COGNITIVE NEUROSCIENCE

Temporal characteristics of global motion processing revealed by transcranial magnetic stimulation

Laura K. Stevens, Paul V. McGraw, Tim Ledgeway and Denis Schluppeck
Nottingham Visual Neuroscience Group, School of Psychology, The University of Nottingham, University Park, Nottingham, NG7 2RD, UK

Abstract

The ability to detect the motion of objects is critical to survival, and understanding the cortical mechanisms involved in this process remains a key challenge in sensory neuroscience. A relatively new approach to this problem is to temporarily disrupt processing at specific cortical sites and measure the behavioural consequences. Several previous studies have shown that transcranial magnetic stimulation (TMS) of human visual area V5/MT disrupts global motion perception, but reports vary widely in the timescale of this effect. To resolve this issue we employed psychophysical techniques to investigate how discrimination of translational, rotational and radial global motion is affected by TMS. Prior to applying TMS we established baseline coherence thresholds for global motion perception. Adopting each observer's coherence level at threshold we examined how TMS delivered to V5/MT modulated performance. Importantly, we measured the influence of single-pulse TMS over a broad temporal range to reveal the fine temporal structure of the disruption profile for global motion perception. Results show that the disruption profile consisted of two distinct epochs during which global direction judgments were reliably impaired, separated by an interval in which performance was unaffected. The bimodal nature of the distribution profiles is consistent with feedforward and feedback processing between visual areas mediating global motion processing. We present a novel quantitative model that characterizes the contribution of each process to visual motion perception.

Introduction

In higher mammals, electrophysiological studies have shown that motion-sensitive neurons are first encountered in primary visual cortex (area 17 or V1; e.g. Hubel & Wiesel, 1968). These neurons project to specialized 'higher' visual cortical areas that pool information, allowing them to respond selectively to more complex image features (e.g. Van Essen & Maunsell, 1983). The response properties of V5/MT neurons reveal that this area is specialised for encoding translational global motion (Zeki, 1974; Newsome & Paré, 1988). Adjacent to area V5/MT is the medial superior temporal cortical area (MST), which contains neurons that respond selectively to more complex global motion representations, such as radial and rotational components of optic flow fields (Tanaka *et al.*, 1989; Duffy & Wurtz, 1991a,b).

In the human visual system, functional magnetic resonance imaging (fMRI) studies have demonstrated a homologue of the monkey global motion complex, often referred to as V5/MT+, thought to contain both MT and adjacent motion-sensitive areas including MST (Zeki *et al.*, 1991; Heeger *et al.*, 1999; Dukelov *et al.*, 2001; Huk *et al.*, 2002; Smith *et al.*, 2006; Beer *et al.*, 2009). It has been reported (Braddick *et al.*, 2001) that area V5/MT+, but not area V1, shows stronger activation to coherent global motion than to random motion, and

neural responses increase linearly with changes in the level of motion coherence (Rees *et al.*, 2000). However, the evidence on this issue is somewhat equivocal (McKeefry *et al.*, 1997; Smith *et al.*, 2006; Baumann & Greenlee, 2007).

Transcranial magnetic stimulation (TMS) has proved to be a useful tool for studying the underlying neural circuitry mediating motion processing in human vision. TMS studies have shown that selective disruption of V5/MT significantly degrades motion perception (Beckers & Homberg, 1992; Hotson *et al.*, 1994; Beckers & Zeki, 1995; Anand *et al.*, 1998; Hotson & Anand, 1999; Sack *et al.*, 2006; Laycock *et al.*, 2007). One of the main advantages of TMS is its temporal resolution, allowing the identification of task-specific temporal disruption windows for different cortical areas. Despite the impressive temporal resolution, the critical window of TMS disruption for area V5/MT in motion-based tasks is far from clear. Taken together, previous reports show substantial variation for the time window during which TMS at V5/MT can disrupt motion perception. Some have shown a relatively early period of disruption (e.g. 30–40 ms prior to motion onset), and others reported later time periods of disruption (up to ∼200 ms after motion onset) with a wide time range. Indeed a few have even reported more than one critical disruption period of V5/MT in the same study (see Laycock *et al.*, 2007 for review). This variability may partly be explained by differences in the visual stimuli used in TMS studies of motion perception. For example, the temporal responses of visual neurons are

heavily dependent on stimulus contrast (Albrecht, 1995; Reich *et al.*, 2001; Conway *et al.*, 2005). Furthermore, V5/MT neurons appear to saturate at relatively low contrast levels whilst those in early visual cortex saturate only gradually with stimulus contrast (e.g. Tootell *et al.*, 1995).

Although stimulus contrast can account for some variability in the reported timing of V5/MT disruption in other studies, there are several other contributory factors. These include relatively coarse sampling of the temporal disruption profile, variations in the type of motion stimuli used and the contribution of TMS-induced eye-blink artefacts.

In the present paper we investigated the contribution of each of these factors to the disruption profile for global motion perception when TMS is delivered to V5/MT. Preliminary data have previously been presented in abstract form (Stevens *et al.*, 2007).

Materials and methods

Participants

Five volunteers (mean age, 29.4 years; range, 23–38 years) participated in the study (MDB, KP, SB, RWD and PVM). All participants had normal or corrected-to-normal vision. PVM is an author while the other participants were naïve to the goals of the study. All participants reliably perceived phosphenes after single-pulse stimulation (1.95T) over the location of area V5/MT, as determined by Sack *et al.* (2006); see section on coil localisation. For all participants there were no contraindications on the Transcranial Magnetic Stimulation Adult Safety Screening questionnaire (Keel *et al.*, 2000), and written informed consent was given after participants were introduced to the equipment and procedure. All experimental procedures met the ethical guidelines of the School of Psychology at the University of Nottingham and adhered to the tenets of the *Declaration of Helsinki*.

Visual stimuli

Global motion random dot kinematograms (RDKs) were computer-generated using an Apple Macintosh G4 and displayed on a Viglen 22″ cathode ray tube monitor (mean luminance, 73.52 cd/m²; vertical refresh rate, 75 Hz), using custom software written in the C programming language. The nonlinear response of the monitor was linearised using the inverse function of the luminance response measured with a standard photometer (Photo Research Inc. PR650 Spectra Scan Colorimeter). Viewing was binocular at a distance of 192 cm.

Each RDK was composed of a sequence of image frames (frame duration 26.67 ms) which, when presented consecutively, produced continuous apparent motion. Each RDK frame comprised 100 non-overlapping black dots [diameter, 7 arcmin; drift rate (if sustained), 1.76°/s] presented within a circular aperture (diameter 6°) on a mid-grey background (luminance 73.52 cd/m²). The luminance of all dots in a RDK was set to be either 0.74 or 71.31 cd/m², resulting in Weber contrasts of 0.99 and 0.03, respectively. These two extreme values were chosen to maximize any potential differential affect of stimulus contrast on neural processing latencies, as measured with TMS. Properties of the dots were selected on the basis of pilot studies and previous investigations of global motion perception (Simmers *et al.*, 2003) to ensure that 'false matches' across successive displacements were negligible, and the correspondence problem minimized (Williams & Sekuler, 1984). Immediately prior to, and following, the presentation of each motion stimulus sequence, a prominent fixation cross was presented in the centre of the display to maintain stable fixation and prevent ocular tracking of the stimulus.

