

COGNITIVE NEUROSCIENCE

Contrasting early visual cortical activation states causally involved in visual imagery and short-term memory

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Abstract

Whether visual imagery and visual short-term memory (STM) share the same neural resources, and the extent to which the early visual cortex (V1/V2) is involved in these processes, has been the subject of much debate. Here, we used transcranial magnetic stimulation (TMS) in two separate experiments to contrast the neural states associated with visual imagery and visual STM in the early visual cortex. In Experiment 1, we investigated V1/V2 activation states at the end of the retention phase in a visual imagery and a visual STM task. V1/V2 TMS facilitated performance in both tasks; the finding that imagery and STM interacted with TMS in the same way suggests that the two processes have similar effects on early visual cortical excitability. In Experiment 2, we investigated V1/V2 activation states at the beginning of the retention phase. V1/V2 TMS impaired performance in the visual STM task, whereas it had no effect on the imagery task. Taken together, our findings show that the late phases of the early visual cortical activation state associated with visual imagery and visual STM are similar; differences between the two processes are apparent in the early phases of the tasks. Our results also suggest that the causal role of the early visual cortex in visual STM includes both the initial translation of the visual input into working memory and the subsequent maintenance of the mental representation. Finally, our findings indicate that visual STM sensory recruitment in working memory might act via excitability modulation of V1/V2 neurons.

Introduction

Visuo-spatial working memory (VSWM), supported by a distributed network within the working memory, processes and represents visuo-spatial information (Baddeley, 2003; Cornoldi & Vecchi, 2003). Short-term visual memory and visual imagery are two major processes subserved by VSWM. Whereas short-term visual memory is defined as encoding and recall of a previously experienced visual percept, visual imagery refers to an internal representation generated after, for instance, a verbal description of the target stimulus (Baddeley & Salame, 1986; Cornoldi & Vecchi, 2003). These are considered to be prototypical functions of VSWM (Zimmer, 2008), and in some cases they are even considered to be equivalent (Kosslyn & Thompson, 2003). However, there is conflicting evidence on whether the structures used for imagery completely overlap with those used in short-term memory (STM). For instance, Quinn & McConnell (2006) found that dynamic visual noise presented concurrently with a visual imagery generation task impaired subjects' performance, whereas no impairment was found when visual noise was presented during an STM task (Andrade *et al.*, 2002; Zimmer & Speiser, 2002). At the 'functional' (or behavioral) level, the overlap between visual STM and mental images is thus unclear.

At the neural level, there is evidence that working memory is mediated by the same neural mechanisms that process the sensory information being retrieved [see the 'sensory recruitment' model of working memory (Awh & Jonides, 2001; D'Esposito, 2007; Serences *et al.*, 2009)]. In a very recent functional magnetic resonance imaging (fMRI) study, participants were engaged in an STM task requiring the retention of either the color or the orientation of a stimulus for subsequent comparison with a second stimulus (Serences *et al.*, 2009). They found activation associated with the memory content in area V1 of the early visual cortex (V1) during the 10-s maintenance interval [see also Harrison & Tong (2009) for similar findings]. In visual imagery, however, the involvement of the early visual cortex has not always been reported. There is some neuroimaging evidence to suggest that retinotopically specific subregions of the primary visual cortex are activated during visual imagery processes (Kosslyn & Thompson, 2003), but numerous other studies have reported evidence to the contrary (Roland & Gulyas, 1995; Ghaem *et al.*, 1997; Knauff *et al.*, 2000; Wheeler *et al.*, 2000). Thus, the overlap in the extent of the early visual cortical involvement in STM and visual imagery is not fully clear.

Here, we investigated the overlap in the neural processes associated with STM and imagery by comparing the effect of these processes on the early visual cortical activation state. This was accomplished using transcranial magnetic stimulation (TMS), a technique that can demonstrate the causal role of cortical areas in cognitive functions (Walsh & Pascual-Leone, 2003; Cowey, 2005), as well as reveal the

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neural activation states associated with these functions (Silvanto & Pascual-Leone, 2008; Silvanto *et al.*, 2008). To investigate neural activation states, we made use of the findings that the behavioral effects of TMS vary with the initial state of the targeted region, and that different psychophysical manipulations (which presumably have different neural bases) interact in different ways with TMS (Silvanto & Muggleton, 2008). For example, after adaptation, TMS facilitates the attributes encoded by the adapted neural populations (Silvanto *et al.*, 2007; Cattaneo *et al.*, 2009), leading to the behavioral effects of adaptation being abolished (Stewart *et al.*, 1999; Théoret *et al.*, 2002). In contrast, after priming, TMS facilitates the detection of attributes encoded by the non-primed neural populations (Cattaneo *et al.*, 2008), abolishing the behavioral impact of priming (Campana *et al.*, 2002, 2006). Interactions between different psychophysical manipulations and the behavioral effects of TMS can thus be used to infer whether these manipulations modulate the initial neural state in similar or different ways.

