Disrupting frontal eye-field activity impairs memory recall

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A large body of research demonstrated that participants preferably look back to the encoding location when retrieving visual information from memory. However, the role of this 'looking back to nothing' is still debated. The goal of the present study was to extend this line of research by examining whether an important area in the cortical representation of the oculomotor system, the frontal eye field (FEF), is involved in memory retrieval. To interfere with the activity of the FEF, we used inhibitory continuous theta burst stimulation (cTBS). Before stimulation was applied, participants encoded a complex scene and performed a short-term (immediately after encoding) or long-term (after 24 h) recall task, just after cTBS over the right FEF or sham stimulation. cTBS did not affect overall performance, but stimulation and statement type (object vs. location) interacted. cTBS over the right FEF tended to impair object recall sensitivity, whereas there was no effect on location recall sensitivity. These findings suggest that the FEF is involved in retrieving object information from scene memory, supporting the hypothesis that the oculomotor system contributes to memory recall. ***NeuroReport*** **00:000–000**

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Introduction

Studies have shown that when mentally visualizing a scene – for example, a Caribbean beach while sitting in an air-conditioned office room – the eyes move according to its content [1], even in complete darkness [2]. Moreover, eye movements are functional for scene recall from memory. When participants were asked to describe a visually or auditorily encoded scene from memory, they were less accurate when asked to maintain fixation compared with free viewing [3]. In the present study, we introduced a novel technique to this research field, by investigating whether visual memory recall is impaired when the activity of an important area in the cortical representation of the oculomotor system, the frontal eye field (FEF), is interfered with.

The FEF is well known for its role in the control and planning of eye movements; in addition to this, it plays a role in a number of cognitive operations (see Vernet *et al.* [4] for a review). To our knowledge, FEF's role in long-term memory has not yet been investigated. However, a functional involvement of this oculomotor brain area in memory can be expected, as many studies showed that eye movements are involved in memory retrieval. A large body of research demonstrates that participants look back to the encoding location when they retrieve visual information from memory [5,6]. However, the role of 'looking back to nothing' during memory recall is still under investigation. Recently, Johansson and Johansson [7] tested whether eye movements are involved in object recall. After encoding arrays of object images, participants were asked to judge statements concerning the orientation or location of certain objects. Crucially, the task was performed under different instructions that affected eye-position. Memory performance was impaired when participants were asked to restrict their eye movements to a region that was incongruent with the encoding location. The authors concluded that eye movements play a functional role in memory recall. Similarly, it has recently been demonstrated that, when answering questions about previously encoded stimuli, participants make fewer errors when they are free to move their eyes during mental image generation compared with fixation [8]. These results suggest that eye movements support the generation of detailed mental images.

To experimentally investigate the functionality of eye movements during recall, previous studies used two different approaches to manipulate gaze behavior. First, researchers compared memory recall accuracy when participants were asked to maintain fixation or were free to move their eyes [3,6–8]. However, as this fixation condition introduces attentional demands in addition to the memory task, cognitive load may be increased. Impaired accuracy might thus occur due to influences other than the imposed oculomotor restriction [9]. This problem can

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potentially be circumvented by modifying the gaze manipulation. Another approach involves participants to keep their eye movements within a specific region of the screen, which could be either congruent or incongruent with respect to the encoding location [5,7]. Nevertheless, restricting eye movements to specific areas does not necessarily prevent participants from using their fixations within these confined areas to regenerate mental images of previously encoded stimuli. Taken together, gaze manipulation approaches pose several problems, and the experiments carried out so far cannot rule out potential confounds. To circumvent these potential caveats, we used a different approach.

