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Highlights

Q2 • Lateral and feedback inputs in V1 contribute to encoding spatiotemporal regularity. • TMS on V1 suppressed the facilitation effect of spatiotemporal regularity. • TMS at different time windows may selectively suppress lateral and feedback inputs. • With randomized predictor orientation TMS disruption was greater on feedback inputs.

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ROLE OF LATERAL AND FEEDBACK CONNECTIONS IN PRIMARY VISUAL CORTEX IN THE PROCESSING OF SPATIOTEMPORAL REGULARITY – A TMS STUDY

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Abstract—Our human visual system exploits spatiotemporal regularity to interpret incoming visual signals. With a dynamic stimulus sequence of four collinear bars (predictors) appearing consecutively toward the fovea, followed by a target bar with varying contrasts, we have previously found that this predictable spatiotemporal stimulus structure enhances target detection performance and its underlying neural process starts in the primary visual cortex (area V1). However, the relative contribution of V1 lateral and feedback connections in the processing of spatiotemporal regularity remains unclear. In this study we measured human contrast detection of a briefly presented foveal target that was embedded in a dynamic collinear predictor-target sequence. Transcranial magnetic stimulation (TMS) was used to selectively disrupt V1 horizontal and feedback connections in the processing of predictors. The coil was positioned over a cortical location corresponding to the location of the last predictor prior to target onset. Single-pulse TMS at an intensity of 10% below phosphene threshold was delivered at 20 or 90 ms after the predictor onset. Our analysis revealed that the delivery of TMS at both time windows equally reduced, but did not abolish, the facilitation effect of the predictors on target detection. Furthermore, if the predictors' ordination was randomized to suppress V1 lateral connections, the TMS disruption was significantly more evident at 20 ms than at 90-ms time window. We suggest that both lateral and feedback connections contribute to the encoding of spatiotemporal regularity in V1. These findings develop understanding of how our visual system exploits spatiotemporal regularity to facilitate the efficiency of visual perception. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: primary visual cortex, spatiotemporal regularity, transcranial magnetic stimulation, lateral connection, feedback connection.

INTRODUCTION

Despite its apparent complexity, natural visual signals are constrained by various statistical regularities. One such regularity is spatiotemporal, whereby objects and scenes around us often occur and move in statistically predictable ways to create a stream of visual inputs which are spatially and temporally coherent (Guo et al., 2004; Hall et al., 2010); such as the trajectory of a car moving on the motorway or an apple falling from a tree. Given our rich experience of these common geometric regularities acquired through evolution and development, our visual system should incorporate and properly exploit them to facilitate visual perception and associated neural computation. For instance, our visual system could expect that a particular feature will be presented at a particular location and time because of the spatial and temporal structure of the current scene, and prior knowledge of the spatiotemporal regularities in the visual world.

This hypothesis has been tested by a number of recent empirical studies using simplified dynamic visual stimuli to mimic natural spatiotemporal regularity (for reviews, see Nobre et al., 2007; Schwartz et al., 2007). When presenting a dynamic stimulus sequence comprising four collinear short bars (predictors) appearing consecutively toward the fovea followed by a target bar at fixation (see Fig. 1 for an example), we found that participants' orientation judgments of the target bar were biased toward the orientation of the predictors. Such bias was much stronger for the predictors were in a highly ordered and predictable sequence than in a randomized order (Guo et al., 2004). Participants also needed less contrast and showed quicker reaction times to detect the foveal target embedded in this predictable spatiotemporal stimulus structure, than in a randomized predictor-target sequence or when presented in isolation without any predictors (Hall et al., 2010). Clearly, the spatiotemporal regularity of the external world is used to interpret our perception of current local visual inputs.

How does our brain compute this spatiotemporal regularity? Using a similar dynamic stimulus structure, recordings of event-related potentials have observed shorter peak latencies of early components (N1/P1) for the target embedded in the predictable predictor-target sequence than in the randomized sequence or presented alone (Pollux and Guo, 2009; Pollux et al., 2011; Hall et al., 2013), suggesting that the spatiotemporal regularity is computed at the early stage of visual perception. Single-cell recordings further confirmed that neurons in primary visual cortex (area V1), the earliest cortical stage in visual processing, is capable of encoding such natural regularity (Guo et al.,

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Abbreviations: ANOVA, analysis of variance; CRF, classical receptive field; FP, fixation point; TMS, transcranial magnetic stimulation.

