Evidence for Fast Signals and Later Processing in Human V1/V2 and V5/MT+: A TMS Study of Motion Perception

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Laycock R, Crewther DP, Fitzgerald PB, Crewther SG. Evidence for fast signals and later processing in human V1/V2 and V5/MT+: a TMS study of motion perception. J Neurophysiol 98: 1253–1262, 2007. First published July 18, 2007; doi:10.1152/jn.00416.2007. Evidence from human and primate studies suggests that fast visual processing may utilize signals projecting from primary visual cortex (V1) through the dorsal stream, to area V5/MT+ or beyond and subsequently back into V1. This coincides with the arrival of parvocellular signals en route to the ventral pathway and infero-temporal cortex. Such evidence suggests that the dorsal stream region V5/MT+ is activated rapidly through the traditional hierarchical pathway and also via a less-well-established direct signal to V5/MT+ bypassing V1. To test this, 16 healthy humans underwent transcranial magnetic stimulation (TMS) of V1/V2 and V5/MT+ while performing a motion-direction detection task. A three-alternate forced-choice design (left/right motion, stationary) allowed analysis of the quality of errors made, in addition to the more usual performance measures. Transient disruption of V1/V2 and V5/MT+ significantly reduced accuracy when TMS was applied at or near motion onset. Most participants also showed disrupted performance with TMS application over V1/V2 ~125 ms post motion onset, and significantly reduced accuracy at 158 ms with V5/MT+ stimulation. The two periods of disruption with V1/V2 TMS are suggestive of feedforward/feedback models, although the earlier period of disruption has not been reported in previous TMS studies. Very early activation of V5/MT+, evidenced by diminished accuracy and reduced perception of motion after TMS may be indicative of a thalamic-extrastriate pathway in addition to the traditionally expected later period of processing. A profound disruption of performance prestimulus onset is more likely to reflect disruption of top-down expectancy than disruption of visual processing.

INTRODUCTION

Hierarchical models of visual processing, largely derived from primate studies, suggest that visual information flows from the retina to the lateral geniculate nucleus (LGN), through to primary visual cortex (V1), and then to extrastriate areas (DeYoe et al. 1994; Felleman et al. 1997; Maunsell 1992; Maunsell and Van Essen 1983; Van Essen et al. 1986). More recently, however, interactive models of visual processing have challenged these classical feedforward-only models by emphasizing the importance of feedback projections from higher- to lower-order areas prior to visual awareness (Bullier 2001; Fenske et al. 2006; Lamme and Roelfsema 2000; Laycock et al. 2006; Tong 2003). In particular, transcortical magnetic stimulation (TMS), a relatively new technique allowing disruption of cortical processing, has been used to demonstrate the necessity of feedback projections from extrastriate cortex into V1 for figure-ground segregation (Heinen et al. 2005) and for perception of movement (Cowey and Walsh 2000; Pascual-Leone and Walsh 2001; Silvanto et al. 2005a).

Recent human event-related potential (ERP) recordings from multiple electrode arrays also indicate that “higher-order” areas are activated much earlier than previously thought (Foxe and Simpson 2002; Lamme and Roelfsema 2000; Vanni et al. 2004a,b). According to a meta-analysis of 48 studies measuring single-unit responses in macaque, the first visual response in V1 was measured at 35 ms post stimuli, whereas in area MT, it was 39 ms (Lamme and Roelfsema 2000). An earlier study by Raiguel, Lagae, Gulyas, and Orban (1989) reported a 5-ms earlier onset of activation of macaque single cells in V5/MT, than in V1. Foxe and Simpson (2002) have also demonstrated that the initial trajectory of visual information through the dorsal stream reaches prefrontal cortex within ~30 ms of leaving occipital cortex with the dorsolateral frontal cortex active within 85 ms post stimulus onset—a latency considerably faster than had been expected from previous human ERP literature. These observations have since been confirmed in other studies and human extrastriate areas shown to be active within 10–15 ms of V1 activation (Di Russo et al. 2002; Foxe and Simpson 2002; Vanni et al. 2001).

Such studies suggest that extrastriate cortex is activated early enough to be able to influence subsequent processing through feedback connections to V1. This was conceptualized as a new feedforward and feedback model of visual processing (Bullier 2001) in which conduction times are sufficiently fast, and activation of single cells in higher-order areas is sufficiently early, to facilitate a role in “top-down” processing. Bullier further proposed that the first-pass global information carried out in higher-level regions, driven by magnocellular projections in the dorsal stream, is retroinjected into V1/V2 rapidly enough to influence and integrate with the first parvocellular projections into V1 and thence into the ventral stream. The dorsal stream may also influence ventral stream processing by direct projection from V5 to V4 in the ventral stream (Chen et al. 2007; Schroeder et al. 1998). This advantage in latency of arrival of magnocellular relative to parvocellular responses in LGN and V1 has been termed the “magnocellular advantage” (Laycock et al. 2006). The magnocellular advantage is suggested to be 10–20 ms in macaque (Bullier et al. 1996; Ohzawa et al. 2002; Tong 2003).
Maunsell et al. 1999; Schmolesky et al. 1998) and ~20 ms in the human VEP (Klistorner et al. 1997).

