Temporal Dynamics of Memory Trace Formation in the Human Prefrontal Cortex

Simone Rossi[1], Iglis Innocenti[1], Nicola R. Polizzotto[2], Matteo Feurra[1], Alberto De Capua[2], Monica Ulivelli[1], Sabina Bartalini[1] and Stefano F. Cappa[3]

[1]Sezione Neurologia, [2]Sezione Psichiatria, Dipartimento di Neuroscienze, Università di Siena, I-53100 Siena, Italy and [3]Centro di Neuroscienze Cognitive, Università Vita-Salute e Istituto Scientifico San Raffaele DIBIT Via Olgettina 58, 20132, Milano, Italy

Address correspondence to Simone Rossi, MD, PhD, Dipartimento di Neuroscienze, Sezione Neurologia, U.O. di Neurofisiopatologia, Policlinico Le Scotte, Viale Bracci, I-53100 Siena, Italy. Email: Rossisimo@unisi.it.

Event-related repetitive transcranial magnetic stimulation (rTMS) can dynamically interfere with the memory encoding of complex visual scenes. Here, we investigated the critical time elapsing from stimulus presentation to the formation of an effective memory trace by delivering rTMS (900 ms at 20 Hz) during the encoding of visual scenes at different poststimulus delays (from 100 to 500 ms) in 28 healthy volunteers. The stimulation delay showed a robust inverse correlation with the correct retrieval of encoded images. In particular, rTMS stimulation delivered with a delay of 500 ms and lasting for 400 ms after stimulus offset resulted in a huge drop in retrieval accuracy. Such a timing suggests that rTMS affects the formation of long-term memory through interference with post-perceptual executive processes, rather than with perceptual analysis of the stimuli. The effect was specific for stimulation of the left dorsolateral prefrontal cortex (DLPFC), whereas rTMS applied to the right DLPFC, vertex (active control site), as well as sham stimulation (placebo) did not affect accuracy. These results confirm the crucial role of the left DLPFC in encoding and provide novel information about the critical timing of its engagement in the formation, consolidation, and maintenance of the memory trace.

Keywords: encoding, memory, prefrontal cortex, rTMS, transcranial magnetic stimulation

Introduction

Lesion studies in patients, as well as functional neuroimaging investigations in normal subjects indicate that a complex anatomic-functional circuit involving prefrontal cortex (PFC), medial temporal lobe (MTL), and posterior association cortices is devoted to the formation of human episodic memories (Fletcher and Henson 2001; Simons and Spiers 2003). A top–down hierarchical, supervising control of the left PFC has been proposed to be required for building up an efficient memory trace of the encoded information. This role of the left PFC is probably transmodal (Innocenti et al., unpublished data) and resistant to ageing since it remains operational during the whole life span (Rossi et al. 2004).

The temporal dynamics of successful encoding of episodes in the human PFC is still not well defined, probably due to methodological constraints. The activation measured with event-related functional magnetic resonance imaging reflects late hemodynamic responses to a stimulus, lacking a sufficient temporal resolution to delineate these extremely fast brain processes. Electromagnetic brain activity covaries with successful encoding along a large time span, from about 300–400 ms up to 1 or even 2 s, depending upon the information content (Paller et al. 1987; Wagner et al. 1999; Paller and Wagner 2002; Campo et al. 2005; Fay et al. 2005). Intracerebral recordings in epileptic patients showed that event-related brain activity underlying declarative memory formation could be sequentially observed within the human MTL from 300 ms (rhinal cortex activity) to 500 ms (hippocampal activity) after the presentation of single words (Fernandez et al. 1999). Unfortunately, the timing of recruitment of PFC could not be addressed in this latter study.

In addition, it must be underlined that these investigations, reporting correlational data, do not allow to conclude whether or not a critical time is required for successful episodic encoding in the human left PFC. Causal information is not provided by lesion studies since it is impossible to disentangle whether a lesion affects encoding or retrieval processes at specific time intervals. The other causal approach is transcranial magnetic stimulation (TMS). Only one previous TMS study has causally investigated some aspects related to the chronometry of phonological episodic encoding (Kahn et al. 2005), suggesting a critical time of ventrolateral PFC (VLPFC) engagement in encoding operations at around 380 ms post-stimulus onset, during the early perceptual analysis of the memoranda. Therefore, a causal investigation by repetitive TMS (rTMS), allowing to dynamically interfere with both early (i.e., during the presentation of the stimuli) and late (i.e., during postperceptual analysis) encoding operations is still lacking.

To this aim, we applied a novel online rTMS protocol to the episodic encoding of complex visual scenes used in previous TMS and electroencephalography studies (Rossi et al. 2001, 2004, 2006; Babiloni et al. 2004, 2006). In a first experiment, 20 Hz rTMS was delivered over the left dorsolateral prefrontal cortex (DLPFC) at encoding. The delay span between rTMS and image presentation was set up in a blocked fashion, with temporal steps from 100 to 500 ms. Depending from the initial delay, the rTMS train (always 900 ms in length) covered from 0 to 400 ms poststimulus offset. Subjects were then asked to perform an old/new judgment discrimination task at retrieval (test phase), in which rTMS was not delivered. Sham stimulation at encoding was included as a control.