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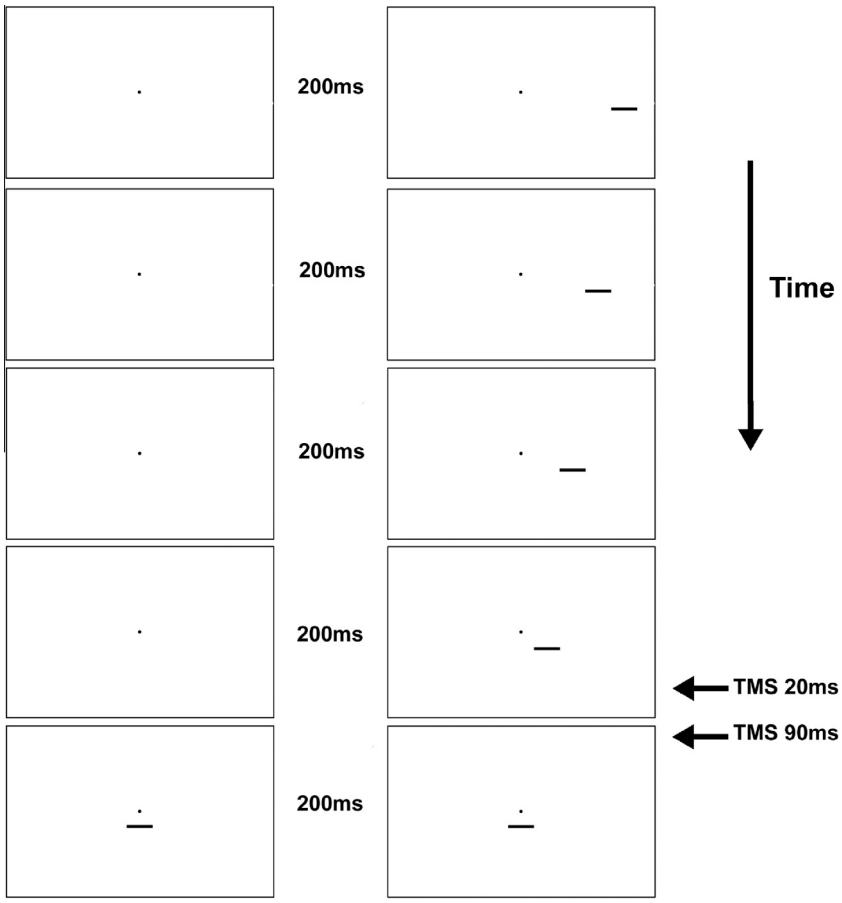

Fig. 1. Demonstration of target alone and predictable sequence used in this experiment.

2007). The responses of most V1 neurons were significantly modulated by the dynamic predictors presented prior to, and distant from, the target stimulation in their classical receptive fields (CRFs). The last predictor in the predictable stimulus sequence presented just outside of the CRF could elicit early neuronal responses for around half of the recorded neurons. Information Theoretic analysis further revealed that these early responses conveyed more mutual information about the predictors' orientation which is available for the neurons to compute the orientation of the oncoming target (Guo et al., 2007). Taken together, it seems that the neural computation of spatiotemporal regularity could start as early as area V1, in which the output of a neuron critically depends on the interaction between current CRF visual input (i.e. the target) and prior information about stimulus statistical regularities (i.e. extra-CRF information about the predictors) processed by other neurons earlier.

As visual neurons are typically embedded in an extensive neural network with feed-forward, lateral and feedback connections (e.g. Albright and Stoner, 2002), the source of this prior information may be the lateral connections within V1 or feedback connections from higher areas. For instance, those V1 neurons with similar orientation preferences, but whose CRFs are arrayed along the predictor trajectory, could communicate with each other through lateral connections about the order of different predictors' appearances. Hence, the spatiotemporal regularity signals over a range of spatial positions could be pooled effectively to inform the recorded V1 neuron about the target onset. Alternatively, neurons in higher cortical areas (e.g. motion-sensitive area V5 and V6, or even frontal and parietal cortex) with larger CRFs could respond to the early predictors and encode the trajectory of the dynamic predictor sequence. Such encoded information could be used by these neurons to make a prediction about the location and timing of the target onset. This predictive cue could then be back-projected to the recorded V1 neuron before the target onset as early neuronal responses such as those observed in Guo et al. (2007). From our current data it is impossible to infer which of the two connections is more influential. In other words, it is unclear how much of the facilitation gained from a spatiotemporal regular structure relies on information from lateral connections in V1 itself or on feedback information from higher brain areas (given the relatively simple stimulus structure and motion trajectory, V5 could be more heavily involved in the processing of this dynamic predictor-target sequence in comparison with other higher brain areas).

Transcranial magnetic stimulation (TMS) is a relatively reliable investigative tool which can be used to study

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functional connectivity for V1 neurons (Walsh and Cowey, 2000). Single-pulse TMS delivered at different time windows after the stimulus onset can transiently disrupt feedforward or feedback processing in V1. Typically, a TMS pulse over the occipital cortex around 100-ms (often between 80 and 120 ms) post-stimulus onset will maximally suppress participants' conscious detection performance of a small grating or single letter presented within the visual hemifield contralateral to the stimulated cortical hemisphere, at a location corresponding to V1 retinotopic organization (e.g. Amassian et al., 1989; Corthout et al., 1999; Sack et al., 2009; de Graaf et al., 2011). This time window is interpreted as consistent with the activity of feedforward processing in V1 neurons (see also Kammer, 2007; de Graaf et al., 2012).

In addition, a number of studies have examined the feedback processing to V1 neurons. Beckers and colleagues (Beckers and Homberg, 1992; Beckers and Zeki, 1995) have demonstrated that TMS over V5 can impair motion direction discrimination much earlier than can TMS over V1. TMS over V1 disrupted performance around 70-ms post-stimulus (ranging from 60 to 80 ms), and with TMS over V5 around 10 ms (ranging from −20 to 20 ms). Given the existence of fast back-projection from V5 to V1 (e.g. could be as quick as 1 or 2 ms; Movshon and Newsome, 1996), it is therefore plausible that feedback from V5 could reach V1 up to 20-ms post-stimulus onset, and might contribute to the activation of V1 neurons. Two recent TMS studies further suggested that disrupting V1 neural activities at the arrival time of feedback information can interfere with the perception of attributes encoded by higher cortical areas. Specifically, TMS over V1 around 20 ms (between 5 and 45 ms) after TMS over V5 or after V5's critical period in processing of motion information significantly disrupted (sometimes abolished) the perception of moving phosphenes (flashes of light) or moving random-dot pattern (Pascual-Leone and Walsh, 2001; Silvanto et al., 2005), suggesting this time window could be crucial for V1 neurons processing feedback information from V5.

