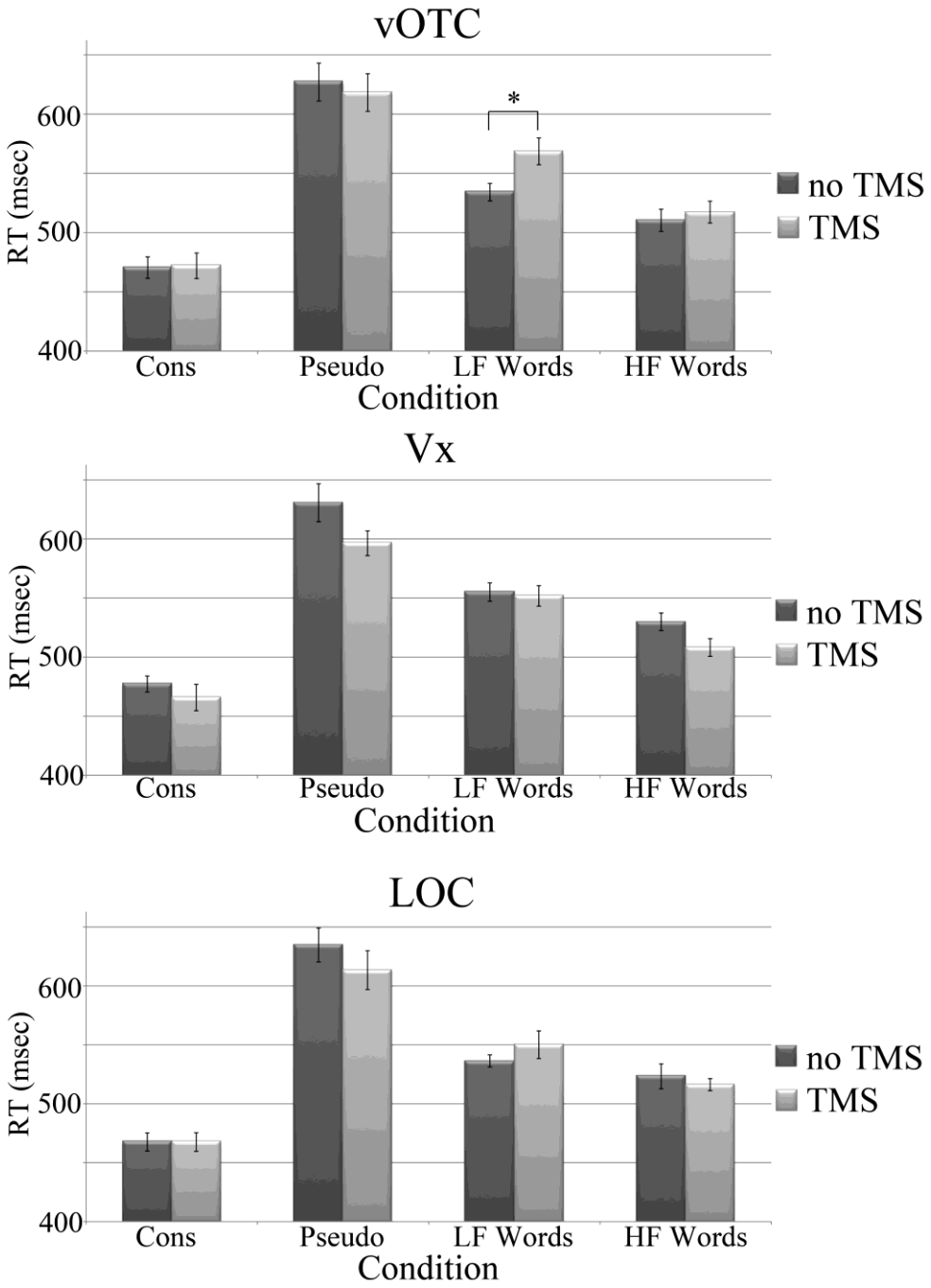


Figure 3-4: Mean RTs (in msec) for rTMS to ventral occipito-temporal cortex (top), vertex (middle), and LOC (bottom) across the four stimulus conditions in Experiment 1 for no TMS (dark bars) and TMS (light bars). Cons = consonant letter strings, Pseudo = pronounceable pseudowords, LF = low frequency words, HF = high frequency words, vOTC = ventral occipito-temporal cortex, and LOC = lateral occipital complex. Error bars represent standard error of the mean, adjusted to accurately reflect the variance in a repeated-measures design (Loftus and Masson 1994). * indicates a significant TMS effect at $p < 0.05$.

3.2.3 Discussion

There are two main findings of the current experiment. First, the depth of vOTC is on average no deeper than the hand area of primary motor cortex, which is easily accessible with TMS (Barker and Jalinous 1985; Pascual-Leone et al. 1994; Rothwell 1997). Second, stimulation of vOTC selectively slowed response times to low frequency words. This pattern was noticeably different than the non-specific facilitation effect seen for vertex stimulation but qualitatively similar to the pattern at LOC.

The specific region of vOTC associated with reading is typically centred on the occipito-temporal sulcus and spreads medially onto the posterior fusiform gyrus (Ben-Shachar et al. 2007; Wright et al. 2008). This area lies at a complex junction between the inferior temporal and fusiform gyri, just superior and lateral to the principle fissure of the cerebellum (see Figure 3-1 and 3-2). As a result, it is possible to orient the TMS coil such that the line of maximum stimulation runs between the cerebellum and inferior temporal gyrus and targets the occipito-temporal sulcus. Due to the smoothly varying topology of the magnetic field generated by a figure-of-eight coil, there is likely to be some stimulation of both inferior temporal gyrus and of cerebellar lobule VI, but the maximum effect targets the occipito-temporal sulcus and lateral posterior fusiform gyrus. Since the scalp-to-target distances for vOTC and hand area of M1 are essentially equivalent, the stimulation intensity necessary to affect the former can be estimated based on motor thresholds. Here we used a fairly conservative measure of motor threshold (i.e. a visible muscle twitch) but lower values based on motor evoked potentials may be sufficient and would help to reduce both the auditory and somatosensory effects of stimulating this region.

That TMS of vOTC resulted in a slowdown in 12 out of 14 participants demonstrates the robustness of the effect. Stimulation slowed responses to low frequency words, while responses to high frequency words showed a non-significant slowdown. In contrast,

stimulation of vOTC had no effect on responses to pseudowords or consonants strings. In other words, the results demonstrate stimulus-specificity since stimulation does not affect all conditions equally. In addition, the results demonstrate site-specificity, as there was a clear difference between the effect of stimulation of vOTC compared to vertex, where there was a non-specific facilitatory effect. In contrast, the results from vOTC stimulation may or may not be different from LOC stimulation, as although LOC stimulation did not result in any significant slowdowns the pattern of the results was qualitatively similar for the two sites.

Given that both vOTC and LOC are activated by visual words (Moore and Price 1999; Price et al. 2006; Duncan et al. 2009) and that the two stimulation sites were only 2cm apart, it is unclear whether there was an actual difference in the effects of TMS between these sites or whether the experiment was under-powered to detect a TMS effect at LOC. Consequently, the second experiment was designed to specifically address this question. Three things were done to increase statistical sensitivity: i) the number of stimuli per condition was doubled, ii) the number of conditions was reduced. Lexical items consisted of only low frequency words (since these produced the largest TMS effect in Experiment 1) and non-lexical items consisted of only pseudowords (as they were unaffected by TMS), and iii) as the aim of the experiment was to determine the site-specificity of vOTC stimulation in relation to LOC stimulation, vertex was not tested. Therefore the design was simplified from 3 x 4 x 2 to 2 x 2 x 2, increasing sensitivity.

In addition, we chose to reduce the stimulation intensity from 110% to 100% of motor threshold based on the similar depths of the hand area of M1 and vOTC. This helped to reduce the discomfort that some participants experienced during stimulation without reducing the likelihood of successfully stimulating the region. Thus the purpose of the second experiment was to further investigate the site-specificity of the slowdown in low frequency word responses observed in the previous. There are two possible outcomes:

1. The TMS effect on low frequency words is site-specific, present only during vOTC but not LOC stimulation. Because the sensation of stimulation is indistinguishable for the two sites, the lack of a TMS effect on LOC would demonstrate that slowdowns in vOTC are a result of the specific neural effects of stimulation rather than peripheral non-specific effects, such as muscle involvement. This scenario would be consistent with the neuropsychological literature where lesions to vOTC but not LOC are associated with reading impairments (Dejerine 1892; Geschwind 1965a; Damasio and Damasio 1983; Binder and Mohr 1992; Philipose et al. 2007). Importantly, this scenario would confirm the feasibility of ventral occipito-temporal stimulation.

2. The effect on low frequency words occurs during stimulation of both vOTC and LOC sites. This possibility would indicate that both vOTC and LOC areas are causally involved in word recognition, consistent with neuroimaging studies that show LOC activation during reading (Price et al. 2006; Wright et al. 2008; Duncan et al. 2009) but inconsistent with the patient data where LOC lesions are not typically associated with reading impairments (Dejerine 1892; Geschwind 1965a; Damasio and Damasio 1983; Binder and Mohr 1992; Philipose et al. 2007).

3.3 Experiment 2

3.3.1 Method

Participants. 26 right handed, native English speakers with normal or corrected to normal vision (13M, 13F, aged 18 to 45, mean = 26) participated. None had any form of dyslexia, a personal history of neurological disease, or a family history of epilepsy according to self-reports. Each gave informed consent after the experimental procedures were explained. The experiments were approved by the Berkshire NHS Research Ethics Committee.

Functional imaging. All participants completed a 1-back task during fMRI scanning in order to localise the precise region of vOTC and LOC to target with TMS in each individual (Table 3-4). The details of the fMRI scans are given in Chapter 2.

Table 3-4: Peak coordinates for the contrasts [Words > Fixation] and [Objects > Scrambled Objects] in vOTC (left) and LOC (right) respectively, in MNI space. Each individual's peak was used as their target for TMS.

vOTC					***LOC***				
Subject	**MNI Coordinates**			***Z*-score**	**Subject**	**MNI Coordinates**			***Z*-score**
	x	***y***	***z***			***x***	***y***	***z***	
1	-44	-63	-23	9.1	**14**	-46	-80	-3	4.9
2	-44	-62	-18	8.4	**15**	-35	-78	-5	2.0
3	-39	-53	-16	6.3	**16**	-47	-71	-9	7.3
4	-34	-48	-24	7.5	**17**	-46	-68	-9	2.2
5	-40	-51	-9	7.1	**18**	-49	-72	-1	11.2
6	-36	-58	-18	9.3	**19**	-45	-73	-13	4.5
7	-36	-60	-14	7.3	**20**	-45	-81	-6	8.0
8	-41	-63	-14	7.2	**21**	-44	-85	1	4.9
9	-42	-56	-18	6.7	**22**	-41	-84	0	7.2
10	-30	-53	-17	11.8	**23**	-44	-72	-10	8.2
11	-43	-66	-8	11.0	**24**	-41	-80	-10	12.4
12	-43	-64	-18	9.1	**25**	-40	-83	-9	5.4
13	-45	-51	-18	4.2	**26**	-44	-63	-22	7.4
Mean	**-41**	**-58**	**-17**	**8.1**	**Mean**	**-44**	**-76**	**-7**	**6.6**
SEM	1.3	1.6	1.3	0.6	**SEM**	1.0	1.9	1.7	0.9

Task and stimuli. As before, participants performed a lexical decision task similar to the first. The primary differences were that i) this experiment used a between-subject design with 13 participants per stimulation site, ii) the number of items per condition was

doubled and iii) only two sites were tested (vOTC and LOC) and iv) only two stimulus conditions were included (low frequency words and pseudowords), each containing 40 items and the same stimuli were used for both sites. Across conditions, the items were balanced for pre-lexical psycholinguistic properties, once again including bigram frequency (Table 3-5). There were two versions whose order was counter-balanced across the stimulation sites. The stimuli were a subset of those used in the previous experiment and were matched across versions for written word frequency, rated familiarity, letter length, number of syllables, bigram frequency and orthographic neighbourhood. Finally, based on the similar depths of the hand area of primary motor cortex and vOTC, the TMS intensity was set to 100% of motor threshold rather than 110% as in the previous experiment.

Table 3-5: Experiment 2. Mean psycholinguistic properties per condition with standard error in parenthesis. LF = low frequency words.

	LF Words	Pseudowords	*t*	*p*
Frequency	5.9 (0.8)	-	-	-
Familiarity	461 (18)	-	-	-
Bigram frequency	1372 (147)	1538 (165)	0.75	0.455
Orthographic neighbourhood	5.5 (0.8)	5.7 (0.6)	0.23	0.817
No. of Letters	4.9 (0.1)	4.9 (0.1)	0.28	0.782
No. of syllables	1.0 (0.0)	1.0 (0.0)	1.00	0.320

Procedure Each trial began with a fixation cross displayed for 500msec, followed by a visual letter string for 200msec and then a blank screen for 2300msec, giving a total duration of 3sec. Subjects indicated whether the letter string formed a real word in English or not by pressing a button using either their right or left index finger. Responses

were fully counter-balanced for response hand across subjects. Accuracy and RTs were recorded.

Testing sessions began by determining the participant's motor threshold using a single pulse delivered to the hand area of primary motor cortex. A practice session, using an independent set of items, followed allowing the participant to become familiar with the lexical decision task. Next, the participant was assigned a testing site and introduced to the sensation of rTMS at that site. After familiarisation with the sensation, the participant performed another practice session with rTMS pseudorandomly delivered on half of the trials to get used to performing the task with concurrent rTMS. As in Experiment 1, participants were unable to distinguish the sensation of stimulation from the two sites.

Analyses. RTs were measured from the onset of the target. No responses were below 300msec and consequently none were trimmed. To minimise the effect of outliers in the RT data, median RTs for correct responses per condition per subject were (Ulrich and Miller 1994). The accuracy scores and median RTs were analysed using a 3-way mixed ANOVA where the within-subjects factors were Condition (words, pseudowords) and TMS (none, rTMS) and the between subjects factor was Site (vOTC, LOC). Post hoc comparisons used two-tailed paired *t*-tests were used with Bonferroni corrections for multiple comparisons.

The data from two participants showed TMS effects of +216 and +201msec (present across conditions), double the next largest effect, over 100msec outside the range of the other participants, suggesting non-specific effects of TMS were impairing responses. Consequently, these subjects' data were excluded from the analysis[7].

3.3.2 Results

Like the first experiment, overall accuracy was high (94%). The only significant main effect on accuracy was for TMS ($F(1,22) = 7.7$, $p = 0.011$), reflecting a small TMS-induced decrease in accuracy (from 95% to 93%) that was present across sites and conditions (Figure 3-5). This is likely due to the peripheral effects of TMS stimulation, which were identical across the two occipito-temporal sites.

[7] Subsequent experiments included a TMS 'pre-test', where prospective participants came for a short introduction to TMS and were able to experience rTMS over both vertex and ventral occipito-temporal sites following Lambon Ralph and colleagues (Lambon Ralph, M., Personal communication, 2009). This helped allay anxiety and identified subjects who experience considerable muscle involvement before they participated in the fMRI session. In addition, subjects were explicitly told that TMS can result in a slowdown, speedup or have no effect, depending on where the stimulation occurs and what the participant is doing. These measures were effective in preventing further instances of implausibly large performance impairments in all subsequent experiments.

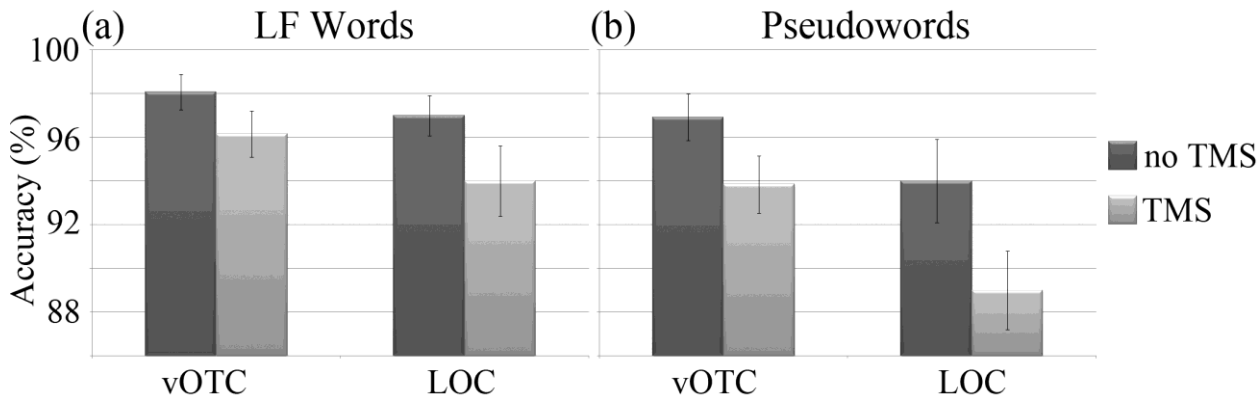


Figure 3-5: Accuracy (%) for a) LF words and b) pseudowords in Experiment 2. LF words = low frequency words, vOTC = ventral occipito-temporal cortex, and LOC = lateral occipital complex. Error bars represent standard error of the mean, adjusted to accurately reflect the variance in a repeated-measures design (Loftus and Masson 1994).

The critical results, however, concerned the TMS effect on RTs. To investigate this, the RT results (shown in Figure 3-6) were analysed with the same omnibus ANOVA. There was a main effect of Condition ($F(1,22) = 43.3$, $p < 0.001$), once again indicating that pseudowords (646msec) were more difficult than low frequency words (585msec). More importantly, the three-way interaction ($F(1,22) = 8.0$, $p = 0.010$) was clearly significant. Further analyses showed that vOTC stimulation significantly slowed RTs for words (+40msec, $t(12) = 3.1$, $p = 0.010$) but had no effect on pseudowords (+8msec, $t(12) = 0.7$, $p = 0.521$). In contrast, LOC stimulation did not significantly affect RTs for words (-15msec, $t(12) = 1.0$, $p = 0.343$) or pseudowords (-1msec, $t(10) = 0.070$, $p = 0.945$).

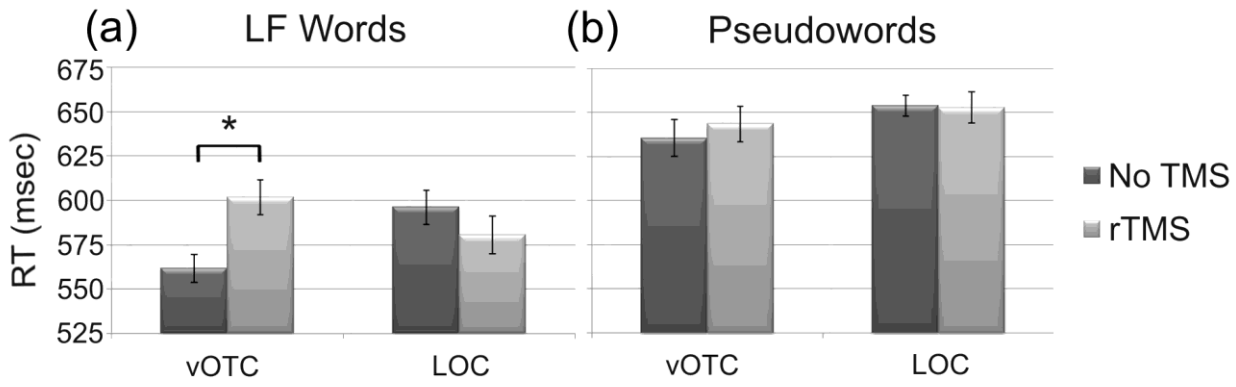


Figure 3-6: Mean RTs (in msec) for a) LF words and b) pseudowords in Experiment 2. The only significant simple TMS effect was a +40msec slow-down for words with ventral occipito-temporal cortex stimulation. Cons = consonant letter strings, Pseudo = pronounceable pseudowords, LF = low frequency words, HF = high frequency words, vOTC = ventral occipito-temporal cortex, and LOC = lateral occipital complex. Error bars represent standard error of the mean, adjusted to accurately reflect the variance in a repeated-measures design (Loftus and Masson 1994). * indicates a significant TMS effect at $p < 0.05$.

3.3.3 Discussion

The results of Experiment 2 confirm that stimulation of vOTC selectively interferes with reading low frequency words and demonstrates the effect is present even at a lower stimulation intensity, with 11 out of 13 participants showing a slowdown. Critically, the findings help to clarify the ambiguous results in the first experiment regarding the effects of LOC stimulation. The experimental design was optimised to maximise sensitivity: i) the number of stimuli per condition was doubled, ii) the number of conditions was reduced, and iii) only vOTC and LOC were tested. Despite this, rTMS over LOC had no significant effect on low frequency words – in fact, if anything LOC stimulation slightly reduced RTs for words – confirming that the interference seen for vOTC stimulation is specific to that site and not a general feature of occipital-temporal stimulation. In other words, peripheral stimulation effects cannot explain the current pattern of results because vOTC stimulation did not affect all stimuli equally; specifically it inhibited word responses without affecting pseudowords. In addition, these effects were not present in LOC where stimulation produced essentially identical peripheral effects. In summary, then, these results

demonstrate that vOTC stimulation successfully and selectively disrupted visual word recognition while LOC stimulation did not.

3.4 General Discussion

The primary goal of the experiments in this chapter was to determine whether it was possible to stimulate a left ventral occipital-temporal region known to be involved in visual word recognition. The results of the two experiments convincingly demonstrate that TMS can be used to successfully stimulate vOTC and reliably interfere with visual word recognition. While the subjective experience of TMS of vOTC and vertex is noticeably different, it is unlikely that the disruption in word reading was a general, peripheral effect of TMS given that the effect was condition-specific and replicated. Moreover, this possibility is rendered even less likely if we consider the difference between vOTC and LOC stimulation in Experiment 2, given that the sensation of TMS is not noticeably different between these two posterior temporal lobe sites. Specifically, stimulation of LOC led to a (non-significant) increase in RTs for low frequency words that became a (non-significant) decrease in the second. The lack of any significant modulation by TMS and the fact that RT changes were not even in a consistent direction, strongly suggests that TMS to LOC had no effect on reading low frequency words, which contrasts with the results of vOTC stimulation. These findings are consistent with the neuropsychological literature which suggests that left hemisphere lesions to either vOTC or the inferior parietal lobule – but not LOC – can result in preferential impairments for reading (Dejerine 1892; Geschwind 1965a; Damasio and Damasio 1983; Binder and Mohr 1992; Philipose et al. 2007) and demonstrate that vOTC, but not LOC, is necessary for visual word recognition. The demonstration that vertex and LOC stimulation have no effect on word reading is strongly suggestive of the site-specific nature of ventral occipito-temporal stimulation. However, in the case of LOC this requires additional stimulation of the temporalis muscle and longer periods of scalp muscle stimulation increase the incidence of adverse effects, particularly

headache, which is undesirable for the participant but also may introduce more variability into performance as the experiment progresses. As such, experiments in subsequent chapters used vertex only.

It is informative to compare the current TMS findings with those from related neuroimaging studies, where there are both similarities and important differences. For instance, amongst alphabetic stimuli consonant strings elicit the least amount of activation in vOTC (Cohen et al. 2002; Devlin et al. 2006), consistent with the finding that vOTC stimulation had essentially no effect on consonant letter strings. Similarly, some imaging studies have demonstrated that activation in vOTC is modulated by word frequency, with greater activation for low than high frequency words (Chee et al. 2003b; Kronbichler et al. 2004). Here, we observed a (non-significant) slow down for high frequency words of +7msec and a larger (significant) effect on low frequency words (+34msec), consistent with the imaging findings. It is possible that with greater statistical sensitivity, we would be able to document a reliable, graded effect of TMS on different classes of orthographic stimuli, but the current findings certainly are consistent with the imaging literature. Pseudowords, on the other hand, elicit robust activation in vOTC activation (Fiez et al. 1999; Hagoort et al. 1999; Xu et al. 2001; Fiebach et al. 2002; Bellgowan et al. 2003; Binder et al. 2003; Mechelli et al. 2003; Binder et al. 2005a; Binder et al. 2005b; Lee et al. 2010) – and yet TMS did not significantly affect responses to pseudowords, despite being matched on prelexical properties with the lexical stimuli. In fact, RT changes to pseudowords were not even in a consistent direction: vOTC stimulation resulted in a 9msec speedup for responses to pseudowords in Experiment 1 but a slowdown of 8msec in Experiment 2. It is worth noting, however, that in a lexical decision task, participants make a different response for words (“yes”) and pseudowords (“no’) which may contribute to the different TMS effects for these two types of stimuli. On the other hand, the same response confound is present in the imaging studies using lexical

decision, so this alone cannot explain the apparent disconnect between the TMS and imaging results. Further studies will be necessary to determine whether TMS differentially affects words and pseudowords even when the response is matched across conditions such as in a naming task. The current findings that vOTC makes different contributions to words and non-words, however, are consistent with previous imaging studies that also found reliable lexicality effects in vOTC (Fiez et al. 1999; Hagoort et al. 1999; Xu et al. 2001; Bellgowan et al. 2003; Binder et al. 2003; Mechelli et al. 2003; Binder et al. 2005a; Binder et al. 2005b; Fiebach et al. 2005; Devlin et al. 2006; Lee et al. 2010; Schurz et al. 2010) and have potentially important implications for understanding vOTC contributions to reading.

How do these findings speak to theories of vOTC function? Lexical frequency (i.e. low > high frequency) and lexicality (i.e. words > pseudowords) effects are both difficult to explain in terms of stored, pre-lexical representations (Cohen et al. 2000; Cohen et al. 2002; McCandliss et al. 2003; Dehaene et al. 2005), particularly when the stimuli were matched on prelexical orthographic factors including bigram frequency. According to this account, neurons in vOTC have receptive fields for bigrams – that is, they are specialised for detecting particular visual stimulus characteristics – and are therefore insensitive to the specific response properties of the task. As a result, any stimuli comprised of legal bigrams should be equally affected by TMS, with no difference between low and high frequency words or pseudowords, irrespective of the response. Clearly the current TMS results, as well as previous imaging findings (Hagoort et al. 1999; Xu et al. 2001; Kronbichler et al. 2004; Fiebach et al. 2005; Devlin et al. 2006; Bruno et al. 2008; Lee et al. 2010; Schurz et al. 2010), are inconsistent with this proposal. An alternate possibility is that vOTC is the site of stored lexical representations of visual words (Kronbichler et al. 2004). Although sufficient to explain the current TMS results, this account is incompatible with previous imaging evidence showing neural repetition priming effects for visually

similar, but lexically distinct word pairs such as “corner-corn” (Devlin et al. 2006). A different possibility is that vOTC acts as an interface, integrating bottom-up, visual form information (that is not specific to written words) with top-down, non-visual properties of the stimulus such as its sound or meaning (Nakamura et al. 2002; Hillis et al. 2005; Price and Friston 2005; Devlin et al. 2006; Xue et al. 2006; Cai et al. 2010). Because low frequency items place greater processing demands than high frequency items, there is greater activation in vOTC and stimulation has a larger disruption effect. In this case, the absence of any effect on pseudoword responses may reflect their relative lack of non-visual properties and the integration process fails regardless of the TMS-induced disruption. The greater activation for pseudowords relative to words reported in a number of imaging studies may reflect the additional processing demands of the search, and subsequent failure, of integration (e.g. what is the meaning of “bocket”?). If true, then this hypothesis predicts that TMS will not affect stimuli when this integration process fails, regardless of the response demanded by the task. An alternative possibility is that the task demands shape the response profile of vOTC, such that during lexical decision the integration of non-visual properties is not required to correctly reject pseudowords as non-lexical items. A close examination of the imaging data is consistent with task demands modulating activity. Studies that used a lexical decision have consistently found greater activation for words (Fiebach et al. 2002; Bellgowan et al. 2003; Binder et al. 2003; Binder et al. 2005b), while studies that used a task that emphasised the phonological properties of the stimuli (e.g. reading, rhyming etc) consistently report greater activation for pseudowords (Fiez et al. 1999; Hagoort et al. 1999; Xu et al. 2001; Mechelli et al. 2003; Binder et al. 2005a; Bruno et al. 2008; Lee et al. 2010). If this is correct, then it predicts that pseudoword processing will be impaired if stimulation occurs during a task which emphasises the processing contribution of vOTC, such as a phonological lexical decision involving pseudohomophones and pseudowords. Clearly further work is needed to better evaluate these theories.

3.5 Conclusion

This chapter demonstrated that TMS can be used to successfully selectively stimulate parts of ventral occipital-temporal cortex and interfere with visual word recognition. These experiments open the door for a systematic exploration of vOTC contributions to reading and its relation to other higher order visual functions (Price and Devlin 2003; Joseph et al. 2006; Starrfelt and Gerlach 2007). Similarly, although we have focused entirely on the left vOTC, this same approach should be useful for investigating right vOTC other categories of visual objects (Haxby et al. 2000; Haxby et al. 2001).

4 Effects of frequency and task

4.1 Introduction

Our ability to recognise words is affected by a number of the psycholinguistic properties that characterise them. These attributes include the number of meanings (Rubenstein et al. 1970) and orthographic neighbours (Coltheart et al. 1977) of a word, the age the word is first learned (Carroll and White 1973; Lyons et al. 1978), its subjective familiarity (Connine et al. 1990) and concreteness (James 1975). However, the factor that has the single greatest effect is the written frequency of the word (Howes and Solomon 1951; Rosenzweig and Postman 1957; Rosenzweig and Postman 1958; Rubenstein et al. 1970; Forster and Chambers 1973; Monsell et al. 1989). Subjects respond more accurately and faster to words which appear more frequently in print relative to those occurring less frequently and this difference in behavioural performance is referred to as the *word frequency effect*. Since lexical frequency is an emergent property of the whole word rather than any sublexical aspects, any behavioural or neurological difference between low and high frequency words can provide information about how words are represented in the brain. Word frequency effects occur during a range of tasks, including lexical decision, semantic decision and naming, suggesting that the effect arises during the process of lexical identification since this is common to all tasks (Morton 1969; Morton 1982). However the word frequency effect interacts with task, such that its magnitude is greatest during lexical decision relative to naming (Forster and Chambers 1973; Frederiksen and Kroll 1976; Balota and Chumbley 1984; Schilling et al. 1998), silent reading (with eye fixation times as dependent measure) (Schilling et al. 1998) and semantic decision (Balota and Chumbley 1984), indicating that frequency also affects processing subsequent to lexical access (i.e. phonological, semantic processing or the mappings between orthography, phonology and semantics) (Balota and Chumbley 1984; Balota and Chumbley 1985; McCann and Besner 1987; Monsell et al. 1989; Besner and Smith 1992). This is consistent with connectionist models, where there is no single locus of the word

frequency effect but rather it reflects the stronger connection strengths of frequently occurring words across the whole network that develop during learning (Seidenberg and McClelland 1989; Plaut et al. 1996).

The distributed nature is also supported by fMRI studies which have demonstrated that multiple brain areas are sensitive to word frequency, including left inferior frontal cortex, left temporoparietal and occipito-temporal areas, bilateral insulae, anterior cingulate/SMA and pre-SMA (Fiebach et al. 2002; Chee et al. 2003a; Chee et al. 2003b; Kuo et al. 2003; Kronbichler et al. 2004; Lee et al. 2004; Carreiras et al. 2006; Nakic et al. 2006; Hauk et al. 2008). In ventral occipito-temporal cortex (vOTC), activity is inversely related to word frequency with the greatest activation for infrequent or novel words (Chee et al. 2003b; Kronbichler et al. 2004). In fact, activation occurs along a continuum, with fixation producing the least activation, followed by checkerboards and strings of meaningless consonants, then high frequency words and finally with low frequency words and pseudowords eliciting the greatest activation (Cohen et al. 2000; Kronbichler et al. 2004). However, although the area shows robust word-related activity, the difference between high and low frequency words is subtle (Chee et al. 2003b; Kronbichler et al. 2004) and in some reported studies, absent (Fiebach et al. 2002; Chee et al. 2003a; Carreiras et al. 2006; Hauk et al. 2008; Carreiras et al. 2009). This may be due to an interaction of the frequency effect and task which has been reported for other areas (Chee et al. 2002; Carreiras et al. 2006). Alternatively, it may be a question of statistical sensitivity as the studies that have reported the effect have used a region-of-interest analysis (Chee et al. 2003b; Kronbichler et al. 2004). However, the one study that used this type of analysis *and* lexical decision did not find an effect of frequency in vOTC (Carreiras et al. 2006), suggesting that other as yet uncharacterised aspects of the experimental design may be important. It should be noted, however, that all studies, whether they

demonstrate an effect of frequency on ventral occipito-temporal activity or not, report activation for high frequency words in the area.

Lexical frequency is an emergent property of the whole word, not its constituent parts. As a result when prelexical properties are matched for high and low frequency words, a frequency effect is incompatible with any prelexical account of ventral occipito-temporal function. As previously noted, these frequency effects together with other neuropsychological and ERP data led to the claim that vOTC a *lexical* visual word form area (Kronbichler et al. 2004).

The experiments in the previous chapter demonstrated that vOTC can be successfully stimulated with TMS, resulting in a disruption of word reading. Interestingly, there was a suggestion that the effect of TMS was modulated by word frequency and that this differential effect was consistent with the neuroimaging reports of greater activation for low versus high frequency words. However, although responses to both low and high frequency words were slowed, only those to low frequency words were significantly affected by TMS. As a consequence of the rather complex design of the experiment (three stimulation sites, four conditions), only ten items per condition were included in the experiment in order to keep the number of TMS pulses within established safety guidelines and subject fatigue to a minimum. Thus it is possible that the experiment lacked sufficient power to identify a significant effect on high frequency words. As a result, the purpose of the first experiment in the current chapter was to further investigate the stimulus selectivity of vOTC using a simpler, more sensitive 2×2 experimental design factorial design with frequency (High, Low) and rTMS (rTMS, none) as independent factors. There are three possible outcomes:

1) Stimulation of vOTC affects low and high frequency words equally as indicated by a significant main effect of TMS and no interaction with frequency. This would be

consistent with the prelexical VWFA hypothesis because the putative bigram detectors should not be sensitive to whole word properties such as frequency. As long as the low and high frequency words are matched for the sub-lexical bigrams frequencies, stimulation should affect both sets of words equally. This would also be consistent with the neuroimaging studies that failed to find a frequency effect (Fiebach et al. 2002; Chee et al. 2003a; Carreiras et al. 2006; Hauk et al. 2008; Carreiras et al. 2009). When considering this outcome alongside the lexical VWFA account and the interface hypothesis, it is apparent that they are both underspecified. In the lexical VWFA model, each word has a lexical entry stored in vOTC, each with a specific threshold that must be reached in order that lexical identification is successful. Stimulation of the area may thus result in inappropriate lexical entries reaching threshold or alternatively suppression of activity in appropriate lexical entries but it is not clear how either of these outcomes may interact with word frequency. Similarly, although vOTC may be required to link the higher order properties to the visual forms of both high and low frequency words, suggesting that TMS should affect all words equally, this process may be more important for word recognition of low frequency words.

2) Stimulation of vOTC affects both low and high frequency words, but differentially, with TMS affecting low frequency words to a greater extent as indicated by a main effect of TMS and a significant supra-additive interaction. As noted above, such an effect of word frequency is incompatible with the idea that the area maintains prelexical abstract representations but is consistent with either a lexical VWFA or interface account. Although this outcome is consistent with the neuroimaging studies showing a frequency effect in vOTC (Chee et al. 2003b; Kronbichler et al. 2004), the lack of effect of TMS on pseudowords in the previous chapter serves as

a timely reminder that fMRI activations do not necessarily represent causal processing.

3) Stimulation of vOTC affects low, but not high, frequency words, as indicated by a significant Frequency × TMS interaction in the absence of a main effect of TMS. Importantly, such a result would be inconsistent with both VWFA accounts since in both cases, vOTC contains representations for high frequency words (either pre-lexical or lexical) that should be affected by stimulation. Although the interface hypothesis doesn't make specific predictions regarding the effect of stimulation on high frequency words, the theory can accommodate an absence of a TMS effect on high frequency words if top-down interactions shape the necessity of vOTC processing such that frequently occurring words can be recognised sufficiently well without the area's processing, even though the area is automatically recruited for any word or word-like stimulus. This would then be similar to the absence of a TMS effect on pseudoword reading reported in the previous chapter, i.e. activation in the absence of causal involvement.

Vertex was also tested to ensure that any disruption was site-specific as was the case in the previous chapter.

4.2 Experiment 1: Frequency effects in lexical decision

4.2.1 Method

Participants. 16 subjects (7M, 9F, aged 20 to 39, mean = 27) participated. All were right handed, native English speakers with normal or corrected to normal vision. None had any form of dyslexia, a personal history of neurological disease, or a family history of epilepsy according to self-reports. Each gave informed consent after the experimental procedures were explained. The experiments were approved by the UCL Research Ethics Committee [UCL #249/001].

Functional imaging. All participants completed a 1-back task during fMRI scanning in order to localise the precise region of vOTC to target with TMS in each individual (Table 4-1). The details of the fMRI scans are identical to those given in Chapter 2.

Table 4-1: Peak coordinates for the contrast [Words > Fixation] in vOTC in MNI space. Each individual's peak was used as their target for TMS.

vOTC				
Subject	**MNI Coordinates**			***Z*-score**
	x	***y***	***z***	
1	-48	-54	-28	5.6
2	-43	-68	-21	9.1
3	-43	-58	-11	11.9
4	-44	-62	-18	8.4
5	-39	-71	-18	6.1
6	-42	-68	-11	7.5
7	-48	-68	-6	7.7
8	-46	-52	-14	4.9
9	-35	-72	-5	10.0
10	-46	-61	-22	7.1
11	-46	-56	-30	7.1
12	-50	-60	-13	9.8
13	-43	-68	-8	7.0
14	-42	-60	-15	6.3
15	-47	-49	-27	5.6
16	-42	-53	-11	2.6
Mean	**-44**	**-61**	**-16**	**7.3**
SEM	0.9	1.8	1.7	0.6

Task and Stimuli. Participants performed a visual lexical decision task while rTMS was delivered to one of two target sites: vOTC and vertex, which was included as a control site where stimulation was not expected to affect responses. In addition to being consistent with the previous chapter, the lexical decision produces the most pronounced word frequency effects (Balota and Chumbley 1984; Balota and Spieler 1999), thus maximising sensitivity to these effects. The lexical decision task consisted of three conditions: 80 low frequency words, 80 high frequency words and 160 pronounceable pseudowords (e.g. “golube”). Low and high frequency words were defined as items having less than 10 or more than 20 occurrences per million, respectively (Table 4-2). Frequency values were obtained from the Celex database of British written English (Baayen et al. 1993). The lexical decision task was divided into two lists (each comprising 40 high frequency, 40 low frequency and 80 pseudowords) and matched for written word frequency (overall and separately for both low and high frequency items) (Baayen et al. 1993), rated familiarity (Coltheart 1981), letter length, number of syllables, bigram frequency and orthographic neighbourhood (Davis 2005). The order of the lists was balanced across subjects and stimulation sites. In addition, an independent set of items was used for practice. The simplified design allowed the number of items per condition to be doubled (from 10 to 20) relative to Experiment 1 in the previous chapter and still remain within established safety parameters (Wassermann 1998; Rossi et al. 2009).

Table 4-2: Mean psycholinguistic properties per condition with standard error in parenthesis. Statistical values refer to Lexical conditions only. Pseudoword data included in table for completeness sake. HF = high frequency words, LF = low frequency words.

	HF Words	LF Words	Pseudowords	*t*	*P*
Frequency	205 (14.13)	4 (0.17)	-	14.24	<0.001
Familiarity	579 (3.43)	492 (4.88)	-	14.47	<0.001
No. of Letters	5.15 (0.08)	5.14 (0.06)	5.06 (0.06)	0.10	0.920
No. of syllables	1.44 (0.06)	1.46 (0.06)	1.41 (0.04)	0.32	0.752
Bigram frequency	1300 (76.5)	1274 (100.5)	1304 (74.6)	0.21	0.837
Orthographic neighbourhood	3.2 (0.38)	3.8 (0.40)	4.0 (0.33)	1.07	0.288

Procedure. Each trial began with a fixation cross displayed for 500msec, followed by a visual letter string for 200msec and then a blank screen for 2300msec, giving a total duration of 3sec. Subjects indicated whether the letter string formed a real word in English or not by pressing a button using either their right or left index finger, with response finger counterbalanced across subjects. Half of all trials had rTMS. Participants were instructed to "respond as quickly as possible while minimising the number of mistakes." Accuracy and reaction times (RTs) were recorded.

The two stimulation sites were tested sequentially in a single session with their order counter-balanced across subjects. Testing began by finding each individual's motor threshold as described previously and this value was used for all subsequent TMS testing. The participant then performed a practice session of the experiment without any TMS to familiarise them with the task. After familiarisation with the sensation, the participant performed a practice session with rTMS pseudorandomly delivered on half of the trials to get used to performing the task with concurrent rTMS. Finally, participants completed a list of the stimuli at each site, again with TMS pseudorandomly delivered on half of all

trials. The details of the TMS apparatus and the method used to localise target sites are the same as previously reported.