On the first frame of each RDK, dots were randomly positioned and were displaced by 2.81 arcmin on each subsequent frame. When a dot reached the edge of the circular display window it was repositioned at a random location within the aperture in the following frame. Dots were either constrained to move globally along a translational (up/down) trajectory (signal dots) or were displaced in random directions on each frame (noise dots). Each RDK was composed of a three-frame global motion sequence (80 ms) in which a fixed proportion of dots were signal dots; the sequence was temporally embedded between a pair of 10-frame (266.65 ms) random motion sequences to limit the disruptive influence of abrupt motion onset/offset transient responses (Newsome & Paré, 1988; Burr & Santoro, 2001; see also Supporting information, Appendix S1, for full details). The strength of the global motion signal, which we term coherence, could be varied by manipulating the relative proportion of signal and noise dots (Fig. 1). The visual stimuli used in conjunction with TMS were presented at a coherence level required to elicit a 75% correct response rate for each individual participant.

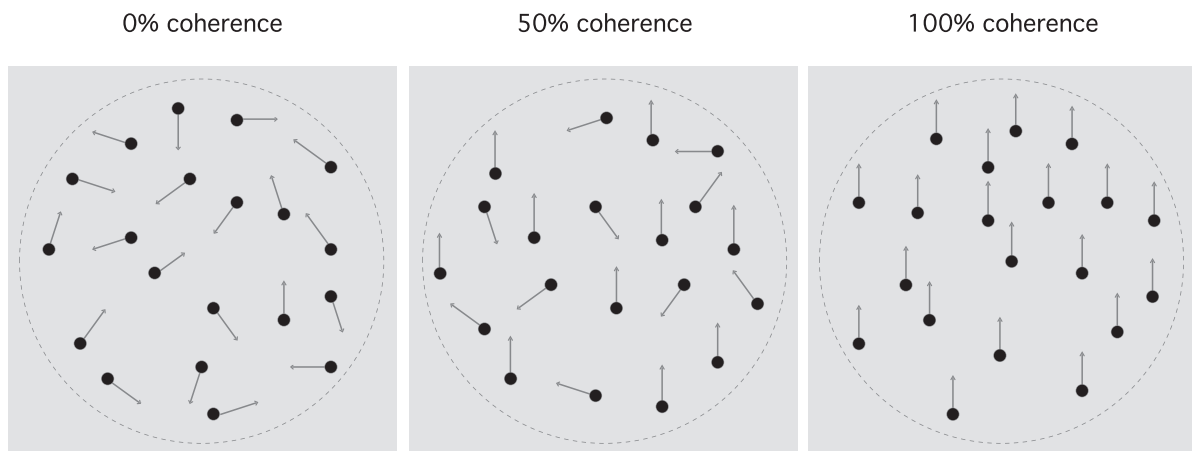0% coherence   50% coherence   100% coherence

FIG. 1. Schematic representation of the global motion stimuli used in the experiment. When coherence is 0% (left panel), all dots are noise dots and there is no net global motion. At 100% coherence (right panel), all dots are signal dots and are displaced along the same global trajectory, in this case upwards. At intermediate coherence levels (centre panel) a fixed proportion (e.g. 50%) of dots are signal dots and are displaced coherently while the rest are displaced in random directions.

On every displacement in the global motion sequence each dot had an equal chance of being selected as a signal dot (Newsome & Paré, 1988; Edwards & Badcock, 1994). For example, at a global motion coherence level of 10%, 10 dots would be displaced coherently over one frame transition but a new sample of 10 dots would be randomly selected to carry the signal into the next frame. At this level of motion coherence, the probability of a dot carrying the signal over two successive frames is 1%. This minimized local 'motion streak' cues (Geisler, 1999) and ensured that spatiotemporal information must be integrated over the entire display to judge global direction. The integration of local motion signals over an extended region of visual space is thought to be a key function of neurons in V5/MT with large receptive fields. The necessary integration of local motion signals renders the task ideal for ensuring functional activation of area V5/MT (Britten *et al.*, 1993).

In addition to simple translational global motion sequences we employed RDKs depicting rotational and radial global motion to ascertain whether the TMS disruption profile for complex components of optic flow is similar to that of translational global motion. Although one might not expect to find major differences in performance for the three types of motion, given that putative MST in humans (as in non-human primates) is adjacent to MT and the spatial resolution of TMS is quite coarse, these stimuli were used because they are well-suited to drive neurons within extrastriate motion areas (Morrone *et al.*, 2000; Smith *et al.*, 2006; Wall *et al.*, 2008).

Rotational and radial global motion stimuli were identical to translational stimuli in every respect other than signal dots were constrained to move coherently along either a rotational (clockwise/anticlockwise) or a radial (expanding/contracting) trajectory. For radial global motion, when a dot reached the centre of the display it was repositioned in a random spatial position within the display aperture in the following frame. Dot displacement magnitude was always constant across space, that is, dot displacement was not larger nearer the edge of the aperture, as it would have been for strictly rigid rotational or radial global motion. This allowed direct comparison of the three global motion types, in line with previous studies (Burr & Santoro, 2001; Simmers *et al.*, 2006).

Coil localisation

The coil position and orientation for area V5/MT stimulation was localised for each individual using a combination of standard functional and anatomical MRI measurements and phosphene-induction methods (see supporting information, Appendix S1, for full details).

TMS procedure

Participants sat in a dimly illuminated laboratory with their head stabilized in a custom-made wooden headrest, which minimized head movement. Biphasic TMS pulses were delivered with one of two custom 55-mm figure-of-eight coils, using a MagStim Rapid stimulator at 80% maximum output (2T; The MagStim Company Ltd., Whitland, UK). The coils had no plastic outer casing, allowing them to be placed in closer proximity to the cortical target site. The handle was parallel to the horizontal plane and pointed toward the back of the head (Hotson *et al.*, 1994; Sack *et al.*, 2006).

The delivery of TMS was time-locked to the vertical refresh rate of the monitor. Single pulses were delivered at a rate of one pulse per RDK stimulus presentation, with a 3-s intertrial interval between each response and the onset of the next RDK sequence. As is typical in psychophysical studies of visual motion, our approach was to obtain reliable estimates of performance by running several thousand trials for each main condition, for a sample of observers. TMS was delivered at 40 randomly interleaved stimulus onset asynchronies (SOAs; from −266 to +253 ms) relative to the onset of the global motion sequence (see Fig. 2), with 100 repetitions per SOA, for each type of global motion. Sessions were run in blocks of 50 RDK stimuli presentations, 40 with TMS, interleaved with 10 without TMS as a control measure. Each block of 50 trials lasted ∼4 min, well within the safety guidelines stipulating rates of safe stimulation (Wassermann, 1998).

