Prefontal cortex in long-term memory: an "interference" approach using magnetic stimulation

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Neuroimaging has consistently shown engagement of the prefrontal cortex during episodic memory tasks, but the functional relevance of this metabolic/hemodynamic activation in memory processing is still to be determined. We used repetitive transcranial magnetic stimulation (rTMS) to transiently interfere with either left or right prefrontal brain activity during the encoding or retrieval of pictures showing complex scenes. We found that the right dorsolateral prefrontal cortex (DLPFC) was crucial for the retrieval of the encoded pictorial information, whereas the left DLPFC was involved in encoding operations. This 'interference' approach allowed us to establish whether a cortical area activated by a memory task actually contributes to behavioral performance.

In vivo investigation of the functional correlates of learning and memory in humans is currently possible with neuroimaging techniques measuring regional cerebral blood flow and metabolism, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). The results of neuroimaging investigations are largely convergent with the clinical findings in amnesic patients[1], which suggest a pivotal role of medial temporal lobe structures—in particular, the hippocampal formation—in long-term episodic memory[2]. More controversial is the neuropsychological evidence for the involvement of the frontal lobe in human episodic memory. Lesions of the frontal lobes are not usually associated with clinically evident amnesia. However, a consistent activation of the prefrontal cortex has been found not only during working memory tasks[3], but also during long-term episodic learning[4,5]. In addition, deficits in source memory[6] or memory for temporal order (recency)[7] have been reported following frontal lobe lesions in man, and meta-analytical evidence exists for impairment in free recall tasks after frontal damage[8].

Imaging studies of episodic memory, mostly for verbal stimuli, suggest a hemispheric encoding–retrieval asymmetry; the left prefrontal cortex is crucial in encoding, and the right prefrontal cortex in retrieval. The hemispheric encoding–retrieval asymmetry (HERA) model[9], developed from these observations, is now the focus of a number of imaging studies that have tried to characterize other factors affecting both the hemispheric asymmetry and the functional neuroanatomical subdivisions of frontal activation. In agreement with clinical neuropsychological evidence[10], prevalent right-sided or bilateral activations have been observed during the encoding of non-verbal items such as unfamiliar faces[11] or complex scenes[12]. However, the the left prefrontal cortex is also activated in response to non-verbal stimuli such as unfamiliar faces or complex figures[13]. Prevalent right prefrontal activation has been associated with successful retrieval[14,15], retrieval effort[16] or monitoring of the retrieved information[17]; left prefrontal activation has also been observed in studies dealing with recognition[18] and source memory[19].

Thus, both the material and the type of memory process may affect the lateralization of frontal activation during memory tasks. In addition, distinct portions within the frontal lobe (such as ventrolateral, dorsolateral and anterior prefrontal cortex) may be engaged in different aspects of memory performance[5]. VLPFC has been associated with the maintenance of information; DLPFC, with manipulation and/or monitoring; and AFC, with selection of processes and/or subgoals.

To better clarify the role of the DLPFC(s) in encoding and retrieval memory process, it might be helpful to use methodologies which do not depend solely on the measurement of the metabolic or hemodynamic response to cognitive challange, but which directly and transiently block the functional participation of a "candidate" brain region. This can be achieved with transcranial magnetic stimulation, a widely used technique for motor control research and clinical testing[20,21]. Repetitive TMS (rTMS) discharges trains of magnetic impulses repetitively in a few hundred milliseconds, reaching cortical regions of interest. This method allows safe interference with the complex neural networks underlying somatosensory perception[22], motor-related cerebral activity[23] and

Table 1. Percentages of hits, false alarms and measures of signal detection (C and d′) in the different experimental conditions.