In two separate experiments, by measuring human contrast detection performance of a briefly presented foveal target bar embedded in the dynamic predictor-target sequences (Fig. 1), we aimed to investigate the relative contribution of lateral and feedback connections in providing spatiotemporally regular information to facilitate detection of the target. Single-pulse TMS was delivered at two different time windows (20 and 90 ms) over the part of the occipital cortex which receives the visual input of the last predictor prior to target presentation. Considering that neurons in higher visual areas (e.g. V5 and V6) could code the trajectory of the dynamic predictor-target sequence based on their responses to the initial 2 or 3 predictors (i.e. 1st, 2nd, and 3rd predictor in Fig. 1), they might be able to generate a prediction about the location and timing of the last predictor (i.e. 4th predictor in Fig. 1) onset and then start to feedback this information to V1 shortly before or around the onset of the last predictor. Consequently, V1 neurons could possess this back-projected information up to 20-ms post last predictor onset, given the existence of fast back-projection from V5 to V1 (Movshon and Newsome, 1996). Based on the early TMS studies on functional connectivity between V5 and V1 (Pascual-Leone and Walsh, 2001; Silvanto et al., 2005) and typical neural response latency in V1 (ranging from 30 to 80 ms and elicited by feedforward inputs; Maunsell and Gibson, 1992; Nowak et al., 1995; Schmolesky et al., 1998), it is anticipated that the early 20 ms TMS might disrupt the feedback information (possibly from V5) about the trajectory of this dynamic stimulus sequence while having minimum impact on the feedforward and lateral connections (Amassian et al., 1989; Corthout et al., 1999; Sack et al., 2009; de Graaf et al., 2011). The 90-ms TMS, on the other hand, might disrupt the feedforward information (Pascual-Leone and Walsh, 2001; Silvanto et al., 2005) about the last predictor and subsequently affect the lateral connections for processing the predictor-target sequence, but might have limited impact on the feedback connections in V1 (as the back-projected prediction about the location and timing of the last predictor onset has already reached V1 neurons before this time window).

EXPERIMENT 1

Experimental procedures

Participants. Eight adult participants (4 females, mean age ± SD = 30 ± 11 years) took part in the study. All participants had normal or corrected-to-normal visual acuity and reported no history of neuropsychiatric illness or epilepsy. Informed consent was obtained from each participant, and all procedures complied with British Psychological Society "Code of Ethics and Conduct", and with the World Medical Association Helsinki Declaration as revised in October 2008.

Visual stimuli and TMS set-up. With the method of constant stimuli, visual stimuli were presented through a ViSaGe Graphics system (Cambridge Research Systems) and displayed on a non-interlaced gamma-corrected monitor (100 Hz frame rate, 40 cd/m^2 background luminance, 1024 × 768 pixel resolution, Mitsubishi Diamond Pro 2070SB). At a viewing distance of 70 cm the monitor subtended a visual angle of 33 × 24°.

The visual stimuli included a predictable predictor-target sequence and a target alone sequence (Fig. 1). The predictable sequence comprised five collinear short bars (1° length, 0.1° width) appearing successively toward the fovea. The first four 'predictor' bars with 15% contrast were presented in the right peripheral visual field. The fifth 'target' bar was presented 1° below a small red fixation point (FP, 0.2° diameter, 10 cd/m^2) in varying contrasts (0%, 0.5%, 1%, 1.5%, 1.75%, 2%, 15%). Each bar was presented for 200 ms. There was no spatial and temporal gap (or spacing) between adjacent bars. The bars were flashed in turn, in a position immediately adjacent (end-to-end) and in a time immediately preceding the next bar at successive

positions. In the target alone sequence, no predictors were presented; only the target in varying contrast was presented at the same time window as in the predictable sequence.

TMS was delivered by using a 70-mm figure-of-eight coil (Medtronic MC-B70 coil) through a Medtronic MagPro X100. The coil location and TMS intensity was determined for each individual participant prior to the testing session. Initially, the TMS intensity was set at 50% of the maximum output, and the coil was placed ~2 cm above and 1 cm left of the inion, with the main axis of the coil oriented parallel to the sagittal plane. After fixating on the central FP, a TMS pulse was administrated manually, and the participant reported whether they experienced a phosphene within a faint thin-line oval which corresponded to the location of the last predictor prior to target onset. The location of the coil and TMS intensity was adjusted according to the reported percept until a reliable phosphene was perceived. The TMS intensity was then reduced to the phosphene detection threshold, defined as the intensity at which the phosphene was reported no more than two out five TMS pulses. Finally, the TMS intensity for the main experiment was set at 10% below the detection threshold at which a phosphene was no longer reported by the participants.

Procedure. To control for artefacts associated with TMS (e.g. auditory click sound, mechanical tapping, and muscle contraction) which may disrupt participants' attention and affect their target detection performance, participants took part in two separate testing sessions: A TMS condition in which the TMS pulses were administered on the left occipital cortex at a location corresponding to the last predictor prior to the target onset, and a control (sham) condition in which the same intensity of TMS pulses were administrated on the right occipital cortex (task unrelated area) which mirrored the stimulation location on the left occipital cortex. Except for the coil location, all experimental parameters (e.g. coil orientation, TMS time windows and intensity) and procedures were the same in both the TMS and control conditions. The order of the testing sessions was counter-balanced across the participants.

