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Craniotopic updating of visual space across saccades in the human posterior parietal cortex

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The neural mechanisms underlying the craniotopic updating of visual space across saccadic eye movements are poorly understood. Previous single-unit recording studies in primates and clinical studies in brain-damaged patients have shown that the posterior parietal cortex (PPC) has a key role in this process. In the present study, we used single-pulse transcranial magnetic stimulation (TMS) to disrupt the processing within the PPC during a task that requires craniotopic updating: double saccades. In this task, two targets are presented in quick succession and the subject is required to make a saccade to each location as accurately as possible. We show here that TMS delivered to the PPC just prior to the second saccade effectively disrupts the craniotopic coding normally observed in this task. This causes subjects to revert to saccades more consistent with a representation of the targets based on their positions relative to one another. By contrast, stimulation at earlier times between the two saccades did not disrupt performance. These results suggest that extraretinal information generated during the first perisaccadic period is not put into functional use until just prior to the second saccade.

Keywords: posterior parietal cortex; transcranial magnetic stimulation; extraretinal signals; craniotopic; double saccade; visuomotor behaviour

1. INTRODUCTION

To direct gaze accurately to objects of interest in extrapersonal space, the central nervous system (CNS) must combine visual information concerning the retinal position of the object image with extraretinal information concerning current eye position. The role of extraretinal signals in this process has been examined by having subjects attempt to make saccades to two targets presented in rapid succession. Humans can quite accurately perform this double-saccade task despite the discrepancy induced by the generation of the first saccade between the retinal location of the second target and the saccade necessary to foveate it (Hallett & Lightstone 1976). This suggests that extraretinal information related to the metrics of the first saccade is used to update the visual representation of the second target in craniotopic coordinates. One consequence of this process is that any inaccuracies in the initial saccade can be compensated for during the second saccade. By contrast, if the updating process did not occur, the CNS would be forced to generate the second saccade based on the positions of the targets relative to one another. This form of coding has been termed exocentric (as opposed to egocentric) or object based. In this case, any inaccuracy in the initial saccade could not be compensated for during the second saccade.

Neurophysiological, brain imaging and brain lesion studies have demonstrated that the posterior parietal cortex (PPC) has a vital role in the updating process. In particular, visual cells in the lateral intraparietal area have been shown to fire in anticipation of saccades that will bring a previously flashed target into their receptive field (Duhamel *et al.* 1992*a*). Functional magnetic resonance imaging studies have shown that the homologous region is activated in human subjects when performing double- or triple-step saccade tasks (Heide *et al.* 2001; Tobler *et al.* 2001). Finally, studies with human subjects suffering from lesions to the parietal cortex, or primates in which this area has been temporarily inactivated, have confirmed that this cortical area is vital to the updating process: such individuals are unable to accurately generate the second saccade in the sequence even when such a saccade is directed into the hemifield ipsilateral to the lesion (Duhamel *et al.* 1992*b*; Heide *et al.* 1995; Li & Andersen 2001). Taken together, these studies demonstrate that the activity occurring in this part of the brain is vital to the updating process. What remains unclear, however, is when in time and for what duration the parietal cortex contributes to the updating process relative to different epochs within the saccade sequence. In the present study, we examined this issue in healthy human subjects by briefly disrupting the pattern of activation in the PPC using single-pulse transcranial magnetic stimulation (TMS) triggered at various latencies after the onset of the initial saccade. By characterizing the effects of the different stimulation times on the saccade sequence it was possible to make strong inferences about the contribution of the parietal cortex to the updating process in a time-resolved manner.

2. METHODS

(a) *Subjects*

Three subjects (two males and one female, mean age: 28.3 years) served as subjects in the experiment after giving informed consent. Each subject was free from neurological impairments affecting ocular control and had normal or

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corrected-to-normal vision. The local ethics committee had approved the experimental procedures.

