ELSEVIER

Acta Psychologica 107 (2001) 275–291

acta psychologica

www.elsevier.com/locate/actpsy

The role of transcranial magnetic stimulation (TMS) in studies of vision, attention and cognition

Lauren Stewart [b], Amanda Ellison [a], Vincent Walsh [a,b,*], Alan Cowey [a]

[a] *Department of Experimental Psychology, University of Oxford, South Parks Rd, Oxford OX1 3UD, UK*
[b] *Institute of Cognitive Neuroscience, Alexandra House, 17 Queen Square, London WC1N 3AR, UK*

Received 2 June 2000; received in revised form 12 January 2001; accepted 12 January 2001

Abstract

Transcranial magnetic stimulation (TMS) can be conceptualized as a virtual lesion technique, capable of disrupting organized cortical activity, transiently and reversibly. The technique combines good spatial and temporal resolution and, moreover, because it represents an interference technique, can be said to have excellent *functional* resolution. The following is a review and discussion of the contribution which TMS has made to the study of vision, attention, development and plasticity and speech and language.

PsycINFO classification: 2323; 2346; 2520

Keywords: Magnetic stimulation; Virtual lesions; Phosphenes; Vision; Plasticity; Speech arrest

1. Introduction

Neuropsychology attempts to draw inferences about normal brain function from the behaviour of patients with brain lesions. The contribution of this approach to what we know about brain function today cannot be overstated; even so, the approach is not without its limitations – brain lesions are often quite diffuse and may

* Corresponding author. Tel.: +44-1865-271326; fax: +44-1865-310447.
E-mail address: vin@psy.ox.ac.uk (V. Walsh).

0001-6918/01/$ - see front matter
PII: S0001-6918(01)00035-X

result in functional reorganization within the brain. Furthermore, the lesions are enduring; we are rarely afforded the opportunity to see how a patient would perform a given task in the absence of their lesion. Transcranial magnetic stimulation (TMS) offers a "virtual lesion" method of investigating the effects of cortical dysfunction that is free of the limitations mentioned above; it can disrupt cognitive functions with a spatial resolution of approximately 1 cm on the scalp and its effects are transient, lasting a few tens of milliseconds, so any effects observed are not masked by reorganization which occurs over much longer time scales. Moreover, the temporal resolution allows one to ask questions about the timing of cortical processing. The term "neural noise" sometimes leads to the question "how can noise stimulate the brain and lead to positive outcomes such as the perception of phosphenes (see below), muscle movements or even paradoxical improvements in performance?" The answer is that *all* these effects are the outcome of the introduction of neural noise. The neuronal firing induced by TMS is likely to be random with respect to the task one is trying to carry out. For example, TMS may be used to demonstrate the reorganization of the motor cortex, but it is highly unlikely that stimulating the motor cortex while subjects are trying to, say, lift an object, will result in a TMS-induced pattern of activity that corresponds with that required for lifting. The TMS is, of course, far more likely to induce activity that conflicts with the organized pattern that is trying to lift the object. The case is similar for vision, indeed it has been argued quite convincingly that the mechanism for producing phosphenes and for disrupting visual processes by stimulation of occipital cortex are identical (Kammer, 1999). Thus, although the effects of TMS may not always disrupt behaviour, since one cannot predetermine the precise pattern of neuronal firing induced, nor predict its fine relationship to ongoing activity, it is consistent to understand it as noise regardless of outcome.

TMS involves applying a brief magnetic pulse, or a train of pulses, to the scalp to induce a local electrical field which, in turn, alters the local electrical field in the underlying surface of the brain. The modern age of magnetic stimulation began as recently as 1985 when Barker and colleagues (Barker, Jalinous, & Freeston, 1985) first stimulated the human motor cortex with a 2 T pulse. The sequence of events in delivery of a single pulse begins with an electrical current of up to 8 kA, generated by a capacitor and discharged into a circular, or figure-of-eight shaped, coil which, in turn, produces a magnetic pulse of up to 2 T. The pulse has a rise time of approximately 0.2 ms and a duration of 1 ms and, due to its intensity and brevity, changes at a rapid rate. The changing magnetic field generates an electric field resulting in neural activity. The net change in charge density in the cortex is zero. In addition to single-pulse stimulation, some stimulators can deliver trains of pulses up to a rate of 50 Hz. Rapid rate stimulation carries a small risk of inducing seizures so stimulation parameters, for example, intensity and rate of repetition must be kept within the recommended safety limits (Wassermann, 1998).

The specificity of TMS is remarkable in both space and time. Fig. 1 shows the resolution of TMS and some of the other techniques used in studying brain function in human subjects and it is clear that there is often a trade-off between space and time. Event-related potentials (ERPs) have good temporal but poor spatial resolu-

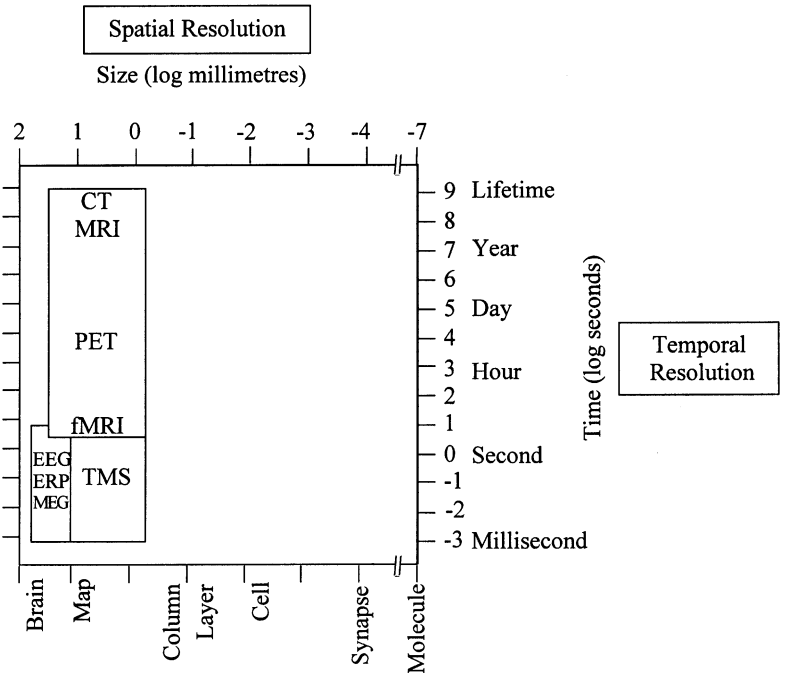

Fig. 1. TMS has spatial and temporal resolution that allows it to occupy an interaction area time and space not accessible to other techniques. Redrawn after Walsh (1998).

tion whereas PET and fMRI have the reverse – good resolution in the spatial but less in the temporal domain. TMS, like magneto-encephalography (MEG), combines intermediate spatial and temporal resolution.