**Visual signals bypassing V1**

Evidence for a direct input from LGN or pulvinar to V5/MT while bypassing striate cortex exists in monkey (Girard et al. 1992; Raiguel et al. 1989; Rodman et al. 1989; Sincich et al. 2004; Standage and Benevento 1983) and in human (Beckers and Zeki 1995; Buchner et al. 1997; ffytche et al. 1995; Holliday et al. 1997).

Buchner et al. (1997), for example, recorded human multichannel visual evoked potentials to checkerboard stimuli and demonstrated a very early VEP with onset before 30 ms, peaking at ~45 ms, suggesting that it originated from V5. This VEP was independent of a second component located over V1 with onset around 50 ms and peaking around 70 ms. One explanation given by these authors for the discrepancy with previous studies showing longer latencies for a visual motion VEP was that the early peak located in the vicinity of V5/MT required such a high signal-to-noise ratio for detection that the small amplitude may have been undetectable in previous studies.

Thus the relative activation and temporal sequence of activation of regions such as V5/MT and V1 has been under debate with more recent literature demonstrating that visual signals project through visual cortex considerably faster than previously thought. Such temporal as well as functional analysis of visual networks is important for understanding how complex processing such as figure-ground segregation can be achieved. Hence this study will use TMS to elucidate the functional connectivity required for motion perception in particular, and in visual processing in general.

**TMS: tracing the visual signal**

TMS has been used to disrupt visual motion perception by stimulating either V5/MT alone (d’Alfonso et al. 2002; Hotson et al. 1994; Sack et al. 2006; Walsh et al. 1998, 1999) or V5/MT and V1 in the same participants (Anand et al. 1998; Beckers and Homberg 1992; Beckers and Zeki 1995; Hotson and Anand 1999; Silvanto et al. 2005b). However, this has resulted in considerable discrepancies in the timing of V5/MT stimulation critical to disruption of motion perception (see Fig. 1). It is possible that the discrepant results may be due to small numbers of participants or different stimulus parameters. Ffytche, Guy, and Zeki (1995) for example, have suggested that the speed of motion differentially activates V5 either before (for fast motion, 22°/s) or after (for slower motion, <6°/s) V1 activation. However, the TMS literature does not seem to support this. Those studies from Fig. 1 showing only a late period of V5 disruption used speeds ranging from 2 to 30°/s. Similarly, the studies finding an early period of disruption also demonstrated a relatively wide range of speeds (4.5–11°/s). Only two studies have demonstrated early and late critical time periods for disturbance of performance; in other studies all possible times of TMS were not probed in depth.

Nevertheless, an analysis of the V5/MT TMS literature indicates two main periods as critical for disruption of motion perception: an early period probably between 30 ms prior to and 30 ms post stimulus presentation and a later more variable period between as early as 70 ms through to ~200 ms post stimulus. Thus in light of the variation and anatomical reports of visual pathways that bypass V1, we sought to trace the timing and relative involvement of V5/MT and V1/V2 in detection of motion direction. Experiment 1 explored the effects of TMS on V1/V2 and V5/MT post stimulus onset over a large range of times, from motion onset to >200 ms later, and experiment 2 investigated in greater detail the effect of very early prestimulus onset of TMS over V1/V2 and V5/MT and possible eye-blink artifacts induced by TMS delivered prior to motion stimulation (Sack et al. 2006).

Different predictions of the time of TMS effects of V1/V2 and V5/MT emerge depending on the techniques and model of visual processing utilized. Most human VEP studies predict lower performance after disruption of V1 with TMS at ~50–55 ms and of V5/MT at ~60–80 ms post stimulus onset (Di Russo et al. 2002; Vanni et al. 2004b), although other electrophysiology (Buchner et al. 1997), and recent MEG results (Inui and Kakigi 2006) as well as anatomical results from primates (Sincich et al. 2004), suggest an early, direct thalamico-cortical signal to V5/MT. Bullier’s (2001) integrative feedforward/feedback model also provides for a second period of disruption in V5/MT to follow the early fast activation of V1 at ~50–55 ms. A synthesis of the preceding literature provides for a hypothesis of an early period of V5/MT processing within 30–40 ms that may be rapidly fed back into V1 within a further 6–7 ms. This presumably magnocellular driven signal may then combine with later arriving parvocellular signals in V1 after 100 ms (Klistorner et
al. 1997). Subsequent motion-related processing in V5/MT suggested by ERP to occur as late as between 160 and 220 ms (Probst et al. 1993), may represent feedback activity from other regions such as frontal cortex (Foxe and Simpson 2002; Ruff et al. 2006; Silvanto et al. 2006).