Previously, Sparing *et al.* (2002) showed, using the phosphene threshold as an indicator of visual cortical excitability, that visual imagery increases the excitability of early visual cortical neurons involved in visual imagery. Specifically, they showed that visual imagery decreased the intensity of TMS required for phosphene induction when the imagined stimulus spatially overlapped with the phosphene. The first aim of the present study was to determine whether visual STM has the same impact on early visual cortical activation state as imagery. In the imagery task, subjects were shown a digital time and were asked to imagine the clock hands associated with this time. In the test phase (after a 2-s imagery period), they were asked to judge whether a target dot appeared inside or outside the imagined clock hands. As imagery increases the excitability of neurons encoding the mental image (Sparing *et al.*, 2002), the application of single-pulse TMS during the mental imagery process should preferentially activate neurons encoding the mental image. We hypothesized that such preferential activation should result in strengthening of the mental image, causing a facilitation of performance. In the memory condition, subjects were presented with the clock hands instead of the digital time at the start of each trial. As in the imagery condition, subjects were asked to judge, after a 2-s retention period, whether a target dot appeared inside or outside the clock hands. If visual STM has the same effect on visual cortical activation state as visual imagery, single-pulse TMS applied during memory retention should have the same effect, that is, preferential activation of neurons encoding the memory item, resulting in strengthening of the visual memory and facilitation of performance.

We also performed a second experiment, contrasting the neural states associated with visual imagery and STM at the beginning of the retention period (Experiment 2).

Materials and methods

All experiments were undertaken with the understanding and written consent of each participant. The study was approved by the institutional review board of University of Pavia, and all subjects were treated in accordance with the Declaration of Helsinki. Two experiments were completed, as follows.

Experiment 1

The objective of this experiment was to determine whether STM, like imagery, increases early visual cortical excitability. This was investigated by applying TMS over the early visual cortex at the end of the imagery/memory period.

Subjects

Fourteen participants (seven males; mean age, 29 years), all of whom were naive with regard to the objective of the study, took part in Experiment 1.

Imagery task

The stimuli were presented on a 17-inch (800 × 600 pixels) monitor. The viewing distance was 57 cm. Each trial began with a black fixation point appearing in the middle of the white screen for 500 ms, after which a time, presented in black digits (with the diameter of each digit being approximately 1° of visual angle), appeared for 1000 ms (see Fig. 1 for a timeline of each trial). The times were: 12.10; 2.20; 4.30; 6.40; 8.50; 10.00; 12.20; 2.30; 4.40; 6.50; 8.00; and 10.10. This was followed by a black circle appearing at fixation (with a diameter of 4° of visual angle; extending 2° into both hemifields), and the subjects were asked to imagine the clock hands depicting the time that had just been presented in digits. Specifically, subjects were explicitly instructed to visualize the hour hand exactly at the position indicated by the hour digit (without correcting for the minutes past the hour; for example, '8.50' was visualized with the hour hand on 8 rather than close to 9). This delay period ('imagery phase') lasted for 2 s, after which a black dot (with a diameter of 0.5° of visual angle) appeared in one of the four quadrants of the circle. Subjects were asked to judge whether this dot appeared inside or outside the area defined by the hour and the minute hand of the clock (proceeding clockwise from the hour hand to the minute hand). In half of the trials the dot was inside this area, and in the other half it was outside. The dot was always presented near the minute hand (approximately 1° of visual angle away from the minute hand). By choosing the minute hand as an 'anchor' for positioning the dot, we aimed to maintain a similar level of difficulty across the different types of trials. In half of the trials the dot appeared on the left side of the circle, and in the other half it appeared on the right side of the circle.

Memory task

The stimuli were presented on a 17-inch (800 × 600 pixels) monitor. The viewing distance was 57 cm. Each trial began with a black fixation point appearing in the middle of the white screen for 500 ms, after which clock hands were presented for 1000 ms (see Fig. 2 for a timeline of each trial). The times were: 12.10; 2.20; 4.30; 6.40; 8.50; 10.00; 12.20; 2.30; 4.40; 6.50; 8.00; and 10.10 (i.e. the same times as used in the imagery experiment). This was followed by a black circle, and the subjects were asked to retain the position of the clock hands over this period. This memory phase lasted for 2 s, after which a black dot appeared in one of the four quadrants of the circle. As in the imagery task, subjects were asked to judge whether this dot appeared inside or outside the clock hands. The only difference between the two tasks, therefore, was that, in the imagery task, subjects were asked to transform the digits into a mental image of clock hands, whereas in the memory task subjects were asked to remember the position of the clock hands.

TMS

TMS was administered with a Magstim model 200 single-pulse stimulator (Magstim Company, UK). The coil was a 70-mm figure-of-eight coil, held with the handle pointing directly upwards. The early visual cortex (V1/V2) was localized using a functional method in which the center of the coil is placed on the surface of the skull such