The participants also took part in a separate control study to investigate the potential role of TMS-induced eye-blink artefacts (Corthout *et al.*, 2000, 2003; Sack *et al.*, 2006). Single-pulse TMS was delivered to the primary motor cortex (hand representation) of the right hemisphere while participants made the same visual direction discrimination judgments using translational RDKs. Global motion stimuli were identical to the visual stimuli described earlier and were presented at each observer's threshold coherence level. TMS pulses were delivered at a time when maximal disruption to performance was observed in the main experiment and all other TMS procedures were as set out before. Each participant completed two sessions, each comprising 40 RDK stimuli presentations: 20 with TMS, interleaved with 20 without TMS, to provide a baseline measure.
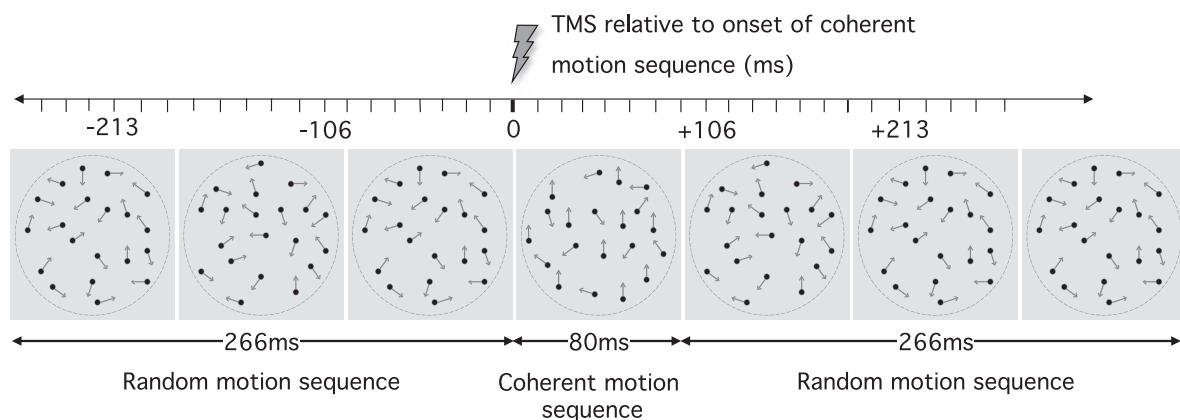

FIG. 2. Single-pulse TMS was delivered once per RDK stimulus presentation sequence at one of 40 times relative to the onset of the global motion sequence (ranging from −266 to +253 ms). The onset of the global motion sequence occurred at 0 ms (duration = 80 ms) and was preceded and followed by random motion sequences, each lasting 266 ms.

As it is known that the temporal response properties of visual neurons vary as a function of stimulus contrast (Shapley & Victor, 1978; Albrecht, 1995; Maunsell *et al.*, 1999), the TMS disruption profile was investigated further using global motion stimuli comprised of lower Weber contrast (0.03) dots (71.31 cd/m^2 dots on a 73.52 cd/m^2 background). All global motion stimulus parameters were identical to the translational RDKs described earlier. During the TMS sessions, visual stimuli were presented at each observer's coherence threshold. Thirteen different SOAs were investigated (from −253 to +226 ms relative to the onset of the global motion sequence), sampled at 40-ms intervals, and participants received 100 stimulations per SOA.

Each participant typically completed no more than two separate experimental sessions of 50 trials each per day (e.g. 40 with TMS, interleaved with 10 without TMS) and the order of testing was randomised across both sessions and participants. Given the large amount of TMS stimuli delivered per single participant, testing took place over a period of ∼6 months.

Results

The effect of TMS delivered to V5/MT whilst performing a translational global motion task was investigated at 40 different SOAs in 13 ms increments (−266 to +253 ms relative to global motion onset). In Fig. 3 the results for the 0.99 Weber contrast motion stimuli are plotted separately for each individual participant and the group mean data ($N = 5$) are also shown. Although there is some variability in the individual participant responses, all participants showed a decrease in performance (a reduction in the percentage of correct responses) on TMS trials. Indeed, the data for each participant clearly reveals two discrete temporal windows where delivery of a single TMS pulse modulates task performance. To quantify the location, height and width of each temporal window, the individual data were fitted with a bimodal function composed of the sum of two inverted Gaussian functions as follows:

$$y = \exp\left\{-[(x-a)/b]^2 \ln 2\right\}\varepsilon + \exp\left\{-[(x-d)/e]^2 \ln 2\right\}f + g \quad (1)$$

where x is TMS onset (in ms), a and d are TMS onsets that cause maximal disruption, b and e are the Gaussian bandwidths (half-width at half-maximum), c and f are the amplitudes (heights) of each Gaussian and g is the performance level for which TMS disruption is minimal. The group data and curve fit, derived from the means of the fitted parameter values, (Fig. 3, bottom-right panel) clearly illustrate two important findings. First, there exists a relatively broad temporal window [mean $b = 70.8$ ms; 95% confidence interval (CI) = ±25.3 ms] in which peak disruption of processing occurred before the global motion sequence onset (mean $a = -72.5$ ms; 95% CI = ±55.1 ms). Second, a narrower temporal window (mean $e = 30$ ms; 95% CI = ±17.7 ms) was also evident, with a smaller peak deficit occurring after the global motion sequence (mean $d = +145.6$ ms; 95% CI = ±27.2 ms). The mean peak performance deficit (c) for the early temporal window was −14.6% (95% CI = ±2.9%) and for the later window the corresponding value (f) was −7.2% (95% CI = ±1.3%), although some individual data showed larger performance deficits. The mean value of g was 75.8% (95% CI = ±3.2%).

To determine whether the early deficit could be attributed to a TMS-induced eye-blink or other muscular artefact, as has been suggested previously (Corthout *et al.*, 2000, 2003; Sack *et al.*, 2006), TMS was delivered to the right hemisphere primary motor cortex prior to the onset of the global motion sequence. For each participant the SOA that produced maximal disruption when TMS was delivered over V5/MT

was tested (mean −37.3 ms). As small sample sizes can increase vulnerability to violating the underlying assumptions of parametric tests (e.g. deviation from the assumption of normality is difficult to detect even when present), a slightly more conservative, non-parametric statistical test, the Wilcoxon signed-rank test, was used to assess differences in performance. Wilcoxon signed-rank tests (all two-tailed) confirmed that TMS delivered at this time reliably disrupted performance when delivered to visual cortex ($T_5 = 0$, $P = 0.04217$), but no significant difference in performance was found between trials in which TMS was delivered to the motor cortex and trials with no TMS at all ($T_3 = 2$, n.s.), as shown in Fig. 4. As an additional control, we used a 30-Hz video camera to record eye blinks of two participants (RWD and PVM) following a TMS pulse, for three conditions: (i) TMS of V5/MT, (ii) TMS of motor cortex, and (iii) sham TMS (coil discharged next to head but not placed on scalp). Each condition was run separately and consisted of 60 stimulations, analysed on a frame-by-frame basis. For each of the two subjects, the percentage of trials in which a blink occurred within a 2 s window following TMS onset was established for each condition: (i) 0% and 3.3%; (ii) 10% and 8.3%; and (iii) 5% and 6.6%. This result makes it extremely unlikely that the performance deficit observed when TMS was delivered to area V5/MT was the result of blink-induced artefacts.

The characteristics of the V5/MT disruption profile were investigated further using lower contrast (0.03 Weber contrast) translational global motion stimuli and the data are presented in Fig. 5. It can be seen that the early period of disruption persisted at lower contrast (mean $a = -69.5$ ms; 95% CI = ±41.3 ms and mean $b = 60.4$ ms; 95% CI = ±17.4 ms), with performance falling close to chance (mean $c = -23.1\%$; 95% CI = ±6%) when TMS was delivered ∼70 ms prior to stimulus onset. The location of the peak of the early period of disruption did not differ significantly for the two different stimulus contrasts ($T_5 = 6$, n.s.), but the magnitude of the performance drop was significantly greater at the lower contrast ($T_5 = 0$, $P = 0.04311$). The late deficit that occurred after stimulus onset had more similar magnitudes for the contrasts tested (for the lower contrast mean $f = -10.6\%$; 95% CI = ±2.9%), but was marginally greater at lower contrast and this difference reached significance ($T_5 = 0$, $P = 0.04311$). In addition the position of the late performance deficit was temporally shifted by ∼23 ms on average towards later SOAs for the lower contrast stimuli (mean $d = +168.2$ ms; 95% CI = ±9.8 ms and mean $e = 21.8$ ms; 95% CI = ±6 ms), and this effect was significant ($T_5 = 2$, $P = 0.04311$). The mean value of g for the 0.03 contrast RDKs was 75.5% (95% CI = ±1.5%).

