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Segregated and Integrated Hemispheric Processes in Vision and Movement

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This thesis is dedicated to my wife,
Ying-Ying Hsieh

ABSTRACT

Anatomical facts dictate that a foveally fixated word is represented by nodes of a neural network distributed across the two hemispheres. However, the mechanisms and implications of this lateralization are poorly understood. This thesis aimed to explore segregated and integrated hemispheric processes in the visual and motor cortices by applying unilateral transcranial magnetic stimulation (TMS) over cortical areas involved in visual and movement perception.

In a visual letter recognition task, unilateral TMS over the visual cortex impaired processing in the contra-, but not ipsilateral visual field. Crucially, such selective contralateral effects were found for the left and right sides of foveal targets. The results imply that each primary visual cortex initially processes the contralateral part of foveal stimuli.

To extend these results from letters to whole word recognition processes, a left or right precue was followed by a word/pseudoword. Visual word recognition was not affected by attentional cues unless the characters were scattered into letter arrays such that word shape was completely distorted. For distorted words, the lateralized cues had significant ipsilateral effects, in line with the single letter recognition findings.

To establish the neural correlates of early hemispheric integration of visual stimuli, the crossed-uncrossed difference (CUD) paradigm was applied. The CUD was increased by inhibiting the crossed latencies, but only when TMS was applied to the hemisphere receiving visual information. Interhemispheric transmission was further studied by recording blood flow change at the unstimulated motor cortex by near infrared spectroscopy. The results revealed that the significantly increased oxy-haemoglobin and slightly decreased deoxy-haemoglobin outlasted the 1 Hz stimulation by up to 40 minutes.

In summary, the results support the split fovea theory that assumes split projection of visual stimuli between the hemispheres, and shed light on the mechanisms and temporal dynamics of interhemispheric transmission of visuospatial stimuli.

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PUBLICATIONS ARISING FROM THESIS

Chiang, T.C., Vaithianathan, T., Leung, T., Delpy, D., Lavidor, M and Walsh, V. (in process) Using near infrared spectroscopy and transcranial magnetic sitmulation to investigate the motor cortex.

Chiang, T.C., Lavidor, M (2005) Magnetic stimulation and the Crossed-Uncrossed difference (CUD) paradigm: Selective effects in the ipsi- and contra-lateral hemispheres. *Experimental Brain Research, 160*, 404-408.

Chiang, T.C., Walsh, V., Lavidor, M. (2004) The cortical representation of foveal stimuli: evidence from quadrantanopia and TMS-induced suppression. *Cognitive Brain Research, 21*,309-316.

CHAPTER 1: INTRODUCTION

If one were to identify the most salient features of the human brain, compared with that of other primates, hemispheric asymmetry would be high on one's list. Views of asymmetry in the primate brain range from claims of no asymmetry in the rhesus monkey, to some asymmetry in chimpanzees and clear left right asymmetry in humans (Yeni-Komshian & Benson, 1976). Other studies of gorillas and other monkeys have reached similar conclusions (Groves & Humphrey, 1973; LeMay & Geschwind, 1975). An intriguing question is whether cerebral asymmetry in humans in any way reflects our uniqueness, in particular because of the lateralisation of language functions. Lateralisation raises many questions about how the hemisphere's share, compete and coordinate to execute cognitive functions. For example, when a word enters the visual cortex, does each hemisphere have the whole word or only the contralateral part? It is well-known that the meaning of the word is generally processed by the left hemisphere but it is not clear whether there are conditions under which the left dominance breaks up. It is also not clear how visual information across the hemispheres is funnelled into action systems. The main aim of this thesis is to investigate hemispheric interactions in vision and language, and in particular to explore the means by which bilateral representation in the visual cortex can produce unitary perceptions and actions.

In the first chapter, I give a brief review of the relevant literature regarding hemispheric asymmetries and their functional meaning. Chapter 2 details the techniques used in my experimental chapters. Chapters 3 to 6 report the results of my empirical work, and in the final chapter I propose an integration of the results and discuss the implications of my findings for future work in this field.

Comparison of the left and right hemispheres

To the naked eye the human brain appears to be made of two similar hemispheres. With the exception of the pineal gland, brain structures in one hemisphere can be found in the other hemisphere, allowing some leeway for minor differences in size and location. Each cerebral hemisphere can be divided into four lobes: Frontal, parietal, temporal and occipital. Much research on hemisphere asymmetries has concentrated on the temporal lobe (see review, Shapleske, Rossell, Woodruff, & David, 1999). The left planum temporale is "... sheetlike, roughly triangular structure, which lies in the superior surface of the temporal lobe within the SF(sylvian fissure)" (p.27 of Shapleske, Rossell, Woodruff, & David, 1999). On average, this is one third longer and travels 3 mm more anterior in the left than the right hemisphere (Geschwind & Levitsky, 1968; Wada, Clark, & Hamm, 1975). This is but one example of gross hemispheric differences, but it has been associated with several uniquely human features, such as late brain development and language functions (Chi, Dooling, & Gilles, 1977; Galaburda, Corsiglia, Rosen, & Sherman, 1987; Rumeau et al., 1994).

A general rule of brain anatomy is that one hemisphere is primarily responsible for information processing and action in contralateral space or by the contralateral part of the body. However, it is clear that this generalisation can be overstressed. For example, even aspects of language, the most lateralised of functions, require the right hemisphere in processing tone, the semantic meaning of concrete nouns, metaphor and humour (see review, Springer & Deutsch, 1997). Clearly, how well we understand brain lateralisation depends on how well we understand the components of cognitive tasks. To illustrate this I will briefly discuss aspects of temporal lobe language functions and parietal lobe attention functions.

Temporal Lobe and Language

The early study of language was restricted to the left hemisphere following the identification of Broca's and Wernicke's areas (Broca, 1861; Wernicke, 1874). Damage to Broca's area (Brodmann area 44/45) results in a productive aphasia. The content of the patients talk contains only keywords despite the fact that they understand spoken and written language very well. In contrast, patients with damage to Werknicke's areas (posterior part of Brodmann area 22) are able to speak fluently, but the content lacks meaning and the comprehension of written and spoken language is poor. If the arcuate fasciculus, connecting these two areas, is damaged, patients will suffer a conduction aphasia in which auditory comprehension and speech articulation are preserved, but patients find it difficult to repeat heard speech (Carlson, 2005). These disorders will not be observed it corresponding regions of the right hemisphere have been damaged. Further, following left hemisphere damage there are often generalised deficits in motor control including in the facial muscles required for speech and in the hands required for sign language (Hickok, Bellugi, & Klima, 1996; Kimura & Watson, 1989). Detailed examinations of motor deficits and brain organisation (Scheibel et al., 1985; Steinmetz, Volkmann, Jancke, & Freund, 1991) have led to the hypothesis that linguistic functions and hand dexterity may share a neural basis (see review, Josse & Tzourio-Mazoyer, 2004). However, at least one case in the literature suggests that writing and verbal naming can be independently controlled by the two hemispheres (Baynes, Eliassen, Lutsep, & Gazzaniga, 1998).

The left hemisphere has more capacity for dealing with written words and this is reflected in higher accuracy and shorter reaction times in word recognition tasks when stimuli are presented in the right rather than the left visual field –subjects to which I will return in my empirical work. In general, processing time will increase or accuracy will decline as the number of letters in a word increases. This is called the length effect and it reveals an interesting difference between the two hemispheres. The response to stimuli in the left visual field increased linearly in time as a function of the number of letters. Stimuli presented in the right visual field, however, do not suffer from this effect (Ellis, 2004; Young & Ellis, 1985). This effect cannot be explained without a good understanding of the processing of written words in the two hemispheres. For example longer words tend to have a smaller neighbourhood size (N-value), which designates as the number of other words of the same length that differ from it by a single letter. Lavidor and Ellis (2002a; , 2002b) manipulated word length and neighbourhood value to examine the interaction with visual field presentation. They found that high neighbourhood value words presented in the left visual field are processed faster than low neighbourhood value words, but there was no effect of neighbourhood value when stimuli were presented in the right visual field. This effect can be eliminated by presenting the stimuli vertically (Bub & Lewine, 1988), in mIxEd CaSe (Fiset & Arguin, 1999), and in stepped format (Young & Ellis, 1985). In contrast, the right hemisphere contributes to lexical processing associated with nouns and metaphor.

Neuropsychological investigations of split brain patients for example, have shown that they can identify nouns with the right hemisphere (Gazzaniga, 1970); and can also identify verbs, adjectives and some grammatical and syntactic structures (Zaidel, 1990). Patients with damage to the right hemisphere may suffer deficits in interpreting metaphors and proverbs (Winner & Gardner, 1977) and in word association (Nakagawa, 1991).

Thus it seems that phonological processes are mainly subserved by left hemisphere brain regions, including Broca's, Wernicke's, the Middle Temporal gyrus and to a lesser extent the right superior temporal regions (Demonet et al., 1992; Mazoyer et al., 1993; Zatorre, Evans, Meyer, & Gjedde, 1992). The right hemisphere specializes in other aspects of language such as rhythm and prosody. Brain imaging studies for example have implicated the right temporal pole (Mazoyer et al., 1993), the right prefrontal cortex (Zatorre, Jones-Gotman, Evans, & Meyer, 1992) and the right superior temporal cortex in a range of language related functions required for interpretation of meaning. Correspondingly, patients with right hemisphere lesions often speak with a flattened intonation and have difficulty in judging the emotional tone of speech (Heilman, Scholes, & Watson, 1975).

Parietal lobe and attention

The parietal lobe is thought to be necessary for the selection and maintenance of attention. Like the left hemisphere specificity for language, the right parietal lobe seems to be dominant in spatial functions. For example, visual neglect, a phenomenon in which there is a misperception of space and objects in space contralateral to the lesion, is primarily associated with right parietal damage and is rarely seen following damage in the homologous region of the left hemisphere (Heilman, Watson, & Valenstein, 1993). Neglect has also been observed in audition (Bellmann, Meuli, & Clarke, 2001) and the somatosensory system (Bellmann, Meuli, & Clarke, 2001) and the right parietal cortex seems to be critical in these modalities as well as in vision. Neglect can gradually recover and evolve into extinction such that patients are able to detect a contralesional stimulus when presented alone but not when a competing stimulus is simultaneously presented in the ipsilesional field. However, although the extinguished stimulus is ignored, information from it can still be processed, presumably in the right hemisphere via the ventral object processing stream (Driver, Vuilleumier, Eimer, & Rees, 2001). For example, patients with right parietal damage are able to successfully compare the extinguished stimulus with the stimulus presented in the ipsilesional visual field (Volpe, Ledoux, & Gazzaniga, 1979), and also to integrate an extinguished stimuli into the perception of an illusory contours (Vuilleumier, Valenza, & Landis, 2001).

The left parietal lobe, in contrast, has been associated with the motor attention. Paying attention to the planned movement of hands induces left lateralised activation in the parietal cortex (Rushworth, Krams, & Passingham, 2001). In addition, compared with single finger responses, independent of hand, a finger choice task cued by the position of a marker on the screen evoked more activation in the left and right intra-parietal sulcus (Schluter, Krams, Rushworth, & Passingham, 2001). Rushworth *et al.* (2001) also showed the effects of parietal lobe damage on motor attention. When the pre-cue correctly predicted the location of the target, patients with either left or right parietal lobe damage performed equally well. However, an incorrect cue yielded large deficits in patients with left parietal damage, thus indicating that these patients are unable to disengage motor attention from the incorrect cued movement. As in the findings on spatial attention, the coverage of motor attention by the left parietal lobe is bilateral in space (Colvin, Handy, & Gazzaniga, 2003).

Rushworth *et al.* (2001) applied transcranial magnetic stimulation (TMS) to differentiate motor and spatial attention in the left and right parietal lobes. Motor attention was only disrupted by TMS on the left supramarginal gyrus and spatial attention was impaired only by TMS of the right angular gyrus. These results provided further evidence that the left parietal lobe was the motor analog, in attentional terms of the right parietal lobe for space.

Interactions between left and right hemispheres

The corpus callosum

Anatomically there are several routes that connect the two halves of the brain: The corpus callosum, the anterior & posterior commissures, the hippocampal commissure and the sub-cortical commissures (Nieuwenhuys, Voogd, & van Huijzen, 1990, p. 365). The Corpus callosum is a thick bundle of fibers connecting cerebral hemispheres and is the major highway of interhemispheric transmission. The anterior commissure lies near the hypothalamus and forms a bridge between the left and right lenticular nuclei, a collective term for the putamen and globus pallidus. The posterior commissure is located between the pineal body and the cerebral aqueduct. The hippocampal commissure, also called the commissure of the fornix, links the left and right hippocampus. The subcortical commissures lie mainly in the diencephalon.

The corpus callosum grows rapidly during the first two years of life, almost reaching the lower end of the adult size range and continues to grow for approximately the first 25 years of life (Pujol, Vendrell, Junque, Marti-Vilalta, & Capdevila, 1993). Its main function is believed to be the exchange of information between the two hemispheres, be it for coordination, facilitation or inhibition (Springer & Deutsch, 1997). Split brain patients are a valuable source of information regarding the exchange of information between the two hemispheres With the corpus callosum being a target site in operations to relieve intractable epilepsy, studies have been able to establish that the anterior regions and posterior regions subserve different information transfer (Funnell, Corballis, & Gazzaniga, 2000; Gazzaniga, 1989; Suzuki et al., 1998). For example, one patient in whom the splenium was sectioned could not name an object presented in the left visual field over several weeks of testing. Subsequently he was able to achieve this transfer of tactile cues via the anterior portion of the corpus callosum. This shared ability was later lost following a second operation in which the anterior corpus callosum was also sectioned (Sidtis, Volpe, Holtzman, Wilson, & Gazzaniga, 1981).

A complete resection of the corpus callosum results in two relatively independent cerebral hemispheres. The examples are dramatic and convincing, and span visual, verbal, tactile and higher cognitive functions. Wolford, Miller and Gazzaniga (2000), for example, have proposed two very different strategies used by the two hemispheres. They have described the left hemisphere as being an interpreter of information, employing knowledge and expectations about the world, whereas the right hemisphere responds on the basis of salience. In one experiment (Wolford, Miller, & Gazzaniga, 2000), subjects were presented with stimuli that could appear in either the upper or lower visual fields with varying probability. When the stimuli were presented to the right hemisphere, the subjects guess where the next stimulus would be simply went for the highest frequency location on every trial. When the stimuli were presented to the left hemisphere, however, the interpreter adopted a frequency matching strategy which resulted in a less successful performance than the right hemisphere. This is an important case because it shows that whether or not a hemisphere is dominant depends on the demands of the task: Here we have the smart, linguistic, hypothesis generating hemisphere performing worse than the "minor" hemisphere. The interpreter can be seen at work again when split brain subjects are presented with two visual stimuli, one in each hemifield, simultaneously. Split brain patients only gave verbal reports of the object presented in the right visual field but were able to rationalise their choices when they reached for a different object presented in the left visual field (Gazzaniga, 2000; see also Baynes, Wessinger, Fendrich, & Gazzaniga, 1995)

In some rare cases there is agenesis of corpus callosum, yet subjects with this condition can grow up with normal cognitive abilities (Springer & Deutsch, 1997), saved for some specific impairments in tasks requiring into hemispheric transfer of motor and visual spatial skills or in some tasks requiring integration of visual and tactial information over both sides of the body (Lassonde, Sauerwein, & Lepore, 1995) in addition the subjects may sometimes have a consistent deficit in phonological processing, although overall language development may be normal (Temple & Isley, 1994). These data suggest that the corpus callosum, although critical in the normal integration of the hemispheres can, over the course of development, be compensated for by the non callosal commissural pathways.

Word recognition

When a word is presented at the centre of fixation, each hemisphere receives the part of the word falling in the contralateral visual field. Lavidor *et al.* (2001) have exploited this in studies of split fovea processing. They adjusted the location around fixation of a centrally presented word in order to manipulate the number of letters appearing in the right or left visual field. They observed longer latencies in a word recognition paradise when more of the letters fell in the left visual field, but no effects of the number of letters following in the right visual field. In a subsequent study (Lavidor, Hayes, Shillcock, & Ellis, 2004), Lavidor's group used words with the same number of letters but a different neighbourhood size on the lead part or end part of the words. The lead part of a centrally presented word will normally be processed by the right hemisphere, and the end part by the left hemisphere. In agreement with 2001 study, they found that right hemisphere processes but not left hemisphere processes were affected by neighbourhood size. The results were taken as evidence that foveal mechanisms of word recognition are the same as those in parafoveal areas. This raises a perennial issue in vision research: is the fovea split in the cortical representation of the visual field? I will return to this question in Chapter 3.

Visuomotor integration

When a visual stimulus triggers a motor response, it involves information transfer between the visual and motor cortices, and this may require interhemispheric transfer. In studying the pathway from vision to action, two topics are of particular relevance to the goals of this thesis. The first concerns time: how long does it take information to travel between the two hemispheres? One mode of measurements adopts Poffenberger's paradigm of comparing reaction times in conditions in which information may be crossed or uncrossed between hemispheres. This is called the crossed-uncrossed difference or CUD. It is well established that responses in uncrossed conditions are faster than responses in uncrossed conditions. In normal subjects the CUD is several milliseconds, and of course this is much larger in split brain and acallosal subjects (Roser & Corballis, 2002). The second topic of particular relevance is the issue of which parts of the corpus callosum are involved in transmission. This seems to depend on specific tasks and stimulus properties. For example, one study mentioned above has shown that the posterior part of the corpus callosum is related to the transmission of visual stimuli. Patients with a lesion of the posterior body of the corpus callosum also show the prolonged CUD (Peru, Beltramello, Moro, Sattibaldi, & Berlucchi, 2003). Recent functional imaging imaging studies, however, have suggested that the genu, in the anterior part of corpus callosum, is activated by crossed conditions (Omura et al., 2004; Weber et al., 2005). It has been argued that the anterior portion is important for motor transmission but these data suggest that other brain areas, including regions of the parietal cortex and some subcortical areas are all so important (Forster & Corballis, 2000; Weber et al., 2005). Other evidence shows an asymmetry in interhemispheric transfer depending on whether the transfer is from left to right or right to left (Forster & Corballis, 2000; Velay & Benoit-Dubrocard, 1999). I will focus on this issue in Chapter 5.

Motor cortex lateralisation

Transmission between hemispheres needs to allow facilitatory and inhibitory signals to keep the two hemispheres functioning in concert. Interhemispheric inhibition has been reported by Ferbert *et al.* (1992) who showed that a single conditioning shock to one hemisphere resulted in a weaker response of the ipsilateral hand by a subsequent test shock six to thirty milliseconds later delivered to the motor cortex of the opposite hemisphere. Increasing the intensity of the conditioning stimulus increases the duration of this interhemispheric inhibition (De Gennaro et al., 2004; Ferbert et al., 1992). Similarly, exercising the hand in normal subjects produces a pre-activation in the corresponding hemisphere and decreased blood flow in the ipsilateral sensory motor cortex (Allison, Meador, Loring, Figueroa, & Wright, 2000; Newton, Sunderland, & Gowland, 2005). This inhibition occurs at the cortical level (Di Lazzaro et al., 1999). For example, patients with an absence or abnormalities of the corpus callosum have delayed or absent inhibition responses (Bonato et al., 1996; Mochizuki, Huang, & Rothwell, 2004; see also Reddy et al., 2000). It seems that the critical site in this transmission is the anterior part of the corpus callosum (Meyer, Roricht, Grafin von Einsiedel, Kruggel, & Weindl, 1995). Further evidence supporting the idea that the anterior half of the corpus callosum mediates between motor regions is found in musicians who have a significant increase in volume of this region (Schlaug, Jancke, Huang, Staiger, & Steinmetz, 1995). However, it has also been suggested, on the basis of neuropsychological patient studies that the posterior half is also critical even though it is more commonly associated with visual functions (Meyer, Roricht, & Woiciechowsky, 1998).

Transcranial magnetic sitmulation has been used to study interhemispheric inhibition and it has been reported that 1 Hz stimulation above motor threshold can increase the excitability of the contralateral, unstimulated hemisphere (Schambra, Sawaki, & Cohen, 2003). However there are some variable results in the study of hemispheric interactions and similar paradigms, using subthreshold stimulation, have reported inhibition (Strens et al., 2002) and facilitation (Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-Leone, 2004). The frequency of magnetic stimulation also has variable effects. Stimulation delivered at 5 Hz was found to magnify the motor evoked potential (MEP) on the ipsilateral hand (Gorsler, Baumer, Weiller, Munchau, & Liepert, 2003), but it did not change the coherence between two hemispehres (Oliviero, Strens, Di Lazzaro, Tonali, & Brown, 2003).

Taken together, the body of psychological, developmental, neuropsychological, electrophysiological, brain stimulation and brain imaging data point to two hemispheres poised in fine balance to enable humans to acquire and utilize a wide range of sensory and cognitive capacities. In this thesis, I address some of the outstanding issues from the level of the very origin of asymmetrical input, that is, in the fovea, through to the integration of visual and motor information, and on to the problem of attentional asymmetries. In doing so it was necessary to establish behavioural parameters, to be able to stimulate the human brain with a fine temporal resolution, to be able to record from the brain using near infrared spectroscopy and to combine magnetic brain stimulation with the recording of the bloodflow. In the next chapter, I will introduce the techniques used in this thesis.

CHAPTER 2: GENERAL METHOD

Transcranial Magnetic Stimulation (TMS)

What TMS is and how it works

TMS uses a magnetic field which crosses the scalp into brain and induces environmental changes outside and inside neurons, thus the influencing the firing rate of the neurons (Nagarajan, Durand, & Warman, 1993). The principle of TMS can be traced back to Michael Faraday's discovery of electromagnetic induction in 1831. In any circuit a rapid current change will produce a magnetic field which in turn induces an electric current in another circuit. In the case of TMS, this second circuit is the brain (Walsh & Rushworth, 1999; see review, Hallett, 2000). To achieve this, a large and rapidly changing current are required to generate a sufficient magnetic field. Figure 1 shows the sequence of events in a typical TMS pulse (Walsh & Cowey, 2000)

The induced electric field depends on the orientation of the cells relative to the direction of the induced field and TMS is, therefore, more likely to stimulate neurons parallel to the cortical surface (Bohning et al., 1999). The effect of TMS on the nervous system can be viewed from an anatomical or functional perspective. Take TMS on the motor cortex for example, and assume the index finger can be slightly raised when the hands are relaxed. TMS can excite the motor cortex and trigger muscles to raise the index finger. However, if volunteers need to use the index finger to precisely press a button, the reaction time would be delayed or accuracy would be impaired: The apparent excitation caused by the TMS would interfere with behaviour. From this behavioural aspect, TMS impairs performance.

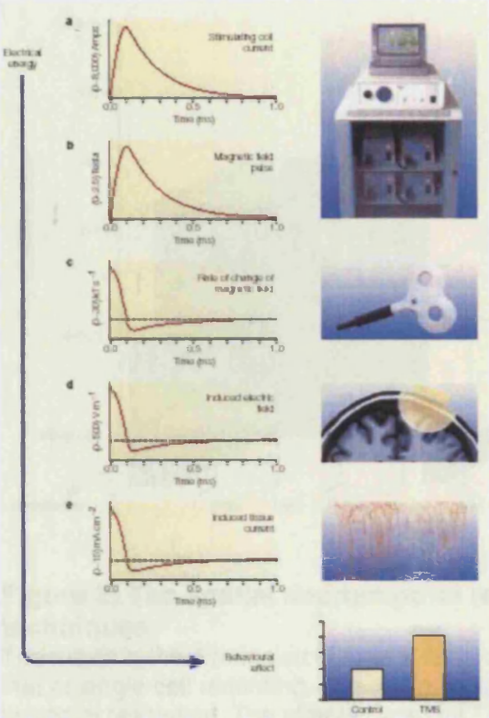

Figure 1: TMS and the brain.
An electrical current of up to 8 kA is generated by a capacitor (a) and discharged into a circular, or figure-of-eight shaped, coil which in turn produces a magnetic pulse of up to 2 T (b). The pulse has a rise time of about 200 μs and a duration of 1 ms and owing to its intensity and brevity changes at a rapid rate (c). The changing magnetic field generates an electric field (d) resulting in neural activity or changes in resting potentials (e). The net change in charge density in the cortex is zero. The pulse shown here is monophasic, but in studies that require repetitive pulse TMS (rTMS), the waveform will be a train of biphasic pulses which allow repeated stimulation. (Figure adapted from Walsh & Cowey, 2000, with permission)

The spatial and temporal resolution of TMS

The spatial and temporal resolution of TMS with respect to other techniques is shown in Figure 2. However, it is also useful to consider what has been called its cognitive or functional resolution (Walsh & Pascual-Leone, 2003). TMS interference effects can help to establish the necessity of an area for a given function and thus complements the correlative data from other techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and event related potentials (ERPs).

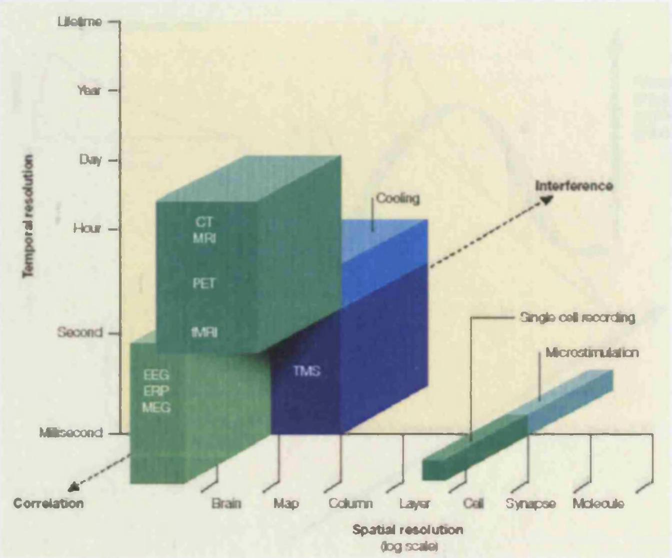

Figure 2: The spatial and temporal resolution of TMS, compared with other techniques.
The x-axis is the dimension of spatial resolution. The stimulated area of TMS is larger than that of single cell recording, and could be smaller than that of EEG. The y-axis is the temporal resolution. The affected area by TMS would be between ms and several minutes. The third dimension is the interference. Unlike fMRI, ERP and single cell recording which passively record the brain activity, TMS actively interferes with the brain activity (Figure adapted from Walsh & Cowey, 2000, with permission).

With respect to temporal resolution, TMS is like EEG, ERP and MEG at the level of a few milliseconds. The rise time of the coil current is less than 200 µs, and the whole duration of a single pulse lasts approximately 1 ms. Nevertheless, the duration of the effect in the cortex is difficult to determine with absolute precision because the neurons stimulated by TMS take time to recover to the normal functional state. Thus, the interaction of the duration of TMS pulses and an area's involvement in a task is a probabilistic issue (Figure 3) (Walsh & Cowey, 2000). Functionally, TMS effects can be distinguished in steps of 10 or 20 ms (Amassian et al., 1989; Pascual-Leone & Walsh, 2001).