Conditions	Hits (mean % ± s.d.)	False alarms (mean % ± s.d.)	Criterion C (mean ± s.d.)	d′ (mean ± s.d.)
R-Enc	65 ± 18	20 ± 13	1.02 ± 0.67	1.44 ± 0.62
L-Enc	54 ± 28	26 ± 14	0.68 ± 0.42	0.79 ± 0.83
Sham	74 ± 19	21 ± 17	1.05 ± 0.82	1.87 ± 0.93
R-Ret	58 ± 29	41 ± 23	0.28 ± 0.65	0.58 ± 0.58
L-Ret	77 ± 15	33 ± 13	0.47 ± 0.39	1.37 ± 0.69
Baseline	76 ± 14	22 ± 15	0.97 ± 0.72	1.86 ± 1.01

L-Enc, left DLPFC rTMS in encoding; no stimulation in retrieval. R-Enc, right DLPFC rTMS in encoding; no stimulation in retrieval. Sham, sham rTMS (left DLPFC in encoding and right DLPFC in retrieval). R-Ret, right DLPFC rTMS in retrieval; no stimulation in encoding. L-Ret, left DLPFC rTMS in retrieval; no stimulation in encoding. Baseline, no stimulation. Each value refers to pooled subjects (13 for each condition).

higher cognitive functions[21,24], and provides direct insights into the involvement of stimulated areas by means of measurable behavioral performance.

Here we used focal rTMS to transiently disrupt the function of the left or right DLPFC, in order to clarify the roles and functional prevalence of these regions in the mechanisms of encoding and retrieval of complex images (**Fig. 1**). Six conditions were studied, R-Enc (right rTMS in encoding, no stimulation in retrieval), L-Enc (left rTMS in encoding, no stimulation in retrieval), sham (left rTMS in encoding and right in retrieval), R-Ret (no stimulation in encoding and right rTMS in retrieval), L-Ret (no stimulation in encoding and left rTMS in retrieval) and baseline (reference condition, no stimulation in encoding or in retrieval). Thus, the effects of right and left prefrontal stimulation applied during encoding and retrieval were compared with baseline and sham rTMS conditions. This interference approach may help to better clarify the functional significance of the frontal lobe in long-term memory.

Results

The two measures 'C' (criterion) and 'd'' (discrimination), derived from signal detection theory, were computed on the behavioral data (**Table 1**). C was inversely related to the proportion of false positives (when, during retrieval, subjects erroneously answered that a distractor had been seen in the encoding phase). The index d′ indicated the ability of subjects to distinguish between 'already seen' and 'never seen' pictures. Both indices significantly varied across experimental conditions (C, $F_{5,60} = 5.224$, $p < 0.001$; d′, $F_{5,60} = 7.921$, $p < 0.001$). However, after Tukey's correction, only in the R-Ret condition did C decrease (versus baseline, $p = 0.012$; versus R-Enc, $p = 0.006$; versus sham, $p = 0.003$), suggesting that subjects tended to be less specific, with more intrusions of unseen pictures during right DLPFC rTMS. None of the other pairwise comparisons were significant. On the other hand, both L-Enc (versus baseline, $p = 0.003$; versus sham, $p = 0.002$) and R-Ret (versus baseline, $p < 0.001$; sham, $p < 0.001$) lowered d′. R-Enc and L-Ret did not produce any significant difference compared to either baseline or sham ($p > 0.40$). These results confirm that the left DLPFC during encoding and right DLPFC during retrieval are involved in the modulation of memory trace strength. However, whereas a specific interference of right DLPFC stimulation was further highlighted by R-Ret versus L-Ret contrast ($p = 0.047$ after Tukey's correction), the L-Enc versus R-Enc contrast was not significant ($p = 0.175$).

Focusing the analysis of variance (ANOVA) on the HERA model (with 'right versus left hemisphere' and 'stimulus side in encoding versus retrieval' as within-subjects factors), the main effects of hemisphere and stimulus were not statistically significant ($F_{1,12} = 0.119$, $p = 0.736$ and $F_{1,12} = 0.435$, $p = 0.552$, respectively), but a significant interaction effect occurred ($F_{1,12} = 35.08$, $p < 0.001$; **Fig. 2a**).