Good spatial and temporal resolution are impressive, but the question to be asked of any technique is, "what new *functional* resolution does it offer?" Can TMS be used to explore functions that could not be studied by other means? Can it offer a more elegant, quicker or less invasive solution to some of the problems that can be addressed through other techniques?

Techniques such as PET, fMRI, ERPs and MEG, can provide a correlation of neural activity with a dependent variable, for example, recorded muscle activity at a distal site, subjective self-report of the subject, behavioural measures such as reaction time or errors on a task. However, since TMS acts as a virtual lesion technique, rather than asking whether activity in a given area is correlated with some dependent variable TMS asks whether or not it is *necessary* for a given function.

2. TMS studies of visual cortex

Amassian et al. (1989) were the first to demonstrate the power of TMS in psychological studies of vision. They delivered single-pulse TMS over the occipital

cortex of subjects while they performed a letter-identification task. Performance was impaired when TMS was applied between 60 and 140 ms after the onset of the presentation of the stimuli and when it was applied between 80 and 100 ms after stimulus onset subjects were incapable of detecting any of the letters. This result was soon replicated and correlated with VEP latencies in clinically normal and abnormal subject groups. Amassian and colleagues also took their experiment a significant stage further by showing that TMS could unmask a visual mask and thus improve performance. In the latter experiment, subjects were presented with the same letter-identification arrays followed, 100 ms later, by a high-contrast visual mask and single-pulse TMS was applied at various intervals after the presentation of the mask. The effect of TMS was to prevent the presentation of the second stimulus from impeding identification of the first stimulus, as was the case without TMS. Fig. 2 shows the reciprocal effects of TMS in the two experiments. In these two experiments lies the foundation for all subsequent studies of visual cognition using TMS: one can either impair visual performance by interfering with the transmission of relevant visual signals or one can improve performance by interfering with the transmission of irrelevant or competing stimuli.

In a recent study, Cowey and Walsh (2000, in press) have shown that TMS can be used to probe the neural substrates of awareness. Phosphenes were induced by TMS to examine the integrity of visual cortex in a peripherally blind subject and to compare the results with those obtained by stimulating the same regions in normally sighted individuals and in a hemianopic subject who possesses blindsight in the impaired field. Phosphenes are sensations of light induced by stimulation of the eye or brain other than by light entering the eye – a poke in the eye or a blow to the head can cause one to "see stars", these stars are phosphenes. The TMS-induced phosphenes obeyed Emmert's law in blindsighted and sighted subjects irrespective of whether the stimulation was applied over the midline of the occipital cortex to produce stationary phosphenes or over visual area V5 to produce moving phosphenes. However, extensive and intensive stimulation of the damaged left hemisphere in the blindsight subject did not yield phosphenes, even when applied to V5 on that side. The phosphenes reported by the peripherally blind subject were as easily elicited and as reproducible as those seen by other subjects but their spatial distribution suggests that retinotopic mapping in this subject's V1 is degraded. Despite the coarser spatial mapping the blind subject showed otherwise normal phosphenes including the perception of movement when V5 was stimulated. The blind subject had lost his sight approximately 8 years prior to the experiment in a road traffic accident in which both optic nerves had been severed. These findings are strongly supportive of the view that visual awareness requires the presence of an intact V1 (see also Lamme, 2001, for further discussion).

The location of extrastriate area V5, just posterior to the meeting point of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus (Watson et al., 1993), makes it particularly accessible to stimulation with TMS and, to date, there have been five studies which have stimulated V5 with the aim of investigating the involvement of this area in visual motion processing. The results of several of these studies have added to already existing evidence from imaging studies

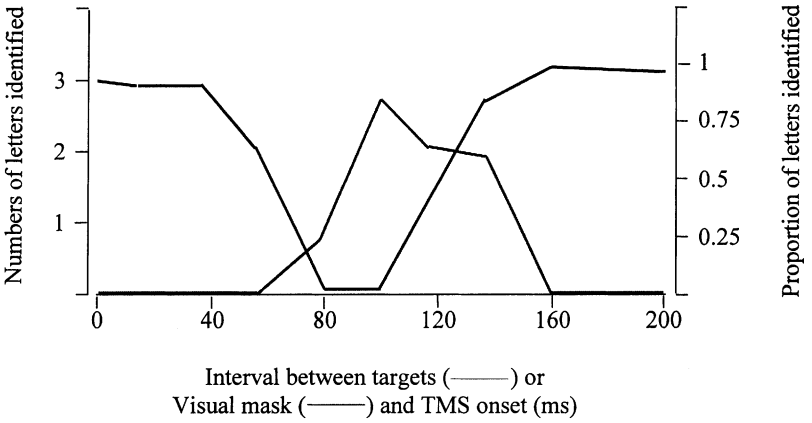

Fig. 2. Amassian's experiments. The U-shaped curve (left ordinate) represents the number of letters correctly identified in trigrams when single-pulse TMS was applied at the time after stimulus onset shown on the absicca. When TMS was applied at 0–40 ms after the onset of the letters there was virtually no effect of TMS on recognition. But TMS applied between 60 and 140 ms after stimulus onset impaired performance and reduced recognition to zero between 80 and 100 ms. The inverted U-shaped curve (right ordinate) shows the proportion of letters correctly identified in the presence of a visual mask when TMS was applied after the mask. This function resembles the inverse of the recognition paradigm. Redrawn after Walsh and Cowey (1998).