The spatial resolution of TMS relies on the type of coil and the neurons underlying the coil. There are two types of coil in common use, circular and figure-of-eight. The bigger the coil, the deeper the penetration of the stimulation (Rudiak & Marg, 1994). The peak of the induced electric field by a circular coil is not in the centre, but around the ring (Figure 4). The induced electric field in the centre is 30% less

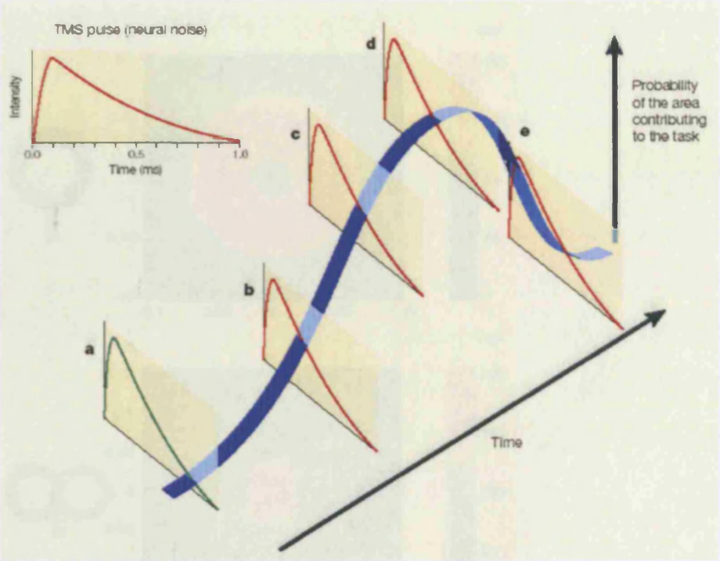

Figure 3: Temporal relationship between transcranial magnetic stimulation and behaviour.
A probabilistic picture of the relationship between pulse strength and behavioural effects. The upper panel shows that the intensity of the transcranial magnetic stimulation (TMS) pulse is greatest close to the time of onset and then declines within one millisecond. The effect this has on behaviour is a function of the intensity of the physiological effects of TMS and the probability that the neurons stimulated are critical to the task. a: The pulse here would not have a behavioural effect because it is applied too early. **b:** The pulse here would interfere with behaviour because an early (that is, high) phase of the TMS noise is applied even though the probability of the area's involvement is low. **c,d:** Similarly, the pulses here would have a behavioural effect because of the high probability of the area's involvement at the time of the pulse. **c,e:** Although the pulses applied here arrive at similar parts of the probability curve, the neural noise at **e** is higher because there is no recovery time. So the product of neural noise and neural necessity would be higher at **e** than at **c.** The appropriate application of TMS may have effects at times well before **b** and **c** or well after **e**, the reported peak. (Figure adapted from Walsh & Cowey, 2000, with permission)

than that adjacent to the coil windings (Bohning, 2000). However, the figure-of-eight coil has increased focality in the centre (Ueno, Tashiro, & Harada, 1988) because the two circular coils carry current in opposite directions, and where the coils meet, there is a summation of the electric field. The end windings of the figure-of-eight coil have only half the intensity of the centre and the focal effective volume, only 3 cm long by 2 cm wide by 2-3 cm deep (Bohning, 2000). Figure 5 illustrates the area affected by the two types of coil.

The precise area affected by the induced field is not easy to define. It is hard to tell, for example, how many neurons traverse the induced field (primary affected area)

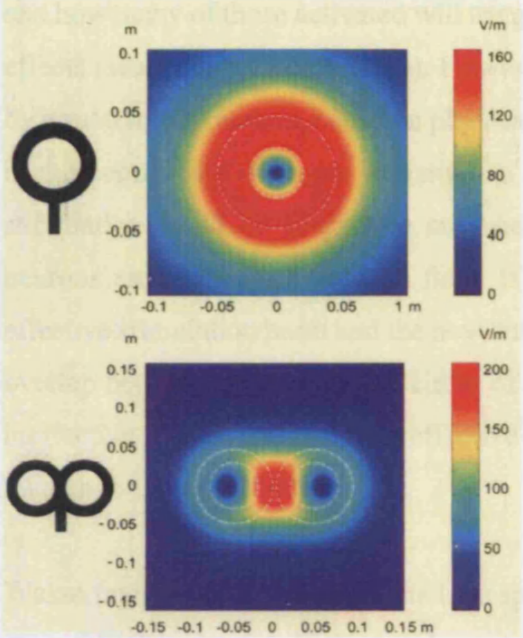

Figure 4: Distribution of the induced electric fields by a circular (top) and figure-of-eight (bottom) stimulating coil.
The circular coil has 41.5 mm inside-turn diameter, 91.5 mm outside turn diameter (mean 66.5 mm) and fifteen turns of copper wire. The figure-of-eight coil has five 6 mm inside-turn diameter, 90 mm outside-turn diameter (mean 73 mm), and nine turns of copper wire on each wing. The outline of each coil is depicted with dashed white lines on the representation of the induced fields. The electric field amplitude is calculated in a plane 20 mm below a realistic model of the coil (dI/dt = 108 A s~1). (Figure created by Anthony Barker; used with permission.)

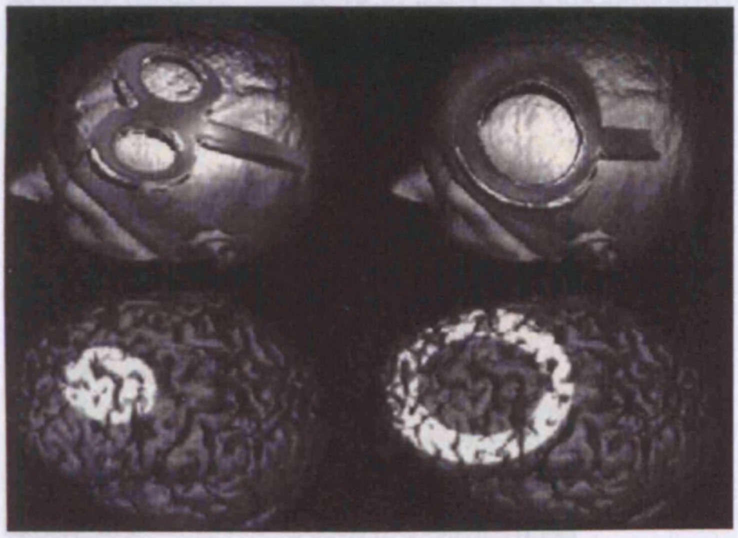

Figure 5: Cartoon-like representation of regions targeted by TMS using a circular or figure-of-eight-shaped coil over the scalp.
Given the differences in induced fields, the results of an experiment done with the figure-of-eight coil may not be reproducible with a circular coil centered over the same brain region because different brain areas would be affected. (Figure adapted from Walsh & Pascual-Leone, 2003, with permission)

and how many of those activated will trigger a series of trans-synaptic transmission effects (secondary affected areas). However, the stimulation areas can be inferred by a subtraction method, based on physical models (Barker, 1999). If a coil located in the central site of figure 6 disrupts a behavioural task, the effective areas of stimulation could be said to be anywhere within, around, or connected to the neurons crossed by the induced field. If the coil is moved to either side of the effective stimulation point and the new sites fail to disrupt the behavioural task, the overlap between the central and either of the two lateral sites can be said to be an ineffective region, and the most effective field is the central sub-region (hot spot) (Walsh & Cowey, 2000).

Wassermann *et al.* (1999) indicated the spatial resolution of TMS was within 5-22 mm of PET activation in the hand primary motor area. Several studies have also shown that TMS effects can be reduced remarkably just by moving a coil a few millimetres away from the 'hot spot' (Barker, Jalinous, & Freeston, 1985; Kammer, 1999; Paus & Wolforth, 1998; Schluter, Rushworth, Passingham, & Mills, 1998). With regard to secondary affected areas, Ilmoniemi *et al.* (1997) observed that the ipsilateral hemisphere was activated (as measured by EEG) 7 ms after the right occipital lobe was stimulated by TMS, and the contralateral hemisphere was then activated 28 ms after TMS.

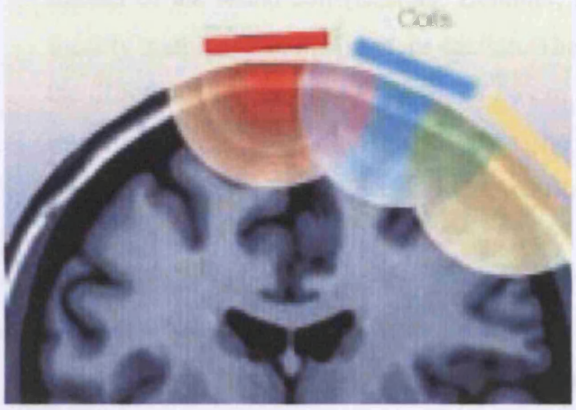

Figure 6: Subtractive lesion analysis applied to TMS.
From models of TMS-induced electric fields one can infer the region of stimulation. By stimulating at neighbouring regions on the scalp the inferences can be refined and, notwithstanding the uncertainty of any one field, reasonable functional anatomical attributions can be made. The 'coils' and induced fields in this figure are illustrative of the methodological rationale and do not represent real configurations and effects. (Figure adapted from Walsh & Cowey, 2000, with permission)

TMS and striate cortex

Since the visual cortex was originally reported as a good target of TMS study (Amassian et al., 1989), subsequent TMS research on the striate cortex can be divided into three major categories: (i) phosphene threshold (PT) studies, (ii) mapping of phosphenes and scotomas and (iii) behavioural tasks. The following will separately introduce TMS studies in each category.

TMS and phosphene threshold (PT)

A "phosphene" is a visual sensation that is produced by something other than light falling on the retina. When poking your eyeball with a finger, you may see spots lines or stars. These are "pressure phosphenes", produced by mechanical stimulation of retinal nerve cells. "Electrical phosphenes" can be produced by passing electric current through the retina, or through the visual cortex of the brain (Wade, 1998; Walsh & Pascual-Leone, 2003). PT is the lowest TMS intensity that makes a subject see phosphenes. The measurement depends on several parameters, such as the coil type, size, location, and TMS pulse frequency and duration. Many PT experiments have adopted the figure-of-eight coil (Boroojerdi et al., 2000; Kammer, 1999; Kammer, Beck, Erb, & Grodd, 2001; Ray, Meador, Epstein, Loring, & Day, 1998; Sparing et al., 2002; Stewart, Walsh, & Rothwell, 2001), instead of the round coil (Kastner, Demmer, & Ziemann, 1998) because of the focality mentioned in the previous section. The size of figure-of-eight coil among the different experiments ranges from 7.5 cm to 10.0 cm in outer diameter. The usual location of TMS stimulation is along the midline of the inion (Ray, Meador, Epstein, Loring, & Day, 1998; Stewart, Walsh, & Rothwell, 2001), or the striate cortex around the inion (Boroojerdi et al., 2000; Kammer, 1999; Kastner, Demmer, & Ziemann, 1998; Sparing et al., 2001). PT remains consistent when measured at weekly intervals (Stewart, Walsh, & Rothwell, 2001) and is reduced by paired TMS pulses (Boroojerdi, 2002; Ray, Meador, Epstein, Loring, & Day, 1998; Sparing et al., 2002). Repetitive TMS evokes phosphenes readily and the higher frequency, the lower PT.

In addition to TMS parameters, ongoing brain activation will have an influence on PT. Visualizing letters reduced PT(Sparing et al., 2002) possibly by raising the base level of activation (Kosslyn et al., 1999). In summary, phosphenes can be induced by TMS over the striate cortex and the threshold will be reduced when more TMS is delivered.

Mapping phosphenes and scotomas

When TMS elicits phosphenes, the phenomenon each volunteer sees will be different. The most common phosphenes are like flashes or spots of light; a simple geometrical figure like a straight or curved line, bar, triangle or circle; and its colour is usually white or grey. There are also some complex phosphenes, like irregular contours, multiple scattered shapes, kinetic phosphenes, and even colours (Fernandez et al., 2002; Kammer, 1999; Ray, Meador, Epstein, Loring, & Day, 1998). There are also some examples of phosphenes experienced as dark on light (Fernandez et al., 2002).

The location of phosphenes is basically contralateral to the site of TMS. When moving the TMS coil laterally, phosphenes move away from the midline. Whereas, when moving the coil dorsally, phosphenes are located in the lower visual field or in both lower and upper visual fields, but rarely exclusively in the upper visual field (Cowey & Walsh, 2000; Kammer, 1999).

If a phosphene occurs at the same time as a visual stimulus, it may impair visual performance; in other words, TMS can induce an artificial scotoma. Mapping scotomas and phosphenes is, therefore, necessary to define the relationship between them. Kammer (1999) found that in 9 out of 15 cases phosphene location matched the scotoma's; the others being either incongruent or not producing a scotoma. Among the nine matched cases, only two had equally sized scotomas and phosphenes, the others having a larger scotoma area (four cases) or a smaller scotoma area (three cases).

To summarize, then, TMS effects in the visual cortex can produce different kinds of phosphenes, from simple geometrical figures to complex forms or colours. The location of phosphenes is basically contralateral to the coil position, and mostly in the lower visual field. Scotomas can be induced by phosphenes to interfere with judgements of visual stimuli. The locations of phosphene and scotomas are sometimes similar.

TMS and cognitive behavioural tasks

The first successful TMS experiment on the human brain was in 1985. Barker *et al.* (1985) placed an excitation coil on a subject's scalp over the motor cortex and recorded muscle-action potentials from the contralateral abductor digitii minimi muscle. The Subject's muscle contraction was observed without discomfort. Subsequently, Amassian *et al.* (1989) interrupted letter recognition contralateral to the TMS coil over the occipital cortex. In the following decade, many varieties of tasks were used in TMS experiments. The discussion below surveys some of the TMS experiments most pertinent to my work.

A simple task is the detection of a non-meaningful visual stimulus. In assessing transmission time across the corpus callosum, subjects only need press a key when detecting a LED. The location of the visual stimulus will interact with the responsding hand, and reaction time (RT) will be faster when the visual stimulus is ipsilateral to the response hand, and slower if the visual stimulus is contralateral to the response hand. This RT difference between the two conditions is the so called cross-uncrossed difference (CUD) and it has been verified in many experiments (Brysbaert, 1994; Chiang, Walsh, & Lavidor, 2004; Fendrich & Gazzaniga, 1989; Harvey, 1978; Lavidor & Ellis, 2003). Marzi *et al.* (1998) applied single pulse TMS over the occipital cortex 50 ms after the presentation of a LED and found that TMS magnified CUD. RT was prolonged when the visual information needed to cross to the contralateral hemisphere that controls the hand to make the response. Epstein and Zangaladze (1996) adopted a similar non-meaningful task, an asterisk disappearing from an array of six asterisks. The maximal impairment by TMS was discovered when applied 62 ms after visual stimulation and the coil displacement was 4 cm above the inion.

The TMS effect seems to be restricted to recent processing event in the brain. Maccabee *et al.* (1991) showed TMS can unmask a visual mask, rather than the visual stimulus. However, a non-linear combination effect of mask and TMS was found recently (Kammer, Scharnowski, & Herzog, 2003).

The effective time of TMS delivery on cognitive tasks was initially found between 80 and 100 ms after the visual stimulus. In the range of SOA=40-140 ms, there was incomplete impairment, and beyond the range there was no effect (Amassian et al., 1989). However, re-examining the differences between SOAs in different experiments it seems clear that some factors need to be considered before directly seeking "magic times" (Walsh & Pascual-Leone, 2003; Walsh & Rushworth, 1999)

TMS intensity has an important influence on timing. In some studies, it has been shown that the shorter the visual simulation, the longer is required for visual processing and transmission, and hence the optimal SOA of impairment is apparently delayed (Amassian et al., 1989; Beckers & Homberg, 1991; Kammer, Scharnowski, & Herzog, 2003; Marzi et al., 1998; Masur, Papke, & Oberwittler, 1993). Task difficulty also plays a role in determining the time window of impairment. Sternberg's short-term-memory scanning task is presumably more difficult than detection of LED or letters and in this task, the impairment of scanning rate occurred at SOAs between 154 or 210 ms (Beckers & Homberg, 1991).

Recently the study of neuronal interactions has shown that back-projections to the striate cortex is necessary for awareness and perception (Pascual-Leone & Walsh, 2001). Further, Juan and Walsh (2003) showed that striate cortex was still important for visual processing up to 200 to 240 ms after visual stimulation offset, in addition to the more common early times around 80-120 ms.

To sum up, varying tasks have all been used to show that TMS can interfere with information processing in the striate cortex. Timing studies indicate that there are at least two critical time zones for TMS impairment, one about 100 ms after visual stimulus offset, indicating the early process of visual information, and the other involved in the back projections from higher cortical areas.

TMS and motor cortex

The demonstrative phenomenon of TMS over the primary motor cortex is the twitch of the contralateral hand muscle. The motor threshold is usually defined as the minimum intensity of TMS to elicit a small (usually 50 μV) motor evoked potential (MEP) at the target muscle in at least half of the trials (Rothwell et al., 1999).

MEPs can be influenced by the parameters of TMS. High frequencies and high intensity of stimulation lead to an increase of MEP excitability, and the effective period after stimulation is positively related to these parameters (Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994; Wu, Sommer, Tergau, & Paulus, 2000). On the other hand, stimulation at below MEP threshold usually requires longer trains to have any lasting effects (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000a; , 2000b).

In contrast, low frequency TMS usually results in suppression of MEP excitability. The stimulation of 0.9 Hz or 1 Hz with high intensity (115% of motor resting threshold) over the primary motor cortex suppressed the MEP input-output curve, and increased resting motor threshold for up to 30 min after the end of stimulation (Chen et al., 1997; Muellbacher, Ziemann, Boroojerdi, & Hallett, 2000). On the other hand, the stimulation with subthreshold intensity (e.g., 85% of motor resting threshold) had a much weaker effect on MEP excitability as compared with suprathreshold rTMS (Fitzgerald, Brown, Daskalakis, Chen, & Kulkarni, 2002). Nevertheless, the EEG result showed, under subthreshold stimulation, that the coherence of alpha band was increased (i.e., lowered EEG power) for up to 25 minutes on the stimulated motor cortex, but not on the contralateral motor cortex (Strens et al., 2002). The discrepancy might be explained if the inhibition of subthreshold stimulation could be restricted to the cortical level, but not extend to the corticospinal connection.

Near Infrared Spectroscopy (NIRS)

What NIRS is and how it works?

Everyday we are surrounded with electromagnetic energy. Some we can sense, like radio, visible light and heat. Some is beyond our sensation, like the Sun's ultraviolet and even gamma rays from stars or radioactive substances. Each type of energy has a different range of wavelengths in the electromagnetic spectrum (figure 7). The visible light is approximately between 400 and 700 nm in wavelength. The infrared waves are just between visible red light and the microwave portion, approximately from 700-100,000 nm, which can be further divided into three sub-categories: near, mid and far. It is generally accepted that near infrared light is approximately below 1,300 nm and the commonest application is the remote control of TVs.

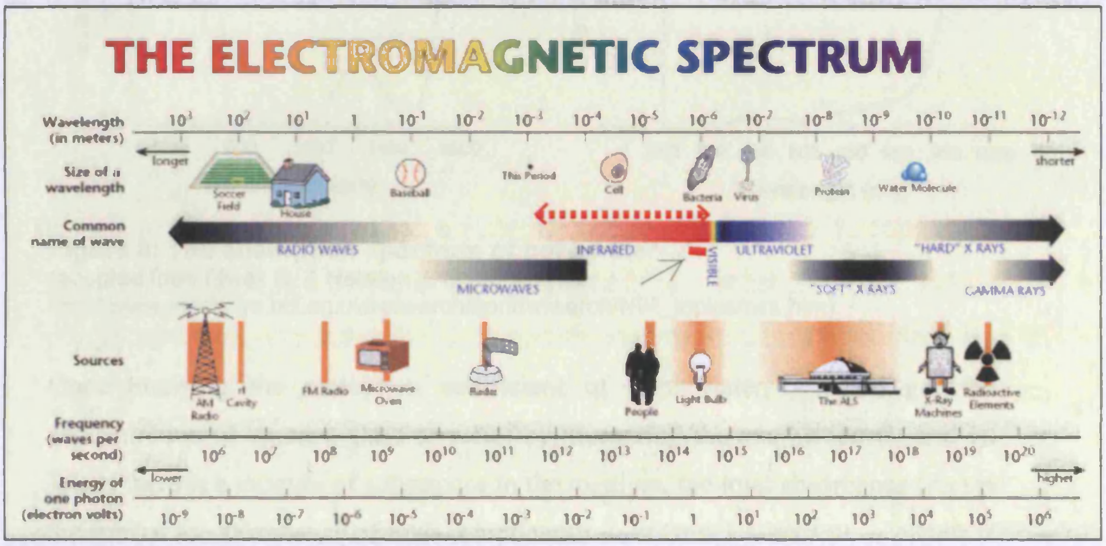

Figure 7: The electromagnetic spectrum
The infrared region of the spectrum is labeled by the red arrow, and the near infrared is next to the visible spectrum (adopted form the website: http://www.lbl.gov/MicroWorlds/ALSTool/EMSpec/EMSpec2.html)

When a light (I_0) transmits through a non-scattering monochrome medium, the output light (I) will be attenuated because some of the light is absorbed by the medium. The phenomenon can be described by the Beer-Lambert Law (named after the two scientists Johann Heinrich Lambert (1728-1777) and August Beer (1825-1863)), which states the light absorbance of the medium (A) has the linear relationship between the concentration of the medium (c) and the distance the light travels through the medium.

$A = acd = -\log_{10}(I_0/I)$ (equation 1)

Where a is the specific extinction coefficient of the medium. By measuring the I_0 and I, we can get the relationship between the extinction coefficient and the absorption spectrum (Sassaroli & Fantini, 2004). For example, water, 80% of adult brain tissues (Woodard & White, 1986), has relatively low absorbance between 200-900 nm. Beyond 900 nm, its absorbance surges up quickly (figure 8).

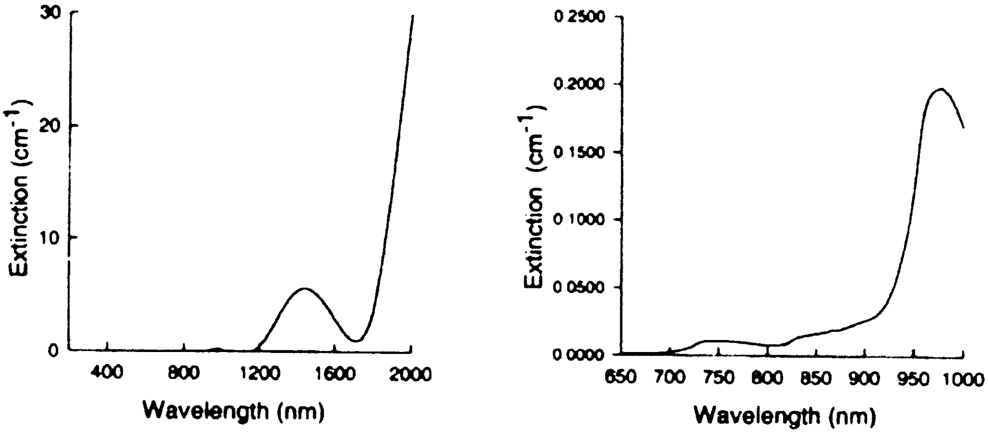

Figure 8: The absorption spectrum of pure water
(adopted form Elwell C. & Hebden J. at the website: http://www.medphys.ucl.ac.uk/research/borl/research/NIR_topics/nirs.htm)

Once knowing the extinction coefficient of pure water, we can get the concentration of another glass of water by measuring the attenuation (I_0 and I). When there is a mixture of substances in the medium, the total absorbance (A_T) is the sum of the absorbance of each component:

$A_T = A_1 + A_2 + A_3 + \ldots + A_n$ (equation 2)

However, light in the medium, especially in biological tissues, could probably be scattered by the cell membranes and the boundaries between various organelles, like mitochondria, ribosomes, fat globules, glycogen and secretory globules. The scattered light increases the travel path in the medium and, as a result, increases the probability of absorption or loss of detection. The effects appear in the Modified Beer-Lambert Law as the following (Chance, Anday, & Nioka, 1998):

$$A = acd*DPF + G = -\log_{10} (I_0/I) \qquad \text{(equation 3)}$$

Where G means light loss and DPF is the differential pathlength factor, accounting for the increased path length. Due to the unknown G, we can't know how much the light is absorbed and scattered when measuring the I_0 and I (attenuation). Thus, the concentration of the medium can't be measured either. However, we can actually get the change in concentration of the medium if we assume G does not change during the measurement.

$$(A_2-A_1) = a(c_2-c_1)d*DPF \qquad \text{(equation 4)}$$

This is the reason why some measured values are differential concentration from the time of initial measurement.

Absorption spectrum of Haemoglobin

It is well known that oxygen is essential for cells to produce energy that it is carried to the cells in the blood stream. Hemoglobin is the key chemical compound that combines with oxygen (oxygenated haemoglobin, O_2Hb) from the lungs and carries the oxygen to cells throughout the body. Once the oxygen has been transmitted to the cells, the O_2Hb will have changed into deoxyhaemoglobin (HHb). The more active the cells are, the more oxygen is needed. The increased need for oxygen means blood flow is required. Thus, the change of haemoglobin may be an index of cell activities.

The absorption spectrum of haemoglobin is shown in figure 9. The left panel indicates the short waves of visible light is absorbed by haemoglobin and, therefore, the arterial blood appears red. The right panel is the enlarged scale of the extinction coefficient which shows in the longer wavelength of near infrared spectrum (800-1,000 nm) that O_2Hb has more absorbance than HHb. Nevertheless, the opposite pattern happens in the shorter wavelength of near infrared spectrum (700-800 nm). Around the 800 nm, both O_2Hb and HHb have the same extinction coefficient. According to equations 2 and 4, the total differential concentration of haemoglobin can be measured independent of tissue oxygenation.

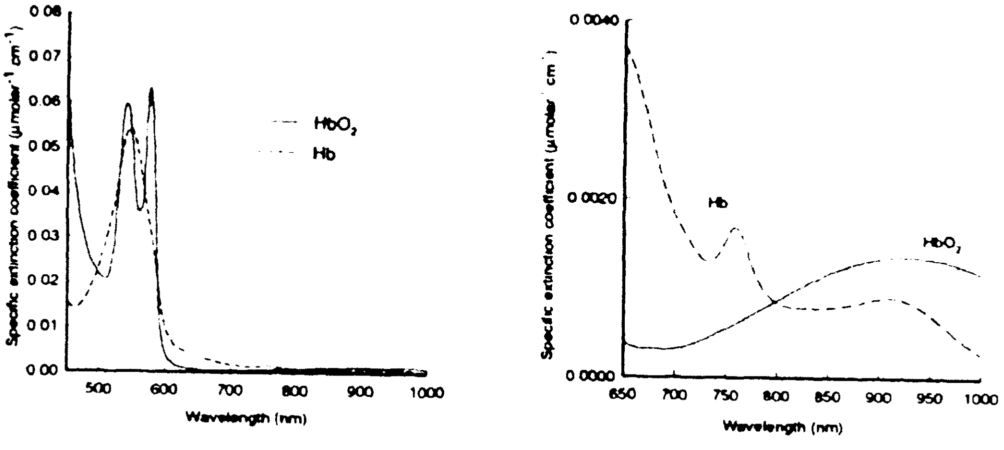

Figure 9: The absorption spectrum of O_2Hb and HHb
(adopted form Elwell C & Hebden J at the website:
http://www.medphys.ucl.ac.uk/research/borl/research/NIR_topics/nirs.htm)

In the range of near infrared wavelength, there are other substances that can be considered as non-interfering in measurement, such as water, lipid and melanin. Water is easily transparent and is clinically considered as a constant absorber. The lipid, though containing 10-40% of tissue, has a similar absorbance spectrum to water. Melanin, an effective absorber of ultraviolet region of spectrum, can also be thought of constant and oxygen independent. Nevertheless, there are some substances that can absorb near infrared as well. Cytochrome oxidase (CO) is an enzyme, existed in the mitochondria membrane, which helps regulate oxygen metabolism of the respiratory chain. Although the detection of its stable concentration in the short term can be resolved by using dual-wavelength spectroscopy, there are some debates and inconsistency with CO measurement in the human (Villringer & Chance, 1997; see review, Obrig & Villringer, 2003). Other substances are also able to absorb near infrared, e.g., haemoglobin compounds, like carboxyhaemoglobin, haemiglobin and sulfhaemoglobin. Despite this, they are either in very low concentrations in normal healthy subjects or have a low extinction coefficient on the near infrared spectrum.

The features of NIRS

NIRS is also a non-invasive tool to measure changes of oxygenation state in the human brain (Jobsis, 1977). Unlike other imaging technologies, like fMRI, PET and MEG, the cost of NIRS is much cheaper in terms of set-up, operation, maintenance and data interpretation. Moreover, the full apparatus can be operated outside the lab or hospitals, and can be conveniently transferred between sites. The portability can suit some patients who can't move into the chamber of fMRI, PET or MEG, and allow researchers to investigate brain-related processes in the natural environment (Miyai et al., 2001; Okamoto et al., 2004).