Analyses. The accuracy of one low frequency word item ('baton') was at chance and thus excluded from the analysis. RTs for "yes" responses were measured from the onset of the target. "No" responses were not analysed but are shown in the figures for completeness sake. Like the results from the previous chapter, TMS did not affect responses to pseudowords, perhaps because of the different response they require (i.e. "no" vs. "yes"). No responses were below 300msec and consequently none were trimmed. To minimise the effect of outliers in the RT data, median RTs for correct responses per condition per subject were used (Ulrich and Miller 1994). The accuracy scores and median RTs were analysed using a 2 × 2 ANOVA with Frequency (high, low) and TMS (rTMS, none) as independent factors.

4.2.2 Results

In the accuracy data, there was a main effect of Frequency ($F(1,15) = 22.458$, $p < 0.001$), indicating that subjects were significantly less accurate for low frequency words (90%) relative to high frequency words (97%, Figure 4-1). There was no main effect of TMS and no interaction, indicating the presence of TMS did not affect accuracy, consistent with the experiments reported in Chapter 3. With regard to the RTs, there was a main effect of Frequency ($F(1,15) = 34.644$, $p < 0.001$) reflecting the advantage for high frequency words (523msec) relative to low frequency words (572msec), consistent with the word frequency effect reported in the previous chapter. There was no main effect of TMS ($F(1,15) = 3.189$, $p = 0.094$) but crucially there was a significant Frequency × TMS interaction ($F(1,15) = 5.953$, $p = 0.028$), reflecting the fact that TMS selectively slowed responses to low frequency words (+23msecs) without significantly affecting high frequency words (+1msec, Figure 4-1).

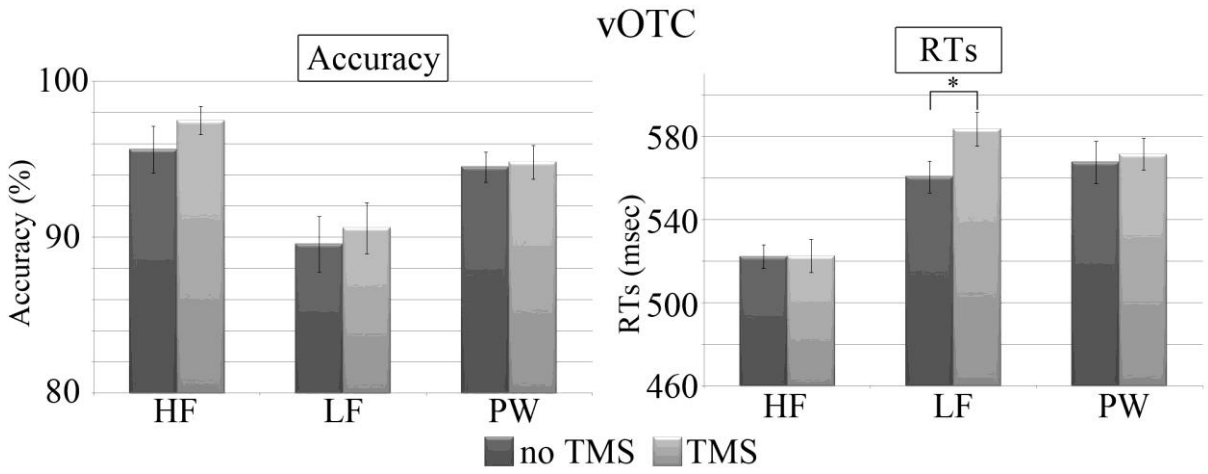


Figure 4-1: Mean accuracy (%) and RTs (msec) for rTMS to ventral occipito-temporal cortex during visual lexical decision task. Each plot shows high (HF) and low (LF) frequency and pseudoword (PW) conditions with TMS (light bars) and without TMS (dark bars). Error bars represent standard error of the mean, adjusted to accurately reflect the variance in a repeated-measures design (Loftus and Masson 1994). * indicates a significant TMS effect at $p < 0.05$.

In contrast, stimulation at the vertex had no significant effects on either accuracy or RTs (Figure 4-2). As expected, there was a main effect of Frequency for both accuracy (98% vs. 91%, $F(1,15) = 19.920$, $p < 0.001$) and RTs (512 vs. 569 msec, $F(1,15) = 90.138$, $p < 0.001$), once again reflecting the advantage for high frequency words relative to low frequency words. Unlike vOTC, there were no main effects of TMS or Frequency × TMS interactions (All $F(1,15) < 2.239$, $p > 0.155$), indicating that TMS had no effect on either low or high frequency words, confirming its appropriateness as a control site.

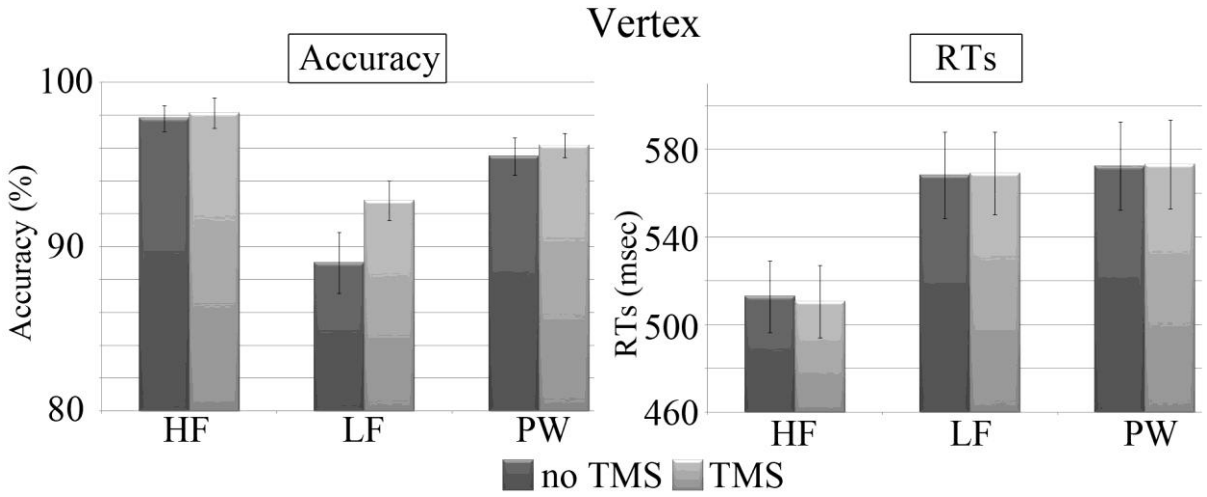


Figure 4-2: Mean accuracy (%) and RTs (msec) for rTMS to vertex during visual lexical decision task. Each plot shows high (HF) and low (LF) frequency and pseudoword (PW) conditions with TMS (light bars) and without TMS (dark bars). Error bars represent standard error of the mean, adjusted to accurately reflect the variance in a repeated-measures design (Loftus and Masson 1994).

In summary, Experiment 1 confirmed that stimulation of vOTC during lexical decision selectively slowed response times to low frequency words without significantly affecting the responses to high frequency words. This pattern was site-specific, as stimulation of vertex had no effect on responses.

4.2.3 Discussion

The aim of this experiment was to investigate the response profile of vOTC to a manipulation of word frequency. Despite using an experimental design optimised to maximise sensitivity, there was no effect of vOTC stimulation on responses to high frequency words during a lexical decision. In contrast, TMS selectively slowed responses to low frequency words thus replicating the response profile reported in the previous chapter. Although the failure to find any effect on high frequency words may still reflect a lack of sensitivity, I consider this unlikely because i) lexical decision was used, ii) the number of trials was doubled iii) the number of participants was increased and iv) consonant strings were dropped from the design, all of which maximises sensitivity. Even

so, it possible that with greater sensitivity, an effect might yet be observed. However, even combining the high frequency data from the previous chapter with that from the current chapter, dramatically increasing the number of subjects, reveals only an non-significant 3msec slowdown ($t(28) = 0.477$, $p = 0.637$). Thus although it is impossible to prove a null result, the significant Frequency $\times$ TMS interaction combined with the optimised experimental design and the fact that pooling the data from two experiments still produces no effect on high frequency words leads to the conclusion that vOTC is not always necessary for recognising high frequency words. The implications of this for the various hypotheses of ventral occipito-temporal function will now be discussed.

First, the results are incompatible with the prelexical visual word form accounts of ventral occipito-temporal function. Since all words are composed of bigrams which should have entries stored in the area, the prelexical account predicts that there should be no difference between high and low frequency words. However, even if the experiment lacked sufficient power to detect an effect of high frequency words, it is apparent that there is a frequency related difference. Furthermore, it is not clear how the prelexical account could be modified to make it consistent with the lexical frequency effects reported here, as well as those reported in the neuroimaging literature (Chee et al. 2003b; Kronbichler et al. 2004). Second, the current data are also incompatible with the lexical word form hypothesis since according to this account, high frequency words are represented in vOTC and thus should be disrupted by stimulation. Although lower activation thresholds of high frequency words may render them more resilient to disruption by TMS, one would still expect some evidence of graded impairment. However, as noted previously, there was no evidence at all for any effect of TMS on high frequency words, and it is hard to conceive of a modification of the lexical word form account that could accommodate this.

Third, the interface account also does not predict the current findings since both low and high frequency words posses higher order properties (such as phonology and semantics) that can be linked to the corresponding visual forms. However, it may be compatible if we consider that correct completion of a visual lexical decision task may or may not require access to these higher order properties. The decision for frequently occurring, over-learned words may be based solely on general characteristics, such as orthographic familiarity, since these characteristics provide sufficient information to reliably distinguish between words and nonwords, whereas lower frequency words place a greater processing burden on semantic and phonological knowledge (James 1975; Shulman et al. 1978; Becker 1979; Waters and Seidenberg 1985; Jared and Seidenberg 1991). Thus the interactions occurring in vOTC are more important for low frequency words while the contribution of the area is minimised when deciding if high frequency words are real or not, consistent with graded activation reported in neuroimaging studies (Chee et al. 2003b; Kronbichler et al. 2004). In fact, considering the current data, it appears that the area is not necessary for deciding on the lexicality of a high frequency word at all. This suggests that other components are sufficient for the task and that rather than occurring within a restricted patch of cortex, visual word recognition occurs across a distributed network. The neuropsychological evidence suggests that in some cases, damage to vOTC has a differential effect on frequency (Behrmann et al. 1998b; Johnson and Rayner 2007) and can even selectively impair low frequency word recognition (Shan et al. 2010; Tsapkini and Rapp 2010) consistent with the current data.

Thus although the current results are incompatible with both visual word form hypotheses, the data are consistent with an elaborated interface hypothesis. This revised interface account makes a clear prediction about the response profile of ventral occipito-temporal: stimulation during a task that boosts the processing demands of vOTC, increasing its contribution will disrupt both high and low frequency words.

The second experiment in this chapter set out to test this prediction by examining the effect of ventral occipito-temporal stimulation during a visual semantic decision task. Relative to lexical decisions, semantic decisions place a greater load on non-orthographic processing, i.e. accessing the meaning of a word. Crucially, semantic decisions require the integration of meaning and visual form regardless of word frequency. Consistent with this is the fact that the behavioural difference between low and high frequency words is diminished during semantic decisions relative to lexical decision (Balota and Chumbley 1984; Schilling et al. 1998). Thus the second experiment investigated the effect of stimulation of vOTC during a visual semantic decision task using a 2×2 experimental design with Frequency (High, Low) and rTMS (rTMS, none) as independent factors. There are two possible outcomes:

1. A main effect of TMS but no interaction would indicate that unlike the lexical decision experiment, vOTC is required for both low and high frequency words during semantic decisions. In this scenario, by increasing the necessity of linking semantic knowledge to the visual form, the semantic decision emphasises the processing contributions of vOTC. Since this integration is required for all words regardless of frequency, disruption of the process affects low and high frequency words. Crucially, this outcome would demonstrate that processing in vOTC is task-dependent – a possibility that is incompatible with models that suggest that processing is stimulus-driven (Kronbichler et al. 2004; Dehaene et al. 2005). If processing in vOTC is stimulus driven it must also be task-independent as task set can only modulate activity if top-down processing interacts with bottom-up input. Rather task-dependency is a hallmark of an interactive system (McClelland and Rumelhart 1981; Rumelhart and McClelland 1982; McClelland 1993) and is a common feature of cognitive models of reading (Rumelhart and McClelland 1982;

Plaut et al. 1996; Coltheart et al. 2001; Jacobs et al. 2003; Harm and Seidenberg 2004; Perry et al. 2007).

2. A significant Frequency × TMS interaction in the absence of a main effect of TMS would indicate that like the lexical decision results, TMS disrupts low but not high frequency words. In other words, processing in vOTC is task-invariant, consistent with feedforward, stimulus-driven models of reading. However, this outcome combined with the result of Experiment 1 would be incompatible with all accounts of vOTC and would require a new hypothesis that could account for the area's stimulus-specificity and task-independence.

Finally, vertex was tested once more to ensure that the effects of stimulation were site-specific.

4.3 Experiment 2: Frequency effects in semantic decision

4.3.1 Method

Participants. 16 subjects (7M, 9F, aged 19 to 35, mean = 24) participated in Experiment 2. All were right handed, native English speakers with normal or corrected to normal vision. None had any form of dyslexia, a personal history of neurological disease, or a family history of epilepsy according to self-reports. Each gave informed consent after the experimental procedures were explained. The experiments were approved by the UCL Research Ethics Committee [UCL #249/001].

Functional imaging. As before, all participants completed a 1-back task during fMRI scanning in order to localise the precise region of vOTC to target with TMS in each individual (Table 4-3). The details of the fMRI scans are identical to those given in Chapter 2.

Table 4-3: Peak coordinates for the contrast [Words > Fixation] in vOTC in MNI space. Each individual's peak was used as their target for TMS.

vOTC				
Subject	**MNI Coordinates**			***Z*-score**
	x	***y***	***z***	
1	-43	-54	-26	7.7
2	-44	-55	-14	11.7
3	-40	-58	-21	6.8
4	-42	-58	-25	6.9
5	-44	-63	-15	7.5
6	-34	-59	-16	6.3
7	-42	-54	-20	7.3
8	-48	-56	-24	4.2
9	-44	-63	-20	4.7
10	-38	-63	-17	11.3
11	-35	-61	-16	8.5
12	-38	-51	-26	11.3
13	-42	-53	-27	8.2
14	-44	-62	-13	5.9
15	-45	-61	-16	8.0
16	-39	-71	-18	6.1
Mean	**-41**	**-59**	**-20**	**7.7**
SEM	0.9	1.3	1.2	0.6

Task and Stimuli. Participants performed a visual semantic decision (semantic decision) task, ("Does the word represent something living?") while one of two target sites was stimulated with rTMS. Once again, these were vOTC (the testing site) and vertex (the

control site where stimulation was not expected to affect responses). The stimuli came from two categories, living and manmade, and there were 80 words per category. These were subdivided into an equal number of low and high frequency words. Due to the relative lack of high frequency living things, it was necessary to use the same items for both stimulation sites such that participants saw each item twice. However, the order of sites was balanced across participants and the order of the items was fully randomised. As before, low and high frequency words were defined as items having <10 and >20 occurrences per million respectively (Table 4-4). The items were not matched across category, as the results from the previous chapter suggest that TMS may differentially affect "yes" and "no" responses, and thus consistent with the lexical decision task in this chapter, they were excluded from the analysis. Within category, the items were matched for letter length, number of syllables, bigram frequency and orthographic neighbourhood (Davis 2005). In addition, an independent set of items was used for practice.

Table 4-4: Mean psycholinguistic properties per condition with standard error in parenthesis. Statistical values refer only to Living items. Manmade items included in table for completeness sake. HF = high frequency words, LF = low frequency words.

	Living		Manmade			
	HF Words	LF Words	HF Words	LF Words	*t*	*P*
Frequency	127 (28.9)	4 (0.4)	76 (11.9)	4 (0.5)	4.26	<0.001
Familiarity	556 (21.1)	476 (38.2)	571 (21.3)	463 (37.4)	5.63	<0.001
No. of Letters	5.2 (0.2)	5.2 (0.2)	5.0 (0.2)	5.2 (0.2)	0.17	0.867
No. of syllables	1.6 (0.1)	1.7 (0.1)	1.4 (0.1)	1.6 (0.1)	0.92	0.359
Bigram frequency	1306 (141)	1254 (175)	1567 (206)	1040 (177)	0.23	0.816
Orthographic neighbourhood	4.3 (0.9)	4.4 (0.9)	6.1 (1.0)	4.8 (0.8)	0.08	0.940

Procedure. The procedure was identical to that of Experiment 1. Each trial began with a fixation cross displayed for 500msec, followed by a visual letter string for 200msec and then a blank screen for 2300msec, giving a total duration of 3sec. Subjects indicated whether the letter string represented a living thing or not by pressing a button using either their right or left index finger, with response finger counterbalanced across subjects. Half of all trials had TMS. Participants were instructed to "respond as quickly as possible while minimising the number of mistakes."Accuracy and RTs were recorded.

The two stimulation sites were tested sequentially in a single session with their order counter-balanced across subjects, with stimulation intensity set to 100% of motor threshold. The participant performed a practice session of the experiment without any TMS to familiarise them with the task. Next, one of the testing sites was chosen and the participant was introduced to the sensation of rTMS at that site. After familiarisation with the sensation, the participant performed a practice session with rTMS pseudorandomly delivered on half of the trials to get used to performing the task with concurrent rTMS. Finally, participants completed the list of the stimuli at each site. The details of the TMS apparatus and the method used to localise target sites are the same as previously reported.

Analyses. The accuracy of one high frequency living item ('grass') was at chance and was consequently excluded from the analysis. Analyses were identical to Experiment 1. RTs for "yes" responses were measured from the onset of the target. To maintain consistency with the lexical decision experiment, "no" responses were not analysed although they are included in the figures for completeness sake. To minimise the effect of outliers in the RT data, median RTs for correct responses per condition per subject were used without any trimming in the statistical analyses (Ulrich and Miller 1994). The accuracy scores and median RTs were analysed using a 2×2 ANOVA with Frequency (high, low) and TMS (rTMS, none) as independent factors.

4.3.2 Results

The results of ventral occipito-temporal stimulation are shown in Figure 4-3. The accuracy scores showed no significant main effects or interactions (all $F(1,15) < 1.000$, $p > 0.333$). The RTs, however, showed a main effect of Frequency ($F(1,15) = 5.815$, $p = 0.029$), reflecting the fact that though accuracy did not differ for low and high frequency words (both 90%), responses to high frequency words were faster (528 vs. 545msec). Crucially, there was a main effect of TMS ($F(1,15) = 11.991$, $p = 0.003$) but no interaction ($F(1,15) = 1.122$, $p = 0.306$), indicating that TMS slowed responses to low frequency words (+18msecs) *and* high frequency words (+32msecs)[8].

[8] In order that the semantic decision analysis be comparable and consistent with that of the lexical decision task, "no" responses were not included in the semantic decision analysis, however, Figure 4-3 suggests that TMS affects the "no" responses in the semantic decision as well as the "yes" responses. Including manmade items in the analysis by collapsing across category (as items were not match across category, it cannot be a separate factor) does not change the result: the main effect of TMS remains ($F(1,15) = 11.407$, $p = 0.004$) in the absence of the interaction ($F(1,15) = 0.287$, $p = 0.600$). This suggests that the absence of a TMS effect on pseudowords does not depend on "no" response per se but rather that, akin to high frequency words, vOTC is not required to determine the lexical status of orthotactically legal but meaningless letter strings.

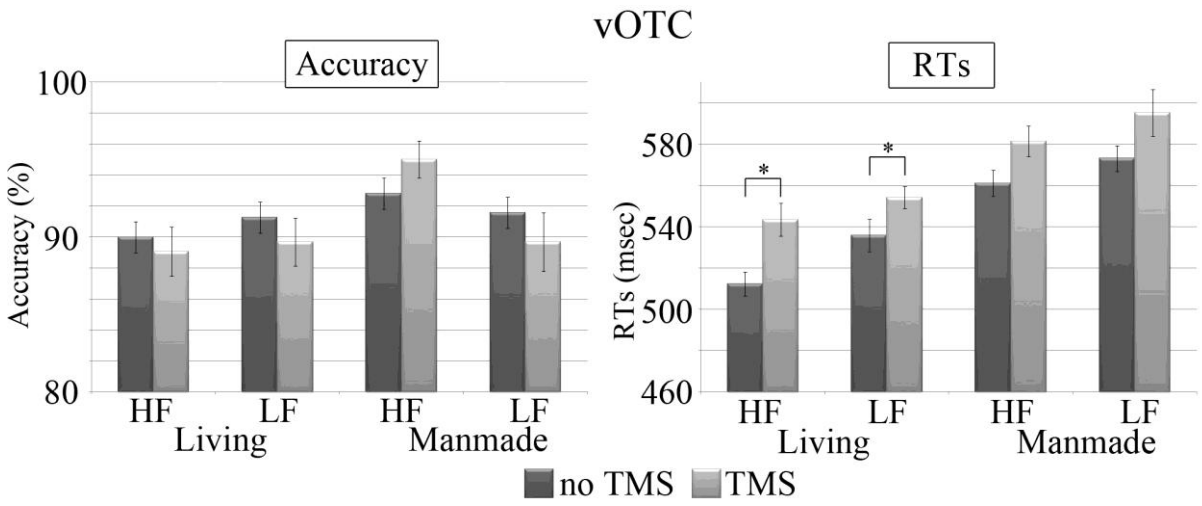


Figure 4-3: Mean accuracy (%) and RTs (msec) for rTMS to ventral occipito-temporal cortex during visual semantic decision task. Each plot shows high (HF) and low (LF) frequency conditions for living and manmade items with (light bars) and without TMS (dark bars). Error bars represent standard error of the mean, adjusted to accurately reflect the variance in a repeated-measures design (Loftus and Masson 1994). * indicates a significant TMS effect at $p < 0.05$.

The effect of rTMS delivered to the vertex is shown in Figure 4-4. Like the ventral occipito-temporal site, there were no significant main effects or interactions in the accuracy data (all $F(1,15) < 1.262$, $p > 0.279$). The RTs showed a main effect of Frequency ($F1,15) = 6.367$, $p = 0.023$), once again demonstrating the advantage of high frequency relative to low frequency words. Unlike the ventral occipito-temporal site, there was no main effect of TMS ($F(1,15) = 0.211$, $p = 0.653$) and no an interaction ($F(1,15) = 0.022$, $p = 0.883$), confirming that suitability of the vertex as a control site.

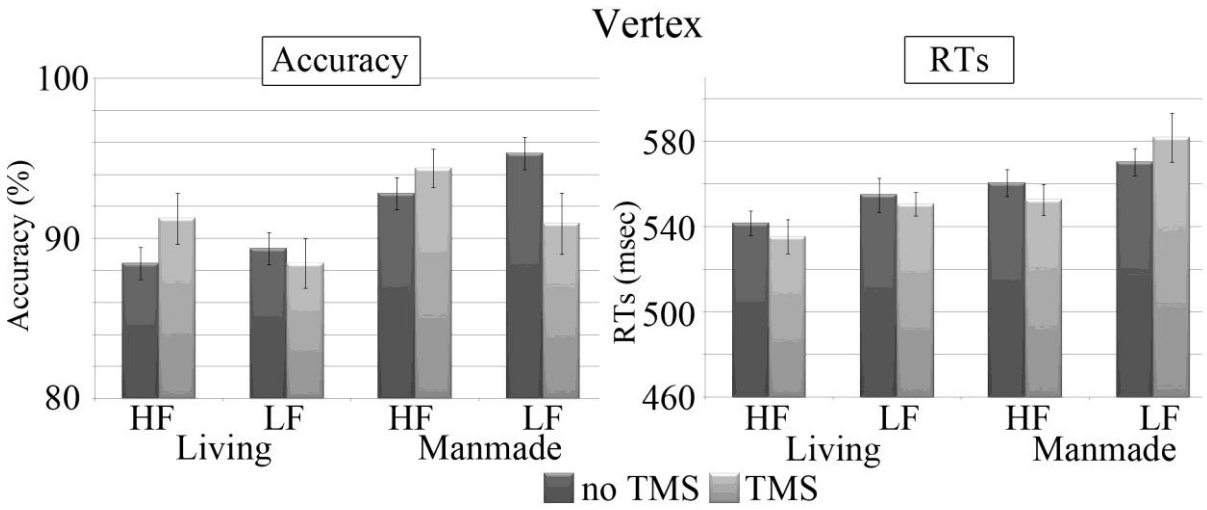


Figure 4-4: Mean accuracy (%) and RTs (msec) for rTMS to vertex during visual semantic decision task. Each plot shows high (HF) and low (LF) frequency conditions for living and manmade items with (light bars) and without TMS (dark bars). Error bars represent standard error of the mean, adjusted to accurately reflect the variance in a repeated-measures design (Loftus and Masson 1994).

In summary, Experiment 2 clearly demonstrates that stimulation of vOTC during semantic decision slowed response times not only to low frequency but also high frequency words. This is markedly different from the pattern observed during stimulation in the lexical decision and, if reliable, indicates task-dependent processing of high frequency words in the area.

4.3.3 Comparison

In order to determine whether the apparent task dependency of vOTC processing of high frequency words was reliable, the median RTs for "yes" responses from both experiments were entered into a mixed ANOVA with Frequency (High, Low) and TMS (none, rTMS) as within subjects factors and Task (lexical decision, semantic decision) as a between subject factor. In addition to the expected main effect of Frequency ($F(1,30) = 36.629$, $p < 0.001$), there was a main effect of TMS ($F(1,30) = 14.121$, $p = 0.001$) indicating that across the two experiments, responses were slowed by TMS to vOTC (no TMS: 533msec, TMS: 551msec). There was also a Frequency × Task interaction ($F(1,30) = 8.641$, $p = 0.006$), indicating the

word frequency effect was larger during the lexical decision task (+50msec) relative to the semantic decision (+17msec), consistent with the behavioural literature (Balota and Chumbley 1984; Schilling et al. 1998). Crucially, there was a Frequency × TMS × Task interaction ($F(1,30) = 5.423$, $p = 0.027$) confirming that the effect of rTMS on low frequency words was consistent across tasks but that the effect on high frequency words was present in the semantic decision (+32msec) but not in the lexical decision (+1msec). The remaining interactions were not significant.

4.3.4 Discussion

This experiment investigated the effect of stimulation of vOTC during a visual semantic decision. TMS administered during the semantic decision task disrupted responses to both low *and* high frequency words. This is in contrast to the lexical decision, where high frequency words were not affected. The 3-way interaction between Frequency, TMS and Task confirmed that this task dependent processing of high frequency words was reliable.

Although lexical decisions involving high frequency words elicit robust activity in vOTC (Fiebach et al. 2002; Chee et al. 2003b; Kronbichler et al. 2004), it is well established that processing of word-like stimuli proceeds beyond merely orthographic processing even in the event that this processing it is not necessary for the current task (Stroop 1935; Van Orden 1987; Van Orden et al. 1988; Price et al. 1996). The task-dependent effect on high frequency words is consistent with top-down influences altering the necessity of vOTC processing and reflects the differing strategies required for the two tasks. Correct completion of a visual lexical decision task may or may not require access to higher order properties such as phonology and semantics. The decision for frequently occurring, over-learned words may be based solely on general characteristics such as the orthographic familiarity since these characteristics provide sufficient information to reliably distinguish between words and nonwords, whereas rarer words place a greater processing burden on

semantic and phonological knowledge (James 1975; Shulman et al. 1978; Becker 1979; Waters and Seidenberg 1985; Jared and Seidenberg 1991). In contrast, the visual properties of a word are not sufficient to correctly complete a semantic decision. Regardless of its frequency or familiarity, the meaning of a word must be processed. This increases the importance of contributions from more anterior temporal areas (Hodges et al. 1995; Vandenberghe et al. 1996; Lambon Ralph et al. 2009) and inferior frontal areas (Roskies et al. 2001; Devlin et al. 2003a; Grindrod et al. 2008) associated with semantic processing, and the integration of this higher order knowledge with the visual form in vOTC (Bokde et al. 2001; Capek et al. 2009).

The existence of task-dependency in vOTC is incompatible with any model that suggests that processing is stimulus-driven as this requires that the response profile is solely determined by the stimuli (not the task). Task set can only modulate activity if top-down processing interacts with bottom-up input. Task-dependency is a hallmark of an interactive system (McClelland and Rumelhart 1981; Rumelhart and McClelland 1982; McClelland 1993). Interactivity of this sort has been reported for reading in both behavioural (Cattell 1886; Reicher 1969; Wheeler 1970) and neuroimaging literature (Flowers et al. 2004; Spironelli and Angrilli 2007; Ruz and Nobre 2008; Proverbio and Adorni 2009) as well as object recognition more generally (Orban et al. 1996; Watanabe et al. 1998; Bar 2003; Bar et al. 2006; Schrader et al. 2009). It is thus not surprising that interactivity is a frequent feature of cognitive models of reading (Rumelhart and McClelland 1982; Plaut et al. 1996; Coltheart et al. 2001; Jacobs et al. 2003; Harm and Seidenberg 2004; Perry et al. 2007). This indicates that neurobiological models of reading, which have concentrated almost exclusively on a feed-forward flow of information (Dejerine 1892; Pugh et al. 1996; Shaywitz et al. 2002; Dehaene et al. 2005), must be updated to reflect the importance of feedback connections.

4.4 Conclusion

This chapter details two experiments aimed at further characterising the response profile of vOTC during reading. Experiment one demonstrated that vOTC is causally involved in visual lexical decisions for low but not high frequency words while experiment two showed that the area is necessary for completion of a semantic decision for both low and high frequency words. The differential effect during the lexical decision and the task dependency is surprising and fundamentally incompatible with any feed-forward model of reading. In addition, they require that the interface account be further elaborated; Top-down interactions not only link higher-order properties to visual form but also determine whether the processing contribution made by the area is necessary or not. This stresses the importance of not only what information is being processed in a region (visual form vs. reading-specific orthography) but also emphasises the processing dynamics – interactive vs. feedforward.

5 Dynamics and specificity

5.1 Introduction

In addition to the virtual lesion mode employed in the previous chapters, TMS can be used in neurochronometric mode. By applying a single pulse or pair of pulses at different onset asynchronies, it is possible to map out the temporal profile of processing within a cortical area. Used in this way, TMS is capable of resolving two critical time windows separated by as little as 40msec (Koivisto et al. 2010). However, its potential has not yet been fully tapped with regard to reading and language. Instead, the absence of invasive single-cell recordings in humans coupled with the fact that non-human animals cannot read has meant that studies of the mental chronometry of visual word recognition have traditionally used purely behavioural measures of accuracy and reaction time (e.g. Reicher 1969; Yap and Balota 2007).

More recently event-related analysis of EEG data has become the predominant methodology (Rugg 1983; Bentin et al. 1999; Cohen et al. 2000; McCandliss et al. 2003; Rossion et al. 2003), providing a direct method of assessing the temporal dynamics of neural events. Viewing a visual stimulus such as a word or object evokes early occipital components at approximately 50-100msec after stimulus onset (Clark et al. 1994; Bentin et al. 1999; Martínez et al. 1999; Di Russo et al. 2003; Rossion et al. 2003) followed by a left occipito-temporal negativity between 170-200msec (Salmelin et al. 1996; McCandliss et al. 1997; Bentin et al. 1999; Tarkiainen et al. 1999; Rossion et al. 2003). The initial components are thought to reflect activity in early visual areas and demonstrate differences between words and objects believed to be a consequence of the pronounced differences in low-level visual properties between the stimuli (Rossion et al. 2003). In contrast, differences in the later component, known as the N170, are thought to reflect specialised neural processing for words that is distinct from other stimulus classes (Rossion et al. 2003). Part of the evidence for this is the topography of the response: bilateral for objects but 'left-lateralised' for words (Rossion et al. 2003), presumably

reflecting the lateralisation of language (Josse and Tzourio-Mazoyer 2004; Cai et al. 2010). Moreover, the left hemisphere N170 elicited by words distinguishes between orthographic and non-orthographic stimuli (Bentin et al. 1999; Cohen et al. 2000), and is modulated by lexical frequency of the stimuli (Neville et al. 1992; Hauk and Pulvermüller 2004). It is these properties that have led some researchers to claim that the N170 reflects the earliest stage of abstract orthographic processing (Cohen et al. 2000; McCandliss et al. 2003; Maurer and McCandliss 2008).

There are, however, a number of reasons to exercise caution with regard to temporal profile estimates for ventral occipito-temporal cortex (vOTC) derived from ERP. First, eye-tracking experiments show fixation on a single word lasts only 200-300msec (Rayner 1998) and thus it seems unlikely that orthographic access is occurs so late in a fixation and so soon before the saccade to the next word (Sereno et al. 2003). Second, activity in vOTC measured by ERP is concurrent with activity in peri-Sylvian regions (Pammer et al. 2004; Pulvermüller and Shtyrov 2006) and preceded by phonological processing in more anterior areas recorded by MEG (Wheat et al. 2010), calling into question whether vOTC activation truly represents the earliest stage of abstract orthographic processing. Finally, invasive recordings in both monkeys (Ashford and Fuster 1985; Richmond et al. 1987; Schroeder et al. 1998; Kiani et al. 2005; Chen et al. 2007) and humans (Yoshor et al. 2007) suggest that activity in this region of extrastriate cortex begins considerably earlier (from 40-100msec post-stimulus onset).

Reliable timing information is crucial in a number of respects. First, it provides information regarding the dynamics of a cortical area, including whether the processing is purely feedforward or some combination of feedforward and feedback. Early activity in an area is generally interpreted as corresponding to feedforward processing while later activity is thought to correspond to processing involving feedback information re-entering the area (Corthout et al. 1999a; Juan and Walsh 2003; Koivisto et al. 2010). Second, knowledge

about when an area is active can inform about the position the area takes within a wider hierarchy of networked areas and whether these areas function in series, parallel or some combination of the two (Pulvermüller et al. 2009). Consequently, it is important to resolve the apparent contradictions regarding the processing dynamics of vOTC, preferably using a methodology that provides an independent measure of the temporal profile during visual word recognition. Here I used paired-pulse, rather than repetitive TMS to take advantage of its more precise temporal resolution (Juan and Walsh 2003; O'Shea et al. 2004; Pitcher et al. 2007) and map the time course of processing in vOTC (Walsh and Pascual-Leone 2003). Although the previous chapters showed TMS can be used to perturb processing in vOTC when administered repetitively, it is not known whether this effect will remain robust when the stimulation is reduced from five to two pulses. Thus the first experiment aimed to test the feasibility of using paired-pulse TMS to map out the temporal profile in vOTC. Pairs of pulses were delivered at different onset asynchronies while participants performed a lexical decision involving low frequency words and pseudowords. The lexical decision was chosen as experiments in previous chapters showed reliable disruptive effects of rTMS. Only one lexical condition was included to maximise sensitivity and low frequency words were chosen because the previous experiments demonstrated they were consistently disrupted by TMS. There are three possibilities regarding the temporal profile of disruption of vOTC (illustrated in Figure 5-1):

1. A single discrete, relatively early period of disruption. This would suggest only feedforward processing occurs in the area, possibly corresponding to the extraction of the abstract visual word form code (Dehaene et al. 2005).

2. Two (or more) discrete periods of disruption with the first reflecting a feedforward wave of activity and the subsequent period reflecting feedback activity.

3. A single prolonged period of disruption, reflecting the ongoing integration of visual form and non-visual properties in the form of concurrent feedforward and feedback processing.

TMS has been used previously to identify profile 1 (O'Shea et al. 2004; Kalla et al. 2008) and profile 2 (Corthout et al. 1999a; Corthout et al. 1999b) but not, to the best of my knowledge, profile 3. Although the second and third possibilities both involve a combination of feedforward and feedback processing, they differ with respect to the onset of feedback. Finally, the onset of disruption may occur at approximately 170msec, consistent with ERP data, or it may begin earlier, consistent with the invasive recording literature.

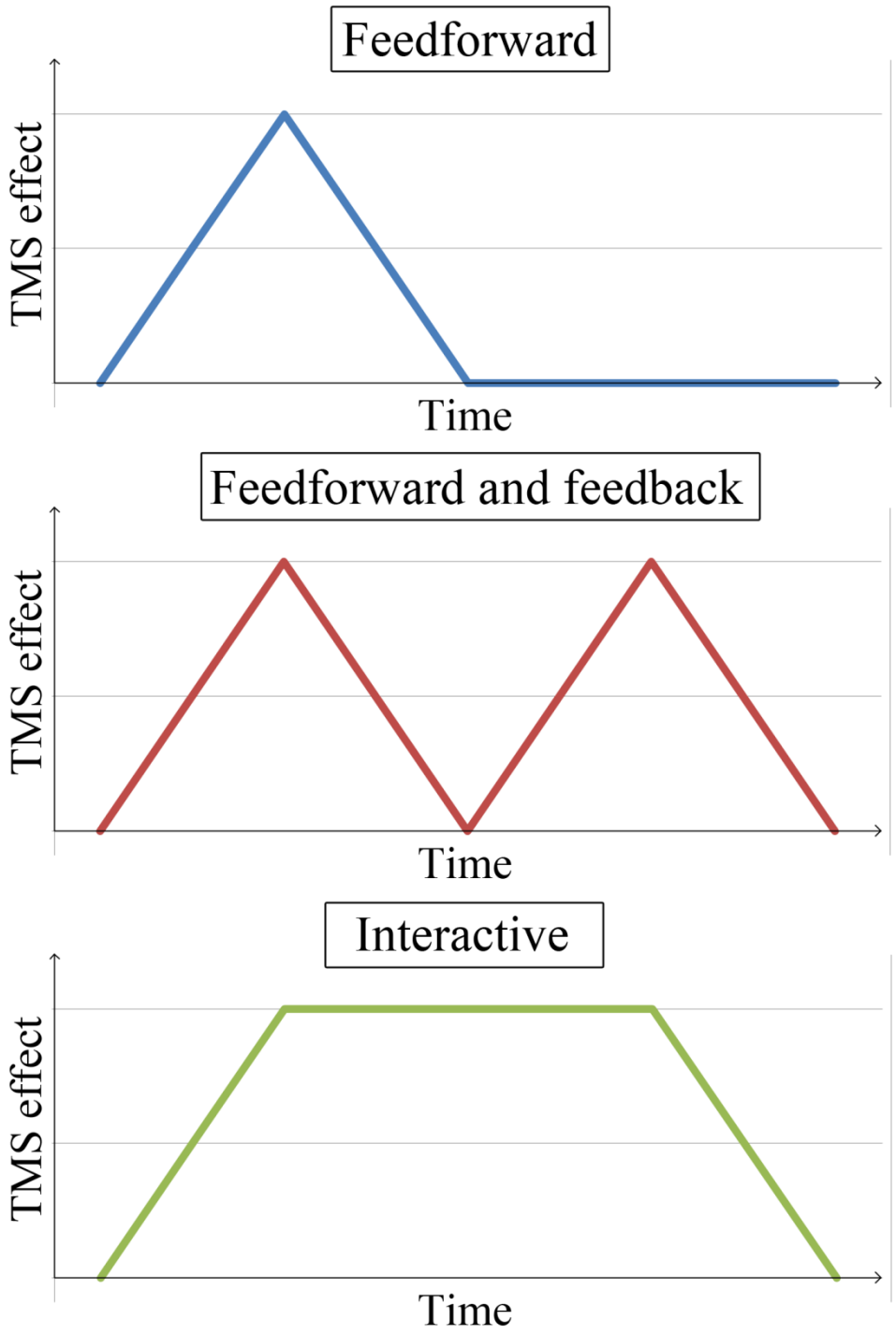


Figure 5-1: Three temporal profiles predicted by feedforward only (top), feedforward and feedback (middle) and ongoing interactive (bottom) accounts of ventral occipito-temporal dynamics.

5.2 Experiment 1

5.2.1 Method

Participants. 24 participants (15M, 9F, aged 19 to 46, mean = 29) took part. All were right handed, native English speakers with normal or corrected to normal vision. None had any form of dyslexia, a personal history of neurological disease, or a family history of epilepsy according to self-reports. Each gave informed consent after the experimental procedures were explained. The experiments were approved by the Berkshire NHS Research Ethics Committee.

Functional imaging. All participants completed a 1-back task during fMRI scanning in order to localise the precise region of vOTC to target with TMS in each individual (Table 5-1). The details of the fMRI scans are given in Chapter 2.