(Reppas, Niyogi, Dale, Sereno, & Tootell, 1997; Smith, Greenlee, Singh, Kraemer, & Hennig, 1998; Tootell et al., 1995; Watson et al., 1993; Zeki et al., 1991) and single-unit recording in monkeys (Britten, Newsome, Shadlen, Celebrini, & Movshon, 1996; Celebrini & Newsome, 1994; Dubner & Zeki, 1971; Mikami, Newsome, & Wurtz, 1986) in reinforcing the specialized role this area has in the processing of visual motion information (see Culham, He, Dukelow, & Verstraten, 2001, for further discussion). Beckers and Homberg (1992), Hotson, Braun, and Boman (1994) and Beckers and Zeki (1995) all used forced-choice motion direction discrimination tasks and found that single-pulse TMS applied over the scalp region known, from imaging studies, to overlie cortical V5, could disrupt or, in some cases (Beckers & Zeki, 1995), abolish subjects' ability to perform this task accurately. The effect was found to be task-specific; a colour discrimination task (Beckers & Homberg, 1992) and an orientation perception task (Beckers & Zeki, 1995) were both unaffected and site-specific. The finding that TMS over V5 can abolish motion direction discrimination builds on results from imaging studies but whilst these have shown a correlation between motion direction perception and activity in V5, the TMS studies demonstrate the necessity of this area for accurate performance on this task.

A recent study by Stewart, Battelli, Walsh, and Cowey (1999) demonstrates that TMS delivered over V5 can elicit moving phosphenes (see Fig. 3 for examples). Stimulation was delivered over points within a 3 cm × 3 cm grid, centered on a point which structural MRI scans have suggested overlies V5. Stimulation intensity was between 30–100% of maximum output and both single- and repetitive-pulse TMS

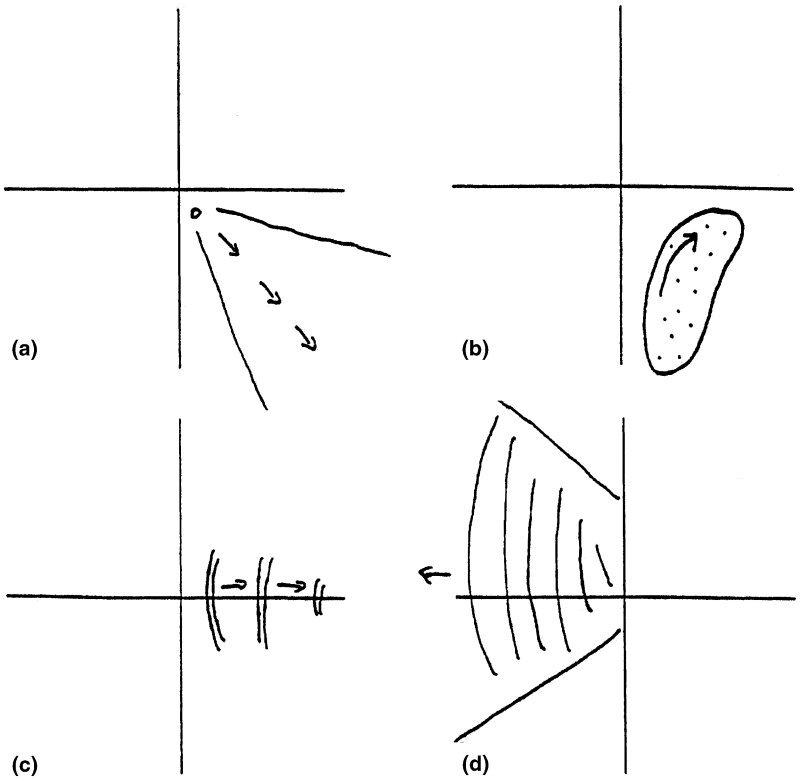

Fig. 3. Moving phosphenes. Four examples of moving phosphenes drawn by subjects following stimulation over V5. (a) The subject described this as "a movement of a single point in a static field": TMS was applied 2 cm dorsal to inion and 6 cm left of the midline at 1.4 T, 5 Hz for 500 ms. (b) Described as "similar to a random dot array; black dots on a white background; appears to move upwards and rightwards". Stimulation site: left hemisphere, 2 cm dorsal and 6 cm lateral to inion; stimulation rate: 5 Hz at 1.8 T for 0.5 s. (c) Described as "drifting right, not continuous". Stimulation site: right hemisphere 2 cm dorsal and 5 cm lateral to inion; stimulation rate 10 Hz at 1.4 T for 1 s. (d) Described as "a block of visual noise that jumps to the left". Stimulation site: right hemisphere, 2 cm dorsal and 4 cm lateral to inion; stimulation rate: single pulse at 1.4 T. Scale bar represents approximately one degree of visual angle. Redrawn after Stewart et al. (1999).

(rTMS) were used. Subjects were asked to indicate when they saw a phosphene, to describe it and to draw it on polar graph paper. Seven out of the nine subjects tested reported seeing phosphenes which moved. Some subjects described a vague impression of movement, for example, "as if the edges of a vertical line seemed to bow inwards" while others described vivid, directional movement, for example, "drifting rightwards, not continuous". The finding that TMS over V5 can elicit moving phosphenes has methodological significance for TMS studies of the kind described above. In TMS studies of the visual system, the absence of any easily measurable output has meant that the coil position on the scalp must be calculated from anatomical MRI scans. However, anatomy and function do not always overlap precisely

and the location of V5 may vary between individuals by up to 2 cm in its anterior–posterior coordinates (Watson et al., 1993). The induction of moving phosphenes in contrast, provides a quick and reliable functional demonstration of V5 location.

The results of both the direction discrimination experiments and the moving phosphene experiment also reveal something about the organization of area V5. In Beckers and Homberg's study, TMS over V5 disrupted direction discrimination only when the moving stimulus was in the hemifield contralateral to the site of stimulation, suggesting that in man, as in monkey, it is the contralateral hemifield that is mapped in each V5. In the moving phosphene experiment, the pattern of phosphenes elicited corresponded to a strictly retinotopically organized system, i.e. stimulation of left V5 produced moving phosphenes in the right visual hemifield and vice versa and moving the coil up and down caused the location of the phosphenes to move down and up, respectively. Results from both these studies also suggest a relative lateralization of motion processing to the left hemisphere. Beckers and Homberg found a much more marked reduction in performance when TMS was applied over left compared to right V5 and moving phosphenes elicited by TMS over V5 were more easily produced with left V5 stimulation than right. A left lateralization of motion processing is in line with PET scanning results (Zeki et al., 1991) but neuropsychological evidence would not seem to support such a lateralization. A possible reason for the disparity between TMS and neuropsychological findings may be the nature of the disruption produced in each instance. The damage sustained by neuropsychological patients is obviously enduring and patients learn to perform tasks using alternative strategies. TMS, in contrast, produces a transient disruption which is too short for any such changes to occur (see Walsh & Cowey, 1998, 2000, and Walsh & Rushworth, 1999, for details).