The effect of TMS over area V5/MT on rotational and radial global motion sensitivity was investigated at 40 SOAs and the data are presented in Fig. 6. The temporal disruption profiles for these additional types of global motion are very similar to that found for translational motion and again consist of an early and a late phase of disruption. The mean peak disruption latencies, derived from Equation 1, occurred at −40.7 ms (95% CI = ±94.3 ms) and +144.1 ms (95% CI = ±81.2 ms) for radial global motion and −55.1 ms (95% CI = ±12.6 ms) and +126.4 ms (95% CI = ±49.2 ms) for rotational global motion (relative to global motion onset), with performance returning to a 75% correct response rate at ∼+50 ms relative to global motion onset.

Discussion

The results of this study clearly reveal two epochs during which delivery of a single TMS pulse to V5/MT disrupted global motion discrimination: an early period which was centred, on average,
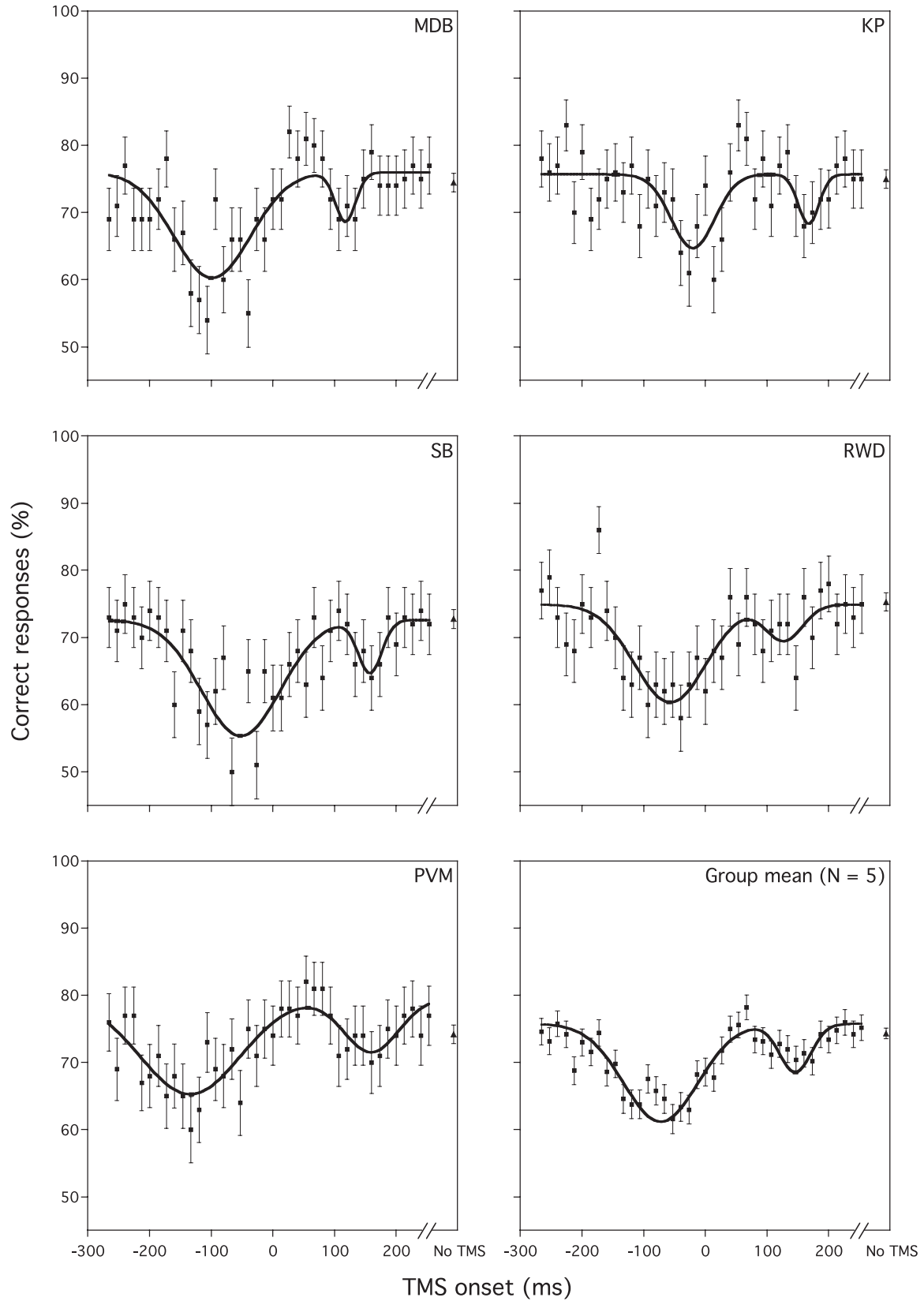
FIG. 3. Performance as a function of TMS onset asynchrony. The first five panels show individual data, the bottom right panel shows the group mean data ($N = 5$). Time 0 ms represents the onset of the global motion sequence. Performance during TMS trials (squares) was impaired relative to no-TMS trials (triangles, presented on the right-hand side of each plot) during two temporal windows, although there were individual differences in the onset and magnitude of the performance deficit. The solid lines show the best-fitting curves, derived from Equation 1, to the data and reveal, relative to global motion onset, a broad early performance deficit and a less marked late deficit. Error bars represent the SE of the percentage.