However, the spatial resolution of NIRS is not as good as fMRI. The input light (I_0) and the output light (I) consist of a pair of optodes 2-4 cm apart and placed on the skull. The depth of light penetration of the optodes is considered to be equal to one-quarter to three quarters of the distance of the optodes (Gratton, Maier, Fabiani, Mantulin, & Gratton, 1994). On the other hand, the temporal resolution of NIRS can reach 50 ms (Gratton, Corballis, Cho, Fabiani, & Hood, 1995), which can monitor real-time change of blood flow in the target area.

When adopting NIRS, there are some practical considerations to improve the validity of measurement (Chance, Anday, & Nioka, 1998). The most concern surrounding NIRS results is the difficulty in identifying the target area associated with the activation measured. The other concern is that of impairing the transmission of emitter optode (I_0) and receiver optode (I) by skin pigmentation and hair color. Dark hair can absorb the light because of the melanin content. The best way to avoid the difficulty is to cut the hair out around the measurement area. Without the hair intervention, the thickness of skull, dura matter and cerebral spinal fluid (CSF) are thought to be causes of interference in the NIRS signal. It may be the reason why some subjects do not give NIRS signal, even if they are bald.

NIRS and the brain

Since Jöbsis (1977) first demonstrated that NIRS could be used to monitor the degree of oxygenation of certain brain areas, several studies have shown the validity of NIRS in the brain research. These will be briefly reviewed in the following.

One of the common tasks used in NIRS study is the finger tapping exercise. The best observation of surging O_2Hb and plunging HHb was exercising finger tapping at least 3 times per second; and the faster the frequency, the better activation in the contralateral motor cortex (Kuboyama, Nabetani, Shibuya, Machida, & Ogaki, 2004; Obrig, Hirth et al., 1996; see also Obrig, Wolf et al., 1996).

To validate NIRS in brain research one must compare the results with that of other imaging techniques, like PET and fMRI. Studies have indicated that the results of NIRS and PET are coherent and the best correlation happens in the outer 1 cm of the brain tissue, i.e., from the gray matter (Hock et al., 1997; Okada et al., 1997; Villringer & Chance, 1997). NIRS also has a strong correlation with fMRI, both in its spatial and temporal dimensions (Hirth et al., 1996; Kato, Izumiyama, Koizumi, Takahashi, & Itoyama, 2002; Mehagnoul-Schipper et al., 2002; Toronov et al., 2001). In some cases, NIRS is even better than fMRI in the detection of the activation areas in the damaged brain (Sakatani, Murata, Fukaya, Yamamoto, & Katayama, 2003).

Little research has been done using the combination of NIRS and TMS. In these studies, NIRS was applied to the motor cortex which had been stimulated by TMS, either immediately or later. Oliveri *et al.* (1999) showed that stimulation over 2 minutes at a low frequency can evoke an increase of O_2Hb in 5 min, although HHb did not change at all. Noguchi *et al.* (2003) used a single pulse of TMS and found that O_2Hb and EMG were dependent on the intensity of stimulation. Supra-threshold stimulation would boost both indices, but sub-threshold stimulation only induced a hameoglobin change.

In summary, NIRS uses optical transmission into the brain to measure blood flow changes, especially haemoglobin and deoxy-haemoglobin. Due to its optical device, the spatial resolution is limited to the outer layers of the cortex, but the temporal resolution is much better than some existing imaging techniques. In addition, the results of NIRS are consistent with PET and fMRI. The other advantages, like low cost, easy manipulation and high mobility, make NIRS a useful prospect in the research of cognitive neuroscience.

CHAPTER 3: THE SPLIT-FOVEA IN THE VISUAL CORTEX

Visual information presented to the right of fixation (in the right visual field or RVF) is projected to the visual cortex of the left cerebral hemisphere (LH) and information presented to the left of fixation (in the left visual field or LVF) is projected to the visual cortex of the right cerebral hemisphere (RH). Because it has been assumed that there is an overlap of the visual fields along the vertical meridian, giving both hemispheres access to foveal stimuli, and because homonymous hemianopia is often accompanied by foveal sparing (wherein anything between 1 and 10 degrees, of central vision is preserved on the same side as the homonymous defect, (Leff, 2004), it is often assumed that the representation of foveal stimuli requires no further exploration (e.g., Brandt, Stephan, Bense, Yousry, & Dieterich, 2000; Petit et al., 1999; Trauzettel-Klosinski & Reinhard, 1998; Victor, Conte, & Iadecola, 1991).

In an influential paper, Leventhal *et al.* (1988) reported that some retinal ganglion cells project to the 'wrong' laminae of the lateral geniculate nucleus. This was particularly so for ganglion cells in the nasal hemiretina. The interpretation was that the crossing of the nasal fibers in the optic chiasm is not complete, allowing some projections from the nasal part of the retinae to reach the ipsilateral hemispheres. Hence foveal stimuli, viewed by the nasal retina, are projected to the contralateral visual cortex. Figure 10 demonstrates the contralateral and ipsilateral projections from the hemiretinae when presented with a foveal target, according to Leventhal *et al.*'s (1988) model. I will term this model here the bilateral projection theory. Other animal studies (Fukuda, Sawai, Watanabe, Wakakuwa, & Morigiwa, 1989; Stone, 1966; Stone, Leicester, & Sherman, 1973) supported this model which is usually taken as an explanation of foveal sparing in hemianopia (Zihl, 1989).

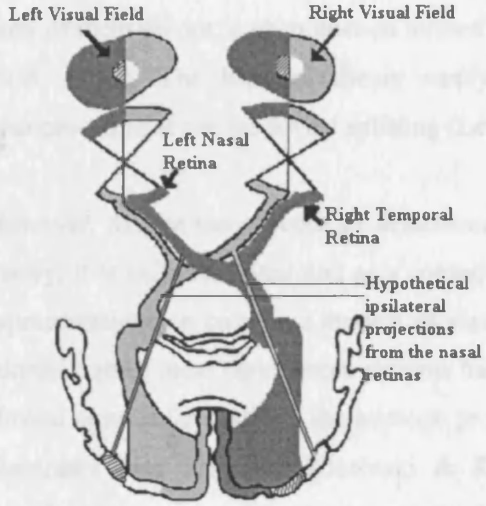

Figure 10: A bilateral projection model of the foveal area assuming ipsilateral projections from the nasal hemiretinae.

A problem for the bilateral projection theory is that behavioral studies have consistently failed to provide evidence of the functional role of the putative bilateral representation of the fovea in humans. Harvey (1978), for example, presented visual targets to the left and right of fixation at various retinal loci and found a separation between crossed and uncrossed responding at all retinal loci. Targets located 0.25° and 0.5° from fixation, i.e. in the region of the nasotemporal overlap, produced a reaction time difference between crossed and uncrossed responding just as large as at the other loci. If an area of functioning overlap projecting to both cerebral hemispheres exists, then the need for interhemispheric crossing would be eliminated (Harvey, 1978; Haun, 1978; Lines & Milner, 1983).

Recent behavioral studies also failed to support the bilateral representation theory (Brysbaert, 1994; Fendrich & Gazzaniga, 1989; Fendrich, Wessinger, & Gazzaniga, 1996; Lavidor, Ellis, Shillcock, & Bland, 2001; Lavidor, Ellison, & Walsh, 2003; Sugishita, Hamilton, Sakuma, & Hemmi, 1994). These studies have suggested that the foveal area is functionally split between the two hemispheres: this alternative is termed the split fovea theory (Shillcock, Ellison, & Monaghan, 2000).

Another challenge to the bilateral view is that although most hemianopia patients have preserved vision of the central area (forveal sparing, see Zihl, 1989), up to 36% of them do not, a phenomenon termed foveal splitting (Celesia, Meredith, & Pluff, 1983). The bilateral theory easily accommodates the foveal sparing phenomenon but not the foveal splitting (Leff, 2004).

However, despite the absence of behavioral evidence for the bilateral projection theory, it is still influential and as a consequence, the implications of split foveal representations on cognitive models of visual recognition are under-explored. In addition, since most hemianopia patients have preserved vision in the central area (foveal or macular sparing), the bilateral projection account of the foveal area still dominates (see Trauzettel-Klosinski & Reinhard, 1998). The chapter aimed therefore to examine the question of the foveal representation by testing visual recognition at different eccentricities in a patient with a lower field quadrantanopia. More importantly, to show that by temporarily disrupt processing in the right and left hemispheres of healthy observers with TMS, it could reproduce the foveal splitting pattern seen in the patient. The goal was to test which of the two theories, the split or the bilateral projection, can better resolve the foveal representation question.

Experiment 1 – Quadrantanopia

A subject VN has a quadrantanopia in her lower RVF, due to a lesion caused by surgical removal of the occipital cortex above the calcarine sulcus in the left hemisphere (Trevethan & Sahraie, 2003).

Static Humphrey perimetry, using the 10-2 programs (Trevethan & Sahraie, 2003), revealed a visual field defect which covered the right lower quadrant of her visual field (see the upper panel of Figure 11). Note that the values in the perimetry diagram that represent VN's perception of targets that are 1° to the right of fixation are well below normal performance yet above threshold (-26 dB in the left eye and -30 dB in the right eye (International Perimetry Standard). Such borderline values allow some vision; hence foveal sparing in certain visual conditions and foveal splitting in other conditions may be found. In light of the borderline values it was important to test the left eye and the right eye of VN separately. In addition, testing VN's monocular performance would allow direct testing of a prediction derived from Leventhal *et al.* (1988) (see Figure 10), who suggested that the ipsilateral projections from the nasal retinae would lead to foveal sparing in the eye contralateral to the lesion, and foveal splitting in the eye ipsilateral to the lesion.

Method

Subject

VN is a 29 year old female who underwent brain surgery aged 21 to remove an arterovenous malformation in her left occipital lobe. Her visual symptoms began when she was aged 15 and she had two posterior cerebral artery emboli 4 months prior to surgery. The lesion is in the left posterior parietal and occipital areas involving the superior aspect of the primary visual cortex. The lesion resulted in a visual field defect which covered the right lower quadrant of her visual field (Trevethan & Sahraie, 2003). VN is right handed according to the Edinburgh handedness questionnaire (Oldfield, 1971).

Stimuli

For the letter/digit classification task, nine digits and nine letters (A, H, M, T, U, V, W, Y, X) were selected. Each stimulus was randomly presented at one of eight presentation locations, four in the upper visual field (0.5° above fixation) and four in the lower visual field (0.5° below fixation). In each upper or lower field, there were four locations: 3° from fixation to the left or right (LVF and RVF, respectively), and 0.5° from fixation to the left or right (foveal-LVF and foveal-RVF, respectively). VN's vision in the upper visual field, within the foveal area, is normal (see Figure 11) and serves as a baseline for comparison with her impaired lower VF.

Because visual acuity declines when stimuli appear at non-foveal locations (Bouma, 1973), para-foveal targets were increased in size. The M-scaling I employed has been verified with behavioral data (Rovamo & Virsu, 1979), and also been applied to digits (Strasburger, Harvey, & Rentschler, 1991) and letters (Goolkasian, 1994). According to the formula, stimuli presented 3^{o} away from fixation were 1.71 times bigger than stimuli presented 0.5^{o} degree from fixation. I piloted the sizes of the foveal and parafoveal targets (N=10 right-handed participants) to ensure equal performance at all eccentricities.

Targets presented foveally were 0.87 cm high (0.5^{o}), and the size of the parafoveal targets was 1.49 cm high (0.85^{o}).

Apparatus and procedures

Stimuli were presented on a PC using E-prime software. The participant sat with her head supported by a chin-rest and head-strap in order to secure head position and stabilize fixation at a distance of 1 m from the screen. There were two blocks of left-eye presentations and two for right-eye presentations. The subject wore an eye-patch to cover the unused eye. Each experimental block considered of 144 trials (nine letters and nine digits in eight presentation locations). Each trial began with a fixation point appearing in the centre of the screen for 500 ms. The fixation point was replaced by a central red circle that was simultaneously presented with the target for 50 ms (based on a pilot study reaching 85% accuracy with this duration). The stimuli (letters or digits) were randomly presented at one of the eight possible eccentricities. After presenting the red circle and the stimulus, a subsequent mask was displayed for 2 seconds at the stimulus location. The participant's task was to decide, as quickly and as accurately as possible the right or left mouse keys (order of response keys was counter-balanced). A blank screen was displayed for 500 ms to end the cycle, followed by the fixation point for the next trial.

Result

VN's 10-2 perimetry and experimental results are presented in Figure 11. In the letter/digit classification, a sequence of χ^2 tests revealed that VN's performance was significantly above chance level (50%) in all conditions except the lower RVF including the foveal region. This was found for the left and right eyes separately.

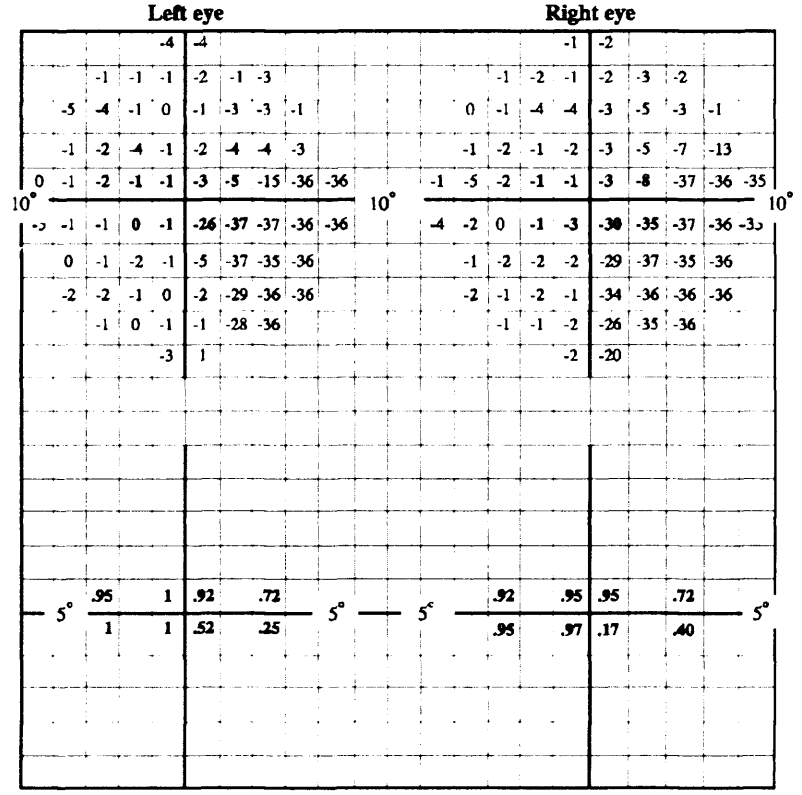

Figure 11: Humphrey 10-2 perimetry and experimental results of VN
The Upper panel was 10-2 perimetry data of VN's right and left eyes. Values represent the difference in decibels (dB) between VN's test result and the expected age-corrected normal values at each point in the central 10^0 of the visual fields. The lower panel presents % of correct letter/digit classification by VN at 8 eccentricities. Note that VN's performance reflects the perimetry data for these eccentricities.

Discussion

VN's performance in the letter/digit classification task reflects foveal splitting and not sparing. Leventhal *et al.* (1988) suggested that the ipsilateral projections from the nasal retinae would lead to foveal sparing in the eye contralateral to the lesion (which is the right eye for VN), and foveal splitting in the eye ipsilateral to the lesion (the left eye for VN). This prediction does not fit VN's data, as the same (poor) results were found in the foveal-RVF targets in both eyes. In fact, many previous studies with hemianopia and quadrantanopia patients have reported results that do not fit Leventhal *et al.*'s model (see Ehlers, 1975; Williams & Gassel, 1962; but see Trauzettel-Klosinski & Reinhard, 1998 for contrasting results).

However I should be cautious as this pattern could be task-dependent and visual tasks that do not require target identification or classification may reveal different results. Given VN's perimetric thresholds, it is possible that the poor vision in the lower RVF would be enough to allow simple target detection, hence foveal sparing may be observed under certain conditions (see Trevethan & Sahraie, 2003). Nevertheless a recent hemianopia case (Upton, Hodgson, Plant, Wise, & Leff, 2003) reported foveal splitting in the contralateral eye, in line with our results and in contradiction to the bilateral projection predictions.

The next stage of the investigation was to test healthy observers with the same task while applying TMS over the right or left visual cortex in order to mimic VN's visual field defect in normal observers with TMS, while investigating the involvement of the two hemispheres in representing foveal targets.

Experiment 2 – TMS Induced Suppression

Amassian *et al.* (1989) were the first to demonstrate suppression of visual perception with TMS; participants were unable to identify visually presented letters when a TMS pulse was given over the occipital pole between 80 ms and 100 ms after the letter was briefly presented. Following Amassian *et al.* (1989) and others' demonstrations of the effects of TMS on visual cortical processing (e.g., Cowey & Walsh, 2000; Kammer, 1999; Lavidor & Walsh, 2003; Pascual-Leone & Walsh, 2001), it should be possible to impair letter/digit classification when stimulating left or right visual cortex to evaluate the extent to which the hemifields overlap along the vertical meridian.

According to the bilateral representation theory, unilateral TMS over the visual cortex would not impair the processing of foveally-presented targets, as a complete copy of the target is still projected to the un-stimulated hemisphere. On the other hand, the split fovea theory prediction is that unilateral TMS would impair target classification processes, as the parts of the target contralateral to TMS are temporarily inaccessible.

Repetitive transcranial magnetic stimulation (rTMS) was applied over the left and right occipital cortex of normal observers during a letter/digit classification task to investigate the extent to which target recognition processes could be accounted for according to the split fovea theory. The targets were presented at four different eccentricities, similar to the eccentricities employed with VN. The experiment tested the prediction that unilateral TMS would interfere with letter/digit classification in the contralateral visual field. Crucially, the split fovea theory predicts that the same patterns would be obtained for the foveal-LVF and foveal-RVF targets.

Method

Design

A 4 x 4 x 2 factorial design (target location: LVF, foveal-LVF, foveal-RVF and RVF) x (TMS: no stimulation, sham-TMS, RH stimulation, or LH stimulation) x (target type: letter, digit) was used in a within-subjects design. Dependent variables were response time and percent of incorrect responses. The application of rTMS occurred in alternating blocks of single hemisphere stimulation. The other variables were randomly applied.

Participants

Nine native English-speaking participants, 5 females and 4 males, took part in the experiment. All of the participants had normal or corrected to normal vision and were aged between 22 and 41 (mean 30.8, sd 6.5). All the participants were right-handed and scored at least 80 in the Edinburgh Handedness Inventory (Oldfield, 1971), with mean score of 94.4 (sd 6).

Before taking part in the experiment, participants signed a consent form and reported absence of epilepsy, or any other neurological conditions as part of the screening procedures. This experiment was reviewed and approved in advance by the Joint UCL/UCLH Committees on the Ethics of Human Research.

Stimuli

For the letter/digit classification task, 9 digits and 9 letters (A, H, M, T, U, V, W, Y, X) were selected. The stimuli were identical to those used with VN. Stimuli were presented at four eccentricities on the horizontal meridian. The 4 locations were 3° to the left of fixation (LVF), 0.5° to the left (foveal-LVF), 0.5° to the right (foveal-RVF) and 3° to the right of fixation (RVF). Stimulus size was scaled for eccentricity (see Experiment 1). Targets presented foveally were 0.87 cm high (0.5°), and the size of the parafoveal targets was 1.49 cm high (0.85°).

TMS equipment

The stimulator used was a Magstim TM model 200 (Super Rapid Magstim, Whitland, Dyfed). Magnetic stimulation was applied at 65% of the maximum using a figure-of-eight 70-mm coil. Previous studies have demonstrated that magnetic stimulation using this type of coil can produce functionally dissociable effects that are restricted to a scalp area within a radius of 0.5-1 cm (Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992). The centre of the coil was positioned over the site to be stimulated such that the windings were at 90° to the scalp and the handle pointed vertically.

Apparatus and procedure

Prior to experiments, TMS-induced phosphenes were used to establish that the magnetic stimulation was localised to the contralateral visual field. Thus in the initial stage of the experiment I probed the occipital cortex with TMS in an attempt to locate left and right field stationary phosphenes, respectively with right and left hemisphere magnetic stimulation. Stationary phosphenes are an established consequence of visual cortical TMS (Hotson, Braun, Herzberg, & Boman, 1994; Kammer, 1999; Marg, 1991), and following Lavidor *et al.* (2003) (see also Stewart, Battelli, Walsh, & Cowey, 1999) can be used to select an area to stimulate in subsequent experiments.

Participants wore a latex swimming cap and sat with their head supported by a chin-rest and head-strap in order to secure head position and stabilize fixation. Stimulation sites were the right and left cortices. The upper edge of the inion was marked on the cap, and another point (the reference point) was marked 2 cm above it. The occipital hemispheric sites that were marked on the cap were 1.5cm to the left of the centre point (left hemisphere site, LH) and 1.5cm to the right of the central point (right hemisphere site, RH). The coordinates were selected initially on the basis of previously successful studies with TMS, that reported stationary phosphenes (Cowey & Walsh, 2000; Kammer, 1999) and the suppression of visual perception tasks with TMS at similar sites (Kammer, 1999; Lavidor & Walsh, 2003).

In a darkened room, participants closed their eyes while TMS was delivered to the RH and LH points. Participants were asked to indicate whenever they saw a phosphene, and to describe its position in space. TMS was applied at increasing intensities until participants reported seeing phosphenes regularly and reliably. For some participants, the magnetic stimulation sites were changed in a 'win-stay/lose-shift' paradigm (Ashbridge, Walsh, & Cowey, 1997) to locate regions on the scalp which resulted in phosphene perception, however the change from the initial 1.5 cm points were minimal (less than 0.5 cm). For the main experiment, the effective phosphene sites were used for each participant with a fixed 65% of the stimulator output, a level selected on the basis of previous experiments, and found to be sufficient to disrupt perception without masking stimuli with overt phosphenes.

At the experimental stage, rTMS was applied at 10 Hz frequency for 500 ms from the onset of the target presentation on the computer screen while participants were performing the letter/digit classification task. See the timeline of the main Experiment in Figure 12.

The experimental trials were employed in 6 blocks, 72 trials in each block. There were two blocks in which rTMS was applied over the right occipital cortex, two blocks with rTMS over the left occipital cortex, two non-TMS blocks and two sham-TMS blocks. The order of the experimental blocks was counter-balanced. In the sham-TMS blocks, the reversed coil was positioned over the left or right visual cortex, with the current directed away from the cortex.

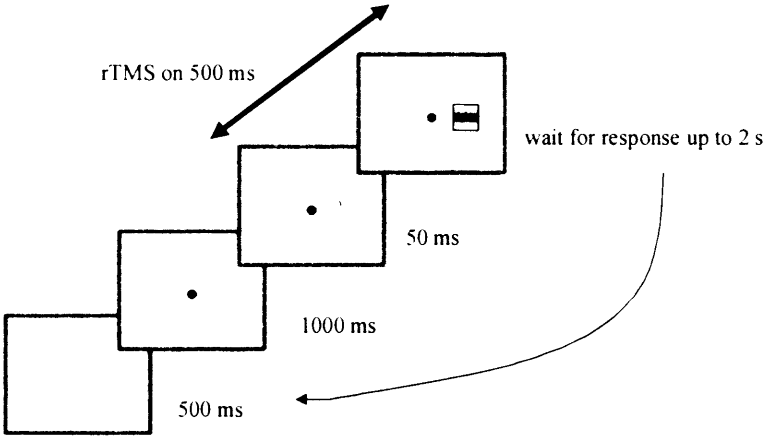

Figure 12: Time line of the TMS experiment (Experiment 2)

Results

Reaction times and percent of incorrect responses to letter/digit classification in the different experimental conditions are summarized in Table 1.

Reaction times

The application of rTMS had a significant effect ($F_{(3,24)}=11.5$, $p<0.01$), with RTs being slowed when TMS was applied to the LH (mean = 564 ms) or to the RH site (mean=570 ms) compared with the no TMS mean of 545 ms or sham-TMS (mean = 547 ms, all post hoc differences were Bonferroni corrected to $p<0.05$). Target location did not have a significant effect on RTs ($F_{(3,24)}=0.85$, ns). Since the no-TMS and the sham-TMS conditions did not differ, I averaged RTs in these two conditions. I calculated the difference between performance under TMS and the baseline conditions, creating two measures, one for TMS over the LH and one for TMS over the RH. These measures that represent the TMS effect size are plotted in Figure 13 as a function of target location. The interaction between rTMS site (RH, LH) and target location was significant ($F_{(3,24)}=3.63$, $p<0.05$), and the patterns of the interaction can be clearly seen in Figure 13. At the RH site, the rTMS effect (i.e., the RT costs) is significantly larger for targets located at the LVF and foveal-LVF locations when compared to RVF or foveal-RVF locations (all post hoc differences were Bonferroni corrected to $p<0.05$). rTMS effects when stimulating the LH site showed the complementary effects.

Table 1: Mean RTs and percent of incorrect responses in Experiment 2. The table displayed the RT and SD (both measured in milliseconds), and the error percent as a function of target eccentricity and TMS condition.

No TMS	LVF	Foveal-LVF	Foveal-RVF	RVF
Mean RT	542	544	555	541
(SD)	97	89	94	98
% error	6	4	5	3
TMS-RH				
Mean RT	596	580	563	542
(SD)	105	86	94	93
% error	4	6	4	6
TMS-LH				
Mean RT	558	550	584	562
(SD)	97	89	95	97
% error	5	5	6	3
ShamTMS				
Mean RT	547	544	557	539
(SD)	88	74	111	83
% error	5	5	4	6

As can be seen in Figure 13, the effects for each visual field are largest when the contralateral hemisphere is stimulated, and there are no differences in the TMS effects between the foveal and more parafoveal targets within each hemifield. Paired *t*-tests with Bonferroni correction for multiple comparisons revealed the following significant differences ($p<0.05$) in accordance with the split fovea theory predictions.

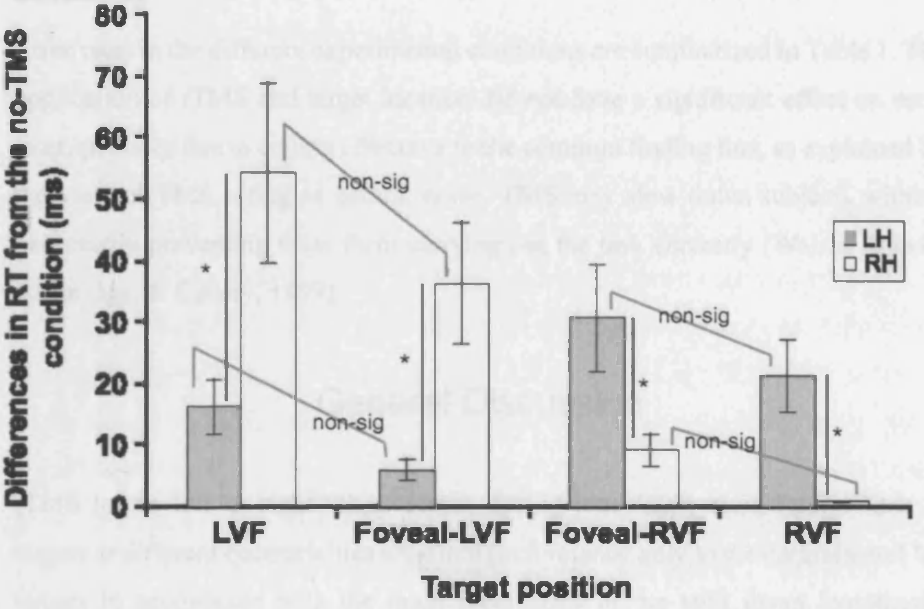

Figure 13: rTMS effect of experiment 2.
rTMS effect is graphed as a function of target eccentricity and the coil location (labeled as the inset). TMS effect is the reaction time change in ms caused by TMS

LVF target classification was significantly more impaired by TMS over the right occipital cortex (52 ms delay relative to the no-TMS condition) than by the ipsilateral TMS (15 ms delay with LH-TMS). Similarly, foveal-LVF targets were significantly more impaired by RH-TMS (36 ms delay) than by the ipsilateral TMS (6 ms delay with LH-TMS).

RVF target classification was significantly more impaired by TMS over the left occipital cortex (22 ms delay relative to the no-TMS condition). This pattern was true for foveal-RVF targets as well (32 ms contralateral delay vs. 9 ms ipsilateral delay).