The characteristic properties of V5 neurons have also been highlighted using TMS. Beckers and Homberg (1992) report that TMS-induced deficits in direction discrimination were most marked for movement away from the fovea than towards it. Similarly, the moving phosphenes elicited by Stewart et al. (1999) were most often reported to be moving away from the fovea. These results are consistent with findings by Albright (1989) that V5 possesses more neurons tuned for motion away from the fovea than towards it; hence stimulation over V5 will affect a greater proportion of centrifugally tuned compared to centripetally tuned neurons.

In addition to revealing some of the properties of V5, TMS has been used to affect V5 function. Stewart et al. (1999) designed an analogue of a motor learning experiment in which TMS had been found to affect the degree of learning in a frequency-specific manner such that low rates of stimulation impeded learning whilst high rates enhanced it (Pascual-Leone, Tarazona, & Keenan, 1999). The study was designed to assess whether TMS could also affect learning in a non-motor modality such as vision. In addition, if TMS applied over V5 could affect the degree to which learning occurred, V5, itself, could be considered to be a neural substrate of learning. TMS was applied over V5 while subjects learned a visual motion task that required detection of a target defined by the conjunction of shape and direction. Three subject groups participated; one group received no TMS, the other two received TMS at 3 Hz and 10 Hz, respectively, during learning which occurred over 4 days (1.5 h/day). While all subjects

learned the task significantly, the 3-Hz stimulation group learned significantly less than either the no TMS group or the 10-Hz stimulation group (see Fig. 4). This frequency-specific effect of TMS on learning suggests that TMS effects on learning may generalize across modalities and that visual motion learning may arise from activity within V5 rather than from some "higher centre" outside sensory cortex.

3. Studies of attention

The role of the parietal cortex in visual attention is a question of central concern. Several imaging and neuropsychological studies point to a particular role for this

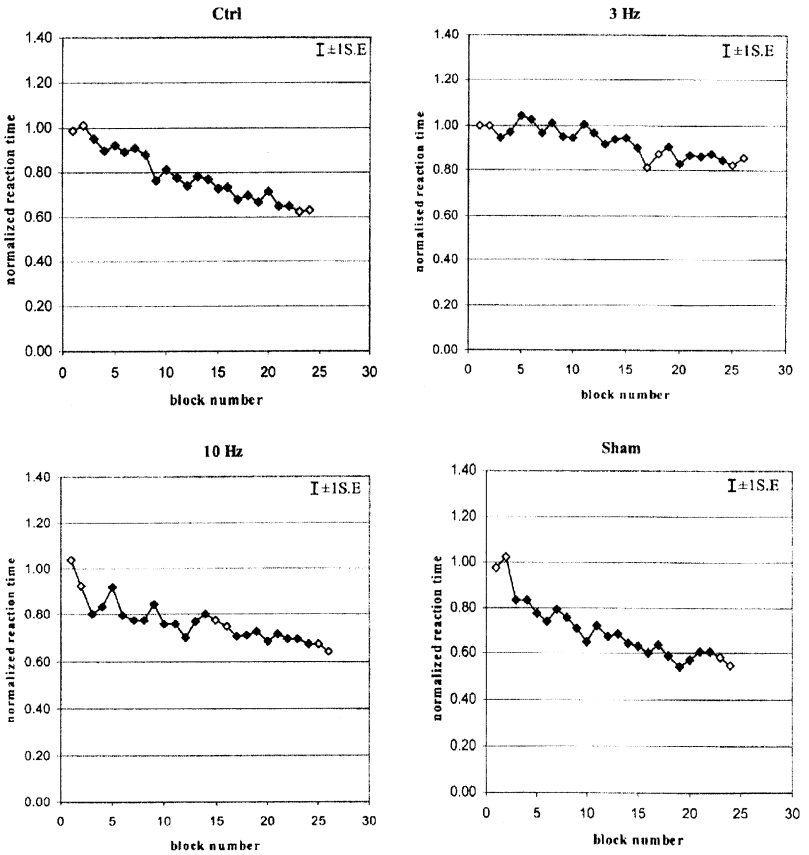

Fig. 4. The effects of different rates of TMS on perceptual learning of visual motion. Subjects practiced for over 100 trials on a motion detection task. The control group did not receive TMS, the sham group received TMS with the coil directed away from the cortex. The two TMS groups received whether 3- or 10-Hz TMS on each trial. At 3 Hz the reaction times improved less than in any of the other groups. It is important to note that the 3-Hz group received fewer TMS pulses than the 10-Hz group (from Stewart et al., 1999).

area in orienting attention while others emphasize its role in visual binding. Frequently the same tasks are used to address the two different issues. Ashbridge, Walsh, and Cowey (1997) applied TMS over the parietal visual cortex of subjects while they were performing "pop-out" or conjunction visual search tasks in arrays containing eight distractors. Magnetic stimulation had no detrimental effect on the performance of pop-out search but did significantly increase reaction times on conjunction search when stimulation was applied over the right parietal cortex 100 ms after the onset of the visual display. Stimulation had no effect on the number of errors made. The results suggest that a sub-region of the right parietal lobe is important for conjunction search but not for pre-attentive pop-out. The timing of the effect indicates that transcranial stimulation disrupts the mechanisms underlying the focal attention necessary for feature binding in conjunction search. The results also highlight the efficacy of TMS as a complement to other spatial and temporal imaging techniques. The role of the parietal cortex, like that of any other area, may change with experience and Walsh, Ashbridge, and Cowey (1998) extended the paradigm used by Ashbridge et al. (1997) to study the effects of learning. Performance on a wide range of perceptual tasks improves with practice. Most accounts of perceptual learning are concerned with changes in neuronal sensitivity or changes in the way a stimulus is represented. Another possibility is that different areas of the brain are involved in performing a task during, as opposed to after, learning it. Walsh et al. observed that single-pulse TMS to the right parietal cortex impaired visual conjunction search when the stimuli are novel (Fig. 5(a)) and require a serial search strategy, but not once the particular search task had been learned (Fig. 5(b)). Hence, the right parietal cortex has a role in novel but not learnt visual conjunction search. The effect of TMS returns when a different, novel, serial search task is presented (Fig. 5(c)).