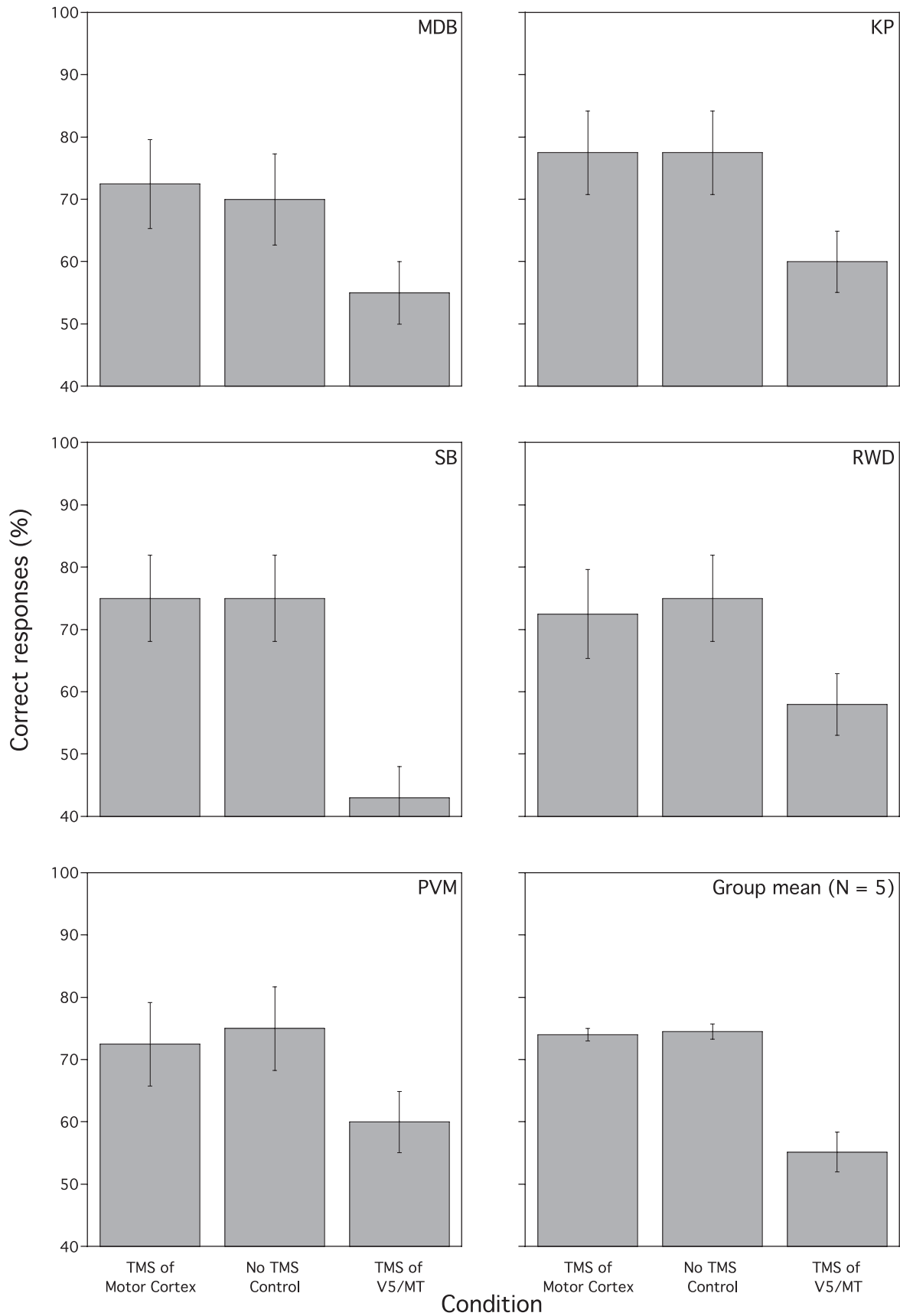
Fig. 4. The percentage of correct responses in baseline (no TMS) trials compared to when TMS was delivered over motor cortex and area V5/MT, prior to global motion onset. The first five panels show individual data and the bottom right panel shows the group mean data (*N* = 5). TMS was delivered at the SOA that resulted in maximal disruption, for each participant, when delivered over V5/MT. Error bars represent the SE of the percentage.
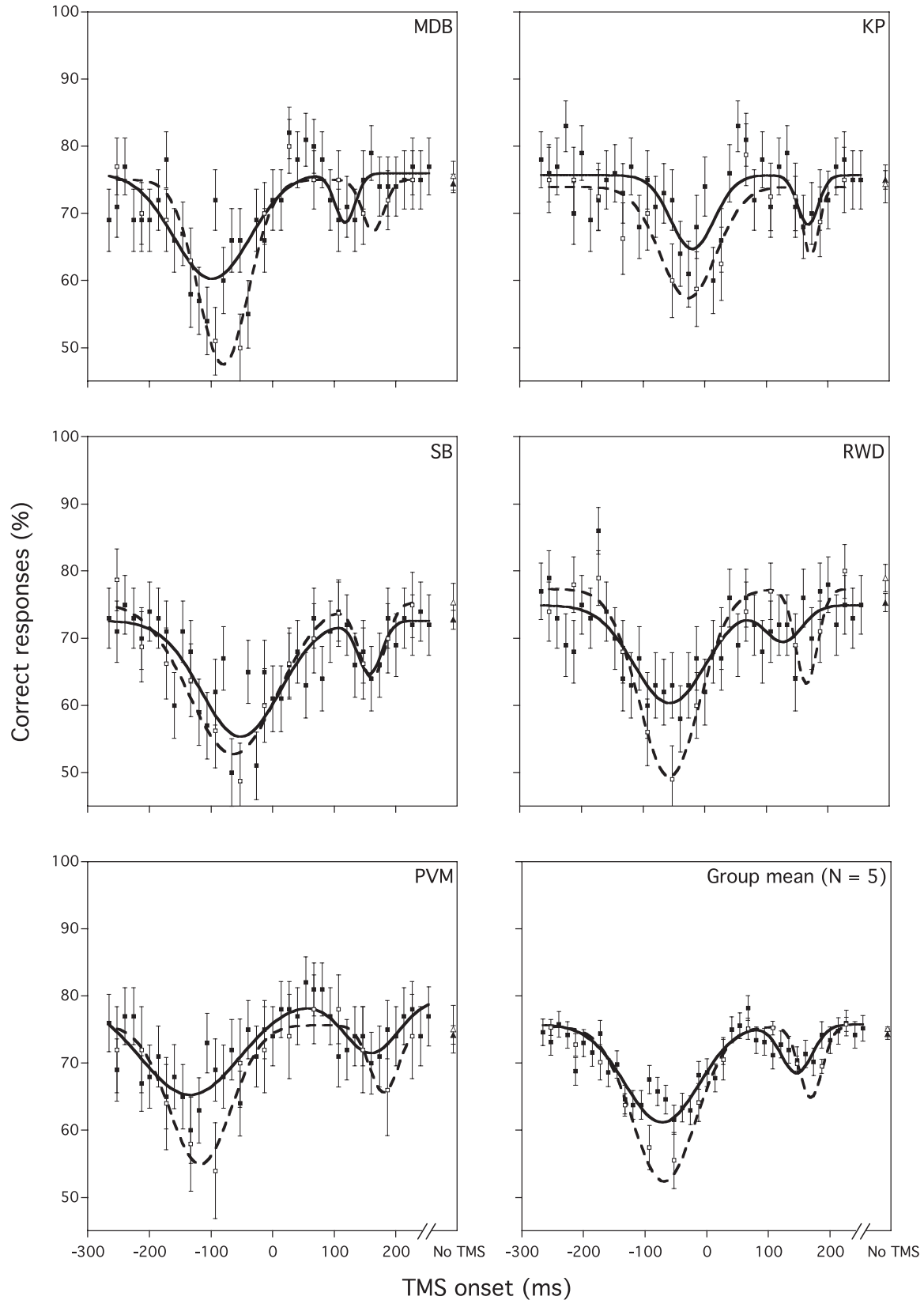
FIG. 5. The percentage of correct responses for high contrast (0.99 Weber contrast; filled symbols and solid line) and low contrast (0.03 Weber contrast; open symbols and broken line) global motion stimuli, fitted with Equation 1. The first five panels show individual data, the bottom right panel shows the group mean data ($N = 5$). Performance was disrupted in TMS trials (squares) compared to no-TMS trials (triangles, presented on the right-hand side of each plot) during an early (pre-global motion) and a late (post-global motion) temporal window. The peak performance deficit during the early temporal window was larger for lower contrast stimuli. The performance deficit during the later temporal window was of similar magnitude for the two stimulus contrasts, although the peak effect was temporally shifted towards greater SOAs for the low contrast stimuli. Error bars represent the SE of the percentage.