We applied a continuous theta burst stimulation (cTBS) protocol to interfere with the activity of the right FEF, an important area in the cortical representation of the oculomotor system. Applying cTBS over the right FEF has been consistently shown to impair oculomotor control in previous studies [10–12]. Participants encoded a complex scene, and they later had to verify or falsify statements about objects and their spatial properties from memory. Although 'looking back to nothing' seems to persist up to 1 week after encoding [5], the functionality of eye movements during recall has not been tested after longer time intervals between encoding and recall. Crucially, in the present study, cTBS was applied over the right FEF immediately before recall was tested, either immediately after encoding or after 24 h, and a control group received sham stimulation. Interfering with an important area in the cortical representation of the oculomotor system using cTBS, instead of restricting eye movements to specific regions, entails the advantage that this manipulation primarily affects the control of eye movements at a cortical level, rather than restricting eye movements per se at the endpoint of the oculomotor loop. On the basis of the hypothesis that eye movements play a functional role in memory recall, we expected that interfering with the activity of an important area in the cortical representation of the oculomotor system such as the FEF would impair memory retrieval.

Methods

Participants

A total of 64 participants were recruited. There were 53 women in the sample. The mean age was 21.75 years (SD = 3.37, range: 18–40). Most participants ($n = 57$) were right-handed. Participants received course credits for their participation. They all gave written informed consent to participate before the experiment and were treated in accordance with the protocol approved by the local ethics committee (KEK-Nr. 220/13) and with the Declaration of Helsinki.

Design

The design of our study embraces three variables: the between factor stimulation (FEF cTBS, sham) and delay between encoding and recall (immediate, 24 h), and the within factor recall statement type (object, location). Thus, four groups of participants took part in the study: immediate recall with cTBS over the right FEF ($n = 16$), immediate recall with sham stimulation ($n = 16$), 24 h delayed recall with cTBS over the right FEF ($n = 16$), and 24 h delayed recall with sham stimulation ($n = 16$). All participants recalled both object and location information from the encoded scene.

Material

The stimulus was a complex scene (Fig. 1b). The basis of the scene was the Virgin music© 75 bands picture (1280 × 1024 pixels; $\sim 27° \times 22°$ visual angle). For the recall task, we formulated statements about the objects in the scene and prerecorded them as audio files. The scene was subdivided into 4 × 4 fields. To increase the complexity of the stimulus and to balance the number of objects across the 16 fields in the image, we modified the scene and added some elements using Adobe Photoshop CS6 (Adobe Systems, San Josè, California, USA). Ninety-six (32 + 64) audio files of object names were created for the encoding task. Importantly, the 32 objects that were later recalled were included in the encoding task along with 64 distractor objects.

Two objects were chosen from each of the 16 fields. One of these two objects was associated with a correct and a false statement about its physical appearance (e.g. 'the zeppelin had a yellow stripe'), and the other object was associated with a correct and a false statement about its location (e.g. 'the coin was in front of the dog'). Thus, a total of 64 statements were prerecorded for the recall task. The statements were specific to the objects in the scene, and could thus not be correctly answered by general knowledge. During recall, the screen remained blank after the presentation of a central fixation cross.