(b) *Apparatus*

The subject was seated in a completely dark room, 114 cm from a screen on which target light-emitting diodes were displayed. Eye movements were recorded with an infrared corneal reflection device (Iris Skalar) with a spatial resolution of 0.1° and sampled at 1000 Hz. The eye movement recording device was calibrated by having the subject fixate targets at known eccentricities prior to and at regular intervals during data collection. The head was stabilized with a chin rest.

(c) *Transcranial magnetic stimulation*

Single magnetic pulses were generated with a Magstim 200 stimulator and delivered through a circular coil (70 mm diameter). The threshold for eliciting visible twitches in the left hand was first determined by stimulating over the right motor cortex. Stimulation of the right PPC was at 120% of the motor threshold. This value was selected to be of sufficient magnitude to influence cortical activity in the PPC, but not so high that it caused blinks or uncomfortable facial twitches. The PPC site was located by moving the coil to a position 3 cm posterior and 3 cm lateral to the vertex. This site corresponds to the P4 location of the international 10–20 system used in electroencephalography studies. Stimulation was given unilaterally so that we could investigate the specificity of the effect for saccades directed ipsilateral and contralateral to the side of stimulation. The subjects did not report any ill effects from the TMS.

(d) *Experimental task*

Subjects performed a rapid double-saccade task (Hallett & Lightstone 1976; Duhamel *et al.* 1992*b*). At the beginning of each trial, a central fixation target appeared for a variable period of time (500–1500 ms). Afterwards, a peripheral target briefly (140 ms) appeared at varying amplitudes (6, 10, 12 and 14°) to the left or right of centre, followed by a second briefly (100 ms) presented peripheral target positioned at varying amplitudes (6, 10, 12 and 14°) in the opposite hemifield. Subjects were instructed to make two saccades in sequence to the locations at which the peripheral targets had appeared. Because the targets appeared and disappeared prior to the onset of the initial saccade, the movements were made in complete darkness and without visual feedback. Figure 1 displays a schematic representation of the events occurring during a left–right target presentation sequence. To reduce errors in direction, the targets appeared in either the right–left order or the left–right order in separate blocks of trials. In separate sessions, TMS was applied at the onset of the first saccade or 100 or 150 ms afterwards. These latter delays were chosen so as to be during the middle and towards the end of the intrasaccadic period, respectively. A saccade velocity threshold was used to trigger the stimulator. Control trials without stimulation were interleaved with the TMS trials during each session. Forty trials with TMS and 40 without were completed for each order of direction for a total of 160 trials in each session.

(e) *Data analysis*

Because the saccade sequence occurred in complete darkness, the first saccade could have a certain degree of variability. Our goal was to quantify the degree to which the second saccade compensated for this variability. This was accomplished in two ways. First, the gain of the first saccade was plotted against the

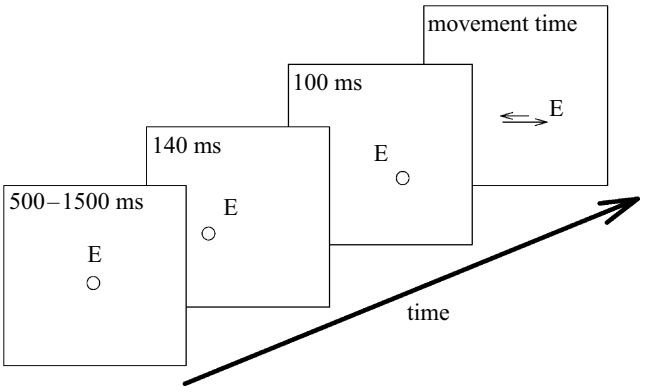

Figure 1. Sequence of events during a left–right trial. The subject initially fixates the target at the central position (E represents the position of the eye). After a variable delay, the target steps to the left and remains stationary for 140 ms. It then steps to the left and disappears after 100 ms. The subject reacts to the target steps by making a rapid double saccade to the position at which each target appeared. Target size is not to scale.