During the experiments, participants sat in a quiet, darkened room and viewed the display binocularly with support of a chin rest. No earplugs were used. The trial was started by a 350 Hz warning tone lasting 150 ms followed by a delay of 1000 ms. A stimulus sequence drawn randomly from either predictable or target alone sequences with varying target contrast was then presented. For instance, in the predictable predictor–target sequence, the four predictors and the target (with varying contrast) were presented on the screen in a highly predictable spatial and temporal order (predictor1 → predictor2 → predictor3 → predictor4 → target). Single-pulse TMS was administered at either 20 ms or 90 ms after the onset of the predictor4. No TMS was administered in the target alone sequence. The participants were instructed to maintain fixation of the FP throughout the trial, and to indicate, by pressing a button in the response box using their dominant hand as quickly as possible, when they were reasonably confident that the target had been presented below the FP within this stimulus sequence (target present/absent detection). No feedback was given to the participant. The trial interval was set to 1500 ms. A minimum of 20 trials were presented for each target contrast in each stimulus sequence (target alone or predictable) for both TMS time windows (20 or 90 ms). Participants were encouraged to have frequent short breaks between testing blocks. Before the formal test, the participants were given a training session (normally 20 trials) to familiarize with the task.

The participants' detection performance (percentage of target detection judgment) was measured as a function of target contrast. Catch trials (0% and 15% target contrast) were used to correct for guessing target detection. Across the participants and stimulus sequences the mean hit rate for the presence of 15% target contrast was 99% ± 3, and the mean false alarm rate for the presence of 0% target contrast was 4% ± 5. The detection rate for target presence with a tested contrast was then calculated as (observed hit rate − false alarm rate)/(1 − false alarm rate)×100 (Norton et al., 2002). Q6

Previous studies have observed an enhanced target detection performance for the low-contrast targets embedded in the predictable sequence than in the target alone sequence (Hall et al., 2010; see Fig. 2 for an example). To examine how this performance enhancement is affected by TMS time windows (20 and 90 ms) and cortical locations (TMS and control condition), for a given target contrast we calculated the differences in normalized target detection rate between predictable and target alone sequences (the gap between two curves in Fig. 2). This represents the enhancement in detection relative to targets presented

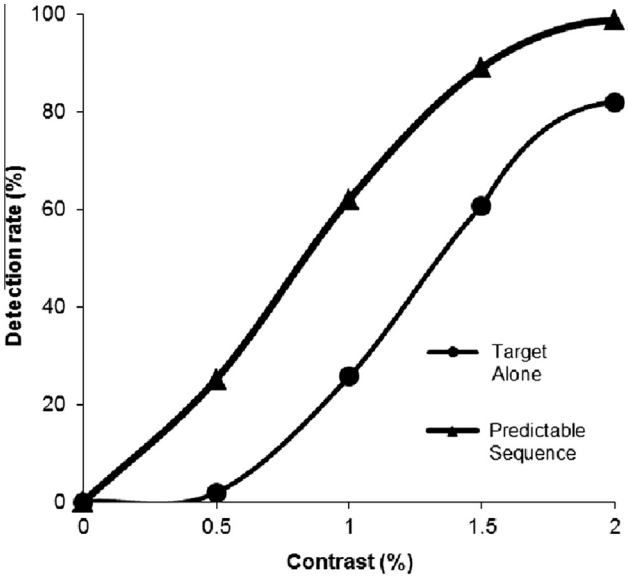

Fig. 2. Detection rate to target with varying contrasts and embedded in predictable and target alone sequences without TMS.

alone (not embedded in a predictable sequence). This percentage of detection enhancement was then compared across different target contrasts and different TMS conditions (TMS 20 ms vs TMS 90 ms vs Control condition; the data collected in the control (sham) condition are labeled as 'Control' in Figs. 3, 4 and 6).

Results. The delivery of TMS significantly reduced but did not abolish the facilitation effect of the dynamic predictors on the target detection. 5 (target contrasts) × 3 (TMS conditions: 20 ms TMS, 90 ms TMS and control condition) repeated measures analysis of variance (ANOVA) with detection enhancement as the dependent variable revealed a significant main effect of TMS condition ($F(2,14) = 14.97$, $p < 0.001$; Fig. 3). Post-hoc tests with Bonferroni correction identified that the enhancement rate was higher in the control condition (TMS on the right occipital cortex, 26.2% ± 20.4) than TMS at 20 ms (10.07% ± 13.3, $p = 0.01$) or 90 ms (13.1% ± 13.4, $p = 0.03$) after the onset of the final predictor. No significant difference was found between TMS delivered at 20 and 90 ms ($p = 0.08$). However, as this difference between TMS at 20 and 90 ms approached significance, the data were examined further (Fig. 4).

Although the group analysis showed that the target detection enhancement was the most evident for 1% target contrast in the control condition (Fig. 3), the optimal target contrast which induced the maximum detection enhancement varied between 0.5% and 1.5% for individual participants. As TMS normally caused more disruption to detect the target presented with the optimal contrast, we further compared this maximum level of enhancement suppression at individual participants' optimal target contrast between different TMS conditions (Fig. 4). A one-way ANOVA followed by Bonferroni post hoc tests showed that the main effect of TMS conditions remained ($F(2,14) = 13.69$, $p < 0.01$), and the enhancement rate was higher in TMS control condition (46.0% ± 17.9) than in 20 ms TMS (18.1% ± 16.1, $p = 0.02$) or 90 ms TMS (19.6% ± 14.0, $p = 0.02$)