Table 5-1: Peak coordinates for the contrast [Words > Fixation] in vOTC in MNI space. Each individual's peak was used as their target for TMS.

vOTC				
Subject	**MNI Coordinates**			***Z*-score**
	x	***y***	***z***	
1	-44	-62	-18	8.4
2	-44	-73	-16	7.7
3	-41	-48	-18	6.3
4	-34	-48	-24	7.5
5	-41	-66	-18	9.4
6	-44	-49	-27	10.6
7	-43	-66	-8	11.0
8	-41	-63	-14	7.3
9	-39	-53	-16	6.3
10	-38	-63	-13	8.5
11	-43	-64	-18	9.1
12	-42	-55	-23	9.3
Mean	**-41**	**-59**	**-18**	**8.4**
SEM	0.9	2.4	3.9	0.4

Task and stimuli. Participants performed a lexical decision task while paired-pulse TMS was delivered to one of two target sites. The lexical decision consisted of two conditions, each comprising 100 items: low frequency words (1-10 occurrences per million), and pronounceable pseudowords. The stimuli were matched across conditions in prelexical properties (Table 5-2). Word frequency values were obtained from the Celex database of British written English (Baayen et al. 1993), while bigram frequency and familiarity values were obtained from N-Watch (Davis 2005). The details of the TMS apparatus and the

method used to localise target sites were reported in the Chapter 2. Every trial had two pulses of TMS separated by 40msec. Subjectively this feels like a single pulse but it induces a more robust interference effect (Juan and Walsh 2003; O'Shea et al. 2004; Pitcher et al. 2007). This experiment used a between-subject design, with one group of 12 participants receiving TMS over vOTC and the other over vertex. Within each group there were five different timing conditions (each including 20 low frequency words and 20 pseudowords) with pulses at either 0 and 40msec, 40 and 80msec, 80 and 120msec, 120 and 160msec, or 160 and 200msec post stimulus onset. To avoid confounding stimulus sets with TMS time windows, each set of items was rotated across each of the 5 timing conditions. Trial order was fully randomised. The five versions of the stimuli contained the same 200 items but each set of 40 items was rotated across each of the 5 timing conditions, in addition to being matched for written word frequency, rated familiarity, letter length, number of syllables and bigram frequency. TMS intensity was set to 100% of the subject's motor threshold.

Procedure. Each trial began with a fixation cross displayed for 500msec, followed by a visual letter string for 200msec and then a blank screen for 1300msec, giving a total duration of 2sec. Subjects indicated whether the letter string formed a real word in English or not by pressing a button using either their right or left index finger. Responses were fully counter-balanced for response hand across subjects. Each trial had TMS in one of the five timing windows. Accuracy and reaction times (RTs) were recorded.

Testing began by determining the participant's motor threshold using a single pulse delivered to the hand area of primary motor cortex. A practice session, using an independent set of items, followed allowing the participant to become familiar with the lexical decision task. Next, the participant was assigned a testing site and introduced to the sensation of paired-pulse TMS at that site. After familiarisation with the sensation, the participant performed a practice session with TMS to get used to performing the task with

concurrent paired-pulse TMS. Finally, participants completed the list of stimuli with TMS delivered to the appropriate site.

Table 5-2: Mean psycholinguistic properties per condition with standard error in parenthesis. LF = low frequency

	LF Words	Pseudowords	t	p
Frequency	5.30 (0.3)	-	-	-
Familiarity	484 (6.6)	-	-	-
No. of Letters	5.1 (0.1)	5.1 (0.1)	0.53	0.598
No. of syllables	1.5 (0.1)	1.5 (0.1)	0.63	0.527
Bigram frequency	1213 (92)	1398 (99	1.37	0.173
Orthographic neighbourhood	3.6 (0.4)	4.4 (0.4)	1.44	0.152

Analyses. RTs were measured from the onset of the target. Responses times shorter than 300msec were trimmed, amounting to 0.2% of the data. To minimise the effect of outliers in the RT data, median RTs for correct responses per condition per subject were used in the statistical analyses (Ulrich and Miller 1994). The accuracy scores and median RTs were analysed using a two-way mixed ANOVA where the within-subjects factor was TMS (0–40, 40–80, 80–120, 120–160, 160–200msec post-stimulus onset) and the between-subjects factor was Site (vOTC, vertex). Planned comparisons used Bonferroni corrected one-tailed paired *t*-tests because the previous experiments showed that TMS to vOTC slowed, rather than speeded, responses.

5.2.2 Results

Accuracy was high with an average score of 94% across conditions. Although pseudowords were included in the task to ensure that participants correctly performed the lexical decision task, they were not included in the analyses as the previous experiments showed no effect of TMS on pseudowords. For the accuracy data, there were no significant main

effects of Time ($F(4,88) = 1.6$, $p = 0.184$) or Site ($F(1,22) = 0.3$, $p = 0.564$) and no interaction ($F(4,88) = 1.6$, $p = 0.174$), indicating that TMS did not affect accuracy (Figure 5-2).

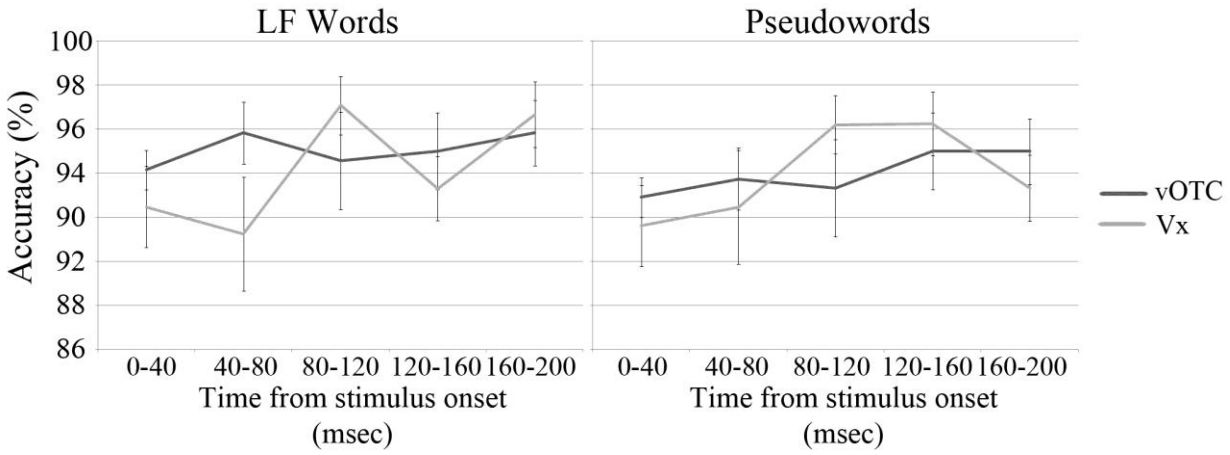


Figure 5-2: Accuracy scores (%) for TMS of vOTC (dark bars) and Vertex (light bars) over 5 time windows, with error bars representing corrected standard error of the means (Loftus and Masson 1994).

RTs for words are shown in Figure 5-3. Here, the 0–40msec time window served as the baseline condition (per testing site) as TMS was not expected to influence reading that early (Maunsell and Gibson 1992; Givre et al. 1994; Schroeder et al. 1998), making it a good baseline for comparison purposes. The two-way mixed ANOVA revealed a main effect of Time ($F(4,88) = 4.2$, $p = 0.004$) but no main effect of Site ($F(1,22) = 0.44$, $p = 0.514$) or Site × Time interaction ($F(4,88) = 1.9$, $p = 0.110$). Visual inspection of Figure 5-3 suggests that the absence of interaction may be caused by an unexpectedly long RT for vertex stimulation in the 160-200msec time window (573msec) compared to the other time windows (range: 544 to 555msec). The +18msec effect, however, did not represent a significant slowdown relative to the 0–40 window ($t(11) = 1.6$, $p = 0.145$), consistent with the results of vertex stimulation in previous chapters and with the functional neuroimaging literature, neither of which demonstrates

vertex involvement in reading at any level. As a result, I chose to exclude the 160-200msec time window from further analyses.

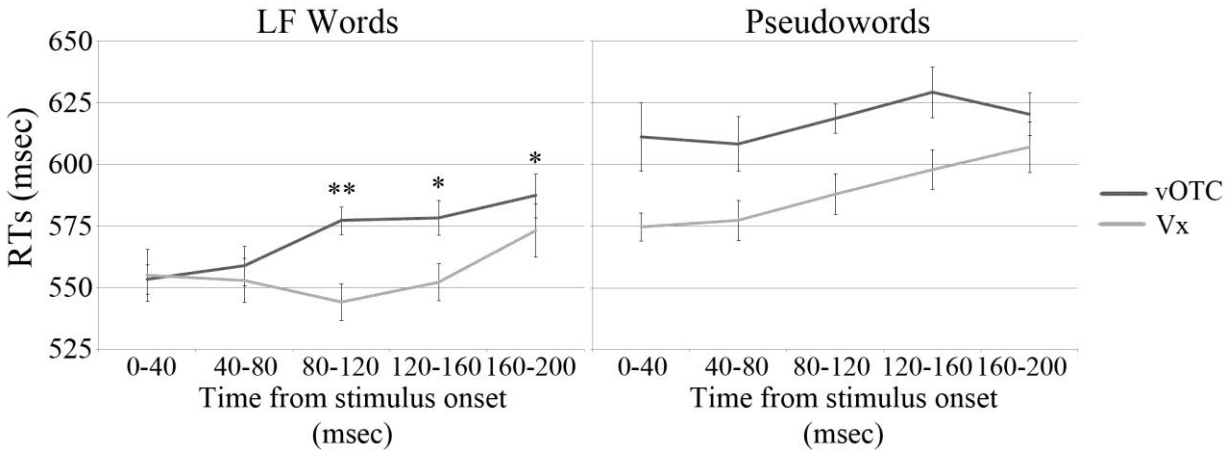


Figure 5-3: Mean RTs (in msec) for TMS of vOTC (dark bars) and Vertex (light bars) over 5 time windows, with error bars representing corrected standard error of the means (Loftus and Masson 1994). ** indicates a significant difference for vOTC stimulation from the 0–40msec time window at p < 0.01; * indicates *p* < 0.05.

When this time window was excluded, there was no main effect of Time ($F(3,66) = 1.1$, $p = 0.369$) or Site ($F(1,22) = 0.5$, $p = 0.501$) but a significant Site × Time interaction ($F(3,66) = 2.9$, $p = 0.044$). Planned comparisons indicated no significant effect at 40–80msec ($t(11) = 0.6$, $p = 0.8205$) but significantly slowed responses for the 80–120 (+24msec, $t(11) = 3.4$, $p = 0.009$) and 120–160msec (+25msec, $t(11) = 2.6$,p = 0.0375) time windows. In contrast, there were no significant effects for stimulation of the vertex at any of the time windows (all $t(11) < 1.3$, $p > 0.72$). Figure 5-3, therefore, illustrates three points. First, the earliest time window where TMS interfered with reading was 80–120msec post-stimulus onset; second, this effect was also present in the subsequent time window of 120–160msec; and third, that this interference effect was specific to the vOTC site.

5.2.3 Discussion

The goal of this experiment was to determine the feasibility of using paired-pulse TMS to map out the temporal profile of vOTC. Clearly, this was successful as similar to the

previous rTMS experiments, responses to low frequency words were slowed by paired-pulse TMS. Despite the reduction from five pulses used in the previous experiments, the effect of stimulation was robust, producing slowdowns in 12/12 participants in 80-160msec period. Thus in addition to being site-, and stimulus- specific and task-dependent, ventral occipito-temporal stimulation is time-specific. This further demonstrates the effect of stimulation is not simply a non-specific effect of ventral TMS as stimulus, task and site remain constant between baseline and the experimental time windows.

The disruption of low frequency word reading was not limited to a single early time window but continued throughout later time windows. This temporal profile suggests that activity in the region is not limited to solely feedforward processing. If the role of the area is to extract abstract codes (orthographic or otherwise) from visual stimuli, then once this has been accomplished and the code sent onwards to higher order areas, the processing in the area would cease (or cease to be causally involved) as there is no need for further visual form analysis. On the contrary, prolonged activity suggests feedback information is re-entering the area and moreover, that this information is critically involved in visual word recognition. Previous TMS studies have found relatively short temporal windows of feedback (for example, Corthout et al. 1999a; Corthout et al. 1999b). Nonetheless, the longer period of feedback seen in the current data is consistent with cognitive models of reading which emphasise both interactive nature but also cascaded activity – i.e. not separate feedforward and then feedback waves. There are however, two alternate explanations for the prolonged period of disruption. The first is that the paired-pulse TMS used in this experiment does not have the ability to resolve two separate time windows. This, however, seems unlikely as stimulation affected processing over a period spanning more than 100msec, particularly as this type of stimulation has previously been used to resolve separate time windows of occurring within a 110msec period (Pitcher et al. 2010). The second explanation is that the slowdown during stimulation in the later time windows

is an artefact of the experimental design. As the trials were fully randomised, some trials with TMS during an early time window may have been followed by trials with TMS during a late time window. This may have resulted in participants consciously or unconsciously waiting for stimulation, artificially slowing the RTs in the later time windows. The numerical slowdown during stimulation of vertex during the 160–200msec time window is consistent with this possibility. Ruling out this possibility requires using an experimental design where the difference in the delay in TMS onset between two consecutive trials is minimised.

Finally, the results demonstrate that stimulation first disrupted processing in the 80-120msec time window, significantly earlier than that expected based on ERP studies. There are two possible reasons for this early disruption:

1. Since the experiment employed a fixed inter-trial interval (ITI), participants may have settled into a rhythm. The slowdown in RTs may therefore have been the result of stimulation disrupting top-down expectation generated by the awareness of the subsequent stimulus onset. In other words, stimulation is not affecting the feedforward wave of activity and visual information is not yet present in vOTC. It is important to note however, that even if this is the case, the paired-pulse TMS successfully disrupted ventral occipito-temporal processing.

2. The stimulation disrupted the feedforward wave of visual information. In other words, visual information is present in ventral occipito-temporal considerably earlier than suggested by the N170 component. This would be consistent with timing estimates suggested by invasive studies of macaque monkeys, where the visual information first arrives in posterior inferior temporal cortex between 40-120msec post-stimulus onset (Ashford and Fuster 1985; Richmond et al. 1987; Schroeder et al. 1998; Kiani et al. 2005; Chen et al. 2007). This possibility would be

confirmed if the early effect is still present when using a variable ITI since this would remove any potential expectation confound.

Thus while it is clear that paired-pulse TMS can successfully disrupt processing in vOTC, the experimental design needs to be optimised to confidently interpret the data. Thus the purpose of Experiment 2 was to not only to optimise and replicate the first experiment but also extend the design to address questions regarding the processing dynamics of ventral occipito-temporal contributions to reading in relation to another higher order visual function, visual object recognition (Price and Devlin 2003; Joseph et al. 2006; Starrfelt and Gerlach 2007). This is of particular interest as the interface hypothesis predicts that i) left ventral occipito-temporal stimulation should affect both visual words and visual objects and moreover ii) that there should be no difference in the temporal profile of different stimulus categories, as regardless of category, the area performs the same function – linking visual form to higher order properties. Therefore, Experiment 2 used paired-pulse TMS to map out the temporal flow of information in vOTC during processing of written words and objects. In addition, although neuroimaging has thus far been unable to spatially dissociate the two stimulus categories within vOTC (Price et al. 2006; Ben-Shachar et al. 2007; Wright et al. 2008), the two appear to dissociate in patients with focal lesions. Damage to the left, but not right, vOTC impairs reading while impaired object recognition (known as visual agnosia) tends to follow bilateral lesions (Sparr et al. 1991; Barton et al. 2004; Karnath et al. 2009). To investigate this discrepancy between neuroimaging and neuropsychological findings, the processing contributions of both left and right vOTC were tested by stimulating each hemisphere independently.

5.3 Experiment 2

5.3.1 Method

Participants. 12 subjects (6M, 6F, aged 21 to 39, mean = 27.8) participated in the experiment. All were right handed, native monolingual English speakers with normal or corrected to normal vision. None had a personal history of neurological disease, a family history of epilepsy or any form of dyslexia, according to self-report. Each gave informed consent after the experimental procedures were explained. The experiments were approved by the UCL Research Ethics Committee [UCL #249/001].

Functional imaging. Nine participants completed a 1-back task and the remaining three participants completed a lexical decision task during fMRI scanning in order to localise the precise region of left and right vOTC to target with TMS in each individual (Table 5-3). The details of the fMRI scans given in Chapter 2.

Table 5-3: Peak coordinates for the contrast [Words > Fixation] in left vOTC (left) and right vOTC (right) respectively, in MNI space. Each individual's peak was used as their target for TMS.

Subject	*Left vOTC*				*Right vOTC*			
	MNI Coordinates			*Z*-score	MNI Coordinates			*Z*-score
	x	*y*	*z*		*x*	*y*	*z*	
1	-46	-52	-14	4.9	45	-60	-13	3.4
2	-46	-56	-20	7.1	49	-52	-10	3.4
3	-35	-72	-5	10.0	40	-65	-7	6.3
4	-40	-58	-14	8.9	48	-62	-20	5.5
5	-48	-68	-6	7.7	48	-58	-11	7.0
6	-41	-61	-16	9.0	45	-63	-19	10.0
7	-48	-54	-28	5.6	50	-48	-28	2.3
8	-43	-68	-21	9.1	44	-59	-22	6.6
9	-39	-71	-18	6.1	35	-75	-11	6.5
10	-42	-59	-13	6.6	41	-60	-13	1.9
11	-42	-53	-11	2.8	41	-50	-20	2.7
Mean	**-43**	**-61**	**-15**	**7.1**	**44**	**-59**	**-16**	**5.0**
SEM	1.2	2.2	2.0	0.7	1.4	2.3	1.9	0.8

Task and Stimuli. Participants performed a visual semantic decision task ("Does the stimuli represent a living thing?") in order to maintain a constant task set across both word and picture stimuli. The stimulus set consisted of 400 items: 200 words and 200 pictures. Each was divided into 100 living things and 100 manmade objects. The words represented the same items as 200 pictures – that is, in the course of a single testing session participants saw both a picture of a baboon and the word "baboon." Half of the items occurred first as a word and then as a picture in one version of the experiment or in the opposite order in the other version. The two versions were counterbalanced across participants. The word

stimuli were divided into five sets and these were matched for written word frequency (mean ± SD, 9.9 ± 24.9, $F(4,195) = 0.14$, $p = 0.97$), letter length (6.1 ± 1.8, $F(4,195) = 0.30$, $p = 0.88$), bigram frequency (918 ± 958, $F(4,195) = 0.36$, $p = 0.84$) and orthographic neighbourhood size (3.0 ± 4.8, $F(4,195) = 0.62$, $p = 0.65$). Frequency values were obtained from the Celex database of British written English (Baayen et al. 1993) while bigram frequency and orthographic neighbourhood size (N) were obtained from N-Watch (Davis 2005). In addition, I conducted a purely behavioural pre-test (i.e. without any TMS) with a separate set of participants (n = 30) to ensure that RTs were matched across stimulus sets. The RTs were entered into an ANOVA with Modality (words, pictures), Category (living, manmade) and List (1, 2, 3, 4, 5) as factors. Critically, there was no main effect of List ($F(4,380) = 1.49$, $p = 0.20$) nor any significant interactions (all $F < 1.74$, $p > 0.19$). There was a significant main effect of both Modality ($F(1,380) = 400.44$, $p < 0.001$) and Category ($F(1,380) = 35.84$, $p < 0.001$), with faster responses to pictures (528 msec) than words (609 msec), and faster responses to living items (556msec) than manmade items (581msec).

For each participant, three sites were test: left vOTC, right vOTC and vertex. The details of the TMS apparatus and the method used to localise target sites were reported in the General Methods. TMS intensity was set to 100% of the subject's motor threshold. Each trial included two pulses of TMS separated by 40msec with the onset delivered at one of five different time points: 0, 40, 80, 120 or 160msec post-stimulus onset, giving five different timing conditions labelled 0–40, 40–80, 80–120, 120–160 and 160–200. Each condition included 80 items (20 words living, 20 words manmade, 20 objects living, 20 objects manmade). To avoid confounding stimulus sets with TMS time windows, each set of 80 items was rotated across each of the 5 timing conditions.

Procedure. Each trial began with a fixation cross displayed for 500msec, followed by a stimulus for 200msec and then a blank screen for a random interval between 1300-

1800msec. The inclusion of a variable ITI, prevents participants from settling into a rhythm, as there is no way of knowing when the next trial will begin and therefore minimises potential top-down expectation effects. Subjects indicated whether the stimulus represented a living or a manmade thing by pressing a button using their right and left index fingers. Response hands were counterbalanced across subjects.

The three stimulation sites were tested in different sessions, each separated by at least one week to avoid any possibility of lingering effect of previous TMS sessions (Hayashi et al. 2004). Their order was fully counter-balanced across subjects. The first session began by measuring the participant's motor threshold using single pulses of TMS delivered to the hand area of left primary motor cortex. Afterwards, and in all subsequent testing sessions, the participant then performed a practice session of the semantic decision experiment without any TMS to familiarise them with the task. Next, one of the three testing sites was chosen and the participant was introduced to the sensation of paired-pulse TMS at that site. After familiarisation with the sensation, the participant performed a practice semantic decision run with paired-pulse TMS to get used to performing the task with concurrent stimulation. None of the items used in either practice run occurred in the main experiment. Finally, they completed the semantic decision experiment for the given site using one of the five stimulus versions. At least one week later, this procedure was repeated using the same stimulation intensity but stimulating a different site with a different stimulus version. On a third session, again at least a week later, the remaining site was tested.

To prevent subject fatigue and coil overheating, the stimuli were divided into 4 runs of 105 items lasting 3mins and 45secs each. Within a run, the items were organised according to modality, with 20 items of the same modality in each block to minimise the cost of switching between words and pictures (Figure 5-4a). The stimulus modality of the first block was counter-balanced across subjects. In addition, each block began with a

dummy trial although participants were not aware of this. Dummy trials (5 per run) were excluded from all analyses to reduce the effects of task-switching between blocks. Within a block, TMS conditions were not arranged randomly but rather were grouped in blocks of four trials which were ordered in either an ascending or descending staircase (Figure 5-4b). This was done to avoid the situation where late stimulation trials (e.g. 160–200) show longer RTs during sham stimulation or control conditions due to participants (implicitly) waiting for stimulation to begin. The current method effectively removed this problem by ensuring that the delay between TMS onset in any two consecutive trials never differed by more than 40msec. Indeed, it became clear during debriefing that participants did not realise there were different stimulation onsets, whereas this is more noticeable when the onsets are randomly ordered, for example in the previous experiment and also Devlin and colleagues (2003a).

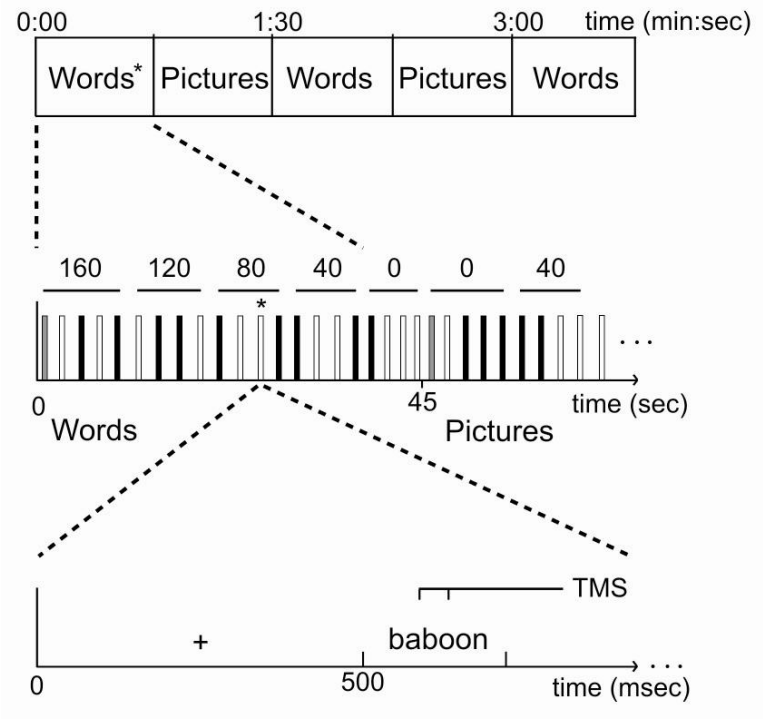


Figure 5-4: The visual semantic decision paradigm. Top: Within a run, words and pictures alternated in 45s blocks with each block beginning with a dummy trial that was not analysed. The stimulus modality of the first block was counter-balanced across subjects. Middle: Within a block, TMS conditions were not arranged randomly but rather were grouped in blocks of four trials which were ordered in either an ascending or descending staircase. Grey bars represent dummy items at the start of each new block while white and black bars represent living and non-living items respectively. Bottom: Time course of a single 80–120 word trial.

Analyses. RTs were measured from the onset of the target. As RTs were generally quicker than in previous experiments no items were trimmed. To minimise the effect of outliers in the RT data, median RTs for correct responses per condition per subject were used (Ulrich and Miller 1994). Repeated-measure analyses of variance (ANOVA) were used to test for effects of interest with three independent factors: Site (left vOTC, right vOTC, vertex) × Modality (word, picture) × Time (0–40, 40–80, 80–120, 120–160, 160–200). Category (living vs. man-made) was not included as a factor since the task was used simply to focus attention on the meaning of the stimulus rather than to dissociate between different categories. Consequently, items were collapsed across category in all analyses. Moreover, the data from the semantic decision in the previous chapter demonstrated that

collapsing responses across category does not affect the pattern of results. To test for significant TMS effects, the four later timing windows were each compared to the 0–40 condition using one-tailed, paired *t*-tests with a Bonferroni correction for multiple comparisons. Finally, the data from one subject were excluded for not following the experimental instructions ("Respond as quickly as you can without making too many mistakes"). This participant traded speed off for accuracy, with mean RTs more than 2 standard deviations slower than the group average but with 100% accuracy across all sites, modalities and stimulation conditions. In contrast, the other participants ranged from 88-98% accuracy but were on average 184msec faster to respond. Consequently, data from this one subject were not included in the group analyses.

5.3.2 Results

fMRI localisation. Figure 5-5 shows the location of the TMS target sites in left and right vOTC. Consistent with previous research, the contrast of words relative to fixation revealed a peak of activation in left vOTC in each participant with a mean *Z* score of 7.1 (range: 2.8 – 10.0, SEM: 0.7). This contrast also produced a peak of activation in a comparable area of right vOTC with a mean *Z* score of 5.0 (range: 1.9 – 10.0, SEM: 0.8). Though the *Z* score in left vOTC (mean $Z = 7.1$, SEM = 0.4) was significantly higher than that of the right (mean $Z = 3.0$, SEM = 0.6; paired t-test: $t(10) = 3.474$, $p = 0.006$), there was no significant difference between hemispheres in the location of the site in any axis (all $t(10) < 1.5$, $p > 0.185$ without Bonferroni correction). The LH mean target coordinate was [–43, –61, –15], while the RH mean was [+44, –59, –16].

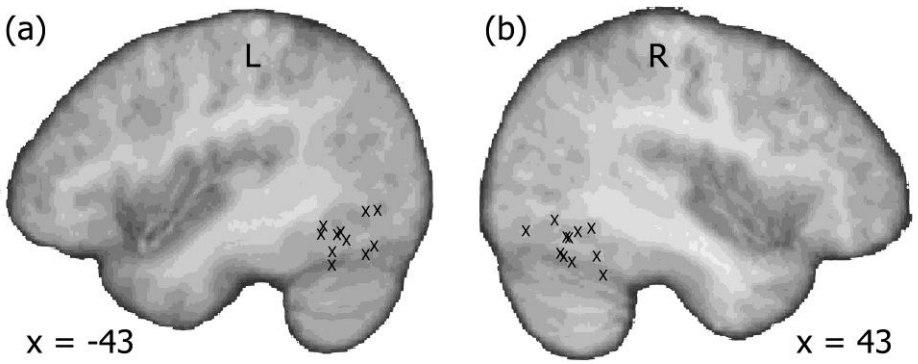


Figure 5-5: Location of TMS stimulation sites in (a) left and (b) right vOTC. For ease of viewing, the sites are projected on to a single slice for each hemisphere. Note that there is no systematic difference in the target locations between hemispheres.

TMS data. Overall accuracy levels were high (95%) indicating that participants had no difficulty performing the task (Figure 5-6). Accuracy scores were entered into an omnibus 3 x 2 x 5 repeated measures ANOVA, with Site (left vOTC, right vOTC, vertex), Modality (words, pictures) and Time (0–40, 40–80, 80–120, 120–160, 160–200). The only significant effect was a main effect of Modality ($F(1,10) = 17.13$, $p = 0.002$), indicating participants were more accurate for pictures (96.9%) than words (92.8%). None of the 2- or 3-way interaction terms reached significance (all $F < 1.4$, $p > 0.2$). In other words, TMS did not significantly affect accuracy.

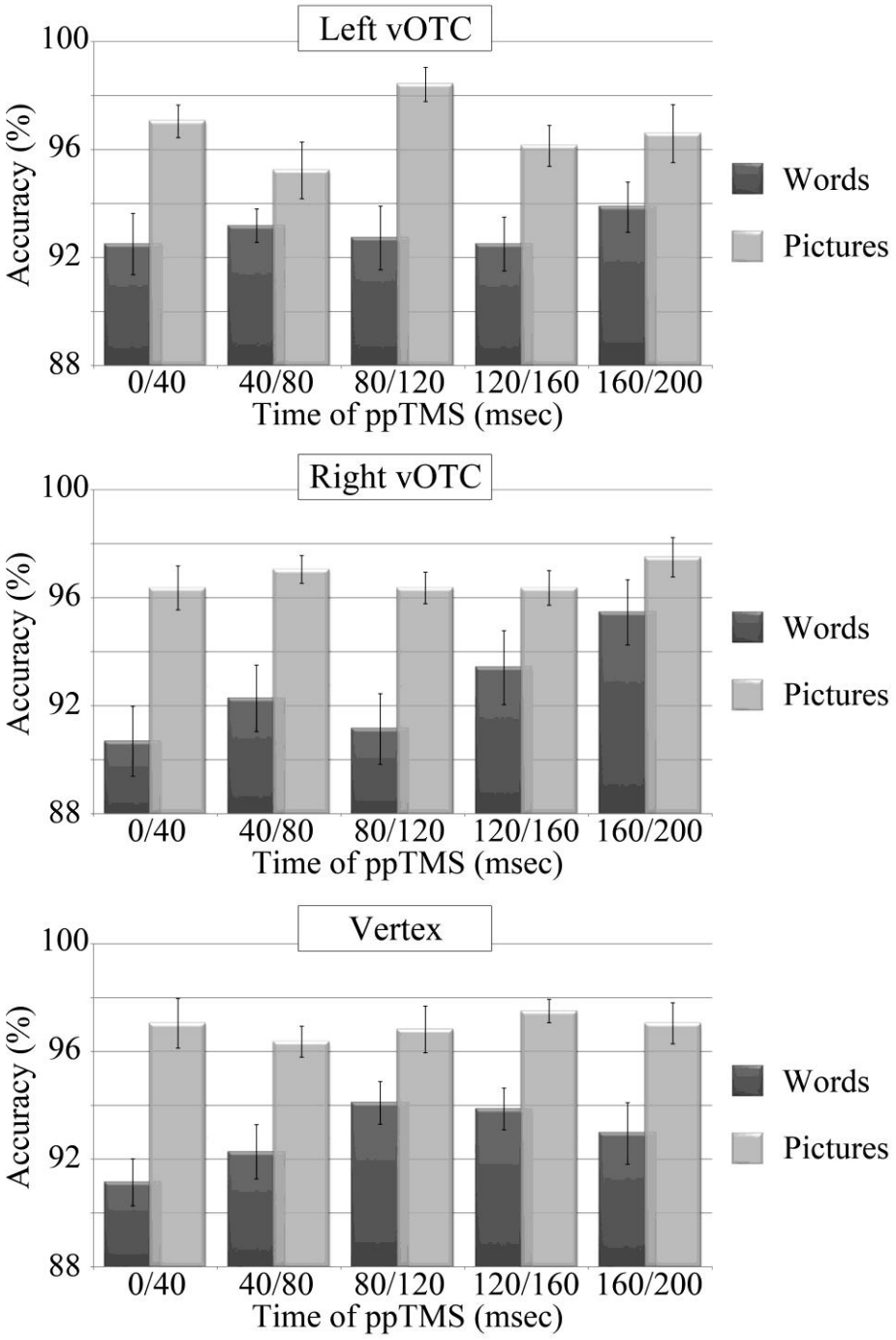


Figure 5-6: Mean accuracy scores (%) for Words (dark bars) and Pictures (light bars) during paired-pulse TMS of left vOTC (top), right vOTC (middle) and vertex (bottom) over 5 time windows, with error bars representing corrected standard error of the means (Loftus & Masson, 1994).

The omnibus ANOVA for RTs revealed two significant main effects. The first was a main effect of Modality ($F(1,10) = 99.76$, $p < 0.001$) indicating that participants responded faster to pictures (447msec) than words (502msec), consistent with the results of the non-TMS pilot. This advantage for pictures is in accordance with the accuracy data above and rules out any speed-accuracy trade-off for words and pictures. Second, there was a significant main effect of Time ($F(4,40) = 4.07$, $p = 0.007$), indicating that TMS significantly affected RTs. The first row of Table 5-4 summarises the main effect of Time by collapsing RTs over Site and Modality for each of the five time windows. Each time point was compared to the 0–40msec baseline condition revealing significant slowdowns at 120–160 ($t(10) = 3.95$, $p = 0.012$) and 160–200msec ($t(10) = 3.17$, $p = 0.036$), after correcting for multiple comparisons using the Bonferroni method. Neither of the three earlier time windows was significantly affected. This main effect of Time, however, was qualified with a significant Site $\times$ Time interaction ($F(8, 80) = 2.20$, $p = 0.036$), indicating that the effect of TMS differed according to the stimulation site. To illustrate this interaction, the data from each Site is presented in a separate row of the table, collapsed over Modality. In addition, to characterise the interaction each of the three testing sites was analysed separately.

Table 5-4: Reaction times (±SEM) across the five time stimulation time windows collapsed over modality. * indicates significantly different from the baseline condition ($p < 0.05$ after Bonferroni correction).

	TMS time window (msec post-stimulus onset)				
	0–40	**40–80**	**80–120**	**120–160**	**160–200**
			All sites		
Mean	464	469	479	478*	481*
SEM	2.4	1.3	4.3	1.5	4.5
			Left vOTC only		
Mean	456	463*	482*	474*	477*
SEM	3.0	2.9	6.3	2.5	5.5
			Right vOTC only		
Mean	471	476	485	489*	492*
SEM	3.1	1.9	6.4	1.7	5.4
			Vertex		
Mean	466	468	469	471	473
SEM	2.9	3.4	2.0	2.8	4.5

Within left vOTC, there was a main effect Modality ($F(1,10) = 50.18$, $p < 0.001$) confirming the advantage for pictures (497 vs. 444msec) and also a main effect of Time ($F(4,40) = 4.75$, $p = 0.003$). The mean (±SEM) RTs are presented in the second row of Table 5-4. Relative to the 0–40msec window, responses in all of the later time windows were significantly slower. For 40–80msec, the slowdown was only +7msec but this was significant even after Bonferroni correction ($p = 0.016$). For the remaining time windows, RTs were slower by +26msec ($p = 0.044$), +18msec ($p = 0.010$) and +21msec ($p = 0.012$). Visual inspection of the raw data (Figure 5-7), however, shows an apparent difference between words and pictures in the 40–80msec time window, with a slowdown for pictures (+18msec) but not for words (-2msec). The difference between words and pictures was primarily driven by a single outlying data point where one participant

showed a 73msec facilitation for words that obscured what would otherwise be an overall increase in RTs. In fact 10–12 participants were slower for words during stimulation at 40–80msec. In other words, the apparent discrepancy between words and pictures is artifactual, as confirmed by the absence of a Modality $\times$ Time interaction ($F(4, 40) = 1.69$, $p = 0.171$).

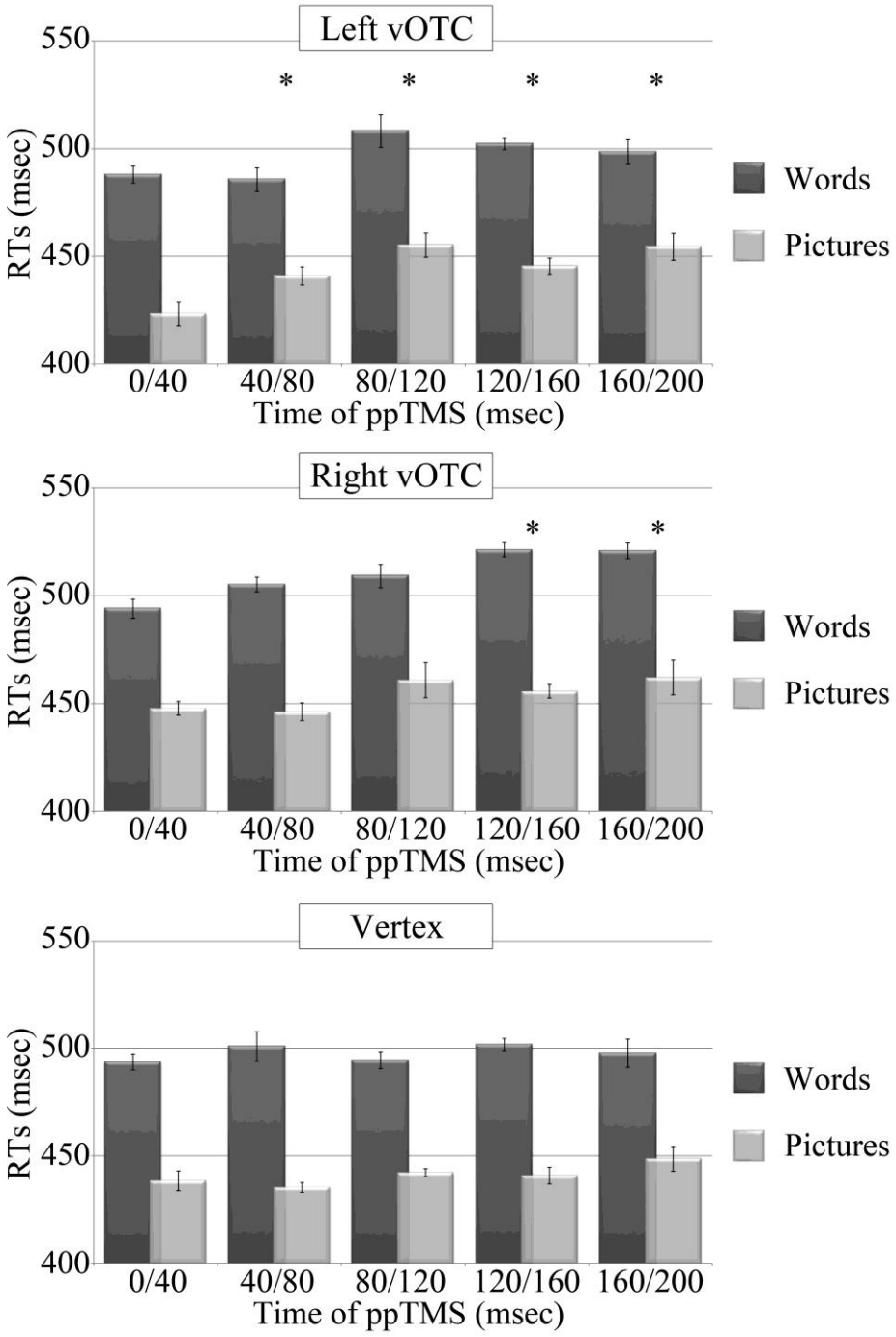


Figure 5-7: Mean RTs (in msec) for Words (dark bars) and Pictures (light bars) during paired-pulse TMS of left vOTC (top), right vOTC (middle) and vertex (bottom) over 5 time windows, with error bars representing corrected standard error of the means (Loftus & Masson, 1994). There was no interaction of Time of paired-pulse TMS with Modality but the two stimulus categories are displayed separately for completeness sake. * indicates a significant difference for vOTC stimulation from the 0–40msec time window at $p < 0.05$.

The pattern of results was similar in right vOTC with a main effect of Modality ($F(1,10) = 93.65$, $p < 0.001$) and a main effect of Time ($F(4,40) = 3.56$, $p = 0.014$). As before, pictures were significantly faster than words (510 vs. 455msec) and there was no significant Modality × Time interaction ($F(4,40) = 1.61$, $p = 0.191$), indicating that words and pictures were equally affected by TMS. Here, however, the TMS-induced slowing occurred later than in the left hemisphere, with significantly longer responses at 120–160 and 160–200msec (+18msec, $p = 0.002$ and +21msec, $p = 0.002$, respectively). To test whether this timing difference was significant, I compared the effect of TMS (relative to the 0–40 baseline condition) for the left and right vOTC sites in the two early time windows. The TMS effect was calculated as the change in RT relative to the 0–40 condition divided by the 0–40 condition and expressed as a percentage. Paired *t*-tests revealed no significant difference in the TMS effects at 40–80 msec (LH vs. RH: +1.7% vs. +0.8%, $t(10) = 0.95$, $p = 0.74$) but a significantly larger effect for left relative to right hemisphere vOTC stimulation at 80–120 (+5.4% vs. +2.6%, $t(10) = 2.72$, $p = 0.044$ after Bonferroni correction). In other words, stimulation of left, but not right, vOTC significantly slowed responses when delivered at 80–120msec post stimulus onset and this difference between the hemispheres was significant.

Finally, when TMS was delivered to the vertex, it had no effect on performance. There was a significant main effect of Modality ($F(1, 10) = 119.59$, $p < 0.001$), re-affirming the advantage for pictures over words (498 vs. 441msec) but no main effect of Time ($F(4, 40) = 0.58$, *n.s.*) nor a significant Modality × Time interaction ($F(4,40) = 0.89$, *n.s.*). The vertex data shown in Table 5-4 and Figure 5-7, make it clear that response times were essentially flat across all five time windows, consistent with the fact the medial superior parietal lobe is not involved in recognizing either pictures or words (Philipose et al. 2007; Duncan et al. 2009).