Our results provide the first evidence in humans for an early period of V1/V2 activity necessary for accurate motion perception after TMS at approximately the time of motion onset. A second critical period post stimulus onset at ~125 ms later was also evident in V1/V2 although this did not reach significance. We have also identified two periods when TMS over the V5/MT region inhibited motion perception. The first raises the possibility of a direct motion pathway bypassing V1, whereas the additional time period at ~160 ms may represent part of the feedforward/feedback loop between V5/MT+ and V1/V2 or alternatively feedback signals from frontal regions. Analysis of the types of errors made by participants allowed us to explore perception with TMS and suggests that stimulation of the V5/MT+ region, in particular at the same time as motion onset, suppresses the perception of motion. Last, we have also shown that TMS prior to motion stimulus onset has a profound effect on performance which we suggest may reflect visual anticipation or expectancy processing.

METHODS

Participants

Sixteen healthy volunteers [age = 24.4 ± 4.9 (SD) yr; 8 female] with normal or corrected-to-normal vision participated in experiment 1, which tested the effects of poststimulus TMS. Six of these participants (26.2 ± 3.3 yr; 2 female) returned for experiment 2, which explored TMS interference with prestimulus onset in V5/MT+. Early onset TMS over V1/V2 was also explored in five participants (26.2 ± 0.73 yr) who had completed experiment 1. Informed consent was provided by all participants, and the study had approval from the relevant ethics committees.

Visual display

Eighty black dots (dot size = 2 × 2 pixels, subtending 0.07°) moved coherently with a velocity of 1.75°/s at 60 cm, leftward, rightward, or presented as stationary within an imaginary square extending 4 × 4° on a gray background for between 53 and 105 ms on an iMac (Apple Computer) with a screen refresh rate of 95 Hz. One-third stationary trials, in addition to the two directions of motion previously used were included to allow investigation of the types of errors in perception made by participants. A relatively slow speed of motion was used to correspond with motion tuning in V1 cells, but perception of the motion signal would presumably still require V5/MT processing (fytche et al. 1995). Visual stimuli were presented centrally as Hotson and Anand (1999) found disruption of motion discrimination in ipsi- and contralateral hemifields with unilateral TMS to human MT. Prominent interhemispheric connections via corpus callosum for MT have been demonstrated, and these results are consistent with Greenlee, Lang, Mergner, and Seeger (1995), who found human subjects displayed bilateral hemifield reduction of motion discrimination after unilateral extrastriate brain lesions. This appears to differ from the primate literature, which suggests a contralateral correspondence between V5/MT hemisphere and visual hemifield.

TMS

TMS was delivered through the use of two MagStim 200 magnetic stimulators (peak magnetic field 2.2T) connected by a BiStim unit (MagStim, Whitland, UK) that controlled the pairs of pulses, which were delivered at 60% of maximum output. This disruption of a discrete population of neurons temporarily impairs function and the effects can last for between 50 and 250 ms (Ettinger et al. 1998; Kammer et al. 2005), although from our own piloting it seems likely that behaviorally significant TMS effects only last perhaps 40–60 ms. Sparing et al. (2005) measured phosphene perception for paired pulses with differing intervals and intensities and found that with inter-stimulus intervals of between 2 and 12 ms phosphene perception was facilitated. In no condition could the authors induce inhibition of phosphene perception, suggesting that the cortical mechanism behind phosphene induction is different to those behind intracortical inhibition and facilitation of motor cortex. Given that the brain structures involved with phosphene induction are believed to be the same as those involved with visual suppression (Kammer et al. 2005), we used paired pulses with an interstimulus interval of 5 ms.

Different shaped magnetic coils were used for V1/V2 and V5/MT stimulation. For V1/V2 stimulation the current study used a 90-mm round coil as this maximizes the chances of stimulating a larger portion of the occipital pole while possibly also stimulating some other visual areas such as V2 and even V3 (Kastner et al. 1998). For stimulation of V5/MT a 70-mm figure-eight coil was used as V5/MT occupies a much smaller region of cortex (Sack et al. 2006; Zeki et al. 1991). A figure-eight coil delivers a more focal area of stimulation than other coil geometries (Roth et al. 1991). The area of stimulation, which is focused from the intersection of the two rings of the coil, has been reported to be within an area 1 cm wide, and to a depth of ~2–3 cm (Beckers and Homberg 1992; Hotson et al. 1994; Jahanshahi and Rothwell 2000; Roth et al. 1991).