To address the hemispheric specificity of the effect and to rule out unspecific rTMS effects, we run a second experiment on a different sample of subjects who were again naive for the memoranda. In such experiment, the right DLPFC and the vertex (as a an additional "active" control) were targeted at encoding, with 3 different temporal delays (i.e., 100, 300, and 500 ms poststimulus onset), based on the results of the previous experiment.

Materials and Methods

Participants

Twenty-eight healthy, fully right-handed volunteers (14 males and 14 females aged 20–35 years) took part in the study: 15 healthy subjects

(7 males) participated in the experiment 1 and 13 (7 males) in the experiment 2. They all had no metallic implants or electrical devices and no previous history of any neurological or psychiatric disorders, drug abuse, or alcoholism. They all gave their written informed consent after approval of the protocol by the local Ethics Committee.

Apparatus and Material

Stimuli were presented centrally on an SVGA 17-inch monitor set at 1024 by 768 resolution and refresh rate of 100 Hz. All stimuli were preprocessed by Adobe Photoshop graphics software. They were of approximately equivalent luminance and contrast. Subjects sat down on a comfortable reclining chair with their head stabilized at a distance of about 60 cm from the center of the monitor. They kept their forearms resting on armchairs with their right index finger resting between 2 buttons spaced 6 cm apart.

Task

In the study phase (encoding), 6 blocks of 16 pictures (8 indoor scenes and 8 outdoor landscapes), previously used in similar studies (Rossi et al. 2001, 2004; Babiloni et al. 2004), were presented for 1 s, with an intertrial interval ranging from 3 to 5 s. Subjects were asked to categorize the images as "indoor" or "outdoor" by pressing the left or right mouse button immediately after the cue disappearance (Fig. 1).

This was an easy task, which was always completed by the subjects without any error, despite the concomitant stimulation.

In the test phase (retrieval), which was carried out 30 min later, subjects were required to discriminate between 8 "old" test images (previously seen in encoding) and 8 new distracters among 16 indoor pictures, with the same intertrial interval of the encoding phase, for each of the 6 corresponding encoding blocks by pressing the left or right mouse button immediately after the image disappearance (Fig. 1). The memory performance was evaluated by collecting accuracy responses (see data analysis). The order of the 6 encoding–retrieval blocks was pseudorandomized between subjects for both the experiments.

Ten minutes of training, performed with a different set of pictures, allowed the subjects to practice the task and familiarize with both sham or active rTMS prior to the actual experimental session. Both the experiments were carried out using the same task.

TMS Protocol

Stimulation was delivered through a MagStim Super Rapid stimulator with 4 external boosters with a maximum output of approximately 2 T (MagStim). A figure-of-eight 70-mm coil was used for the stimulation. It was held by hand tangential to the scalp with the handle pointing backward and laterally at a 45° angle from the middle sagittal axis of the
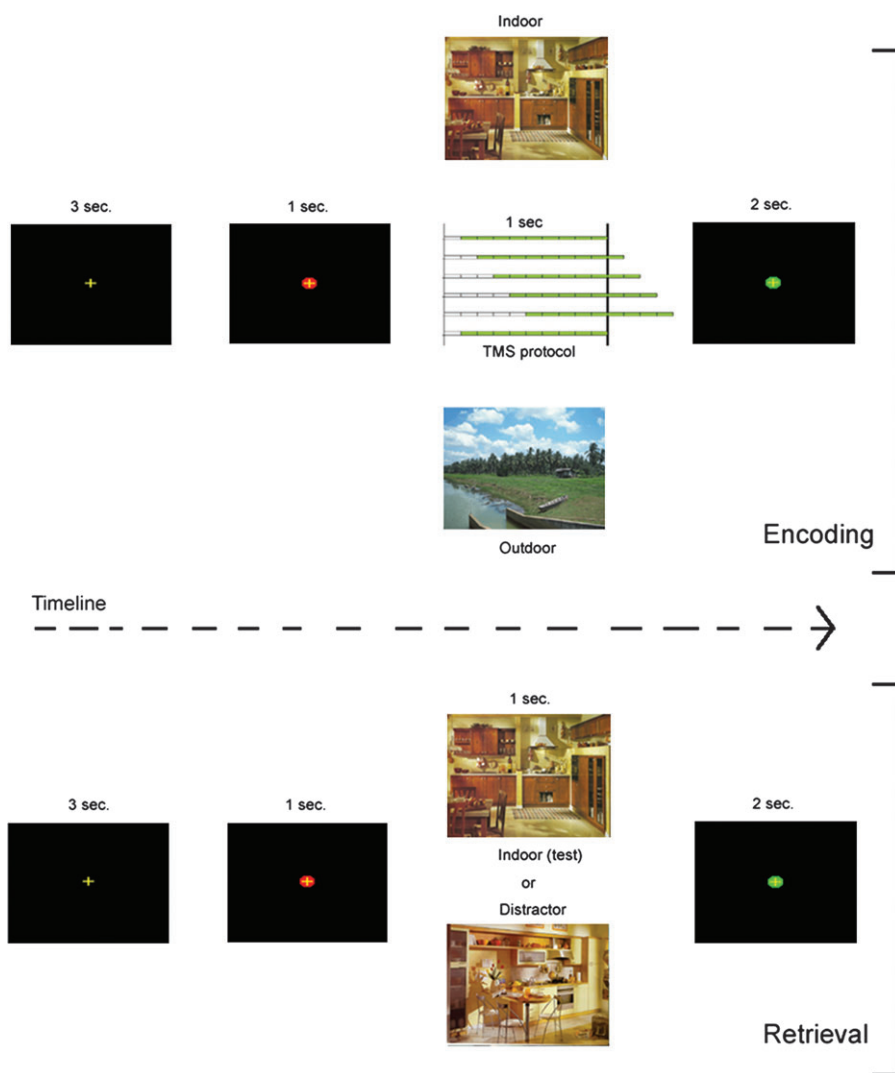