'retinal' gain of the second saccade. The gain of the first saccade was defined as the amplitude of this saccade divided by the amplitude between the central fixation target and the first peripheral target. The retinal gain of the second saccade was defined as the amplitude of this saccade divided by the amplitude between the first and second targets. If the brain craniotopically codes the location of the two targets, then it will be able to take into account any variability in the metrics of the first saccade and compensate with the second saccade. As a result, a linear regression calculated for the relationship between the first saccade gain and the second saccade retinal gain should have a positive slope (figure 2*a*). Second, if the brain codes the targets in an object-based frame of reference—that is, one target relative to the other—then any variability in the first saccade will not be compensated for and the slope of the relationship between the first saccade gain and the second saccade retinal gain should approach zero (figure 2*b*).

Although this type of analysis provides a valuable insight into the basic processing that underlies the updating of the visual representation of space, it relies on results from a group of trials to generate a single slope value. However, because the compensatory process occurs within individual trials we also wished to quantify it on a trial by trial basis. This has the advantage that the values obtained for the compensation can then be compared with the time at which TMS was delivered relative to the second saccade (which vary quite substantially for any given stimulation time relative to the first saccade). Thus, for our second method of quantification we measured the 'compensatory' gain of the second saccade relative to the delay between TMS delivery and second saccade onset. Compensatory gain was defined as the amplitude of the saccade that is generated divided by the amplitude required given the first saccade gain. Perfect compensation, again reflecting craniotopic coding of the targets, would yield a value of one; whereas values of less than one would reflect target coding in a more object-based frame of reference.

3. RESULTS

Figure 3 displays the slope values from the analysis of the relationship between the first saccade gain and the

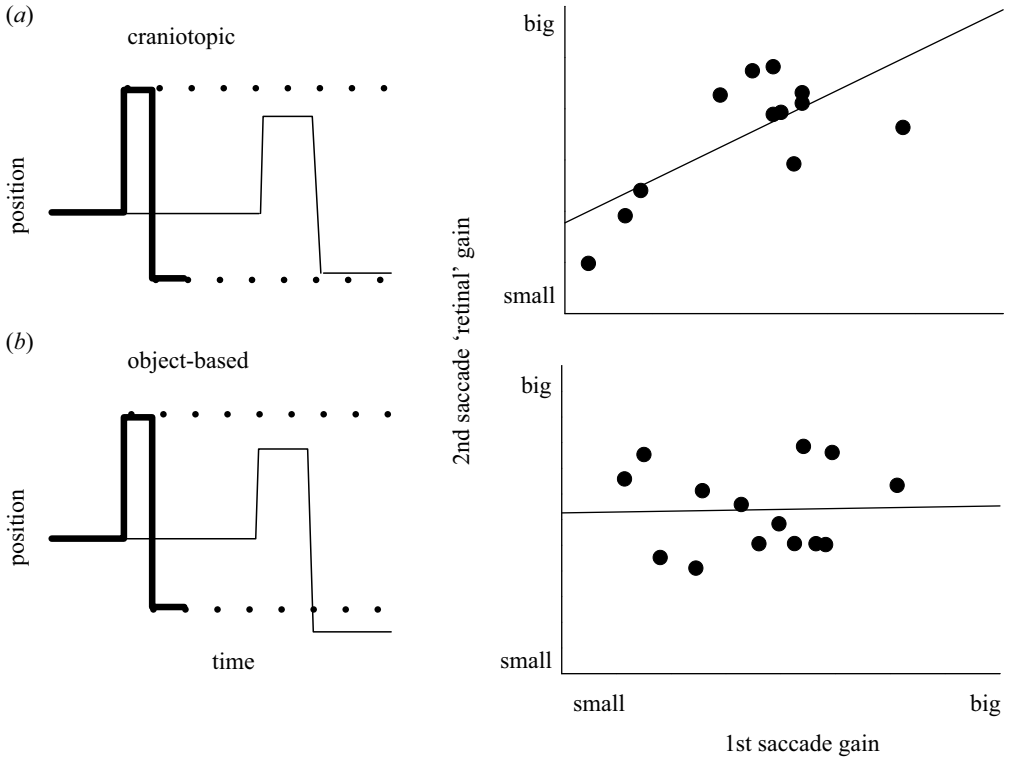

Figure 2. Hypothetical trials (left diagrams) showing saccade trajectories (thin lines) when first saccade undershoots the target (thick lines). If the CNS codes targets in a craniotopic frame of reference (*a*), the second saccade compensates, but if an object-based frame of reference is used (*b*), no compensation occurs. Graphs on the right show corresponding hypothetical plots of first saccade gain versus second saccade retinal gain over several trials. Craniotopic coding results in a positive slope between these two variables, whereas object-based coding results in a slope of zero.