Location of stimulation

Before the TMS phase of the experiment, cortical localization was established through the induction of phosphenes. For V5/MT localization, a 3 × 3 grid of nine points, 1 cm apart was marked on a latex cap, centered 3 cm dorsal and 5 cm lateral to the inion. A relative lateralization of motion processing in the left hemisphere has been suggested by studies using TMS (Antal et al. 2003; Beckers and Homberg 1992; Stewart et al. 1999). Thus we used left V5/MT for all stimulation. Participants sat in a dim room with eyes closed while the stimulator intensity was gradually increased, and the coil was moved to each point on the grid. Participants were asked to indicate if a phosphene was seen and if so, to describe its shape, position, and movement. The location where the most distinctive phosphene perception was described was recorded for each participant, with the average position 3.1 cm dorsal and 4 cm lateral to the inion. For the purposes of this report, this area will henceforth be referred to as V5/MT+. Seven participants reported perceiving a moving phosphene, the rest a stationary phosphene. An identical procedure was followed for the localization of V1/V2 with the coil moved in 1- cm steps directly above the inion until the brightest stationary phosphene percept was described. On average, this position was 2.1 cm dorsal to the inion.

In cortical areas other than motor or visual cortical areas where physical responses (motor twitch or visual phosphene, respectively) are induced with TMS, it is more difficult to localize accurately and neuravigation techniques, which utilize functional imaging scans to accurately target previously identified regions (e.g., Sack et al. 2006) may be required. However, the use of phosphenes for localization in the visual areas of interest, allows a high degree of confidence that the TMS coil was accurately placed over the region of interest (Classen et al. 1998; Denslow et al. 2005; Schenk et al. 2005; Stewart et al. 1999). We would also argue that although use of a control stimulation site such as the vertex or an “off-V5/MT+” site would enhance the appearance of the current study design, the extra time and demands of sustained attention for participant comfort were not justifiable.
Procedure

Participants sat in a dimly illuminated laboratory 60 cm from the computer monitor. For both the pre-TMS psychophysics and the TMS sessions, participants sat in a portable massage chair with their face resting against a face cradle. This setup was used to minimize head movement, expose the scalp above occipital cortex for TMS application, and stabilize viewing of the computer monitor in front of the participant.

In a pre-TMS training session, participants were familiarized with the motion direction discrimination task, and the number of motion stimulus frames required to perform ≥80% correct was determined. Over the sample, this averaged 7.1 frames (75 ± 3.3 (SE) ms); however, in the TMS session, the task was adjusted for each participant based on their performance in the pre-TMS training session.

In the TMS phase of the experiment, participants were seated, and the TMS coil was located on a stand against the head above V1/V2 or V5/MT+. During the experiment, head position relative to coil position was monitored by the experimenter. In experiment 1, 15 trials in each of eight different stimulation onset asynchrony (SOA) conditions were presented with TMS applied randomly at different onset asynchronies from the visual stimulus of 0, 32, 63, 95, 126, 158, 189, and 221 ms (see Fig. 2). Participants were instructed to indicate as quickly and accurately as possible if they saw dots moving right, left or stationary.

Responses were recorded by keyboard press using a three-alternate forced-choice (3AFC) design. A space-bar was used to initiate the next trial, which appeared ~4 s later. In experiment 1, the task was run in two blocks, the order of which was counterbalanced across participants (0, 63, 126, and 189 ms in block 1; 32, 95, 158, and 221 ms in the other block).

Experiment 2 explored different SOA times, including prestimulus TMS for the same motion direction detection task used in experiment 1. Localization of V1/V2 and V5/MT+ was achieved with the same technique of inducing phosphenes as described in experiment 1. The pre-TMS session was repeated to determine stimulus duration required for 80% performance. Double-pulse TMS was applied with different SOAs than was used in experiment 1 (for V5/MT+ stimulation, pulses were triggered 105, 42, and 10 ms prior to motion stimulus onset and 10, 21, 42, 84, 147, and 263 ms post motion stimulus onset, although to reduce pulse dosage, each participant viewed only 6 or 7 of the 10 potential SOA conditions; for V1/V2 TMS, pulses was triggered 105, 42, and 10 ms prior to motion stimulus onset and 10 and 63 ms post motion stimulus onset).

In pilot experiments, null trials with no TMS were included among the regular TMS trials but were found to disturb participant performance unevenly due to expectation. Sham TMS was not included as a suitable control is not yet available that can replicate both the auditory and sensory experience of real TMS. As TMS was not expected to disrupt performance at all SOA conditions, intersubject control could nevertheless be made with these SOA conditions.