Reaction times for each response were consistently faster in encoding than in retrieval. Logistic regressions in search of correlations between reaction time and error rate were not statistically significant. However, taking reaction time as dependent variable

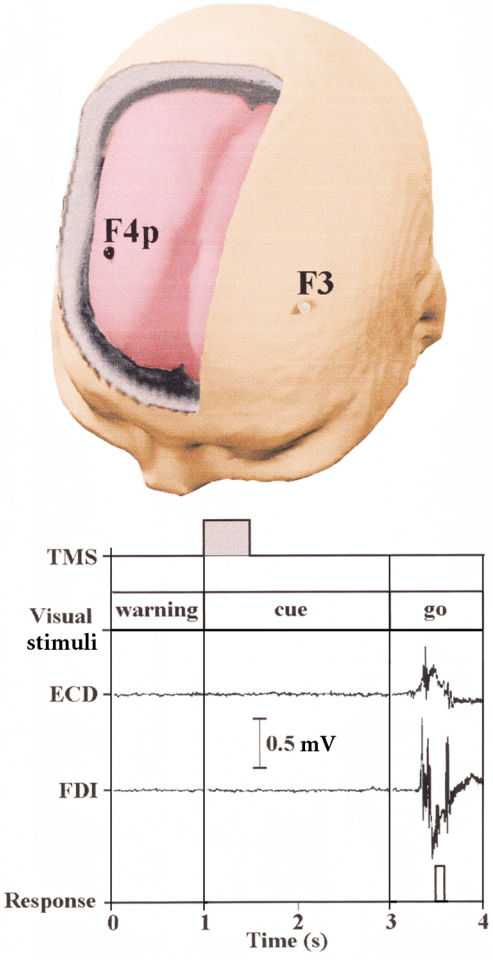

Fig. 1. Sites of TMS and experimental timing. Top, position of scalp electrode site F3 (10–20 International EEG system) on a scalp model, and position of the perpendicular projection of F4 on a cortical model (F4p). Models were obtained by averaging the magnetic resonance images of 152 subjects (SPM96). Talairach coordinates for F4p are (42, 32, 31), which correspond to superior frontal gyrus/Brodmann area 9. Analogous results can be obtained with the projection of F3 on the scalp model. This allows a rough localization of the cortical site stimulated by rTMS with the focal coil. Bottom, typical time course of the experimental condition with respect to visual and rTMS stimulations; EMG of the ECD and FDI muscles and of the motor response. rTMS stimulation applied to the scalp electrode site F3 did not elicit EMG activity.

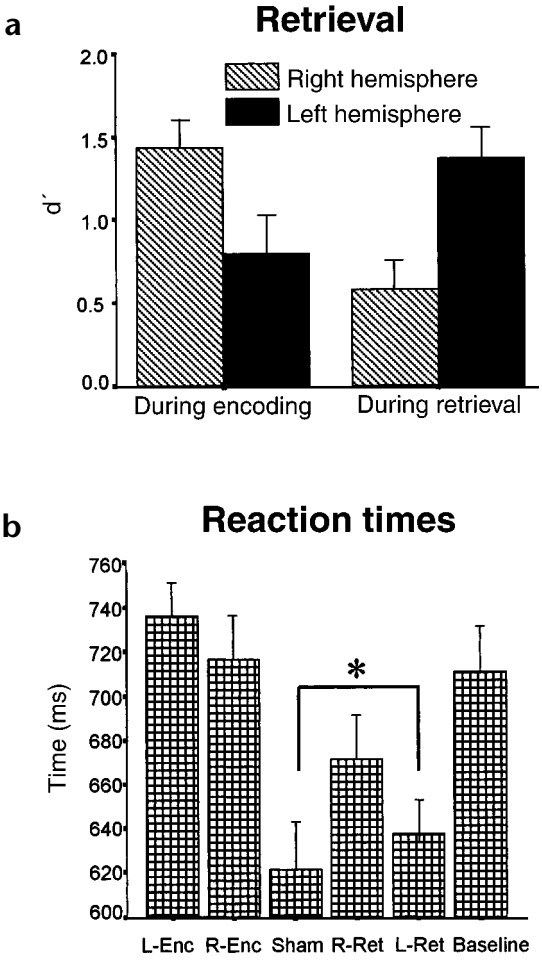

Fig 2. Effects of rTMS on retrieval and reaction time. (**a**) Hemispheric interaction of rTMS effects on d´. (**b**) Mean values of reaction times in the different conditions of retrieval. The presence of rTMS, either active or sham, shortens reaction times, irrespective of the stimulated site. See text for statistical evaluations.