Apparatus

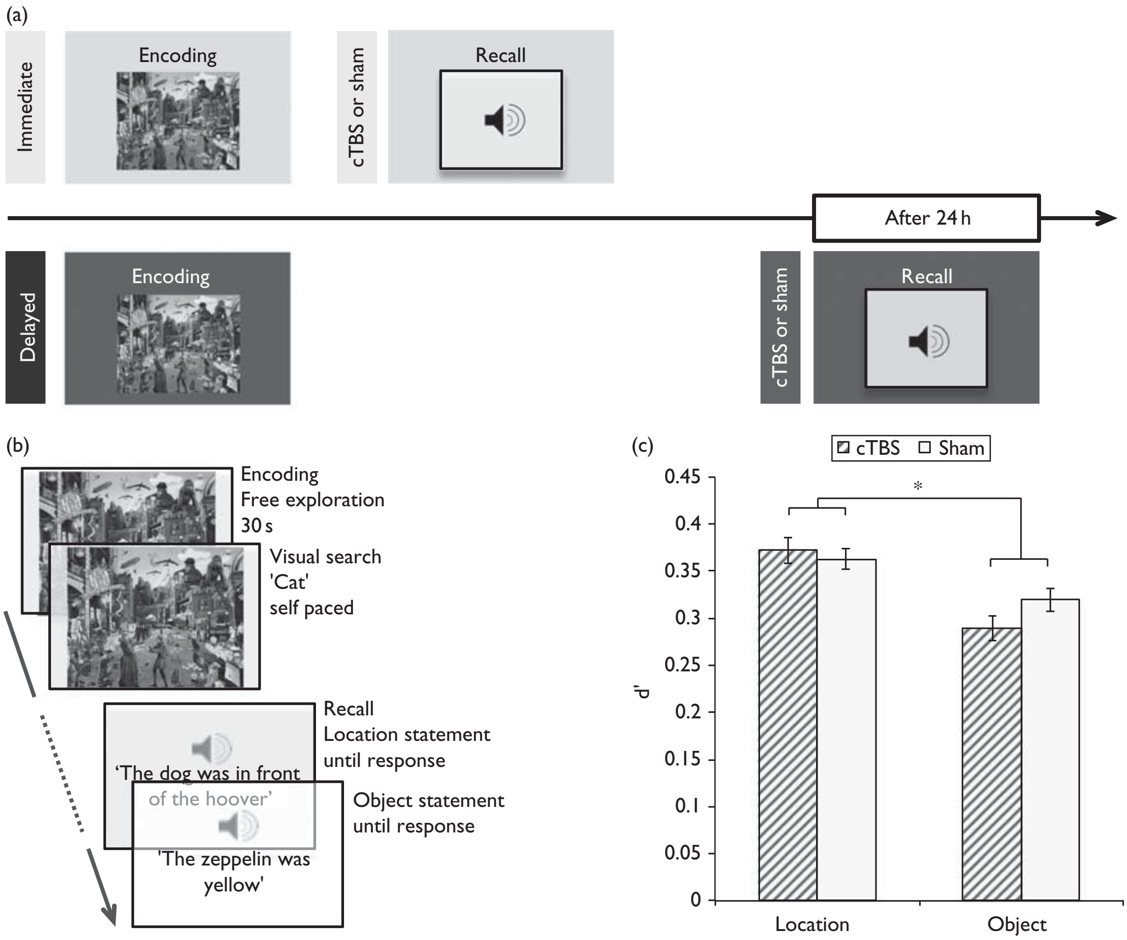
cTBS was applied by means of a MagPro × 100 stimulator (MagVenture, Farum, Denmark) using a figure-of-eight coil (Magnetic Coil MC-B70; Medtronic Functional Diagnostics, Skovlunde, Denmark) or a sham coil (Magnetic Coil MC-P-B70; Medtronic).

Procedure

An overview of the procedure is provided in Fig. 1a. Half of the sample completed the experiment (consisting of an encoding and a recall task) in one session; the other half of the sample performed the encoding task on day 1, and received brain stimulation and completed the recall task after 24 h.

In the encoding task (Fig. 1b), participants were presented with a complex scene for 30 s. They were instructed to look at the scene carefully and to memorize as many details as possible. To deepen encoding, after freely viewing the scene (30 s), the participants were

Fig. 1



(a) The experiment consisted of two phases, an encoding phase and a recall phase. Participants either performed the recall task immediately after encoding or after 24 h. Just before the recall task started, participants received cTBS over the right FEF or sham stimulation. (b) In the first phase of the study, participants encoded a complex scene and performed a visual search task to deepen encoding. In the second phase, participants were presented with statements about the objects or their location in the scene while they were looking at a blank screen. Importantly, participants received cTBS over the FEF or sham stimulation right before the recall task started. (c) cTBS over the FEF impaired object memory recall sensitivity, across delay groups. *Significant interaction (0.05 level) between stimulation (sham, FEF cTBS) and statement (location, object recall). cTBS, continuous theta burst stimulation; FEF, frontal eye field.

informed that they would hear object names through the loudspeakers, and were instructed to search the corresponding objects in the scene and to point at them. In total, 96 objects (32 that later appeared in the recall task plus 64 distractors) had to be searched. When the participant pointed at the correct object in the scene, the experimenter triggered the audio file corresponding to the next object name. The order of the objects to be searched was random. On average, the encoding task took $M = 13{:}42$ (SD = 1:27) min.