An important methodological concern relates to whether “dips” in performance at certain SOA times actually represent functional disruption of the specific cortical region rather than an artifact reflecting eye blink or muscle contraction. Previous reports have suggested that visual suppression somewhere around 30–60 ms prior to the visual stimulus onset reflects eye blink rather than specific TMS effects (Corthout et al. 1999; Sack et al. 2006). This explanation, however, seems unlikely given the long duration of eye blinks (200–300 ms) found in a comprehensive investigation of eye-blink physiology from VanderWerf et al. (2003).

RESULTS

Experiment 1: comparison of V1/V2 and V5/MT + TMS

For V1/V2 stimulation, one participant, and for V5/MT+ stimulation, two participants showed highly inconsistent performance across conditions and were not included in further analysis. It seemed likely that this substandard performance, particularly during V5/MT+ stimulation, was a reflection of eye or facial twitching that some participants experience with more anterior stimulation over V5/MT+.

V1/V2 stimulation

TMS to V1/V2 disrupted motion perception in a very early time window and also in a second, later period of time (see Fig. 3A). As the first and second dips in performance were separated by a period of >80% correct performance, it was assumed that the two dips represent different periods of processing and so could be analyzed separately. Mean performance at SOA = 0 ms was significantly different from SOA = 32 ms, t(14) = −3.8, P < 0.02, Bonferroni corrected; and SOA = 32 ms was not significantly different from SOA = 63 ms, t(14) = −1.8, P = 0.097—although a trend toward impaired performance was apparent.

Concerning the second, later period of processing, a repeated-measures ANOVA showed that the effect of TMS on V1/V2 over time (SOA = 63–221 ms) approached significance, F(14,5) = 2.21, P = 0.06. As is seen in Fig. 3A, the curve shows a trend toward reduced performance at SOA = 126 ms. Inspection of individual data suggests that the individual variation in the latency of dips in performance around this period of time may explain the failure to reach significance. Eleven of 15 participants demonstrate a decrease in performance with 8 having an effect at 126 ms, including 3 also at 95 ms, and 3 showing reduced performance only at 158 ms.
Error analysis

The use of a 3AFC procedure enabled analysis of the types of errors that characterized the dips in performance. Thus for trials with a moving stimulus, an error implies either an incorrect estimation of motion direction or a sensation of lack of motion. Figure 4 shows the types of errors made by participants across different SOA times for V1/V2 and V5/MT+ stimulation. Considering only trials where motion was presented, the figure illustrates the percentage of incorrect trials where no motion was perceived (i.e., participants reported a given trial as stationary rather than motion in the wrong direction).

Single sample t-tests were run to determine if the percentage of trials where no motion was perceived deviated significantly from a bias-adjusted baseline level. Given that there are two
types of errors possible, this baseline level should be chance (i.e., 50%). However, from the data it is apparent that there is a tendency for more responses to be classified as stationary than motion in the wrong direction. It is unclear if this is an inherent bias in the participants’ response or if this is an induced bias due to TMS across all SOAs. The bias-adjusted baseline was calculated from the mean score from three SOAs that did not show an increased number of errors (i.e., SOA = 63, 95, and 189 ms). For V1/V2 stimulation, the bias-adjusted baseline was 74.6%, whereas for V5/MT+ stimulation, the new baseline score was 72.9%. We then compared this adjusted baseline to SOAs for which TMS disrupted overall accuracy (i.e., for V1/V2 at SOA = 0 and 126 ms; for V5/MT+ at SOA = 0 and 158 ms). Bonferroni corrected alpha after making two planned comparisons was 0.025.

After TMS over V1/V2, the number errors reported as stationary at SOA = 0 ms did not differ from the bias adjusted baseline level (P = 0.80). Significantly more errors were reported as stationary at SOA = 126 ms (P < 0.02) as seen in Fig. 4A. By comparison, stimulation over V5/MT+ resulted in significantly more errors reported as stationary at SOA = 0 ms (P < 0.0001) but not at SOA = 158 ms (P = 0.88) as seen if Fig. 4B.

To determine if the quality of motion perceived differed when TMS was applied to V5/MT+ or V1/V2 at SOA = 0 ms (where detection accuracy was reduced for both sites), a t-test was run on percent errors reported as stationary for motion trials. A significant increase in stationarity was found for V5/MT+ compared with V1/V2 (P < 0.05).

Experiment 2: V1/V2 and V5/MT+ TMS interference at negative SOAs

Figure 5A shows that the early period of disruption to motion detection found in experiment 1 extends to negative SOA times as well. Repeated-measures ANOVA demonstrated significant inhibition of performance by TMS, F(4,4) = 6.90, P < 0.01. Dunn’s post hoc tests suggested that this was largely a result of TMS at SOA = −42 and −10 ms (P < 0.01). Error analysis demonstrated an increased number of errors classified as stationary compared with the bias-adjusted baseline level of 53.1% (calculated from mean error scores at SOA = −100 and 63 ms) with TMS at SOA = −42 ms (P < 0.002).