Following damage to the right parietal cortex, patients often exhibit neglect of the left side of space or the left side of objects. One possible explanation for this is that, because the two hemispheres operate in a mutually inhibitory manner, damage to the right cortical hemisphere not only leads to a reduced capacity to orient to information in the left-world, but also to disinhibition of the left parietal cortex and thus an exaggerated tendency to attend to the right-world. By applying single-pulse TMS to the parietal cortex 50 ms before subjects were required to detect a small electrical stimulus delivered to the fingers, Seyal, Ro, and Rafal (1995) were able to demonstrate that sensitivity to tactile stimuli was *increased* in the hand ipsilateral to stimulation. Using rTMS, Pascual-Leone et al. (1994) modelled visual extinction, another feature of parietal cortex damage. Subjects were presented with either one or two asterisks to detect on a computer monitor and received trains of pulses contralateral to the stimulated hemisphere only when targets were presented in both hemifields simultaneously.

Another clinical phenomenon which TMS may be able to model is visual neglect. Neglect is widely studied in neuropsychological patients but there are many differences between patients and the tendency is for the phenomenon to be transient. In a study by Fierro et al. (2000), subjects were briefly presented (50 ms) with horizontal lines which had been divided by a vertical line and required to judge whether the left,

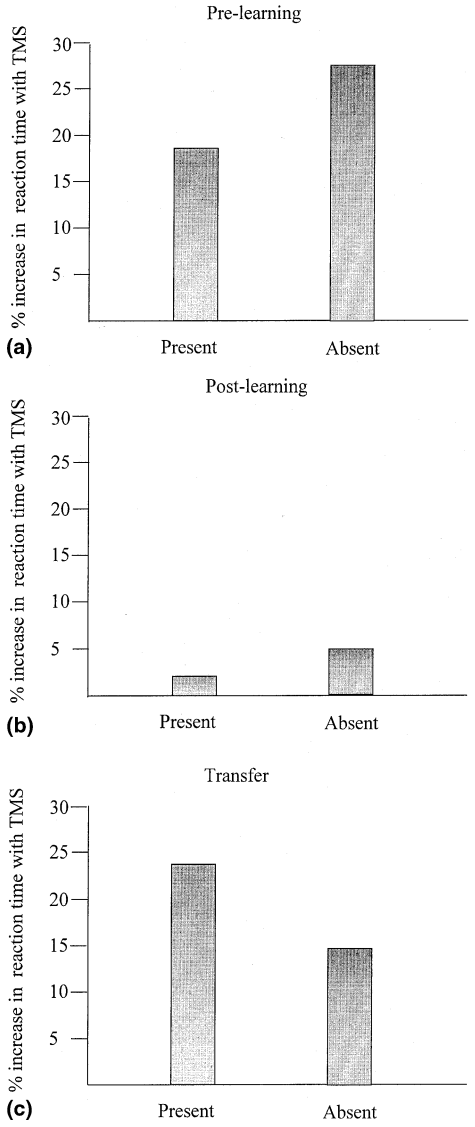

Fig. 5. TMS can be used to assess the role of cortical areas at different stages of learning and expertise. Walsh et al. (1998) applied TMS over posterior parietal cortex during the performance of visual search tasks. (a) When subjects are presented with a previously unseen visual search task there are large costs in reaction times for both target present and target absent trials. (b) After subjects have trained to become efficient on the search task the deficits are no longer induced by TMS. (c) When the same subjects are again presented with a new visual search task, the effects of TMS are reinstated.

right or neither side was longer. In control trials there was a pseudoneglect tendency, consistent with right hemisphere bias to report the left as longer. On TMS trials, pulses were delivered at 115% of motor threshold at 25 Hz for 400 ms over left or

right parietal cortex at the time of stimulus onset. Right parietal stimulation corrected the pseudoneglect but left parietal and sham TMS (in which the coil is discharged near to the subject's head or at an angle which directs the inducing field away from the head) did not change the subjects' behaviour. Being able to reproduce neglect is an important step in modeling the phenomenon and one wonders whether a reaction time approach might increase the sensitivity of this particular assay. At the other end of the clinical scale, Oliveri et al. (1999) have reversed rather than reproduced a neuropsychological phenomenon. They studied patients with right or left hemisphere brain lesions and gave TMS to frontal or parietal cortex of the intact hemisphere 40 ms after the subjects were presented with unilateral or bilateral tactile stimuli to be detected. Those patients with right hemisphere lesions showed a reduction in extinction when TMS was given over the left frontal region, thus supporting the interpretation of Kinsbourne (1977) and Seyal et al. (1995).

4. Studies of development and plasticity

A good example of the use of TMS in correlating stimulation effects with behaviour comes from a study in which juvenile monkeys received TMS over the motor cortex and electrical activity was recorded distally from one finger (Flament, Hall, & Lemon, 1992). Over time, between birth and 4.5 months of age, the strength of the TMS pulse required to elicit activity at the finger declined by approximately 60% and then remained stable. The onset of this stability coincided with the onset of fine finger movements in the monkey. In a similar experiment with human subjects between the ages of 8 months and 55 years, the threshold to elicit EMG activity initially decreased by 4 years of age (when fine independent finger movements develop) and continued to decrease until adolescence – up to which time myelination of the human pyramidal tract continues. This result stands in contrast to the results of TMS to the cervical spine; here thresholds matured within the first 2 years of life, indicating the completion of development. The experiments point to two further advantages of TMS – it can be used with very young human subjects, and comparable experiments can be carried out in humans and non-human primates.

TMS has also been successful in mapping long- and short-term reorganization of sensory maps in people who lack sensory input in a particular domain. Pascual-Leone and Torres (1993) applied single-pulse TMS over the scalp of Braille readers and sighted readers and measured the ability to detect small electrical stimuli applied to the reading or non-reading fingers. When TMS was applied over the cortical regions representing the Braille reading fingers, TMS at many more sites disrupted tactile perception – a clear demonstration that use of the Braille reading finger had led to an expanded representation in the sensorimotor cortex.