The contralateral TMS effects for LVF and foveal-LVF targets did not differ significantly (52 ms and 36 ms, respectively). Also the ipsilateral TMS effects in these locations did not differ (15 and 6 ms, respectively).

The contralateral TMS effects for RVF and foveal-RVF targets did not differ significantly (22 and 32 ms, respectively). Also the ipsilateral TMS effects in these locations did not differ (0.5 and 9 ms, respectively).

Error rates

Error rates in the different experimental conditions are summarized in Table 1. The application of rTMS and target location did not have a significant effect on error rates, possibly due to ceiling effects or to the common finding that, as explained by the view of TMS acting as neutral noise, TMS may slow down subjects without necessarily preventing them form carrying out the task correctly (Walsh, Ellison, Ashbridge, & Cowey, 1999).

General Discussion

rTMS to the left or right visual cortex during letter/digit classification task to targets at different eccentricities impaired performance only to the contralateral VF targets in accordance with the main predictions of the split fovea hypothesis. Crucially, the results of this chapter have shown that the predicted contralateral rTMS effects were also true for foveal targets. The practical implication of this finding is that the functional visual fields start immediately to the left and right of fixation (see also Brysbaert, 1994).

The TMS effects of this chapter for the briefly presented targets are consistent with other TMS findings with occipital stimulation in which TMS is only able to disrupt perceptual judgements if the relative duration of presentation is short (e.g., Amassian et al., 1989), or stimuli are close to luminance detection thresholds (see Kammer & Nusseck, 1998). I did not find significant TMS effects on accuracy, however when using cognitive tasks simple accuracy changes are less common than RT (see Walsh & Pascual-Leone, 2003, p84-89 for discussion of why RT deficits can occur, indeed be predicted to occur, without any effect on errors).

One possible concern is whether the reported TMS effects were confounded with a potential alerting bias induced by auditory or somatosensory artefacts of TMS. Auclair and Siéroff (2002), for example, have shown recently that a lateralised cue (a brief presentation of LVF or RVF digit, in their study) improved identification of letters that were ipsilateral to the cue. The noise a TMS coil makes during stimulation, may act as an exogenous spatial cue, being a right cue when TMS is applied over the right occipital cortex, and a left cue when TMS is applied over the left occipital cortex. However this was not the case, as sham rTMS did not affect performance.

This chapter has shown that a subject suffering from a partial lesion in her left occipital cortex failed to discriminate letters from digits when targets were presented 0.5^{0} to the right and below fixation, and hence did not show foveal sparing in this task. However the main novelty reported here is not the patient data (such cases have been reported before, for a review see Leff, 2004), but rather the direct testing, by TMS, of a prediction from Leventhal's work in monkeys. I found significant behavioral disruption induced by TMS during letter/digit classification for a group of normal observers (experiment 2) that replicated VN's performance. Letters and digits that were only half a degree away from fixation were affected by contra, but not ipsilateral TMS. This also speaks to the fact that the TMS current effects did not spread to the un-stimulated hemisphere.

These results suggest it is unlikely that two complete copies of the centrally presented word were processed in each hemisphere. However, independent representations do not preclude interactions between the two hemispheres and when the target is presented in the region of greatest representational overlap (i.e., at fixation in the midline) it may be the case that any disruption to the processing may interfere with either competition or co-operation between the hemispheres that is a feature of normal processing (e.g., Hilgetag, Theoret, & Pascual-Leone, 2001; Seyal, Ro, & Rafal, 1995; Walsh, Ellison, Ashbridge, & Cowey, 1999). Thus the results obtained here cannot preclude the possibility of some functional role for the nasal ipsilateral projection, as the unilateral TMS may disrupt processing of the foveal stimuli due to its (possible) effects on the co-operative hemispheric interactions across the foveal region. However, interhemispheric interactions seem an unlikely explanation of our results since other studies suggest that secondary activations are too weak to be behaviorally effective (Kammer, Beck, Erb, & Grodd, 2001; Pascual-Leone et al., 1999; Walsh & Pascual-Leone, 2003).

The contralateral inhibitory effects found were the results of a temporary stimulation of the (healthy) primary visual cortex. When a person with a permanent lesion in her left visual cortex (VN) was tested with the same task, she failed to discriminate letters from digits when targets were presented in her lower RVF, contralateral to the lesioned cortex. This failure was not surprising as it reflected the lesion location. However, in line with the split fovea predictions, the same failure occurred with foveal targets, that were only slightly to the right of fixation. This is a strong test of the split fovea predictions, as the same subject was able to respond accurately to targets that were in the upper RVF, near or far from fixation, but not to targets at the lower RVF, near or far from fixation.

Although VN's results clearly show she has foveal splitting rather than foveal sparing, there is still a need to offer an alternative account for the phenomenon of foveal sparing other than the bilateral projection. This is because more than 60% of hemianopic patients show foveal sparing rather then splitting (Celesia, Meredith, & Pluff, 1983). It has been suggested that central vision occupies a larger area of the visual cortex than peripheral vision and that this area is less likely to be affected by random damage (such as strokes). According to this alternative view, foveal sparing would not be due to the fact that a unilateral stroke leaves the contralateral brain tissue unaffected but to the fact that the stroke spares some of the ipsilateral brain tissue responsible for central vision (Leff, 2004). The alternative explanation is in line with the recently shown correlation between foveal sparing and spared ipsilateral brain tissue as revealed by magnetic resonance imaging (Gray, Galetta, Siegal, & Schatz, 1997). Additional alternative arguments have been put forward to account for macular sparing, suggesting that the phenomenon reflects: (a) incomplete damage to the visual pathways (e.g., Wilbrand, 1926 cited in Bischoff, Lang, & Huber, 1995; Horton & Hoyt, 1991), (b) some immunity from infarcts of occipital pole due to overlap of the blood supplies from the middle and posterior cerebral arteries (e.g., Smith & Richardson, 1966) or (c) results from unusual fixation strategies adopted by hemianopic patients (Bischoff, Lang, & Huber, 1995).

I conclude that central vision is not bilaterally represented in the primary visual cortex - an observation that has repercussions for any anatomically constrained psychological model of visual processing (Brysbaert, 2004). The nature and quality of the bilateral information may be further tested with different visual tasks that require different resolution, from simple target detection to the whole word recognition.

CHAPTER 4: WORD AND NON-WORD RECOGNITION AND THE SPLIT FOVEA

The main argument of the split fovea theory (that was presented in Chapter 3) is that the representation of foveal stimuli is split down the midline between the two cerebral hemispheres (see Shillcock, Ellison, & Monaghan, 2000, for a review). A number of recent theories of word identification have taken the "split fovea" into account, with the two hemispheres dealing with the beginnings and ends of words in different ways (Brysbaert, 1994; Brysbaert, 2004; Ellis, 2004; Lavidor, Ellis, Shillcock, & Bland, 2001; Lavidor, Ellison, & Walsh, 2003; Lavidor, Hayes, Shillcock, & Ellis, 2004; Lavidor & Walsh, 2003). However, as Bowers and Turner (2005) commented, it is interesting to note that most word recognition researchers have not taken this anatomical constraint into consideration in their studies. The implicit assumption has been that information presented to the fovea is bilaterally projected, with two hemispheres processing complete words separately. Here I will explore the implications of the split fovea theory on word recognition processes, in particular when spatial cueing procedes word presentation. Spatial cueing is particularly relevant to the split fovea theory because, if one assumes that the processing of words is initially split between the two hemispheres, right and left sided spatial cues might have selective effects on word segments (that is right and left segments) rather than on whole words.

Spatial attention (SA) is a well-researched area and, although there are many similes to describe its effects, it is generally accepted that spatial attention involves bringing into the 'spotlight' of active processing some object or location. A popular paradigm to study spatial attention is the Posner paradigm (Posner, 1980). In this paradigm, an observer must detect a signal at one of two locations, with a precue indicating the probable signal location. A 'valid' cue (signal at the cued location) typically leads to faster and more accurate responses, compared to an 'invalid' cue. Common explanations of the cueing effect hinge upon the concept of a limited attentional resource unevenly distributed across the visual field, causing an increase of perceptual quality at the attended (cued) location relative to the unattended (uncued) location.

Despite much research, spatial attention effects on visual word recognition (VWR) are still unclear. McCann, Folk and Johnston (1992) argued that spatial attention and visual word recognition operated independently and that spatial attention must be focused on the letter string in order to support word recognition processes. This independence means that the lexical status of the cued words does not matter, because the spatial cueing can improve performance for all word types, including high-frequency words, low-frequency words and pseudowords (McCann, Folk, & Johnston, 1992). A similar conclusion was reported by Ortells, Tudela, Noguera and Abad (1998), in a divided visual field study, where all the attentional manipulations were effective, but they did not interact with word familiarity.

Alternatively, others described SA and VWR as interactive, for example Stolz and McCann (2000); that is, attention has selective effects on VWR which depend on the lexical status of the word target, the semantic context, and has significantly larger facilitatory effects on pseudowords when compared with words. An earlier ERP study (McCarthy & Nobre, 1993) also concluded that spatial selective attention can modulate the degree to which words are processed.

The interactive attentional effects on VWR may take place either during the initial uptake of orthographic information (Stolz & McCann, 2000) or during later stages in word recognition where, according to the late-selection theories, spatial attention can operate after stimulus identification and semantic processing (Sieroff & Posner, 1988). The implication of late-selection theories is that word identification would be unaffected by whether or not spatial attention is focused on the word.

Within the framework of early attentional effects on word recognition, two theories explain how the familiarity of the letter string can modulate the influence of spatial attention. The replacement theory considers that letter processing may be less affected by spatial attention in words than in pseudowords because letters in words can be partially activated and recovered by top-down processes (Mozer & Behrmann, 1990) The redistribution theory suggests that the lexical status of a letter string directly affects the distribution of attention in reading. According to the redistribution theory, the deployment of attention is different in the case of words and pseudowords. For words, letter identification may benefit from a deployment of spatial attention from the cue location to the entire spatial extent of the stimulus, which would assist letter identification in the un-cued side as well. The identification of pseudowords, on the other hand, would require a sequential process and would not be influenced by a redistribution of attention on the whole letter string (Auclair & Sieroff, 2002).

To distinguish between the two contrasting theories regarding SA and VWR (independent or interactive effects), Auclair and Sieroff (2002) have used the Sieroff and Posner (1988) cueing procedure. A lateralized cue indicated in advance either the beginning (left) or the end (right) of foveally presented letter strings that participants were instructed to read aloud. Results showed that the precue had a stronger influence on pseudoword than on word identification, with letter recognition in the left segment of the centrally-presented target affected by a left but not a right cue, and complementary, the right cue affected the right segment of the centrally-presented target but not the left cue. However, results showed that shorter words were also influenced by the cue location when exposure duration was reduced. Auclair and Sieroff (2002) concluded that their results are compatible with an early role of spatial attention in letter string processing, but they also suggested that the lexical status of a letter string can directly influence the distribution of attention before the identification process is completely achieved. Although orienting of spatial attention seemed heavily involved in pseudoword identification, some spatial attention mechanism also operated in the case of familiar words.

Auclair and Sieroff were focusing on the attentional aspects of their study and their theoretical framework is spatial attention theory; however, by predicting lateralized cueing effects on foveally presented targets they implicitly assume (although did not discuss it) that representation of centrally presented words is split between the two cerebral hemispheres along the vertical midline. Without such an assumption, there is no reason to predict that the left segment of centrally presented words will be affected by a left but not right cue, and, correspondingly, that the right segment would be affected by right but not left cue. If two segments are bilaterally projected to both hemispheres, then left and right cues should have the same effect as all the letters of the target are both in the left and right hemispheres. Note that the position and the brief duration (83 ms) of the left and right cues in Auclair and Sieroff's study, imply that the cues are presented in the left or right visual field (respectively), therefore initially projected to the contralateral hemisphere. Presenting the lateralized cues and referring to the left and right segments of centrally presented words, as reported in Auclair and Sieroff (2002), actually links their research with a different discipline - lateralized word recognition.

A typical finding in lateralization studies of visual word recognition is a robust right visual field (RVF) advantage, that is performance to words presented to the right visual field is better than to words presented to the left visual field (for a review see Ellis, 2004). Several explanation were offered to account for this robust RVF advantage, for example, that it reflects that left hemisphere (LH) superiority in language tasks (Gazzaniga, 2000) or that differences in the visual acuity of the initial letters benefit the right but not the left visual field (Kirsner & Schwartz, 1986), or reading habits in English (Battista & Kalloniatis, 2002).

Alternatively, Nicholls and colleagues (Lindell & Nicholls, 2003; Nicholls & Wood, 1998; see also Mondor & Bryden, 1992) have suggested that the hemisphere's different word recognition strategies place different demands on attentional resources. The LH's parallel encoding process is specialized for the recognition of whole words (Chiarello, 1988), and is capable of identifying large chunks of information even in the absence of directed spatial attention (LaBerge & Brown, 1989).

To assess the contribution of attention to the LH's observed superiority for word recognition. Lindell and Nicholls (2003) have employed a spatial cueing paradigm with divided visual field word presentation. They manipulated the cue position relative to the target word. There were three types of cues that appeared either to the left of the lateralized word (beginning cue), or to the right of the target word (end cue), or at both visual fields (a neutral cue). The results indicated no effect of cue position on RVF/LH performance, consistent with the idea that the LH enjoys an attentional advantage by its ability to deploy attention in parallel across the stimulus. In contrast, there was a facilitative effect of the beginning cue in the LVF/RH (where the cue was presented about 6° to the left of fixation) which was significantly larger than the cueing effect of the end cue (which was presented about 1.5° to the left of fixation). The authors argued that for LVF/RH words, the beginning cue draws spatial attention to the initial letter cluster, enabling efficient implementation of the RH's sequential strategy. In addition, Lindell and Nicholls's (2003) results implied that lexical processes might be facilitated by paying attention to the beginning of words, rather than the end of words, in line with the claim that spatial attention is involved in the lexical processing of words (McCann, Folk, & Johnston, 1992).

Lindell and Nicholls's (2003) results contrasted Auclair and Sieroff's (2002) on several points. First, the facilitatory cueing effects Lindell and Nicholls reported occurred for words, while Auclair and Sieroff did not find cueing effects for words (relative to pseudowords). Second, Lindell and Nicholls reported that only left cues did affect performance, while Auclair and Sieroff found symmetrical (ipsilateral) cueing effects for both the left and right cues.

By presenting left and right precues before centrally presented words, and assuming that the split fovea theory is valid, there are two contrasting predictions derived from Auclair and Sieroff (2002) and Lindell and Nicholls (2003) studies. According to the split fovea theory, the left segment of the centrally presented word is projected to the RH, while the right segment is projected to the LH. According to Auclair and Sieroff, both visual fields would benefit from the cueing, with a left cue more beneficial to LVF stimuli (i.e., left segment) than a right cue, and a right cue more beneficial to RVF stimuli (i.e., right segment) than a left cue. However, a prediction derived from Lindell and Nicholls theory would claim that the left cue would benefit the left segment, as Auclair and Sieroff predicts, however, there will be no cueing effect for the right segment by the right cue as there are no additive attentional effects in the RVF/LH.

A third contrasting prediction is that if the split fovea theory is not valid, there will be no cueing effects at all, as the centrally presented words are bilaterally projected to both hemispheres, therefore eliminating the potential facilitation from a spatial cue to the left or right visual field.

The experiments in this chapter aim to explore these contradictory predictions. The reported experiments manipulated pre-cue positions in order to test how spatial cueing modulates lexical processing of words and pseudowords within the framework of the split fovea theory. Subjects were presented with a sequence of a pre-cue, a rapid visual stimulus (letter strings) and a mask. The task was to report the letters of the visual stimulus. The manipulations of the pre-cue included types (digits, arrows or squares, see Experiments 1 to 4), locations (right, left, far left and far right, Experiments 3 and 4), and salience (bigger and different colours for the right cues, Experiments 5 to 7). Aiming to increase cueing effects, Experiments 8 and 9 presented mis-aligned letter strings and the task was letter search.

Experiments 1 and 2

Since Auclair and Sieroff (2002) did not consider the split fovea theory, I first aim to replicate Experiment 1 in their paper but from the split fovea point of view. Another justification for this replication is the need to establish the lateralized cueing patterns with English words (Auclair and Sieroff used French words).

Method

Design

A 2 x 2 x 2 factorial design (cue location: LVF, RVF) x (stimulus length: 6 or 8 letters) x (stimulus type: real or pseudo-words) was used in a within-subjects design. In Experiment 1 the precues were digits, and in Experiment 2 the precues were arrows, '>' on the left visual field and '<' on the right.

Participants

Experiment 1. Twelve native English-speakers, 8 females and 4 males, aged between 21 and 29 (mean 24.4, sd 2.8). All but two the participants were right-handed and the mean score was 79.6 (sd 31) in the Edinburgh Handedness Inventory (Oldfield, 1971).

Experiment 2. Six native English-speakers, 2 females and 4 males, aged between 22 and 35 (mean 26.5, sd 5.2). All the participants were right-handed and the mean score was 97.5 (sd 4.2) in the Edinburgh Handedness Inventory (Oldfield, 1971).

All participants of both experiments had normal or corrected to normal vision and were naïve to the paradigm and the purpose of the experiments.

Stimuli

Eighty English content words (nouns, verbs and adjectives) and eighty pseudowords were used as stimuli. Half of the words had six letters and half had eight letters. Real word sets were matched on written frequency (Kucera & Francis, 1967), imageability and age of acquisition. The pseudowords were generated from the ARC nonword database (Rastle, Harrington, & Coltheart, 2002). Pseudowords were also made of six and eight letters in equal proportion. The stimuli for Experiments 1 and 2 are presented in Appendix 1.

The stimuli (words and pseudowords) were presented in 21-point uppercase Courier New font. The letters appeared white on a black background to minimize flicker. The stimuli were presented for 30 ms at screen centre. Figure 14 illustrated the size and distances (in visual angle) of the precues and the visual stimuli.

Apparatus and procedure

Stimuli were presented on a 17-inch CRT (800 x 600 pixels) triggered by E-prime software. Each participant sat with their head supported by a chin-rest and head-strap in order to secure head position and stabilize fixation at a distance of 1 m from the screen. Each experiment consisted of 172 trials, including 12 trials for

Figure 14: The visual angle of cues and stimuli
The black numbers represent stimuli size in Experiment 1, which were nearly identical to the sizes reported by Auclair & Sieroff's (2002), denoted by grey numbers. The values before and after the slash were the visual angle for the 6 or 8-letter stimuli, respectively.

practice at the beginning. Each trial began with a fixation point appearing in the centre of the screen for 500 ms. The fixation point was replaced by digits or arrows on the left or right visual field for 80 ms. Following the lateralized precue, the stimuli (words or pseudowords) were randomly and centrally presented for 30 ms. After presenting the stimulus, a subsequent mask was displayed at the stimulus location. The mask was big enough to cover the previous cue areas. The participant's task was to report, as accurately as possible, the digit (only in Experiment 1) and the letters of the stimulus (oral report). Participants' responses were recorded for further analysis. Pressing the space bar was required to initiate the next trial. Figure 15 illustrated the timeline of the experiments.

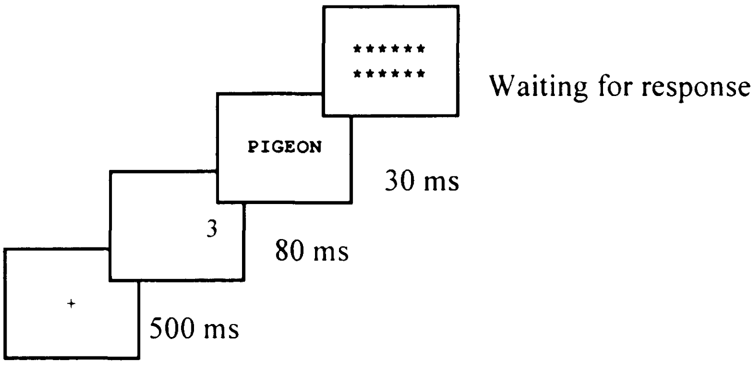

Figure 15: Timeline of Experiments 1 and 2
Each trial started with a fixation cross presented for 500 ms, followed by a pre-cue to the left or right of fixation for 80 ms, immediately replaced by a 30 ms target stimulus. A mask was presented on the screen until participants' responses. The timeline was also applicable to all the experiments in this chapter, with the exception of Experiments 6 & 7.

Data Analysis

Participants' responses was scored according to Sieroff and Posner's (1988) and Auclair and Sieroff's (2002) scoring methods. Each letter string was first divided into two parts, left segment that included the letters to the left of fixation (3 and 4 in case of 6- and 8-letter strings, respectively) and right segment with the right of fixation letters. The percentage of correctly recognized letter was then calculated separately for the left and right halves of the stimuli. The differences in performance between the left and right parts was calculated using the Laterality Index, defined as $100 \times (R - L)/(R + L)$, in which R represented the mean percentage of letters correctly identified for right segment trials. A negative L-Index implies that more letters were recognized in the left than the right segment. A positive L-Index implies that more letters were recognized in the right than the left segment. A null L-index means equal performance at the left and right segments of the centrally presented letter strings.

Results and discussion

In Experiment 1, the responses were calculated and analyzed only when the pre-cue (digit) was correctly reported. All subjects were at least 95% correct, with total mean percentage of 98.23, (sd 0.014). The results of Experiment 1 are presented in Table 2.

There was a significant lexicality effect, ($F_{(1,11)}=8.48$, $p<0.05$), with a more negative laterality index for pseudowords than for words (i.e., better performance at the left than the right segment). There were no further significant main effects or interactions.

In line with Auclair and Sieroff (2002), the results of Experiment 1 reflect laterality effect for pseudowords but not for words. However, in contrast to Auclair and Sieroff (2002), there were no cueing effect for pseudowords. In Auclair and Sieroff's (2002) study, the right precue changed the Laterality Index towards the positive values: for the 6- and 8-letter pseudowords, the Laterality Indices were 3.79 and 10.85, respectively. In contrast, in the current Experiment 1, the corresponding values are -13.71 and -11.31 for the 6- and 8-letter pseudowords, respectively.

Table 2: Percentage of letters correctly recognized in the left and right segments and the Laterality Index as a function of stimuli lexicality, length and cue location (Experiment 1).

			Segment					
			Left		Right		Laterality Index	
Stimuli	Length	Cue loc	M	SD	M	SD	M	SD
Words	6	Left	97.30	2.71	94.95	5.39	-1.28	1.90
		Right	95.36	4.72	94.95	4.59	-0.21	1.83
	8	Left	93.05	10.16	91.69	8.78	-0.64	3.85
		Right	92.02	8.54	87.69	14.74	-2.93	5.04
Pseudo words	6	Left	81.63	12.17	68.79	16.05	-9.31	9.99
		Right	82.52	11.67	64.22	17.43	-13.71	10.93
	8	Left	64.50	15.29	57.56	17.55	-6.27	17.82
		Right	68.47	14.27	55.43	17.33	-11.31	14.79

The significant advantage of letter identification at the left segment of centrally presented pseudowords (and words) might suggest that subjects tended to scan the letters from left-to-right, a tendency affected by natural reading habits, that overrides the predicted cueing effects. In an effort to minimize scanning habits and encourage right-to-left scanning of the stimuli following the right cue, Experiment 1 was replicated, with informative arrows as precues rather than digits (Experiment 2). The results are summarised in Table 3.

There was a significant lexicality effect, with negative laterality index for pseudowords but not for words ($F_{(1,5)}=7.49$, $p<0.05$). In addition, stimuli length interacted with lexicality ($F_{(1,5)}=14.12$, $p<0.05$). Simple effect analysis revealed that 8-letter pseudowords had a more negative Laterality Index than 6-letter pseudowords (-11.68 versus -7.66, $F_{(1,5)}=27.03$, $p<0.01$), but there was no differences in laterality index for 6- and 8-letter words (-1.00 versus -0.92, $F_{(1,5)}=0.01$, $p>0.05$). There were no further significant main effects or interaction.

Table 3: Percentage of letters correctly recognized in the left and right segments and the Laterality Index as a function of stimuli lexically, length and cue location (Experiment 2).

			Segment					
			Left		Right		Laterality Index	
Stimuli	Length	Cue loc	M	SD	M	SD	M	SD
Words	6	Left	98.91	1.93	96.31	5.28	-1.39	1.89
		Right	99.52	0.75	98.30	1.96	-0.62	0.89
	8	Left	97.74	3.52	94.99	6.99	-1.52	2.07
		Right	97.37	2.79	96.85	5.12	-0.31	1.83
Pseudo	6	Left	88.71	10.72	79.30	14.54	-6.02	5.72
words		Right	88.75	11.34	75.37	19.99	-9.30	10.82
	8	Left	82.21	12.96	67.11	19.93	-11.67	12.05
		Right	81.32	6.38	65.18	12.95	-11.69	8.39

Both Experiment 1 and 2 showed similar patterns of absolute advantage for letter recognition in the left segment of centrally presented letter strings, a left bias that was stronger than the potential cueing effects even when the cue was a clear right-to-left arrow (Experiment 2). The slightly odd results of Experiment 2 of the better performance for the longer pseudowords might result from the small sample size. However, it is clear from both experiments that the ipsilateral cueing effects reported by Auclair and Sieroff (2002) were not replicated.

Experiment 3

The failure to replicate Auclair and Sieroff's (2002) results led me to design a new experiment (Experiment 3), where a different cueing paradigm was used, following Lindell and Nicholls's (2003). They used four cue positions combined with divided visual field presentation and reported selective cueing effects.

Method

Design

A 4 x 2 x 2 factorial design (cue location: left-far, left-near, right-near, right-far) x (stimulus length: 6 or 8 letters) x (stimulus type: real or pseudo-words) was used in a within-subject design. Pre-cues format, size and location are illustrated in Figure 16.

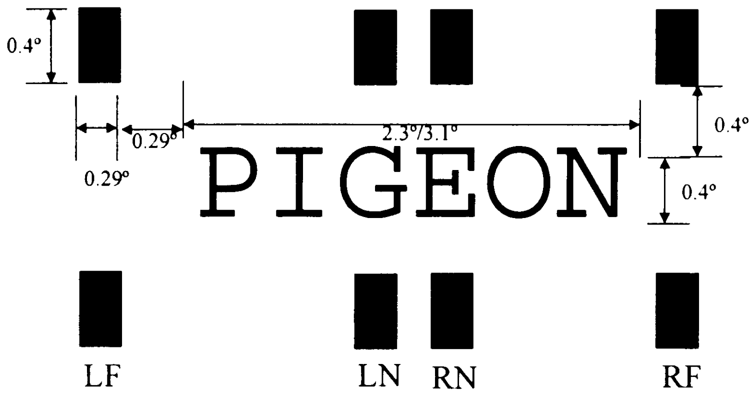

Figure 16: The arrangement of pre-cues and stimuli in Experiments 3 & 4
The pre-cue was a pair of two rectangles which would appear at one of four possible locations: left-far (LF), left-near (LN), right-near (RN) and right-far (RF), following Lindell and Nicholls (2003). The black numbers represent stimulus size, the values before and after the slash were the visual angle of 6 or 8-letter stimuli, respectively.

Participants

Six native English-speakers, 3 females and 3 males, aged between 21 and 27 (mean 24.3, sd 2.2). All participants were right-handed and scored at least 90 in the Edinburgh Handedness Inventory (Oldfield, 1971), with total mean score of 96.7 (sd 5.2). All participants had normal or corrected to normal vision and were naïve to the paradigm and the purpose of the experiments.

Stimuli

In total, one hundred and thirty-two English content words (nouns, verbs and adjectives) and one hundred and thirty-two pseudowords were used as stimuli. Half of the words had six letters and half had eight letters. The stimuli included the 160 letter strings used in Experiments 1 and 2, and additional stimuli, which are presented in Appendix 2. The word sets were matched on written frequency (Kucera & Francis, 1967), imageability and age of acquisition.

Apparatus and procedure

Apart from the precues format and location, the procedure was similar to the procedure of Experiments 1 and 2.

Results and discussion

Table 4 displays the mean percentage of letters correctly identified at the left and right segments of the stimuli, and the Laterality Index.