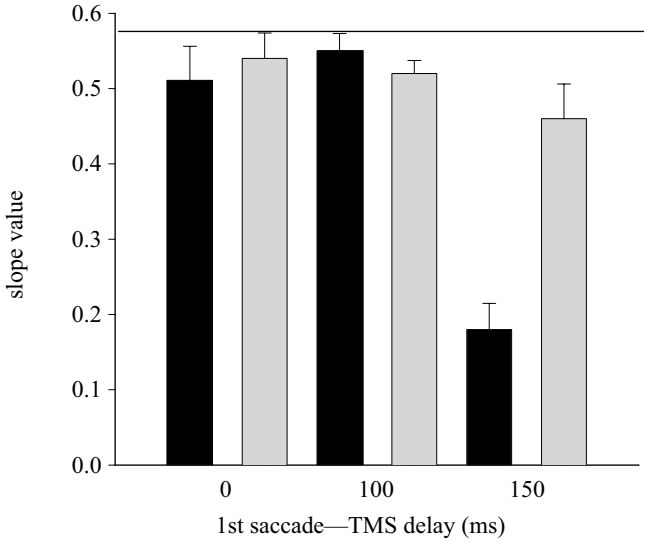

Figure 3. Group means for the slope values of the linear regression between the first saccade gain and the second saccade retinal gain plotted for each stimulation time (0, 100 and 150 ms after the first saccade onset). Black bars represent saccade sequences in which the first saccade was directed contralateral and the second saccade ipsilateral to the side of stimulation. Grey bars represent the opposite sequence. The horizontal line shows the slope value when no TMS is given. Error bars show one intersubject s.e.

second saccade retinal gain, plotted separately for each stimulation time and order of saccade direction relative to the side of stimulation. When the stimulation occurred coincident with or 100 ms after the onset of the first saccade, the slope values were the same as those generated when no TMS was given. This was true regardless of whether the saccades occurred in a contralateral–ipsilateral or ipsilateral–contralateral sequence relative to the side of stimulation. However, when the TMS was delivered 150 ms after the first saccade (i.e. just prior to the second saccade), the slope was markedly reduced for saccades occurring in a contralateral–ipsilateral order. This was not the case for ipsilateral–contralateral sequences. This pattern of results was confirmed with a 2×3 repeated measures ANOVA, which revealed a significant main effect of stimulation time ($F_{2,12} = 9.13$, $p = 0.004$). A post-hoc Tukey's test demonstrated that the slope value when TMS was delivered 150 ms after the first saccade and the saccades were performed in a contralateral–ipsilateral order was significantly smaller than the slope values for all the other conditions, except the opposite sequence with TMS given at the same time. The slope value in this latter condition was not significantly different from those occurring for any of the other combinations of stimulation time and saccade order. This pattern of results indicates that the ability to update the location of targets in a craniotopic frame of reference is compromised when activity in the PPC is disrupted just prior to the generation of an ipsilaterally directed saccade.