5.3.3 Discussion

The current experiment used neurochronometric TMS of left and right vOTC to map out the temporal flow of information during visual word and object processing. Consistent with the previous experiments, vertex stimulation had no effect. In contrast, responses to both pictures and words were slowed by stimulation of either left or right vOTC but the temporal profile of the two hemispheres differed significantly. There were no significant differences between words and objects either anatomically (left vs. right) or temporally (across the five time windows). Stimulation first disrupted processing during the 40–80msec time window in the left hemisphere but at 120–160msec in the right. This is the first time that right vOTC has been shown to be causally involved in reading in normal, healthy skilled readers.

The interface hypothesis suggests that left vOTC integrates visual form and higher non-visual properties of visual stimuli. An important aspect of this theory that separates it from visual word form accounts is that the role of the area is the same for all visual stimuli, including both words and objects. The current data is consistent with this as left ventral occipito-temporal stimulation slowed responses to both words and objects and the temporal profile for the two stimulus categories was not significantly different. Since it is impossible to prove a null result, the absence of a difference between words and objects may result from a lack of sensitivity, however, it is consistent with the neuroimaging literature, where a direct comparison produces no reliable differences (Price et al. 2006; Ben-Shachar et al. 2007; Wright et al. 2008). Furthermore, when patients with left hemisphere vOTC lesions are tested with sensitive psychophysical measures they show deficits in reading *and* object recognition (Behrmann et al. 1998a; Starrfelt et al. 2009), again in agreement with the current data. For both stimulus types, the disruption first occurred during the 40–80msec time window. This is earlier than reported in the previous experiment, where words were first disrupted during the 80–120msec period. This

difference may reflect the change in task, as the RTs in the lexical decision are in the 550-600msec range compared to the considerably faster RTs observed in the current experiment (400-500msec).

Although TMS affected both words and pictures it is possible that there are distinct but spatially overlapping sub-populations of neurons: one for processing words and one for processing pictures (Dehaene et al. 2002; McCandliss et al. 2003). If true, although TMS would lack the spatial resolution to identify these intermixed subpopulations, single or paired-pulse TMS could potentially resolve them *temporally* if their dynamics differed. The current data however, provide no evidence of such a temporal dissimilarity. Moreover, high resolution imaging (Wright et al. 2008) and fMRI adaptation (Kherif et al. 2010) found no evidence for such neuronal specialisation. Although, invasive cellular recordings during awake human neurosurgery (Lenz et al. 2002; Mukamel et al. 2010) could yet provide evidence of sub-populations of word and object neurons there is currently no existing evidence of such specialisation.

With regard to reading, the right vOTC, and indeed more generally the right hemisphere is frequently overlooked. Indeed, studies have reported that while reading elicits robust activity in the left, there is either less activity (Dehaene et al. 2002; Fiebach et al. 2002) or even no activation at all in right vOTC (Cohen et al. 2002; though see Ben-Shachar et al. 2007; Cai et al. 2010). Moreover, lesions to the right are not typically associated with reading impairment and in the few reported cases, it is attributed to an atypical language network (Davous and Boller 1994; Tsapkini et al. 2005). As a result the role of right vOTC is often assumed to be limited to either a compensating in the event of damage to the left (Pugh et al. 1996; Shaywitz et al. 2002; Cohen et al. 2003; Shaywitz et al. 2004) or basic feature analysis (Dehaene et al. 2005; Vinckier et al. 2007). In either of these scenarios, the disruptive effect of right ventral occipito-temporal stimulation could be explained by cross-callosal spreading of the induced current. None of this, however, is consistent with

the current data which suggest a more central role for right vOTC in reading. If right vOTC is limited to basic feature analysis, then disruption would be expected to occur either before or, at the very latest, concurrently with, the first period of disruption in left vOTC since this basic feature analysis is suggested to precede word form analysis (Dehaene et al. 2005; Vinckier et al. 2007). However, this is not the case: disruption first occurred during the 120–160msec time window, significantly later than the first period of disruption in the left. Moreover, this hemispheric asymmetry in timing is also inconsistent with the cross-callosal current spread explanation as it predicts that stimulation of the right hemispheric should disrupt reading either slightly before – since the induced current must cross the callosum – or at the same time as stimulation of the left hemisphere – since callosal transfer times are likely to be shorter than the temporal resolution of paired-pulse TMS[9].

The hemispheric asymmetry in timing is unexpected but may reflect the 'privileged' status of the left hemisphere in language tasks. Correctly solving the semantic decision task, for both visual objects and words, requires accessing predominantly left lateralised non-visual linguistic knowledge, which may have introduced a top down bias, emphasising left hemisphere processing. This hypothesis makes testable predictions:

1. Running the same experimental task on a cohort of *right hemisphere dominant* subjects would reverse the pattern of results: disruption of right vOTC would occur earlier than left vOTC (c.f. Cai et al. 2010).

2. Though the functional connectivity of vOTC would be similar across hemispheres, the connection strengths in LH vOTC would be stronger, reflecting the greater contribution of LH knowledge. This can be measured using Dynamic Causal Modeling (DCM).

[9] Estimates of callosal transfer times vary across studies but are on the order of 10msec (Saron and Davidson 1989; Braun 1992; Lo and Fook-Chong 2004; Li et al. 2010).

3. A task that relied preferentially on RH knowledge would attenuate or reverse the pattern, though such a task may be difficult to design for words.

Although further work is required test these possibilities the hemispheric asymmetry is consistent with recent timing estimates obtained from beamformed MEG. Cornelissen and colleagues (2009) reported that passive viewing of words elicits a peak in beta band synchrony in left vOTC at approximately 140msec, with a weaker response occurring in right vOTC after 150msec[10].

Two of the current findings stand in apparent contrast to the neuropsychological literature. First, as already noted, responses to words were slowed during right hemisphere stimulation but lesions in that hemisphere are not associated with reading impairment. Second, responses to objects were slowed during stimulation of either hemisphere – that is, a unilateral perturbation. In contrast, visual agnosia is associated with either extensive unilateral (Barton et al. 2004) or bilateral damage (Sparr et al. 1991; Humphreys and Rumiati 1998; James et al. 2003; Kohler et al. 2004; Karnath et al. 2009) to vOTC.

These discrepancies may reflect the differences between patient and TMS studies. First, in this thesis, TMS produced consistent but relatively small changes in RTs (i.e. on the order of tens of milliseconds), which may go undetected in single case studies. Second, unlike patients, the healthy participants in TMS studies serve as their own controls which increases the sensitivity and probability of detecting a difference. Third, post-lesion functional reorganisation is likely to occur in patients, complicating any interpretation of their deficits. For example, following a unilateral lesion, these plastic changes may allow for the recovery particularly for object recognition reflecting the lack of any hemispheric asymmetry for this stimulus class. Functional re-organisation may also lead to a recovery

[10] However this difference was not subjected to a statistical test.

in performance in word recognition when the lesion affects right vOTC but is less likely to do so when the lesion affects left vOTC, reflecting the hemispheric asymmetry for language. There is, however, insufficient time for such plasticity following TMS.

Therefore, it may be the case that a subtle deficit in the recognition of words (in the event of right hemisphere damage) or objects (in the event of unilateral damage) may be detected if highly sensitive measures (Mycroft et al. 2009; Starrfelt et al. 2009; Starrfelt et al. 2010) are employed soon after the damage occurs[11].

In summary, this experiment clearly demonstrates that vOTC is commonly involved in both visual word and object recognition with no difference the two modalities in either hemisphere or time. This suggests that vOTC of either hemisphere is not specialised for one type of stimuli or the other but rather is important for processing higher order visual information (presumably visual *form* information) which is critical for both types of stimuli.

5.4 General Discussion

This chapter detailed two experiments aimed at characterizing the temporal dynamics of vOTC. Both experiments demonstrated that paired-pulse TMS can disrupt ventral occipito-temporal processing during visual word recognition, providing a novel means of directly assessing the area's temporal profile. This is important as, in the absence of single cell recordings comparable to those available from macaque monkeys, previous attempts to assess the temporal dynamics of the region have relied on EEG or MEG.

In both experiments reported in this chapter and for both words and objects in Experiment 2, disruption of vOTC occurred over a prolonged period of time. The TMS effect during the later time windows is inconsistent with the area being limited to

[11] This approach will be further complicated however, by the effects of swelling and other acute effects of the damage.

feedforward processing and rather suggests that feedback information re-enters the region. Furthermore, the relatively long and unbroken period of disruption suggests that the area does not have separate feedforward and feedback waves, consistent with interactive cascaded activity.

ERP and MEG studies demonstrate that both written words and pseudowords evoke an early midline occipital positivity at approximately 50-100msec post-stimulus, followed by a left occipito-temporal negativity between 170-200msec (Salmelin et al. 1996; McCandliss et al. 1997; Bentin et al. 1999; Tarkiainen et al. 1999; Rossion et al. 2003). The initial positive component may reflect activity in V1 and is common to all visual stimuli whereas the second (negative) component is thought to arise in vOTC and distinguishes between orthographic and non-orthographic stimuli (Bentin et al. 1999; Cohen et al. 2000) and is sensitive to word frequency manipulations (Neville et al. 1992; Hauk and Pulvermüller 2004). Thus it is typically assumed that vOTC is activated by an excitatory feedforward volley of activity spreading ventro-laterally from V1 to V2 and V4 and then into left vOTC at approximately 170-200msec post stimulus onset (McCandliss et al. 2003; Dehaene et al. 2005). My results, however, suggest that information is present in vOTC substantially earlier – possibly as early as 40msecs after the stimulus appears on the retina. Even if the first pulse anticipated the feedforward volley of action potentials, its disruptive effect is believed to last at most 30-40msecs (Amassian et al. 1989; Ilmoniemi et al. 1997; Corthout et al. 1999a), which suggests a time lag between the TMS and ERP/MEG latency values. Interestingly, the TMS results better match those from multi-unit recordings in awake monkeys. For instance, the onset latencies for action potentials in V1 are between 20-30msec (Maunsell and Gibson 1992; Givre et al. 1994; Schroeder et al. 1998) which matches TMS-induced disruption (Corthout et al. 1999a; Paulus et al. 1999; Kammer et al. 2003; Corthout et al. 2007) but anticipates the C1 component from ERPs (Clark et al. 1994; Martínez et al. 1999; Di Russo et al. 2003). Similarly, in monkeys the initial action

potentials from the ascending visual pathway appear in posterior inferotemporal cortex between 40-120msec post-stimulus onset (Ashford and Fuster 1985; Richmond et al. 1987; Schroeder et al. 1998; Kiani et al. 2005; Chen et al. 2007), consistent with the current TMS findings but much earlier than suggested by the N170 component. In other words, the time at which TMS exerts its disruptive effect precedes the peak times reported in ERP/MEG experiments. Presumably this reflects the fact that these components arise from large-scale neuronal synchrony across activity in multiple structures and therefore lag behind the earliest wave of activity in any given structure (Schroeder et al. 1998; Walsh and Cowey 2000). As a consequence, chronometric TMS studies may offer a more accurate measure of absolute regional timings than ERP or MEG, despite their poorer temporal resolution (i.e. tens of milliseconds vs. milliseconds). Furthermore if this lag is not consistent across regions or within the same region across tasks, then the interpretation of ERP timing data becomes complicated, even for estimating relative timing. In fact, a consideration of ERP and TMS data for V1 and vOTC would seem to suggest that the difference between the earliest detectable activity in an area and its peak ERP component may differ across regions. For instance, the discrepancy between ERP and TMS estimates of V1 activity (ERP: 50-55msec. TMS: 30msec) is considerably smaller than that for vOTC (ERP: 170-200msec. TMS: 40-120msec). However, further work comparing timing estimates within-subject is clearly needed.

6 Consistency and variability in functional localisers

"In choosing a localiser to define an ROI, the researcher is making an ontological assumption that this localizer contrast picks out a meaningful functional unit in the brain (i.e., a natural kind). Like other ontological assumptions in science, the utility of a particular functionally defined ROI is determined by the consistency of the data that emerge from it and the richness of the theoretical progress those data support". Saxe, Carey and Kanwisher (2004), pages 91-92.

6.1 Introduction

Increasingly, functional neuroimaging studies are moving away from traditional brain mapping studies designed to identify the cortical topography of a function and towards designs that investigate the response properties of specific neuroanatomical regions. This approach requires a robust method for identifying the region under investigation, however, macro-anatomic landmarks are not especially good predictors of functionally homogenous cortical fields (Uematsu et al. 1992; Amunts et al. 2000; Farrell et al. 2007). The early visual fields are a good example. V1 is primarily located in the calcarine sulcus but its borders do not correspond to clear sulcal landmarks while V2 and V3 are even more difficult to distinguish based purely on local landmarks (Amunts et al. 2000; Wohlschlager et al. 2005). The inability to define a region unambiguously is a major impediment to investigating it. Consequently, a typical solution is to localise the region functionally based on its response properties, for instance, using retinotopy (Sereno et al. 1995; Larsson and Heeger 2006), somatotopy (Blankenburg et al. 2006; Pulvermüller et al. 2006; Huang and Sereno 2007), or tonotopy (Wessinger et al. 1997; Bilecen et al. 1998; Wessinger et al. 2001; Talavage et al. 2004). Even higher order association areas can be defined in this way with "functional localisers" routinely used to identify the set of voxels sensitive to faces (O'Craven and Kanwisher 2000; Haxby et al. 2001; Levy et al. 2001; Downing et al. 2006; Jiang et al. 2007; Yovel et al. 2008; Mei et al. 2010), speech (Miller and D'Esposito 2005; Szycik et al. 2008), objects (Kourtzi and Kanwisher 2000; Haxby et al. 2001; Levy et al. 2001; Culham et al. 2003; Jiang et al. 2007; Eger et al. 2008; Yovel et al. 2008), body parts (Downing et al. 2006; Saxe et al. 2006b), scenes (Epstein and Kanwisher 1998; Downing et al. 2006), or written words (Baker et al. 2007; Ben-Shachar et al. 2007; Mei et al. 2010). In most cases this involves collecting additional scans in which participants perform a different task solely for the purpose of functionally identifying the

anatomical region and then using it in summary mode as a way of evaluating the response profile of a functionally defined region-of-interest (fROI).

Although there is some debate regarding the most efficient method for doing this (Friston et al. 2006; Saxe et al. 2006a), relatively little attention is paid to the validity of a key underlying assumption – namely, how consistently does the scan localise a functional area? Obviously the tacit assumption is that the same task in the same subject will identify essentially the same set of voxels despite various sources of physiological and scanner noise (Aguirre et al. 1998; Kruger and Glover 2001; Handwerker et al. 2004). If there is considerable variability between runs within the same session, then the basic idea of functional localisation becomes suspect because the localised set of voxels may not correspond well to those being tested in the main experimental run, decreasing sensitivity and increasing both false positives and false negatives.

One of the few studies to investigate this issue examined the consistency of activation for faces in the fusiform and occipital face areas (FFA and OFA), scenes in the parahippocampal place area (PPA), and body parts in the extrastriate body area (EBA) (Peelen and Downing 2005b). They found all stimuli produced peak voxels that were consistent in both location and *t*-value across runs. They did not, however, report the consistency of the activation itself, which is important because most studies that use functional data to identify a region-of-interest define it based on the cluster of voxels within a given anatomical area activated by a particular contrast (Kanwisher et al. 1999; O'Craven and Kanwisher 2000; Grill-Spector et al. 2004; Downing et al. 2006; Spiridon et al. 2006; Jiang et al. 2007; von Kriegstein et al. 2008; Yovel et al. 2008). One study which did investigate the consistency of activation for faces found that although the location of the

peak voxel was stable, there was less than 40% overlap[12] in the number of active voxels between localiser runs (Kung et al. 2007), suggesting that functionally defined ROIs may be more variable than commonly assumed.

It should be noted at this point that while the intrinsic reliability of the BOLD signal is of relevance to the issue of the reliability of functional localisers – in that it sets the upper limit of reliability (see Bennett and Miller (2010)) – it is important not to conflate the two issues. One addresses the theoretical issue of the reproducibility of a pattern of activation over a set of voxels while the other provides a practical method for identifying a set of voxels. For the former, intra-class correlation (ICC) and Pearson correlations can be used to compute a similarity value over a set of unthresholded voxels in an a priori defined region. In contrast, the aim of functional localiser scans is to define a set of functionally relevant voxels within a broadly defined anatomical region by setting an arbitrary threshold to separate "active" from "inactive" voxels in a statistical map. So while it's clear that the practice of using functional localiser scans depends, in part, on the intrinsic reproducibility of the fMRI signal, it also depends on many other factors under the experimenter's control, such as which task is used, the amount of data to be collected, the optimal method for data analysis and so on. Here I am concerned solely with these latter (practical) issues and consequently will not focus on the theoretically important, but slightly tangential, issue of fMRI reproducibility in general.

As a result of using fMRI to localise the target sites in the TMS experiments in this thesis, I had the opportunity to evaluate consistency and variability associated with functionally localising reading- and object-sensitive areas of left occipito-temporal cortex (OTC). fMRI

[12] This value was based on Kung et al.'s (2007) Figure 5a and uses a formula sensitive to differences in the number of active voxels between runs (as is used in our own analyses). The overlap value increases when this difference in voxel numbers is ignored but even so, remains less than 50%.

was used to localise a region of the ventral OTC associated with visual word recognition (Price and Mechelli 2005) and a lateral OTC region associated with visual object recognition (Malach et al. 1995; Grill-Spector et al. 1999) in a fairly large sample of volunteers (n = 45). To empirically evaluate the assumption that functional localisation of category-sensitive cortical regions is robust and consistent, I calculated three different measures of consistency between two functional localiser runs: (1) the distance between peak voxels in the two runs; (2) the amount of spatial overlap in activations and (3) the amount of overlap in contiguously activated voxels within a spherical ROI centred on the peak voxel.

6.2 Experiment 1

6.2.1 Method

Participants. 45 (23 M, 22 F) healthy, monolingual English speakers participated. Their ages ranged from 19 to 38 (mean = 25), and all were right handed with normal or corrected-to-normal vision. None had a personal or family history of any neurological disease, and each gave informed consent after the experimental procedures were explained. This experiment was approved by the Berkshire NHS Research Ethics Committee.

Experimental paradigm. A one-back task was used with four categories of visual stimuli: written words, pictures of common objects, scrambled pictures of the same objects, and consonant letter strings (Figure 6-1). Subjects were instructed to press a button if the stimulus was identical to the preceding stimulus and 12.5% of the stimuli were targets. A block design was used to maximize statistical sensitivity. Each block consisted of 16 trials from a single category presented one every second. A trial began with a 650msec fixation cross, followed by the stimulus for 350msec. In between blocks, subjects viewed a fixation cross for 16 sec. The stimuli were divided equally into two lists, with the order counter-

balanced across subjects such that 50% of subjects saw the first list of stimuli during run 1 and the remaining 50% during run 2. In total there were 192 stimuli per category including targets. Using a one-back task has the advantage that stimulus category can be varied without changing the task, maintaining a constant cognitive set – the specific stimuli are almost incidental to the task. In addition, it is commonly used for functional localisation (for example Kanwisher et al. 1999; Gazzaley et al. 2005; Peelen and Downing 2005a; Baker et al. 2007; Downing et al. 2007).

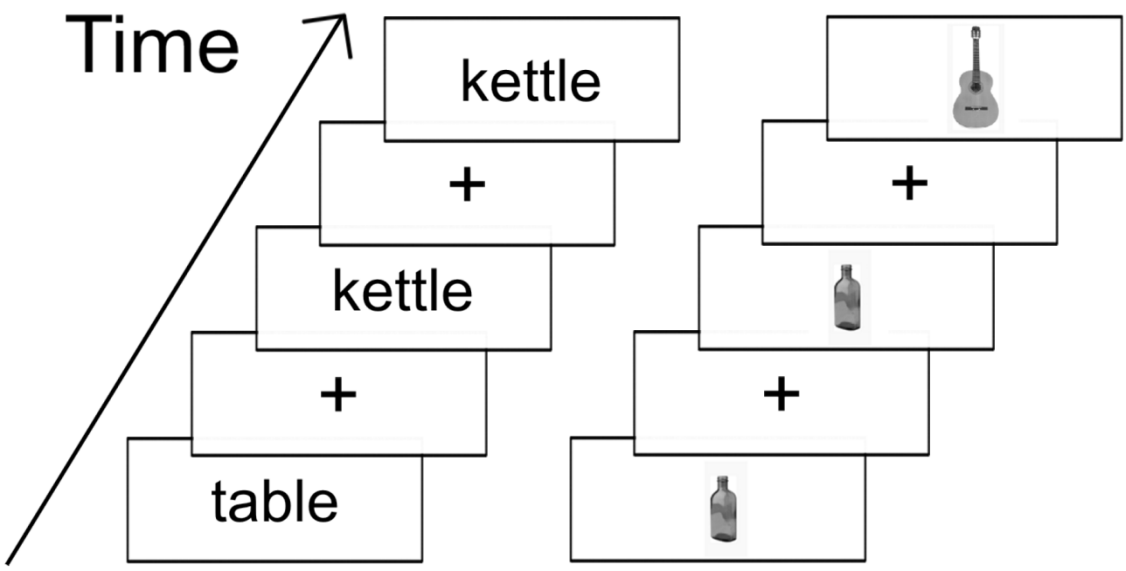


Figure 6-1: The 1-back paradigm used to functional localise word and object sensitive regions. Note that this image is not to scale. Words were presented in 32pt Helvetica font and subtended a visual angle of 4°. Pictures were 200 x 250 pixels and subtended a visual angle of 4°. Permission to reproduce this figure has been granted by Elsevier.

Word stimuli (n = 168) were obtained from the MRC Psycholinguistic database (Coltheart 1981) and consisted of 4 or 5 letter words with regular spellings (e.g. “hope”). All words had familiarity ratings between 300 and 500 (Coltheart 1981), were either one or two syllables, and had a British English written word frequency value of 40 or less (Baayen et al. 1993). The stimuli in the two runs were fully matched for frequency, familiarity, imageability, number of letters, and number of syllables (Table 6-1). Object stimuli consisted of black and white pictures (200 × 250 pixels) of easily recognizable objects such

as a boat, tent, nail, etc. The scrambled objects were generated by dividing the pictures into 10 × 10 pixel squares and permuting their placement within the image. None of the resulting images were recognizable after scrambling. Finally, consonant letter strings were unpronounceable strings randomly generated to exactly match the length of the word stimuli.

Table 6-1: Mean psycholinguistic properties per condition with standard error in parenthesis.

	Run	Words	Consonants
Letters	1	4.5 (0.05)	4.5 (0.05)
	2	4.5 (0.05)	4.5 (0.05)
Syllables	1	1.3 (0.05)	-
	2	1.3 (0.05)	-
Frequency	1	8 (0.79)	-
	2	7 (0.74)	-
Familiarity	1	431 (8.1)	-
	2	408 (11.6)	-
Imageability	1	452 (11.7)	-
	2	448 (15.2)	-

Functional imaging. Whole-brain imaging was performed on a Siemens 1.5 Tesla MR scanner at the Birkbeck-UCL Neuroimaging (BUCNI) Centre in London. The functional data were acquired with a gradient-echo EPI sequence (TR = 3000msec; TE = 50msec, FOV = 192 × 192, matrix = 64 × 64) giving a notional resolution of 3 × 3 × 3mm. Each run consisted of 164 volumes and as a result, the two runs together took 16.4 minutes. In addition, a high-resolution anatomical scan was acquired (T1-weighted FLASH, TR = 12 msec; TE = 5.6msec; $1mm^3$ resolution) for anatomically localising activations in individuals.

Data processing was carried out using FSL 4.0 (www.fmrib.ox.ac.uk/fsl). To allow for T1 equilibrium, the initial two images of each run were discarded. The data were then realigned to remove small head movements (Jenkinson et al. 2002), smoothed with a Gaussian kernel of FWHM 6mm, and pre-whitened to remove temporal auto-correlation (Woolrich et al. 2001a). The resulting images were entered into a general linear model with four conditions of interest corresponding to the four categories of visual stimuli. Blocks were convolved with a double gamma "canonical" hemodynamic response function (Glover 1999) to generate the main regressors. In addition, the estimated motion parameters were entered as covariates of no interest to reduce structured noise due to minor head motion. Linear contrasts of [Words > Fixation] and [Objects > Scrambled objects] identified reading- and object-sensitive areas, respectively. First level results were registered to the MNI-152 template using a 12-DOF affine transformation (Jenkinson and Smith 2001) and all subsequent analyses were conducted in the MNI standard space. A second level fixed-effects model combined the two first level runs into a single, subject-specific analysis which was then entered into a third level, mixed effects analysis to draw inferences at the population level (Beckmann et al. 2003; Woolrich et al. 2004).

Note that consonant strings were originally intended to serve as a baseline condition for words analogous to scrambled pictures for objects. Although the contrast [words>consonants] produced activation in vOTC at the random effects level similar to previous studies (Cohen et al. 2002; Devlin et al. 2006), the activation was not reliable for individuals (see also Cohen et al. 2002; Vigneau et al. 2005; Baker et al. 2007) and therefore [words > fixation] was used to identify reading-sensitive areas instead.

Regions-of-interest. In order to restrict the analyses to the ventral and lateral OTC, two anatomical masks were drawn in standard space. The ventral OTC mask encompassed the posterior portion of the left fusiform gyrus, occipito-temporal sulcus (OTS), and medial parts of the inferior temporal gyrus (ITG) – areas consistently activated by visual word

recognition tasks (Price et al. 1994; Price et al. 1996; Herbster et al. 1997; Rumsey et al. 1997; Fiez and Petersen 1998; Fiez et al. 1999; Shaywitz et al. 2004). The standard space coordinates were: *X* = –30 to –54, *Y* = –45 to –70 and *Z* = –30 to -4. The lateral OTC mask encompassed lateral posterior fusiform gyrus, posterior OTS and lateral parts of posterior ITG – areas consistently activated by visual objects and collectively known as the "lateral occipital complex" (LOC) (Malach et al. 1995; Grill-Spector et al. 1999). The standard space coordinates were X = –33 to –56, Y = –67 to –89 and Z = –20 to +4. Within each mask, only voxels with at least a 20% chance of being grey matter were included based on an automatic tissue segmentation algorithm (Zhang et al. 2001).

6.2.2 Results

***Behaviour**: 1-back performance.* Behavioural data from six subjects were lost due to a problem recording button press responses while in the scanner. The data from the remaining subjects (n = 39) were analysed using signal detection theory as hits and false alarms. The mean hit rate was 0.791 and the false alarm rate was 0.011, indicating that participants performed the task adequately (see Table 6-2). In addition, d-prime (d') scores were calculated to measure sensitivity for detecting repeated items (Table 6-2). These were then entered into 2 × 4 repeated measures ANOVA examining the effects of Category (words, consonant strings, objects, scrambled objects) and Run (first, second). A main effect of Category ($F(3,114) = 77.9$, $p < 0.001$) indicated that detecting repetitions of scrambled objects was most difficult, but there was no difference between words or objects ($t(38) = 0.05$, $p = 0.961$. Importantly, neither the main effect of Run ($F(1,38) = 0.494$, $p = 0.486$) nor the Category × Run interaction ($F(3,114) = 1.665$, $p = 0.179$) was significant, indicating that participants' performance did not significantly change from the first to the second run. The same pattern was present in the reaction times to correct detections (i.e. "hits"). Again, there was a main effect of Category ($F(3,114) = 5.4$, $p = 0.002$) but no main effect of Run ($F(1,38) = 0.09$, $p = 0.765$) and no Category × Run

interaction ($F(3,114) = 1.169$, $p = 0.325$). In other words, there was no behavioural evidence for task learning that might confound the activation patterns across runs.

Table 6-2: Behavioural data from the 1-back task for Experiment 1. The top section presents overall performance in terms of hit and false alarm rates. The second section presents sensitivity scores (d'-values) for detecting item repetitions while the third presents the reaction times for correctly detecting repeated items.

	Words	Consonants	Objects	Scrambled
Hit Rate	0.866	0.842	0.854	0.602
False Alarms	0.006	0.006	0.002	0.030
D-Prime Scores (±SEM)				
Run 1	4.03 (0.15)	3.96 (0.13)	4.05 (0.13)	2.43 (0.14)
Run 2	4.16 (0.15)	3.83 (0.14)	4.14 (0.13)	2.64 (0.14)
Median RTs (±SEM)				
Run 1	582 (14.1)	560 (13.0)	568 (13.2)	599 (15.6)
Run 2	578 (11.9)	562 (12.7)	585 (11.7)	600 (13.1)

Imaging results: *Group effects.* Consistent with previous research, the peak activation in ventral OTC for words relative to fixation was located in the occipito-temporal sulcus (–42, –50, –20; $Z = 7.7$), extending both medially onto the convexity of the posterior fusiform gyrus and laterally onto the inferior temporal gyrus. To visualise this activation, the group results were projected onto an inflated surface of an "average" brain (i.e. Freesurfer's fsaverage subject) to illustrate that activation was not limited to the ventral surface but also present inside the occipito-temporal sulcus (Figure 6-2B). As reported previously (Bookheimer et al. 1995; Moore and Price 1999; Price et al. 2006; Wright et al. 2008), objects relative to scrambled objects also activated this same region (–40, –58, –20; $Z = 7.9$; Figure 6-2D) and although activation for objects was numerically larger than for words, there was no significant difference between them. Within the lateral OTC, objects produced strong activation in LOC (–41, –78, –9; $Z = 7.5$), although once again, there was a

comparable activation for words (–37, –84, –11; *Z* = 6.9; Figure 6-2B). Here, objects did lead to significantly greater activation than words (*Z* = 5.9; Figure 6-2D), but this was part of a much larger cluster encompassing almost the entire occipital lobe and extending ventrally through large parts of the inferior temporal lobe bilaterally (c.f. Moore and Price 1999). In other words, the group results demonstrate that the task and stimuli were appropriately able to identify ventral and lateral OTC areas and confirm previous studies that demonstrate greater activation for objects than words in OTC regions (Bookheimer et al. 1995; Moore and Price 1999; Price et al. 2006; Wright et al. 2008).

Imaging results: *Inter-subject variability.* To assess how closely activation from individuals matched the group results, their peak responses for words and objects were compared to the group results. For words, all 45 participants showed a peak response within ventral OTC with a *Z*-score of at least 3.5, although the specific location varied considerably (Table 6-3). The left panel of Figure 6-2C illustrates the spatial distribution of peaks within ventral OTC. Individual subject peaks are shown as orange dots. Each peak has been projected onto a single brain that has been inflated to show not only the crests of the gyri (light grey) but also the depths of the sulci (dark grey) using Freesurfer (http://surfer.nmr.mgh.harvard.edu/). Note that the sharp demarcations between gyri and sulci do not accurately reflect the anatomical variability present in the group; instead the figure illustrates the spatial distribution of peaks relative to a single "average" brain. Consequently, the specific anatomical location of each peak was assessed relative to that individual's structural scan in standard space. The greatest consistency is in the medial-lateral direction, with the majority of peaks (n = 20) falling within the occipito-temporal sulcus. Another 18 were located on the crest of the posterior fusiform gyrus and 7 were in on the crest of the inferior temporal gyrus. In contrast, the largest variation was in the rostro-caudal direction while the variation in z-axis is mostly due to the depth of the OTS.

On average, the Euclidean distance from an individual subject's peak to the group peak was 15mm (±5mm).

Table 6-3: Summary of inter-subject variability in peaks coordinates for words and objects. Coordinates are in the MNI152 space and the Z-score is for the peak voxel.

	X	Y	Z	*Z*-score	Distance to group peak (mm)
Words in ventral OTC					
Range	-52…-30	-70…-46	-25…-5	3.5…12.7	5.7…23.9
Mean	-42	-62	-16	8.8	15.2
S.D.	5	7	5	2.5	5.2
Objects in lateral OTC					
Range	-55…-34	-87…-68	-19…3	2.7…13.9	4.1…18.5
Mean	-43	-77	-8	7.1	9.2
S.D.	5	6	6	2.4	3.5

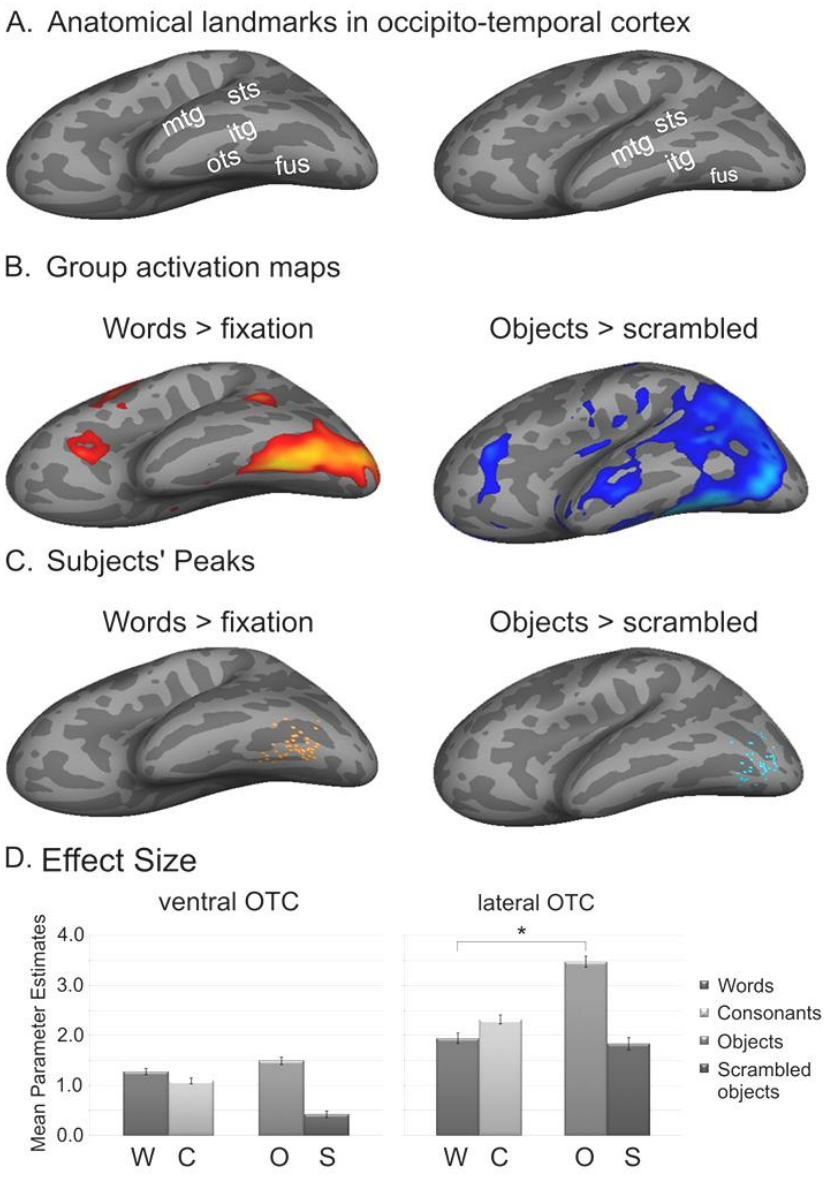


Figure 6-2: Results of functional localising word- and object-sensitive areas of occipito-temporal cortex. (A) An inflated left hemisphere of a single brain illustrating the main anatomical landmarks in the OTC. Sulci are shown in dark gray and gyri in light gray. (B) Group activation for [Words > Fixation] and [Objects > Scrambled] projected on to the inflated left hemisphere of the Freesurfer "fsaverage" brain. (C) The spatial distribution of individual subject peaks for [Words > Fixation] in ventral OTC (orange dots) and for [Objects > Scrambled] in lateral OTC (blue dots). Note that the sharp demarcations between gyri and sulci do not accurately reflect the anatomical variability present in the group. Instead the figure illustrates the spatial distribution of peaks relative to a single brain. (D) Effect sizes for words, consonant strings, objects and scrambled objects relative to fixation in ventral and lateral OTC. Error bars represent standard error of the mean. * indicates a significant difference at $p < 0.001$. Abbrevs: mtg = middle temporal gyrus, sts = superior temporal sulcus, itg = inferior temporal gyrus, ots = occipito-temporal sulcus, fus = fusiform gyrus; W = words, C = consonant strings, O = objects, and S = scrambled objects. Permission to reproduce this figure has been granted by Elsevier.

There was slightly less variability in the peak coordinates for objects within LOC. Once again, all 45 participants showed a clear peak in the ROI with *Z*-scores of 2.7 or higher and these are illustrated in the right panel of Figure 2C. The majority of peaks for objects lay in lateral occipital cortex (n = 26) and the remaining ones were located in posterior fusiform cortex (n = 19). Unlike the reading peaks, these were spread more evenly around group peak and on average, the Euclidean distance from an individual subject's peak to the group peak was 9mm (±3mm).

Imaging results: *Intra-subject consistency.* The most critical analyses for evaluating the consistency assumption underlying functional localisers concerned within-subject consistency. This was calculated in three ways. Because studies often define functional ROIs using a sphere with a fixed radius centred on the peak voxel (Miller and D'Esposito 2005; Blankenburg et al. 2006; Pulvermüller et al. 2006; Jiang et al. 2007), the first measure examined the spatial reliability of the peak voxel since this determines the fROI. The coordinates of peak voxels were extracted for each participant from both runs and the distance between peaks was calculated using the standard Euclidean distance measurement. On average, peaks for words were separated by 7.4mm while peaks for objects were 8.3mm apart. It is worth noting that at the resolution of the acquired data (3 × 3 × 3mm), these peaks would be 2–3 voxels apart in space, although this figure varied considerably across participants. A number of subjects showed peaks within 1 voxel of each other (words: n = 17; objects: n = 11) however many subjects had peaks more than 4 voxels (>12mm) apart (words: n = 12; objects: n = 12). The coordinates of the peak depend on many factors, however, and only one is the size of the underlying neurophysiological response. Therefore, peak locations are highly susceptible to random fluctuations (Aguirre et al. 1998; Kruger and Glover 2001; Handwerker et al. 2004). Consequently, the second analysis focused on the set of voxels within the ROI that were activated by both runs.

The most common method for defining an fROI is based on the volume of activated voxels within a particularly region (Kanwisher et al. 1999; Grill-Spector et al. 2004; Spiridon et al. 2006; Jiang et al. 2007; Szycik et al. 2008; Yovel et al. 2008). Consequently, the second measure assessed consistency in terms of the volume of commonly activated cortex between runs in both ventral and lateral OTC. This was computed as the ratio (R_{ij}) of commonly activated voxels to the total number of activated voxels in two runs, *i* and *j*:

Equation 6-1: $$\mathbf{R_{ij}} = \frac{\mathbf{2 \times V_{ij}}}{\left(\mathbf{V_i + V_j}\right)}$$

where V_{ij} is the number of voxels within the ROI which were active in both runs *i* and *j* while V_i and V_j are the number of voxels within the ROI that were active in runs *i* and *j*, respectively. A value of 1.0 indicates identical sets of voxels while 0.0 represents completely disjoint sets. This definition, however, treats voxels as "active" or not based on an essentially arbitrary threshold. To avoid conditioning the results by an arbitrary choice, five thresholds were used spanning a typical range: i) $Z > 1.64$ ($p < 0.05$ uncorrected), ii) $Z > 2.3$ ($p < 0.01$ uncorrected) iii) $Z > 3.09$ ($p < 0.001$ uncorrected), and iv) $Z > 4.0$, (roughly $p < 10^{-4}$, which is fairly conservative) and v) $Z > 5.0$ (roughly $p < 10^{-6}$, which would conservatively correct for multiple comparisons across the whole brain with a family-wise $\alpha < 0.05$). Mean (± SEM) consistency ratios were similar in both ventral and lateral OTC regions with the highest values (0.64 ± 0.03 and 0.60 ± 0.04) for the lowest statistical threshold (Figure 6-3a). Raising the statistical threshold *decreased* the amount of overlap between runs, and this is illustrated in Figure 6-4. In this figure, data from two representative subjects show how the increasingly conservative statistical threshold influences the overlap (yellow) between runs (shown in red and green). At lenient thresholds, there is widespread activation within both the ventral and lateral occipito-temporal ROIs, leading to considerable overlap (the consistency score is shown in the

upper right corner of the panel). At higher thresholds, however, two things typically happened. First, the number of active voxels in one or both runs decreased dramatically. Second, the active clusters from the two runs tended to separate spatially, leaving. These two factors together mean that increasingly conservative thresholds result in smaller and smaller regions of common activation. At the two most conservative statistical thresholds ($Z > 4.0$ and $Z > 5.0$) the mean consistency scores were 0.30 ± 0.05 and 0.21 ± 0.05, respectively. In addition, higher thresholds meant fewer subjects with significantly activated voxels. For instance, at the most conservative threshold it was impossible to identify an fROI for words or objects in 8 and 18 (out of 45) participants, respectively. In sum, overlap scores were surprisingly low with more conservative statistical thresholds yielding even less overlap and fewer subjects in which an fROI could be defined.