Cortical reorganization can also occur as a consequence of losing as well as using a body part. Cohen, Bandinelli, Findley, and Hallett (1991) used TMS to study cortical plasticity following amputation of an upper limb. The motor reorganization that occurs after amputation includes an increase in the motor excitability of muscles close to the stump. Consistent with this, Cohen and colleagues found that stimula-

tion over the motor area contralateral to the stump elicited activity in nearby muscles more easily (at lower stimulation intensities and at more sites on the scalp) than stimulation over the motor cortex ipsilateral to the stump elicited activity in the corresponding muscles of the intact arm.

5. Studies of speech and language functions

Speech arrest is perhaps the most powerful example of TMS in its virtual lesion mode and several groups have achieved this by stimulating over left frontal areas (rTMS can cause a disruption or cessation of normal speech referred to as speech arrest). However, with the exception of Epstein et al. (1999), who used an iron-cored coil, the stimulation parameters required are much greater than those commonly used in TMS experiments, for example, rates of between 8–50 Hz, durations between 1 and 10 s and intensities between 80% and 100% of maximum stimulator output. Even with these parameters, speech arrest is not always achieved, for example, Michelucci et al. (1994) and Jennum, Friberg, and Dam (1994) found it in only 7/14 and 14/21 subjects, respectively, giving support to the notion that language processing is extremely robust in the human brain. Of the groups who have successfully achieved speech arrest with TMS, there is debate regarding the locus of the effect. Epstein et al. (1999), for example, claim that, despite the lateralization of the speech arrest effect to the left hemisphere, the sites at which the effect can be achieved overlap with sites at which TMS can produce contraction of the orbicularis oris muscle of the face and hence attribute the speech arrest to an effect on the muscles innervating the jaw and mouth. Pascual-Leone et al. (1993), on the other hand, believe the effect to be mediated by interference with language processing, per se. It would not be surprising if speech arrest could be achieved by an effect on either the motor or the language components of speech. Indeed, using direct electrical stimulation, Penfield and Rasmussen (1949) noted that speech arrest could be achieved by stimulation of rolandic cortex of the right and left hemisphere, or by stimulation at a more anterior site on the left hemisphere alone. Presumably, TMS should be able to reveal similar effects, given the right stimulation parameters and coil type such that current spread did not preclude dissociation of "motor" effects from "language" ones (see Munhall, 2001 for a related discussion). Such a demonstration would be important because it would mean that subsequent studies could use sub-threshold stimulation in reaction-time-based paradigms to further probe the role of such areas in other types of linguistic tasks that do not require verbal output (see Stewart, Walsh, Frith, & Rothwell, 2001).

TMS has also been used to look at aspects of linguistic processing lying upstream of speech output. Single- and rTMS have been used with picture naming tasks (see Humphreys & Price, 2001, for a discussion of different methods applied to this area). Topper, Mottaghy, Brugmann, Noth, and Huber (1998), reported that single-pulse TMS applied between 500–1000 ms before stimulus presentation at intensities of 35–55% maximum output significantly reduced picture-naming latency when delivered over Wernicke's area. Wassermann et al. (1999) gave trains of

pulses at 10 Hz at an intensity corresponding to subjects' motor threshold. They found that stimulation over frontal and temporal sites of the left hemisphere produced increased error rates which were accompanied by reduced naming latencies with stimulation over temporal and frontal sites of the left hemisphere and the frontal site of the right hemisphere. Mottaghy et al. (1999) using trains of 20 Hz at intensities of 55% maximum stimulator output, found that picture-naming latency was significantly facilitated when TMS was given over Wernicke's area, but not over its right hemisphere homologue or Broca's area. Finally, Flitman et al. (1998) used a paradigm in which the measured response involved a manual rather than a verbal response to eliminate the possibility that any TMS effect was due to an effect on speech output. Subjects were required to indicate, by a keypress, whether a picture/word combination was congruent or not. Stimulation over two left hemispheric sites, one at which speech arrest had been produced and a temporoparietal site produced an increase in reaction time. Such disparate findings make interpretation difficult. While it is clear that language processing can be affected by TMS, it is not at all clear which sites are most vulnerable to disruption nor under what circumstances facilitation, rather than disruption, is achieved. This highlights one of the major problems with TMS studies at this point in time – different groups often use similar tasks but use quite different stimulation parameters, coil types and target areas.

6. A note on safety

The use of TMS is rightly subject to approval by local ethical committees and there are some precautions which must be taken in all studies using the technique. The safety of single pulse stimulation is well established but further precautions should be taken when using rTMS. rTMS can cause seizures.

The magnetic field produced by stimulating coils can cause a loud noise and temporary elevations in auditory thresholds have been reported. The use of ear plugs is recommended in all experiments. Some subjects may experience headaches or nausea or may simply find the face twitches and other peripheral effects of TMS too uncomfortable. Such subjects obviously should be released from any obligation to continue the experiments. More serious are the concerns that TMS may induce an epileptic seizure. There are a number of cases of epileptic fits induced by rTMS and caution is necessary. As a guide, any subject with any personal or family history of epilepsy or other neurological condition should be precluded from partaking in an experiment which does not involve investigation of that condition. Pascual-Leone et al. (1993) assessed the safety of rTMS and noted that seizures could be induced in subjects who were not associated with any risk factors. The paper presents some guidelines for the use of rTMS and familiarity with this paper should be a prerequisite of using rTMS. The paper is only one guide and it is not exhaustive. The study deals only with three sites of stimulation and expresses pulse intensity as a percentage of motor threshold. Studies which apply rTMS to the prefrontal or occipital visual areas cannot merely lift criteria from this paper and assume they transfer to other

conditions. We also recommend that anyone wishing to use rTMS visit the TMS website (http://www.pni.unibe.ch/maillist.htm). The TMS community is constantly reviewing safety procedures and this website is a starting point for access to sound information. A more recent paper (Wassermann, 1998) summarizes the consensus that exists within the community. The adverse effects recorded include seizures (though these are rare), some enhancement effects on motor reaction time and verbal recall, and effects on affect (some subjects have been reported to cry following left prefrontal rTMS and others to laugh). There is little information about potential longer-term problems with rTMS but the issue cannot be ducked. If, on one hand, rTMS is potentially useful in the alleviation of depression (George et al., 1995), it must be conceded that rTMS can have longer term effects. It would be disingenuous to suggest that all long-term effects are likely to beneficial rather than deleterious. It should be noted, however, that the improvements in mood as a result of rTMS follow several sessions of magnetic stimulation and that the effects may be cumulative. A simple precaution that may be taken is to prevent individual subjects from taking part in repeated experiments over a short period of time. As with the paper by Pascual-Leone et al. (1993), the use of rTMS should follow a close reading of Wassermann's report.