As can be seen from Fig. 5B, participants showed a similar pattern of early disruption with V5/MT+ stimulation as in experiment 1. With TMS prior to motion onset (SOA = −42 and −10 ms), accuracy was reduced, and at 105 ms prior to visual presentation onset, no effect in accuracy was seen. Repeated-measures ANOVA demonstrated significant inhibition of performance by TMS, F(5,8) = 13.17, P < 0.0001. Dunn’s post hoc tests showed this to be mainly due to TMS at SOA = −42 ms (P < 0.0001), SOA = −10 ms (P < 0.01), and SOA = 10 ms (P < 0.05). Error analysis demonstrated an increased number of errors classified as stationary compared with a bias-adjusted baseline level of 65.8% (calculated from mean error scores at SOA = −100, 42, and 84 ms) at SOA = −10 ms (P < 0.002), and a trend was apparent at SOA = 10 ms (P = 0.09).

Transient disruption of visual areas V1/V2 and V5/MT+ by TMS demonstrates a number of times critical for accurate perception of direction of motion. Both areas V1/V2 and V5/MT+ appear to contribute to accurate detection and discrimination of motion direction with the two regions showing both very early and later periods of TMS-induced disruption. Error analysis indicated that TMS at these critical times, in particular the early period with stimulation over V5/MT+, diminished the subjective perception of motion as indicated by more errors classified as stationary. Recent anatomical evidence would support the likelihood of an early period of performance inhibition in V5/MT+; however, the finding of such a period in V1/V2 was unexpected, having not been previously reported. The later period of disruption of motion perception uncovered by TMS for V1/V2 and V5/MT+ was expected based on previous reports. We have also found disruption of perceptual processing with TMS prior to motion stimulus onset that will be discussed in terms of expectation processing.
after considering the effects of TMS on V1/V2 and V5/MT+ separately.

**Two critical periods for motion perception in V1/V2**

Our results provide evidence for a very early activation of V1/V2 suggesting V1/V2 plays a role in the “gating” of feedforward projections involved in motion processing in V5/MT+. Our results are consistent with human MEG timing (Inui and Kakigi 2006) as well as primate single-cell physiology (Lamme and Roelfsema 2000). Although such an early time period for occipital TMS effects has been reported in TMS studies of nonmotion visual stimuli (Corthout et al. 1999, 2003), previous TMS studies of motion perception have not demonstrated such an early effect (see Fig. 1). This novel finding of early V1/V2 inhibition of performance may suggest a very fast signal through the more traditional geniculo-striate route to V5/MT+, or if considered in conjunction with the early V5/MT+ activation (discussed further in the next section), this early V1/V2 activation may represent fast feedback to V1/V2 following direct thalamic activation of attention via V5/MT+. Primate single-cell physiology has previously demonstrated that visual signals are sufficiently rapid to allow such feedback to occur (Girard et al. 2001). However, our data cannot decisively determine which hypothesis is most likely.

A later nonsignificant period of disruption (126 ms) is less likely to reflect initial feedback projections from V5/MT+ to V1/V2 given the rapidity of visual processing across the entire scalp (Foxe and Simpson 2002). Rather it may reflect either late arrivals of parvocellular signals (Klistorner et al. 1997) or feedback from other higher extrastriate or frontal cortical regions apart from V5/MT+ (Ruff et al. 2006; Silvanto et al. 2006). Despite the lack of significance, a number of participants’ individual data demonstrated an apparent interruption of performance at this later period between 95 and 158 ms, and in fact, this inter-participant variability in the timing of the TMS effects may explain the lack of group significance in this time window. Moreover it is apparent that despite the variation, the probability of this being a significant time for processing of motion by V1/V2 is increased by evidence of a corresponding increased number of errors reported as stationary rather than motion in the wrong direction.

The variation between subjects could be predicted following the use of the same TMS intensity (60% of maximum stimulator output) for all participants. Kammer et al. (2005) have shown that the time window for TMS-induced disruption is dependent on stimulation intensity. Thus given that participants would be expected to show variation in cortical excitability, the 32- to 63-ms variation in the critical period for TMS-induced disruption could be expected. Nevertheless, this does not alter our conclusion that V1/V2 is involved with motion processing at an early period and, at a second distinct period, potentially associated with re-entrant signals from V5/MT+ or from other areas of cortex.

**Two periods of V5/MT+ disruption also suggests a fast input and a second period of cortical feedback into extrastriate cortex**

The early TMS onset time reported here appears the most critical for functional activation of V5/MT+. At this time, an increase in motion discrimination errors and also by an increase in errors subjectively reported as having no motion and appearing stationary was found. Recent primate anatomical work would suggest this may reflect a direct input from LGN or the pulvinar, bypassing striate cortex (Sinich et al. 2004). Such a direct anatomical pathway would facilitate rapid processing of motion in the visual system. Girard et al. (1992) found that 80% of macaque V5/MT sites remained responsive after reversible cooling of V1, suggesting that there is a significant nonstriate projection into V5/MT.