Table 4: Percentage of letters correctly recognized in the left and right segments and the Laterality Index as a function of stimuli lexicality, length and cue location (Experiment 3).

			Segment					
			Left		Right		Laterality Index	
Stimuli	Length	Cue loc	M	SD	M	SD	M	SD
Words	6	LF	95.06	8.74	95.68	7.58	0.38	1.02
		LN	97.78	5.44	96.32	6.54	-0.79	0.97
		RN	96.39	7.92	94.88	11.62	-1.00	2.45
		RF	97.45	3.65	96.68	4.83	-0.42	1.55
	8	LF	96.54	6.55	93.38	8.58	-1.74	3.27
		LN	91.41	13.79	86.82	17.49	-3.09	4.04
		RN	91.14	12.65	86.90	16.31	-2.77	3.49
		RF	98.61	3.40	93.17	6.51	-2.91	3.49
Pseudo words	6	LF	82.72	11.69	73.42	19.30	-7.29	9.89
		LN	76.74	14.18	62.80	23.63	-13.06	15.14
		RN	75.30	20.80	61.07	19.07	-10.97	6.08
		RF	80.28	13.32	63.75	18.58	-12.94	11.22
	8	LF	60.72	18.77	61.02	21.93	-0.77	7.01
		LN	63.01	24.57	51.51	28.89	-13.72	17.83
		RN	62.24	19.34	55.23	29.68	-11.71	17.11
		RF	62.01	19.64	57.28	27.51	-7.67	17.20

Statistical tests showed a significant main effect of cue locations ($F_{(3,15)}=3.39$, $p<0.05$), where a significant difference was found only between the left-far cues (LF) and the left-near cues (LN) (-2.36 versus -7.66, Turkey's HSD test). However, stricter post-hoc comparison (like Bonferroni t-test and Scheffe's test) did not show any significant differences between the four cue locations.

There was a length by stimulus type interaction ($F_{(1,5)}=12.28$, $p<0.05$). Simple effect results revealed that the 8-letter pseudowords had less negative Laterality Index than 6-letter pseudowords (-8.47 versus -11.05 $F_{(1,5)}=7.29$, $p<0.05$), and there was no difference between 6- and 8-letter words (-0.46 versus -2.63, $F_{(1,5)}=5.09$, $p>0.05$). There were no further significant main effects or interactions.

Auclair and Sieroff's (2002) findings would imply that the left cues (LF and LN) will have a negative Laterality Index; and the right cues (RN and RF) will have a Laterality Index towards the positive range (right segment advantage). Applying Lindell and Nicholls's (2003) conclusions to Experiment 3, on the other hand, would imply that only the left-far cue (LF) will improve the report on the left segment (i.e., a more negative Laterality Index). However, when only pseudowords were extracted into the statistical analysis, no cueing effects were found, not even trends in the predicted directions. In order to verify that the failure to get cueing effects in 3 consecutive experiments thus far is not an artefact of the particular stimuli, I designed Experiment 4 with stimuli that were used previously and yielded ipsilateral cueing effects (Sieroff & Posner, 1988).

Experiment 4

Sieroff and Posner (1988) successfully demonstrated that cues in the right visual field improved letter recognition in the right segment of centrally presented pseudowords, and as a result, alleviated the negative Laterality Index, (however, subjects were still recognizing more letters at the left segment of the pseudowords). On the other hand, my previous experiments in this chapter did not clarify what the 'right' cue contributes to the letter recognition. Experiment 4 therefore is going to employ the exact visual stimuli of Sieroff and Posner (1988) in order to verify whether the failure to generate right cueing effects might be due to the particular stimuli I used.

Method

Design

A 4 x 2 x 2 factorial design (cue location: left-far, left-near, right-far, right-near) x (stimulus length: 6 or 8 letters) x (stimulus type: real or pseudo-words) was used in a within-subjects design. Pre-cues format, size and location were identical to the cue specifications in Experiment 3.

Participants

Six native English-speakers, 2 females and 4 males, aged between 19 and 30 (mean 23.0, sd 4.5). All but one participants were right-handed and the mean score was 76.7 (sd 33.3) in the Edinburgh Handedness Inventory (Oldfield, 1971).

Stimuli

Sixty 8-letter words and eighty 8-letter pseudowords were taken from Sieroff and Posner (1988), and are presented in Appendix 3. To allow length manipulation I added sixty-six 6-letter words and sixty-six 6-letter pseudowords (taken from Experiment 3).

Apparatus and procedure

Apart from the different stimuli, the procedure was similar to the procedures of Experiment 3.

Results and discussion

Table 5 displays the mean percentage of letters correctly identified at the left and right segments of the stimuli, and the Laterality Index.

There was a significant lexicality effect, with more negative value for pseudowords (-0.71 for words versus -9.95 for pseudowords, $F_{(1,5)}=15.07$, $p<0.05$). There were no further significant main effects or interactions.

Table 5: Percentage of letters correctly recognized in the left and right segments and the Laterality Index as a function of stimuli lexicality, length and cue location (Experiment 4)

			Segment					
			Left		Right		Laterality Index	
Stimuli	Length	Cue loc	M	SD	M	SD	M	SD
Words	6	LF	97.07	3.83	98.09	2.71	0.54	1.52
		LN	97.94	4.17	97.07	2.79	-0.42	1.59
		RN	99.15	2.09	96.84	4.10	-1.20	1.80
		RF	99.39	0.96	96.61	2.89	-1.43	1.10
	8	LF	98.08	3.53	97.44	3.99	-0.33	1.33
		LN	94.51	4.90	93.04	8.88	-0.92	3.00
		RN	95.55	5.32	93.55	7.21	-1.12	1.68
		RF	97.67	2.85	96.15	4.21	-0.80	2.36
Pseudo words	6	LF	92.12	5.87	77.46	11.58	-8.98	5.37
		LN	85.25	12.86	78.71	12.15	-3.96	5.36
		RN	86.79	8.54	77.83	15.08	-6.05	5.80
		RF	89.68	9.12	84.52	9.75	-3.04	2.65
	8	LF	75.55	22.48	59.12	21.23	-13.28	8.85
		LN	80.00	16.30	61.87	22.72	-14.52	15.29
		RN	77.67	19.86	61.73	21.40	-12.88	9.45
		RF	82.23	14.71	61.74	23.84	-16.90	16.76

Experiment 4, that employed the 8-letter pseudowords from Sieroff and Posner (1988), also failed to replicate the cuing effect reported by Sieroff and colleagues, or the alternative cueing effects predicted from Nicholls and colleagues. The Laterality Index of right-far (RF) cues was -16.90, sliding down from -13.28 of left-far (LF) cues. It is not in agreement with Sieroff and Posner's results (1988), where the right cue decreased laterality from -21.7 (following a left cue) to -12.2. However, Experiments 1-4 systematically indicated that the right cue did not alleviate the negative Laterality Index. Because Experiment 4 employed the same stimuli as Sieroff and Posner (1988), it is clear that the failure to create cueing effects was not due to the stimuli used in Experiments 1-3. In the following experiments (5-7) I aim to present a more salient right cue in order to generate the cueing effects reported by Sieroff and colleagues.

Experiments 5,6 and 7

One of the best ways to capture attention is to present a salient stimulus which would be automatically detected because some of its features, e.g., colour, size or orientation, are considered to be primary and be processed in parallel by special modules (Treisman, 1988). In order to magnify the differences between the left and right cues, the cues on the right visual field will be presented in a red colour in Experiments 5 and 6, and be widened into bars as well in Experiment 7. In addition, the left cues were smaller (0.29° of visual angles rather than 0.4° as in Experiments 1-4).

Method

Design

A 4 x 2 x 2 factorial design (cue location: left-far, left-near, right-near, right-far) x (stimulus length: 6 or 8 letters) x (stimulus type: real or pseudo-words) was used in a within-subjects design. However, the pre-cues differed from the previous experiments. The cues on the left side (LF and LN) were reduced from 0.4° into 0.29° of visual angles in length. Their colour was black (as in the previous experiment). The right cues in Experiments 5 and 6 were kept in the original size (0.4° of visual angles, see Figure 16), but were presented in red. In Experiment 7, the cues were widened into bars of 1.9° x 0.4° (see details in Figure 17). There was, therefore, no difference between RN and RF locations, since there was only one location (R) on the right visual field due to the increased cue size.

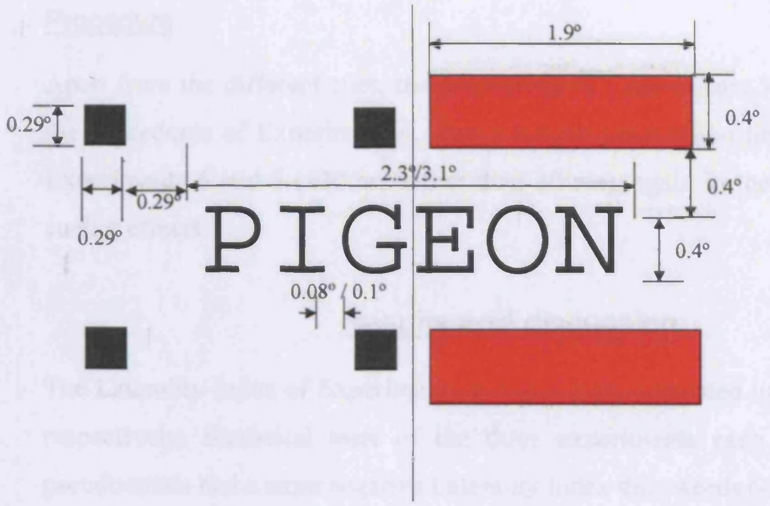

Figure 17: The arrangement of pre-cues and stimuli in Experiment 7
The pre-cue was a pair of two rectangles which would appear at one of two possible locations to the left of fixation: left-far (LF), left-near (LN), and in one location to the right of fixation. The right, red cues were extended to 1.9° width. The black numbers represent stimuli size, the values before and after the slash were the visual angle for the 6 or 8-letter stimuli, respectively.

Participants

Experiment 5. Six native English-speakers, 2 females and 4 males, aged between 20 and 26 (mean 21.2, sd 2.4). All but two participants were right-handed and the mean score was 65.0 (sd 44.9) in the Edinburgh Handedness Inventory (Oldfield, 1971).

Experiment 6. Six native English-speakers, 3 females and 3 males, aged between 19 and 26 (mean 24.0, sd 2.6). All but one participants were right-handed and the mean score was 74.1 (sd 24.8) in the Edinburgh Handedness Inventory (Oldfield, 1971).

Experiment 7. Six native English-speakers, 4 females and 2 males, aged between 19 and 27 (mean 21.7, sd 3.3). All but one participants were right-handed and the mean score was 79.2 (sd 25.2) in the Edinburgh Handedness Inventory (Oldfield, 1971).

Stimuli

The visual stimuli of Experiments 5, 6 and 7 were identical to the stimuli used in Experiment 4.

Procedure

Apart from the different cues, the procedures of Experiments 5-7 were similar to the procedures of Experiment 4, with a longer presentation time for pre-cues in Experiments 6 and 7 (120 ms rather than 80 ms), again in the effort to produce cueing effects.

Results and discussion

The Laterality Index of Experiments 5, 6 and 7 are presented in Table 5, 6 and 7, respectively. Statistical tests of the three experiments each showed that the pseudowords had a more negative Laterality Index than words (-11.71 versus -0.20, $F_{(1,5)}=11.47$, $p<0.05$ in Experiment 5; -10.00 versus -1.04, $F_{(1,5)}=7.40$, $p<0.05$ in Experiment 6; -12.34 versus -5.34, $F_{(1,5)}=6.23$, $p=0.055$ in Experiment 7). There were no further statistically significant main effects and interactions.

Table 6: Percentage of letters correctly recognized in the left and right segments and the Laterality Index as a function of stimuli lexicality, length and cue location (Experiment 5)

			Segment					
			Left		Right		Laterality Index	
Stimuli	Length	Cue loc	M	SD	M	SD	M	SD
Words	6	LF	98.91	1.84	98.80	2.10	-0.06	1.55
		LN	98.43	2.73	96.83	6.68	-0.91	3.68
		RN	99.65	0.85	98.11	2.30	-0.79	0.80
		RF	99.35	1.60	97.36	4.54	-1.05	2.61
	8	LF	98.90	1.94	99.21	1.94	0.16	0.38
		LN	97.40	5.13	96.93	3.93	-0.22	1.50
		RN	96.18	6.77	98.16	2.88	1.11	2.72
		RF	97.59	3.88	97.96	3.18	0.20	0.49
Pseudo words	6	LF	91.05	7.28	76.80	11.78	-8.84	4.66
		LN	90.85	9.80	76.86	18.22	-9.24	9.87
		RN	91.49	5.90	76.34	18.57	-10.17	11.74
		RF	93.38	6.21	78.58	14.85	-9.25	7.54
	8	LF	79.88	15.00	62.18	16.64	-13.07	10.25
		LN	76.07	15.10	57.77	16.34	-14.25	12.53
		RN	76.49	14.84	56.16	20.81	-16.96	12.89
		RF	76.41	20.68	59.04	15.10	-11.88	19.48

Table 7: Percentage of letters correctly recognized in the left and right segments and the Laterality Index as a function of stimuli lexicality, length, and cue location (Experiment 6)

			Segment					
			Left		Right		Laterality Index	
Stimuli	Length	Cue loc	M	SD	M	SD	M	SD
Words	6	LF	97.29	3.41	94.80	5.70	-1.10	2.16
		LN	95.59	5.36	92.92	8.19	-1.36	3.84
		RN	97.39	4.27	94.14	5.35	-2.01	2.43
		RF	97.61	3.19	93.28	8.04	-2.61	4.11
	8	LF	88.23	17.06	89.06	20.85	-0.46	7.01
		LN	88.48	13.56	86.57	16.40	0.09	1.52
		RN	94.46	6.83	93.53	8.87	-1.29	1.94
		RF	93.11	8.01	92.74	7.71	0.38	1.06
Pseudo words	6	LF	83.85	10.67	68.74	18.92	-11.95	15.02
		LN	79.68	12.88	57.72	27.03	-17.00	21.00
		RN	81.23	11.79	60.16	27.06	-15.89	18.35
		RF	72.17	15.92	63.79	23.13	-4.88	13.26
	8	LF	57.53	24.26	51.61	21.19	-6.28	10.91
		LN	57.63	19.66	48.41	21.42	-7.47	9.96
		RN	58.45	18.63	47.81	20.79	-13.44	16.74
		RF	55.43	22.15	48.16	20.37	-3.07	10.43

Table 8: Percentage of letters correctly recognized in the left and right segments and the Laterality Index as a function of stimuli lexicality, length and cue location (Experiment 7)

			Segment					
			Left		Right		Laterality Index	
Stimuli	Length	Cue loc	M	SD	M	SD	M	SD
Words	6	LF	77.91	26.47	74.42	26.20	-2.31	4.48
		LN	79.20	28.89	69.26	37.02	-12.03	16.59
		RN	76.27	27.93	65.41	36.13	-13.73	18.30
		RF	76.77	24.98	71.56	32.23	-6.69	10.49
	8	LF	72.91	28.00	73.97	27.24	1.16	7.88
		LN	66.84	37.63	62.54	40.45	-5.04	12.59
		RN	62.91	33.31	60.05	37.82	-6.68	10.38
		RF	66.08	34.10	66.56	31.51	2.63	10.74
Pseudo words	6	LF	61.15	30.44	46.05	30.98	-17.77	15.23
		LN	62.03	25.75	49.73	28.81	-17.49	18.02
		RN-RF	57.40	30.88	46.67	27.24	-11.05	13.85
	8	LF	45.80	25.30	34.72	16.45	-10.45	13.64
		LN	40.06	25.15	31.53	17.34	-7.80	19.27
		RN-RF	39.14	26.40	31.74	20.53	-9.45	7.26

Comparative analysis of Experiments 1-7

Figure 18 presents the Laterality Index of Experiments 5, 6 and 7. The right, rectangular red cues (RF) of Experiment 5, presented for 80 ms, did not alleviate the laterality of the LF cues for the 6-letter pseudowords (-9.25 versus -8.84), but slightly did so for the 8-letter pseudowords (-11.88 versus -13.07). When increasing the presentation time of the cues to 120 ms in Experiment 6, the right-far cues (RF) decreased the negative Laterality Index of both 6-letter and 8-letter pseudowords, compared with the left-far cues (LF). A similar pattern of decreased negative values (i.e., smaller LVF advantage following a right cue) was found in Experiment 7 (-11.05 versus -17.77 for 6-letter stimuli; -9.45 versus -10.45 for

8-letter stimuli). This tendency of reversing the laterality index direction in Experiments 5-7 was not found in Experiments 1-3 (see Figure 19).

The combined results of Experiments 1-3 showed a significant interaction between the stimulus type and cue location ($F_{(1,23)}=5.02$, $p<0.05$). Simple main effect analysis revealed that for pseudowords, right-far cue (RF) yielded more negative Laterality Index than the left-far cue (LF) (-11.20 versus -7.06, $F_{(1,23)}=10.56$, $p<0.01$). However, both cues did not generate different Laterality Index for words (-1.11 versus -1.00, $F_{(1,23)}=0.01$, $p>0.05$).

In fact, the trend of the interaction is totally reversed between the first three experiments (Experiments 1, 2 and 3) and the last two experiments (Experiments 6 and 7). The statistical results of the combined data of Experiments 6 and 7 revealed the same interaction effect between stimulus type and cue locations ($F_{(1,11)}=10.74$, $p<0.01$). However, the trend is reversed with reduced laterality effects for pseudowords following a right-far cue (RF) (-7.11 versus -11.61 with left cue, $F_{(1,11)}=14.94$, $p<0.01$). No such differences were found for words (-1.57 versus -0.68, $F_{(1,11)}=0.59$, $p>0.05$).

The comparison of the first three and the last two experiments indicates that the duration of the pre-cue may be of importance. Experiments 1 to 5 have manipulated the visual stimuli and the types of pre-cues, but none of them replicated the cueing effects predicted by Sieroff and Posner's (1988). In Experiments 6 and 7, the more salient right cues resulted in a less negative laterality index.

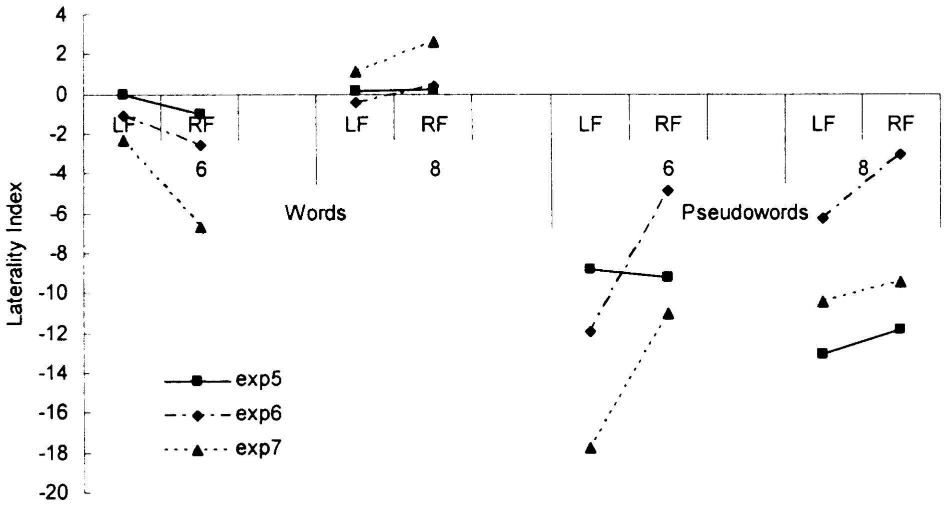

Figure 18: The Laterality Index of Exp 5,6 & 7 as a function of stimuli lexicality, length and cue location

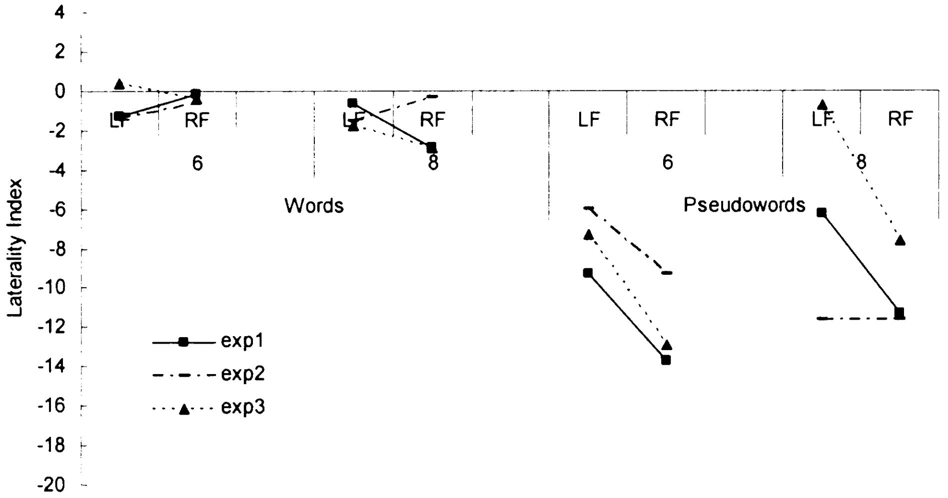

Figure 19: The Laterality Index of Exp 1, 2 & 3 as a function of stimuli lexicality, length and cue location.

Experiment 8

The previous experiments (1-7) have revealed that subjects tended to report more letters from the left than the right segment of centrally presented letter strings. This tendency was so strong that it overrode potential cueing effects from right-sided pre-cues, that were predicted based on Auclair and Sieroff's (2002) findings. It is possible that the left segment advantage in my experiments was the result of reading habits in English, which proceed from left to right in natural reading. When presented with words and pseudowords, subjects tended to scan the stimuli according to the normal reading direction that is from left to right. Such directional scanning under conditions of brief exposure and masking (as in Experiments 1-7) might account for the superior recognition of the left-of-fixation letters.

Experiment 8 was designed in order to eliminate possible scanning effects in a spatial cueing letter recognition task. The idea was to present letters in a scattered array, such that letters are not arranged in a word format, as were the words and pseudowords of the previous experiments. If the scanning from the left tendency only accompanies word recognition processes, it will not be evident with the scattered letter arrays, allowing therefore potential spatial cueing effects at the right side of fixation (following a right cue). The task was letter search in letter array of 2, 4 or 8 letters, where target letters were located to the left or right of fixation, following spatial cues that were presented to the left or right of fixation. Apart from the distortion of word shape by scattering the letters, Experiment 8 was similar in terms of cue location and duration, and target exposure duration to Experiments 1-7.

Method

Design

A 2 x 3 x 2 factorial design (cue location: LVF, RVF) x (stimulus size: 2, 4, or 8 letters) x (target location: LVF, RVF) was used in a within-subjects design. The dependent variables were percentage of correct responses (ACC) and reaction time (RT). Cue and target location were identical at 80% of all trials (valid cues).

Participants

Twenty four participants, 13 females and 11 males, aged between 22 and 34 (mean 25.8, sd 3.1). All but one participants were right-handed and the mean score was 91.3 (sd 15.6) in the Edinburgh Handedness Inventory (Oldfield, 1971). Every participant had normal or corrected to normal vision and was naïve to the paradigm and the purpose of the experiments.

Stimuli

One hundred trials of 2-, 4- and 8-letter arrays were used as stimuli. Every array consisted of one target letter (A, B, C, X, Y, Z) and some flankers (H, I, M, O, T, U, V, W), all randomly selected for every trial. The visual array was scattered in a square, 3 x 3 degrees in size, such that in each trial the target letter was presented randomly to the left or right of the fixation point. The letter arrays were presented in 10-point Courier New font, black on a white background.

Apparatus and procedure

Stimuli were presented on a PC using E-prime software. Each participant sat with their head supported by a chin-rest and head-strap in order to secure head position and stabilize fixation at a distance of 1 m from the screen. The experiment consisted of 340 trials, including 40 trials for practice at the beginning. Each trial began with a fixation point appearing in the centre of the screen for 500 ms. The fixation point was replaced by a star sign (pre-cue) for 80 ms, to the right or left of fixation. The letter arrays was then presented for 30 ms, randomly with 2, 4 or 8 letters that included the target letter presented to the left or right of fixation. The participant's task was to press 'Y' key as quickly as possible if they detected a target letter in the array. Then the participant was requested to take time to report what the target letter s/he detected and where (right or left) the target letter appeared. Participants' responses were recorded for further analysis. Figure 20 illustrated the timeline of the experiment.

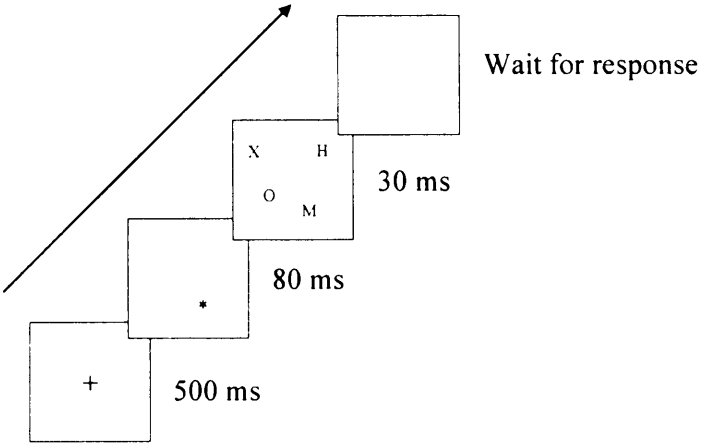

Figure 20: Timeline of Experiment 8
Each trial started with a fixation cross presented for 500 ms, followed by a pre-cue on the target location (80% of trials) for 80 ms, immediately replaced by a 30 ms letter arrays. A blank screen replaced the letter arrays until participant's responses. In the example illustrated in Figure 20, the target letter is X at the LVF, and the cue is not valid (20% of trials) since it was presented at RVF. The manipulation of cue location and target location was aimed to test the ipsilateral cueing effects predicted by Auclair and Sieroff (2002).

Data Analysis

RTs were analyzed only for correct responses. Reaction times that were less than 140 ms or longer than 2000 ms were discarded either as anticipatory or excessively lengthy, respectively. There were 110 discarded trials out of 5687 trials (1.93%).

Results and discussion

The results are plotted in Figure 21 and Figure 22. In the accuracy data (Figure 21), there was a significant effect of array size ($F_{(2,46)}=75.56$, $p<0.01$), and the three categories were each different (88%, 75% and 56% for 2, 4 and 8 letters, respectively). There was an interaction between cue and target location ($F_{(1,23)}=28.67$, $p<0.01$). Simple main effect analysis showed that recognition of the left target letter was better following a left cue (80%) than a right cue (67%), $F_{(1,23)}=11.24$, $p<0.01$. In contrast, recognition of the right target letter was better following a right cue (81%) than following a left cue (64%), $F_{(1,23)}=17.89$, $p<0.01$. Finally, a three-way interaction of array size, cue and target location was significant ($F_{(2,45)}=16.78$, $p<0.01$). As was shown in Figure 21, the interaction of cue and target location increased with array size. For 2-letter arrays, cue and target location did not interact. For 4-letter arrays, recognition of the left target letter was better following a left cue (83%) than a right cue (70%), $F_{(1,45)}=9.23$, $p<0.01$. In contrast, recognition of the right target letter was better following a right cue (84%) than following a left cue (66%), $F_{(1,45)}=22.90$, $p<0.01$. For 8-letter arrays, recognition of the left target letter was better following a left cue (67%) than a right cue (41%), $F_{(1,45)}=26.31$, $p<0.01$. In contrast, recognition of the right target letter was better following a right cue (70%) than following a left cue (43%), $F_{(1,45)}=46.55$, $p<0.01$.