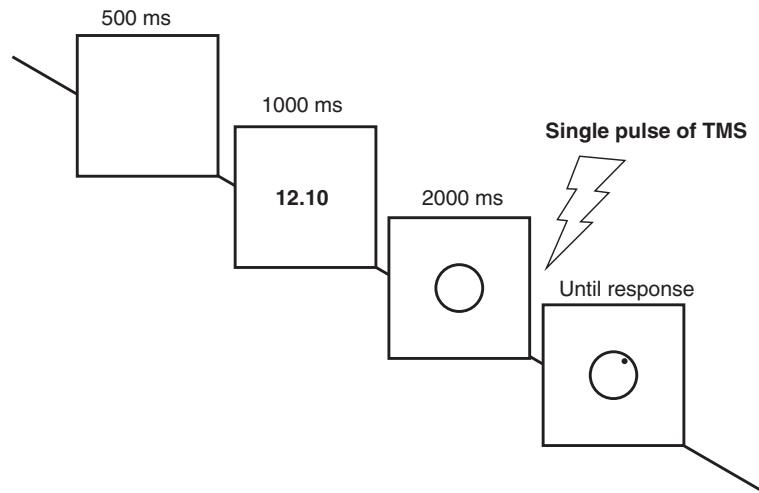


FIG. 1. Timeline of an experimental trial in the imagery task. At the beginning of each trial, subjects were presented with a digital time. Their task was then to visualize the clock hands associated with this time inside a circle representing the clock face. After a 2-s imagery period, a dot appeared inside the circle, and subjects were asked to judge whether the dot appeared inside or outside the imagined clock hands. In Experiment 1, transcranial magnetic stimulation (TMS) was applied at the end of the imagery period; in Experiment 2, TMS was applied at the start of the imagery period.

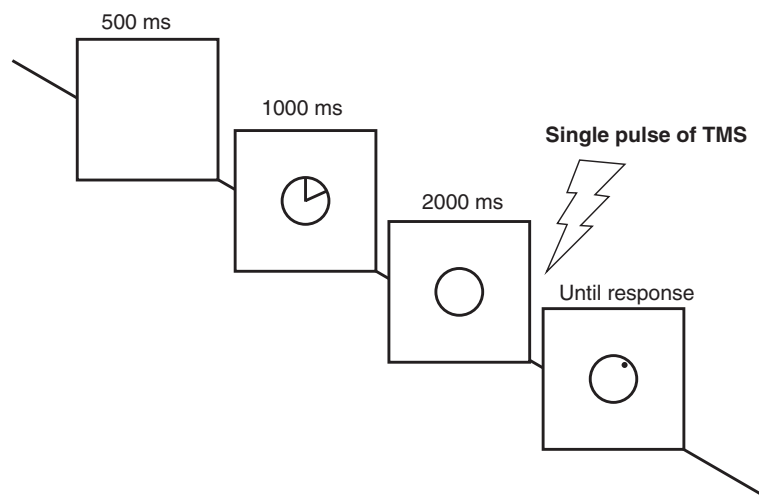


FIG. 2. Timeline of an experimental trial in the memory task. At the beginning of each trial, subjects were presented with clock hands, which they were asked to remember. After a 2-s retention period, a dot appeared inside the circle, and subjects judged whether the dot appeared inside or outside the clock hands. In Experiment 1, transcranial magnetic stimulation (TMS) was applied at the end of the retention period; in Experiment 2, TMS was applied at the start of the retention period.

that the stimulation elicits phosphenes that intrude on the center of the visual field, that is, the target location [for a discussion of this method, see Walsh & Pascual-Leone (2003); see Campana *et al.* (2002) and Silvanto *et al.* (2005a,b) for examples]. The starting point for the functional localization was the medial early occipital cortex, because stimulation of this site induces phosphenes intruding into both hemifields (as did the clock stimulus in the present study). The average coil position for V1 stimulation was 2.1 cm [standard deviation (SD) = 0.92] dorsal and 0.6 cm (SD = 0.61) lateral from theinion. The mean TMS intensity required for inducing phosphenes was 79% (with a range of 68–85%). To control for non-specific effects of TMS, the vertex was used as a control site. In the TMS conditions, a single pulse of TMS was applied at the end of the imagery/memory period, at the onset of the target dot. A fixed TMS intensity of 65% of maximum stimulator output was used on the basis of a number of previous studies (e.g. Campana *et al.*, 2002; O'Shea *et al.*, 2004; Silvanto *et al.*, 2005b; Muggleton *et al.*, 2006). This intensity was

well below the reported mean TMS intensity required to induce phosphenes in our sample of participants. Furthermore, previous studies (e.g. Bestmann *et al.*, 2007) have shown that phosphenes are less likely to be perceived when subjects are not attending to them. Accordingly, and similarly to what was found in previous studies in which occipital TMS was applied while subjects were fixating at a computer screen and performing a visual task (e.g. Campana *et al.*, 2002; Silvanto *et al.*, 2005a,b), none of the subjects reported perceiving phosphenes during the experiment.

Procedure

At the beginning of the session, subjects performed a block of 24 practice trials for each task to familiarize themselves with the task. After training, the TMS sites were localized. Participants responded with their index and middle fingers by pressing '1' and '2' on the number pad of a PC keyboard. These buttons were chosen so that

the subjects could rest their wrists on the desk, thus minimizing discomfort. Half of the subjects pressed '1' for inside and '2' for outside; for the other half, the order was reversed. Each condition (V1/V2 TMS, vertex TMS, no TMS) was tested in a block of 48 trials. All participants responded with the right hand.

Control experiment

The objective of this experiment was to determine whether any effects observed in Experiment 1 could be merely due to TMS facilitating the detection of the target dot, rather than TMS interacting with visual imagery or memory. To investigate this, we determined whether TMS applied at target onset facilitates the localization of the target dot in the absence of a memory/STM memory task.