On the other hand evidence for such a direct pathway to V5/MT+ has only been previously suggested in a few reports in human (Beckers and Zeki 1995; Buchner et al. 1997; Fink et al. 1996; Holliday et al. 1997). The current data do not allow speculation on whether a direct input into human area V5/MT+ traverses the pulvinar, superior colliculus, or LGN.

It is possible that a second period of disruption may reflect interruption of processing of the more traditional geniculo-striate pathway and from V1 through the dorsal stream to V5/MT+. However, although consistent with the ERP literature (Probst et al. 1993), this period (158 ms) is presumably too late to represent initial feedforward processing and may instead be associated with feedback signals from higher frontal cortical regions such as the frontal eye field or parietal cortex (Foxe and Simpson 2002; Ruff et al. 2006; Silvanto et al. 2006). Although it has been demonstrated that regions within frontal cortex are rapidly activated much earlier than this late period we report, there are numerous regions potentially involved with top-down processing, and these show a wide ranging activation range well within the range consistent with producing feedback into V5/MT+ in the time range we have shown (see for example Fig. 1B from Bullier 2001). In particular, Bar et al. (2006) have shown that orbitofrontal cortex was activated ~130 ms after object onset, but 50 ms before activation of object recognition areas in the ventral stream, suggesting that top-down frontal processes could indeed explain our TMS effect in V5/MT+ at 158 ms. Alternatively, given that V1/V2 appears to be necessary for accurate perception at 126 ms, the subsequent disruption of V5/MT+ at 158 ms may represent ongoing processing and updating through the V1/V2-V5/MT loop. This feedforward/feedback loop has been suggested to be important for visual awareness (Bullier 2001; Lamme and Roelfsema 2000; Laycock et al. 2006; Tong 2003).

Two periods of necessary processing in V5/MT+ for a motion-direction task has only been suggested in two previous TMS reports (d’Alfonso et al. 2002; Sack et al. 2006), although the theoretical implications of two discrete periods of activation were not discussed. On the one hand, Beckers and Homberg (1992) and Beckers and Zeki (1995) established disruptive effects at ~0 ms, whereas on the other hand, Anand et al. (1998), Sack et al. (2006), and Silvanto et al. (2005b) found the disruptive effects to lie ~100–150 ms.

Last, with stimulation of V1/V2 and V5/MT+ 221 ms post presentation of the motion display, a small but significant reduction in performance was seen. This very late interruption of performance was perplexing as times post 200 ms are unlikely to be necessary for bottom-up visual cortical processing. Two possibilities to explain this result immediately spring to mind. First, TMS may have directly or indirectly disrupted signals associated with motor responses that have been shown to be manipulable in the 200-to 300-ms range (Renault et al.
Experiment 2

A somewhat surprising result seen for both V1/V2 and V5/MT+ TMS was the profound disruption to normal motion-detection performance well before the motion stimulus even began. This dip in performance, which appears to be maximal 42 ms prior to motion onset is unlikely to be associated with direct visual processing of motion (as the visual system has not seen any visual stimuli yet) or with eye-blink artifact as discussed in the following text, but rather, as suggested by an anonymous reviewer, it is likely that this profound inhibition of accurate motion perception may be associated with TMS-induced disruption of expectation or attentional processing as participants were required to fixate on the monitor between each trial. Indeed it has often been demonstrated with fMRI that expectation of a visual stimulus activates frontal and parietal regions which then exert a top-down influence on visual areas (including V5/MT and V1) (Hopfinger et al. 2000; Kastner et al. 1999; Macaluso et al. 2003; Ress et al. 2000). In particular Taylor, Nobre, and Rushworth (2007) have recently shown that TMS over FEF during the cuing period of an attentional orienting task affected the evoked responses to visual stimuli and the ongoing neural activity recorded in anticipation of the visual stimuli.

Although not directly tested, we suggest that the prestimulus effect we found is likely to be dissociable from the TMS disruption to early visual processing evident with stimulation closer to motion onset. Although TMS at, for example, motion onset is still ~30 ms before the first visual signal reaches visual cortex, the disruption to a population of neurons may last between 40 and 60 ms (according to our pilot data), which would be long enough for the first frame of motion to be missed. Consequently, disruption to visual processing of motion per se could be expected at this time.

The long duration previously reported for eye blinks (200–300 ms) (VanderWerf et al. 2003) makes it likely that specific cortical effects rather than artifact explain TMS-induced disruption at 30- to 40-ms prestimulus found by Sack et al. (2006). Experiment 2 here demonstrated that stimulation over V1/V2 and V5/MT+105 ms prior to motion stimulus onset did not show disruption of performance as would be expected if eye blinks had been induced.