To better understand when in time the updating process occurs, we measured the 'compensatory' gain of the second saccade on a trial by trial basis and plotted it against the time at which TMS was delivered relative to the onset of the second saccade. The resulting graphs are

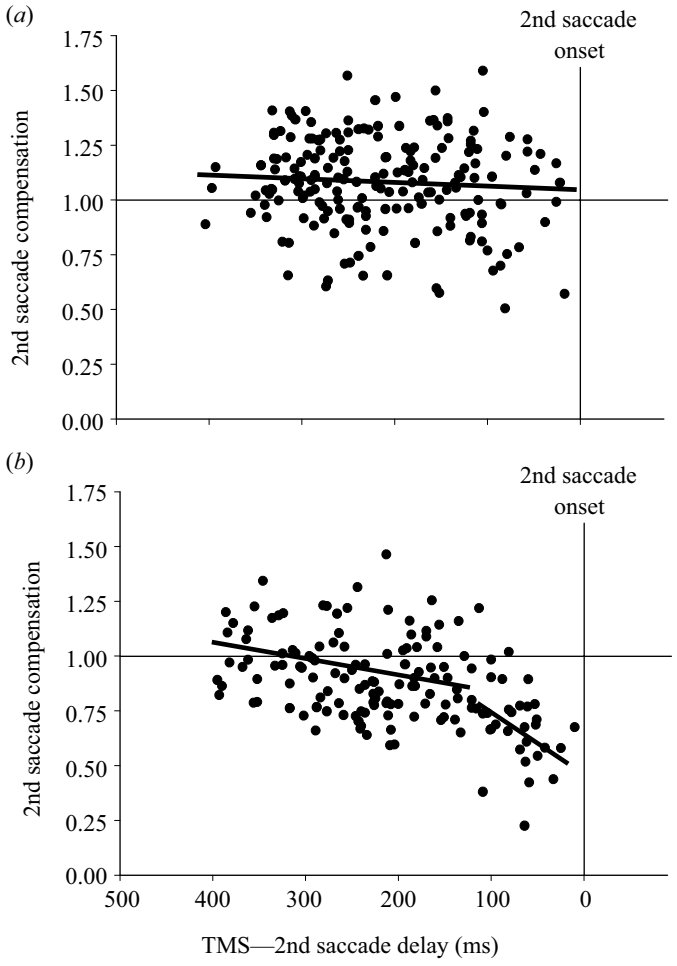

Figure 4. Compensatory gain of the second saccade plotted as a function of the delay between delivery of TMS and onset of the second saccade during individual trials for all three subjects. Data from trials with saccades generated in the ipsilateral–contralateral order are shown in (*a*) and in the contralateral–ipsilateral order in (*b*). The horizontal lines represent perfect compensation. The vertical lines represent onset of the second saccade. The thick solid lines represent lines of best fit through the data. For the contralateral–ipsilateral condition (*b*), the data have been broken into two segments before and after the break-point at 116 ms prior to the second saccade.

shown for saccades performed in the ipsilateral–contralateral (figure 4*a*) and contralateral–ipsilateral (figure 4*b*) sequences. In both cases, when the TMS was delivered well before the onset of the second saccade there was perfect compensation. Although the degree of over- or under-compensation varied quite substantially across trials, on average the compensatory gain during this period was close to one. However, as the TMS was delivered closer in time to the onset of the second saccade, the compensatory gain began to decrease for saccade sequences generated in the contralateral–ipsilateral order. This decrease did not occur when the saccades were made in the opposite order. The break-point at which this decrease occurred was quantified in the following manner. First, 20-point running averages were obtained for each condition. The 20-point running average was chosen because it sufficiently smoothed the data while still retaining the essential changes in the data across the different TMS–second saccade delays. Next, the mean and standard deviation for the ipsilateral–contralateral condition were calculated and used as a baseline with which to compare when changes occurred in the contralateral–ipsilateral condition. Finally, we defined the break-point as the time after which the running average for the contralateral–ipsilateral condition was more than two standard deviations below that of the ipsilateral–contralateral condition. These steps are analogous to those used in single-unit recording studies to define if and when a neuron changes its activity during a task. Using this approach we found that the break-point occurred 116 ms prior to the onset of the second saccade. Across the three subjects this break-point had a range of 106–134 ms. Linear regressions for the segments of data before and after this break-point show markedly different slopes. This pattern of results implies that, at this time, the PPC started to make functional use of the extraretinal information generated during the first saccade to accurately prepare the second saccade. As a result, when TMS was delivered to the PPC at or after this time, the second saccade no longer compensated for any inaccuracies in the first saccade.