Before the recall task, half of the sample (each $n = 32$) received cTBS over the right FEF, whereas the other half received sham stimulation. Because stimulating the right FEF leads to more bilateral effects [13,14], we applied cTBS or sham stimulation to the right and not the left FEF. In half of each stimulation group (each $n = 16$), the stimulation was applied immediately after encoding, and after 24 h in the other half. cTBS was delivered at 80% of each participant's individual resting motor threshold, using a cTBS protocol [12]. The protocol consisted of 801 pulses, delivered in 267 bursts of three pulses at 30 Hz each, with an interburst interval of 100 ms. The total duration of the protocol was 44 s. This offline approach was chosen due to its relatively long-lasting offline effects (up to 30 min after stimulation [12]). The right FEF was localized as previously described [10,15]. In brief, the resting motor threshold of the right motor cortex was determined using single pulses. The coil (with the handle pointing backwards) was then shifted 2 cm anteriorly from this area. Participants in the sham group received sham stimulation according to the same protocol, delivered with a figure-of-eight sham coil.

The sham coil generated similar discharge noises as during real stimulation, and produced a mild cutaneous sensation, but did not affect the activity of the underlying cortical tissue.

Immediately after brain stimulation, memory recall (Fig. 1b) was tested. During recall, the screen was blank. Participants listened to statements about the scene, and were asked to judge whether these statements were correct or wrong. Before each audio file was presented, a central fixation cross appeared for 500 ms. There were 64 statements (two statements for each of the 32 objects) in total, presented in random order. Participants were asked to press the key 'K' on a keyboard if the statement was correct, and the key 'F' if the statement was false. On average, the duration of the recall task was $M=7{:}15$ (SD = 0:54) min.

Results

To test the hypothesis that cTBS over FEF would impair memory recall, we computed a three-factorial mixed analysis of variance on memory performance, as measured using d' (proportion of hits minus proportion of false alarms), with stimulation (FEF cTBS, sham) and delay (immediate, 24 h) as between factors, and statement type (location, object) as within factor. The results revealed a main effect of statement type [$F(1, 60)=55.422$, $P<0.001$, $\eta_p^2=0.48$], indicating that performance was generally higher in location compared with object recall trials. Furthermore, performance was generally higher immediately after encoding compared with that after 24 h, as indicated by the main effect of delay [$F(1, 60)=4.882$, $P=0.031$, $\eta_p^2=0.075$]. Stimulation did not affect overall performance [$F(1, 60)<1$] but stimulation and statement type significantly interacted [$F(1, 60)=5.287$, $P=0.025$, $\eta_p^2=0.081$] (for an illustration, see Fig. 1c). Bonferroni-corrected post-hoc comparisons revealed that FEF cTBS, compared with sham stimulation (immediate and delayed recall groups pooled), impaired object memory recall sensitivity by trend ($P=0.095$), but did not affect location memory recall sensitivity ($P=0.589$). No other interaction reached significance, all P values were greater than 0.122.