Subjects

Eleven participants (four males; mean age, 25 years), all of whom were naive to the objective of the study, took part in the control experiment. Five of these subjects had taken part in Experiment 1, and five of them took part in Experiment 2.

Detection task

The stimuli were presented on a 17-inch (800 × 600 pixels) monitor. The viewing distance was 57 cm. Each trial began with a black fixation point appearing in the middle of the white screen for 500 ms; this was followed by a blank circle being presented for 2 s, after which a black dot appeared in one of the four quadrants of the circle. The locations of the target dot were the same as in the imagery and memory tasks. Subjects were asked to report whether the target dot appeared on the left or the right side of the circle. Each condition (V1/V2 TMS, vertex TMS, no TMS) was tested in one block of 48 trials. All participants responded with the right hand.

TMS

TMS was administered as in Experiment 1, with a single pulse applied over the early visual cortex or vertex at the onset of the target dot.

Procedure

At the beginning of the session, subjects performed a block of 24 practice trials to familiarize themselves with the task. After training, the TMS sites were localized. Participants responded with their index and middle fingers by pressing '1' and '2' on the number pad of a PC keyboard: half of the subjects pressed '1' for left and '2' for right; for the other half, the order was reversed.

Experiment 2

The objective of this experiment was to determine the effect of TMS on visual imagery and STM when TMS is applied at the beginning of the imagery/memory period.

Subjects

Fourteen participants (seven males; mean age, 24 years), all of whom were naive with regard to the objective of the study, took part in

Experiment 2. Five of these subjects had taken part in the control experiment.

Imagery and memory tasks and TMS

The imagery and memory tasks were identical to those used in Experiment 1. TMS was carried out as in Experiment 1, with the difference that the TMS pulse was applied at the onset of the imagery/memory period.

Procedure

At the beginning of the session, subjects performed a block of 24 practice trials for each task to familiarize themselves with the task. After training, the TMS sites were localized. Participants responded with their index and middle fingers by pressing '1' and '2' on the number pad of a PC keyboard: half of the subjects pressed '1' for inside and '2' for outside; for the other half, the order was reversed. Each condition (V1/V2 TMS, vertex TMS, no TMS) was tested in one block of 48 trials. All participants responded with the right hand.

Results

To obtain a measure reflecting the tradeoff between accuracy and reaction times, we analysed the data by dividing each subject's reaction times by the detection accuracy in each condition. This method has been repeatedly used in a number of other studies, and is well established (e.g. Townsend & Ashby, 1983). To remove outliers, responses with reaction times more than two SDs from the mean of that particular condition (for that subject) were removed from the analysis. No more than three trials were removed for any of the subjects in any of the conditions.

Experiment 1

The mean detection accuracies in the imagery task were as follows: no TMS, 0.93; occipital TMS, 0.92; and vertex TMS, 0.90. A repeated-measures ANOVA revealed no significant main effect of TMS condition on accuracy ($F_{2,26} = 1.15$; $P = 0.23$; $\eta^2 = 0.11$).

Figure 3 shows the mean reaction times in the imagery task as a function of the TMS condition. A repeated-measures ANOVA with TMS site as the main factor indicated a significant effect ($F_{2,26} = 6.54$; $P = 0.005$; $\eta^2 = 0.34$). *Post hoc* pairwise comparisons indicated that TMS applied over the occipital cortex enhanced performance relative to the no-TMS condition ($t_{13} = 2.86$; $P = 0.013$) and the vertex-TMS condition ($t_{13} = 3.24$; $P = 0.006$). Performance in the vertex-TMS condition did not significantly vary from that in the no-TMS condition ($t_{13} = 0.2$; $P = 0.85$).

The mean detection accuracies in the memory condition were as follows: no TMS, 0.91; occipital TMS, 0.91; and vertex TMS, 0.90. A repeated-measures ANOVA revealed no significant main effect of TMS condition on accuracy ($F_{2,26} = 0.61$; $P = 0.55$; $\eta^2 = 0.05$).

Figure 4 shows the mean reaction times in the memory task as a function of the TMS condition. A repeated-measures ANOVA with TMS site as the main factor indicated a significant effect ($F_{2,26} = 8.80$; $P = 0.001$; $\eta^2 = 0.40$). *Post hoc* pairwise comparisons indicated that TMS applied over the occipital cortex enhanced performance relative to the no-TMS condition ($t_{13} = 3.52$; $P = 0.004$) and the vertex-TMS condition ($t_{13} = 3.33$; $P = 0.005$). Performance in the vertex-TMS