4. DISCUSSION

Human beings possess a remarkable ability to accurately determine the egocentric location of external targets and generate eye or limb movements to those targets. We are able to perform this task despite the fact that the images of external objects on the retina are displaced each time the eye moves. Because these abrupt alterations in the retinal image do not significantly impair our performance, it implies that the brain monitors the metrics of eye movements that intervene between the presentation of a target and the response made towards it, as has been shown experimentally with double-saccade tasks (Hallett & Lightstone 1976). Clinical and neurophysiological studies have demonstrated that the PPC has a key role in this monitoring process (Duhamel *et al.* 1992*a*,*b*; Heide *et al.* 1995; Li & Andersen 2001). In the present study, we sought to determine exactly when and under what circumstances the PPC makes this contribution. This was accomplished by disrupting the pattern of activation in the PPC using TMS while subjects attempted to perform a double-saccade task. TMS has the advantage of being able to demonstrate that activity in a specific region of the brain is necessary for a particular task to be performed correctly. In addition, by delivering the TMS pulse at precise intervals relative to events within the task, it becomes possible to determine when a specific area is necessary (Pascual-Leone *et al.* 1999; Walsh & Rushworth 1999).

The fact that humans can perform double-saccade tasks quite accurately implies that the position of each target is coded in a craniotopic—or head-centred—frame of reference. For this to occur, the retinal information related to the position of the second target must be combined with extraretinal information concerning the metrics of the first saccade. In addition, this information must be integrated in a rapid manner because the second saccade typically is generated within a few hundred milliseconds after the completion of the first saccade. For the present study, we used the concept of compensation to identify the extent to which craniotopic coding occurred. In particular, we

assumed that because of the nature of the task, there would be some variability in the end-point of the first (and second) saccade. If a craniotopic frame of reference were in use, then any inaccuracy in the first saccade would be compensated for by an appropriate increase or decrease in the amplitude of the second saccade. However, if the craniotopic coding failed, then the degree of compensation would be reduced. Our two compensation indices demonstrated that the craniotopic coding failed when the pattern of activity within the PPC was disrupted with TMS during a *ca*. 100 ms period prior to the onset of the second saccade. Moreover, this failure occurred only during saccadic sequences directed initially contralateral and subsequently ipsilateral to the side of stimulation. This pattern of results implies that the PPC is normally involved in the integration of retinal and extraretinal information related to contralaterally directed saccades for functional use in preparing ipsilaterally directed saccades, just prior to the generation of those saccades. Previous TMS studies have also shown that the PPC is involved early during the saccade preparation process (Müri *et al*. 1996; Terao *et al*. 1998). In addition, clinical studies in patients with parietal damage have shown a similar deficit in monitoring the metrics of a contralesionally directed initial saccade for computing an ipsilesionally directed second saccade, but not in generating a contralesionally directed second saccade (Duhamel *et al*. 1992*b*).

The degree of compensation that did occur under these circumstances was consistent with the coding of target locations in an object-based frame of reference (Behrmann & Tipper 1999; Olson 2001). In particular, subjects appeared to be able to determine the position of the second target with respect to the first target and use this purely visual information to generate saccades that were appropriate for the retinal distance between the two target images. This contrasts with purely retinotopic coding, in which the position of the second target is calculated with respect to the distance of its image from the fovea during the initial fixation period. If retinotopic coding were used the second saccade would have markedly undershot the target on every trial. This would have been reflected by second saccade retinal gain scores with an average value across trials of 0.5 (because of the combinations of saccade amplitudes that were required). Instead, the average of the second saccade retinal gain values was 1.2. In other words, the subjects tended to overshoot the second target during a typical trial and rarely generated a second saccade that reflected coding using a retinotopic frame of reference.