with condition as an independent variable, two patterns distinguishing the effects of rTMS on performance from that on reaction time emerged. First, reaction times in retrieval were significantly associated with condition ($F_{5,60.76} = 2.884$, $p = 0.021$). Second, the Tukey's procedure identified two statistically different ($p < 0.001$) subsets that were internally homogeneous: blocks in which real or sham TMS were applied during retrieval (sham, R-Ret and L-Ret; $p = 0.188$) and blocks without stimulation ($p = 0.857$); (**Fig. 2b**).

Discussion

rTMS transiently and safely interferes with the function of cortical networks involved in cognitive processes; this offers advantages for the investigation of the neurophysiological mechanisms underlying cognitive task performance. PET and fMR, indeed, are able to detect regional 'activations' with excellent spatial resolution, but their relatively low time discrimination does not allow for tracing the hierarchical organization in a distributed network. Moreover, it is difficult to determine unequivocally if the detected metabolic changes result in a net facilitatory or inhibitory effect on behavior. In contrast, if the transient interference induced by rTMS results in the worsening of behavioral performance, this may provide strong evidence for the active involvement of the stimulated brain area in the process under study[25] and for its place in a functional hierarchy. Nevertheless, the intimate mechanisms of rTMS interference—and its selectivity within functional subregions—still need to be fully determined. The present findings provide direct evidence for a functional role of the prefrontal cortex in long-term episodic memory processes. The hemispheric asymmetry effects observed in this study seem to extend the HERA model of verbal episodic memory organization in the brain[26] to the visuospatial domain.

The high error rate after right stimulation during retrieval (**Table 1**) suggests that the rTMS-induced disrupting effect is direct, as it takes place immediately after the stimulation period, while the retrieval effort is active. In other words, the interference of rTMS persisted for at least 1.5 seconds after the end of stimulation (**Fig. 1**), and was associated with an increased number of false positive responses. Patients with frontal lesions tend to produce more 'false alarms' in recognition memory tasks[27,28]. Taken together, these findings indicate a selective specialization of the right DLPFC in the monitoring phase of retrieval[17] during yes/no recognition tasks of complex visuospatial stimuli.

Left rTMS applied during the encoding process significantly reduced the probability of successful retrieval of the encoded information (**Table 1**), providing direct confirmation of previous neuroimaging evidence suggesting that the left DLPFC is crucial in encoding mechanisms[29]. This finding is striking, considering that the encoded information (complex scenes) has shown prevalence in the right hemisphere[12]. The effect might result from less efficient ('shallow') encoding and/or from a faster decay of the information, due to concomitant rTMS. However, as the L-Enc versus R-Enc contrast was not significant (despite the finding that R-Enc, unlike L-Enc, did not differ between sham and baseline), the present findings suggest that a bilateral PFC engagement, with left functional prevalence, is associated with encoding of pictorial material memory traces.

The regions affected by rTMS in the present study are probably the same as those engaged in working memory tasks[5,30,31]. Many neuroimaging investigations during working memory tasks have suggested that the DLPFC is crucial in the short-term retention of information. In particular, Brodmann area 46 seems to be associated with the selection of response, whereas areas 9 and 8 seem crucial for the maintenance of the representations[32]. These regionally specific nodes within the working memory distributed neuronal network are capacity-constrained in the physiological domain[31]; rTMS might transiently disable the processing contribution of DLPFC and adjacent structures to the circuitry of working memory, inducing a dramatic decrement of its capacity in the active manipulation of information[5]. Indeed, pictures were always available during the task (**Fig. 1**), so that working memory processes might occur only during self-monitoring of the responses in the previous trials or together with an influence on executive frontal functions (management of instructions, visuomotor transformation and response selection). The location of the activations associated with material specificity, however, seems to be in the VLPFC[5], which was unlikely to be directly affected by rTMS of middle/superior frontal regions. This part of the PFC may be less sensitive than the VLPFC to the nature of information content, and seems to show a left-sided functional prevalence.