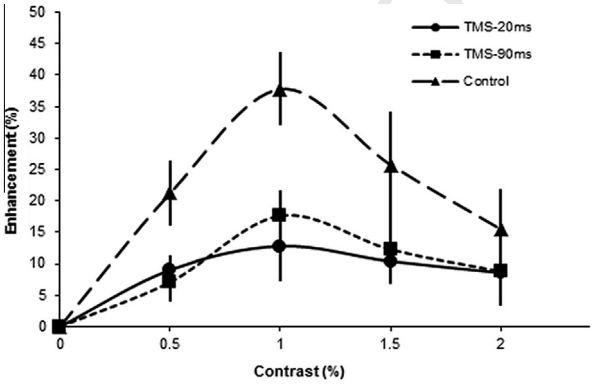

Fig. 3. Enhancement of detection rate to target with varying contrasts and embedded in predictable sequences compared to target alone sequences with and without TMS. Error bar represents standard error of mean.

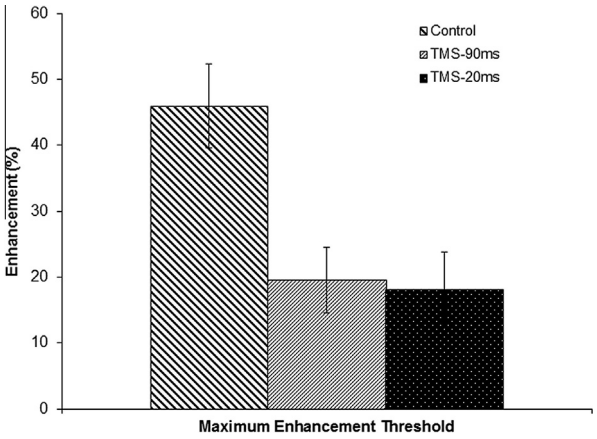

Fig. 4. Enhancement of detection rate to target embedded in predictable sequences compared to target alone sequences with and without TMS at maximum enhancement threshold. Error bar represents standard error of mean.

conditions. No difference was found between 20 and 90 ms TMS conditions ($p = 1.00$).

Taken together, the single TMS pulse administrated at 20 and 90 ms after the onset of the last predictor induced the same level of disruption to detect the low-contrast target in the predictable collinear predictor-target sequence. As TMS at 20 or 90 ms is thought to suppress the feedback or lateral inputs, respectively (Amassian et al., 1989; Corthout et al., 1999; Pascual-Leone and Walsh, 2001; Silvanto et al., 2005; Sack et al., 2009; de Graaf et al., 2011), perhaps both are disrupted. If so there is a disruption of both the priming at the target location in V1 from overall stimulus trajectory detection by higher brain regions and from the common orientation priming via lateral connections in V1. To further separate feedback and lateral inputs in detecting the target bar, we randomized the orientation of the predictors in Experiment 2. As a result, the four predictor bars were presented in a non-collinear trajectory, but still in a temporally predictable sequence (Fig. 5). Compared to the sequence used in Experiment 1, this random orientation sequence should disrupt lateral connections in V1. Given the feedback inputs (e.g. from V5 and V6) are less sensitive to orientation of the moving parts and could still provide useful information about the trajectory of this dynamic sequence, we predicted that TMS at 20 ms would cause more suppression effect than TMS at 90 ms.

EXPERIMENT 2

Experimental procedures

Participants. Eight adult participants (4 females, mean age ± SD = 33 ± 6 years) took part in the study. Five of them also participated in Experiment 1. All participants had normal or corrected-to-normal visual acuity and reported no history of neuropsychiatric illness or epilepsy. Informed consent was obtained from each participant, and all procedures complied with British

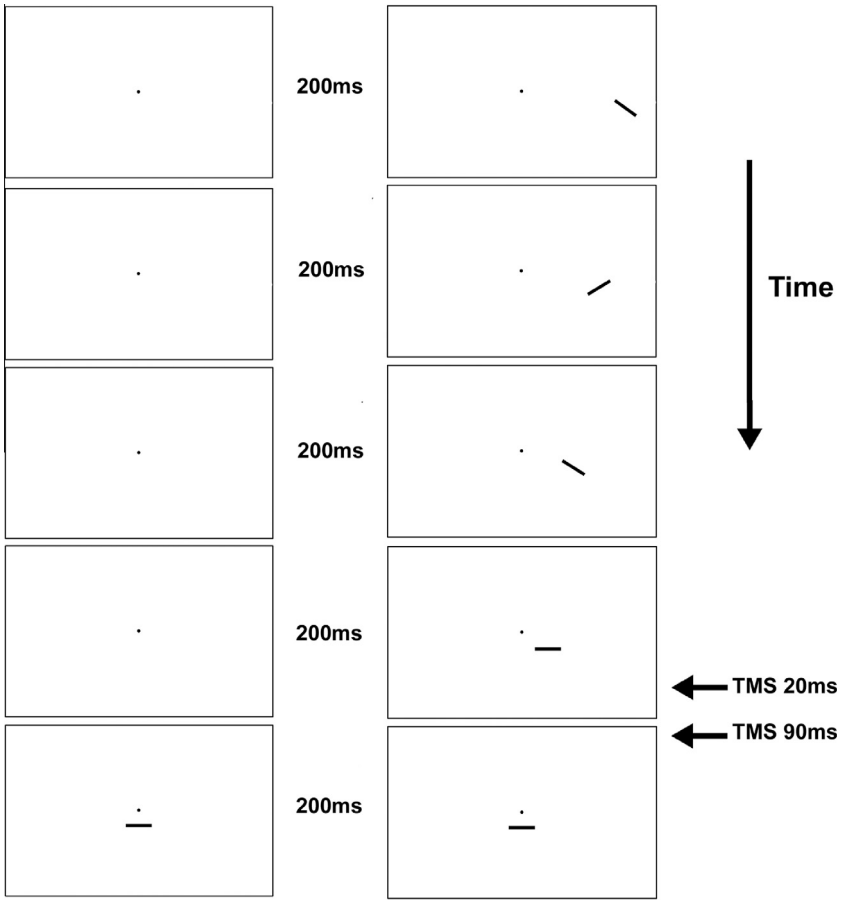

Fig. 5. Demonstration of target alone and random sequence used in this experiment.