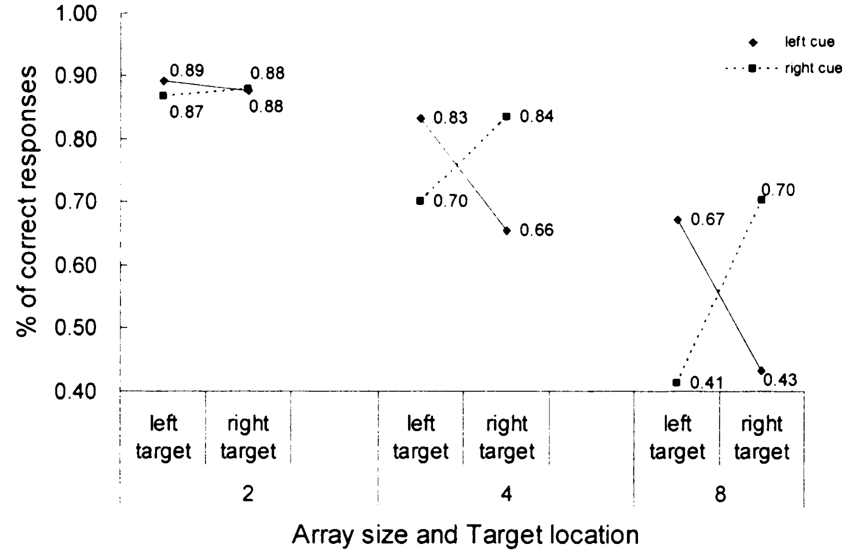

Figure 21: Percentage of letters correctly recognized in the left and right segments of the letter arrays as a function of array size, target location and cue location (Experiment 8)
On the Y axis, 1 indicates 100% and 0.5 indicates 50% correct responses.

In the RT data (Figure 22), there was a significant effect of array size ($F_{(2,46)}=7.93$, $p<0.01$), in which responses to 2-letter array (659.5 ms) were faster than to 8-letter array (726.6 ms), however, both were indifferent from 4-letter array (703.6 ms). There was an interaction between cue and target location ($F_{(1,23)}=60.66$, $p<0.01$). Simple main effects analysis showed that recognition of the left target letter was faster following a left cue (593.8 ms) than following a right cue (806.2 ms), $F_{(1,23)}=32.86$, $p<0.01$. In contrast, recognition of the right target letter was faster following a right cue (607.9 ms) than following a left cue (805.8 ms), $F_{(1,23)}=29.09$, $p<0.01$. There was no three-way interaction ($F_{(2,38)}=0.15$, $p>0.05$), as the interaction patterns were alike for each array size.

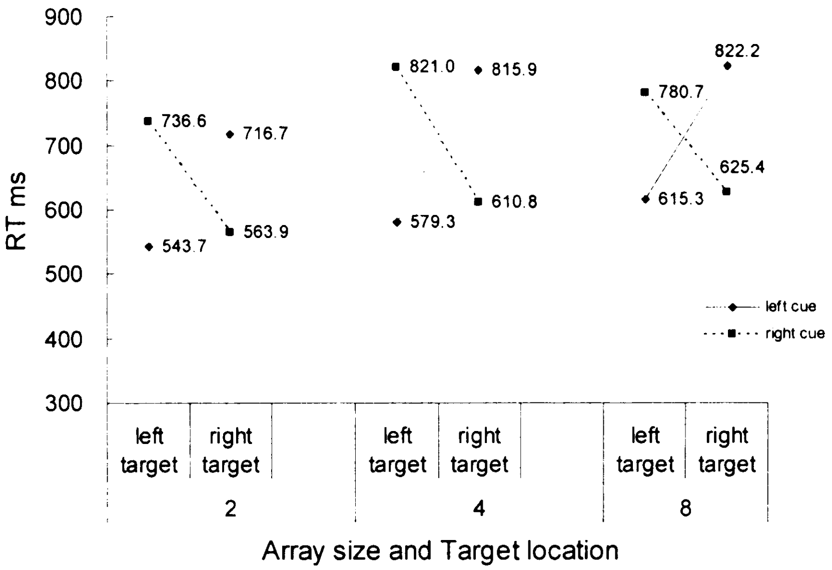

Figure 22: Response times to letters correctly recognized in the left and right segments of the letter arrays as a function of array size, target location and cue location (Experiment 8)

In Experiment 8, a significant ipsilateral cueing effect, in RT and accuracy, was found, with better performance in the LVF arrays following a left but not a right cue, and the complementary pattern for RVF arrays following a RVF but not LVF cue. This significant ipsilateral pattern reflects the predicted cueing effects (Auclair & Sieroff, 2002; but notLindell & Nicholls, 2003) that were not found in Experiments 1-7. Since the cueing procedure in Experiment 8 was similar to the paradigms employed in Experiments 1-7, apart from the way the target letters were presented (in wordlike format in Experiments 1-7 or in a scattered letter array in Experiment 8), the conclusion is that the ipsilateral cueing has increased effects when target letters are not grouped in word shapes. The cueing effect also increased when the to-be-searched array included more letters. The result implies that left-to-right scanning that is associated with natural reading interfered with potential spatial cueing effects during word recognition. However, when the form of the word was disassembled in a way that made left-to-right scanning uninformative, the spatial cues played a role in guiding attention to the letter array and improved performance in the cued locations.

Experiment 9

The parafoveal display of Experiment 8 served to establish the cueing effects in less-than optimal locations, where I predicted (and found) facilitatory ipsilateral cueing effects when the form of a word was disassembled, based on a spatial orientation paradigm (Posner, 1980). To determine whether the cortical representation of foveal stimuli is split or bilaterally represented in both hemispheres, I replicated Experiment 8 but with a foveal display (Experiment 9). The foveal display served as the critical test for the split fovea theory, where I predicted ipsilateral facilitatory effects for the left- and right-of-fixation letters following a left or right cue, respectively. This is because if I assume that briefly presented foveal information is bilaterally projected to both hemispheres, then unilateral cues will become uninformative.

The prediction that the ipsilateral cues would have facilitative effects on the left and right segment of the foveal letter array is based on Auclair and Sieroff's findings (Auclair & Sieroff, 2002) and on the facilitative cueing effects I found in Experiment 8 for the parafoveal displays. However, there is an alternative prediction, which still supports the split fovea theory yet predicts *inhibitory* ipsilateral cueing effects. Recently it was suggested that attention enhances spatial resolution in the cued location (Lee, Itti, Koch, & Braun, 1999; Talgar, Pelli, & Carrasco, 2004; Yeshurun & Carrasco, 1998). These authors showed facilitatory cueing effects when higher resolution was required for the task, but also *inhibitory* cueing effects when resolution at the cued location was higher than the optimal needed for the task. For a texture segregation task, Yeshurun and Carassco (1998) observed that attention improved performance at peripheral locations where spatial resolution was too low, but impaired performance at central locations where spatial resolution was too high. Therefore, in visual search tasks in which observers' performance is slower and less accurate as target eccentricity increases, due to the lower spatial resolution of the periphery, cueing the target location diminished this eccentricity effect.

If the split fovea theory is valid, then left cues should affect performance to stimuli presented just left of fixation, and correspondingly, right cues should affect performance to stimuli just right of fixation. If, however, stimuli in the foveal area are bilaterally projected, lateralized cues should not affect performance as there is not a single 'valid' location (right or left). Whether this cueing effect is facilitatory (Posner, 1980) or inhibitory (Yeshurun & Carrasco, 1998) is a function of the spatial resolution at target location and of the task at hand.

For the letter search task in unstructured letter arrays, it was established that performance is optimal at foveal rather than parafoveal locations (Bertera & Rayner, 2000). That implies that enhancing further the resolution in foveal letter arrays may impair performance, as resolution would become too high (Yeshurun & Carrasco, 1998), like watching a picture from a too-close distance. Therefore inhibitory ipsilateral cueing are predicted for foveal arrays based on spatial resolution enhancement theory (Yeshurun & Carrasco, 1998).

The letter array in Experiment 9 was reduced to 0.5 degree to the left and right of fixation to ensure foveal presentation. Because the reduced scattered area only accommodates 4 letters at most, presentation of 8-letter arrays was not possible.

Method

Design

A 2 x 2 x 2 factorial design (cue location: LVF, RVF) x (stimulus size: 2, 4 letters) x (target location: LVF, RVF) was used in a within-subjects design. The dependent variables were percentage of correct responses (ACC) and reaction time (RT). Cue and target location were identical at 80% of all trials (valid cues).

Participants

Twenty eight participants, 18 females and 10 males, aged between 19 and 35 (mean 24.4, sd 4.5). All but two participants were right-handed and the mean score was 88.21 (sd 22.9) in the Edinburgh Handedness Inventory (Oldfield, 1971). Every participant had normal or corrected to normal vision and was naïve to the paradigm and the purpose of the experiments.

Stimuli

One hundred and fifty trials of 2- and 4-letter arrays were used as stimuli. Every array consisted of one target letter (A, B, C, X, Y, Z) and some flankers (H, I, M, O, T, U, V, W), all randomly selected for every trial. The visual array was scattered in a square, 1 x 1 degrees in size, such that in each trial the target letter was presented randomly to the left or right of the fixation point. The letter arrays were presented in 7-point Courier New font, black on a white background.

Apparatus and procedure

Apart from the array size, the procedure was similar to the procedure of Experiment 8.

Data analysis

Due to disk faults, there was no RT data in 8 out of 28 participants, but accuracy data were kept for all participants. RTs were analyzed only for correct responses. Reaction times that were less than 140 ms or longer than 2000 ms were discarded either as anticipatory or excessively lengthy, respectively. There were 53 discarded trials out of 5023 trials (1.06%).

Results and discussion

The results are plotted in Figure 23 and Figure 24. In the accuracy data, there was a significant effect of array size ($F_{(1,27)}=13.43$, $p<0.01$), with better recognition of 2-letter array (86%) than 4-letter array (81%).

There was a significant interaction between cue and target location ($F_{(1,27)}=4.46$, $p<0.05$). Simple main effect analysis did not reveal any significant differences in the recognition of the target letter following a left or a right cue. However, recognition of the left target letter was worse following a left cue (82%) than a right cue (85%). Complementary, the recognition of the right target letter was worse following a right cue (81%) than a left cue (84%).

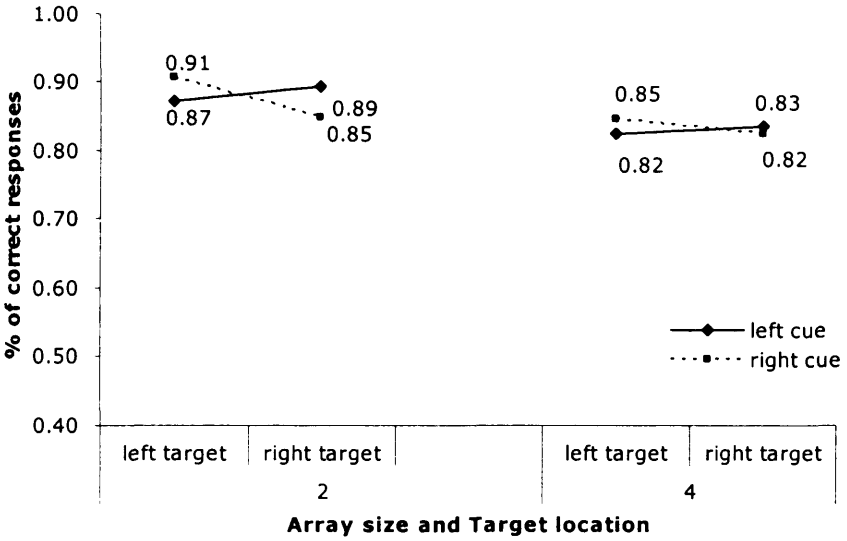

Figure 23: Percentage of letters correctly recognized in the left and right segments of the letter arrays as a function of array size, target location and cue location (Experiment 9)

On the Y axis, 1 indicates 100% and 0.5 indicates 50% correct responses.

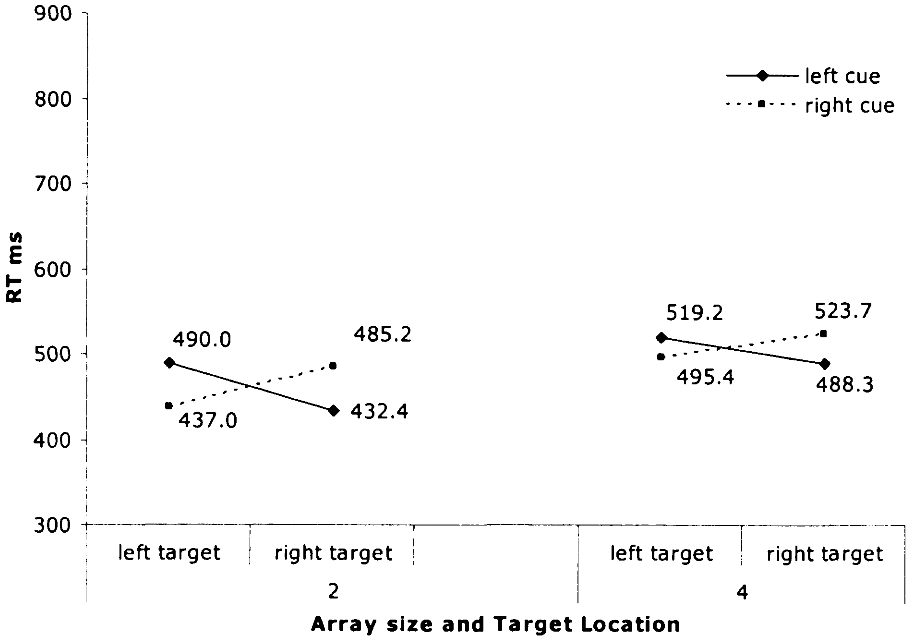

Figure 24: Response times to letters correctly recognized in the left and right segments of the letter arrays as a function of array size, target location and cue location (Experiment 9)

In the RT data (Figure 24), there was a significant effect of array size ($F_{(1,19)}$=13.72, p<0.01), with a faster recognition of 2-letter array (469.58 ms) than 4-letter array (514.37 ms). There was a significant interaction between cue and target location ($F_{(1,19)}$=4.84, p<0.05). Simple main effects analysis did not reveal any significant differences in the recognition of the target letter following a left or a right cue. However, the data showed that the recognition of the left target was slower following a left cue (509.79 ms) than following a right cue (475.24 ms). In contrast, recognition of the right target letter was slower following a right cue (513.41 ms) than following a left cue (469.45 ms).

In Experiment 9, a significant interaction between cue location and target location was found. However, the cueing effects, both in RT and accuracy, were inhibitory. In other words, the cue ipsilaterally preceding the target letter inhibited the recognition of the target letter. Even though this is contrary to the results of Experiment 8 which reported the facilitatory cueing effects of the cue on the ipsilateral target letter, the results of Experiment 9 further confirmed the prediction of the split fovea theory because ipsilateral parafoveal cueing effects, though negative, were found for foveal displays.

Previous research has demonstrated the phenomenon of inhibitory cueing effects on foveal displays (Yeshurun & Carrasco, 1998) by arguing the spatial resolution in the fovea was highly enhanced by attention. According to Yeshurun and Carrasco's (1998) results, the function of attention (pre-cue) was to enhance the spatial resolution of the visual stimulus (signal enhancement), and the attention effect actually depended on the match between the enhanced signal and the size of the filter. The enhanced stimulus (that is following the cue) will improve performance when the stimulus exceeds filter size. In contrast, the enhanced stimulus would impair performance when it located within the filter. Yeshurun and Carrasco have shown that the cue impaired performance at about 1° of visual angle in the viewing distance of 57 cm, but the impairment reduced to 0.66° when the viewing distance was increased to 228 cm. In my Experiment 9, the viewing distance was 100 cm, the dropping performance by cued stimulus would definitely happen within the scattered visual array, i.e., in the fovea area. Thus, the negative cueing effects of Experiment 9 are compatible with Yeshurun & Carrasco (1998) and with the split fovea theory.

Another possible reason for the negative cueing effects would be the abrupt onset of the pre-cue. Breitmeyer and Valberg (1979) found that the oscillation of peripheral grating only impaired the visibility of the foveal area, but not the visibility of the peripheral visual field. In Experiment 9, the visual array followed immediately by the pre-cue, and both were black on a white background. It might be that the pre-cue served as the abrupt onset before the visual array.

In summary, the visual search task in the foveal area was affected by parafoveal cueing, which complied with the prediction of the split fovea theory. Although the ipsilateral cueing effects were inhibitory, rather than facilitative as in Experiment 8, it may be explained by the spatial resolution enhancement theory or the abrupt onset of the pre-cue. In any case, the ipsilateral cueing effects found in Experiments 8 and 9 are both in line with the split fovea theory.

General Discussion

In the present experiments, I aimed to explore the role of spatial cues in the processing of visual words/pseudowords within the framework of the split fovea theory. Experiments 1 to 5 showed that more letters at the left than at the right segment of centrally presented pseudowords were correctly reported, whether the cue was in the left or right visual field. Experiments 1-5 failed to replicate the predicted cueing effects (i.e., Auclair & Sieroff's prediction) where recognition of the left letters was supposed to be improved following a left but not a right cue, and vice versa for the right of fixation letters. In addition, the results of Experiments 1 to 5 showed no cueing effects for words, as opposed to Lindell and Nicholls's (2003) findings. In experiments 6 and 7, I increased the salience of the pre-cue and increased the cue duration from 80 ms to 120 ms. The change did not alter the result pattern for words, however, there were cueing effects for pseudowords, in line with Auclair and Sieorff (2002), and Sieorff and Posner (1988). In Experiments 8 and 9, when the word shape of the letter strings was broken into a scattered visual array, significant cuing effects emerged, both in the para-fovea and fovea areas, in line with the split fovea theory. The conclusions are that visual word recognition is not easily modulated by the passive exogenous cues, unless the cues are salient enough and are presented for long enough to allocate attention; or the standard word shape is disassembled.

The findings reported here support the view that spatial attention affects visual word recognition, in line with Stolz and MaCann (2000), because there were selective attentional effects on word recognition which depended on the lexical status of the word target. Visual word recognition has been argued to be obligatory and rapid, it would be triggered by the appearance of the stimulus in the visual field (Brown, Gore, & Carr, 2002). However, the automatic notion has been also challenged by some research (e.g., Manwell, Roberts, & Besner, 2004; Risko, Stolz, & Besner, 2005; Stolz & McCann, 2000). For example, Stolz and McCann (2000) found that the semantic priming effect occurred mainly when the prime cue shared location with the target word (e.g., 80% of valid trials). When the number of valid trials was reduced to 50%, the spatial precuing and semantic priming did not interact. Risko *et al.* (2005) also showed that Stroop effect happened only when the target word was the colour carrier; however, when the colour was carried by a separated word or a bar, no Stroop effect was found. The lack of Stroop effect implied that the target word would not be automatically activated.

In the word recognition and attention experiments mentioned in the previous paragraph, the spatial cues had dual function: not merely a spatial cue which passively reduced the uncertainty of target's location, but also a stimuli which is actively associated with the target word, for example semantic priming or a colour name. In contrast, in Sieroff and Posner (1988), Auclair and Sieroff (2002) and the experiments in this chapter, the cue was not associated with the centrally presented target words. It is possible that the cues were more prone to be ignored by subjects when having no association with the target. In line with this possibility, previous research had shown that pre-cues do not necessary capture attention (Yantis & Jonides, 1990) and could be modulated by endogenous attention (Fenske & Stolz, 2001; Folk, Remington, & Johnston, 1992). In the current experiments, participants did not need to attend to the exogenous cue, unless it was coloured and lasted long enough (Manwell, Roberts, & Besner, 2004). Even when the colour distractor was a digit string, it did not affect word recognition processing (Roberts & Besner, 2005, experiment 8). The failure of Experiments 1-7 here to produce cueing effects is therefore in line with previous studies that have used similar types of cues (Manwell, Roberts, & Besner, 2004; Roberts & Besner, 2005).

When the target string becomes a pseudoword, the reciprocal loop between the lexicon and the letters would be broken because pseudowords could not activate the lexicon to assist letter recognition. The lack of top-down support implied that pseudowords required a sequential process and were spelled out. It was shown that attentional scanning is influenced by reading direction (Battista & Kalloniatis, 2002), therefore, the left-to-right scanning made the beginning letters/left part of pseudowords the key features of lexical access. That scanning bias might explain the significant left segment advantage that was found over and above the cueing effects (as measured by the negative laterality index) in Experiments 1-5. Only when salient cues were employed in Experiments 6 and 7 was the laterality index reduced. In addition, a salient exogenous cue might not trigger spatial attention to intervene in lexical processing (Roberts & Besner, 2005), until it has lasted for a minimum period (Auclair & Sieroff, 2002; Manwell, Roberts, & Besner, 2004). Indeed the longer cue duration in Experiments 6 and 7 increased the cueing effects on letter recognition.

As opposed to Experiments 1-7, significant ipsilateral cueing effects emerged when word shape was distorted (Experiments 8 and 9). Previous research has indicated that distorted word shape, for instance vertical presentation, case alternation or stepped format would interfere with the lexical access (Bub & Lewine, 1988; Ellis, Brooks, & Lavidor, 2005; Fiset & Arguin, 1999; Young & Ellis, 1985). Indeed when in experiments 8 and 9 characters were scattered such that word shape was completely distorted, letter search was significantly modulated by the spatial cue.

In summary, word recognition appears to be an autonomous process and resistant to passively exogenous cues. Subjects' strategy and the task demand could dominate the process. However, pseudowords or the deformed words would leave the autonomous process vulnerable to salient and longer exogenous cues, and modulate lexical process, thus producing cuing effects on letter identification in pseudowords. The ipsilateral parafoveal cueing effects on foveal targets found in Experiments 8 and 9 are in line with the split fovea theory.

CHAPTER 5: CROSSED-UNCROSSED DIFFERENCE (CUD) IN THE VISUOMOTOR CORTICES

The cross-uncrossed difference (CUD) is a method for studying the transfer of sensory and motor visuomotor information across the corpus callosum (Marzi, Bisiacchi, & Nicoletti, 1991). When the visual stimulus is presented to one hemifield, the reaction time (RT) when using the ipsilateral hand (uncrossed response) is faster than when responding with the contralateral hand (crossed response) and the CUD represents the time taken to transfer information from one hemisphere to the other (Lavidor & Ellis, 2003).

Marzi *et al.* (1998) employed transcranial magnetic stimulation (TMS) over the occipital cortex to investigate the callosal basis of the CUD and found a significant TMS effect in delaying RT only when visual information had to be transferred across the brain. The results were based on comparisons between the crossed and uncrossed conditions, but without further separation between the contralateral and ipsilateral TMS effects. In chapter 3, I have shown contralateral, but not ipsilateral, TMS effects on visual targets located in the right and left visual field (RVF and LVF, respectively)- repetitive TMS (rTMS) over the right occipital cortex had a significant inhibitory effect on letter/digit decision performance for left, but not right, visual field targets, and the complementary pattern of rTMS effect was obtained with left hemisphere stimulation which significantly impaired lexical decision to RVF, but not LVF targets (Chiang, Walsh, & Lavidor, 2004). Similar selective patterns were found, either for a letter/digit task (Amassian et al., 1989), or a lexical decision task (Lavidor & Walsh, 2003). The aim of the current study was therefore to study the CUD effect with TMS over the occipital cortex, while distinguishing between ipsilateral and contralateral TMS effects.

Methods

Design and stimulus

A 5 x 2 x 2 factorial design (TMS: no stimulation, RH stimulation, LH stimulation, and two sham-TMS conditions) x (target position: LVF or RVF) x (responding hand: right or left) was used for the experiment; all within subject variables. The application of repetitive transcranial magnetic stimulation (rTMS) was presented in alternating blocks of single hemisphere stimulation. Responding hand was manipulated in fixed blocks, and target position was randomly manipulated.

The combination of responding hand, TMS location, and target position created the CUD experimental conditions, which are shown in Figure 25. In the crossed condition, the hemifield and hand were on opposite sides, while in the uncrossed condition, the hemifield and hand were on the same side.

The stimulus was a white circle with 0.86 degree in diameter, presented for 110 ms 5° to the left or right of fixation (LVF and RVF, respectively). Four blocks of 92 trials were used, where no stimulation (60 trials) and rTMS (32 trials) were randomly delivered. In order to avoid continuous responses, 12 additional trials in each block were catch trials, without any visual stimulus. Half of trials were combined with rTMS. For the sham conditions, another four blocks of 27 trials were delivered, where eight out of 24 trials and three catch trials were accompanied by sham rTMS. The total number of trials for each participant was 524, including 60 catch trials.

Participants

Eleven neurologically healthy participants, 6 females and 5 males, and aged between 22 and 34 (mean 26.3, sd 3.9) with normal or corrected to normal vision, took part in the experiment. All participants were right-handed, scoring at least 75 in the Edinburgh Handedness Inventory (Oldfield, 1971), with total mean score of 94.6 (sd 7.5). The experiment was reviewed and approved in advance by the Joint UCL/UCLH Committees on the Ethics of Human Research, and all participants signed the informed consent form.

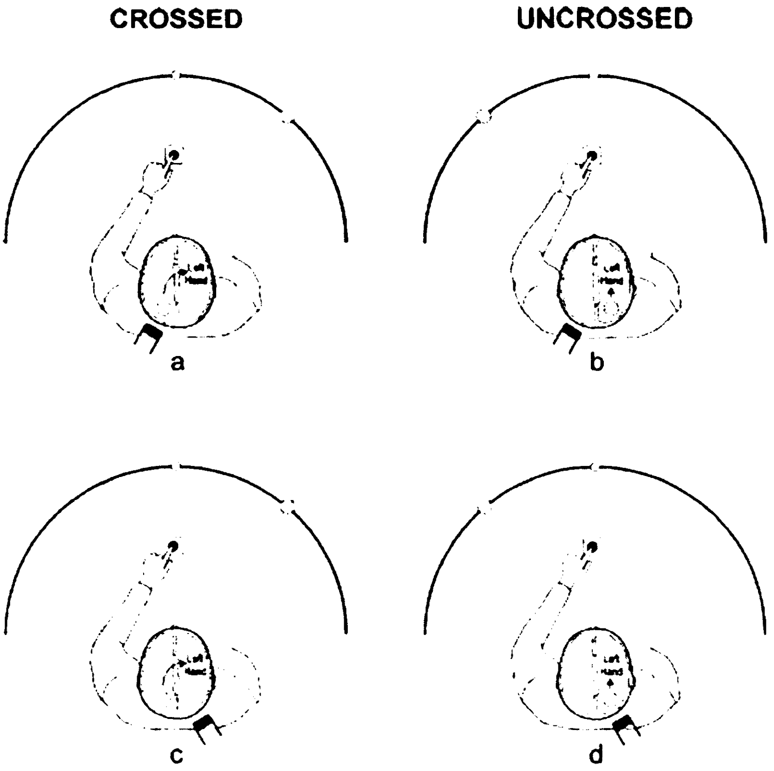

Figure 25: Crossed-uncrossed conditions of visual cortex stimulation and responding hand
For convenience, only responses using the left hand are shown, although both hands were used in a balanced sequence. In the crossed condition, visual cortex stimulation and hand are on opposite sides, while in the uncrossed condition, the hemifield and the hand are on the same sides. **a,d**: rTMS applied to the same side as the visual cortex processing the visual stimulus; **b, c**: rTMS applied to the visual cortex not involved in stimulus detection (from Marzi et al., 1998, with permission)

Apparatus and procedure

For the TMS trials, rTMS was applied by using 70 mm figure-of-eight coil for 500 ms (10 Hz, 60% of the maximum output of about 2-T, MagStim model 200, Magstim, Whitland, Dyfed, UK). Before the experiment was conducted, the coil was first positioned 2 cm laterally and 2 cm above the inion, then moved to find the best place where it produced contralateral phosphenes (Kammer, 1999; Marg, 1991). The location was then fixed for the participant during the whole experiment.

For the sham trials, two figure-of-eight coils were attached together. The inactive coil was placed on the same stimulation location, and an active coil was placed at 90^{0}, through which no current was passed to the inactive coil. Because the active coil was away from the skull, the brain was not stimulated but participants were exposed to the unilateral click and to the vibration of the active coil.

The experiment was conducted in a dark room. Stimuli were presented on a PC using E-prime software (Psychology Software Tools). Each participant sat with their head supported by a chin-rest and head-strap in order to secure head position and stabilize fixation at a distance of 1 m from the screen. Every trial began with a cross (10 point Courier New font) appearing in the centre of the screen for 500 ms. At random intervals (from 300 ms to 900 ms), the cross was replaced with no stimulus or a white circle for 110 ms on the LVF or RVF. Following the target disappearance, a blank screen of 1000 ms was presented while waiting for the participant's responses, replaced again by a new sequence of fixation, target and blank screen. On the rTMS trials, stimulation was given for 500 ms at the time of target appearance. Participants were requested to fixate the cross and press a space bar with the index finger as quickly as possible when the target (i.e., the white circle) was detected.