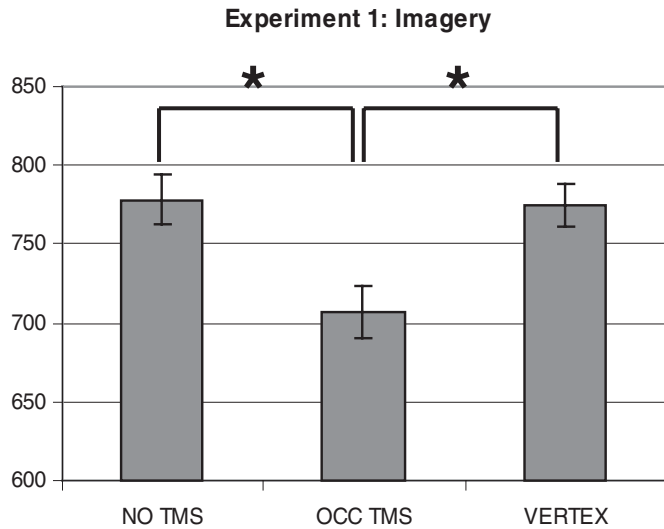


FIG. 3. The mean ($n = 14$) of subjects' reaction times (RTs) (corrected by accuracy) in the imagery task as a function of the transcranial magnetic stimulation (TMS) condition. TMS was applied at the end of the imagery period. TMS applied over the early visual cortex (OCC TMS) facilitated performance relative to the no-TMS (NO TMS) and the control (VERTEX) TMS conditions. The error bars, indicating ± 1 standard error of the mean, have been adjusted to remove between-subjects variance (Loftus & Masson, 1994). * $P < 0.05$.

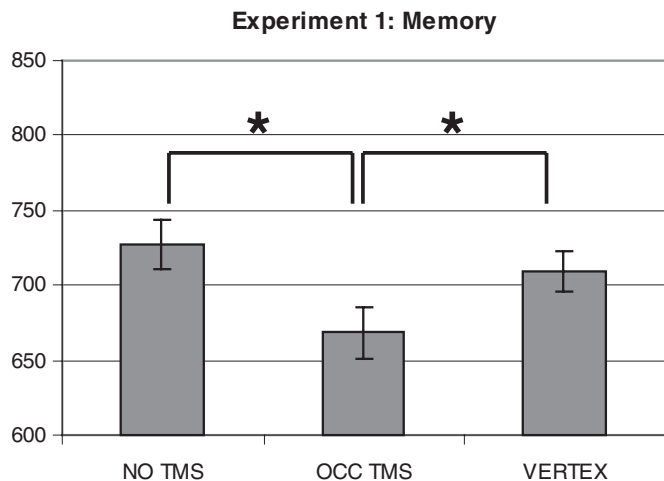


FIG. 4. The mean ($n = 14$) of subjects' corrected reaction times (RTs) in the memory task as a function of the transcranial magnetic stimulation (TMS) condition. TMS was applied at the end of the retention period. TMS applied over the early visual cortex (OCC TMS) facilitated performance relative to the no-TMS (NO TMS) and the control (VERTEX) TMS conditions. The error bars, indicating ± 1 standard error of the mean, have been adjusted to remove between-subjects variance (Loftus & Masson, 1994). * $P < 0.05$.

condition did not significantly differ from that in the no-TMS condition ($t_{13} = 1.33$; $P = 0.21$).

Control experiment

The mean detection accuracies were as follows: no TMS, 0.99; occipital TMS, 0.99; and vertex TMS, 0.99. A repeated-measures ANOVA revealed no significant main effect ($F_{2,20} = 1$; $P = 0.386$; $\eta^2 = 0.09$). Figure 5 shows the mean reaction times as a function of the TMS condition. A repeated-measures ANOVA with TMS site as the

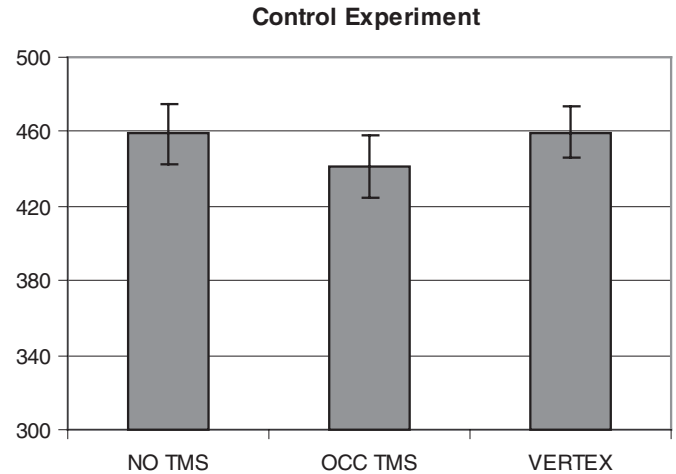


FIG. 5. The mean \pm SEM ($n = 11$) of subjects' corrected reaction times (RTs) in the dot detection task as a function of the transcranial magnetic stimulation (TMS) condition. TMS had no significant effect on subjects' performance. NO TMS, no-TMS condition; OCC TMS, TMS applied over the early visual cortex; VERTEX, control TMS condition.

main factor indicated no significant effect ($F_{2,20} = 0.89$; $P = 0.43$; $\eta^2 = 0.08$). This result shows that TMS did not facilitate the detection of the target dot.

Experiment 2

The mean detection accuracies in the imagery task were as follows: no TMS, 0.92; occipital TMS, 0.93; and vertex TMS, 0.92. A repeated-measures ANOVA revealed no significant main effect of TMS condition on accuracy ($F_{2,26} = 0.09$; $P = 0.92$; $\eta^2 = 0.01$). Figure 6 shows the reaction times in the imagery task as a function of the TMS condition. A repeated-measures ANOVA with TMS site as the main factor indicated no significant effect ($F_{2,26} = 0.17$; $P = 0.85$; $\eta^2 = 0.01$).