The low error rate in retrieval during left rTMS ruled out the possibility that any interference of rTMS with frontal eye fields (affecting the accuracy of saccades[33] needed to scan the picture) contributed to recognition errors.

Reaction times were consistently faster during encoding than during retrieval, reflecting the expected different cognitive demand. Concomitant rTMS, either sham or active, ipsi- or contralateral to the moving hand, significantly shortened reaction times (**Fig. 2b**). This suggests no direct motor-related effects of this type of rTMS, but rather, a nonspecific arousal effect that did not influence the cognitive process, but intersensory facilitation mechanisms[34] due to the noise of the coil discharging cannot be ruled out.

However, the physical effect of low-intensity TMS is to induce currents in the brain that flow almost parallel to the cortical surface. These currents result in an immediate trans-synaptic activation of a discrete brain volume underneath the coil[35] followed by activation of other regions functionally connected with the stimulated one[23,36,37,38]. The observed interference effect of the rTMS might take place on the whole distributed neural cortical network that is involved in a particular task. In this framework, it is difficult to ascertain whether some remote effects of DLPFC stimulation might extend to more ventral regions through extant functional connections, whereas the low intensity and the selectivity of stimulation make improbable a direct spread of the magnetic stimulus to VLPFC and AFC. This might explain the relatively low specificity of the effects induced by rTMS of DLPFC(s). Indeed, the same site of brain stimulation may lead to interference with other aspects of memory function, including working memory[38,39], procedural learning[40] and semantic memory[41].

Possible trans-synaptic effects of rTMS on memory processes, including an 'at distance' (diaschisis) interference on hippocampal function, could not be addressed in the present protocol, but may be amenable to investigation using combined PET–TMS protocols.

Methods

Subjects. Thirteen healthy volunteers (9 female), 22 to 41 years old (average, 30.1), naive to the pictures presented, gave their written informed consent for the study, after the approval of the protocol by the local Ethics Committee. All were right handed (mean dexterity, 89%) according to the Edinburgh handedness inventory[42]. Their medical history and examination were normal, and they had never taken neuroactive drugs.

Subjects sat on reclining chairs with their heads stabilized by restraints, in front of a 17-in monitor. Their right index finger rested between 2 buttons spaced 6 cm apart.

Experimental conditions. Six blocks of encoding were followed by six blocks of retrieval, and the order of presentation was pseudorandomized and counterbalanced among subjects. For each block of the encoding phase, 16 complex colored magazine pictures (8 interiors and 8 external landscapes) were randomly presented on the monitor for 2 s each, with 2 intertrial intervals (18 or 25 s long, 8 and 5 subjects, respectively). Images were preceded by a visual warning stimulus (a red spot lasting 1 s). Subjects were instructed to press with their right index finger one of the two buttons (left, to indicate internal; right, external) as quickly as possible after the presentation of a green circle in the middle of each picture (the 'go' signal), which appeared 1 s after the picture presentation (**Fig. 1**).

One hour after encoding, the corresponding retrieval blocks occurred in which 16 pictures of interiors were again randomly presented. Eight of these pictures had previously been seen (tests), and eight were novel (distractors). The timing of warning and go signals, picture presentation and intervals were the same as in the encoding blocks. Subjects were again asked, in a yes–no recognition task, to discriminate between the pictures by pressing one of two buttons (left, test; right, distractor) immediately after the go stimulus. The correct choice in encoding and in retrieval (test) was always the left button. The encoding and the retrieval phases lasted 28 to 38 min each, depending on the interstimulus interval used. Each picture and each response produced an appropriate trigger signal. A 10-min training session, performed with a different set of pictures, allowed the subjects to practice with the task and with either sham or active rTMS (both left and right DLPFCs) before the actual experimental session.

The six encoding/retrieval blocks (R-Enc, L-Enc, sham, R-Ret, L-Ret and baseline) were labeled according to the type (active or sham) and the side (left/right) of the rTMS applied on the DLPFCs.