Data Analysis

When the response rate for catch trials was greater than 15% or the missing responses rate to the visual target was over 10%, the data were deleted, resulting in nine valid participants out of the original eleven. RTs that were less than 140 ms or longer than 800 ms were discarded either as anticipatory or excessively lengthy, respectively. Discarded trials were 0.7% of the total RTs.

Because the aim of the study was to examine potential TMS effects on the CUD and not to test hemispheric differences in target identification per se, the results from targets presented to RVF and LVF were pooled together and analyzed in 5 x 2 repeated measures ANOVA, with TMS condition (five levels) and CUD (crossed, uncrossed) as the within-subject variables.

Results

The results are plotted in Figure 26. Analysis of RT data showed a main effect of TMS ($F_{(4,32)}=13.74$, $p<0.001$). Scheffe's post-hoc comparisons ($p < 0.05$) revealed that the no-TMS condition was significantly slower than the TMS or the sham conditions. Although the main effect of the CUD was not significant, the results were in the expected direction with faster responses in the uncrossed than the crossed condition (278 ms versus 284 ms, $F_{(1,8)}=2.8$, $p=0.1$).

Of greater interest was the significant interaction of the CUD and the TMS condition ($F_{(4,32)}=2.81$, $p<0.05$). Simple main effects of the interaction revealed that the only condition where the crossed and uncrossed conditions differ significantly occurred when TMS was applied over the contralateral visual cortex under the crossed response.

To investigate further the individual contribution of each hemisphere to the CUD inhibition induced by TMS applied over the contralateral visual cortex, I separated the crossed and uncrossed responses to RVF and LVF trials (only for the contralateral rTMS stimulation). A repeated measures ANOVA revealed a significant CUD effect ($F_{(1,8)}=6.22$, $p<0.01$), but no visual field effect. In addition, visual field did not interact with the crossed-uncrossed responses, and the CUD effect size was similar in both visual fields.

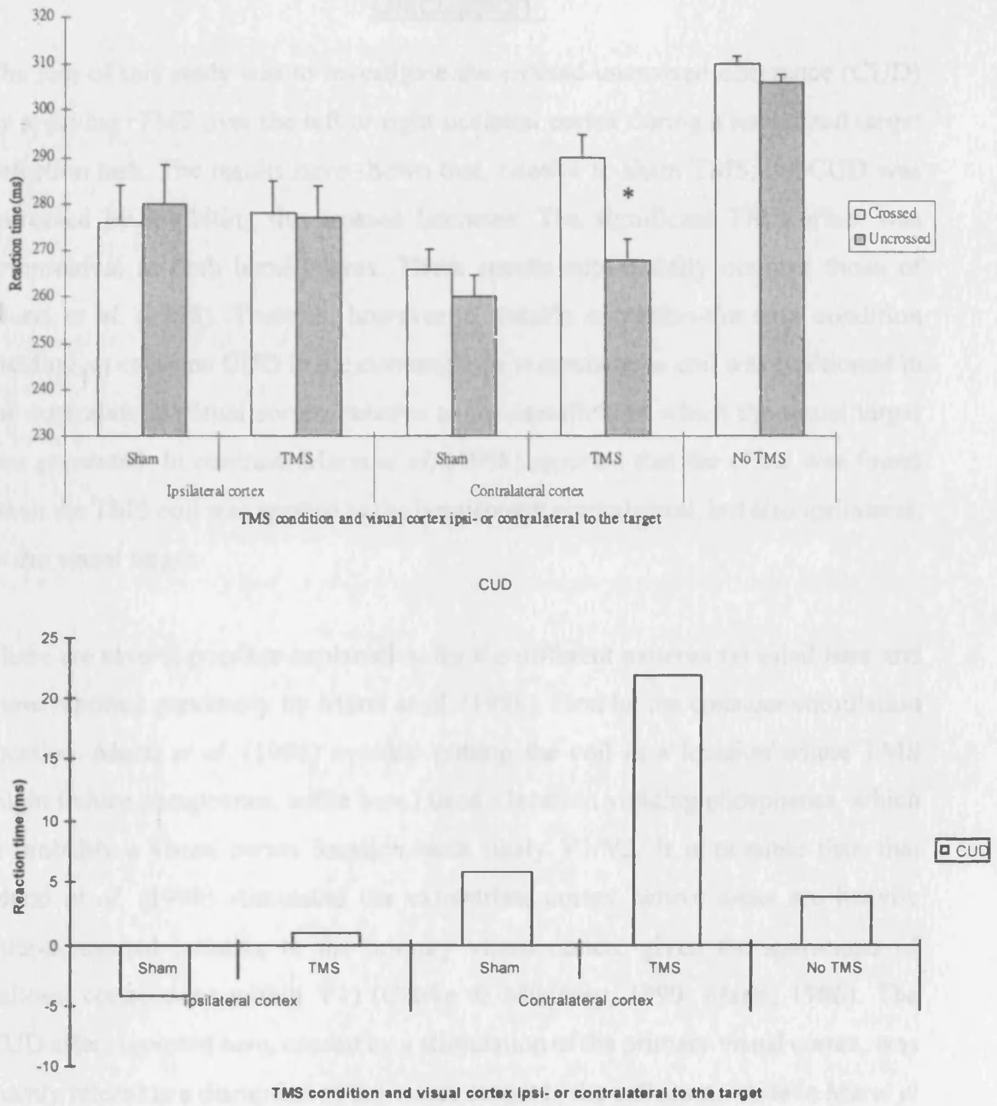

Figure 26: Reaction time (RT) of the uncrossed and crossed conditions as a function of target position and magnetic stimulation (top panel) and TMS effect on the CUD (lower panel)

Top panel: The left two bars were RTs when rTMS was applied to the occipital cortex ipsilateral to the visual stimulus. The contralateral conditions were rTMS treatment on the occipital cortex contralateral to the visual target. The sham condition was exposing participants to the click sound produced by the rTMS but not the magnetic stimulation. The magnetic condition was real rTMS treatment over the occipital cortex processing (contralateral) or non-processing the visual target (ipsilateral). The right pair of bars represents the no-TMS condition. Error bar is the standard error of each condition. Lower panel: RT differences between the crossed and uncrossed conditions. The positive bars denoted that the RT at the crossed condition were slower than RT at the uncrossed condition, while negative bars represented faster RT in the crossed than the uncrossed condition.

Discussion

The aim of this study was to investigate the crossed-uncrossed difference (CUD) by applying rTMS over the left or right occipital cortex during a lateralized target detection task. The results have shown that, relative to sham TMS, the CUD was increased by inhibiting the crossed latencies. The significant TMS effect was symmetrical at both hemispheres. These results substantially confirm those of Marzi *et al.* (1998). There is, however, a notable exception-the only condition yielding an enlarged CUD in the current study was when the coil was positioned in the contralateral visual cortex, relative to the hemifield in which the visual target was presented. In contrast, Marzi *et al.* (1998) reported that the effect was found when the TMS coil was applied to the hemisphere contralateral, but also ipsilateral, to the visual target.

There are several possible explanation for the different patterns revealed here and those reported previously by Marzi *et al.* (1998). First let me consider stimulation location. Marzi *et al.* (1998) avoided putting the coil in a location where TMS might induce phosphenes, while here I used a location yielding phosphenes, which is probably a visual cortex location most likely V1/V2. It is possible than that Marzi *et al.* (1998) stimulated the extrastriate cortex, where areas are heavily inter-connected (relative to the primary visual cortex, given the sparseness of callosal connections within V1) (Clarke & Miklossy, 1990; Marzi, 1986). The CUD effect reported here, caused by a stimulation of the primary visual cortex, was mainly related to a disruption of the visual output to the callosum, while in Marzi *et al.* (1998) there was a disruption of the callosal transmission in the inter-connected areas of the extrastriate cortex. In line with this account, while Marzi *et al.* (1998) adopted intensity of 80% of output, here I applied only 60%. The higher intensity might also contribute to the TMS effects on the other, non-stimulated hemisphere via the transcranial connections in areas 18 and 19.

Another general difference between the two TMS-CUD studies is, obviously, the TMS procedure: Marzi *et al.* (1998) employed a single-pulse TMS, while here I employed repetitive TMS. However, the implications of the different procedures warrant further investigation.

Both the sham and rTMS manipulations sped up response times, when compared with the no-TMS control condition, in accordance with Marzi *et al.* (1998). This feature of TMS is well documented (Walsh & Pascual-Leone, 2003, pp84-89), and might result from alertness or inter-sensory facilitation (Hershenson, 1962; Nickerson, 1973).

One possible concern is whether the reported TMS effects were confounded with potential attentional bias induced by auditory or somatosensory artefacts of TMS. Auclair and Sieroff (2002), for example, have shown that a lateralized cue improved identification of letters that were ipsilateral to the cue. The noise a TMS coil makes during stimulation, might act as an exogenous spatial cue, being a right cue when TMS is applied over the right occipital cortex, and a left cue when TMS is applied over the left occipital cortex. However, this was not the case, because the significant CUD effect was found with a real, but not sham stimulation.

The CUD task might include, in addition to the intrahemispheric and the interhemispheric transmission, sensory-motor integration, decision-making and preparation of motor response in the premotor cortex (Iacoboni & Zaidel, 2004; Marzi et al., 1999; Tettamanti et al., 2002). The stronger activation of the following areas was observed in the crossed, but not uncrossed conditions: the superior parietal cortex (Iacoboni & Zaidel, 2004; Marzi et al., 1999), premotor cortex (Tettamanti et al., 2002) and the occipital cortex (Marzi et al., 1999). In contrast, there was no clear activation in the uncrossed condition, except anterior to the ventral anterior commissure plane (Marzi et al., 1999). In addition, the superior parietal cortex is heavily interconnected, both anatomically and functionally, with the dorsal premotor cortex (Wise, Boussaoud, Johnson, & Caminiti, 1997). I will term those areas required in the crossed condition as "the contralateral pathway", and the areas involved in the uncrossed condition "the ipsilateral pathway". It is possible that weaker visual output, resulting from a TMS application over one visual cortex, might not, or barely, activate "the contralateral pathways". In contrast, the same residual visual information might be sufficient to activate "the ipsilateral pathway" because it might be either resistant to the decay of the visual information, or compensated for the TMS-induced weaker visual information. In line with this account, some studies have shown that the ipsilateral hemisphere can be activated by TMS over the occipital cortex (Ilmoniemi et al., 1997), and the intra-cortical facilitation can happen at the motor cortex when TMS is applied over the premotor area (Munchau, Bloem, Irlbacher, Trimble, & Rothwell, 2002). Moreover, TMS over the motor cortex can elicit suppression of the contralateral motor cortex via transcallosal route (Trompetto et al., 2004).

In summary, the interhemispheric transfer of visuomotor information was found here to be affected by TMS only when the hemisphere contralateral to the visual stimuli was involved. The results show, therefore, that interhemispheric transfer can be affected by interfering with the activity of a primary sensory area. However, further research is required to disentangle the consequences of interference to the interhemispheric information transfer at the primary visual cortex, the extrastriate and perhaps the pre-motor areas.

CHAPTER 6: USING NEAR INFRARED SPECTROSCOPY AND TRANSCRANIAL MAGNETIC STIMULATION TO INVESTIGATE THE MOTOR CORTEX

Repetitive transcranial magnetic stimulation (rTMS) can modulate cortical function by enhancing or decreasing cortical excitability depending on the parameters of stimulation. Generally, high frequency stimulation (>= 5 Hz) facilitates cortico-spinal excitability, but low frequency stimulation (<= 1 Hz) inhibits it (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000a; Pascual-Leone et al., 1998). Although inhibition by 1 Hz TMS has been reported at the stimulation site and can outlast the stimulation by 15-30 minutes (Chen et al., 1997; Fitzgerald, Brown, Daskalakis, Chen, & Kulkarni, 2002; Muellbacher, Ziemann, Boroojerdi, & Hallett, 2000; Pal et al., 2005; Plewnia, Lotze, & Gerloff, 2003), there is no consensus about the induced change at the homologous site in the unstimulated hemisphere. Some researchers have noted activation (Gilio, Rizzo, Siebner, & Rothwell, 2003; Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-Leone, 2004; Pal et al., 2005; Pascual-Leone et al., 1998; Plewnia, Lotze, & Gerloff, 2003; Schambra, Sawaki, & Cohen, 2003), but deactivation has also been observed (Wassermann, Wedegaertner, Ziemann, George, & Chen, 1998).

The interhemispheric connections between the motor cortices have been examined in several previous studies (Ferbert et al., 1992; Meyer, Roricht, Grafin von Einsiedel, Kruggel, & Weindl, 1995; Meyer, Roricht, & Woiciechowsky, 1998). One proposal is that 1 Hz repetitive stimulation reduces interhemispehric inhibition and thus activates the contralateral motor cortex (Gilio, Rizzo, Siebner, & Rothwell, 2003; Pal et al., 2005). However, one imaging study showed that, at the stimulated site, rCBF gradually increased by up to 20% during 30 minutes of 1 Hz TMS, and then gradually decreased down to 6% in the 10 minutes following stimulation. Furthermore, decreased rCBF in the opposite hemisphere was also detected during stimulation, but no data have shown how long the negative effect may last after stimulation (Fox et al., 1997). Another imaging technique, near infrared spectroscopy (NIRS), has also been used to study

TMS effects. Single pulse TMS activated the motor cortex by increasing the oxyhaemoglobin (O_2Hb) level (Noguchi, Watanabe, & Sakai, 2003). Applying low frequency rTMS for 2 minutes also increased the O_2Hb level in the stimulation area (Oliviero et al., 1999). According to the Fick principle, the increase in O_2Hb concentration can be considered as an index of raised blood flow. Nevertheless, the increased O_2Hb level in these two studies (Noguchi, Watanabe, & Sakai, 2003; Oliviero et al., 1999) only recorded for a maximum of 5 minutes after stimulation, far shorter than the behavioral effects. For example, Kobayashi *et al.* (2004) indicated that ipsilateral finger movements were improved for at least 10 minutes following 1 Hz TMS. Moreover, little research has concentrated on the haemoglobin changes, especially at the homologous non-stimulated motor cortex after 1 Hz stimulation. This chapter aims to use NIRS to investigate how long the effects of 1 Hz stimulation in the contralateral hemisphere can last.

Method

Design

A 2 x 6 factorial design (TMS: sham and real) x (time block: before TMS, after TMS 1, 2, 3, 4 and 5) was used in a within subject design. The task was to move the right thumb as quickly as possible to sequentially press hard on the index, middle, fourth and little finger, and then reverse the sequence. The task was self-paced. A full block consisted of 10 cycles of 30-second moving (on-state) and then 60-second rest (off-state). Inter-block interval was 10 minutes (see the details in Figure 27). NIRS was fixed over the hand area of left motor cortex and TMS was delivered over the right motor cortex.

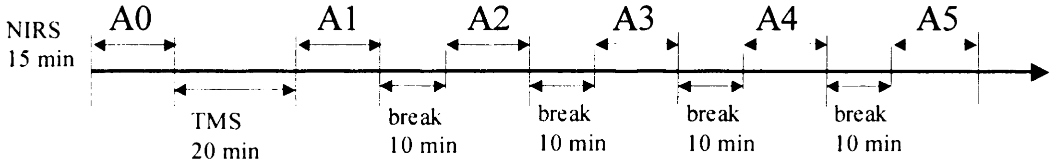

Figure 27: Time line of NIRS measurement
NIRS was applied over the left motor cortex and blood flow changes recorded before TMS (A0) and after TMS in 5 different blocks (A1 to A5). Every block was 15 minutes long, consisting of 10 cycles of 30 seconds in the on-state and 60 seconds in the off-state. Inter-block interval was 10 minutes.

Participants

Five healthy male subjects, aged between 24 and 40 (mean 32.4, sd 8.5), participated in the experiment. All participants were right-handed and scored at least 90 in the Edinburgh Handedness Inventory (Oldfield, 1971), with total mean score of 96.0 (sd 4.1). The experiment was reviewed and approved in advance by the Joint UCL/UCLH Committees on the Ethics of Human Research, and subjects signed a consent form.

TMS and NIRS apparatus

TMS was applied using a 70 mm figure-of-eight coil for 20 minutes (1Hz, 115% of the motor threshold; MagStim model 200, Magstim, Whitland, Dyfed, UK). The TMS coil was placed over the right motor cortex and the motor threshold was determined by the MOBS algorithm (Tyrrell & Owens, 1988) (I would like to thank Dr. Kai Thilo, Department of Physiology, University of Oxford, for providing the software used in the threshold procedure).

For the sham condition, two figure-of-eight coils were attached together. The inactive coil was placed on the same stimulation location, and an active coil was placed at 90^o, through which no current was passed to the inactive coil. Since the active coil was away from the skull, the brain was not stimulated but subjects were exposed to the unilateral click and to the vibration of the active coil.

A NIRO-200 monitor (Hamamatsu Photonics K.K., Japan) was used to monitor concentration change of O_2Hb and deoxy-hemoglobin (HHb) at 6 Hz sampling rate. Briefly, a laser source emits light guided to the subjects' head through a fiber-optic bundle, a so-called "optode". Optodes were positioned over the left motor cortex. Interoptode distance was 3 cm. The placement of optodes was across the motor cortex and with the emitter at the posterior, which was in line with the best orientation of the probe to obtain robust measurements of O_2Hb and HHb (Toronov et al., 2001).

Procedure

The experiment began with the localization of motor cortices with BrainSight system (Magstim, Whitland, Dyfed, UK). The hand area was found by locating the superior genu, convex anteriority, of the motor cortex (Pizzella, Tecchio, Romani, & Rossini, 1999). Those subjects who did not have structural images had the motor cortex located by TMS. Final verified locations were conducted by TMS to find out the best coil position for the production of contralateral finger twitches. The locations were then fixed through the whole experiment. Participants were then instructed to do the finger tapping task. Every subject was told when to start moving fingers and when to stop, total 10 cycles of 30-second moving (on-state) and then 60-second rest (off-state). After the first block of 10 cycles, 1 Hz TMS (or sham-TMS) was applied over the right motor cortex for 20 minutes. After stimulation, another 5 blocks of 10 cycles of finger tapping were recorded, with an inter-block interval of 10 minutes. Every subject had to come back on a second day to repeat the same procedure except for the TMS treatment. Three subjects were treated with 1 Hz TMS on the first day and the sham-TMS on the other day. Two subjects received the opposite order of treatments.

Data Analysis

Because the NIRO-200 monitor does not allow for absolute quantification of baseline values, data were related to a baseline of zero calculated from the 10 seconds before stimulation (finger moving) onset. To cope with the delayed change of the physiological data, the sampling period of the off-state was the combination of two periods: 10 seconds before the onset of the on-state and 10 seconds starting from 20 seconds after the onset of off-state. The period of activation was sampled for 20 seconds starting from 5 seconds after the onset of the on-state. A regression line was plotted, based on the sampling data of the off-state, to eliminate the fluctuation of the baseline over time. Each data point (including on- and off states) was subtracted from the corresponding value on the regression line. The sampling period of on-state and off-state is graphed in Figure 28.

The folding average cycle in one block was the median value of 10 cycles of off- and on-states, represented as rest and activation, respectively in order to avoid sudden spikes from unknown factors. The mean of each folding average cycle was calculated and the difference between the off-state and on-state was used for Statistical analysis (two-way repeated measure ANOVA).

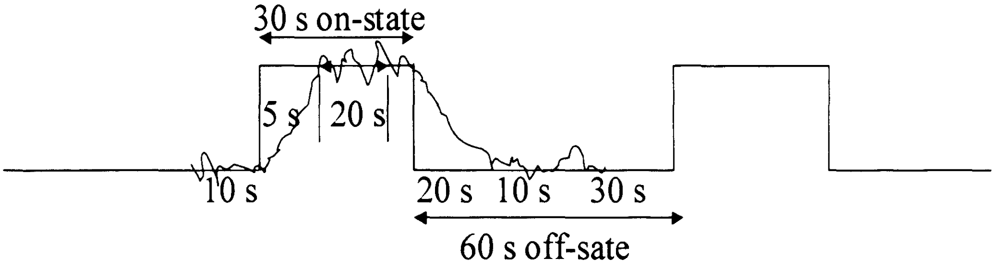

Figure 28: Sampling period of on-state and off-state for every cycle
The blue trace figuratively represents as the actual curve from NIRS 200. The red line marks the sampling period of the activation. The green lines marks the sampling periods of the off-state: the first part was 10 seconds before the on-state and the second part was 10 seconds starting from 20 seconds after the off-state.

Results

The results are plotted in Figures 3, 4 and 5. In the ΔO_2Hb data (Figure 29), there was a significant interaction between TMS and time block ($F_{(5,20)}=4.55$, $p<0.01$). Simple main effect analysis showed that, during the time block of A1 (i.e., the first 15 minutes after stimulation), the increase of ΔO_2Hb was higher following 1 Hz TMS (1.10 μM) than the sham stimulation (0.64 μM), $F_{(1,20)}=29.61$, $p<0.01$. Similarly during the period A2, the increased ΔO_2Hb level was still higher for the 1 Hz (0.99 μM) than the sham stimulation (0.72 μM), $F_{(1,20)}=10.58$, $p<0.01$. There were no differences between the TMS and the sham stimulation in other time blocks (i.e., A0, A3, A4 and A5).

For ΔHHb the data are plotted in Figure 30. There were no significant main effects or interactions for either indices. However, in the time block of A0 (before stimulation), the levels of ΔHHb change varied between the TMS and the sham stimulation. In order to reveal the stimulation effect on the ΔHHb change, the values of ΔHHb change in A1 to A5 were subtracted from those at A0. This showed that, in the time block of A1, ΔHHb level decreased more following TMS (-0.037 μM), compared with the increase following the sham stimulation (0.028 μM).

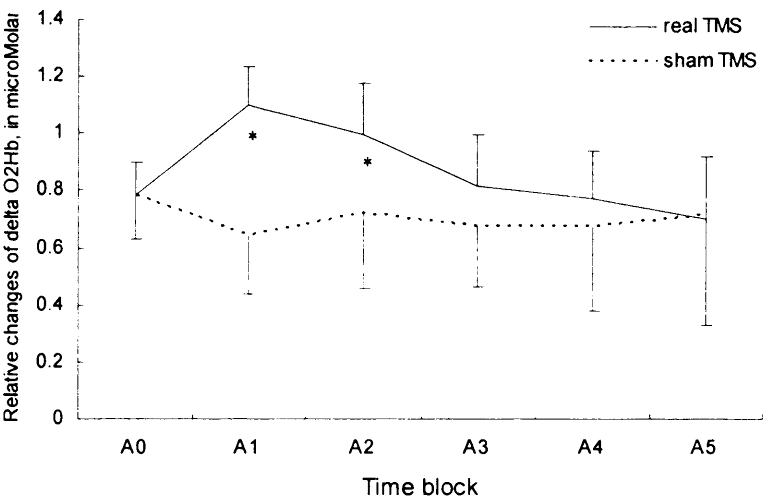

Figure 29: The concentration of ΔO_2Hb as a function of recording time block and TMS

The symbols, A0-A5, on the X axis indicate 15-minute periods of NIRS recording, A0 marks the recording before stimulation, and A1 to A5 the recording after stimulation, with an inter-block interval of 10 minutes. The asterisks each show that the level of ΔO_2Hb is significantly higher following real stimulation than sham stimulation, at the time block of A1 and A2. Bars show the standard error for each data point.

The sum of ΔO_2Hb and ΔHHb, plotted in Figure 31, can be integrated as the total change of blood volume (ΔBL) (Delpy et al., 1988). There was a significant interaction between TMS and time block ($F_{(5,20)}=3.49$, $p<0.05$). Simple main effect analysis showed that, during the time block of A1 (i.e., the first 15 minutes after stimulation), the increase of ΔBL was higher following 1 Hz TMS (0.87 μM) than the sham stimulation (0.58 μM), $F_{(1,20)}=10.94$, $p<0.01$. During the period of A2, the increased level of ΔBL was still higher for the 1 Hz (0.83 μM) than the sham stimulation (0.64 μM), $F_{(1,20)}=4.48$, $p<0.05$. There were no differences between the TMS and the sham stimulation in other time blocks (i.e., A0, A3, A4 and A5).

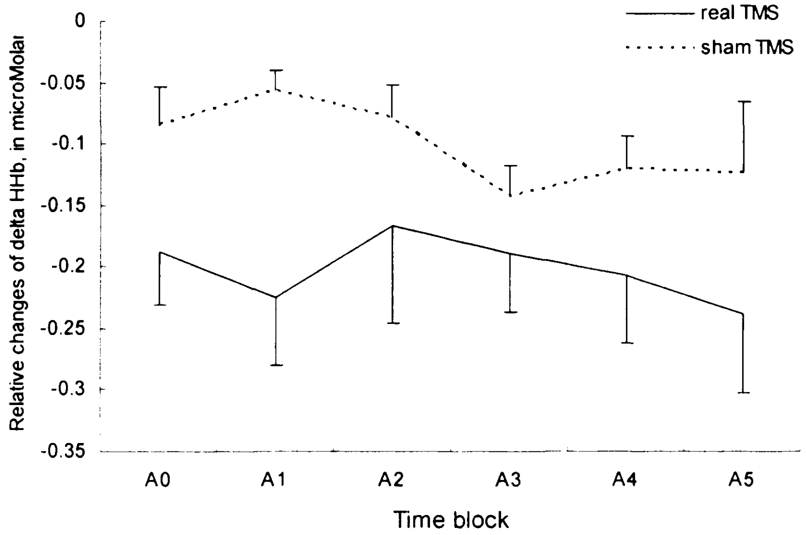

Figure 30: The concentration of ΔHHb as a function of recording time block and TMS

The symbols, A0-A5, on the X axis indicate 15-minute periods of NIRS recording, A0 marks the recording before stimulation, and A1 to A5 the recording after stimulation, with an inter-block interval of 10 minutes. Bars show the standard error for each data point.

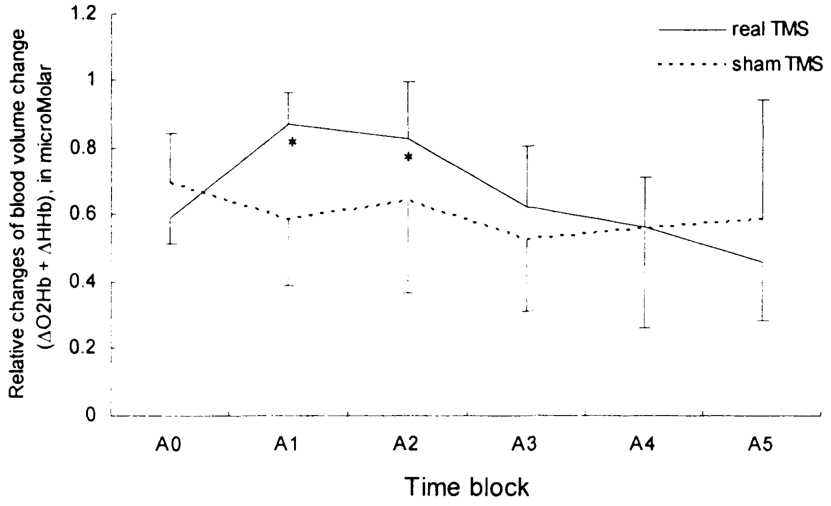

Figure 31: The relative change of blood volume as a function of time block and TMS

The sum of ΔHHb and ΔO_2Hb was considered as the relative change of the blood volume (ΔBL). The symbols, A0-A5, on the X axis indicate means 15-minute periods of NIRS recording, A0 marks the recording before stimulation, and A1 to A5 the recording after stimulation, with an inter-block interval of 10 minutes. Bars show the standard error for each data point.