Significance of similarity between V1/V2 and V5/MT+ timing

A final issue to consider is whether the similarity in the performance curve between TMS to V1/V2 and V5/MT+ is artifactual or theoretically salient as we originally hypothesized. It is acknowledged that the use of the round coil for V1/V2 stimulation could spread as far as V5/MT+ particularly in participants with smaller head size, whereby the perimeter of the 90-mm round coil may have in fact rested near the V5/MT+ region. However, the second dip seen in performance of both V1/V2 and V5/MT+ argues for scientific reliability of all the results as this appears to be centered ~126 ms post motion onset for V1/V2 and 158 ms for V5/MT+ stimulation. Furthermore, an analysis of types of errors made for V1/V2 TMS compared with V5/MT+ TMS for the SOA = 0 ms condition depicted in Fig. 4 indicates a significant difference in perception between V1/V2 and V5/MT+. The error analysis actually discriminates the early dips in accuracy with V5/MT+ TMS as representative of a perception of no motion, whereas performance with V1/V2 TMS is closer to equal probability of a perception of incorrect motion or stationary. This would suggest that different cortical regions were in fact being stimulated. It may therefore be parsimonious to draw the conclusions outlined in the preceding text implicating fast visual processing and an associated rapid feedforward/feedback signal from V5/MT+ to V1/V2 that may facilitate and enhance transient attention. On the other hand, simultaneous activity in striate and extrastriate cortex has previously been suggested both in an early and a late period of time that roughly corresponds to the two periods established in the current study. Morand et al. (2000) discussed this in terms of the rapid feedforward/feedback signals in the visual system in which it is likely that a continuously updating feedback loop is required to perceive a rapidly changing visual scene.

Reconciliation of timing of visual processing

There remains some discrepancy within the literature as to the exact time course of visual processing in lower cortical areas although much of this may be understood as relating to the different techniques used for measuring cortical activity. Our results, using TMS, suggest a very early activation (within 32 ms of motion onset) of both V5/MT+ and V1/V2 is necessary for accurate perception. This time frame is consistent with some human VEP and MEG studies showing V1 onset within 30–50 ms and V5 onset as early as 30 ms (Buchner et al. 1997; ffytche et al. 1995; Inui and Kakigi 2006). Similarly, the intracranial monkey single-cell literature also suggests both V1 and V5 have a minimum latency of 20–40 ms (Chen et al. 2007; Kawano et al. 1994; Marcus and Van Essen 2002; Maunsell and Gibson 1992; Raiguel et al. 1989).

On the other hand, most visual-evoked potential (VEP) studies tend to show slightly longer onset times of ~50–55 ms over V1 and 60–80 ms over extrastriate cortex (Di Russo et al. 2002; Vanni et al. 2004b). Walsh and Cowey (2000) however, have argued it would be unlikely for TMS timing data to correspond with ERP times due to the time it takes for cortical activity to build up to the peak component. We would suggest, therefore, that single-cell physiology provides a better comparison of temporal activation with TMS than ERP data.

Our data are also consistent with a number of TMS studies showing an early period of activation of V5/MT+ at motion onset (SOA = 0 ms), although other reports have not uncovered such an early period of visual suppression (see Fig. 1). Of the four studies cited in our Fig. 1 that found only a later period of V5 disruption, none tested the early time intervals in question. On the other hand, the two studies which only found an early period of disruption only tested time intervals ≤100 or 160 ms, respectively, and thus may have “missed” any later
period of V5 processing. It is therefore suggested that the most likely factor influencing previous discrepancies in the literature may have simply been the range of TMS onset times tested.

Conclusions

It is now increasingly apparent that the visual system is equipped to process information extremely rapidly (Buchner et al. 1997; Foxe and Simpson 2002; current data). In addition, we have demonstrated that area V5/MT+—part of the dorsal projection stream to parietal cortex—is necessary for accurate perception of motion as early as, if not before, V1/V2 activation. TMS administered just before and at motion onset likely represents sustained TMS effects lasting at least until motion onset—possibly meaning that the V5/MT+ region is necessary to capture and direct attention to the first frame or so of motion. This is compatible with Bullier’s (2001) conception of a fast magnocellular feedforward/feedback loop through the dorsal stream being necessary for attentional capture. Such fast activation of V5/MT+ would allow rapid feedback signals into V1/V2 and would also be necessary for nonmotion visual processing not traditionally expected to require V5/MT+ activation, allowing for an initial global analysis of the scene before further processing through the ventral stream into infero-temporal cortex (Bullier 2001; Lamme and Roelfsema 2000; Laycock et al. 2006; Tong 2003).

REFERENCES