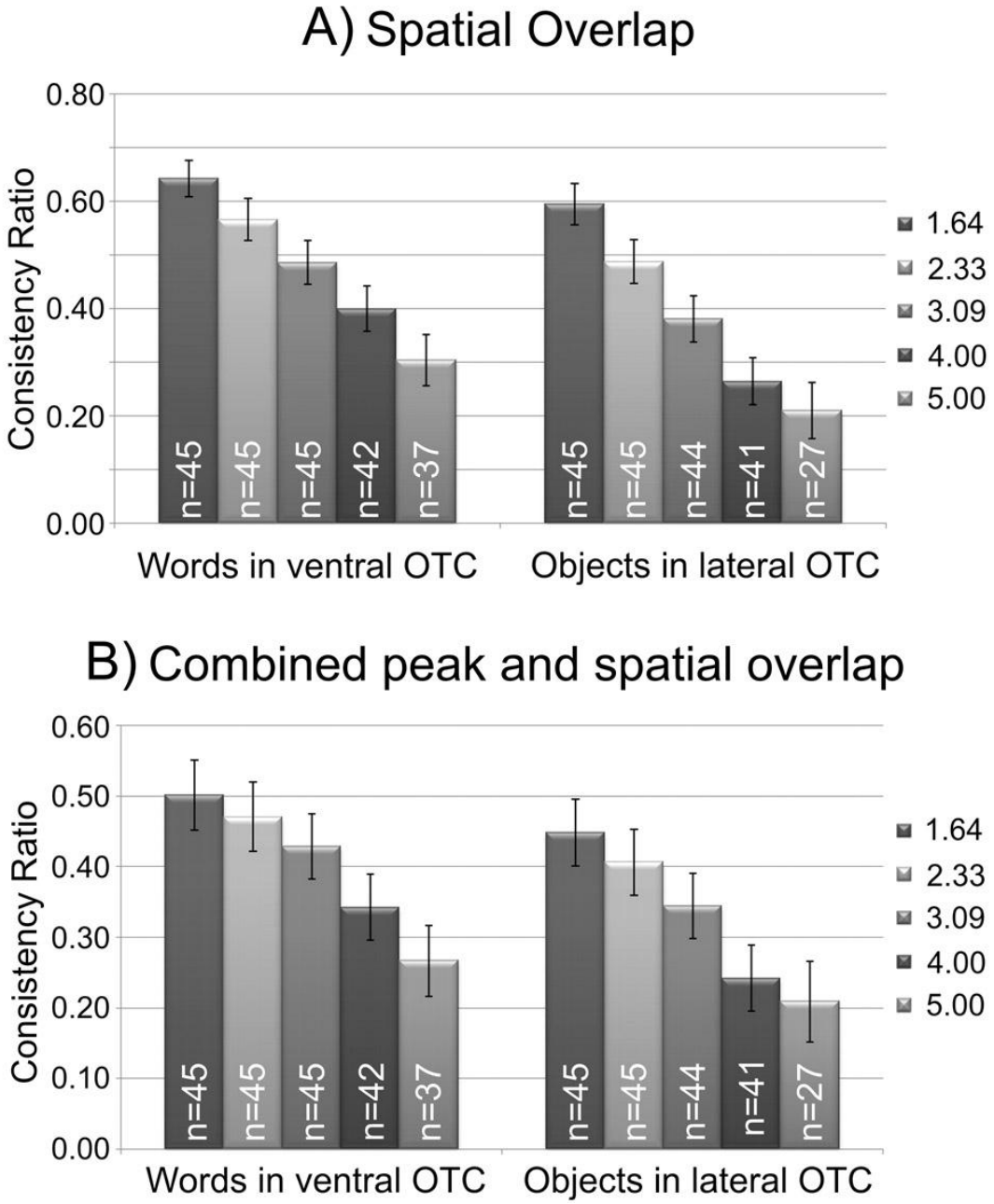


Figure 6-3: Consistency of fROI activation when different statistical thresholds were used to define "active" voxels. A) These bar plots show consistency scores based on spatial overlap between the two localiser runs. Activation thresholds ranged from lenient ($Z > 1.64$, $p < 0.05$ uncorrected) to conservative ($Z > 5.0$, $p < 10^{-6}$). At the lowest thresholds, all participants had active voxels in the ROI but as the threshold increased, some subjects needed to be excluded from the analyses due to lack of activation at that threshold. The numbers in white refer to the number of subjects who were included in the analysis at each level (out of 45). B) In these plots, consistency was evaluated on the set of contiguously activated voxels within 9mm of the peak response. Error bars represent standard error of the means. Permission to reproduce this figure has been granted by Elsevier.

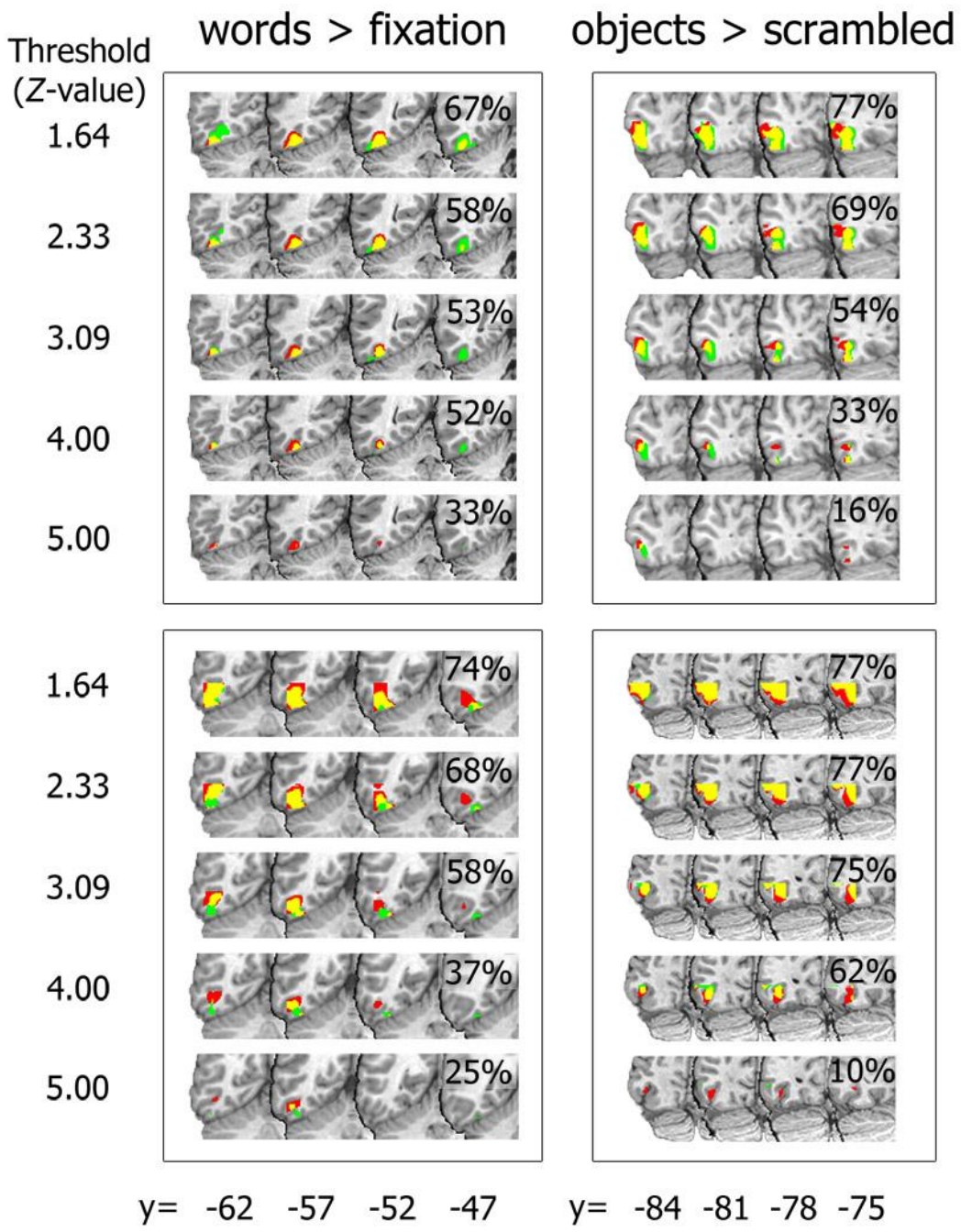


Figure 6-4: An illustration of how consistency interacts with statistical thresholding in two representative participants. The left column shows activation for [Words > Fixation] in the left ventral occipito-temporal region for two runs at multiple thresholds while the right column shows the same for [Objects > Scrambled] in the left lateral occipital complex. Voxels that were only activated in the first and second runs are coloured green and red, respectively, while voxels that were active in both runs are coloured yellow. Note that increasing the threshold decreases the overlap. Permission to reproduce this figure has been granted by Elsevier.

Finally, it is possible to combine peak and volume measures to define an fROI as the set of active voxels that are contiguous with the peak activation (Downing et al. 2006). This approach will help to reduce variability between runs as long as the two peaks fall within overlapping clusters. To assess the consistency of this method, I defined fROIs as the set of contiguous active voxels (using the same set of five thresholds as above) that included the peak voxel and were within a 9mm radius of the peak voxel following Downing and colleagues (2006). The results are shown in Figure 6-3b. Again, the highest consistency values were for the lowest statistical threshold. For the contrast [Words > Fixation] in ventral OTC, the mean consistency ratio (R_{ij}) was 0.50 (SEM = 0.05) and for the contrast [Objects > Scrambled], the mean R_{ij} was 0.45 (SEM = 0.05). Increasing the threshold to $Z > 5$ reduced the overlap to 0.27 ± 0.05 for words and 0.21 ± 0.06 for objects and precluded identifying an fROI in 8 and 18 of the participants.

6.2.3 Discussion

The aim of this experiment was to evaluate the consistency associated with functionally localising reading- and object-sensitive areas of left occipito-temporal cortex. At the group level, the current results closely match previous reports with peak activations located in the posterior occipito-temporal sulcus for written words (Cohen et al. 2000; Kronbichler et al. 2004; Shaywitz et al. 2004; Price and Mechelli 2005; Devlin et al. 2006; Ben-Shachar et al. 2007) and in the lateral occipital region for visual objects (Malach et al. 1995; Grill-Spector et al. 1999). In other words, the ability to localise these regions at the group level is highly consistent across studies. At the individual level, however, localization was considerably less consistent, with peaks varying in location by as much as 20mm in any direction. This finding replicates previous studies and demonstrates the importance of using functional data to localise a specific region of interest when characterizing its response properties (Kanwisher et al. 1997; Saxe et al. 2006a; Wright et al. 2008). But in order for functional localisation to be meaningful, it must be robust and consistent *within*

subjects. The current findings suggest that this consistency was surprisingly poor, regardless of the specific method used to evaluate consistency:

Peak voxels. Roughly 33% of the participants had peaks at essentially the same location in both localiser runs whereas another 27% had peaks that were at least 12mm apart. The remainder fell within those two extremes. In other words, for one quarter of the subjects tested here, an fROI based on the peak voxel response may not even overlap with the activation seen in the main experimental task.

Spatial overlap. The most commonly used method for defining an fROI is to select the voxels within a region activated by a given contrast. Clearly this depends critically on the definition of "active voxels" and this varies from study to study. Over a wide range of activation thresholds ($p < 0.05$ to $p < 10^{-6}$), consistency scores were surprisingly low, ranging from 64% to 21%, respectively. The most lenient definition of "active" voxels produced the greatest consistency across runs, but even so, roughly one third of the data from the fROI are coming from noisy or unreliable voxels. Equally problematic is the fact that lenient statistical thresholds lead to only minimal category-selectivity in the ROI (Golarai et al. 2007; Fox et al. 2008). Conservative statistical thresholds ($p < 10^{-3}$ to 10^{-6}) are more common but yield very low consistency values, with less than half of the voxels present in both runs. As a result, the majority of the data being investigated comes from unreliable voxels.

Peak plus spatial extent. In theory, combining the first two methods has the advantage that small displacements of the peak voxel do not necessarily change the fROI, assuming they fall within a common cluster of active voxels. In practice, the results were qualitatively and quantitatively similar to the previous method because of the small numbers of active voxels common to both runs.

One potential explanation for the low levels of overlap between runs is that participants may acclimate to the task and therefore show less activation in their second run. There was, however, no evidence of task learning in the behavioural data. This was also true for the imaging data where I analysed the number of active voxels per contrast with Run (first, second) and Threshold (1.64, 2.33, 3.09, 4.0, 5.0) as independent factors. Predictably there was a main effect of Threshold on the number of active voxels for both contrasts (words: $F(4, 179) = 229.3$, $p < 0.001$; objects: $F(4, 179) = 192.9$, $p < 0.001$) but there was no main effect of Run (words: $F(1,44) < 0.1$, $p = 0.936$; objects $F(1,44) = 1.2$, $p = 0.287$) and no Run $\times$ Threshold interaction (words: $F(4,176) = 0.3$, $p = 0.896$; objects: $F(4,176) = 0.8$, $p = 0.520$). In other words, task learning did not appear to significantly contribute to the relatively low consistency between runs.

The single largest source of variability appeared to be spatial shifts in activation (see Figure 6-4), which help to explain the surprising finding that overlap decreased with more conservative statistical thresholding (see also Kung et al. 2007). Initially, I assumed that higher statistical thresholds would converge on the most selective category-sensitive voxels which I expected would be stable across runs. In practice, however, the highest thresholds showed the lowest consistency scores resulting in a trade-off between category-selectiveness and consistency. One potential limitation of the current experiment is only two types of category-selectivity were tested and only in two anatomical areas, so it is possible that the results may not generalise to other areas. On the other hand, despite being sensitive to different categories of stimuli, both regions showed essentially the same pattern and this pattern matched those of Kung et al. (2007) who found at best 50% consistency in face-sensitive areas.

This variability for category-sensitive visual areas stands in contrast to the consistency seen for retinotopically-defined visual areas, which appear remarkably stable within individuals (M. I. Sereno, personal communication). One striking difference between

retinotopic vs. category-sensitive localisers is the amount of data typically collected. Studies of retinotopy often collect an order of magnitude more data (Table 6-4). For instance, it is not uncommon to functionally localise category-sensitive regions based on one or more scans that take a total of 20 minutes or less. In contrast, retinotopy is typically defined using six to twelve scans that together take an hour or more, so perhaps it is not surprising that the results are more consistent. On other hand, it is possible that the observed variability in visual association areas accurately reflects functional-anatomic variability in these regions due to neuronal firing patterns becoming increasingly distant from the stimulus they are intended to represent.

Table 6-4: Summary of functional localiser scans from selected studies. Note that this is not intended to be an exhaustive list of studies employing functional localisers but a representative sample.

Study	Localising	Task	Vols per condition	Runs
Early Visual Areas				
Sereno et al. (1995)	Retinotopy	Passive viewing	128	8
Tootell et al. (1997)	Retinotopy	Passive viewing	128	6-12
Larsson & Heeger (2006)	Retinotopy	Passive viewing	168	10
Higher Order Visual Areas & Non-Visual Areas				
O'Craven & Kanwisher (2000)	Faces	Naming	60	2
Haxby et al. (2001)	Faces, objects, etc	1-back	10	12
Yovel et al. (2008)	Faces, objects, etc	1-back	64	1
Levy et al. (2001)	Faces, objects, etc	1-back	21	1
Von Kriegstein et al. (2008)	Faces, object	Passive viewing	25	2
Szycik et al. (2008)	Speech	Semantic decision	90	1
Pulvermüller et al. (2006)	Motor	Movement	40	1
Blankenburg et al. (2006)	Somatotopy	Cutaneous stimulation	38	1
Saxe & Kanwisher (2003)	Theory of mind	ToM task	60	3
Jiang et al. (2007)	Faces, cars	Passive viewing	30	2
Baker et al. (2007)	Words	Passive viewing / 1-back	40	4

To investigate this further, the second experiment investigated how the reliability of a functional localiser scan is affected by increasing the number of volumes included in the analysis. Ideally, one would compare the voxels identified by functional localiser scans using increasing amounts of data with the true set of activated voxels. Clearly, this is not possible and in lieu of actually knowing what voxels constitute the "true set of active voxels", I used a within-subject random effects (RFX) analysis of ten runs (per subject) as the "gold-standard". Localiser scans based on increasing amounts of data were compared to the results of this RFX analysis and assessed for reliability in terms of peak location and activated voxels.

6.3 Experiment 2

6.3.1 Method

Participants. 4 (2 M, 2 F) healthy, monolingual English speakers participated in the study. Their ages ranged from 25 to 39 (mean = 33), and all were right handed with normal or corrected-to-normal vision. These subjects had participated in the previous experiment. None had a personal or family history of any neurological disease, and each gave informed consent after the experimental procedures were explained. This experiment was approved by the by the UCL Research Ethics Committee.

Experimental procedures. The experimental paradigm was similar to Experiment 1. However, unlike Experiment 1, each participant completed 10 runs, with two runs per session and each session separated by a minimum of one week. Consonant strings were replaced by faces because the inclusion of faces allowed me to test face sensitive areas, i.e. the fusiform face area (FFA), that are perhaps the most commonly functionally localised brain regions (O'Craven and Kanwisher 2000; Haxby et al. 2001; Levy et al. 2001; Downing et al. 2006; Jiang et al. 2007; Yovel et al. 2008; Pourtois et al. 2009; Mei et al. 2010). Face stimuli consisted of greyscale images (300 x 300 pixels) of front-view male and female

faces of a variety of ethnicities. Object-, reading- and face- sensitive areas were identified by the linear contrasts [Words > Fixation], [Objects > Scrambled objects] and [Faces > Objects] respectively.

Image analysis. There were two types of analysis, both performed within subject. First, the 10 runs were combined using a random effects (RFX) analysis to identify the "gold-standard" voxels per contrast, per subject. RFX analyses model both the within and between run variability and as a result approximates the "true" activation(s) for a particular subject (when the runs are all within subject). Second, I computed functional localiser (FL) scans based on within subject fixed effects (FFX) analyses using different numbers of run (1-9) to assess how the amount of data collected influenced the consistency of the localization. To avoid order effects or selection biases, each analysis was conducted multiple times by randomly sampling the available data and reporting the mean consistency scores across the samples. In general, there are there are $\left(\frac{10}{m}\right)$ possible choices for m=[1…9]:

Equation 6-2 $$\left(\frac{\boldsymbol{N}}{\boldsymbol{m}}\right) = \left(\frac{\boldsymbol{N}!}{(\boldsymbol{N}-\boldsymbol{m})!\boldsymbol{m}!}\right)$$

Although the number of possible choices can be large, an upper limit in the number of possible choices without resampling is set by $m = 1$ and $m = 9$, i.e. $\left(\frac{10}{9}\right) = \left(\frac{10}{1}\right) = 10$. Consequently, FLs were computed based on 10 random samples of m runs, yielding $FL_{m,i}$ where *m* is the level (1…9) and *i* is the instantiated FL (1…10) at level *m*. Next, reliability of the FL was assessed by two means both of which were calculated per subject, per stimulus class, per hemisphere. First, the Euclidean distance between the peak voxel for $FL_{m,i}$ and the peak voxel identified by the RFX analysis was calculated. Second, the volume of activated cortex common between $FL_{m,i}$ and the RFX analysis was calculated (Equation 6-1). As before, whether a voxel is active or not is dependent on the thresholding. The

same five thresholds used in Experiment 1 were used for the FFX analyses ($Z > 1.64$, $Z > 2.3$, $Z > 3.09$, $Z > 4.0$ and $Z > 5.0$). The exact Z value for each subject for each ROI that would give a corrected $p < 0.05$ at the voxel level was calculated based on the number of resels in the subject- and ROI-specific mask. This provided a range of values from $Z = 2.60$ to 3.02. As $p < 0.001$ is often used heuristically as a threshold in *a priori* ROIs, I chose $Z > 3.09$ ($p < 0.001$) as a fixed threshold in all of the overlap calculations for the RFX analyses as this conservatively corrected for multiple comparisons.

The following pseudocode describes the process and would be applied to each participant in turn:

```
for m = 1…9 # Levels
     for i = 1…10 # Instantiation
         Randomly select m runs from the 10 collected
         Compute FLm,i using a FFX analysis on the m runs
         # Compute the peak comparisons
         Calculate peak coordinate for FLm,i per ROI
         Calculate distance to RFX peak voxel coordinates
         # Compute the overlap comparisons
         Calculate overlap between FLm,i and RFX
       Done
     # Aggregate the peak and overlap results from the 10 samples
     Calculate mean distance (± SEM) from peaks in FLm,i to RFX
     Calculate mean overlap (± SEM) between FLm,i and RFX
done
```

Regions-of-interest. As before, anatomical masks were drawn in standard space for each stimulus type. However, in the current experiment a mask was drawn for each hemisphere. The masks for words encompassed the posterior portion of the fusiform gyrus, occipito-temporal sulcus (OTS), and medial parts of the inferior temporal gyrus (ITG) (Price et al. 1994; Price et al. 1996; Herbster et al. 1997; Rumsey et al. 1997; Fiez and Petersen 1998; Fiez et al. 1999; Shaywitz et al. 2004). The standard space coordinates

were: X = (±)30 to (±)54, Y = –45 to –70 and *Z* = –30 to -4. The masks for objects encompassed lateral posterior fusiform gyrus, posterior OTS and lateral parts of posterior ITG (Malach et al. 1995; Grill-Spector et al. 1999). The standard space coordinates were X = (±)33 to (±)56, Y = –67 to –89 and *Z* = –20 to +4. Finally, the masks for faces encompassed a similar area to the 'words masks' but slightly more anterior (Kanwisher et al. 1997). The standard space coordinates were: X = (±)31 to (±)51, Y = -36 to -60 and *Z* = -31 to *Z* = -4. These generic masks were then customised for each subject by manually removing voxels of the mask that overlapped the subject's cerebellum, ventricles and non-neural voxels. In summary, there were six masks per participant, one for each hemisphere for objects, words and faces.

6.3.2 Results

Behaviour*: 1-back performance.* Behavioural data from one session for Subject 3 was lost due to a problem recording button press responses while in the scanner. The data from the remaining sessions were analysed using signal detection theory. The mean hit rate was 0.72 and the false alarm rate was 0.006 (Table 6-5), demonstrating that participants performed the one-back task adequately. D-prime (d') scores were calculated to measure sensitivity for detecting repeated items. These were then entered into 4 × 5 × 2 repeated measures ANOVA examining the effects of Category (words, objects, scrambled objects, faces), Session (1, 2, 3, 4, 5) and Run (first, second). A main effect of Category ($F(3,6) = 19.578$, $p = 0.02$) indicated that detecting repetitions of scrambled objects were most difficult, but there was no difference between the other stimuli types (all $t(37) < 1.24$, $p > 0.223$). There was no main effect of Session ($F(4,8) = 0.557$, $p = 0.700$) or Run ($F(1,2) = 5.710$, $p = 0.139$) and no interactions (all $F < 1.5$, $p > 0.130$), indicated that participants' performance did not significantly change across runs or sessions. Reaction times to correct detections (i.e. "hits") showed a similar pattern. Again, there was a main effect of Category ($F(3,6) = 7.589$, $p = 0.018$) but no main effect of Run ($F(1,2) = 4.872$,

$p = 0.158$) or Session ($F(4,8) = 0.160$, $p = 0.953$) and no interactions (all $F < 1.02$, $p > 0.462$). In other words, there was no behavioural evidence for task learning that might affect the activation patterns across runs or sessions.

Table 6-5: Behavioural data from the 1-back task in Experiment 2. The top section presents overall performance in terms of hit and false alarm rates. The second section presents sensitivity scores (d'-values) for detecting item repetitions while the third presents the reaction times for correctly detecting repeated items.

		Words	Objects	Scrambled	Faces
Hit Rate		0.794	0.800	0.553	0.818
False Alarms		0.005	0.000	0.018	0.001
D-Prime Scores (± SEM)					
Session 1	*Run 1*	3.84 (0.35)	4.23 (0.50)	2.68 (0.67)	4.12 (0.54)
	Run 2	4.38 (0.48)	3.88 (0.67	2.27 (0.76)	4.07 (0.58)
Session 2	*Run 1*	3.26 (0.52)	4.11 (0.53)	1.73 (0.67)	3.70 (0.50)
	Run 2	3.47 (0.49)	3.80 (0.42)	1.53 (0.57)	3.32 (0.59)
Session 3	*Run 1*	4.05 (0.53)	4.65 (0.38)	2.79 (0.29)	4.65 (0.38)
	Run 2	3.21 (0.16)	3.90 (0.00)	2.42 (0.18)	3.54 (0.20)
Session 4	*Run 1*	3.55 (0.61)	3.88 (0.67)	2.70 (0.47)	3.16 (0.39)
	Run 2	3.29 (0.72)	2.62 (0.51)	1.78 (0.60)	3.43 (0.78)
Session 5	*Run 1*	3.49 (0.58)	3.44 (0.57)	2.46 (0.52)	4.18 (0.28)
	Run 2	2.95 (0.17)	3.02 (0.29)	2.61 (0.61)	3.53 (0.59)
Median RTs (± SEM)					
Session 1	*Run 1*	483 (32.4)	537 (36.5)	625 (83.6)	507 (23.0)
	Run 2	521 (34.7)	556 (38.0)	447 (150.9)	545 (29.2)
Session 2	*Run 1*	528 (17.6)	525 (27.8)	675 (71.9)	484 (27.7)
	Run 2	538 (12.4)	490 (35.0)	646 (43.7)	492 (23.0)
Session 3	*Run 1*	507 (23.0)	498 (21.5)	560 (25.1)	518 (19.3)
	Run 2	564 (10.7)	528 (15.0)	559 (18.2)	523 (21.3)
Session 4	*Run 1*	519 (14.7)	510 (18.0)	551 (26.1)	478 (16.7)
	Run 2	584 (59.5)	530 (65.4)	461 (161.3)	557 (30.2)
Session 5	*Run 1*	491 (5.2)	552 (41.9)	584 (33.6)	468 (26.6)
	Run 2	523 (27.2)	487 (46.3)	571 (31.4)	497 (30.0)

Imaging results: *Random effects analyses.* All contrasts produced bilateral activation in all participants. Words relative to fixation produced a peak with a *Z*-score of at least 4.46 and 4.05 in left and right vOTC, respectively. Objects relative to scrambled objects strongly activated LOC, producing a peak of at least $Z = 3.93$ and $Z = 3.45$ in the left and right hemispheres, respectively (Table 6-6). Faces relative to objects activated bilateral FFA, producing a peak *Z*-score of at least 2.45 and 3.84 in left and right hemispheres, respectively. In Subjects 3 and 4, the left hemisphere activation did not reach significance ($Z < 3.09$). Consequently, it was not possible to conduct overlap analyses for faces in the left hemisphere for these subjects. There were, however, recognisable peaks in activation within the anatomical ROI that were used for computing peak reliability.

Table 6-6: Peak coordinates for RFX analysis for each subject for each contrast. Coordinates are in MNI152 space and the Z-score is for the peak voxel.

	Left Hemisphere				*Right Hemisphere*			
Subject	**x**	**y**	**z**	***Z*-score**	**x**	**y**	**z**	***Z*-score**
[Words > Fixation]								
1	-44	-64	-22	4.46	45	-62	-18	4.75
2	-46	-54	-17	5.04	48	-60	-23	4.58
3	-40	-56	-21	5.37	44	-59	-22	4.92
4	-42	-54	-13	4.76	49	-47	-30	4.05
[Objects > Scrambled]								
1	-45	-75	-18	5.42	44	-70	-18	5.00
2	-39	-82	-5	5.45	50	-72	-13	5.46
3	-44	-82	-9	5.59	42	-75	-17	5.74
4	-51	-75	-5	3.93	42	-76	-16	3.45
[Faces > Objects]								
1	-39	-48	-26	4.86	41	-45	-25	5.47
2	-40	-51	-16	4.04	44	-48	-25	4.65
3	-42	-59	-28	2.45	43	-46	-30	3.84
4	-46	-44	-28	3.08	45	-48	-25	4.15

Effect of amount of data on location of peak voxel. To facilitate understanding and ease comparison with existing studies the analysis refers the number of volumes included in the analyses rather than the number of runs, since the number of volumes in a run varies by study. There were 32 volumes per condition per run in the current study consequently the values along the *x*-axis of the plots are multiples of 32.

The first analysis examined how the number of volumes included in a FL affected the reliability of the peak voxel relative to the "true" (i.e. RFX) peak. Figure 6-5 plots the average distance between the peak voxel from a FL and the "true" peak in each of the three ROIs. Increasing the number of volumes collected resulted in a decrease in the Euclidean distance between the peaks. In other words, increasing the amount of data resulted in the peak voxel from the functional localiser getting closer to the "true" peak, however, the two did not converge and after approximately 192 volumes, additional data had little impact on the location of the FL peak. For both words and objects, the discrepancy between the FL and "true" peak remained > 4mm on average and did not differ between the left and right hemispheres. In contrast, for faces the localiser did a good job identifying the peak coordinate in the non-dominant (i.e. left) hemisphere, but was less good in the dominant hemisphere where the discrepancy was just over 8mm.

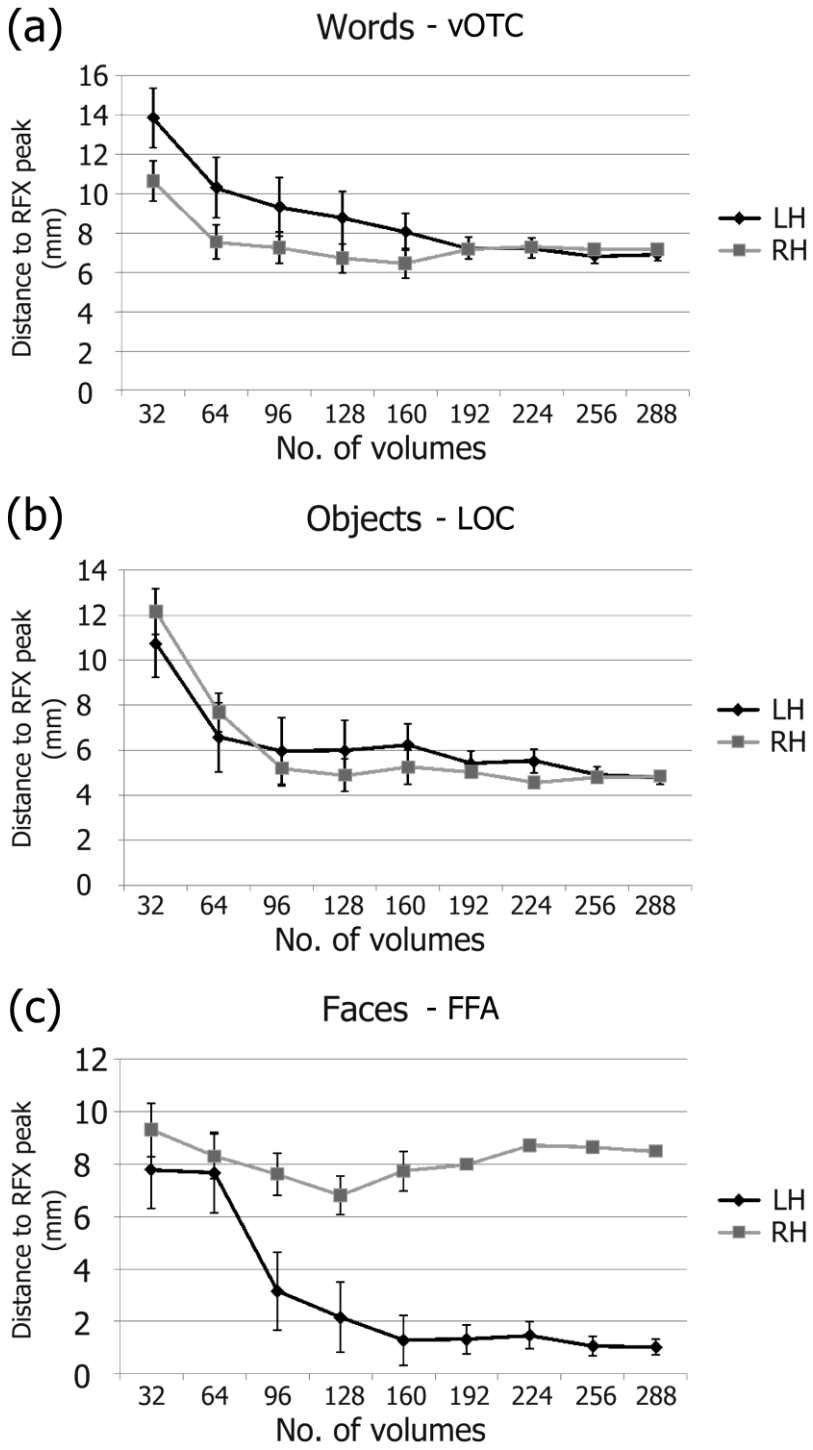


Figure 6-5: Graphs showing the distance (mm) from the RFX peak to the peaks identified by the FFX analyses of increasing numbers of volumes for (a) Words, (b) Objects and (c) Faces in left hemisphere (dark grey) and right hemisphere (light grey).

The group results, however, obscure individual differences that are particularly apparent for words and faces where FL successfully identified the "true" peak in the non-dominant more often than in the dominant hemisphere. For instance, the FL scans found the "true" peak in 3 out of 4 cases in the right (i.e. non-dominant) hemisphere as compared to 1 out of 4 in the left (i.e. dominant). Similarly, the face localisers converged on the left hemisphere peak in all four participants but did not find the "true" peak in the right hemisphere in any of them. In both cases, this advantage for the non-dominant hemisphere arose because it typically only contained a single peak whereas the dominant hemisphere typically had multiple peaks within the anatomical ROI, namely the most significant RFX peak and [1-3] additional peaks with slightly lower *Z*-scores (Figure 6-6). Because the fixed-effects analyses used to compute functional localisers do not take inter-run variance into account, it is easy for the analysis to find a local maximum (i.e. peak) rather than the global maximum (Friston et al. 1999), resulting in a sub-optimal localization.

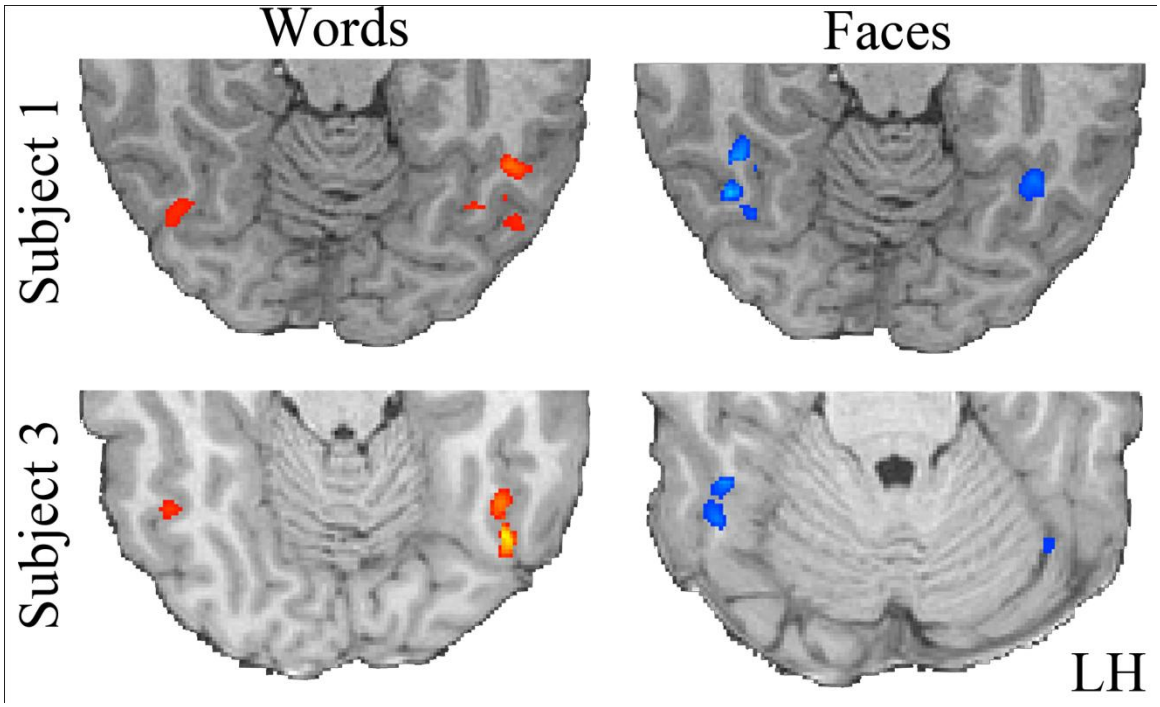


Figure 6-6: Areas of cortex suggested to be sensitive to a stimulus type often have multiple peaks. Thus for words (left) and faces (right) the dominant hemispheres typically have more peaks than the non-dominant hemisphere.

As the amount of data included in the analysis increases, the FL peak gets closer to the main "true" peak on average, but individual analyses are flipping between peaks in the area and this is reflected in the large error bars. With even more data, however, the FL analyses tend to identify a single peak, but there is no guarantee that it will be the global maximum. Indeed, as Figure 6-5 illustrates, in the majority of cases the functional localiser found a local maximum instead. The reason the FL was more reliable in the right hemisphere for words and in the left hemisphere for faces was because non-dominant hemispheres typically have fewer local maxima to get stuck in. Consequently, the FL has a greater chance of identifying the "true" peak. This also explains why the FL did a poor job identifying the "true" peak for objects (in either hemisphere) as objects typically engage LOC bilaterally with multiple peaks in both hemispheres (reflecting this lack of hemispheric asymmetry).

Interestingly, this analysis may be informative with regard to the TMS data reported in previous chapters. All four subjects also participated in the first experiment in Chapter 3 and their vOTC stimulation site was identified based on a short FL scan. For Subjects 1 & 2, the FL used for the TMS experiment identified a peak that was greater than 1cm from the RFX peak. For these subjects, TMS did not disrupt word reading. In contrast, for Subjects 3 & 4, the FL for used for the TMS experiment identified a peak less than 1cm from the RFX peak and for both subjects, TMS disrupted word reading. In other words, the short FL scan used to target TMS may identify a peak voxel whose distance to the RFX peak is greater than the spatial resolution of TMS.

In summary, although including increasing the amount of data included in a FL decreases the distance from the FL to the "true" peak, no amount of data ensured that the two would converge. This problem is compounded in cases where there are multiple peaks within the anatomical ROI.

Effect of amount of data on spatial overlap. The second analysis investigated whether increasing amounts of data improves the reliability of the FL when measured in terms of their spatial overlap. The group results are shown in Figure 6-7 for the different stimulus types in each hemisphere. Within each panel, the five coloured lines represent how the spatial overlap was affected by thresholding at the different levels (i.e. Z = 1.64, 2.33, 3.09, 4 and 5). In general, increasing the amount of data included in the localiser improved consistency up to a point, after which the consistency began to slowly decline. This was true of all three ROIs in both hemispheres, independent of the statistical threshold used to define "active" voxels. For instance, consider the red lines (corresponding to a $Z > 2.33$ threshold) in Figure 6-7. In each of the panel, the red line reaches its maximum consistency score between 96 and 160 voxels (3-6 runs in the current experiment) and then gradually trails off as even more data are included in the functional localiser. This same trajectory can be clearly seen for all three of the lowest statistical thresholds and

appears to be presented for the purple ($Z > 4.0$) and light blue ($Z > 5.0$) curves as well, although these are clearly shifted such that they only reach their maxima at approximately 256-288 volumes (i.e. 8-9 runs). These diminishing returns are a consequence of using fixed effects analyses to compute the functional localiser. Increasing the amount of data without taking into account the inter-run variance, artificially inflates the resulting statistical maps resulting in more and more voxels passing threshold. As a result, these voxels inflate the total number of voxels included in the denominator of Equation 6-1 without necessarily affecting the numerator (i.e. the voxels common to both analyses), thus reducing the overall consistency score. Indeed, if all the active voxels in the RFX analysis are already present in the FL analysis, then adding additional data (and thus increasing the number of active voxels) can only reduce the consistency ratio. This is illustrated for vOTC in a single subject in Figure 6-8. Here, the yellow lines indicate the border of "truly" active voxels identified in the RFX analysis while blue voxels are "active" voxels from the functional localiser scan. Two different amounts of data were used: either 96 or 288 volumes (i.e. 3 or 9 runs) and "active" voxels were determined with either a $Z > 2.33$ or $Z > 5.0$ threshold. The figure illustrates two points. First, that as additional data are included in the FL analysis, the set of "active" voxels in the anatomical ROI exceeds the "truly" activated voxels, reducing consistency. Second, the best consistency in terms of maximizing overlap occurs either for the combination of relatively small amounts of data with a lenient statistical threshold (i.e. 96 volumes, $Z > 2.3$) or with the largest amounts of data and most stringent statistical threshold (i.e. 288 volumes, $Z > 5.0$). Indeed, this point is clear from Figure 6-7 where the consistency ratio is typically reached after 96 volumes of data for lower statistical thresholds. When using a high threshold such as $Z = 4.0$ (purple line) and 5.0 (light blue line), increasing the number of volumes does improve overlap *but* reaches a maximum only marginally better than the maximum overlap achieved with low thresholding.