Discussion

The results showed that, following 1 Hz TMS over the motor cortex, blood flow increased in the homologous, unstimulated motor cortex in the contralateral hemisphere, as evidenced by the raised level of ΔO_2Hb for 40 minutes after the stimulation. The change was not produced by the sham stimulation. Although the changes of ΔHHb level were not coupled with ΔO_2Hb and not statistically significant, the trend revealed that, compared with the levels before stimulation (A0), a decrease in ΔHHb was observed in the A1 period (i.e., 15 minutes after stimulation).

The value of ΔHHb was small and could be easily influenced by other factors. For example, the smaller decrease of ΔHHb may have been compensated by the over-supply in oxygen demand for the finger tapping, a fast and localized increase in blood flow in the respective cortical area (Fox, Raichle, Mintun, & Dence, 1988; Villringer & Dirnagl, 1995). In line with the prediction, the estimated blood volume change (= ΔO2Hb + ΔHHb) (Delpy et al., 1988) increased during the finger movement.

The results are in line with past research indicating increased activation in the contralateral non-stimulated motor cortex following TMS (Gilio, Rizzo, Siebner, & Rothwell, 2003; Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-Leone, 2004; Pal et al., 2005; Pascual-Leone et al., 1998; Plewnia, Lotze, & Gerloff, 2003; Schambra, Sawaki, & Cohen, 2003), but also extend past imaging studies using low frequency magnetic stimulation which recorded blood flow only at the stimulation site (Fox et al., 1997; Noguchi, Watanabe, & Sakai, 2003; Oliviero et al., 1999). The data also offer physiological evidence of a basis for behavioural effects up to 10 minutes after stimulation (e.g., Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-Leone, 2004). The longer lasting effect in my results may be due to the difference of TMS intensity. Unlike Kobayashi et al's experiment (2004) which used 90% of motor threshold (MT), the current experiment adopted 115% MT. The suprathreshold stimulation caused muscle twitches and one might argue that the twitches changed the ongoing afferent input or influence the non-stimulated motor cortex. However, past research using suprathreshold stimulation found decreased motor excitability without effects on motor performance, e.g. pinch force/acceleration, finger-tapping speed, or learning ability (Chen et al., 1997; Muellbacher, Ziemann, Boroojerdi, & Hallett, 2000; Muellbacher et al., 2002). Further, inhibition by 1 Hz TMS at the site of stimulation has been considered a cortical effect rather than due to efferent effects (Chen et al., 1997; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000b; Touge, Gerschlager, Brown, & Rothwell, 2001). Similarly, TMS effects on the non-stimulated motor cortex have been interpreted as cortical in orgin (Daskalakis, Christensen, Fitzgerald, Roshan, & Chen, 2002; Ferbert et al., 1992; Hanajima et al., 2001). For example, Plewnia *et al.*, (2003) used suprathreshold stimulation and activated the non-stimulated homologous motor cortex through the reduction of intra-cortical inhibition, but without changes in MEP at hand muscles.

In a PET study, Fox *et al.* (1997) found increased blood flow in the stimulated motor cortex and decreased blood flow on the contralateral site, which was different from the current results; however, Fox *et al.*, monitored blood flow change during the magnetic stimulation and it provides evidence of inhibitory interhemispheric pathways between motor cortices (Gerloff et al., 1998; Meyer, Roricht, Grafin von Einsiedel, Kruggel, & Weindl, 1995; Pal et al., 2005). This kind of pathway would also explain the crossed decrease in excitability of Wassermann *et al.*'s results (1998). Additionally, the inhibitory interhemispheric connections may compromise the crossed increase effects on the non-stimulated motor cortex (Chen et al., 1997; Muellbacher, Ziemann, Boroojerdi, & Hallett, 2000; Plewnia, Lotze, & Gerloff, 2003; Schambra, Sawaki, & Cohen, 2003) by claiming that 1 Hz TMS reduced the excitability in the stimulated motor cortex, which would then decrease the inhibitory influence on the homologous area (Pal et al., 2005). As a result, the raised activity occurred in the non-stimulated motor cortex.

In the current study, only one channel was placed over the non-stimulated motor cortex. More channels in further studies, e.g., on the stimulated motor cortex and adjacent areas in both hemispheres, to monitor the blood flow change over time may yield better measures of the relationship between the two hemispheres and of the effects of 1 Hz TMS on behaviour.

In summary, 1 Hz TMS inhibited the motor cortex and its inhibitory interhemisphreic pathway; as a result, the homologous motor cortex in the unstimulated hemisphere was enhanced in terms of activated blood flow by voluntary finger tapping, as evidenced by the increased O_2Hb and slightly decreased HHb. The effects lasted for 40 minutes after stimulation.

CHAPTER 7: CONCLUSIONS AND FURTHER RESEARCH DIRECTIONS

The experiments reported in this thesis were designed to explore segregated and integrated hemispheric processes in the visual and motor cortices. The main method was applying unilateral transcranial magnetic stimulation (TMS) over various cortical areas while subjects performed a range of tasks, from visual recognition of letters, visuomotor speed responses, to finger tapping.

Within the framework of interhemispheric integration, the main research question for the visual modality was the nature of foveal representation in the primary visual cortex. In particular, subjects' focus on a word presented in the centre of a screen to test the hypothesis that the cortical representation of the word in the striate visual cortex contains all the letters (bilateral projection theory) or only the contralateral segment of the word (split fovea theory). The visual tasks included letter/digit discrimination (Chapter 3), cued letter search (Chapter 4) and word recognition tasks (Chapter 4). In general, visual stimuli were presented in the screen centre in these experiments while TMS was applied over the right or left visual cortex. Using these strategies, the experiments aimed to answer the following questions.

Split fovea theory and word recognition

1. Is the cortical representation of words in the early visual cortex functionally split along the vertical meridian?
2. Is the process of word recognition (for centrally presented words) affected by lateralized attentional pre-cues?

In the visuomotor task (Chapter 5), subjects made a speeded response while detecting a stimulus appearing on either side of the screen. The crossed-uncrossed difference (CUD) paradigm was used to assess the information transferring from one hemisphere to the other. As in the visual task, unilateral TMS over the visual cortex was applied during the CUD paradigm, aiming to answer the following questions:

Crossed and uncrossed differences (CUD)

3. Is the stimulus represented in one or both visual cortices?
4. Is the information transferring to the other hemisphere via the corpus callosum (the crossed route) more vulnerable to TMS than the uncrossed route?

Interhemispheric integration was also studied using a pure motoric task (Chapter 6). Subjects moved their right thumb to tap on the other right fingers before and after low-frequency TMS over the ipsilateral motor cortex, aiming to answer the following research questions.

TMS effects on the un-stimulated motor cortex

5. What is the TMS effect on the homologous motor cortex of the other (un-stimualted) hemisphere, as measured by oxy-hemoglobin (O_2Hb), deoxy-hemoglobin (HHb) and blood flow change (BL)?
6. How long will the TMS effect last after stimulation?

The following sections discuss the results of each of these investigations and their interpretation and suggest potential future research directions.

Split fovea theory and word recognition

The split fovea theory asserts that the representation of the foveal area in the primary visual cortex is split along the vertical meridian. The right side of the vertical meridian is projected to the left visual cortex and vice versa. The split representation of the foveal area is similar to the contralateral projection of the left and right visual fields to the right and left visual cortices respectively. Therefore, the whole visual field can be grouped into two parts: the left and right sides of fixation. In accordance with the main predictions of the split fovea hypothesis, the results of Chapter 3 showed that rTMS to the left or right visual cortex during letter/digit classification impaired performance only to the contralateral (to stimulation) visual field targets. Crucially, the results have shown that the predicted contralateral rTMS effects were also true for foveal targets. The practical implication of this finding is that the functional visual fields start immediately to the left and right of fixation. However, it is yet to be determined whether the representation of the vertical meridian itself is split. Anatomical evidence indicated that some retinal ganglion cells near the fovea could project to both hemispheres (Leventhal, Ault, & Vitek, 1988). Nevertheless, even for stimuli presented only 0.25° away from fixation, there was no functioning overlap projection to both cerebral hemispheres (Harvey, 1978). Visual stimuli so close to fixation is practically the vertical midline area, therefore, even if there were bilateral cortical projections within 0.25° in the retina, it would have no significance.

In order to reach the recognition of a word, the left and right segments of a word need to be integrated across hemispheres to access orthographic, phonological and semantic information. Due to the lateralization of language to the left hemisphere (Cohen et al., 2000), the left segment (i.e., letters in the left visual field) need to be transferred through the splenium of the corpus callosum to the language structures uniquely within the left hemisphere (for a review see Bub, Arguin, & Lecours, 1993). In particular, the mid-portion of the left fusiform gyrus may correspond to the visual word form (VWF) system (Cohen et al., 2000; Warrington & Shallice, 1980).

The function of the VWF system has been reported for visual letter strings, in which the letter string can be identified independently of the visual fields of presentation, the colour or geometric features, such as case, size and font type (Cohen et al., 2002; Warrington & Shallice, 1980). In addition, pseudowords would activate the VWF area as well as real words, but not consonant strings (Cohen et al., 2002; Dehaene, Le Clec, Poline, Le Bihan, & Cohen, 2002; Rees, Russell, Frith, & Driver, 1999; Xu et al., 2001). The main difference between pseudo- and real words lies in the semantic meaning. However, both obey phonological and orthographic letter combination rules. In contrast, consonant strings, unlike real and pseudo-words, do not follow letter combination rules and can not translate into phonology. This suggests that VWF area would be a stage prior to semantic analysis.

Pammer *et al.*, (2004) used magnetoencephalography (MEG) to record brain activities during the first 500 ms of a lexical decision task and found that interhemisphere transfer happened in the first 200 ms post stimulus, predominately in the left posterior fusiform gyrus (BA 18/19, posterior to the VWF), and greater synchrony for words than pseudowords (anagrams of real words in that study) in the anterior part of the fusiform gyrus, en route to VWF area. The VWF area was then activated in the temporal range of 100-300 ms post stimulus, in line with the 250 ms post stimulus activation which was found to be correlated with behavioural lexicality effects (Cohen et al., 2000; Nobre, Allison, & McCarthy, 1994). However, areas in the frontal lobe (inferior frontal gyrus, BA44/6, IFG) responded before VWF area, especially for anagrams and might be associated with phonological processing. Based on these results, Pammer *et al.* (2004) suggested that word recognition may be represented in a parallel distributed network, and not by an orderly sequence of transformation from visual input to motor output.

I have shown that the two cerebral hemispheres differ in the way they process letter strings. In addition, spatial attention might have different effects on visual word recognition in the two hemispheres. Some researchers have argued that spatial attention must be focused on the letter string in order to support word recognition processes (McCann, Folk, & Johnston, 1992; Risko, Stolz, & Besner, 2005). The results of Chapter 4 showed that visual word recognition was not easily modulated by passive exogenous cues. It is possible that subjects were in a highly focused attentional state (i.e., paying attention to the word strings) and the abrupt onsets (i.e., precues) did not automatically capture attention (Yantis & Jonides, 1990). The word recognition occurred in the reciprocal loop between the lexicon and the letters. When the target string becomes a pseudoword, the reciprocal loop between the lexicon and the letters would be broken because pseudowords could not activate the lexicon to assist letter recognition. In line with our findings, recent research showed that a salient exogenous cue might not trigger spatial attention to intervene in lexical processing (Roberts & Besner, 2005), unless it lasted long enough (Auclair & Sieroff, 2002; Manwell, Roberts, & Besner, 2004; Nicholls & Wood, 1998).

Future research might consider how other factors interact with the split fovea representation, for example sub-cortical contributions (Sergent, 1987), gender differences (Shaywitz et al., 1995) and right-to-left reading habits, e.g., in Hebrew (Deutsch & Rayner, 1999). In addition, the implication of split fovea theory can be applied to normal reading behaviours (for a review, see Shillcock, Ellison, & Monaghan, 2000), or extend out to face and object recognition (Lavidor & Walsh, 2004).

Crossed and uncrossed differences (CUD)

Jeeves (1969) pointed out that crossed motor responses to lateralized visual input were abnormally long in acallosal subjects. The CUD paradigm aimed to study the transfer of sensory and motor (visuomotor) information across the corpus callosum (Marzi, Bisiacchi, & Nicoletti, 1991; Poffenberger, 1912). Chapter 5 used the CUD paradigm and applied rTMS over the left and right occipital cortex during a target detection task. The results showed symmetrical rTMS effects in both hemispehres. The magnetic stimulation increased the CUD only when the coil was positioned in the contralateral visual cortex, relative to the hemifield in which the visual target was presented.

The results emphasized two points. First, the rTMS effects were found in the the contra, but not ipsilateral hemifield. TMS effects did not spread to the un-stimulated hemisphere, in line with TMS studies on the visual cortex (Amassian et al., 1989; Epstein, Verson, & Zangaladze, 1996; Walsh & Cowey, 2000). Second, it is unlikely that the visual stimulus was processed in both hemispheres. Were the stimulus represented in both hemispheres, there would not be any TMS effects on the CUD because the un-stimulated hemisphere would have a copy of the stimulus and could complete the task without interference. However, the results of Chapter 5 did not support such a prediction.

Several imaging studies of the CUD paradigm have shown that activation in the right superiror parietal area (BA7) was highly correlated with the crossed conditions (Iacoboni & Zaidel, 2004; Marzi et al., 1999; Tettamanti et al., 2002; Weber et al., 2005). In addition, right parietal lesions typically impair interhemispheric transfer in the CUD paradigm (Marzi, Bongiovanni, Miniussi, & Smania, 2003). These data also suggest that some areas of the corpus callosum transferring the information to the right BA7, might be the site of interhemispheric transfer for the CUD paradigm. It has been suggested that the splenium of the corpus callosum contains the fibers interconnecting the posterior parietal area, e.g., BA7 (de Lacoste, Kirkpatrick, & Ross, 1985). Lesions in the posterior body of the corpus callosum markedly prolonged the CUD (Corballis, Corballis, & Fabri, 2004; Iacoboni, Ptito, Weekes, & Zaidel, 2000; Peru, Beltramello, Moro, Sattibaldi, & Berlucchi, 2003). However, other imaging studies (Marzi et al., 1999; Tettamanti et al., 2002), together with neuropsychological (Thut et al., 1999) as well as electrophysiological (Milner & Lines, 1982; Rugg, Lines, & Milner, 1984; Thut et al., 1999) data suggest that interhemispheric transfer occurred in the anterior part of the corpus callosum. There is evidence based on a patient with a corpus callosum lesion, where the splenium was spared, and the CUD effect for this patient was similar to those with complete corpus callosotomy (Tomaiuolo, Nocentini, Grammaldo, & Caltagirone, 2001).

There might be more than one specific site for the transfer of visuomotor information. Looking at the crossed condition only, when the visual stimulus is presented to the right hemifield and reached the left visual cortex, it needs to cross the hemispheres to the right superior parietal lobule (BA7), and then to the right motor cortex via an intrahemispheric route to command the left hand. The site of interhemispheric transfer would in this case be at the splenium of the corpus callosum (de Lacoste, Kirkpatrick, & Ross, 1985). In contrast, when the visual stimulus is in the left hemifield, the site of interhemispheric transfer would be different. The right BA7, receiving the ispilateral projection from the right visual cortex, needs to get information to the opposite motor cortex to command the right hand. In this case, the interhemispheric transfer would more likely be in the anterior corpus callosum, due to heavy interconnections between the premotor cortices (Wise, Boussaoud, Johnson, & Caminiti, 1997). Future research is required to explore the sites of this visuomotor information.

TMS effects on the un-stimulated motor cortex

TMS can not only influence stimulated areas, but also affect remote un-stimulated areas by triggering a series of trans-synaptic transmission (Ilmoniemi et al., 1997). Chapter 6 used low-frequency (1 Hz) stimulation on the right motor cortex to measure the activity of the left motor cortex with the indices of oxyhaemoglobin (O_2Hb) and deoxyhaemoglobin (HHb). The results found significant increases in O_2Hb and blood flow change (the sum of O_2Hb and HHb) that lasted 40 minutes after stimulation, and slightly decreased HHb in the first 15 minutes following stimulation.

The interhemispheric inhibitory connections between the motor cortices have been previously observed (Ferbert et al., 1992; Meyer, Roricht, Grafin von Einsiedel, Kruggel, & Weindl, 1995; Meyer, Roricht, & Woiciechowsky, 1998). Activation of one motor cortex with a single stimulation would induce an inhibition on the opposite un-stimulated motor cortex. However, 1 Hz repetitive stimulation would reduce the interhemispehric inhibition by activating the contralateral motor cortex (Gilio, Rizzo, Siebner, & Rothwell, 2003; Pal et al., 2005). Ipsilateral finger movements were improved for at least 10 minutes following 1 Hz TMS (Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-Leone, 2004). In line with these data, Chapter 6 revealed changes of O_2Hb and HHb in the homologous motor cortex contralateral to the stimulated hemisphere.

In addition to 1 Hz stimulation, another way to study the interhemispheric inhibition is to apply paired pulse TMS. The standard method of paired stimulation is to place a suprathreshold conditioning TMS pulse (CS) over the motor cortex, which then inhibits the size of motor evoked potential (MEP) produced by the test TMS (TS) of the opposite motor cortex. The interval between CS and TS was around 6-50 ms (Ferbert et al., 1992). Less than 6 ms caused facilitatory effects (Hanajima et al., 2001). Interhemispheric inhibition between motor cortices appeared to be mediated to a large extent by transcallosal excitatory connections that terminated inhibitory interneurons (Daskalakis, Christensen, Fitzgerald, Roshan, & Chen, 2002; Ferbert et al., 1992; Hanajima et al., 2001). The CS activated the stimulated motor cortex, and then enhanced the excitatory interconnection which triggered inhibitory interneurons on the opposite motor cortex. As a result, decreased activity occurred in the un-stimulated motor cortex. 1 Hz stimulation, in contrast, inhibited the stimulated motor cortex first, which induced the low activity of the inhibitory interneurons in the un-stimulated motor cortex. The effect, therefore, made hand movement easier to elicit and activate the un-stimulated motor cortex.

Further research of the effects 1 Hz stimulation and measuring resulting haemoglobin changes requires recording from more channels over areas adjacent to the motor cortex. This may reveal other areas also affected by stimulation and allow one to map the haemoglobin change among these areas over time post-TMS. In addition to fundamental research on TMS effects on physiology, 1 Hz stimulation is being investigated as a potential treatment of some motor disorders, like Parkinson's disease (Buhmann et al., 2004) and amyotrophic lateral sclerosis (ALS) (Di Lazzaro et al., 2004). Furthermore, the possibility that 1 Hz stimulation changed activity in the contralateral hemisphere has been applied to other topics, e.g., hemispatial neglect (Brighina et al., 2003), tactile extinction (Oliveri et al., 1999) and aphasia (Martin et al., 2004).

Conclusions

The thesis aimed to explore how the two hemispheres operate to execute different tasks, from encoding visual input to producing motor output. In the visual word recognition task (Chapter 3), centrally presented words tested the split fovea theory, which predicted that each primary visual cortex only processes the contralateral part of the stimulus. Methods included disrupting one side of the visual cortex with TMS in normal subjects, and examining a subject with a quadrantanopia. The results broadly supported the prediction of the split fovea theory.

To extend the results to whole word recognition processes, Chapter 4 requested subjects to report the letters of a word/pseudoword preceded by a precue in the left or right visual field. The results suggested that visual word recognition was not affected by attentional cues (i.e., automatic reading) unless the characters were scattered such that word shape was completely distorted. Letter search was then significantly modulated by spatial cues and the ipsilateral parafoveal cueing effects on foveal targets further supported the split fovea theory.

In the visuomotor task, the CUD paradigm was chosen to reveal the information flow from visual output to motor input. Information transferring via the corpus callosum originally takes more time than intracortical information transmission. The results of Chapter 5 showed that the TMS effect only occurred when the visual stimulus was in the contralateral hemifield. In addition, the crossed condition was more vulnerable to the TMS interference than the uncrossed condition, which increased reaction times for the crossed condition.

Previous research reported that the interhemispheric connection between the motor cortices has been reported as inhibitory. Chapter 6 aimed to understand information transfer between the left and right motor cortices. 1 Hz TMS was applied to the right motor cortex and the activity of the un-stimulated (left) motor cortex was monitored with NIRS while subjects were doing finger tapping task. The results showed that the significantly increased oxy-haemoglobin and slightly decreased deoxy-haemoglobin outlasted the 1 Hz stimulation by up to 40 minutes. The results not only supported the notion that 1 Hz stimulation activated the un-stimulated motor cortex through the interhemispheric communication, but also provided long-lasting physiological evidence of changes in the un-stimulated motor cortex.

In summary, the two hemispheres process visual information independently in the early stages of visual processing and subsequently cooperate via the corpus callosum to achieve full word recognition or to make a speeded response with the hand contralateral to the visual stimulus. The motor cortex can also be activated through the corpus callosum by magnetic stimulation to the opposite motor cortex. These experiments reported in this thesis therefore tested several hypotheses regarding the segregation and integration of visual and visuomotor processes, and have established a number of new findings relevant to further progress in this field.

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Appendix 1

Stimuli for Experiments 1 and 2 (Chapter 4)

6 - letter stimuli		8 - letter stimuli	
words	pseudowords	words	pseudowords
AERIAL	BULCKS	ABSTRACT	BLEIZZED
AUTUMN	DRYFTS	ALTITUDE	CLEIMBED
BORDER	FORLTS	ALUMINUM	COUGHQUE
CASTOR	FRIECE	ANGLICAN	CWAILLED
CHAPEL	FURSTE	APPLAUSE	FLEIGHCS
CHERRY	GHIRDS	BATHROOM	FROUNNED
DECEIT	GHRAIN	BROCHURE	GHOUDGED
DENIAL	GHRILL	CHAMPION	GHREABES
GOSPEL	GHULCH	CHARCOAL	GHREATTS
HUNGER	GNORTS	CHEERFUL	GHROATTS
INSECT	GOARLE	CLARINET	HEIGHLED
IODINE	GOUGHZ	CURRENCY	KLIGHMBS
KENNEL	HOURLS	DEFINITE	KWAILLED
LUXURY	JIGHBS	DOWNPOUR	KWEIGHKS
MAIDEN	KAICKS	DRAWBACK	NIGHNTHS
MARVEL	KNYQUE	EXTERNAL	PEIGHNTE
MISERY	KRUNCH	FACILITY	PHEASSED
MORTAL	LARSTE	FAREWELL	PHOUGHCK
MOTIVE	LEAKKS	FULLNESS	PHRENTCH
OUTFIT	PHIFES	GRADUATE	PREUGNED
PACKET	PHOPCE	HESITATE	PRIGHCED
PARDON	PLAGNS	HITHERTO	PSAUGHST
PIPING	PREUNS	ILLUSION	PSAUGHTS
POISON	PSINCS	LOVELORN	PSEEMBED
POLISH	QUERNE	MODERATE	QUAIKKED
PRIEST	RHEPED	MOMENTUM	QUEIGHCS
REPAIR	RHOAPS	NORTHERN	QUEIGHLD
SAVAGE	RHOOLS	NUMEROUS	RHUISSED
SHAKER	SAUTTS	OVERSHOT	SCKUILDE
SHOWER	SMYTHS	PARTICLE	SHAIPPED
SQUIRE	SNOURS	PATIENCE	SHAUGHDE
STARCH	SPOADE	PRECINCT	SHRIEQUE
STATUE	SQUOBB	PURCHASE	SKWEEQUE
TAILOR	STAUMS	REAFFIRM	SKWIEKES
THREAD	TEUTTS	SCULPTOR	STOUGHZE
THRILL	TRICTE	SENTENCE	THRORLES
TIMBER	WRAISE	SUBURBAN	WHAUGHDE
TRANCE	WREACK	UNSTEADY	WHOARKED
TYRANT	WRYQUE	UPSTAIRS	WREIGHND
VIOLET	YAUNDE	WITHERED	WROUGHST

Appendix 2

Added stimuli for Experiment 3 (Chapter 4)

6-letter stimuli		8-letter stimuli	
words	pseudowords	words	pseudowords
BOTHER	BAULDE	ABSOLUTE	CREINNED
BURIAL	BENTCH	ALLIANCE	FLEIGHDE
CHROME	BOARLS	BARBECUE	FREIGHDE
CRAVEN	CHORKE	BINOMIAL	GHLYNTSE
DEPUTY	CWERGN	CAUTIOUS	KNEIGHED
DESPOT	DAIMES	CHANDLER	KNOAZZED
ENIGMA	DAUNTE	CHARMING	NOUGHTCH
FRENZY	FIRGNS	CIVILIAN	PHALNQUE
LABOUR	GHORLD	COMPRISE	PHLORNTE
MARBLE	HAWNTE	CUSTOMER	RHAILLED
MARGIN	JIGNED	ELEGANCE	RHARPHED
MEADOW	PHLEKS	FAITHFUL	RHAUSSED
PIGEON	PHLYNT	FEMININE	RHOALLED
PLANET	PLITES	GRUESOME	SCKAILES
PLUNGE	QUAKTE	HONESTLY	SCKEUPED
RACKET	SHAQUE	MARGINAL	SCKOOLDE
SCREAM	SKRUDE	MINSTREL	SCKOULED
SHIELD	SLAITS	MOISTURE	SCKWIRMS
SHIVER	STORZE	MUSICIAN	SHRUNQUE
SHRIEK	SUNQUE	PAVEMENT	SKRIMPCE
SINGER	THYNZE	PERIODIC	SKRIMPTE
SKETCH	VORNTE	REGIONAL	SMERCHED
STRIDE	WHINZE	SHOWROOM	SPUNDGED
STRIPE	WOUGHK	SURVIVAL	SQUINTCE
TUMBLE	WREUMB	VAULTING	STAUGHLD
UNREST	WRUCHE	VIOLENCE	WHAULLED

Appendix 3

8-letter visual stimuli from Sieroff & Posner (1988)

noncompound words		pseudowords	
ABRUPTLY	ENDEAVOR	ACKORBOD	MINATANI
ABSOLUTE	FACILITY	ALPETAMY	MIRCHANG
ABSTRACT	GENEROUS	BENOKANT	MOCRATEC
ACADEMIC	HERITAGE	BIMCOGEN	MOSELENO
ACCIDENT	INCREASE	BLANIFER	MOTAMERO
ACCURACY	INDUSTRY	CALONIMP	NACKNEMI
ACTIVITY	KANGAROO	CHULSEDE	NETONBAK
ACTUALLY	MAINTAIN	CLADARNE	NOBREKUN
ALTHOUGH	MONUMENT	COROMEVE	NOBYDURA
AMERICAN	PARADISE	CREDORER	PASHDACT
ASSEMBLY	PECULIAR	CRONSEDI	PERSGORS
ATTORNEY	PERSUADE	DACIMOCE	PHOSKROW
BECOMING	PROGRESS	DACTINCE	PORYPURT
BEWILDER	PROPERTY	DARMLANK	PYBURTAL
BOUNDARY	REAPPEAR	DEVINARY	RALECNAD
BUSINESS	RECEIVER	DORULESH	ROBATHOM
CALENDAR	RECORDER	DOSYMOBE	ROLEVODA
CAPACITY	REGISTER	DOWLADON	RUESDAPE
CATEGORY	RESOLUTE	ENTAROST	RUSOTRES
CHARMING	SCHEDULE	FEROWIRK	RYGOKAIT
COMPLAIN	SHEPHERD	FETIMALK	RYNDUSTI
CONSIDER	SHOULDER	GERETRIS	SEDLENES
CONTRAST	SQUIRREL	GURLISER	SENABIRE
DAUGHTER	SURGICAL	HENILASE	SETASIRO
DECEMBER	SYMPHONY	HEWTARVE	SHOLESPE
DELIVERY	TELEGRAM	HOTHAGUL	SIBSUNES
DEMOCRAT	THOROUGH	HOWAMEST	SISTREDA
DISASTER	TOMORROW	HUROGHOT	SUROLEFY
DISPATCH	TROUSERS	KAWDBARC	SURONEGE
ELEPHANT	UNBROKEN	KOBIRADE	TABCRAST
		KOBROKAM	TAMERGOL
		LARCIGUS	TELUSOBA
		LARODIRA	TESUROLE
		LAWBLONS	TONTSARC
		LEASAFERS	UGADRETH
		LEBULBEL	VOREDANE
		LODERBOL	WARTHWID
		LYTACULA	WEVERHEN
		MAKMIDAL	WODELIRB
		MANALIND	YEDLERIV