7. Conclusion

As the papers in this special issue show, there are many different ways of addressing a neuropsychological question. As should also be clear, however, *every* technique has limitations that are defined by the spatial and temporal resolutions of the methods and also by whether the technique interferes with brain processes or records them. Satisfactory answers to scientific questions rarely, if ever, yielded to a single technique and the future value of the methods discussed in this special issue is perhaps determined by the extent to which the methods are complementary. For example, progress has already been made in combining TMS with PET (Paus et al., 1997) and fMRI (Bohning, Pecheny, & Epstein, 1997; Bohning, Shastri, & McConnell, 1998), advances that will be important for understanding the physiological fundamentals of the effects of TMS as well as the behavioural effects. The use of brain imaging to investigate necessity and sufficiency of brain areas for task performance (Price, Mummery, Moore, Frackowiak, & Friston, 1999) also provides an area of interface between the different techniques. Where TMS does have a special role is in generating reversible, virtual lesions that can add real time analysis to the neuropsychologist's research program.

Acknowledgements

The authors' works are supported by the Medical Research Council, The Dr. Hadwen Research Trust and the Royal Society.

References

Albright, T. D. (1989). Centrifugal directional bias in the middle temporal visual area (MT) of the macaque. *Visual Neuroscience*, *2*(2), 177–188.

Amassian, V. E., Cracco, R. Q., Maccabee, P. J., Cracco, J. B., Rudell, A. P., & Eberle, L. (1989). Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroencephalography and Clinical Neurophysiology*, *74*, 458–462.

Ashbridge, E., Walsh, V., & Cowey, A. (1997). Temporal aspects of visual search studied by transcranial magnetic stimulation. *Neuropsychologia*, *35*, 1121–1131.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet*, *i*, 1106–1107.

Beckers, G., & Homberg, V. (1992). Cerebral visual motion blindness: transitory akinetopsia induced by transcranial magnetic stimulation of human area V5. *Proceedings of the Royal Society of London, Series B*, *249*, 173–178.

Beckers, G., & Zeki, S. (1995). The consequences of inactivating areas V1 and V5 on visual motion perception. *Brain*, *118*, 49–60.

Bohning, D. E., Pecheny, A. P., & Epstein, C. M. (1997). Mapping transcranial magnetic stimulation (TMS) fields with MRI. *Neuro Report*, *8*, 2535–2538.

Bohning, D. E., Shastri, & McConnell, K. (1998). Echoplanar BOLD fMRI of brain activation induced by concurrent transcranial magnetic stimulation (TMS). *Investigative Radiology*, *33*, 336–340.

Britten, K. H., Newsome, W. T., Shadlen, N. M., Celebrini, S., & Movshon, J. A. (1996). A relationship between behavioural choice and the visual responses of neurons in macaque MT. *Visual Neuroscience*, *13*(1), 87–100.

Celebrini, S., & Newsome, W. T. (1994). Neuronal and psychophysical sensitivity to motion signals in extrastriate area MST of the Macaque monkey. *Journal of Neuroscience*, *14*(7), 4109–4124.

Cohen, L. G., Bandinelli, S., Findley, T. W., & Hallett, M. (1991). Motor reorganization after upper limb amputation in man. *Brain*, *114*, 615–627.

Cowey, A., & Walsh, V. (2000). Magnetically induced phosphenes in sighted, blind and blindsighted observers. *NeuroReport*, *11*, 3269–3273.

Cowey, A., & Walsh, V. Tickling the brain: studies of visual sensation, perception and cognition by transcranial magnetic stimulation. *Progress in Brain Research* (in press).

Culham, J., He, S., Dukelow, S., & Verstraten, F. (2001). Visual motion and the human brain: what has neuroimaging told us? *Acta Psychologica*, *107*, 69–94.

Dubner, R., & Zeki, S. M. (1971). Response properties and receptive fields of cells in an anatomically defined region of the superior temporal sulcus in the monkey. *Brain Research*, *35*, 528–532.

Epstein, C. M., Meador, K. J., Loring, D. W., Wright, R. J., Wiseman, J. D., Sheppard, S., Lah, J. J., Puhlavich, F., Gaitan, L., & Davey, K. R. (1999). Localization of speech arrest with transcranial magnetic brain stimulation. *Journal of Clinical Neurophysiology*, *110*(6), 1073–1079.

Fierro, B., Brighina, F., Oliveri, M., Piazza, A., Bua, V., Buffa, D., & Bisiach, E. (2000). Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *NeuroReport*, *11*, 1519–1521.

Flament, D., Hall, E. J., & Lemon, R. J. (1992). The development of corticomotorneuronal projections investigated using magnetic brain stimulation in the infant macaque. *Journal of Physiology*, *447*, 755–768.

Flitman, S. S., Grafman, J., Wassermann, E. M., Cooper, V., O'Grady, J., Pascual-Leone, A., & Hallett, M. (1998). Linguistic processing during repetitive transcranial magnetic stimulation. *Neurology*, *50*, 175–181.

George, M. S., Wassermann, E. M., Williams, W. A., Callahan, A., Ketter, T. A., Basser, P., Hallett, M., & Post, R. M. (1995). Daily repetitive transcranial magnetic stimulation improves mood in depression. *NeuroReport*, *6*, 1853–1856.

Hotson, M., Braun, D. W., & Boman, D. (1994). Transcranial magnetic stimulation of extrastriate cortex degrades human motion direction discrimination. *Vision Research*, *34*, 2115–2123.

Humphreys, G. W., & Price, C. (2001). Cognitive neuropsychology and functional brain imaging: implications for functional and anatomical models of cognition. *Acta Psychologica*, *107*, 119–153.

Jennum, P., Friberg, L. A., & Dam, M. (1994). Speech localization using repetitive transcranial magnetic stimulation. *Neurology*, *44*, 269–273.