This general pattern applies to all three stimulus types in both hemispheres, though the dominant hemisphere for words (LH) shows considerably better overlap than the non-dominant hemispheres. In contrast, there are no apparent hemispheric differences in the FL reliability for objects, once again reflecting the lack of hemispheric asymmetry in object processing.

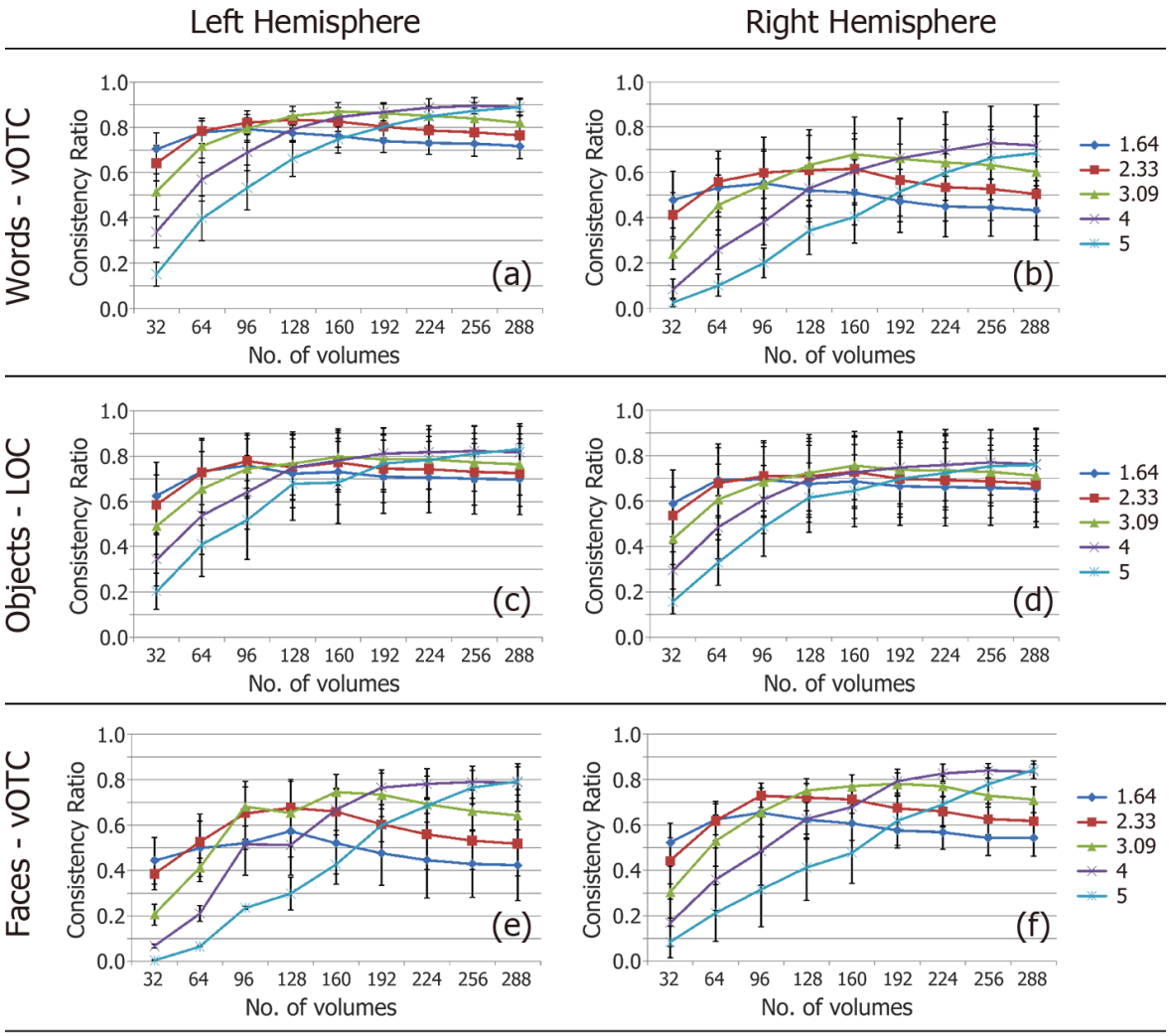


Figure 6-7: Graphs showing the degree of overlap for the words (a and b), objects (c and d) and faces (e and f) for the two hemispheres. Note that as the number of volumes included in the FFX analysis increases, the consistency ratio increases reaching a maximum when a large number of volumes are included and threshold stringently. However, including a much lower number of volumes and using a considerably less stringent threshold has approximately the same outcome. Note that as there was no significant LH RFX activation for [Faces > Objects] for Subjects 3 and 4 they are not included in the relevant graph.

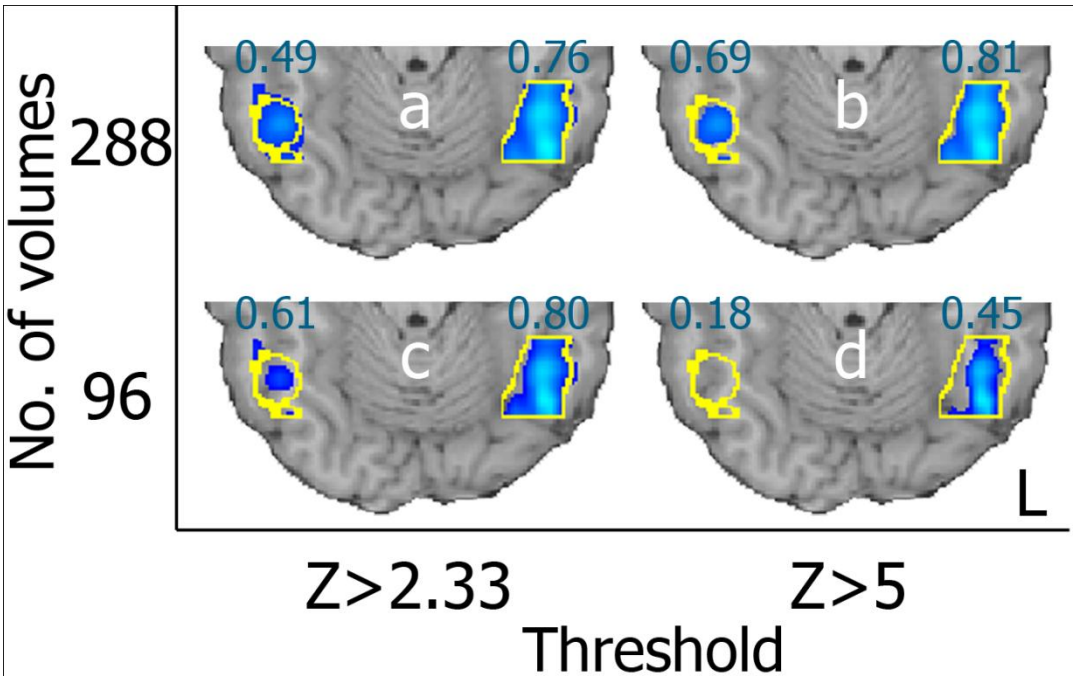


Figure 6-8: The effect of volumes and thresholds on overlap for words for Subject 3. The yellow outline represents the area identified by the "gold-standard" RFX analysis while the blue corresponds to FFX analyses for 288 volumes (top) thresholded at $Z > 2.33$ (a) and $Z > 5$ (b) and 96 volumes (bottom) thresholded at $Z > 2.33$ (c) and $Z > 5$. Note that particularly for the left hemisphere stringent thresholding of large numbers of volumes (b) gives a similar result to a more tolerant thresholding of a much smaller number of volumes (c). Also note that large numbers of volumes with a low threshold results in extraneous voxels being included in the fROI (a), while stringent thresholding of a low number volumes erroneous excludes voxels (d). Consistency ratios are shown in blue.

6.3.3 Discussion

Motivated by the results of Experiment 1 (and Kung and colleagues 2007) which showed poor consistency of functional localisers, the aim of the current experiment was to evaluate whether this consistency results from an inadequate number of volumes being collected. By scanning participants multiple times I was able to compare the peak voxel location and overlap between the "true" results (obtained via a subject-specific "gold-standard" RFX analysis) and those of typical standard functional localiser scans based on different quantities of acquired data.

The first analysis demonstrated that increasing the amount of data included in a FL decreases the distance from the FL peak voxel to the "true" peak, although the two rarely converged. Instead, because functional localisers rely on fixed effect analyses, they are liable to get trapped in local maxima when an anatomical region exhibits multiple peaks in response to a particular stimulus category. Additional data leads to a monotonic increase in the voxel-based statistical results, maintaining the local maxima. Indeed, in the current data, once a stable maxima was found, increasing the amount of data never produced a change in the peak voxel (Figure 6-5). In other words, the current findings, together with those of Experiment 1 in this chapter and those reported by Berman et al. (2010), make it clear that defining a fROI as a sphere of fixed radius centred on the peak voxel of a FL analysis is suboptimal, potentially compromising the analysis of the main experiment. On the other hand, research groups using peak voxels to identify the functional ROI may manually intervene to select a peak based on their experience and anatomical expertise. This need not always be the most significant peak in the area. Although this approach would be susceptible to external sources of bias and may suffer from poor reproducibility, even within a single lab, it offers an alternative to the problem of local maxima in fixed-effect analyses.

The second assessment of consistency demonstrated how different amounts of data in the FL localiser analysis affected the reliability (i.e. the spatial overlap) of the fROI and how this relationship was modulated by the choice of threshold (from $p < 0.05$ to $p < 10^{-6}$). Using a relatively small number of volumes in conjunction with a low threshold produced fROIs of approximately the same reliability as using a more stringent threshold with large quantities of data and this was true for all three stimulus classes and for fROIs in both hemispheres. Perhaps surprisingly, the use of a high threshold with relatively small amounts of data resulted in very poor consistency because the use of a high threshold did not ensure that only "true" activations remained. Instead it simply biased the results

towards one particular sub-peak within a cluster and this was often different from the "true" peak.

These findings confirm that functional localiser scans that are independent from the main experimental data acquisition suffice to identify an fROI despite considerable inter-scan variability in activated voxels but place an upper limit on the accuracy of this identification. The most cost-efficient method involves collecting a relatively small amount of data (~10mins) and using a lenient statistical threshold to identify all voxels in a given region that are sensitive to the process-of-interest. At best, however, there appears to be roughly 80% overlap with those in the main task, indicating a fairly substantial amount of "noise" in the fROI analyses.

6.4 General Discussion

The chapter investigated the reliability and consistency of functional localiser scans. These scans are commonly used to isolate a functionally defined ROI based on its response properties. The first experiment found poor consistency between two essentially identical scans, in terms of both the location of the peak voxel and the spatial overlap of activated voxels, particularly when higher statistical thresholding was used. The second experiment tested the hypothesis that this poor consistency results from the small amount of data typically included in a functional localiser. As expected, increasing the amount of data improved consistency when the fROI was based on the activated voxels. However, this relationship between consistency and amount of data is strongly affected by the statistical threshold used. In contrast, no amount of data made the peak voxel of the localiser scan reliable, strongly suggesting this method of defining an fROI is suboptimal. These findings highlight the important of the (implicit) consistency assumption when interpreting results based on independent functional localiser scans.

These results illustrate the importance of careful experimental design for functional localisers as well as the value of empirically checking their effectiveness. While one may intuitively feel that higher statistical thresholds will result in more reliable and trustworthy fROIs, this is only true if impractically large amounts of data are collected. Moreover, the reliability achieved in this manner is only marginally greater than using a lenient threshold on much smaller amounts of data. In addition to this, reducing sources of variability (Friston and Henson 2006), and optimising both stimuli and tasks (Fox et al. 2008) will all improve the consistency of the results.

Furthermore, given the increasing use and importance of functional localiser scans, their exact details should be reported clearly and in detail, rather than as an afterthought, thus assisting readers in evaluating the robustness of the findings. At a minimum, these could include clear information about the amount of data collected as well as the details of how the fROI was defined. For instance, in many cases it is unclear what anatomical criteria (if any) are used to limit the extent of the fROI to the region under investigation. Functional localisers currently play an important role in cognitive neuroscience, and no doubt will become even more important in the future. Consequently, it will be increasingly important to optimise the practice to provide consistent localisation within individuals in order to maximise sensitivity and avoid potential sources of bias.

Finally, our results also have important implications for TMS studies. There are several options when choosing a method for targeting stimulation, including using fMRI-based neuro-navigation, using standard space coordinates from published imaging studies, or using heuristic methods such as the 10-20 system. Recent empirical studies have shown that although all three methods work, the latter two are sub-optimal, requiring higher stimulation intensities and/or larger numbers of subjects (Sparing et al. 2008; Sack et al. 2009). This is almost certainly due to the considerable inter-subject variability in the location of peak responses (current results; Kanwisher et al. 1997; Wright et al. 2008)

rendering stimulation based on group coordinates less efficient. This problem is further compounded by a heuristic approach to targeting because of the inherent variability between the measurement system (e.g. the 10-20 system) and the underlying anatomy (Steinmetz et al. 1989). Clearly, an optimal targeting method will take into account inter-subject variability either through fMRI-based neuro-navigated TMS (Andoh et al. 2006; Duncan et al. 2010) or by localising the stimulation directly with TMS (Devlin et al. 2003a; Gough et al. 2005; Ellison et al. 2007; Taylor et al. 2007; Pattamadilok et al. 2010). While neuro-navigation based on fMRI is often thought to be the superior option, our current results suggest that may not necessarily be an entirely reliable method due to the spatial variability of the peak voxel inherent in short, fixed localiser scans. In other words, using fMRI to localise a TMS target may still result in an inappropriate area being stimulated, a problem exacerbated by the spatial distortions in EPI images due to magnetic field inhomogeneties and draining veins (Jezzard and Balaban 1995; Terao et al. 1998; Duong et al. 2001; Turner 2002; Devlin et al. 2003a). This extent of this problem becomes exacerbated if the distance between the localised voxel and the genuine target is greater than the spatial resolution of TMS. Instead, a TMS-based functional localiser probably represents the optimal method for targeting stimulation as it avoids all of these sources of error and provides a direct measure of the effect of stimulation across a range of target sites. However, it should be noted that in some circumstances, an independent TMS localiser maybe undesirable, for example, if there is a need to limit the amount of stimulation one area receives. For instance, TMS of certain sites, including the ventral sites targeted in this thesis, is associated with muscle stimulation which over long periods of time can become uncomfortable.

7 General Discussion

Reading is a complex activity involving the delicate orchestration of visual, phonological, and semantic properties. Ventral occipito-temporal cortex (vOTC) is an area that encompasses the posterior aspect of the fusiform gyrus along with the adjacent occipito-temporal sulcus. This area of the ventral visual stream, lying between posterior visual areas such as V4 and more anterior ventral temporal areas, shows robust activity in neuroimaging studies of visual word recognition (Price et al. 1996; Herbster et al. 1997; Rumsey et al. 1997; Fiez and Petersen 1998; Cohen et al. 2000; Sakurai et al. 2000; Cohen et al. 2002; Kuo et al. 2003; Kronbichler et al. 2004) and lesions to the area can cause impairments which appear to preferentially affect reading (Dejerine 1892; Damasio and Damasio 1983; Binder and Mohr 1992; Beversdorf et al. 1997; Leff et al. 2001; Gaillard et al. 2006). It is not surprising, then, that modern neurological models of reading agree that vOTC plays an important role. However, what contributions the area actually makes is still the matter of considerable debate (McCandliss et al. 2003; Price and Devlin 2003; Cohen and Dehaene 2004; Kronbichler et al. 2004; Price and Devlin 2004; Dehaene et al. 2005).

The uncertainty surrounding the function of vOTC arises in part due to the difficulty separating its contributions from other areas of the reading network, highlighting the need for a method to temporarily and non-invasively perturb the information processing in this area to investigate the causal relations between activation and reading. TMS offers such a tool (Barker and Jalinous 1985; Pascual-Leone et al. 1999; Sack 2006), but it was commonly thought that the location of vOTC on the ventral surface of the brain would make stimulation impossible (for example, Simos et al. 2008).

The experiments in this thesis used transcranial magnetic stimulation (TMS) to disrupt vOTC in normal, healthy participants while they performed tasks that engaged visual word recognition. These experiments comprise the first reported attempts to disrupt vOTC using TMS and demonstrated that the effect of ventral occipito-temporal stimulation is

reliable and robust – disrupting word recognition in six independent experiments For instance, I demonstrated:

- Stimulation of left vOTC impaired responses during a lexical decision task. Importantly, this effect was stimulus-specific as TMS did not affect pseudowords or high frequency words.

- TMS of vertex did not impair responses, demonstrating the effect of vOTC stimulation was also site-specific. Furthermore, TMS of a nearby lateral occipito-temporal site, LOC, also did not slow responses, demonstrating that the effect of vOTC stimulation is not a general effect of ventral TMS.

- Stimulation of left vOTC during a semantic decision task also slowed responses. However, in contrast to the effect during the lexical decision, TMS affected both low *and* high frequency words, demonstrating that vOTC processing is task dependent.

- Neurochronometric TMS revealed that the temporal profile of left vOTC and suggested that processing in vOTC is both interactive and cascaded and that the area is active considerably earlier than indicated by ERP studies.

- The temporal profile of vOTC was consistent for words and objects but showed a hemispheric asymmetry, with activity in left vOTC preceding right.

7.1 Implications

7.1.1 Theories of ventral occipito-temporal function

There are three hypotheses regarding the contribution left vOTC makes to reading. The first two propose that the area contains neurons that are specific to reading and contain abstract orthographic information which is used to process the wave of feedforward

activity arriving from lower visual areas. The prelexical visual word form hypothesis suggests that these neurons are attuned to letter bigrams (McCandliss et al. 2003; Cohen and Dehaene 2004; Dehaene et al. 2005) while the lexical visual word form hypothesis suggests that the neurons are attuned to whole words (Kronbichler et al. 2004). In contrast the third hypothesis proposes that ventral occipito-temporal neurons perform the same function on words and other non-lexical stimuli. This theory suggests that left vOTC interacts with other regions during reading, acting as an interface associating feedforward visual form information critical for orthographic processing with higher order properties of the stimuli by way of feedback connections (Nakamura et al. 2002; Hillis et al. 2005; Price and Friston 2005; Devlin et al. 2006; Xue et al. 2006; Cai et al. 2010).

The prelexical word form account is plainly incompatible with much of the data presented in this thesis. The prelexical nature of the abstract codes putatively stored in vOTC means that these neurons must be blind to stimulus properties that emerge at the lexical level, such as lexicality and frequency. However, the experiments in Chapters 3 and 4 demonstrate that this is not the case. Thus, the prelexical account fails not only to explain the TMS data in this thesis but also the differential effect of frequency reported in neuroimaging studies (Chee et al. 2003b; Kronbichler et al. 2004) and in patients with damage to vOTC (Behrmann et al. 1998b; Johnson and Rayner 2007; Shan et al. 2010; Tsapkini and Rapp 2010). In contrast, the lexical word form hypothesis is compatible with a TMS effect on words but not pseudowords since only real words should be represented in the area. However, although the lexical account predicts a graded effect of word frequency, it also predicts that *both* low and high frequency words should be affect by vOTC stimulation since the area stores abstract representations of all words. However, there was no evidence for this. Indeed, although the effect of stimulation was dependent on word frequency, there was no effect of TMS on high frequency words in two independent lexical decision experiments, consistent with reports of vOTC lesions that

selectively impair low frequency words (Shan et al. 2010; Tsapkini and Rapp 2010). Furthermore, although responses to high frequency words and low frequency words were slowed during semantic decisions, there was still no graded effect of frequency.

Moreover, the task-dependency and temporal profile of left vOTC are inconsistent with either the prelexical or lexical word form hypotheses, since in both these accounts vOTC processing is stimulus-driven with no feedback from higher areas. Clearly, these visual word form accounts require reformulation in order to explain the data presented in this thesis. In fact, the only modification that would suffice would be incorporating feedback connections. Nevertheless, an interactive visual word form hypothesis (either prelexical or lexical) would still require distinct but spatially overlapping subpopulations of word- and object- specific neurons to be consistent with the neuroimaging and neuropsychological literature and of course the consistent effect of TMS on words in objects demonstrated in this thesis. Definitive proof of word specific neurons and object specific neurons would require intracellular recordings (Lenz et al. 2002; Mukamel et al. 2010), but the opportunities for this are rare in patients and non-existent in neurologically normal people. There is currently, therefore, no evidence for such neuronal specialisation (Wright et al. 2008; Kherif et al. 2010).

A more parsimonious account of vOTC function is that the neuronal population is not segregated, but rather a single population of neurons that performs essentially the same function: representing complex visual form information, which is subsequently linked with non-visual properties of the stimulus. The data presented in this thesis allows the further refinement of the interface theory. First, the relative contribution of the area depends on the demands of the stimuli and task. Second, this integration is, in effect, the same for both left and right vOTC.

Stimuli and tasks that accentuate the importance of the non-visual properties of visual stimuli emphasise the role of vOTC. For example, the contribution of left vOTC during lexical decisions depends on the frequency of the word, as correct responses can be generated for high frequency words and pseudowords without resort to non-visual properties – diminishing the causal relevance of processing in left vOTC. In contrast, correct responses to low frequency words requires non-visual properties be accessed and integrated with the visual form, increasing the importance of left vOTC processing. Thus, the interface hypothesis is consistent with the differential effect of frequency reported in neuroimaging, where rarer words produce more activation, and neuropsychological literature, where low frequency words are more susceptible to impairment. In fact, while lesions to left vOTC can affect low frequency words during a lexical decision, impairments in word reading are independent of word frequency (Tsapkini and Rapp 2010), reflecting the necessity of left vOTC to integrate visual form with phonology. In addition, the effect of lexicality on the area also appears to depend on task. Like high frequency words, visual form is of particular importance when performing a lexical decision on pseudowords, diminishing the contribution of vOTC, consistent with the lack of any disruptive effect of TMS and the greater activation for words observed in neuroimaging studies (Fiebach et al. 2002; Bellgowan et al. 2003; Binder et al. 2003; Binder et al. 2005b). In contrast, tasks that stress the phonological properties of the stimuli tend to elicit greater activation for pseudowords relative to words (Fiez et al. 1999; Hagoort et al. 1999; Xu et al. 2001; Mechelli et al. 2003; Binder et al. 2005a; Bruno et al. 2008; Lee et al. 2010).

Counter to most neurological models of reading, the data presented in this thesis support a central role for right vOTC. That TMS disrupted both words and objects during stimulation of either hemisphere suggests that the function of left and right hemisphere vOTC may essentially be the same. This, however, seems to be at odds with the asymmetry in activation strength reported in the neuroimaging literature and the

asymmetry in the effect of vOTC lesions reported in the neuropsychological literature. However, a consequence of the left hemisphere dominance for language may be that during tasks that emphasise linguistic properties of stimuli (such as reading), the contribution of left vOTC is relatively more important since it is interacting with brain areas associated with linguistic knowledge (Lambon Ralph et al. 2001; Cai et al. 2010).

7.1.2 Cognitive models of reading

The data in this thesis are informative with regard to cognitive models of reading and their neurological validity. Although there are many differences between the two main classes of models (dual-route and connectionist), there are a number of similarities. For example, orthographic processing is interactive and cascaded, consistent with the data reported in this thesis. Furthermore, as can be seen in Figure 7-1, both types of models contain orthographic-specific components. In contrast, however, the experiments in this thesis together with neuroimaging (Wright et al. 2008; Kherif et al. 2010) and neuropsychological (Behrmann et al. 1998a; Starrfelt et al. 2009) data suggest that this assumption may be incorrect. With regard to the connectionist model, the orthographic specific aspect could be replaced by processing that was not specific to lexical stimuli; in other words, the model could perform the same operations on visual words and objects, consistent with the neurological data. In contrast, modifying the dual-route models may prove difficult given the presence of an “orthographic input lexicon.”

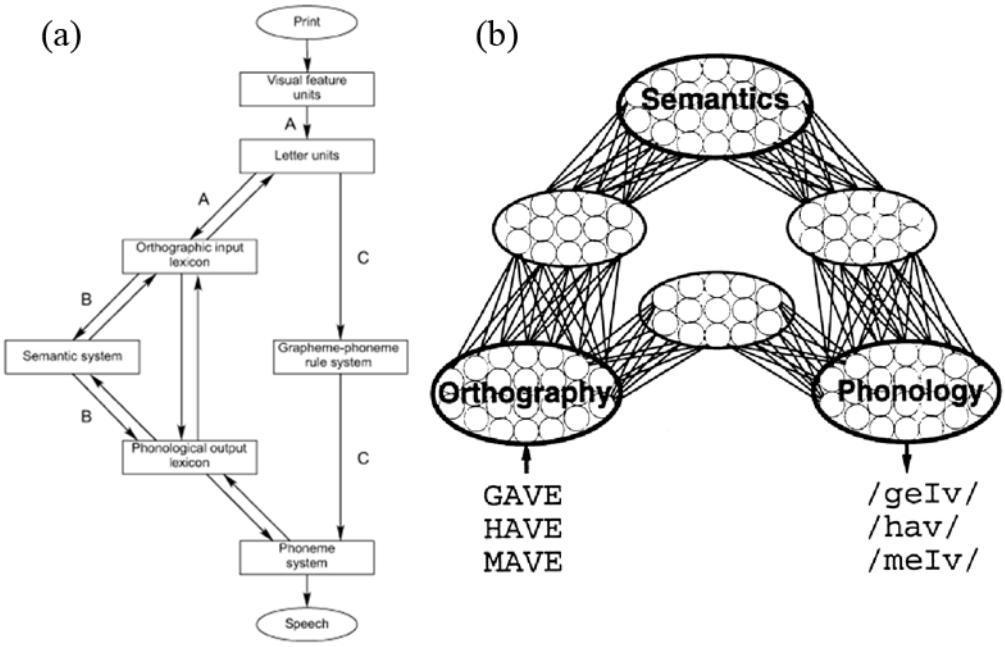


Figure 7-1: Examples of cognitive models of reading: (a) DRC model. Note that there are distinct levels of orthographic representation, with serial and parallel connections (Coltheart et al. 2001), figure adapted from (Sakurai et al. 2006) Permission to reproduce this figure has been granted by Elsevier (b) a mixture of feed-forward and feed-back connections. Distributed-connectionist model (Seidenberg and McClelland 1989). Large arrows depict the inputs and outputs of the system. Note that both types of model contain reading-specific units. Permission to reproduce this figure has been granted by Taylor & Francis.

7.1.3 Transcranial Magnetic Stimulation

7.1.3.1 Optimising target localisation

Although localising the target in TMS experiments can be done in a number of ways, only fMRI and TMS localisation take account of inter-subject variability. The importance of functionally localising the target site (with either fMRI or TMS) in each participant is highlighted in Chapter 6 which, consistent with previous research (Kanwisher et al. 1997; Wright et al. 2008) demonstrated considerable inter-subject variability in the location of the peak of activity. In fact, for a number of participants, the distance between the group peak and the subject-level peak may be greater than the spatial resolution of TMS. Choosing a target site based on group coordinates or using a heuristic approach (such as the 10-20 system) may therefore result in an inappropriate site being stimulated,

consequently increasing the number of subjects required in the study and/or the stimulation intensity (Sparing et al. 2008; Sack et al. 2009).

The choice of whether to use fMRI or TMS to functionally localise the target site will depend on the particulars of the experiment. Although we used fMRI to functional localise the area of vOTC to stimulate in each participant, this was not strictly necessary. Pilot work indicated that it was possible to functionally localise the optimal stimulation site using short TMS experiments before proceeding to the main experiment as previously done for other stimulation sites (e.g. Devlin et al. 2003a; Gough et al. 2005; Ellison et al. 2007; Taylor et al. 2007; Pattamadilok et al. 2010). In practice, however, some participants found the extra stimulation uncomfortable, making fMRI localisation the superior choice in this case. However, for other sites where there is less discomfort, TMS localisers may actually be superior to using fMRI. Localising the target site with TMS ensures that an appropriate site is stimulated in the main experiment. In contrast, the results of Chapter 6 illustrate that localising the target with a short fMRI run may result in an inappropriate area being stimulated, since the peak voxel in the fMRI localiser is unlikely to correspond to the "true" peak. This problem is compounded by the presence of multiple peaks in areas of cortex sensitive to a particular stimulus, since the experimenter will have to use their expertise to select which peak to target. However, the spatial resolution of TMS is such that this will only be problematic when there is a substantial discrepancy between the target site and the true peak.

7.1.3.2 Neurochronometric studies

The experiments in Chapter 5 highlight the importance of using neurochronometric TMS to independently evaluate ERP timings. However, certain precautions must be taken when designing these experiments in order that the results can be easily interpreted. In this regard, this thesis features two innovative experimental design features: the staircase ordering of time windows and random ITI.

Neurochronometric studies have typically randomly intermixed the time windows of TMS (for example, Corthout et al. 1999b; Devlin et al. 2003a; Camprodon et al. 2009; Prime et al. 2010). A consequence of this, however, is that trials with TMS in an early time window may be followed by trials with TMS in a late time window which makes it more likely that participants become aware there are different TMS onset asynchronies. In addition, the subject may consciously or unconsciously wait for stimulation before responding, artificially slowing the RTs in the late conditions. The staircase design used in Chapter 5, i.e. grouping trials in blocks which are ordered in either an ascending or descending staircase effectively removed this problem since the delay between TMS onset asynchrony in any two consecutive trials is minimised. Moreover, participants reported that they were not aware of any difference in the timing of TMS over the experiment.

The use of a fixed ITI in neurochronometric TMS experiments can result in participants knowing (consciously or unconsciously) when the next trial will begin. Consequently, if is impossible to determine whether TMS related changes in performance result from disruption of bottom-up activity or top-down expectation effects. In contrast, when the ITI is randomised it is not possible to know when the onset of the next trial is, minimising expectation.

7.1.3.3 Spatial resolution of TMS

The clear dissociation between stimulation of vOTC and LOC, two occipito-temporal regions separated by approximately 2cm provides empirical evidence regarding the spatial resolution of TMS. This is consistent with the growing literature suggesting that the functional resolution of the technique is sufficient to distinguish contributions from relatively focal patches of neocortex, separated by as little as 1-2cm (Brasil-Neto et al. 1992; Schluter et al. 1999; Gough et al. 2005; Pitcher et al. 2009).

7.1.4 fMRI

The data presented in this thesis have two implications for the use of fMRI. First, the data illustrate the importance of triangulating information from different methodologies. Despite the many advantages of fMRI, it is unable to determine the causal influence of brain activity on behaviour and consequently incapable of differentiating essential from other co-activated areas, complicating the interpretation of fMRI data. This shortcoming is highlighted by the lack of any TMS effect during vOTC stimulation for pseudowords and high frequency words in lexical decisions and during LOC stimulation for words or pseudowords, despite the fMRI activity seen for each of these situations. In other words, care must be taken when drawing conclusions based solely on data from one methodology.

Second, the data presented in Chapter 6 provide much needed guidelines regarding the optimisation of functional localiser scans. A critical assumption underlying the use these increasingly used functional localiser scans is that the voxels identified as the functional region-of-interest are reliable. These scans can be optimised by collecting approximately 10mins of data and, somewhat counter-intuitively, using a lenient statistical threshold. In contrast, previous studies that have used a functional localiser scan frequently collect approximately 10mins of data but use a conservative threshold (for example, Jiang et al. 2007; Axelrod and Yovel 2010). An additional issue with the use of functional localiser scans is the generally poor standard of reporting the details of the scan. At a minimum, researchers could include clear information about the amount of data collected as well as the details of how the functional region-of-interest was defined. Without these details, a satisfactory interpretation of the results of the main experiment remains difficult.

7.2 Future directions

Representations. Although this thesis presents data that strongly suggests that vOTC does not contain bigram or word detectors, it remains unclear how information is represented in vOTC. One possibility is that the representations may be something similar to spectral receptive fields (SRF) that characterise the responses of neurons in macaque V4 (David et al. 2006). SRFs characterise neuronal tuning in terms of the orientation and spatial frequency power spectrum and are independent of spatial phase. SRFs can be used for any visual stimuli, since all visual stimuli possess such a power spectrum. In addition, independence from spatial phase means that SRFs can explain neuronal tuning for neurons that show position-invariant responses. Clearly, these properties must also be true of any hypothesised neuronal tuning in vOTC, as the area activates to any visual stimulus, and is invariant of the stimulus position on the retina. However, in higher-order areas the cross species correspondence is relatively poor. The macaque homologue for human vOTC may be posterior inferior temporal cortex but could conceivably be superior temporal sulcus (Van Essen 2003). It is unlikely, however, to be V4 which may correspond to more posterior aspects of occipito-temporal cortex. Clearly, further work is required to establish what relationship, if any SRFs have to human vOTC neuronal tuning and how information is represented in the area.

In the absence of invasive neuronal recordings, state-dependent TMS could potentially provide valuable insights into the nature of representations in vOTC. By manipulating the activation state, either through adaptation or priming, prior to stimulation, spatially overlapping but functionally distinct neuronal subpopulations can be differentiated. This has previously been used to selectively stimulate sub-populations of MT neurons with different directional tuning. For example, the motion sensitive area MT contains neurons that have preferences for particular directions of motion. These subpopulations of neurons cannot be easily distinguished using TMS. However, Cattaneo and Silvanto (2008)

manipulated the activation state in the area by asking participants to view coherently moving dots for one minute thus decreasing activity levels in neurons with a preference for motion in this particular direction. Next participants received a single pulse of TMS over MT immediately before an 80msec presentation of more coherently moving dots. Performance for dots moving in the same direction as the adapting stimulus was improved, while the performance for dots moving in the opposite direction was impaired (relative to no TMS). In other words, by manipulating the activation state prior to stimulation, the authors were able to selectively stimulate a subpopulation of neurons within an area. Using this approach, it may be possible to investigate whether SRFs, or something akin to them, characterise neuronal response properties within vOTC since visually dissimilar stimuli that share a SRF may be processed by the same neuronal subpopulation.

Interactions. In everyday life, words are rarely, if ever, confused for objects and vice versa. There is no evidence for super-specialised word- and object- specific neurons in vOTC, suggesting that the difference in neural representation must lie elsewhere. TMS delivered to other cortical areas involved in reading and object recognition, could determine the relative contributions of these areas to the two stimulus types. For example, if the phonological properties are more important to word processing compared to the processing of objects (Price et al. 2006), then stimulation of areas implicated in phonological processing, such as pars opercularis and supramarginal gyrus, may be more disruptive for words. Furthermore, if TMS was employed in its neurochronometric mode, the temporal profiles for these different areas could be mapped. This may reveal differences between words and objects while also providing valuable constraints on models of word and object recognition.

An alternative approach would be to investigate differences across the whole network using Dynamic Causal Modelling (DCM). Though the functional connectivity of vOTC for words and objects would be similar, the connection strengths between the different

regions may differ, reflecting the fact that different properties of each stimulus type may be more or less important.

TMS and DCM could also investigate the origin of the hemispheric asymmetry in timing reported in this thesis. One possibility would be to use neurochronometric TMS to compare hemispheric asymmetries in subjects who are left dominant for language versus subjects who are right hemisphere dominant. If the hemispheric asymmetry for timing reported in this thesis reflects the greater contribution of left hemisphere knowledge, it should reverse in subjects who are right dominant. Alternatively, delivering neurochronometric TMS while participants perform a task that emphasises right hemispheric knowledge, such as a task involving words of high emotional valence, may result in the timing asymmetry being diminished or reversed, such as reading of highly emotional words (Nagae 1998; Landis 2006).

DCM could also investigate the hemispheric asymmetry reported in this thesis, where the effect of left vOTC was earlier than its right homologue. If this reflects the greater contribution of left hemisphere knowledge for linguistic tasks then although the functional connectivity would be similar across hemispheres, the connection strengths for left vOTC would be stronger.

Methodological. The neurochronometric studies in this thesis highlighted a temporal lag between estimates of timings suggested by ERP. If this varies across different cortical locations or even across tasks within the same location then the interpretation of ERP timing data becomes complicated, even for estimating relative timing. Although, the data from this thesis in conjunction with previously published studies support a variable lag, a convincing demonstration would require a within subjects design, obtaining temporal profiles from both ERP and TMS.