~60 ms prior to global motion onset and a relatively late period which occurred ~150 ms after global motion onset. These two disruption periods were separated by an interval during which TMS has little or no effect on performance. The early period was broader in its temporal
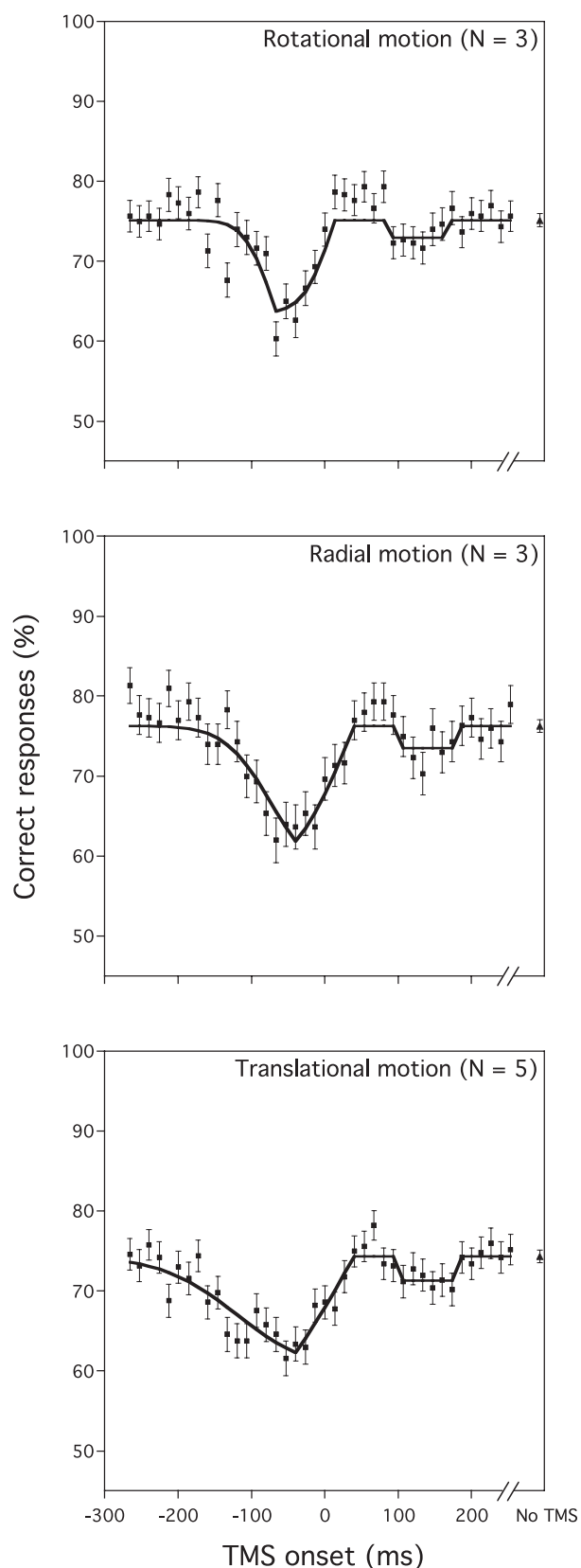
extent and TMS delivered at or around this time produced a deficit of approximately twice the magnitude of that in the late period. These disruption windows persisted at different stimulus contrast levels and were present for both translational and more complex types of global motion.

Several other studies have reported reduced performance on motion tasks when TMS is delivered to V5/MT, during either exclusively early (Beckers & Homberg, 1992; Beckers & Zeki, 1995) or late (Hotson *et al.*, 1994; Anand *et al.*, 1998; Hotson & Anand, 1999) windows. This is primarily because the range of SOAs at which TMS was delivered simply did not extend to both critical periods found in the present study, and/or the sampling of SOAs was too coarse to reveal the performance drop. Nonetheless, three previous studies also found two periods during which TMS of V5/MT impaired the ability to discriminate translational global motion direction (d'Alfonso *et al.*, 2002; Sack *et al.*, 2006; Laycock *et al.*, 2007). Although d'Alfonso and colleagues found some evidence for both an early and a late period of TMS disruption, relative to stimulus onset, the results exhibited considerable variability between the two participants tested. Furthermore they offered no explanation for the two temporal disruption windows found. Laycock *et al.* (2007) and Sack *et al.* (2006) were more comprehensive in their approach, but there are marked differences in methodology and interpretation between these studies and ours and these are considered in more detail below.

Sack and colleagues reported impaired performance when TMS was delivered 30–40 ms prior to, and 130–150 ms following, motion onset. The timescale of the later disruption period is very similar to our own findings, in terms of when it occurs and the temporal extent. They attributed the late deficit to the direct disruptive action of TMS on processes mediating integration of motion signals in V5/MT. Sack *et al.* (2006) and others (Corthout *et al.*, 2000, 2003), suggested that the early deficit was probably the result of a TMS-induced blink artefact rather than disruption of cortical processing. This was because TMS causes motor neurons to depolarize and can produce facial twitching that could potentially include ocular muscles. At first glance, blink duration (typically 200–300 ms) and the active suppression of visual information associated with blinks (~200 ms) appear consistent with the temporal extent of the early window (Ridder & Tomlinson, 1993; VanderWerf *et al.*, 2003). However, we have shown that this early deficit was absent for stimulation at a control site, even though it elicited considerable facial twitching. Moreover, when stimulus contrast was reduced the early performance deficit was even larger. If early disruption was the result of TMS-induced blinks, changing a stimulus characteristic (contrast) should not lead to more severe disruption. Although blinks cannot explain the early deficit, it remains to be seen whether other types of eye movements (e.g. saccades) induced by, or correlated with, TMS of V5/MT could account for this result. Sack *et al.* (2006) reported deficits of similar magnitude when TMS was delivered before and after motion onset. However, we found that the early deficit was always greater in magnitude than the late deficit for all three types of global motion tested.

Fig. 6. Group mean (*N* = 3) percentage correct responses for rotational (top panel) and radial (middle panel) global motion. For comparison, the group mean correct responses for translational global motion are re-plotted (bottom panel). Solid lines represent the best-fitting curves derived from applying a simple feedforward–feedback model of TMS disruption to the data (see Equations 2, 3 and 4 and the text for further details). In keeping with the previous data, performance for each motion task, relative to a no-TMS baseline, was disrupted during an early and a late temporal window. The disruption profiles for each type of global motion show very good agreement. Error bars represent the SE of the percentage.

Laycock *et al.* (2007) reported reduced performance with TMS at SOAs between −42 and +10 ms, and +158 ms, relative to motion onset. However, aspects of their study make interpretation of the results problematic. In the first experiment, the duration of the global motion stimulus was set at a level designed to produce 80% correct performance. Their data show that this threshold level is unstable, with the vast majority of participants performing considerably better than this on the task. As they neglected to measure baseline thresholds (i.e. trials without TMS) during the experiment, it is difficult to separate shifts in participants' baseline performance from TMS-induced deficits unless the latter are very large. To highlight this point, the late disruption was not replicated in a second experiment despite stimulation of the same site (V5/MT) at the same latency (158 ms after motion onset). They do, however, report a large performance deficit when TMS was delivered before and just after motion onset. Unfortunately, the authors do not specify SOAs were defined with respect to their double-pulse technique.