Kammer, T. (1999). Phosphenes and transient scotomas induced by magnetic stimulatio of the occiptal lobe: their topographic relationship. *Neuropsychologia*, *37*, 191–198.

Kinsbourne, M. (1977). Hemi-neglect and hemisphere rivalry. *Advances in Neurology*, *18*, 41–49.

Lamme, V. A. F. (2001). Blindsight: the role of feedforward and feedback corticocortical connections. *Acta Psychologica*, *107*, 209–228.

Michelucci, R., Valzania, F., Passarelli, D., Santangelo, M., Rizzi, R., Buzzi, A. M., Tempestini, A., & Tassinari, C. A. (1994). Rapid-rate transcranial magnetic stimulation and hemispheric language dominance: usefulness and safety in epilepsy. *Neurology*, *44*, 1697–1700.

Mikami, A., Newsome, W. T., & Wurtz, R. H. (1986). Motion selectivity in macaque visual cortex. I. Mechanisms of direction and speed selectivity in extrastriate area MT. *Journal of Neurophysiology*, *55*(6), 1308–1327.

Mottaghy, F. M., Hungs, M., Brugmann, M., Sparing, R., Boroojerdi, B., Foltys, H., Huber, W., & Topper, R. (1999). Facilitation of picture naming after repetitive transcranial magnetic stimulation. *Neurology*, *53*, 1806–1812.

Munhall, K. G. (2001). Functional imaging during speech production. *Acta Psychologica*, *107*, 95–117.

Oliveri, M., Rossinin, P. M., Traversa, R., Cicinella, P., Filippi, M. M., Pasqualetti, P., Tomaiulo, F., & Caltagirone, C. (1999). Left frontal transcranial magnetic stimulation reduces contralateral extinction in patients with unilateral right brain damage. *Brain*, *122*, 1731–1739.

Pascual-Leone, A., Gomez Tortosa, E., Grafman, J., Alway, D., Nichelli, P., & Hallett, M. (1994). Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal lobe. *Neurology*, *44*, 494–498.

Pascual-Leone, A., & Torres, F. (1993). Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. *Brain*, *116*, 39–52.

Pascual-Leone, A., Houser, C. M, Reese, K., Shotland, L. I., Grafman, J., Sato, S., Valls-Sole, J., Brasil-Neto, J. P., Wassermann, E. M., & Cohen, L. G. (1993). Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Journal of Electroencephalography and Clinical Neurophysiology*, *89*, 120–130.

Pascual-Leone, A., Tarazona, F., & Keenan, J. (1999). Transcranial magnetic stimulation and neuroplasticity. *Neuropsychologia*, *37*(2), 207–217.

Paus, T., Jech, R., Thompson, C. J., Comceau, R., Peters, T., & Evans, A. C. (1997). Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *Journal of Neuroscience*, *17*, 3178–3184.

Penfield, W., & Rasmussen, T. (1949). Vocalization and arrest of speech. *Archives of Neurological Psychiatry*, *61*, 21–27.

Price, C. J., Mummery, C. J., Moore, C. J., Frackowiak, R. S. J., & Friston, K. J. (1999). Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. *Journal of Cognitive Neuroscience*, *11*, 371–382.

Reppas, J. B., Niyogi, S., Dale, S. M., Sereno, M. I., & Tootell, R. B. H. (1997). Representation of motion boundaries in retinotopic human visual cortical areas. *Nature*, *388*, 175.

Seyal, M., Ro, T., & Rafal, R. (1995). Increased sensitivity to ipsilateral cutaneous stimuli following transcranial magnetic stimulation of the parietal lobe. *Annals of Neurology*, *38*, 264–267.

Smith, A. T., Greenlee, M. W., Singh, K. D., Kraemer, F. M., & Hennig, J. (1998). The processing of first- and second-order motion in human visual cortex assessed by functional magnetic resonance imaging (fMRI). *Journal of Neuroscience*, *18*(10), 3816–3830.

Stewart, L. M., Battelli, L., Walsh, V., & Cowey, A. (1999). Motion perception and perceptual learning: a magnetic stimulation study. *Journal of Electroencephalography and Clinical Neurophysiology*, *51*, 334–350.

Stewart, L. M., Walsh, V., Frith, U., & Rothwell, J. C. (2001). TMS produces two dissociable types of speech production. *NeuroImage*, *13*, 472–478.

Tootell, R. B. H., Reppas, J. B., Dale, A. M., Look, R. B., Sereno, M. I., Malach, R., Brady, T. J., & Rosen, B. R. (1995). Visual motion after effect in human cortical area MT revealed by functional magnetic resonance imaging. *Nature*, *375*, 139–141.

Topper, R., Mottaghy, F., Brugmann, M., Noth, J., & Huber, W. (1998). Facilitation of picture naming by focal transcranial magnetic stimulation of Wernicke's area. *Experimental Brain Research*, *121*, 371–378.

Walsh, V. (1998). Faradization of the Mind. *Current Biology*, *8*, R8–R11.

Walsh, V., Ashbridge, E., & Cowey, A. (1998). Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. *Neuropsychologia*, *36*, 45–49.

Walsh, V., & Cowey, A. (1998). Magnetic stimulation studies of visual cognition. *Trends in Cognitive Science*, *2*, 103–110.

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience*, *1*, 73–79.

Walsh, V., & Rushworth, M. (1999). A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia*, *37*(2), 125–136.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. *Journal of Electroencephalography and Clinical Neurophysiology*, *108*(1), 1–16.

Wassermann, E. M., Blaxton, T. A., Hoffman, E. A., Berry, C. D., Oletsky, H., Pascual-Leone, A., & Theodore, W. H. (1999). Repetitive transcranial magnetic stimulation of the dominant hemisphere can disrupt visual naming in temporal lobe epilepsy patients. *Neuropsychologia*, *37*, 537–544.

Watson, J. D, Myers, R., Frackowiak, R. S., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., Shipp, S., & Zeki, S. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cerebral Cortex*, *3*(2), 79–94.

Zeki, S., Watson, J. D. G., Lueck, C. J., Friston, K. J., Kennard, C., & Frackowiak, R. S. J. (1991). A direct demonstration of functional specialization in human visual cortex. *Journal of Neuroscience*, *11*, 641–649.