The mean detection accuracies in the memory task were as follows: no TMS, 0.93; occipital TMS, 0.88; and vertex TMS, 0.93. A

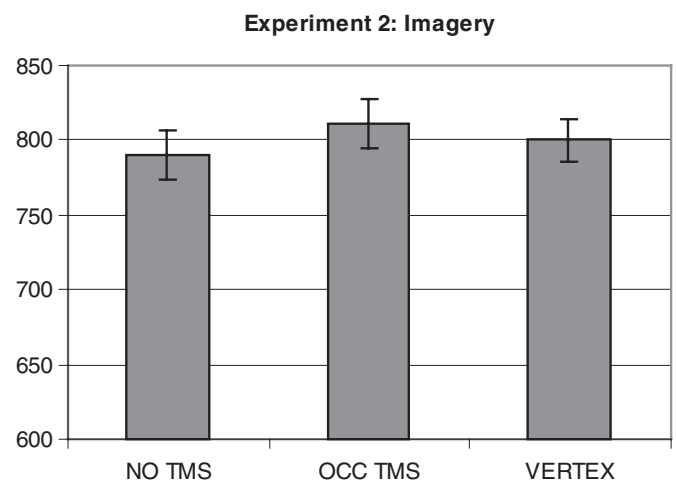


FIG. 6. The mean \pm SEM ($n = 14$) of subjects' corrected reaction times (RTs) in the imagery task as a function of the transcranial magnetic stimulation (TMS) condition. TMS was applied at the start of the imagery period. TMS had no effect on subjects' performance. NO TMS, no-TMS condition; OCC TMS, TMS applied over the early visual cortex; VERTEX, control TMS condition.

repeated-measures ANOVA revealed a significant main effect ($F_{2,26} = 5.70$; $P = 0.009$; $\eta^2 = 0.31$). *Post hoc* pairwise comparisons indicated that TMS applied over the occipital cortex impaired performance relative to the no-TMS condition ($t_{13} = 2.96$; $P = 0.011$) and to the vertex-TMS condition ($t_{13} = 2.30$; $P = 0.038$). Performance in the vertex-TMS condition did not significantly vary from that in the no-TMS condition ($t_{13} = 0.32$; $P = 0.75$). These comparisons show that occipital TMS impaired memory performance.

Figure 7 shows the mean of subjects' corrected reaction times in the memory task as a function of the TMS condition. A repeated-measures ANOVA with TMS site as the main factor indicated a significant effect ($F_{2,26} = 5.72$; $P = 0.009$; $\eta^2 = 0.31$). Pairwise comparisons indicated that TMS applied over the occipital cortex impaired performance relative to the no-TMS condition ($t_{13} = 2.76$; $P = 0.016$) and the vertex-TMS condition ($t_{13} = 2.94$; $P = 0.012$). Performance in the vertex-TMS condition did not significantly differ from that in the no-TMS condition ($t_{13} = 0.29$; $P = 0.78$).

An additional analysis was performed to directly contrast the differential effects of early (Experiment 2) and late (Experiment 1) TMS on the imagery and STM tasks. As the data for the two experiments did not have a homogeneous variance (STM task, Box's test of equality of covariance matrices, $P = 0.041$; imagery task, Box's test of equality of covariance matrices, $P = 0.006$), reaction times in the two TMS conditions (vertex and occipital) were normalized relative to the baseline no-TMS condition; this normalization was done by dividing the reaction time in the TMS condition by the reaction time in the corresponding no-TMS condition. These transformed data had the homogeneous variance required for the performance of a between-subjects ANOVA. A mixed repeated-measures ANOVA was performed for both the memory and imagery experiments, with TMS site (occipital, vertex) as within-subjects condition, and TMS time point (late TMS vs. early TMS) as between-subjects variable. There was a significant interaction for both the memory and imagery experiments (memory task, $F_{1,26} = 16.93$, $P < 0.001$, $\eta^2 = 0.39$; imagery task, $F_{1,26} = 4.34$, $P = 0.047$, $\eta^2 = 0.14$). This pattern of results confirms that 'late' occipital TMS facilitates both

imagery and STM performance, whereas 'early' occipital TMS impairs memory performance but has no effect on imagery task.

Discussion

The objective of Experiment 1 was to investigate the visual cortical activation states causally associated with visual imagery and STM at the end of the imagery/retention phase. In both tasks, we observed a facilitation of performance, indicating that TMS strengthened the imagery/memory representation; this shows that neurons in V1/V2 are causally involved in the maintenance of the mental image in both imagery and STM, and that these processes are associated with an increase in visual cortical excitability. The causal involvement of V1/V2 in memory maintenance is consistent with the studies by Harrison & Tong (2009) and Serences *et al.* (2009), which reported activation associated with the memory content in the early visual cortex (V1). Moreover, the finding that, in the control experiment, TMS did not facilitate the detection of the target dot in the absence of an imagery/memory task demonstrates that the TMS-induced facilitation in Experiment 1 was not due to TMS simply facilitating the processing of the target dot. Rather, the results of Experiment 1 are more likely to reflect an interaction between the effects of TMS and the early visual cortical activation state associated with visual imagery and STM.