Laycock *et al.* (2007) proposed two alternative accounts for the early disruption, neither of which is based on blink artefacts. First, they suggest that TMS disrupts the rapid propagation of motion signals, via a direct pathway from the lateral geniculate nucleus (LGN) to V5/MT, which bypasses V1. Primate studies have provided anatomical and physiological evidence of projections from subcortical structures such as the LGN directly to V5/MT (Girard *et al.*, 1992; Sincich *et al.*, 2004). Disruption of this fast motion pathway (ffytche *et al.*, 1995, 2000; Buchner *et al.*, 1997), if it exists in humans (see Anderson *et al.*, 1996), would be consistent with reduced performance just after motion onset. They then propose that earlier deficits, found prior to motion onset (42 ms in their case), are unlikely to be associated with motion processing *per se*, but reflect disruption of attention or expectation. Although disruption of endogenous (sustained, voluntary and top-down) attention may lead to some deterioration in performance, it is unclear why this would be restricted to the earliest SOAs tested. Indeed, a general TMS-induced cognitive impairment could not easily explain why performance in the current study returned to baseline levels when TMS was applied at certain SOAs. Although it is possible that TMS prior to motion onset engages exogenous (transient, involuntary and stimulus-driven) attention and this temporally distracts participants, the fact that disruption was absent when stimulation was delivered over a control site is problematic for a simple explanation based on expectancy and attention. Laycock *et al.* (2007) also differ from Sack *et al.* (2006) in their interpretation of the late disruption window. They speculate that this deficit is associated with disruption of feedback signals from higher cortical regions (e.g. top-down processing from parietal cortex and frontal eye fields) to V5/MT.

Here we present a parsimonious and physiologically plausible scheme of how TMS influences direction perception, at different time intervals relative to global motion onset, based upon a simple feedforward–feedback model. In essence the model assumes that the late performance deficit is due to direct TMS interference of processing in V5/MT and early disruption reflects backward propagation of TMS from V5/MT to V1. The main features of our explanation are outlined schematically in Fig. 7 and proceed as follows. Following a period of global motion (80 ms, in this study) the first cortical stage of visual analysis occurs in V1 (Hubel & Wiesel, 1968). To encode global motion direction, V5/MT neurons integrate local motion over successive frames, thereby collating information over the entire extent of the coherent sequence (80 ms). Taking these estimates into account and considering a feedforward model of information transfer, TMS of V5/MT should disrupt motion signals sometime after motion onset. The precise time at which disruption occurs will depend on response latencies of neurons at each of the precortical and cortical visual areas involved. Estimates of response latencies in primates vary widely from study to study (for reviews see Bullier, 2001, 2003) but typically fall within the range ∼25–120 ms for V1 and ∼45–130 ms for V5/MT. Furthermore, as the temporal responses of visual neurons can be influenced by external factors (e.g. stimulus contrast), providing a definitive estimate of the response latency of different visual areas in humans is not straightforward. Nonetheless if the late deficit reflects impairment of ongoing motion processing in V5/MT, and the deleterious effect of a TMS pulse is initially maximal and falls exponentially to zero over time (Walsh & Cowey, 2000), then disruption in performance can be quantified by the following equation:

$$D_{\text{late}} = \begin{cases} \sum_{n=1}^{3} \exp\{-[(x-a-b-26.67n)/c]^2 \ln 2\}d & x \leq a+b+80 \\ 0 & x > a+b+80. \end{cases} \quad (2)$$

where x is TMS onset (in ms), a is the response latency (in ms) of V1 (i.e. the time at which visual evoked global motion activity first arrives at V1), b is the latency (in ms) of the feedforward connection between V1 and V5/MT, n is frame number (either 1, 2 or 3) containing coherent global motion, c is the half-life (persistence) of the TMS-induced V5/MT 'noise' and d is a scaling factor.

To explain the early deficit we adopted a novel, but somewhat speculative, feedback-based approach. It is known that the effects of TMS rapidly spread to functionally connected cortical areas, as demonstrated in studies combining TMS with fMRI (Bohning *et al.*, 1999), PET (Paus *et al.*, 1997) and EEG (Ilmoniemi *et al.*, 1997). For example, a combined TMS/EEG study reported a response in right occipital cortex 20 ms after TMS was delivered to left occipital cortex (Ilmoniemi *et al.*, 1997). As feedback connections exist between V5/MT and V1 (Maunsell & Van Essen, 1983; Shipp & Zeki, 1989), and feedforward and feedback fibres show similar conduction velocities (Nowak *et al.*, 1997), one prediction is that the effects of TMS delivered to V5/MT will propagate to V1 via feedback connections, arriving sometime later. If it takes roughly the same time for information to travel from V1 to V5/MT as it does for recurrent signals to return in the opposite direction, then the disruptive influence of TMS-induced feedback 'noise' in V1 can be expressed as follows:

$$D_{\text{early}} = \begin{cases} \sum_{n=1}^{3} \exp\{-[(x+b-a-26.67n)/e]^2 \ln 2\}f & x \leq a+b+80 \\ 0 & x > a+b+80 \end{cases} \quad (3)$$

where x and a are the same parameters as those used in Equation 2, b is the latency (in ms) of the feedback connection between V5/MT and V1 (in this case identical to the feedforward latency), n is frame number (either 1, 2 or 3) containing coherent global motion, e is the half-life (persistence) of the TMS-induced V1 feedback 'noise' and f is a scaling factor.

Consequently the total TMS-induced disruption for a given TMS onset is then found by combining Equations 2 and 3 to give:

$$D_{\text{total}} = D_{\text{late}} + D_{\text{early}} + P_{\text{baseline}} \quad (4)$$

where P_{baseline} is the performance level obtained on the global motion direction task when TMS is absent (ideally ∼75% correct). In this relatively straightforward feedforward–feedback model the disruption produced by a TMS pulse is simply a function of the degree of temporal overlap between the presence of TMS-induced 'noise' and global motion-evoked activity within a particular visual area.
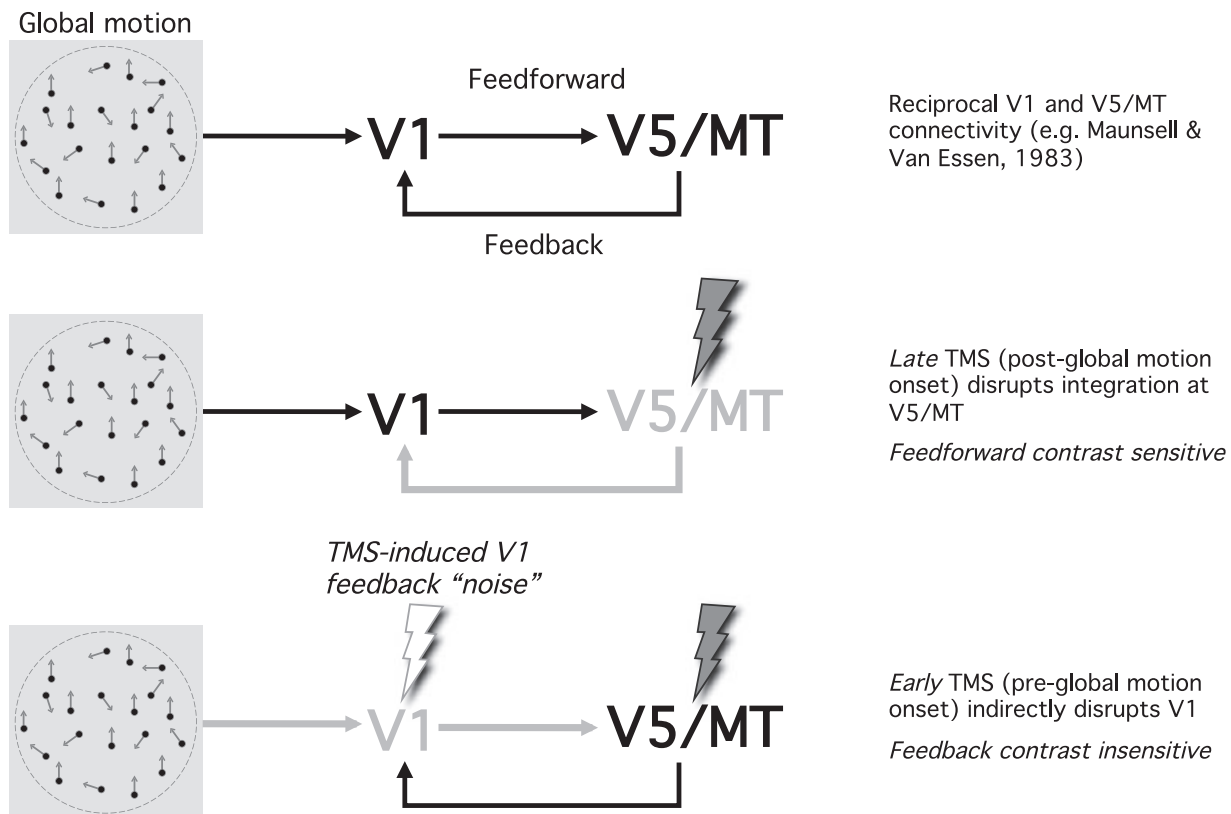
FIG. 7. An outline of how TMS could disrupt global motion perception within a simple feedforward–feedback framework. During presentation of a coherent motion sequence V1 neurons are activated and then the activation propagates through the visual cortical hierarchy, arriving at area V5/MT sometime later. Disruption of global motion processing in area V5/MT (late temporal window) occurs when the presence of TMS-induced neural 'noise' coincides with the arrival of task-related activity at area V5/MT, and motion perception is consequently disrupted. Disruption of processing in area V1 (early temporal window) occurs when TMS-induced neural activity is transmitted from area V5/MT back to area V1, via recurrent feedback connections. The arrival of indirect V1 feedback 'noise' disrupts the local motion signals being processed at the level of V1.