To ensure that the effect of cTBS on object recall sensitivity did not occur due to a speed-accuracy tradeoff, we calculated an analysis of variance on the median reaction time data (in ms) of hits, with the within factor statement type (location, object), and the between factor stimulation (FEF cTBS, sham) and delay (immediate, 24 h). Generally, reaction times in object recall trials were faster ($M=4109$, SD = 499) than that in location recall trials ($M=4882$, SD = 636), as indicated by the significant main effect of statement type [$F(1, 60)=114.376$, $P<0.001$, $\eta_p^2=0.656$]. Importantly, there was no significant interaction between statement type and stimulation ($P=0.340$), indicating that the effect of cTBS on memory performance (d') did not occur due to a speed-accuracy trade-off. However, the three-way interaction (stimulation × delay × statement type) reached significance [$F(1, 60)=5.747$, $P=0.020$, $\eta_p^2=0.087$]. Bonferroni-corrected post-hoc comparisons revealed reaction time differences between the immediate ($M=4456$, SD = 482) and the delayed ($M=5022$, SD = 608) cTBS group ($P=0.002$), and the immediate sham group ($M=5112$, SD = 822, $P=0.009$) on location trials. No other main effect or interaction reached significance; all P values were greater than 0.069.

Discussion

In the present study, we investigated whether an important area in the cortical representation of the oculomotor system, the FEF, is functionally involved in memory recall. We applied cTBS over the FEF, and this influenced recall performance. This study is motivated by a large body of research demonstrating that, when people retrieve visual or verbal information from memory, they tend to look back to the location where this information has been encoded [5–6,16–20]. However, purely behavioral studies present several potential confounds that limit their conclusions.

The results of our study suggest that cTBS over the FEF tended to impair object recall sensitivity. Impaired recall performance after interfering with the oculomotor system is in line with the findings of previous studies. These studies have demonstrated that retrieval is worse when eye movements are restricted to a specific region of the screen [2–3,6–8,20]. Specifically, recent findings indicate that object recall accuracy is impaired during central fixation compared with free viewing [8]. Although memory performance decreases in previous studies, manipulating gaze position, could be explained by a spatial mismatch between encoding and recall locations, here we provide evidence that memory is impaired when the FEF, an important area in the cortical representation of the oculomotor system, is interfered with. This finding supports the hypothesis that oculomotor mechanisms are a critical component for reinstating visual images from memory [6,8].

The application of inhibitory cTBS over the right FEF before recall impaired retrieval sensitivity (d') across delay groups. Previous studies investigating the functional significance of eye movements during recall on a blank screen typically tested memory only shortly after encoding. An exception is the study by Martarelli and Mast [5], who asked participants to encode images at different locations of the screen and tested recall 1 week after encoding. Participants still spent more time fixating the encoding location during recall. Our findings complement and extend this effect, indicating that oculomotor mechanisms do not only support short-term recall but are also functional after longer encoding–retrieval intervals. Paradoxically, cTBS seemed to shorten reaction times on location trials immediately after encoding. As this was an unexpected effect, we can only speculate about its theoretical meaning with caution and we plead for more research to verify this possible effect of cTBS on response times.

Given that typical oculomotor parameters (e.g. saccade latencies) are difficult to measure in a 'blank screen paradigm' (as no perceptual information is presented and thus processed), we do not report eye-tracking data in this manuscript. Previous studies consistently found increased saccade latencies applying exactly the same cTBS protocol over the FEF [11,12]. However, we cannot exclude that the influence of brain stimulation on object recall might have been modulated by other cognitive functions that depend on the FEF. The FEF is not only an important cortical area for planning, programming, and executing eye movements but it is also involved in cognitive mechanisms such as spatial priming, working memory, and memory search (see Vernet *et al.* [4] for a review). Critically, the FEF is also prominently involved in spatial attention (see Crowne [21] for a review), and several studies suggest that both oculomotor and attentional mechanisms are supported by FEF neurons [22–24]. Thus, it is plausible that cTBS over the FEF also affected some of these cognitive functions, and this, in turn, contributed to impaired memory recall.

Here, we showed that inhibiting the activity of the right FEF by means of cTBS impairs memory recall. Our findings provide evidence that the FEF is involved in memory, supporting the hypothesis that oculomotor mechanisms contribute to mental visualization of stimuli from memory [6,8].

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Conflicts of interest
There are no conflicts of interest.

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