The objective of Experiment 2 was to compare the early visual cortical activation states associated with visual imagery and STM at the beginning of the imagery/retention phase. In the memory task, the application of TMS immediately after the offset of the visual stimulus impaired performance, demonstrating a causal role for the early visual cortex in the initial encoding of the item to be remembered. In psychological terms, this might reflect a disruption of iconic memory, a very brief visual memory in which visual information from a recent image is stored for up to 1 s before 'reaching' STM (e.g. Sperling, 1960). This is also consistent with neuroimaging evidence showing that the occipital cortex is active during iconic memory, thus suggesting that neural activity in visual cortices can persist over several hundred milliseconds after the disappearance of the visual stimulus (Ruff *et al.*, 2007). No effect of TMS was found in the imagery task of Experiment 2, indicating that the early visual cortex is not strongly involved in the earliest stages of visual imagery.

The active transformation of a mental representation and the maintenance of a mental image are two distinct processes that are both subserved by working memory (Baddeley & Salame, 1986; Cornoldi & Vecchi, 2003). The latter process is required in both the imagery and memory tasks, and the finding that TMS had the same effect on the imagery and memory tasks when applied at the end of the delay period (Experiment 1) suggests that imagery and STM were mediated at that stage by similar cortical mechanisms. In contrast to the memory task, the imagery task required active transformation of a digital time into a corresponding iconic representation at the start of the delay period. The finding that there was no TMS effect in the imagery condition of Experiment 2 suggests that the early visual cortex is not causally involved in this active conversion.

Accordingly, previous findings have demonstrated that the actual transformation of the digital time to a mental image is subserved by a fronto-parietal network (e.g. Sack *et al.*, 2002, 2008) and that the involvement of the occipital cortex only occurs at a later stage in the conscious maintenance of this image (Kosslyn *et al.*, 2001). In particular, in the functional connectivity study by Sack *et al.* (2008), participants were asked to sequentially construct and spatially transform a mental visual object on the basis of either verbal or visual information. Only the 'visual' condition elicited early bottom-

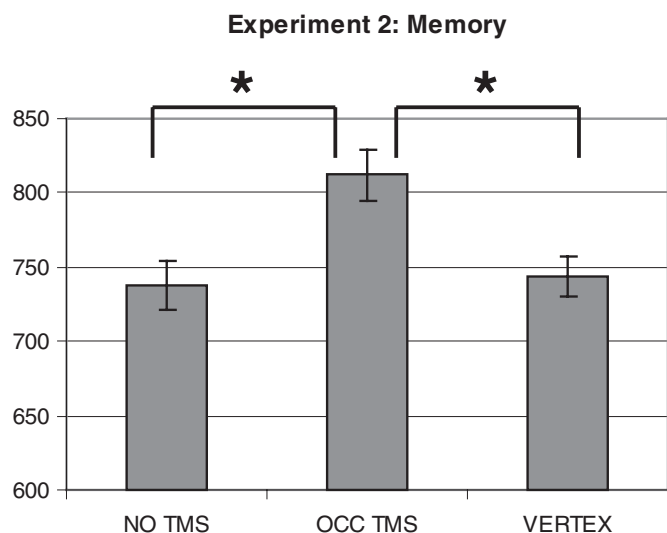


FIG. 7. The mean \pm SEM ($n = 14$) of subjects' corrected reaction times (RTs) in the memory task as a function of the transcranial magnetic stimulation (TMS) condition. TMS was applied at the start of the retention period. TMS applied over the early visual cortex (OCC TMS) impaired performance relative to the no-TMS (NO TMS) and the control (VERTEX) TMS conditions. $*P < 0.05$.

up activity in the occipito-temporal complex; this activation was interpreted to reflect online assembling of the serially presented visual inputs into a final, emerging visual object (Sack *et al.*, 2008). The disruptive 'early' TMS effect in our memory task is consistent with the view that there is an initial bottom-up transfer of visual information from occipital regions to higher cortical regions involved in memory maintenance (reflecting a transfer of the visual input from iconic memory to STM). However, when the mental image is not based on purely visual input, but requires more abstract manipulation (subserved by fronto-parietal areas), the 'early' visual cortical involvement is not critical (Sack *et al.*, 2008). Our study extends these findings by shedding light on the causal role of the early visual cortex in the 'early' and 'late' phases of imagery and memory.

Our results beg the question of how TMS can either facilitate behavior (as in Experiment 1) or impair behavior (as in the memory condition of Experiment 2). The answer is likely to lie in the interaction between TMS effects and the initial state of the targeted region. A number of behavioral studies (e.g. Silvanto *et al.*, 2007, 2008; Cattaneo *et al.*, 2008) suggest that single-pulse TMS may preferentially activate neurons in a low initial activation state (i.e. low firing rate) relative to more active neuronal populations. This conclusion is supported by modeling work demonstrating that a neuron in a high initial activation state (i.e. firing strongly in response to a visual stimulus) can be less excitable in response to strong external stimulation (such as a TMS pulse) than a neuron in a lower initial activation state (Mathews, 1999) [see also Siebner *et al.* (2009)]. In other words, there is a dissociation between neuronal excitability (i.e. susceptibility to external stimulation) and the initial activation state. On the basis of this dissociation, it has been argued that single-pulse TMS may, under certain circumstances, be more effective in affecting neurons in a low initial activation state than neurons strongly responding to visual stimulation (Siebner *et al.*, 2009).