Although few studies have addressed the issue of TMS persistence (embodied by parameters c and e in Equations 2 and 3), what little evidence there is suggests that the effects of a TMS pulse on visually evoked activity, albeit in feline cortex, can last for up to 200 ms (Moliadze *et al.*, 2003).

Applying the model to the mean data obtained for the three types of global motion (solid lines in Fig. 6) illustrates that it readily characterizes the periods of early and late TMS disruption [mean values of a, b, c, d, e and f are 30.1 ms (95% CI = ±20.9 ms), 74.6 ms (95% CI = ±3.3 ms), 79.4 ms (95% CI = ±103.9 ms), −3 (95% CI = ±2.3), 3.9 ms (95% CI = ±5.8 ms) and −3.5 (95% CI = ±3), respectively and the mean r^2 value of the fits = 0.79 (95% CI = ±0.16)]. The estimated values of a and b are comfortably within the range of visual latencies in monkey cortex (Bullier, 2001, 2003) and similar to onset latencies in humans derived from EEG (Di Russo *et al.*, 2001) and magnetoencelphalography (Inui & Kakigi, 2006).

Importantly, the feedback-based explanation of the early deficit predicts that the peak of the disruption window will be less sensitive to contrast-mediated changes in neural response latency as, unlike the feedforward connections, the propagation of TMS disruption to V1 will be unaffected by changes to stimulus characteristics. The results in Fig. 5 support this, as there was no consistent shift in the peak of the early deficit but all participants showed a shift for the late deficit for low-contrast stimuli. Indeed, one might expect the peak of the late deficit to be most strongly affected by stimulus contrast if contrast-dependent latency effects are, to some extent, cumulative along the feedforward visual pathway. Furthermore, when the stimulus contrast was reduced the magnitude of the performance deficit during the early window increased but that of the late period was less affected. This is also compatible with the feedback mechanism in the proposed model; as contrast response functions of V1 neurons are typically shallower and saturate at higher contrasts than those in V5/MT (e.g. Tootell *et al.*, 1995), it is reasonable to suppose that V1 will be much less visually responsive to the lower contrast than the higher contrast RDK and thus more susceptible to disruption by TMS-induced feedback 'noise'. However, an alternative explanation based on proactive or forward masking of visual information in V5/MT by TMS-induced phosphenes may, in principle, accommodate this contrast-dependent effect. The larger performance deficit found during the early window for the low contrast stimuli would be consistent with this notion, as interference might be stronger on weaker stimuli (we are grateful to an anonymous reviewer for this suggestion). This explanation does not require the existence of a feedback loop from V5/MT to V1, but necessarily assumes that moving phosphenes elicited by TMS persist and interfere with visual motion signals arriving subsequently in V5/MT. Although this could explain some aspects of the data it is important to note that only one participant readily perceived moving phosphenes (RWD), while the others saw static phosphenes, as in other studies (see supporting information, Appendix S1). Whether induced phosphenes are an epiphenomenon of the disruptive visual effects of TMS or a cause of them has yet to be determined.

Another notable aspect of the data is that the early deficit is not only greater in magnitude, but it occurs over a broader range of SOAs than the late deficit. This is likely to reflect the fact that TMS delivered much later than stimulus onset provides sufficient time for cortical network dynamics to recover and restabilise. Furthermore, TMS delivered after V5/MT has integrated local motion signals is unlikely to have any effect on motion perception as the relevant information will have been transmitted to the next stage of visual analysis. Beckers & Homberg (1992) noted that the disruption window is broader when TMS is delivered to V1 than to V5/MT. They concluded that this occurs because TMS of V1 disrupts not only local motion signals at V1 but also the arrival of feedback signals from V5/MT. Here we show a similar effect but, critically, one that arises without any change in stimulation site. Although a role for feedback modulation of V1 from higher visual areas, in monkeys and humans, has been suggested previously (e.g. Hupe *et al.*, 1998; Pascual-Leone & Walsh, 2001; Super *et al.*, 2001; Ro *et al.*, 2003; Heinen *et al.*, 2005; Ruff *et al.*, 2006), a crucial prediction of the model outlined in Fig. 7 is that V1 processing should always be impaired when TMS is delivered to V5/MT, at an appropriate time, due to feedback connections. This prediction may be testable by employing a task that requires only V1, and not V5/MT, but devising such a precise task remains a challenge for future research. Indeed, emerging evidence suggests that many tasks expected to depend on the ventral stream also engage dorsal stream processing (e.g. Laycock *et al.*, 2009).

The TMS disruption profiles established in our optic flow (rotational and radial global motion) conditions are clearly similar to those found for translational global motion. Given the spatial resolution of TMS and the propagation of TMS effects to interconnected cortical areas, it is likely that the fidelity of motion signals are compromised in the entire V5/MT+ complex.

In summary, we have characterized comprehensively the temporal disruption profile for global motion perception when single-pulse TMS is delivered to V5/MT. Our results provide some of the clearest evidence to date for the existence of two distinct epochs during which global direction judgments can be reliably disrupted. We interpret these data in relation to known cortical circuitry, with a particular emphasis on the role and timing of feedforward and feedback connections between visual areas mediating motion processing.

Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix S1. Supplementary methods.

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Abbreviations

CI, confidence interval; fMRI, functional magnetic resonance imaging; RDK, random dot kinematogram; SOA, stimulus onset asynchrony; TMS, transcranial magnetic stimulation.

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