Recording and stimulating procedures. Triggers and electromyographic (EMG) signals were recorded continuously and off-line analyzed. EMG signals were recorded with surface electrodes glued on the skin in a short bipolar montage, with the active electrode placed on the motor points of the right and left first dorsal interosseous muscles (FDI) and on the right extensor communis digitorum (ECD).

Before applying rTMS, individual resting excitability thresholds for motor cortex stimulation were determined for both hemispheres by measuring the amplitude of motor twitches evoked by single TMS stimuli in the contralateral FDI muscle. Threshold was defined as the minimal intensity of the stimulator output (Mag-Stim Super Rapid, Carmarthenshire, Wales, UK) capable of evoking a motor evoked potential (MEP) greater than 50 μV with 50% probability (see International Standard Guidelines[43]). The stimulating figure-eight coil was tangential to the area of scalp surface corresponding to the primary motor cortex (C3 or C4 positions of the 10–20 EEG international system), with its handle pointing backward and angled about 45° from the midline. Excitability threshold measurements were taken after the presentation of the warning stimulus, as during the experimental setup. Once individual thresholds were determined (mean, 62.6 ± 9.2%, without interhemispheric differences), the intensity of stimulation was reduced by 10%. Thus, left and right DLPFC were stimulated, when required, with a subthreshold intensity for eventual motor cortex activation that would have overtly interfered with motor performance (mean intensity of stimulation used, 55.7 ± 9.1%). Then, left and right DLPFCs were stimulated by lining up the tip of the middle bar of the coil on F3 and F4, respectively[37,38], corresponding to the Brodmann area 9 (**Fig. 1**). A mechanical arm fixed the coil in that position (marked on the scalp) and its correct position was checked by an experimenter repeatedly throughout the session. Trains of 10% subthreshold rTMS (500 ms, 20 Hz) were delivered, when required by the experimental design, at the same time as picture presentation (**Fig. 1**). The same intensity and timing of rTMS was used for sham stimulation. In this case, the coil was still centered on F3 and F4, but it was held perpendicularly to the scalp surface, so that scalp contact and discharging noise were similar to the active stimulation, but the induced magnetic field did not activate cortical neurons[39].

Data analysis. For each subject's answer, the trial-to-trial performance (wrong/right choice) and reaction time (from the go signal to the first EMG burst, either in the right FDI or ECD muscles) were considered. The cutoff to define effective the earliest EMG activation was a burst greater than 50 μV in one of the two muscles, taking into account possible different response strategies of subjects.

Behavioral data were initially composed in a spreadsheet with 1248 rows (13 subjects × 16 answers × 6 blocks) and then grouped in two categories. The first category grouped variables derived from the experimental design, including subjects, sequence and type of blocks, order of the stimuli within each block, and type of picture (interiors or externals in encoding, and internal test or distractor in retrieval). The second category included variables related to the response to each stimulus during either encoding or retrieval (right or wrong), with corresponding reaction times.

To take into account all possible sources of variations of the first group (plus the reaction time as continuous covariate) on the two dependent dichotomous variables (failure during encoding and retrieval), two logistic regressions were applied. The 'forward likelihood-ratio' method was chosen as a screening procedure, by individuating which variables could play a role and, therefore, to limit the factors to be included in the ANOVA models. Thereafter, ANOVA for repeated measures (with experimental blocks as within-subjects factor) was applied to two psychometric measures (C and d′) commonly used to describe the ability to reject distractors during retrieval and to discriminate between the two items (tests and distractors). These measures can be obtained by applying a simple algorithm derived by the signal detection theory[44]. C can be interpreted as an index of 'specificity' (the 'willingness' of a subject to endorse items as old); d′ can be considered as the 'true memory strength' (the

ability of subjects to distinguish between already seen or novel pictures).

After verifying the differences between blocks with active rTMS and control conditions (baseline and sham), a specific two-way ANOVA for repeated measures ('hemisphere' and 'side of stimulus in encoding and retrieval' as within-subjects factors) was applied to better address the HERA model. Throughout ANOVA for repeated measures, Mauchly's test did not allow rejection of the sphericity assumption. Thus, no attempt to correct the degrees of freedom (Greenhouse–Geisser procedure) was made. Tukey's method was used for *post hoc* comparisons.

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