Psychological Society "Code of Ethics and Conduct", and with the World Medical Association Helsinki Declaration as revised in October 2008.

Procedure. The experimental set-up, testing procedure, TMS stimulation and participants' tasks were the same as those used in Experiment 1. The only difference was the change of the predictor-target stimulus structure, from predictable sequence to random orientation sequence. In this random orientation sequence (Fig. 5), the first three predictors with random orientation (0–150° in steps of 30°) appeared successively toward the fovea, followed by the last predictor with horizontal orientation, and finally by the horizontal target with a varying contrast.

Results. As in Experiment 1, we first identified the optimal target contrast which had induced the maximum detection enhancement in the TMS control condition for individual participants, and then compared the TMS disruption effect at this target contrast between different TMS conditions (Fig. 6). Repeated measures ANOVA demonstrated a significant main effect of TMS condition ($F(2,14) = 6.72$, $p < 0.01$). Bonferroni post hoc tests revealed that in comparison with the TMS control condition (37.0% ± 16.3), the target detection enhancement was significantly suppressed by TMS administrated at 20 ms (20.7% ± 12.2, $p < 0.05$). Consistent with the hypothesized feedback input at this time window, TMS had a similar disrupting type effect as seen in Experiment 1. In Contrast, there was no hypothesized input at 90 ms from lateral connections in this experiment and consequently no significant

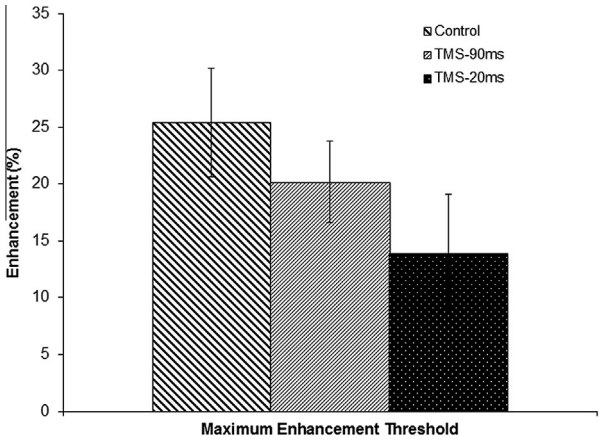

Fig. 6. Enhancement of detection rate to target embedded in random sequences compared to target alone sequences with and without TMS at maximum enhancement threshold. Error bar represents standard error of mean.

disruption was seen. That is, no difference was observed between the control condition and TMS at 90 ms (27.9% ± 14.4, $p = 0.37$). There was a trend but no significant difference between TMS at 20 and 90 ms ($p = 0.06$).

DISCUSSION

Our previous studies have demonstrated that the human visual system could exploit geometric spatiotemporal regularities to facilitate target detection and discrimination (Guo et al., 2004; Hall et al., 2010), and these regularities could be computed at an early stage of visual processing (Pollux and Guo, 2009; Pollux et al., 2011; Hall et al., 2013), possibly starting at area V1 (Guo et al., 2007). In this study, we employed TMS to explore the relative contribution of lateral and feedback connections in V1 neural computation of collinear spatiotemporal regularity.

In comparison with the target alone sequence, our participants' low-contrast target detection performance was significantly enhanced by the target embedded in the collinear predictable sequence in the TMS control condition. A single TMS pulse administrated at 20 or 90 ms after the onset of the last predictor prior to target presentation, however, had the same degree of deteriorative effect on the target detection performance (Figs. 3 and 4). As the TMS at 90 ms could suppress visual perception of the last predictor (Amassian et al., 1989; Corthout et al., 1999; Sack et al., 2009; de Graaf et al., 2011) and subsequently disrupt V1 lateral connections which integrate spatially and temporally separated individual predictors into a coherent dynamic collinear contour, and the TMS at 20 ms could disrupt feedback information from V5 about the trajectory of the sequent predictor presentation (Pascual-Leone and Walsh, 2001; Silvanto et al., 2005), it seems that both lateral and feedback inputs have contributed to the enhanced target detection in the predictable sequence. This conclusion was further supported by our observation in Experiment 2 when we randomized the predictors' orientation to minimize the involvement of V1 lateral connections (lateral connections predominately connect neurons sharing similar response properties, such as orientation selectivity; Lamme et al., 1998). The result showed that TMS at 90 ms had negligible impact on target detection in comparison with TMS control conditions, whereas TMS at 20 ms significantly reduced the participants' sensitivity to perceive the low-contrast targets (Fig. 6). This finding also confirms that stimulation at 90 ms was interrupting lateral connections in Experiment 1. Furthermore, as significant enhancement ($\geqslant$21%) in the target detection was still evident for TMS at 20 or 90 ms (Fig. 6), the non-significant TMS effect at 90 ms in Experiment 2 is therefore unlikely due to a 'floor effect' in which TMS at 90 ms cannot significantly interfere with the already weaker lateral connections caused by the predictors with randomized orientation. Taken together, our findings not only confirm the capability of V1 neurons in computing collinear spatiotemporal regularity (Guo et al., 2007), but also directly demonstrate the involvement of both lateral and feedback inputs in such neural computation.