The behavioral impairments and facilitations induced by TMS in the present study can be explained in the context of this state-dependency. TMS impaired performance in the memory task when applied at the very beginning of the delay period, immediately after the offset of the visual presentation of the memory item (Experiment 2). At this time point, neurons in V1/V2 encoding the memory item were presumably still firing in response to its visual presentation. The above model of state-dependency suggests that TMS applied at this time point was likely to preferentially activate neurons not strongly driven by the memory item (as these neurons were less active than neurons firing in response to its visual presentation and thus more excitable). This preferential activation of neurons not involved in encoding the memory item may have reduced the signal-to-noise ratio of the memory trace, producing the behavioral impairment. Such a state-dependent effect has been previously used to explain the disruptive effect of TMS on motion detection (Silvanto & Muggleton, 2008).

At the end of the delay period, neurons in V1/V2 were presumably no longer responding to the visual presentation of the memory item. Therefore, as the initial neural state in the memory task at the time of TMS application was different in Experiments 1 and 2, the impact of TMS is likely to be different as well. But why did TMS facilitate both imagery and memory tasks in Experiment 1? Visual imagery has been shown to make neurons more excitable in response to external stimulation [that is, neurons engaged in imagery are preferentially activated by TMS relative to other neurons; see Sparing *et al.* (2002)]. This preferential activation of neurons engaged in imagery is likely to strengthen the mental image and thus facilitate behavior. The novel finding in Experiment 1 is that TMS interacted with the memory task in the same way as it did with imagery (that is, there was a behavioral facilitation), suggesting that, at the end of the delay period, neurons

encoding the memory item were also more excitable. The important point to stress is that neurons in V1/V2 were unlikely to be firing in response to the visual presentation of the memory item at the end of the delay period. V1/V2 neurons were thus likely to be less active (but more excitable) at the end of the delay period than at its beginning. This difference in initial states could explain why TMS impaired memory in Experiment 2, but facilitated it in Experiment 1.

Our findings may seem to partially contradict those of Serences *et al.* (2009), who found a steady pattern of V1 activity associated with a memory item over a 10-s delay period, and that the pattern of the memory-related activity was similar to that associated with the encoding of the sensory stimulus. In fact, our findings suggest that the V1 activation state in visual STM changes over the delay period, with the excitability of neurons encoding the memory item increasing. From a theoretical perspective, our results suggest that the 'sensory recruitment hypothesis' of working memory might act via modulation of the excitability of neurons in V1 [rather than maintaining a tonic representation of the visual stimulus representation, as suggested by the findings of Serences *et al.* (2009)]. The discrepancy between our results and the findings of Serences *et al.* (2009) might result from the fact that TMS and fMRI give insights into slightly different aspects of neural activity. Because TMS is a tool for modifying rather than measuring neuronal activity, it is useful for investigating how excitable neurons involved in visual STM are in response to external stimulation. In contrast, fMRI may tell us more about the spatial distribution of neurons involved in STM in a given area, but less about the excitability states of those neurons.

Given that the application of TMS modulates neural activity in anatomically connected regions (e.g. Valero-Cabré *et al.*, 2005, 2007), it could be argued that the effects reported here reflect the impact of TMS on a network of cortical areas. However, the TMS literature does not support the view that the behavioral effects of TMS are generally due to such network effects. There are, indeed, plenty of examples of how the application of TMS over two different nodes within a network induces differential effects. For example, the visual areas V1 and V5/MT share strong anatomical connections, but the application of TMS over these areas induces different functional consequences (e.g. Mathews *et al.*, 2001; Thompson *et al.*, 2009). Similarly, the application of TMS over different nodes of the fronto-parietal network, the angular gyrus and the frontal eye fields induces distinct behavioral effects (e.g. Ruff *et al.*, 2008). Therefore, although the activation induced by TMS spreads to anatomically connected areas, there is no evidence that these network effects account for the functional effects of TMS [see also Sack (2009) for a detailed discussion of this issue].

In summary, our findings reveal the causal role of the early visual cortex in the 'early' and 'late' phases of visual imagery and STM. The results of Experiment 1 suggest that imagery and STM have similar excitatory effects on the activation state of the early visual cortical neurons, demonstrating that the two tasks recruit overlapping neural processes. This finding is consistent with the view that one mechanism, such as the 'visual buffer' (a structure embodying the conscious visual image in a depictive form) (Kosslyn & Ochsner, 1994), subserves both imagery and STM (Kosslyn *et al.*, 1999), and that this mechanism corresponds to the activity of visual cortical areas. As described in the Introduction, the psychological literature is in disagreement as to whether the structures used for these two functions overlap, and the present findings provide neural evidence for the view that such an overlap exists. Experiment 2 showed that the early visual cortex plays a causal role during the earliest stage of the retention period in visual STM; in contrast, this region had no such early involvement in visual imagery.

Abbreviations

fMRI, functional magnetic resonance imaging; SD, standard deviation; STM, short-term memory; TMS, transcranial magnetic stimulation; V1, area V1 of the early visual cortex; V2, area V2 of the early visual cortex; VSWM, visuo-spatial working memory; WM, working memory.

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