References

Aguirre GK, Zarahn E, D'Esposito M (1998) The variability of human, BOLD hemodynamic responses. NeuroImage 8: 360-369

Allen EA, Pasley BN, Duong T, Freeman RD (2007) Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. Science 317: 1918-1921

Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell A, Eberle L (1989) Suppression of visual perception by magnetic coil stimulation of human occipital cortex. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section 74: 458-462

Amunts K, Malikovic A, Mohlberg H, Schormann T, Zilles K (2000) Brodmann's Areas 17 and 18 Brought into Stereotaxic Space--Where and How Variable? NeuroImage 11: 66-84

Andoh J, Artiges E, Pallier C, Rivière D, Mangin JF, Cachia A, Plaze M, Paillère-Martinot ML, Martinot JL (2006) Modulation of language areas with functional MR image-guided magnetic stimulation. NeuroImage 29: 619-627

Antal A, Nitsche MA, Kincses TZ, Lampe C, Paulus W (2003) No correlation between moving phosphene and motor thresholds: A transcranial magnetic stimulation study. NeuroReport 15: 297-302

Arguin M, Bub DN (1993) Single-character processing in a case of pure alexia. Neuropsychologia 31: 435-458

Arias-Carrion O (2008) Basic mechanisms of rTMS: Implications in Parkinson's disease. International Archives of Medicine 1: 2

Ashford JW, Fuster JM (1985) Occipital and inferotemporal responses to visual signals in the monkey. Experimental Neurology 90: 444-466

Axelrod V, Yovel G (2010) External facial features modify the representation of internal facial features in the fusiform face area. NeuroImage 52: 720-725

Aydin-Abidin S, Moliadze V, Eysel UT, Funke K (2006) Effects of repetitive TMS on visually evoked potentials and EEG in the anaesthetized cat: dependence on stimulus frequency and train duration. Journal of Physiology-London 574: 443-455

Aydin-Abidin S, Trippe J, Funke K, Eysel UT, Benali A (2008) High- and low-frequency repetitive transcranial magnetic stimulation differentially activates c-Fos and zif268 protein expression in the rat brain. Experimental Brain Research 188: 249-261

Baayen RH, Piepenbrock R, Van Rijn H (1993) The CELEX lexical database [CD-ROM]. The CELEX Lexical Database (CD-ROM)

Baker CI, Liu J, Wald LL, Kwong KK, Benner T, Kanwisher N (2007) Visual word processing and experiential origins of functional selectivity in human extrastriate cortex. Proceedings of the National Academy of Sciences 104: 9087-9092

Balota DA, Chumbley JI (1984) Are lexical decisions a good measure of lexical access? The role of word frequency in the neglected decision stage. Journal of Experimental Psychology: Human Perception and Performance 10: 340-357

Balota DA, Chumbley JI (1985) The locus of word-frequency effects in the pronunciation task: Lexical access and/or production? Journal of Memory and Language 24: 89-106

Balota DA, Spieler DH (1999) Word frequency, repetition, and lexicality effects in word recognition tasks: Beyond measures of central tendency. Journal of Experimental Psychology: General 128: 32-55

Bar M (2003) A cortical mechanism for triggering top-down facilitation in visual object recognition. Journal of Cognitive Neuroscience 15: 600-609

Bar M, Kassam KS, Ghuman AS, Boshyan J, Schmidt AM, Dale AM, HÃ¤mÃ¤lÃ¤inen MS, Marinkovic K, Schacter DL, Rosen BR, Halgren E (2006) Top-down facilitation of visual recognition. Proceedings of the National Academy of Sciences of the United States of America 103: 449-454

Barker AT, Jalinous R (1985) Non-invasive magnetic stimulation of human motor cortex. Lancet 1: 1106-1107

Barton JJS, Cherkasova MV, Press DZ, Intriligator JM, O'Connor M (2004) Perceptual functions in prosopagnosia. Perception 33: 939-956

Becker CA (1979) Semantic context and word frequency effects in visual word recognition. Journal of Experimental Psychology: Human Perception and Performance 5: 252-259

Beckmann CF, Jenkinson M, Smith SM (2003) General multilevel linear modeling for group analysis in FMRI. NeuroImage 20: 1052-1063

Behrmann M, Nelson J, Sekuler EB (1998a) Visual complexity in letter-by-letter reading: 'Pure' alexia is not pure. Neuropsychologia 36: 1115-1132

Behrmann M, Plaut DC, Nelson J (1998b) A literature review and new data supporting an interactive account of letter-by-letter reading. Cognitive Neuropsychology 15: 7-51

Bellgowan PSF, Saad ZS, Bandettini PA (2003) Understanding neural system dynamics through task modulation and measurement of functional MRI amplitude, latency, and width. Proceedings of the National Academy of Sciences of the United States of America 100: 1415-1419

Ben-Shachar M, Dougherty RF, Deutsch GK, Wandell BA (2007) Differential Sensitivity to Words and Shapes in Ventral Occipito-Temporal Cortex. Cereb. Cortex 17: 1604-1611

Bennett CM, Miller MB (2010) How reliable are the results from functional magnetic resonance imaging? Annals of the New York Academy of Sciences 1191: 133-155

Benson DF, Geschwind N (1969) The alexias. Handbook of Clinical Neurology 4: 112-140

Bentin S, Mouchetant-Rostaing Y, Giard MH, Echallier JF, Pernier J (1999) ERP manifestations of processing printed words at different psycholinguistic levels: Time course and scalp distribution. Journal of Cognitive Neuroscience 11: 235-260

Berman MG, Park J, Gonzalez R, Polk TA, Gehrke A, Knaffla S, Jonides J (2010) Evaluating functional localizers: The case of the FFA. NeuroImage 50: 56-71

Besner D, Smith MC (1992) Models of Visual Word Recognition: When Obscuring the Stimulus Yields a Clearer View. Journal of Experimental Psychology: Learning, Memory, and Cognition 18: 468-482

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J (2004) Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. European Journal of Neuroscience 19: 1950-1962

Beversdorf DQ, Ratcliffe NR, Rhodes CH, Reeves AG (1997) Pure alexia: Clinical-pathologic evidence for a lateralized visual language association cortex. Clinical Neuropathology 16: 328-331

Bilecen D, Scheffler K, Schmid N, Tschopp K, Seelig J (1998) Tonotopic organization of the human auditory cortex as detected by BOLD-fMRI. Hearing Research 126: 19-27

Binder JR, McKiernan KA, Parsons ME, Westbury CF, Possing ET, Kaufman JN, Buchanan L (2003) Neural correlates of lexical access during visual word recognition. Journal of Cognitive Neuroscience 15: 372-393

Binder JR, Medler DA, Desai R, Conant LL, Liebenthal E (2005a) Some neurophysiological constraints on models of word naming. NeuroImage 27: 677-693

Binder JR, Mohr JP (1992) The topography of callosal reading pathways. A case-control analysis. Brain 115: 1807-1826

Binder JR, Westbury CF, McKiernan KA, Possing ET, Medler DA (2005b) Distinct brain systems for processing concrete and abstract concepts. Journal of Cognitive Neuroscience 17: 905-917

Blankenburg F, Ruff CC, Deichmann R, Rees G, Driver J (2006) The cutaneous rabbit illusion affects human primary sensory cortex somatotopically. PLoS Biology 4: 459-466

Bohning DE, Pecheny AP, Epstein CM, Speer AM, Vincent DJ, Dannels W, George MS (1997) Mapping transcranial magnetic stimulation (TMS) fields in vivo with MRI. NeuroReport 8: 2535-2538

Bokde ALW, Tagamets MA, Friedman RB, Horwitz B (2001) Functional interactions of the inferior frontal cortex during the processing of words and word-like stimuli. Neuron 30: 609-617

Bookheimer SY, Zeffiro IA, Blaxton T, Gaillard W, Theodore W (1995) Regional cerebral blood flow during object naming and word reading. Human Brain Mapping 3: 93-106

Brasil-Neto JP, McShane LM, Fuhr P, Hallett M, Cohen LG (1992) Topographic mapping of the human motor cortex with magnetic stimulation: Factors affecting accuracy and

reproducibility. Electroencephalography and Clinical Neurophysiology - Electromyography and Motor Control 85: 9-16
Braun CMJ (1992) Estimation of interhemispheric dynamics from simple unimanual reaction time to extrafoveal stimuli. Neuropsychology Review 3: 321-365
Broca P (1861) Perte de la parole, ramollissement chronique et destruction partielle du lobe antérieur gauche du cerveau. Bull Soc Anthropol 2: 235-238
Brodmann K (1909) Vergleichende lokalisationslehre der grosshirnrinde. In: Garey LJ (ed) Brodmanns Localisation in the Cerebral Cortex. Imperial College Press, London
Bruno JL, Zumberge A, Manis FR, Lu ZL, Goldman JG (2008) Sensitivity to orthographic familiarity in the occipito-temporal region. NeuroImage 39: 1988-2001
Buckner RL, Raichle ME, Petersen SE (1995) Dissociation of human prefrontal cortical areas across different speech production tasks and gender groups. Journal of Neurophysiology 74: 2163-2173
Cai Q, Paulignan Y, Brysbaert M, Ibarrola D, Nazir TA (2010) The left ventral occipito-temporal response to words depends on language lateralization but not on visual familiarity. Cerebral Cortex 20: 1153-1163
Camprodon JA, Zohary E, Brodbeck V, Pascual-Leone A (2009) Two Phases of V1 Activity for Visual Recognition of Natural Images. Journal of Cognitive Neuroscience 22: 1262-1269
Capek C, Poonian S, Devlin JT (2009) Effective functional connectivity of phonological and semantic processing during word reading. In: CNS, San Francisco, USA
Carreiras M, Mechelli A, Price CJ (2006) Effect of word and syllable frequency on activation during lexical decision and reading aloud. Human Brain Mapping 27: 963-972
Carreiras M, Riba J, Vergara M, Heldmann M, Münte TF (2009) Syllable congruency and word frequency effects on brain activation. Human Brain Mapping 30: 3079-3088
Carroll JB, White MN (1973) Word frequency and age of acquisition as determiners of picture-naming latency. The Quarterly Journal of Experimental Psychology 25: 85-95
Cattaneo Z, Silvanto J (2008) Investigating visual motion perception using the transcranial magnetic stimulation-adaptation paradigm. NeuroReport 19: 1423-1427
Cattell JM (1886) The time it takes to see and name objects. Mind 11: 63-65
Chee MWL, Hon NHH, Caplan D, Hwee LL, Goh J (2002) Frequency of concrete words modulates prefrontal activation during semantic judgments. NeuroImage 16: 259-268
Chee MWL, Venkatraman V, Westphal C, Siong SC (2003a) Comparison of block and event-related fMRI designs in evaluating the word-frequency effect. Human Brain Mapping 18: 186-193
Chee MWL, Westphal C, Goh J, Graham S, Song AW (2003b) Word frequency and subsequent memory effects studied using event-related fMRI. NeuroImage 20: 1042-1051

Chen C-M, Lakatos P, Shah AS, Mehta AD, Givre SJ, Javitt DC, Schroeder CE (2007) Functional Anatomy and Interaction of Fast and Slow Visual Pathways in Macaque Monkeys. Cereb. Cortex 17: 1561-1569

Chen M, Mogul DJ (2009) A structurally detailed finite element human head model for simulation of transcranial magnetic stimulation. Journal of Neuroscience Methods 179: 111-120

Clark VP, Fan S, Hillyard SA (1994) Identification of early visual evoked potential generators by retinotopic and topographic analyses. Human Brain Mapping 2: 170-187

Cohen L, Dehaene S (2004) Specialization within the ventral stream: the case for the visual word form area. NeuroImage 22: 466-476

Cohen L, Dehaene S, Naccache L, Lehericy S, Dehaene-Lambertz G, Henaff MA, Michel F (2000) The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain 123 (Pt 2): 291-307

Cohen L, Lehéricy S, Chochon F, Lemer C, Rivaud S, Dehaene S (2002) Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area. Brain 125: 1054-1069

Cohen L, Martinaud O, Lemer C, Lehèricy S, Samson Y, Obadia M, Slachevsky A, Dehaene S (2003) Visual Word Recognition in the Left and Right Hemispheres: Anatomical and Functional Correlates of Peripheral Alexias. Cerebral Cortex 13: 1313-1333

Cohen LG, Roth BJ, Nilsson J, Dang N, Panizza M, Bandinelli S, Friauf W, Hallett M (1990) Effects of coil design on delivery of focal magnetic stimulation - technical considerations. Electroencephalography and Clinical Neurophysiology 75: 350-357

Coltheart M (1981) The MRC psycholinguistic database. Quarterly Journal of Experimental Psychology 33 A: 497-505

Coltheart M, Davelaar E, Jonasson JT, Besner D (1977) Access to the internal lexicon. In: Dornic S (ed) Attention and Performance VI. Academic Press, London, pp 535-555

Coltheart M, Rastle K, Perry C, Langdon R, Ziegler J (2001) DRC: A dual route cascaded model of visual word recognition and reading aloud. Psychological Review 108: 204-256

Conforto AB, Z'Graggen WJ, Kohl AS, Rösler KM, Kaelin-Lang A (2004) Impact of coil position and electrophysiological monitoring on determination of motor thresholds to transcranial magnetic stimulation. Clinical Neurophysiology 115: 812-819

Connine CM, Mullennix J, Shernoff E, Yelen J (1990) Word familiarity and frequency in visual and auditory word recognition. Journal of experimental psychology. Learning, memory, and cognition 16: 1084-1096

Cornelissen PL, Kringelbach ML, Ellis AW, Whitney C, Holliday IE, Hansen PC (2009) Activation of the left inferior frontal gyrus in the first 200 ms of reading: Evidence from Magnetoencephalography (MEG). PLoS ONE 4

Corthout E, Hallett M, Cowey A (2007) TMS-induced scotomata: Time-based neglect. Clinical Neurophysiology 118: 1895-1898

Corthout E, Uttl B, Walsh V, Hallett M, Cowey A (1999a) Timing of activity in early visual cortex as revealed by transcranial magnetic stimulation. NeuroReport 10: 2631-2634

Corthout E, Uttl B, Ziemann U, Cowey A, Hallett M (1999b) Two periods of processing in the (circum)striate visual cortex as revealed by transcranial magnetic stimulation. Neuropsychologia 37: 137-145

Cukic M, Kalauzi A, Ilic T, Miskovic M, Ljubisavljevic M (2009) The influence of coil–skull distance on transcranial magnetic stimulation motor-evoked responses. Experimental Brain Research 192: 53-60

Culham J, Danckert S, Souza JXD, Gati J, Menon R, Goodale M (2003) Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. Experimental Brain Research 153: 180-189

Damasio AR, Damasio H (1983) The anatomic basis of pure alexia. Neurology 33: 1573-1583

David SV, Hayden BY, Gallant JL (2006) Spectral receptive field properties explain shape selectivity in area V4. Journal of Neurophysiology 96: 3492-3505

Davis CJ (2005) N-watch: A program for deriving neighborhood size and other psycholinguistic statistics. Behavior Research Methods 37: 65-70

Davous P, Boller F (1994) Transcortical alexia with agraphia following a right temporo-occipital hematoma in a right-handed patient. Neuropsychologia 32: 1263-1272

Deblieck C, Thompson B, Iacoboni M, Wu AD (2008) Correlation between motor and phosphene thresholds: A transcranial magnetic stimulation study. Human Brain Mapping 29: 662-670

Dehaene S, Cohen L, Sigman M, Vinckier F (2005) The neural code for written words: A proposal. Trends in Cognitive Sciences 9: 335-341

Dehaene S, Le Clec'H G, Poline JB, Le Bihan D, Cohen L (2002) The visual word form area: A prelexical representation of visual words in the fusiform gyrus. NeuroReport 13: 321-325

Dehaene S, Naccache L, Cohen L, Bihan DL, Mangin JF, Poline JB, Rivière D (2001) Cerebral mechanisms of word masking and unconscious repetition priming. Nature Neuroscience 4: 752-758

Dejerine J (1891) Sur un cas de cécité verbale avec agraphie, suivie d'autopsie. C R Séances Mém Soc Biol 3: 197-201

Dejerine J (1892) Contribution à l'étude anatomo-pathologique et clinique des différentes variétés cécité verbale. Comptes Rendus Hebdomaladaires des Séances et Mémoires de la Société de Biologie 4: 61-90

Denslow S, Lomarev M, George MS, Bohning DE (2005) Cortical and subcortical brain effects of Transcranial Magnetic Stimulation (TMS)-induced movement: An

interleaved TMS/functional magnetic resonance imaging study. Biological Psychiatry 57: 752-760

Devanne H, Lavoie BA, Capaday C (1997) Input-output properties and gain changes in the human corticospinal pathway. Experimental Brain Research 114: 329-338

Devlin JT (2008) Current perspectives on imaging language. In: Kraft E, Gulyas B, Poppel E (eds) Neural Correlates of Thinking. Springer-Verlag, Berlin, pp 121-137

Devlin JT, Jamison HL, Gonnerman LM, Matthews PM (2006) The Role of the Posterior Fusiform Gyrus in Reading. J. Cogn. Neurosci. 18: 911-922

Devlin JT, Matthews PM, Rushworth MFS (2003a) Semantic Processing in the Left Inferior Prefrontal Cortex: A Combined Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation Study. J. Cogn. Neurosci. 15: 71-84

Devlin JT, Matthews PM, Rushworth MFS (2003b) Semantic processing in the left inferior prefrontal cortex: A combined functional magnetic resonance imaging and transcranial magnetic stimulation study. Journal of Cognitive Neuroscience 15: 71-84

Di Russo F, Martinez A, Hillyard SA (2003) Source analysis of event-related cortical activity during visuo-spatial attention. Cerebral Cortex 13: 486-499

Downing PE, Chan AWY, Peelen MV, Dodds CM, Kanwisher N (2006) Domain specificity in visual cortex. Cerebral Cortex 16: 1453-1461

Downing PE, Wiggett AJ, Peelen MV (2007) Functional Magnetic Resonance Imaging Investigation of Overlapping Lateral Occipitotemporal Activations Using Multi-Voxel Pattern Analysis. J. Neurosci. 27: 226-233

Duncan KJ, Pattamadilok C, Devlin JT (2010) Investigating occipito-temporal contributions to reading with TMS. Journal of Cognitive Neuroscience 22: 739-750

Duncan KJ, Pattamadilok C, Knierim I, Devlin JT (2009) Consistency and variability in functional localisers. NeuroImage 46: 1018-1026

Duong TQ, Kim D-S, Uğurbil K, Kim S-G (2001) Localized cerebral blood flow response at submillimeter columnar resolution. Proceedings of the National Academy of Sciences of the United States of America 98: 10904-10909

Eger E, Ashburner J, Haynes J-D, Dolan RJ, Rees G (2008) fMRI Activity Patterns in Human LOC Carry Information about Object Exemplars within Category. Journal of Cognitive Neuroscience 20: 356-370

Ellison A, Lane AR, Schenk T (2007) The Interaction of Brain Regions during Visual Search Processing as Revealed by Transcranial Magnetic Stimulation. Cereb. Cortex 17: 2579-2584

Epstein R, Kanwisher N (1998) A cortical representation the local visual environment. Nature 392: 598-601

Farah MJ (2004) Visual Agnosia. MIT Press, Cambridge, Massachusetts

Farah MJ, Wallace MA (1991) Pure Alexia as a Visual Impairment: A Reconsideration. Cognitive Neuropsychology 8: 313-334

Farrell DF, Burbank N, Lettich E, Ojemann GA (2007) Individual variation in human motor-sensory (rolandic) cortex. Journal of Clinical Neurophysiology 24: 286-293

Fiebach CJ, Friederici AD, Muller K, von Cramon DY (2002) fMRI evidence for dual routes to the mental lexicon in visual word recognition. Journal of Cognitive Neuroscience 14: 11-23

Fiebach CJ, Gruber T, Supp GG (2005) Neuronal mechanisms of repetition priming in occipitotemporal cortex: Spatiotemporal evidence from functional magnetic resonance imaging and electroencephalography. Journal of Neuroscience 25: 3414-3422

Fiez JA (1997) Phonology, semantics, and the role of the left inferior prefrontal cortex. Human Brain Mapping 5: 79-83

Fiez JA, Balota DA, Raichle ME, Petersen SE (1999) Effects of lexicality, frequency, and spelling-to-sound consistency on the functional anatomy of reading. Neuron 24: 205-218

Fiez JA, Petersen SE (1998) Neuroimaging studies of word reading. Proceedings of the National Academy of Sciences of the United States of America 95: 914-921

Flowers DL, Jones K, Noble K, VanMeter J, Zeffiro TA, Wood FB, Eden GF (2004) Attention to single letters activates left extrastriate cortex. NeuroImage 21: 829-839

Forster KI, Chambers SM (1973) Lexical access and naming time. J.Verb.Learn.Verb.Behav. 12: 627-635

Fox C, Iaria G, Barton J (2008) Defining the face processing network: Optimization of the functional localizer in fMRI. Human Brain Mapping 9999: NA

Fox P, Ingham R, George MS, Mayberg H, Ingham J, Roby J, Martin C, Jerabek P (1997) Imaging human intra-cerebral connectivity by PET during TMS. NeuroReport 8: 2787-2791

Frederiksen JR, Kroll JF (1976) Spelling and sound: Approaches to the internal lexicon. Journal of Experimental Psychology: Human Perception and Performance 2: 361-379

Friedman RB, Alexander MP (1984) Pictures, images, and pure alexia: a case study. Cognitive Neuropsychology 1: 9-23

Friston KJ, Henson RN (2006) Commentary on: Divide and conquer; a defence of functional localisers. NeuroImage 30: 1097-1099

Friston KJ, Holmes AP, Worsley KJ (1999) How many subjects constitute a study? NeuroImage 10: 1-5

Friston KJ, Rotshtein P, Geng JJ, Sterzer P, Henson RN (2006) A critique of functional localisers. NeuroImage 30: 1077-1087

Frost SJ, Sandak R, Mencl WE, Landi N, Moore D, Della Porta G, J.G. R, Katz L, Pugh KR (2008) Neurobiological studies of skilled and impaired word reading. In: Grigorenko EL, Naples AJ (eds) Single-Word Reading: Behavioral and Biological Perspectives Taylor & Francis Group, New York, pp 355-376

Gaillard R, Naccache L, Pinel P, Clemenceau S, Volle E, Hasboun D, Dupont S, Baulac M, Dehaene S, Adam C, Cohen L (2006) Direct intracranial, fMRI, and lesion evidence for the causal role of left inferoternporal cortex in reading. Neuron 50: 191-204

Gazzaley A, Cooney JW, McEvoy K, Knight RT, D'Esposito M (2005) Top-down Enhancement and Suppression of the Magnitude and Speed of Neural Activity. Journal of Cognitive Neuroscience 17: 507-517

Gerwig M, Kastrup O, Meyer BU, Niehaus L (2003) Evaluation of cortical excitability by motor and phosphene thresholds in transcranial magnetic stimulation. Journal of the Neurological Sciences 215: 75-78

Geschwind N (1965a) Disconnexion syndromes in animals and man. I. Brain : a journal of neurology 88: 237-294

Geschwind N (1965b) Disconnexion syndromes in animals and man. II. Brain : a journal of neurology 88: 585-644

Givre SJ, Schroeder CE, Arezzo JC (1994) Contribution of extrastriate area v4 to the surface-recorded flash vep in the awake macaque. Vision Research 34: 415-428

Glover GH (1999) Deconvolution of Impulse Response in Event-Related BOLD fMRI. NeuroImage 9: 416-429

Göbel S, Walsh V, Rushworth MFS (2001) The mental number line and the human angular gyrus. NeuroImage 14: 1278-1289

Golarai G, Ghahremani DG, Whitfield-Gabrieli S, Reiss A, Eberhardt JL, Gabrieli JDE, Grill-Spector K (2007) Differential development of high-level visual cortex correlates with category-specific recognition memory. Nat Neurosci 10: 512-522

Gough PM, Nobre AC, Devlin JT (2005) Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. Journal of Neuroscience 25: 8010-8016

Grainger J, Ziegler J (2008) Cross-Code Consistency in a Functional Architecture for Word Recognition. In: Grigorenko EL, Naples AJ (eds) Single-Word Reading: Behavioral and Biological Perspectives Taylor & Francis Group, New York, pp 129-157

Grill-Spector K, Knouf N, Kanwisher N (2004) The fusiform face area subserves face perception, not generic within-category identification. Nat Neurosci 7: 555-562

Grill-Spector K, Kushnir T, Edelman S, Avidan G, Itzchak Y, Malach R (1999) Differential processing of objects under various viewing conditions in the human lateral occipital complex. Neuron 24: 187-203

Grill-Spector K, Kushnir T, Hendler T, Edelman S, Itzchak Y, Malach R (1998) A sequence of object-processing stages revealed by fMRI in the human occipital lobe. Human Brain Mapping 6: 316-328

Grindrod CM, Bilenko NY, Myers EB, Blumstein SE (2008) The role of the left inferior frontal gyrus in implicit semantic competition and selection: An event-related fMRI study. Brain Research 1229: 167-178

Hagoort P, Indefrey P, Brown C, Herzog H, Steinmetz H, Seitz RJ (1999) The neural circuitry involved in the reading of German words and pseudowords: A PET study. Journal of Cognitive Neuroscience 11: 383-398

Handwerker DA, Ollinger JM, D'Esposito M (2004) Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. NeuroImage 21: 1639-1651

Harm MW, Seidenberg MS (2004) Computing the meanings of words in reading: Cooperative division of labor between visual and phonological processes. Psychological Review 111: 662-720

Hauk O, Davis MH, Pulvermüller F (2008) Modulation of brain activity by multiple lexical and word form variables in visual word recognition: A parametric fMRI study. NeuroImage 42: 1185-1195

Hauk O, Pulvermüller F (2004) Effects of word length and frequency on the human event-related potential. Clinical Neurophysiology 115: 1090-1103

Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293: 2425-2430

Haxby JV, Hoffman EA, Gobbini MI (2000) The distributed human neural system for face perception. Trends in Cognitive Sciences 4: 223-233

Hayashi T, Ohnishi T, Okabe S, Teramoto N, Nonaka Y, Watabe H, Imabayashi E, Ohta Y, Jino H, Ejima N, Sawada T, Iida H, Matsuda H, Ugawa Y (2004) Long-term effect of motor cortical repetitive transcranial magnetic stimulation induces. Annals of Neurology 56: 77-85

Herbsman T, Forster L, Molnar C, Dougherty R, Christie D, Koola J, Ramsey D, Morgan PS, Bohning DE, George MS, Nahas Z (2009) Motor threshold in transcranial magnetic stimulation: The impact of white matter fiber orientation and skull-to-cortex distance. Human Brain Mapping 30: 2044-2055

Herbster AN, Mintun MA, Nebes RD, Becker JT (1997) Regional cerebral blood flow during word and nonword reading. Human Brain Mapping 5: 84-92

Hillis AE, Newhart M, Heidler J, Barker P, Herskovits E, Degaonkar M (2005) The roles of the "visual word form area" in reading. NeuroImage 24: 548-559

Hodges JR, Graham N, Patterson K (1995) Charting the progression in semantic dementia: implications for the organisation of semantic memory. Memory (Hove, England) 3: 463-495

Hoeft F, Wu DA, Hernandez A, Glover GH, Shimojo S (2008) Electroncally switchable sham transcranial magnetic stimulation (TMS) system. PLoS ONE 3

Howes DH, Solomon RL (1951) Visual duration threshold as a function of word probability. Journal of Experimental Psychology 41: 401-410

Huang RS, Sereno MI (2007) Dodecapus: An MR-compatible system for somatosensory stimulation. NeuroImage 34: 1060-1073

Humphreys GW, Rumiati RI (1998) Agnosia without prosopagnosia or Alexia: Evidence for stored visual memories specific to objects. Cognitive Neuropsychology 15: 243-277

Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Na?a?ta?nen R, Katila T (1997) Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. NeuroReport 8: 3537-3540

Ino T, Nakai R, Azuma T, Kimura T, Fukuyama H (2009) Recognition and reading aloud of kana and kanji word: an fMRI study. Brain Res Bull 78: 232-239

Jacobs AM, Graf R, Kinder A (2003) Receiver operating characteristics in the lexical decision task: evidence for a simple signal-detection process simulated by the multiple read-out model. J Exp Psychol Learn Mem Cogn 29: 481-488

James CT (1975) The Role of Semantic Information in Lexical Decisions. Journal of Experimental Psychology: Human Perception and Performance 1: 130-136

James TW, Culham J, Humphrey GK, Milner AD, Goodale MA (2003) Ventral occipital lesions impair object recognition but not object-directed grasping: An fMRI study. Brain 126: 2463-2475

Jared D, Seidenberg MS (1991) Does Word Identification Proceed From Spelling to Sound to Meaning? Journal of Experimental Psychology: General 120: 358-394

Jeffrey JB, John W, Branham RK, Sofia R-G, Caroline H, Heather B, Scott TR, Alok M, Harold S, Mark SG (2008) Development and evaluation of a portable sham transcranial magnetic stimulation system. 1: 52-59

Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17: 825-841

Jenkinson M, Smith S (2001) A global optimisation method for robust affine registration of brain images. Medical Image Analysis 5: 143-156

Jezzard P, Balaban RS (1995) Correction for geometric distortion in echo-planar images from B-0 field variations. Magnetic Resonance in Medicine 34: 65-73

Jiang X, Bradley E, Rini RA, Zeffiro T, VanMeter J, Riesenhuber M (2007) Categorization training results in shape- and category-selective human neural plasticity. Neuron 53: 891-903

Johnson RL, Rayner K (2007) Top-down and bottom-up effects in pure alexia: Evidence from eye movements. Neuropsychologia 45: 2246-2257

Joseph JE, Cerullo MA, Farley AB, Steinmetz NA, Mier CR (2006) fMRI correlates of cortical specialization and generalization for letter processing. NeuroImage 32: 806-820

Josse G, Tzourio-Mazoyer N (2004) Hemispheric specialization for language. Brain Research Reviews 44: 1-12

Juan C-H, Walsh V (2003) Feedback to V1: a reverse hierarchy in vision. Experimental Brain Research 150: 259-263

Kalla R, Muggleton NG, Juan CH, Cowey A, Walsh V (2008) The timing of the involvement of the frontal eye fields and posterior parietal cortex in visual search. NeuroReport 19: 1067-1071

Kammer T, Scharnowski F, Herzog MH (2003) Combining backward masking and transcranial magnetic stimulation in human observers. Neuroscience Letters 343: 171-174

Kanwisher N, Chun MM, McDermott J, Ledden PJ (1996) Functional imaging of human visual recognition. Cognitive Brain Research 5: 55-67

Kanwisher N, McDermott J, Chun MM (1997) The fusiform face area: A module in human extrastriate cortex specialized for face perception. Journal of Neuroscience 17: 4302-4311

Kanwisher N, Stanley D, Harris A (1999) The fusiform face area is selective for faces not animals. NeuroReport 10: 183-187

Karnath HO, RÃ¼ter J, Mandler A, Himmelbach M (2009) The anatomy of object recognition - Visual form agnosia caused by medial occipitotemporal stroke. Journal of Neuroscience 29: 5854-5862

Kherif F, Josse G, Price CJ (2010) Automatic Top-Down Processing Explains Common Left Occipito-Temporal Responses to Visual Words and Objects. Cereb Cortex

Kiani R, Esteky H, Tanaka K (2005) Differences in Onset Latency of Macaque Inferotemporal Neural Responses to Primate and Non-Primate Faces. J Neurophysiol 94: 1587-1596

Kinsbourne M, Warrington EK (1962) A disorder of simultaneous form perception. Brain : a journal of neurology 85: 461-486

Kinsbourne M, Warrington EK (1963) The localizing significance of limited simultaneous visual form perception. Brain 86: 697-702

Kohler S, Paus T, Buckner RL, Milner B (2004) Effects of Left Inferior Prefrontal Stimulation on Episodic Memory Formation: A Two-Stage fMRI-rTMS Study. J. Cogn. Neurosci. 16: 178-188

Koivisto M, Mäntylä T, Silvanto J (2010) The role of early visual cortex (V1/V2) in conscious and unconscious visual perception. NeuroImage 51: 828-834

Kourtzi Z, Kanwisher N (2000) Cortical regions involved in perceiving object shape. Journal of Neuroscience 20: 3310-3318

Kriegeskorte N, Mur M, Ruff DA, Kiani R, Bodurka J, Esteky H, Tanaka K, Bandettini PA (2008) Matching Categorical Object Representations in Inferior Temporal Cortex of Man and Monkey. Neuron 60: 1126-1141

Kronbichler M, Hutzler F, Wimmer H, Mair A, Staffen W, Ladurner G (2004) The visual word form area and the frequency with which words are encountered: Evidence from a parametric fMRI study. NeuroImage 21: 946-953

Kruger G, Glover GH (2001) Physiological noise in oxygenation-sensitive magnetic resonance imaging. Magnetic Resonance in Medicine 46: 631-637

Kung CC, Peissig JJ, Tarr MJ (2007) Is region-of-interest overlap comparison a reliable measure of category specificity? Journal of Cognitive Neuroscience 19: 2019-2034

Kuo WJ, Yeh TC, Lee CY, Wu YT, Chou CC, Ho LT, Hung DL, Tzeng OJL, Hsieh JC (2003) Frequency effects of Chinese character processing in the brain: An event-related fMRI study. NeuroImage 18: 720-730

Lambon Ralph MA, McClelland JL, Patterson K, Galton CJ, Hodges JR (2001) No right to speak? The relationship between object naming and semantic impairment: Neuropsychological evidence and a computational model. Journal of Cognitive Neuroscience 13: 341-356

Lambon Ralph MA, Pobric G, Jefferies E (2009) Conceptual knowledge is underpinned by the temporal pole bilaterally: Convergent evidence from rTMS. Cerebral Cortex 19: 832-838

Landis T (2006) Emotional Words: What's so Different from Just Words? Cortex 42: 823-830

Larsson J, Heeger DJ (2006) Two retinotopic visual areas in human lateral occipital cortex. Journal of Neuroscience 26: 13128-13142

Lee CY, Huang HW, Kuo WJ, Tsai JL, Tzeng JLO (2010) Cognitive and neural basis of the consistency and lexicality effects in reading Chinese. Journal of Neurolinguistics 23: 10-27

Lee CY, Tsai JL, Kuo WJ, Yeh TC, Wu YT, Ho LT, Hung DL, Tzeng OJL, Hsieh JC (2004) Neuronal correlates of consistency and frequency effects on Chinese character naming: An event-related fMRI study. NeuroImage 23: 1235-1245

Leff AP, Crewes H, Plant GT, Scott SK, Kennard C, Wise RJS (2001) The functional anatomy of single-word reading in patients with hemianopic and pure alexia. Brain 124: 510-521

Lenz FA, Jaeger CJ, Seike MS, Lin YC, Reich SG (2002) Single-Neuron Analysis of Human Thalamus in Patients With Intention Tremor and Other Clinical Signs of Cerebellar Disease. J Neurophysiol 87: 2084-2094

Levy I, Hasson U, Avidan G, Hendler T, Malach R (2001) Center-periphery organization of human object areas. Nature Neuroscience 4: 533-539

Li Y, Bin G, Hong B, Gao X (2010) A coded VEP method to measure interhemispheric transfer time (IHTT). Neuroscience Letters 472: 123-127

Lichtheim L (1885) On aphasia. Brain 7: 433-484

Liu R, Ueno S (1998) Stimulation of the influence of tissue inhomogeneity on nerve excitation elicited by magnetic. Proceedings - 20th Annual International Conference - IEEE/EMBS 6: 2998-3000

Lo YL, Fook-Chong S (2004) A transcranial magnetic stimulation study of the ipsilateral silent period in lower limb muscles. Neuroscience Letters 368: 337-340

Loftus GR, Masson MEJ (1994) Using confidence intervals in within-subject designs. Psychonomic Bulletin and Review 1: 476-490

Lyons AW, Teer P, Rubenstein H (1978) Age-at-acquisition and word recognition. Journal of Psycholinguistic Research 7: 179-187

Maccabee PJ, Amassian VE, Eberle LP, Cracco RQ (1993) Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerve in vitro: Locus of excitation. Journal of Physiology 460: 201-219

Malach R, Reppas JB, Benson RR, Kwong KK, Jiang H, Kennedy WA, Ledden PJ, Brady TJ, Rosen BR, Tootell RBH (1995) Object-related activity revealed by functional magnetic-resonance-imaging in human occipital cortex. Proceedings of the National Academy of Sciences of the United States of America 92: 8135-8139

Manenti R, Cappa SF, Rossini PM, Miniussi C (2008) The role of the prefrontal cortex in sentence comprehension: An rTMS study. Cortex 44: 337-344

Martínez A, Anllo-Vento L, Sereno MI, Frank LR, Buxton RB, Dubowitz DJ, Wong EC, Hinrichs H, Heinze HJ, Hillyard SA (1999) Involvement of striate and extrastriate visual cortical areas in spatial attention. Nature Neuroscience 2: 364-369

Maunsell JHR, Gibson JR (1992) Visual response latencies in striate cortex of the macaque monkey. Journal of Neurophysiology 68: 1332-1344

Maunsell JHR, Newsome WT (1987) Visual processing in monkey extrastriate cortex. Annual Review of Neuroscience Vol. 10: 363-401

Maurer U, McCandliss BD (2008) The Development of Visual Expertise for Words: The Contribution of Electrophysiology. In: Grigorenko EL, Naples AJ (eds) Single Word-Reading. Taylor & Francis Group, New York

McCandliss BD, Cohen L, Dehaene S (2003) The visual word form area: Expertise for reading in the fusiform gyrus. Trends in Cognitive Sciences 7: 293-299

McCandliss BD, Posner MI, Givon T (1997) Brain plasticity in learning visual words. Cognitive Psychology 33: 88-110

McCann RS, Besner D (1987) Reading Pseudohomophones: Implications for Models of Pronunciation Assembly and the Locus of Word-Frequency Effects in Naming. Journal of Experimental Psychology: Human Perception and Performance 13: 14-24

McClelland JL (1993) Toward a Theory of Information Processing in Graded, Random and Interactive Networks. In: Meyer DE, Kornblum S (eds) Attention and Performance XIV: Synergies in Experimental Psychology, Artificial Intelligence, and Cognitive Neuroscience. MIT Press, Cambridge, MA, pp 655-688

McClelland JL, Rumelhart DE (1981) An interactive activation model of context effects in letter perception: Part 1. An account of basic findings. Psychological Review 88: 375-407

McConnell KA, Nahas Z, Shastri A, Lorberbaum JP, Kozel FA, Bohning DE, George MS (2001) The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: A replication in healthy adults comparing two methods of assessing the distance to cortex. Biological Psychiatry 49: 454-459

Mechelli A, Gorno-Tempini ML, Price CJ (2003) Neuroimaging studies of word and pseudoword reading: Consistencies, inconsistencies, and limitations. Journal of Cognitive Neuroscience 15: 260-271

Mei L, Xue G, Chen C, Xue F, Zhang M, Dong Q (2010) The "visual word form area" is involved in successful memory encoding of both words and faces. NeuroImage

Miller LM, D'Esposito M (2005) Perceptual fusion and stimulus coincidence in the cross-modal integration of speech. Journal of Neuroscience 25: 5884-5893

Moliadze V, Giannikopoulos D, Eysel UT, Funke K (2005) Paired-pulse transcranial magnetic stimulation protocol applied to visual cortex of anaesthetized cat: Effects on visually evoked single-unit activity. Journal of Physiology 566: 955-965

Moliadze V, Zhao YQ, Eysel U, Funke K (2003) Effect of transcranial magnetic stimulation on single-unit activity in the cat primary visual cortex. Journal of Physiology-London 553: 665-679

Monsell S, Doyle MC, Haggard PN (1989) Effects of Frequency on Visual Word Recognition Tasks: Where Are They? Journal of Experimental Psychology: General 118: 43-71

Moore CJ, Price CJ (1999) Three distinct ventral occipitotemporal regions for reading and object naming. NeuroImage 10: 181-192

Morton J (1969) Interaction of information in word recognition. Psychological Review 76: 165-178

Morton J (1982) Disintegrating the lexicon: An information processing approach. Perspectives on Mental Representation: 89-109

Mouchawar GA, Nyenhuis JD, Geddes LA, Schaefer DJ, Riehl ME (1993) Magnetic stimulation of excitable tissue: calculation of induced eddy-currents with a three-dimensional finite-element model. IEEE Transactions on Magnetics 29: 3355-3357

Mukamel R, Ekstrom AD, Kaplan J, Iacoboni M, Fried I (2010) Single-Neuron Responses in Humans during Execution and Observation of Actions. Current Biology 20: 750-756

Mycroft RH, Behrmann M, Kay J (2009) Visuoperceptual deficits in letter-by-letter reading? Neuropsychologia 47: 1733-1744

Naccache L, Dehaene S (2001) The priming method: Imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. Cerebral Cortex 11: 966-974

Nagae S (1998) Processing of emotional kanji words in the right hemisphere and the effect of handedness on the processing. Shinrigaku Kenkyu 69: 39-46

Nagarajan SS, Durand DM (1995) Analysis of magnetic stimulation of a concentric axon in a nerve bundle. Ieee Transactions on Biomedical Engineering 42: 926-933

Nagarajan SS, Durand DM (1996) A generalized cable equation for magnetic stimulation of axons. Ieee Transactions on Biomedical Engineering 43: 304-312

Nakamura K, Honda M, Hirano S, Oga T, Sawamoto N, Hanakawa T, Inoue H, Ito J, Matsuda T, Fukuyama H, Shibasaki H (2002) Modulation of the visual word

retrieval system in writing: A functional MRI study on the Japanese orthographies. Journal of Cognitive Neuroscience 14: 104-115

Nakic M, Smith BW, Busis S, Vythilingam M, Blair RJR (2006) The impact of affect and frequency on lexical decision: The role of the amygdala and inferior frontal cortex. NeuroImage 31: 1752-1761

Neville HJ, Mills DL, Lawson DS (1992) Fractionating language: Different neural subsystems with different sensitive periods. Cerebral Cortex 2: 244-258

Noble CE (1954) The familiarity-frequency relationship. Journal of Experimental Psychology 47: 13-16

Nobre AC, Allison T, McCarthy G (1994) Word recognition in the human inferior temporal lobe. Nature 372: 260-263

Norris D, McQueen JM, Cutler A (2000) Merging information in speech recognition: Feedback is never necessary. Behavioral and Brain Sciences 23: 299-325+363-370

O'Craven KM, Kanwisher N (2000) Mental imagery of faces and places activates corresponding stimulus-specific brain regions. Journal of Cognitive Neuroscience 12: 1013-1023

O'Shea J, Muggleton NG, Cowey A, Walsh V (2004) Timing of target discrimination in human frontal eye fields. Journal of Cognitive Neuroscience 16: 1060-1067

Orban GA, Dupont P, Vogels R, De Bruyn B, Bormans G, Mortelmans L (1996) Task dependency of visual processing in the human visual system. Behavioural Brain Research 76: 215-223

Pammer K, Hansen PC, Kringelbach ML, Holliday I, Barnes G, Hillebrand A, Singh KD, Cornelissen PL (2004) Visual word recognition: The first half second. NeuroImage 22: 1819-1825

Pascual-Leone A, Bartres-Faz D, Keenan JP (1999) Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions'. Philosophical Transactions of the Royal Society of London Series B-Biological Sciences 354: 1229-1238

Pascual-Leone A, Vallssole J, Wassermann EM, Hallett M (1994) Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117: 847-858

Pascual-Leone A, Walsh V, Rothwell J (2000) Transcranial magnetic stimulation in cognitive neuroscience - virtual lesion, chronometry, and functional connectivity. Current Opinion in Neurobiology 10: 232-237

Pasley BN, Allen EA, Freeman RD (2009) State-Dependent Variability of Neuronal Responses to Transcranial Magnetic Stimulation of the Visual Cortex. Neuron 62: 291-303

Pattamadilok C, Knierim IN, Kawabata Duncan KJ, Devlin JT (2010) How Does Learning to Read Affect Speech Perception? J. Neurosci. 30: 8435-8444

Paulus W, Korinth S, Wischer S, Tergau F (1999) Differential inhibition of chromatic and achromatic perception by transcranial magnetic stimulation of the human visual cortex. NeuroReport 10: 1245-1248

Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC (1997) Transcranial magnetic stimulation during positron emission tomography: A new method for studying connectivity of the human cerebral cortex. Journal of Neuroscience 17: 3178-3184

Paus T, Sipila PK, Strafella AP (2001) Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: An EEG study. Journal of Neurophysiology 86: 1983-1990

Peelen MV, Downing PE (2005a) Is the extrastriate body area involved in motor actions? Nat Neurosci 8: 125-125

Peelen MV, Downing PE (2005b) Within-subject reproducibility of category-specific visual activation with functional MRI. Human Brain Mapping 25: 402-408

Perry C, Ziegler JC, Zorzi M (2007) Nested incremental modeling in the development of computational theories: The CDP+ model of reading aloud. Psychological Review 114: 273-315

Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME (1988) Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature 331: 585-589

Philipose LE, Gottesman RF, Newhart M, Kleinman JT, Herskovits EH, Pawlak MA, Marsh EB, Davis C, Heidler-Gary J, Hillis AE (2007) Neural regions essential for reading and spelling of words and pseudowords. Annals of Neurology 62: 481-492

Phillips JA, Humphreys GW, Noppeney U, Price CJ (2002) The neural substrates of action retrieval: An examination of semantic and visual routes to action. Visual Cognition 9: 662-684

Pitcher D, Charles L, Devlin JT, Walsh V, Duchaine B (2009) Triple Dissociation of Faces, Bodies, and Objects in Extrastriate Cortex. Current Biology

Pitcher D, Duchaine B, Walsh V, Kanwisher N (2010) TMS evidence for feed forward and feedback mechanisms of face and body perception. In: Vision Sciences Society,, Florida, U.S.A

Pitcher D, Garrido L, Walsh V, Duchaine BC (2008) Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. The Journal of neuroscience : the official journal of the Society for Neuroscience 28: 8929-8933

Pitcher D, Walsh V, Yovel G, Duchaine B (2007) TMS evidence for the involvement of the right occipital face area in early face processing. Current Biology 17: 1568-1573

Plaut DC, McClelland JL, Seidenberg MS, Patterson K (1996) Understanding Normal and Impaired Word Reading: Computational Principles in Quasi-Regular Domains. Psychological Review 103: 56-115

Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JDE (1999) Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. NeuroImage 10: 15-35

Postle BR, Ferrarelli F, Hamidi M, Feredoes E, Massimini M, Peterson M, Alexander A, Tononi G (2006) Repetitive transcranial magnetic stimulation dissociates working memory manipulation from retention functions in the prefrontal, but not posterior parietal, cortex. Journal of Cognitive Neuroscience 18: 1712-1722

Pourtois G, Schwartz S, Spiridon M, Martuzzi R, Vuilleumier P (2009) Object Representations for Multiple Visual Categories Overlap in Lateral Occipital and Medial Fusiform Cortex. Cereb. Cortex 19: 1806-1819

Price CJ (2000) The anatomy of language: Contributions from functional neuroimaging. Journal of Anatomy 197: 335-359

Price CJ, Devlin JT (2003) The myth of the visual word form area. NeuroImage 19: 473-481

Price CJ, Devlin JT (2004) The pro and cons of labelling a left occipitotemporal region: "the visual word form area". NeuroImage 22: 477-479

Price CJ, Friston KJ (2005) Functional ontologies for cognition: The systematic definition of structure and function. Cognitive Neuropsychology 22: 262-275

Price CJ, McCrory E, Noppeney U, Mechelli A, Moore CJ, Biggio N, Devlin JT (2006) How reading differs from object naming at the neuronal level. NeuroImage 29: 643-648

Price CJ, Mechelli A (2005) Reading and reading disturbance. Current Opinion in Neurobiology 15: 231-238

Price CJ, Mummery CJ, Moore CJ, Frackowiak RSJ, Friston KJ (1999) Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. Journal of Cognitive Neuroscience 11: 371-382

Price CJ, Wise RJ, Frackowiak RS (1996) Demonstrating the implicit processing of visually presented words and pseudowords. Cereb Cortex 6: 62-70

Price CJ, Wise RJS, Watson JDG, Patterson K, Howard D, Frackowiak RSJ (1994) Brain activity during reading The effects of exposure duration and task. Brain 117: 1255-1269

Prime SL, Vesia M, Crawford JD (2010) TMS Over Human Frontal Eye Fields Disrupts Trans-saccadic Memory of Multiple Objects. Cereb. Cortex 20: 759-772

Proverbio AM, Adorni R (2009) C1 and P1 visual responses to words are enhanced by attention to orthographic vs. lexical properties. Neuroscience Letters 463: 228-233

Pugh KR, Shaywitz BA, Shaywitz SE, Constable RT, Skudlarski P, Fulbright RK, Bronen RA, Shankweiler DP, Katz L, Fletcher JM, Gore JC (1996) Cerebral organization of component processes in reading. Brain 119: 1221-1238

Pulvermüller F, Huss M, Kherif F, Moscoso del Prado Martin F, Hauk O, Shtyrov Y (2006) Motor cortex maps articulatory features of speech sounds. Proceedings of the National Academy of Sciences 103: 7865-7870

Pulvermüller F, Shtyrov Y (2006) Language outside the focus of attention: The mismatch negativity as a tool for studying higher cognitive processes. Progress in Neurobiology 79: 49-71

Pulvermüller F, Shtyrov Y, Hauk O (2009) Understanding in an instant: Neurophysiological evidence for mechanistic language circuits in the brain. Brain and Language 110: 81-94

Pyun SB, Sohn HJ, Jung JB, Nam K (2007) Differential reorganization of fusiform gyrus in two types of Alexia after stroke. Neurocase 13: 417-425

Rayner K (1998) Eye Movements in Reading and Information Processing: 20 Years of Research. Psychological Bulletin 124: 372-422

Reicher GM (1969) Perceptual recognition as a function of meaningfulness of stimulus material. Journal of Experimental Psychology 81: 275-280

Reimer JF, Lorsbach TC, Bleakney DM (2008) Automatic semantic feedback during visual word recognition. Memory and Cognition 36: 641-658

Reuter-Lorenz PA, Brunn JL (1990) A prelexical basis for letter-by-letter reading: A case study. Cognitive Neuropsychology 7: 1-20

Richmond BJ, Optican LM, Podell M, Spitzer H (1987) Temporal encoding of two-dimensional patterns by single units in primate inferior temporal cortex .1. Response characteristics. Journal of Neurophysiology 57: 132-146

Rosenberg K, Liebling R, Avidan G, Perry D, Siman-Tov T, Andelman F, Ram Z, Fried I, Hendler T (2008) Language related reorganization in adult brain with slow growing glioma: FMRI prospective case-study. Neurocase 14: 465-473

Rosenzweig MR, Postman L (1957) Intelligibility as a function of frequency of usage. Journal of Experimental Psychology 54: 412-422

Rosenzweig MR, Postman L (1958) Frequency of usage and the perception of words. Science 127: 263-266

Roskies AL, Fiez JA, Balota DA, Raichle ME, Petersen SE (2001) Task-dependent modulation of regions in the left inferior frontal cortex during semantic processing. Journal of Cognitive Neuroscience 13: 829-843

Rossi S, Ferro M, Cincotta M, Ulivelli M, Bartalini S, Miniussi C, Giovannelli F, Passero S (2007) A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). Clinical Neurophysiology 118: 709-716

Rossi S, Hallett M, Rossini PM, Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical Neurophysiology 120: 2008-2039

Rossion B, Joyce CA, Cottrell GW, Tarr MJ (2003) Early lateralization and orientation tuning for face, word, and object processing in the visual cortex. NeuroImage 20: 1609-1624

Rotem A, Moses E (2008) Magnetic stimulation of one-dimensional neuronal cultures. Biophysical Journal 94: 5065-5078

Roth BJ, Saypol JM, Hallett M, Cohen LG (1991) A theoretical calculation of the electric-field induced in the cortex during magnetic stimulation. Electroencephalography and Clinical Neurophysiology 81: 47-56

Roth Y, Amir A, Levkovitz Y, Zangen A (2007) Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. Journal of Clinical Neurophysiology 24: 31-38

Roth Y, Zangen A, Hallett M (2002) A coil design for transcranial magnetic stimulation of deep brain regions. Journal of Clinical Neurophysiology 19: 361-370

Rothwell JC (1997) Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. Journal of Neuroscience Methods 74: 113-122

Rubenstein H, Garfield L, Millikan JA (1970) Homographic entries in the internal lexicon. Journal of verbal learning and verbal behavior 9: 487-494

Rugg MD (1983) Further study of the electrophysiological correlates of lexical decision. Brain and Language 19: 142-152

Rumelhart DE, McClelland JL (1982) An interactive activation model of context effects in letter perception: II. The contextual enhancement effect and some tests and extensions of the model. Psychological Review 89: 60-94

Rumsey JM, Horwitz B, Donohue BC, Nace K, Maisog JM, Andreason P (1997) Phonological and orthographic components of word recognition - A PET-rCBF study. Brain 120: 739-759

Ruohonen J, Ilmoniemi RJ (2002) Physical principles for transcranial magnetic stimulation. In: Pascual-Leone A, Davey NJ, Rothwell JC, Wassermann EM, Puri BK (eds) Handbook of Transcranial Magnetic Stimulation. Arnold, London

Rushworth MFS, Ellison A, Walsh V (2001) Complementary localization and lateralization of orienting and motor attention. Nat Neurosci 4: 656-661

Ruz M, Nobre AC (2008) Attention modulates initial stages of visual word processing. Journal of Cognitive Neuroscience 20: 1727-1736

Sack AT (2006) Transcranial magnetic stimulation, causal structure-function mapping and networks of functional relevance. Current Opinion in Neurobiology 16: 593-599

Sack AT, Kadosh RC, Schuhmann T, Moerel M, Walsh V, Goebel R (2009) Optimizing functional accuracy of TMS in cognitive studies: A comparison of methods. Journal of Cognitive Neuroscience 21: 207-221

Sakurai Y, Momose T, Iwata M, Sudo Y, Ohtomo K, Kanazawa I (2000) Different cortical activity in reading of Kanji words, Kana words and Kana nonwords. Cognitive Brain Research 9: 111-115

Sakurai Y, Yagishita A, Goto Y, Ohtsu H, Mannen T (2006) Fusiform type alexia: Pure alexia for words in contrast to posterior occipital type pure alexia for letters. Journal of the Neurological Sciences 247: 81-92

Salinas FS, Lancaster JL, Fox PT (2009) 3D modeling of the total electric field induced by transcranial magnetic stimulation using the boundary element method. Physics in Medicine and Biology 54: 3631-3647

Salmelin R, Service E, Kiesila P, Uutela K, Salonen O (1996) Impaired visual word processing in dyslexia revealed with magnetoencephalography. Annals of Neurology 40: 157-162

Sandak R, Mencl WE, Frost SJ, Pugh KR (2004) The neurobiological basis of skilled and impaired reading: Recent findings and new directions. Scientific Studies of Reading 8: 273-292

Sandrini M, Rossini PM, Miniussi C (2008) Lateralized contribution of prefrontal cortex in controlling task-irrelevant information during verbal and spatial working memory tasks: rTMS evidence. Neuropsychologia 46: 2056-2063

Saron CD, Davidson RJ (1989) Visual Evoked Potential Measures of Interhemispheric Transfer Time in Humans. Behavioral Neuroscience 103: 1115-1138

Saxe R, Brett M, Kanwisher N (2006a) Divide and conquer: A defense of functional localizers. NeuroImage 30: 1088-1096

Saxe R, Carey S, Kanwisher N (2004) Understanding other minds: Linking developmental psychology and functional neuroimaging. Annual Review of Psychology 55: 87-124

Saxe R, Jamal N, Powell L (2006b) My body or yours? The effect of visual perspective on cortical body representations. Cerebral Cortex 16: 178-182

Saxe R, Kanwisher N (2003) People thinking about thinking people: The role of the temporo-parietal junction in "theory of mind". NeuroImage 19: 1835-1842

Schilling HEH, Rayner K, Chumbley JI (1998) Comparing naming, lexical decision, and eye fixation times: Word frequency effects and individual differences. Memory and Cognition 26: 1270-1281

Schluter ND, Rushworth MFS, Mills KR, Passingham RE (1999) Signal-, set-, and movement-related activity in the human premotor cortex. Neuropsychologia 37: 233-243

Schrader S, Gewaltig MO, Körner U, Körner E (2009) Cortext: A columnar model of bottom-up and top-down processing in the neocortex. Neural Networks 22: 1055-1070

Schroeder CE, Mehta AD, Givre SJ (1998) A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. Cerebral Cortex 8: 575-592

Schurz M, Sturm D, Richlan F, Kronbichler M, Ladurner G, Wimmer H (2010) A dual-route perspective on brain activation in response to visual words: Evidence for a length by lexicality interaction in the visual word form area (VWFA). NeuroImage 49: 2649-2661

Seidenberg MS, McClelland JL (1989) A Distributed, Developmental Model of Word Recognition and Naming. Psychological Review 96: 523-568

Sekuler EB, Behrmann M (1996) Perceptual Cues in Pure Alexia. Cognitive Neuropsychology 13: 941-974

Sereno MI, Dale AM, Reppas JB, Kwong KK, Belliveau JW, Brady TJ, Rosen BR, Tootell RBH (1995) Borders of multiple visual areas in humans revealed by functional magnetic-resonance-imaging. Science 268: 889-893

Sereno SC, Brewer CC, O'Donnell PJ (2003) Context Effects in Word Recognition: Evidence for Early Interactive Processing. Psychological Science 14: 328-333

Shan C, Zhu R, Xu M, Luo B, Weng X (2010) Implicit reading in Chinese pure alexia. Brain and Language In Press, Corrected Proof

Shaywitz BA, Shaywitz SE, Blachman BA, Pugh KR, Fulbright RK, Skudlarski P, Mencl WE, Constable RT, Holahan JM, Marchione KE, Fletcher JM, Lyon GR, Gore JC (2004) Development of left occipitotemporal systems for skilled reading in children after a phonologically-based intervention. Biological Psychiatry 55: 926-933

Shaywitz BA, Shaywitz SE, Pugh KR, Mencl WE, Fulbright RK, Skudlarski P, Constable RT, Marchione KE, Fletcher JM, Lyon GR, Gore JC (2002) Disruption of posterior brain systems for reading in children with developmental dyslexia. Biological Psychiatry 52: 101-110

Shulman HG, Hornak R, Sanders E (1978) The effects of graphemic, phonetic, and semantic relationship on access to lexical structures. Memory and Cognition 6: 115-123

Siebner HR, Hartwigsen G, Kassuba T, Rothwell JC (2009) How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. Cortex 45: 1035-1042

Silvanto J, Muggleton N, Walsh V (2008) State-dependency in brain stimulation studies of perception and cognition. Trends in Cognitive Sciences 12: 447-454

Simos PG, Billingsley-Marshall R, Papanicolaou AC (2008) Single-Word Reading: Perspectives From Magnetic Source Imaging. In: Grigorenko EL, Naples AJ (eds) Single-Word Reading: Behavioral and Biological Perspectives Taylor & Francis Group, New York, pp 211-232

Skarratt PA, Lavidor M (2006) Magnetic stimulation of the left visual cortex impairs expert word recognition. Journal of Cognitive Neuroscience 18: 1749-1758

Smith RC, Dixon TR (1971) Frequency and the judged familiarity of meaningful words. Journal of Experimental Psychology 88: 279-281

Sparing R, Buelte D, Meister IG, Paus T, Fink GR (2008) Transcranial magnetic stimulation and the challenge of coil placement: A comparison of conventional and stereotaxic neuronavigational strategies. Human Brain Mapping 29: 82-96

Sparr SA, Jay M, Drislane FW, Venna N (1991) A historic case of visual agnosia revisited after 40 years. Brain 114: 789-800

Spiridon M, Fischl B, Kanwisher N (2006) Location and spatial profile of category-specific regions in human extrastriate cortex. Human Brain Mapping 27: 77-89

Spironelli C, Angrilli A (2007) Influence of Phonological, Semantic and Orthographic tasks on the early linguistic components N150 and N350. International Journal of Psychophysiology 64: 190-198

Starrfelt R, Gerlach C (2007) The visual what for area: Words and pictures in the left fusiform gyrus. NeuroImage 35: 334-342

Starrfelt R, Habekost T, Gerlach C (2010) Visual processing in pure alexia: A case study. Cortex 46: 242-255

Starrfelt R, Habekost T, Leff AP (2009) Too Little, Too Late: Reduced Visual Span and Speed Characterize Pure Alexia. Cereb. Cortex: bhp059

Steinmetz H, Fürst G, Meyer B-U (1989) Craniocerebral topography within the international 10-20 system. Electroencephalography and Clinical Neurophysiology 72: 499-506

Stewart LM, Walsh V, Rothwell JC (2001) Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study. Neuropsychologia 39: 415-419

Stokes MG, Chambers CD, Gould IC, English T, McNaught E, McDonald O, Mattingley JB (2007) Distance-adjusted motor threshold for transcranial magnetic stimulation. Clinical Neurophysiology 118: 1617-1625

Stokes MG, Chambers CD, Gould IC, Henderson TR, Janko NE, Allen NB, Mattingley JB (2005) Simple metric for scaling motor threshold based on scalp-cortex distance: Application to studies using transcranial magnetic stimulation. Journal of Neurophysiology 94: 4520-4527

Stone GO, Vanhoy M, Van Orden GC (1997) Perception is a two-way street: Feedforward and feedback phonology in visual word recognition. Journal of Memory and Language 36: 337-359

Stroop JR (1935) Studies of interference in serial verbal reactions. Journal of Experimental Psychology 18: 643-662

Szycik GR, Tausche P, Münte TF (2008) A novel approach to study audiovisual integration in speech perception: Localizer fMRI and sparse sampling. Brain Research 1220: 142-149

Talavage TM, Sereno MI, Melcher JR, Ledden PJ, Rosen BR, Dale AM (2004) Tonotopic organization in human auditory cortex revealed by progressions of frequency sensitivity. Journal of Neurophysiology 91: 1282-1296

Tarkiainen A, Helenius P, Hansen PC, Cornelissen PL, Salmelin R (1999) Dynamics of letter string perception in the human occipitotemporal cortex. Brain 122: 2119-2131

Taylor PCJ, Nobre AC, Rushworth MFS (2007) FEF TMS Affects Visual Cortical Activity. Cereb. Cortex 17: 391-399

Terao Y, Ugawa Y, Sakai K, Miyauchi S, Fukuda H, Sasaki Y, Takino T, Hanajima R, Furubayashi T, Putz B, Kanazawa I (1998) Localizing the site of magnetic brain stimulation by functional MRI. Experimental Brain Research 121: 145-152

Terao Y, Ugawa Y, Suzuki M, Sakai K, Hanajima R, GembaShimizu K, Kanazawa I (1997) Shortening of simple reaction time by peripheral electrical and submotor-threshold magnetic cortical stimulation. Experimental Brain Research 115: 541-545

Thut G, Pascual-Leone A (2010) A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. Brain Topography 22: 219-232

Tokay T, Holl N, Kirschstein T, Zschorlich V, Köhling R (2009) High-frequency magnetic stimulation induces long-term potentiation in rat hippocampal slices. Neuroscience Letters 461: 150-154

Tootell RBH, Mendola JD, Hadjikhani NK, Ledden PJ, Liu AK, Reppas JB, Sereno MI, Dale AM (1997) Functional Analysis of V3A and Related Areas in Human Visual Cortex. J. Neurosci. 17: 7060-7078

Tranchina D, Nicholson C (1986) A model for the polarization of neurons by extrinsically applied electric fields. Biophysical Journal 50: 1139-1156

Trippe J, Mix A, Aydin-Abidin S, Funke K, Benali A (2009) Theta burst and conventional low-frequency rTMS differentially affect GABAergic neurotransmission in the rat cortex. Experimental Brain Research 199: 411-421

Tsapkini K, Dimos O, Katsarou Z (2005) Pure alexia without agraphia after a lesion at the right hemisphere: A case study. Brain and Language 95: 239-240

Tsapkini K, Rapp B (2010) The orthography-specific functions of the left fusiform gyrus: Evidence of modality and category specificity. Cortex 46: 185-205

Turner R (2002) How much cortex can a vein drain? Downstream dilution of activation-related cerebral blood oxygenation changes. NeuroImage 16: 1062-1067

Uematsu S, Roberts DW, Lesser R, Fisher RS, Gordon B, Hara K, Krauss GL, Vining EP, Webber RW (1992) Motor and sensory cortex in humans - topography studied with chronic subdural stimulation. Neurosurgery 31: 59-72

Ueno S, Tashiro T, Harada K (1988) Localized stimulation of neural tissues in the brain by means of a paired configuration of time-varying magnetic fields. Journal of Applied Physics 64: 5862-5864

Ulrich R, Miller J (1994) Effects of Truncation on Reaction Time Analysis. Journal of Experimental Psychology: General 123: 34-80

Valero-Cabre A, Payne BR, Rushmore J, Lomber SG, Pascual-Leone A (2005) Impact of repetitive transcranial magnetic stimulation of the parietal cortex on metabolic brain activity: a C-14-2DG tracing study in the cat. Experimental Brain Research 163: 1-12

Valero-Cabré A, Payne BR, Rushmore J, Lomber SG, Pascual-Leone A (2005) Impact of repetitive transcranial magnetic stimulation of the parietal cortex on metabolic brain activity: A 14C-2DG tracing study in the cat. Experimental Brain Research 163: 1-12

Van Der Werf YD, Paus T (2006) The neural response to transcranial magnetic stimulation of the human motor cortex. I. Intracortical and cortico-cortical contributions. Experimental Brain Research 175: 231-245

Van Essen D (2003) Organization of visual Areas in Macaque and Human Cerebral Cortex. In: Chalupa L, Werner J (eds) The Visual Neurosciences. MIT Press

Van Orden GC (1987) A ROWS is a ROSE: spelling, sound, and reading. Memory and Cognition 15: 181-198

Van Orden GC, Johnston JC, Hale BL (1988) Word Identification in Reading Proceeds From Spelling to Sound to Meaning. Journal of Experimental Psychology: Learning, Memory, and Cognition 14: 371-386

Vandenberghe R, Price C, Wise R, Josephs O, Frackowiak RSJ (1996) Functional anatomy of a common semantic system for words and pictures. Nature 383: 254-256

Vigneau M, Jobard G, Mazoyer B, Tzourio-Mazoyer N (2005) Word and non-word reading: What role for the Visual Word Form Area? NeuroImage 27: 694-705

Vinckier F, Dehaene S, Jobert A, Dubus JP, Sigman M, Cohen L (2007) Hierarchical Coding of Letter Strings in the Ventral Stream: Dissecting the Inner Organization of the Visual Word-Form System. Neuron 55: 143-156

Vogels R, Orban GA (1985) The effect of practice on the oblique effect in line orientation judgments. Vision Research 25: 1679-1687

von Kriegstein K, Dogan O, Gruter M, Giraud AL, Kell CA, Gruter T, Kleinschmidt A, Kiebel SJ (2008) Simulation of talking faces in the human brain improves auditory speech recognition. Proceedings of the National Academy of Sciences of the United States of America 105: 6747-6752

Wagner TA, Zahn M, Grodzinsky AJ, Pascual-Leone A (2004) Three-dimensional head model simulation of transcranial magnetic stimulation. Ieee Transactions on Biomedical Engineering 51: 1586-1598

Walsh V, Cowey A (1998) Magnetic stimulation studies of visual cognition. Trends in Cognitive Sciences 2: 103-110

Walsh V, Cowey A (2000) Transcranial magnetic stimulation and cognitive neuroscience. Nature Reviews Neuroscience 1: 73-79

Walsh V, Pascual-Leone A (2003) Transcranial Magnetic Stimulation: A Neuroschronometrics of Mind. MIT Press

Walsh V, Rushworth M (1999) A primer of magnetic stimulation as a tool for neuropsychology. Neuropsychologia 37: 125-135

Warrington EK, Shallice T (1980) Word-form dyslexia. Brain 103: 99-112

Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalography and Clinical Neurophysiology - Evoked Potentials 108: 1-16

Watanabe T, Harner AM, Miyauchi S, Sasaki Y, Nielsen M, Palomo D, Mukai I (1998) Task-dependent influences of attention on the activation of human primary visual cortex. Proceedings of the National Academy of Sciences of the United States of America 95: 11489-11492

Waters GS, Seidenberg MS (1985) Spelling-sound effects in reading: time-course and decision criteria. Memory & cognition 13: 557-572

Wernicke C (1874) Der Aphasische Symptomenkomplex

Wessinger CM, Buonocore MH, Kussmaul CL, Mangun GR (1997) Tonotopy in human auditory cortex examined with functional magnetic resonance imaging. Human Brain Mapping 5: 18-25

Wessinger CM, VanMeter J, Tian B, Van Lare J, Pekar J, Rauschecker JP (2001) Hierarchical Organization of the Human Auditory Cortex Revealed by Functional Magnetic Resonance Imaging. Journal of Cognitive Neuroscience 13: 1-7

Wheat KL, Cornelissen PL, Frost SJ, Hansen PC (2010) During visual word recognition, phonology is accessed within 100 ms and may be mediated by a speech production code: Evidence from magnetoencephalography. Journal of Neuroscience 30: 5229-5233

Wheeler DD (1970) Processes in word recognition. Cognitive Psychology 1: 59-85

Wilson SA, Thickbroom GW, Mastaglia FL (1993) Transcranial magnetic stimulation mapping of the motor cortex in normal subjects - the representation of 2 intrinsic hand muscles. Journal of the Neurological Sciences 118: 134-144

Wohlschlager AM, Specht K, Lie C, Mohlberg H, Wohlschlager A, Bente K, Pietrzyk U, Stocker T, Zilles K, Amunts K, Fink GR (2005) Linking retinotopic fMRI mapping and anatomical probability maps of human occipital areas V1 and V2. NeuroImage 26: 73-82

Woolrich M, Ripley B, Brady J, Smith SM (2001a) Temporal autocorrelation in univariate linear modelling pf FMRI data. NeuroImage

Woolrich MW, Behrens TEJ, Beckmann CF, Jenkinson M, Smith SM (2004) Multilevel linear modelling for FMRI group analysis using Bayesian inference. NeuroImage 21: 1732-1747

Woolrich MW, Ripley BD, Brady M, Smith SM (2001b) Temporal Autocorrelation in Univariate Linear Modeling of FMRI Data. NeuroImage 14: 1370-1386

Wright N, Mechelli A, Noppeney U, Veltman D, Rombouts S, Glensman J, Haynes J-D, Price C (2008) Selective activation around the left occipito-temporal sulcus for words relative to pictures: Individual variability or false positives? Human Brain Mapping 29: 986-1000

Xu B, Grafman J, Gaillard WD, Ishii K, Vega-Bermudez F, Pietrini P, Reeves-Tyer P, DiCamillo P, Theodore W (2001) Conjoint and extended neural networks for the computation of speech codes: The neural basis of selective impairment in reading words and pseudowords. Cerebral Cortex 11: 267-277

Xue G, Chen C, Jin Z, Dong Q (2006) Language experience shapes fusiform activation when processing a logographic artificial language: An fMRI training study. NeuroImage 31: 1315-1326

Yap MJ, Balota DA (2007) Additive and interactive effects on response time distributions in visual word recognition. Journal of Experimental Psychology: Learning Memory and Cognition 33: 274-296

Yoshor D, Bosking WH, Ghose GM, Maunsell JHR (2007) Receptive fields in human visual cortex mapped with surface electrodes. Cerebral Cortex 17: 2293-2302

Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P (1997) Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain 120: 141-157

Yovel G, Tambini A, Brandman T (2008) The asymmetry of the fusiform face area is a stable individual characteristic that underlies the left-visual-field superiority for faces. Neuropsychologia 46: 3061-3068

Yue L, Xiao-lin H, Tao S (2009) The effects of chronic repetitive transcranial magnetic stimulation on glutamate and gamma-aminobutyric acid in rat brain. Brain Research 1260: 94-99

Zangen A, Roth Y, Voller B, Hallett M (2005) Transcranial magnetic stimulation of deep brain regions: Evidence for efficacy of the H-Coil. Clinical Neurophysiology 116: 775-779

Zhang YY, Brady M, Smith S (2001) Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. Ieee Transactions on Medical Imaging 20: 45-57

Appendix A

fMRI INFORMATION SHEET

Tracing Language Circuits in the Brain

Berkshire Research Ethics Committee06/Q1602/20, Version 3.0, 29/08/2007

Dear Research Volunteer,

You are being invited to take part in a research study using a brain scan called functional magnetic resonance imaging (fMRI). fMRI is a specific type of magnetic resonance imaging (MRI) brain scan and this sheet provides some information regarding fMRI to help you to decide whether you'd like to participate. If you have any further questions, please do not hesitate to contact Dr. Joseph Devlin (0207 679 5414, joe.devlin@ucl.ac.uk). This study has been reviewed by the Berkshire Research Ethics Committee who raised no objections on ethical grounds.

You can find out more information about what we do from our web site http://joedevlin.psychol.ucl.ac.uk/index.php). You can also find out more about MRI from The Health Protection Agency (http://www.hpa.org.uk/radiation).

What is MRI ?

MRI is a relatively recently developed technique which combines the use of magnetic fields and radio-waves to image the body. MRI does not use ionizing radiation.

Participants are asked to fill out a ***MRI Safety Screening Questionnaire***, and to remove metallic items before entering the magnet room. The screening form is included with this information sheet. If you would like to volunteer, please go through it before arriving at the Centre to determine whether there are any safety issues associated with your participation. If you are uncertain, please do not hesitate to contact Dr. Devlin (0207 679 5414, joe.devlin@ucl.ac.uk) before arriving.

fMRI uses similar methods to clinical MRI except that instead of giving good anatomical images of the brain, it provides information about the activated parts of the brain as the volunteer performs some simple task like reading. The technique relies on measuring changes in oxygen levels in brain tissue.

The MRI Scanner

The scanner is a large cube shape and has a tube (bore) running through the middle which is open at both ends. The participant enters the scanner tube laid down, head-first, with their lower legs outside the magnet's bore. Subjects who are concerned about feeling ***claustrophobic*** during the scan may wish to discuss this with the Researcher before their arrival. Volunteers can often be nervous initially, but we do everything we can to ensure comfortable and a relaxed environment during the scan, including keeping in visual and verbal contact during scanning. In addition, special glasses are provided which enable the volunteer to see out of the magnet during the test.

Starting the Scanning Procedure

Once the volunteer is comfortable in the scanner, the Researcher and Radiographer will go into the adjoining room (where the control equipment is located) and get started. This involves checking that the 2-way headphone communication system is working clearly and making sure the volunteer is comfortable. Participants may, of course, come out of the magnet or leave at any time without having to give any reason.

During the Scan

During the scanning participants hear some tapping noises (which can be noisy so ear protection is supplied). This is the normal sound of the magnet taking pictures. Different types of scan sequences make different noises. Before scans begin and after they are completed, the Radiographer and Researcher typically speak with the participant to let them know what to expect and to answer any questions that may come up. If during scanning, the participant wants to speak, (s)he has a call button which can be pressed to stop the scan and communicate with the Radiographer and Researcher.

During fMRI, participants will be asked to perform simple language tasks such as reading words on a computer screen or listening to sentences over the headphones. The Researcher will provide precise details of the particular experiment and a chance to practice outside of the scanner, before starting. In addition, we typically collect a structural scan (a picture of the anatomy of the brain) which does not require the participant to do anything other than lie still and relax, so participants may choose to listen to music or the radio through our specially designed headphones. Participants are invited to bring a CD of their choice. The choice of music does not affect the results because it is only on during the anatomical scan.

Participants receive £10 per hour for their time. The total time will always be no more than 2 hours.

Results of the Research

The data collected will be anonymised and securely stored to be analysed as part of a larger group study. The results will be published by researchers at this centre in international journals of excellence, most of which are able to be purchased, or sometimes free. More information can be found at our web site (http://joedevlin.psychol.ucl.ac.uk/index.php).

While these images of the brain are for specific research purposes only and are not meant to be diagnostic of any condition, you should be aware there is a possibility that they may reveal an unexpected result that may have relevance to your health. They do not form any part of official hospital medical records, but in the unlikely event that any unusual findings are noted incidentally, you would be notified immediately and if necessary your GP informed.

After the Scan

There are no after-effects from being scanned. Once participants have collected their belongings and spoken to the Researcher/Radiographer, they may leave.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. In fact, the data will be anonymous so that even if it could be accessed, it would not be attributable to any individuals.

TMS INFORMATION SHEET

Tracing Language Circuits in the Brain

Berkshire Research Ethics Committee06/Q1602/20, Version 3.0, 29/08/2007

Dear Research Volunteer,

You are being invited to take part in a research study using transcranial magnetic stimulation (TMS). TMS is a non-invasive method using magnetic fields to stimulate specific parts of the brain to measure whether this has any effect on performance during simple tasks such as reading words presented on a computer screen. This information sheet broadly describes the TMS procedure and answers some common questions. If you have further questions, please do not hesitate to contact Dr. Joseph Devlin (0207 679 5414, joe.devlin@ucl.ac.uk). This study has been reviewed by the Berkshire Research Ethics Committee who raised no objections on ethical grounds.

You can find out more information about what we do from our web site http://joedevlin.psychol.ucl.ac.uk/index.php.

What is transcranial magnetic stimulation (TMS)?

TMS is a non-invasive method by which a magnetic field is used to stimulate a small area of a person's brain. This is done by applying magnetic pulses to a person's scalp. These magnetic pulses pass through the skull and stimulate the brain area lying underneath the stimulating coil.

What are the side effects of TMS?

TMS is a painless procedure, but it can be noisy and can cause muscular twitches. These effects can be minimized by wearing ear plugs and by the researcher adjusting the position of the stimulating coil. TMS can also temporarily slow down finger press responses such as pressing buttons. These effects are very small (in the order of milliseconds), but sometimes people notice them. This is the measure that we use to tell us how the brain is functioning. The effects are temporary and will not out-last the testing session. This TMS study includes both **SINGLE** pulses and **REPETITIVE** magnetic pulses. It is safe to say that there are no risks or side effects known for single pulse magnetic stimulation. Under some conditions however, such as at high stimulation rates (50Hz), repetitive pulse magnetic stimulation can induce seizures. For this reason, people with any family history of epilepsy or mental illness, you should NOT take part in this study. The stimulation rates in this experiment are much lower at 10Hz and lower. If you wish to read papers on this matter I would be happy to provide them to you.

What are the possible disadvantages and risks of taking part?

It may not be safe to have TMS if you have any metal in your body because of the strong magnetic fields used. Other than dental fillings, all other metal in the body

including dental work should be discussed with the researcher beforehand. All participants are asked to fill out a TMS Safety Screening Questionnaire for their safety. The screening form is included with this information sheet. Please go through it before arriving at the Centre to determine whether there are any safety issues associated with your participation. If you are uncertain, please do not hesitate to contact Dr. Devlin (0207 679 5414, joe.devlin@ucl.ac.uk) before arriving.

It is possible that if TMS pulses are given to a pregnant woman it may harm the unborn child. Therefore, if there is a possibility that you are pregnant, you must NOT take part in this study.

TMS uses non-ionising energy in the radio frequency spectrum. Unlike X-rays, TMS does not damage chemical bonds or DNA so it does not harm cells. Instead, a small portion of the energy is transformed into heat which is dissipated normally by the body. The amount of energy absorbed by a volunteer in a typical TMS experiment is approximately 10 times less than that absorbed from using a digital cell phone. In other words, the electro-magnetic energy in TMS is well within currently safety limits and does not have harmful effects.

What should I expect if I decided to participate?

Before taking part in any TMS, you would be asked to fill out a TMS safety screening questionnaire. These questionnaires would ask you about your medical history, any medication you are currently on, and about recent alcohol, caffeine and recreational drug use. They would also ask you whether you might be pregnant. You would be required to fill out these questionnaires and to sign a consent form before any testing takes place. In addition, both alcohol and caffeine can temporarily increase an individuals' susceptibility to a seizure, so to avoid this we ask that volunteers abstain from drinking more than 2 units of alcohol in the 24 hours before TMS testing and avoid all caffeine (e.g. tea, coffee, colas, etc.) in the hour before testing.

Testing will take place in the Psychology Department at UCL. A friend or relative could accompany you to the centre. We have a waiting area for friends and relatives who wish to come along. After arriving, the researcher would explain the procedure and go through the TMS Safety Screening Form with you. Then TMS would be introduced and you would have the opportunity to become familiar with the sound it makes and the sensation of magnetic stimulation. You would also have the opportunity to practice the computer task until you were comfortable with it. The tasks are not designed to be difficult and the researcher will be present to answer any questions you may have with either TMS in general or with the specific study.

You would be paid £10 per hour for your time. The total time you would spend in a session will be no more than 2 hours. And at all times, you would be welcome to stop participating without providing any advanced notice nor an explanation.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research would be kept strictly confidential. In fact, the data will be anonymous so that even if it could be accessed, it would not be attributable to any individuals.

What will happen to the results of the research study?

We aim to publish the results of this study in a scientific journal. We may also present the results at a scientific conference or a seminar in a university. We may also publish results on our website but it would not be possible to identify you in any report or publication. We would be happy to discuss the results of the study with you and to send you a copy of the published results.

Who is organising the research?

This research study is organised by Dr. Joseph Devlin at the Dept. of Psychology, UCL – a brain scientist with lots of experience performing TMS studies.

Contact information:

Dr. Joseph Devlin
Department of Psychology
University College London
Gower Street
London WC1E 6BT
Phone: 0207 679 5414
Email: joe.devlin@ucl.ac.uk

Appendix B

Department of Psychology, UCL
Gower Street, London, WC1E 6BT
***Telephone:* 0207-679-5414**

TMS Safety Screening Form (Confidential)

If you agree to take part in this study, please answer the following questions. The information you provide is for screening purposes only and will be kept completely confidential.

Subject Questionnaire

1. Have you ever suffered from any neurological or psychiatric conditions? If YES please give details (nature of condition, duration, current medication, etc).	YES/NO
2. Have you ever suffered from epilepsy, febrile convulsions in infancy or fainted?	YES/NO
3. Does anyone in your immediate or distant family suffer from epilepsy? If YES please state your relationship to the affected family member.	YES/NO
4. Have you ever undergone a neurosurgical procedure (including eye surgery)? If YES please give details.	YES/NO
5. Do you currently have any of the following fitted to your body? Heart pacemaker Cochlear implant Medication pump Surgical clips	YES/NO
6. Are you currently taking any unprescribed or prescribed medication? If YES please give details.	YES/NO
7. Are you currently undergoing anti - malarial treatment?	YES/NO
8. Have you drunk more than 3 units of alcohol in the last 24 hours?	YES/NO
9. Have you drunk alcohol already today?	YES/NO
10. Have you had more than one cup of coffee, or other sources of caffeine, in the last hour?	YES/NO
11. Have you used recreational drugs in the last 24 hours?	YES/NO
12. Did you have very little sleep last night? This would be two or more hours less than your usual amount. For someone who typically sleeps 8 hours, "very little sleep" would be 6 or fewer hours.	YES/NO
13. Have you already participated in a TMS experiment today?	YES/NO
14. Are you left or right handed?	Left/Right
15. Date of Birth	__/__/__

Subject Consent

I (please give full name in CAPITALS)_____
confirm that I have read the TMS information sheet and have completed the above questionnaire. The nature, purpose and possible consequence of the procedures involved have been explained. I understand that I may withdraw from the study at any time.

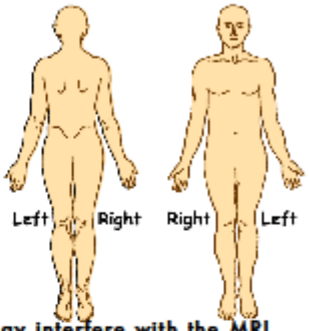
Signature_____ Date_____

Please note: All data arising from this study will be held and used in accordance with the Data Protection Act (1984). The results of the study will not be made available in a way that could reveal the identity of individuals.

Version 3, 17/10/06

JOINT MRI RESEARCH CENTRE
BIRKBECK COLLEGE &
UNIVERSITY COLLEGE LONDON

MRI RESEARCH SUBJECT PRE-SCREENING FORM 1



Principal Investigator / Lab _____

Subject Weight in Kilograms ____ Subject Number _____

Name _____
Last name First name M.I.

Birthdate _____ Email Address _____

Address _____ City _____

Postcode _____

Phone _____ _____ _____
Home Work Mobile

⚠ **Some of the following items may be hazardous to your safety or may interfere with the MRI scan. Please check the correct answer for each of the following. If you checked yes, please give more information. E.g. Type of material? How long ago? Use the diagram to indicate where on your body?**

1. ☐ Yes ☐ No Do you have a heart pacemaker?
2. ☐ Yes ☐ No Is there a possibility of metal in your head? (e.g. aneurysm clips, but not dental work like fillings)
3. ☐ Yes ☐ No Is there a possibility of metal in your eyes or have you ever needed an eyewash having worked with metals?
4. ☐ Yes ☐ No Do you have an implanted medical device? (e.g. cochlear implant, metal ear tubes, tens unit, bone stimulator, insulin or other medication pump, automatic defibrillator, internal pacing wires).
5. ☐ Yes ☐ No Have you had any metallic dental implants (e.g. posts, crowns) within the last 6 weeks?
6. ☐ Yes ☐ No Have you had any bone, tendon, spine or joint surgery within the last 6 weeks?
7. ☐ Yes ☐ No Do you weigh more than 300 lbs (135 kg)?
8. ☐ Yes ☐ No Is there any possibility that you may be pregnant?
9. ☐ Yes ☐ No Do you suffer from claustrophobia?
10. ☐ Yes ☐ No Do you have any medical problems when you lie flat on your back? (e.g. breathing problems, back pain,
11. ☐ Yes ☐ No Do you have an IUD that may contain copper, or a contraceptive diaphragm?
12. ☐ Yes ☐ No Have you had any stents, clips or surgery to any of any of your vessels (e.g. carotid artery vascular clamp, coronary stent, aortic clips, IVC filter, coils for blocked arteries)
13. ☐ Yes ☐ No Do you have metal anywhere else in your body? (e.g. spinal rods, dental work, piercings, shrapnel, buckshot, bullets) – please indicate where on your body using the diagram above
14. ☐ Yes ☐ No Do you have any piercings that can't be removed?
15. ☐ Yes ☐ No Do you have a cerebrospinal fluid (CSF) shunt? (e.g. treatment for hydrocephalus or water on the brain)
16. ☐ Yes ☐ No Do you have tattooed eyeliner, tattooed eyebrows or Bigen hair dye?
17. ☐ Yes ☐ No Have you had any medical condition that has prevented you from completing an MRI exam in the past?
18. ☐ Yes ☐ No Are you currently suffering from asthma, or do have allergies to any medication you have taken recently?
19. ☐ Yes ☐ No Have you had any previous surgery? (give details, and indicate where on your body using the diagram
    Details: _____ Date: ___/___/___
    Details: _____ Date: ___/___/___
20. ☐ Yes ☐ No Do you have a transdermal medicated patch? (e.g. nicotine patch, contraceptive patch, medicated pain relief)
21. ☐ Yes ☐ No Do you wear a hearing aid or dentures?

_____ _____ ___/___/___
Name of person completing form (please print) Signature Date

_____ _____ ___/___/___
Name of MR Operator Signature Date