From data shown in Figs. 3 and 4, it would be tempting to conclude that lateral and feedback inputs in V1 had an equal role in computing collinear spatiotemporal regularity. The selective disruption observed in Experiment 2 strengthens this interpretation further. This idea, however, should be treated with caution. Although a single TMS pulse in a critical time window could abolish conscious perception of a visual stimulus, the degree of this TMS-induced masking effect is dependent upon many experimental variables, such as coil parameters, TMS pulse timing, and complexity of visual stimuli (e.g. Kammer, 2007; de Graaf et al., 2012). Furthermore, to avoid eliciting an illusory phosphene which would interfere with the target-detection task, the TMS intensity in this project was set at 90% of the minimum intensity required for phosphene induction. It is plausible that feedback or lateral inputs to the targeted V1 neurons would not be totally suppressed by the TMS pulse delivered with this intensity at the 20- or 90-ms time window. It should also be noted that feedback inputs could come from multiple cortical areas which are sensitive to motion and are capable of making a prediction about the location and timing of the target onset (e.g. V5, V6, or even frontal and parietal cortex). As these feedback signals might arrive at V1 at different time windows, it is possible that TMS at 20 ms would not suppress all these feedback inputs. Given this inherent nature of TMS methodology, it is difficult to precisely quantify the contribution of lateral and feedback inputs for encoding spatiotemporal regularity in V1 from the current study.

Furthermore, although TMS at around 90-ms post-stimulus over V1 is commonly assumed to disrupt feedforward processing (e.g. Pascual-Leone and Walsh, 2001; Silvanto et al., 2005), it is argued that the time window of 80–130 ms after stimulus onset might already reflect V1 neural activities driven by both feedforward inputs and feedback signals from higher visual areas; as recurrent processing could start only tens of milliseconds after the initial feedforward projection (e.g. Nowak and Bullier, 1997; Vanni et al., 2001; Kammer, 2007). The latency of feedback processing in V1 could further depend on the nature and complexity of visual stimuli (de Graaf et al., 2012). Given TMS at 90 ms had a significant detrimental effect on the target detection in experiment 1 but had negligible impact in experiment 2 – in which the predictors' orientation was randomized to minimize the involvement of V1 lateral connections – it is likely that with our stimulus structure, TMS at 90 ms heavily suppressed the feedforword processing of the last predictor. However, the current design does not allow us to determine to what degree the feedback inputs at 90 ms contributed to the processing of the last predictor.

Nevertheless, the fact that both lateral and feedback connections are utilized in processing the predictable dynamic stimulus sequence has shed light on the origin of our perceptual sensitivity to natural geometric

spatiotemporal regularities. The lateral or horizontal connections interconnect V1 neurons with similar orientation preferences across a large cortical distance, and these connections are strongest when neurons' CRFs are also co-axially aligned (Lamme et al., 1998). As these connections have the ability to provide both excitatory and inhibitory inputs to their postsynaptic neurons, and thus modulate their discharges (McGuire et al., 1991), the coherent orientation or contour signals over a range of spatial positions can be pooled effectively. It is plausible this inherent anatomical cortical structure is shaped by the evolutionary pressure to compute natural geometric regularities more efficiently.

On the other hand, the feedback connections could provide top-down modulation originating in high-order cortical areas – such as V5, V6 or even frontal and parietal cortex (Nobre et al., 2007; Watanabe, 2007; Summerfield and Koechlin, 2008) – on the integration of coherent but spatially and temporally separated visual signals. In our experiments the top-down expectation of the target presentation, derived from prior experience of natural regularities, could be projected backward to area V1. Consequently, the immediate sensory input would be interpreted within the context of a prior expectation (Bar, 2007). Previous studies have revealed that our knowledge of natural statistics can be acquired through perceptual learning (e.g. Schwarzkopf et al., 2009). Even short-term training of contour integration and detection based on familiar or unfamiliar natural regularities could induce learning-dependent neural changes in V1 which engages top-down facilitation mechanisms (Gilbert and Li, 2013). It seems that in comparison with lateral inputs which are probably from evolutionary-driven hard-wired connections, feedback predictive inputs are probably more subject to a developmental or learning process. Future studies might clarify this speculation by comparing TMS interference between trained and untrained tasks of detecting novel natural statistics.

CONCLUSION

Our findings not only confirmed the capability of V1 neurons in the computation of collinear spatiotemporal regularity (Guo et al., 2007), but also directly demonstrated the contribution of feedback and lateral connections in such neural computation. These findings further the understanding of how our visual system exploits spatiotemporal regularity to facilitate the efficiency of visual perception.

UNCITED REFERENCES

Bullier (2001), Hupe et al. (1998), Simoncelli and Olshausen (2001) and Young (2000).