The fact that relative retinal information could still be used to generate saccades coded in object-based coordinates implies that the TMS disrupted the other source of information required for craniotopic coding—extraretinal signals. Several areas within the PPC are known to possess cells that carry extraretinal information (e.g. Andersen 1997; Duhamel *et al*. 1992*a*; Snyder *et al*. 1998). It appears that TMS disrupted the integration of retinal and extraretinal information and thus reduced the extent to which craniotopic coding of the targets was possible. Therefore, the present results confirm that craniotopic coding is used to update the visual representation of space across saccadic eye movements and demonstrate for the first time, to our knowledge, that this process occurs during a critical period just prior to the second saccade.

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REFERENCES

Andersen, R. A. 1997 Multimodal integration for the representation of space in the posterior parietal cortex. *Phil. Trans. R. Soc. Lond.* B **352**, 1421–1428.

Behrmann, M. & Tipper, S. P. 1999 Attention accesses multiple reference frames: evidence from visual neglect. *J. Exp. Psychol. Hum. Percept. Perform.* **25**, 83–101.

Duhamel, J. R., Colby, C. L. & Goldberg, M. E. 1992*a* The updating of the representation of visual space in parietal cortex by intended eye movements. *Science* **255**, 90–92.

Duhamel, J. R., Goldberg, M. E., Fitzgibbon, E. J., Sirigu, A. & Grafman, J. 1992*b* Saccadic dysmetria in a patient with a right frontoparietal lesion. The importance of corollary discharge for accurate spatial behaviour. *Brain* **115**, 1387–1402.

Hallett, P. E. & Lightstone, A. D. 1976 Saccadic eye movements to flashed targets. *Vision Res.* **16**, 107–114.

Heide, W., Blankenburg, M., Zimmermann, E. & Kompf, D. 1995 Cortical control of double-step saccades: implications for spatial orientation. *Ann. Neurol.* **38**, 739–748.

Heide, W., Binkofski, F., Seitz, R. J., Posse, S., Nitschke, M. F., Freund, H. J. & Kompf, D. 2001 Activation of frontoparietal cortices during memorized triple-step sequences of saccadic eye movements: an fMRI study. *Eur. J. Neurosci.* **13**, 1177–1189.

Li, C.-S. R. & Andersen, R. A. 2001 Inactivation of macaque lateral intraparietal area delays initiation of the second saccade predominantly from contralesional eye positions in a double-saccade task. *Exp. Brain Res.* **137**, 45–57.

Müri, R. M., Vermersch, A. I., Rivaud, S., Gaymard, B. & Pierrot-Deseilligny, C. 1996 Effects of single-pulse transcranial magnetic stimulation over the prefrontal and posterior parietal cortices during memory-guided saccades in humans. *J. Neurophysiol.* **76**, 2102–2106.

Olson, C. R. 2001 Object-based vision and attention in primates. *Curr. Opin. Neurobiol.* **11**, 171–179.

Pascual-Leone, A., Bartres-Faz, D. & Keenan, J. P. 1999 Transcranial magnetic stimulation: studying the brain–behaviour relationship by induction of 'virtual lesions'. *Phil. Trans. R. Soc. Lond.* B **354**, 1229–1238.

Snyder, L. H., Grieve, K. L., Brotchie, P. & Andersen, R. A. 1998 Separate body and world referenced representations of visual space in parietal cortex. *Nature* **394**, 887–891.

Terao, Y., Fukuda, H., Ugawa, Y., Hikosaka, O., Hanajima, R., Furubayashi, T., Sakai, K., Miyauchi, S., Sasaki, Y. & Kanazawa, I. 1998 Visualization of the information flow through human oculomotor cortical regions by transcranial magnetic stimulation. *J. Neurophysiol.* **80**, 936–946.

Tobler, P. N., Felblinger, J., Burki, M., Nirkko, A. C., Ozdoba, C. & Muri, R. M. 2001 Functional organisation of the saccadic reference system processing extraretinal signals in humans. *Vision Res.* **4**, 1351–1358.

Walsh, V. & Rushworth, M. 1999 A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia* **37**, 125–135.