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REFERENCES

Albright TD, Stoner GR (2002) Contextual influences on visual processing. Annu Rev Neurosci 25:339–379.
Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell A, Eberle L (1989) Suppression of visual perception by magnetic coil stimulation of human occipital cortex. Electroen Clin Neuro 74:458–462.
Bar M (2007) The proactive brain: using analogies and associations to generate predictions. Trends Cogn Sci 11:280–289.
Beckers G, Homberg V (1992) Cerebral visual motion blindness: transitory akinetopsia induced by transcranial magnetic stimulation of human area V5. Proc R Soc B 249:173–178.
Beckers G, Zeki S (1995) The consequences of inactivating areas V1 and V5 on visual motion perception. Brain 118:49–60.
Bullier J (2001) Integrated model of visual processing. Brain Res Rev 36:96–107.
Corthout E, Uttl B, Ziemann U, Cowey A, Hallett M (1999) Two periods of processing in the (circum) striate visual cortex as revealed by transcranial magnetic stimulation. Neuropsychologia 37:137–145.
de Graaf TA, Cornelsen S, Jacobs C, Sack AT (2011) TMS effects on subjective and objective measures of vision: stimulation intensity and pre-versus post-stimulus masking. Conscious Cogn 20:1244–1255.
de Graaf TA, Goebel R, Sack AT (2012) Feedforward and quick recurrent processes in early visual cortex revealed by TMS? Neuroimage 61:651–659.
Gilbert CD, Li W (2013) Top-down influences on visual processing. Nat Rev Neurosci 14:250–363.
Guo K, Nevado A, Robertson RG, Pulgarin M, Thiele A, Young MP (2004) Effects on orientation perception of manipulating the spatio–temporal prior probability of stimuli. Vision Res 44:2349–2358.
Guo K, Robertson RG, Pulgarin M, Nevado A, Panzeri S, Thiele A, Young MP (2007) Spatio–temporal prediction and inference by V1 neurons. Eur J Neurosci 26:1045–1054.
Hall S, Pollux PM, Guo K (2010) Exploitation of natural geometrical regularities facilitates target detection. Vision Res 50:2411–2420.
Hall S, Pollux PMJ, Roebuck H, Guo K (2013) ERP evidence for human early visual sensitivity to co-linearity compared to co-circularity. Neurosci Lett 556:46–51.
Hupe JM, James AC, Payne BR, Lomber SG, Girard P, Bullier J (1998) Cortical feedback improves discrimination between figure and background by V1, V2 and V3 neurons. Nature 394:784–787.
Kammer T (2007) Masking visual stimuli by transcranial magnetic stimulation. Psychol Res 71:659–666.
Lamme VAF, Super H, Spekreijse H (1998) Feedforward, horizontal, and feedback processing in the visual cortex. Curr Opin Neurobiol 8:529–535.
Maunsell JH, Gibson JR (1992) Visual response latencies in striate cortex of the macaque monkey. J Neurophysiol 68:1332–1344.
McGuire BA, Gilbert CD, Rivlin PK, Wiesel TN (1991) Targets of horizontal connections in macaque primary visual cortex. J Comp Neurol 305:370–392.
Movshon JA, Newsome WT (1996) Visual response properties of striate cortical neurons projecting to area MT in macaque monkeys. J Neurosci 16:7733–7741.
Nobre AC, Correa A, Coull JT (2007) The hazards of time. Curr Opin Neurobiol 17:465–470.
Nowak LG, Bullier J (1997) The timing of information transfer in the visual system. In: Rockland KS, Kaas JH, Peters A, editors. Cerebral cortex, vol. 12: extrastriate cortex in primates. New York, London: Plenum Press. p. 205–241.
Nowak LG, Munk MHJ, Girard P, Bullier J (1995) Visual latencies in areas V1 and V2 of the macaque monkey. Vis Neurosci 12:371–384.
Pascual-Leone A, Walsh V (2001) Fast backprojections from the motion to the primary visual area necessary for visual awareness. Science 292:510–512.

Pollux PM, Guo K (2009) Event-related potential correlates of spatiotemporal regularities in vision. Neuroreport 20:525–530.
Pollux PMJ, Hall S, Roebuck H, Guo K (2011) Event-related potential correlates of the interaction between attention and spatiotemporal context regularity in vision. Neurosci 190:258–269.
Sack AT, van der Mark S, Schuhmann T, Schwarzbach J, Goebel R (2009) Symbolic action priming relies on intact neural transmission along the retino-geniculo-striate pathway. Neuroimage 44:284–293.
Schmolesky MT, Wang YC, Hanes DP, Thompson KG, Leutgeb S, Schall JD, Leventhal AG (1998) Signal timing across the macaque visual system. J Neurophysiol 79:3272–3278.
Schwartz O, Hsu A, Dayan P (2007) Space and time in visual context. Nat Rev Neurosci 8:522–535.
Schwarzkopf DS, Zhang J, Kourtzi Z (2009) Flexible learning of natural statistics in the human brain. J Neurophysiol 102:1854–1867.
Silvanto J, Lavie N, Welsh V (2005) Double dissociation of V1 and V5/MT activity in visual awareness. Cereb Cortex 15:1736–1741.
Simoncelli EP, Olshausen BA (2001) Natural image statistics and neural representation. Annu Rev Neuro 24:1193–1216.
Summerfield C, Koechlin E (2008) A neural representation of prior information during perceptual inference. Neuron 59:336–347.
Vanni S, Tanskanen T, Seppa M, Uutela K, Hari R (2001) Coinciding early activation of the human primary visual cortex and anteromedial cuneus. Proc Natl Acad Sci U S A 98:2776–2780.
Walsh V, Cowey A (2000) Transcranial magnetic stimulation and cognitive neuroscience. Nat Rev Neurosci 1:73–79.
Watanabe M (2007) Role of anticipated reward in cognitive behavioural control. Curr Opin Neurobiol 17:213–219.
Young MP (2000) The architecture of visual cortex and inferential processes in vision. Spat Vis 13:137–146.

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