Figure 1. Experimental task. In the study phase (encoding), outdoor or indoor visual scenes were presented to subjects, who performed a discrimination task. rTMS (900 ms at 20 Hz) was delivered at different poststimulus onset delays, according to the TMS protocol (see Fig. 2). In the test phase (retrieval), previously presented indoor scenes (tests) had to be recognized along new indoor images (distractors). Subjects had to perform an old/new discriminations task without any rTMS interference.

participants' head. Every 2 blocks of encoding, the coil was changed to prevent heating.

First, individual resting excitability thresholds for left and right motor cortex stimulation were determined by using the same coil and stimulator; then, the intensity was reduced by 10% to minimize discomfort during DLPFC stimulation.

The left (experiment 1) or the right (experiment 2) DLPFC was stimulated during encoding by placing the wings junction of the coil on the scalp regions corresponding to Brodmann area 9, according to a previously detailed anatomical localization procedure (Rossi et al. 2006). Additionally, the Vertex stimulation site (experiment 2) was defined as a point midway between the inion and the nasion and equidistant from the left and right intertragal notches. Since this region is not involved in learning and memory processes, it was considered as a control site for possible unspecific somatosensory, acoustic, or arousal effects of active TMS. No rTMS was delivered during the retrieval phase.

Experiment 1: 20 Hz rTMS was applied at encoding to the left DLPFC for 900 ms (intensity 90% below individual threshold of stimulation), starting with a delay of 100, 200, 300, 400, or 500 ms from the cue presentation), therefore covering all the remaining time of picture presentation on the screen (block 1), and including also stimulation for 100 (block 2), 200 (block 3), 300 (block 3), or 400 (block 4) ms after the stimulus disappearance (Fig. 2). A sham control condition was included at a 100 ms delay from stimulus onset (covering all the remaining time of cure presentation) to provide a control for any unspecific effects of rTMS.

Experiment 2: the same frequency and intensity of rTMS were used, while changing site of stimulation and delays: the 6 blocks of encoding included active rTMS applications to the right DLPFC or to the vertex at 100, 300, 500 ms delays from the cue presentation. Thus, the second experiment served as a control for experiment 1, both in terms of possible hemispheric asymmetry and timing of engagement of DLPFC at encoding (Fig. 2).

The combination of intensity, frequency, and intertrain intervals of rTMS stimulations was within safety margins (Rossi et al. 2009).

Data Analysis

The number of correctly recognized test images presented during the 6 encoding blocks (Hits rate, H) and of false recognitions of novel pictures (False Alarms rate, FA) was used to analyze the subjects' performance for each corresponding block of the retrieval phase.

Additionally, in the framework of signal detection theory (Wickens 2002), d-prime (d') and criterion (C) allowed to measure the ability to distinguish between "true" items and distracters and to reject distracters during the recognition memory task. Hence, d' can be interpreted as the ability to discriminate between already seen and novel words and C can be considered as an index of the "willingness" of a subject to endorse images as old.

In order to assess the role of the different explanatory variables of interest, their variance was partitioned into components: Sidak corrected one-way analysis of variance (ANOVA) for repeated measures served to assess differences across blocks (Shapiro–Wilk test confirmed normality, Levene's test assessed homoscedasticity). Given that the design of the experiment 2 was partly based on the results of the experiment 1, we did not run a single between-subjects ANOVA, but rather 2 separate analyses. The effect of delay of stimulation was investigated through bivariate correlation when blocks related to the same stimulation site were different. General linear modeling extended both approaches and allowed to assess interactions between site and delay of stimulation; moreover, it was used to confirm the fixed effects and investigate the role of random effects in a unified picture. Data management and analysis were performed using Matlab (The Mathworks) and SPSS 17.0 (SPSS Inc.) software packages. The level of significance was set at 0.05.

Results

The procedure was well tolerated by subjects and no side effects were reported with the exception of mild discomfort at the stimulation site in 4 subjects, which was, however, always transient.
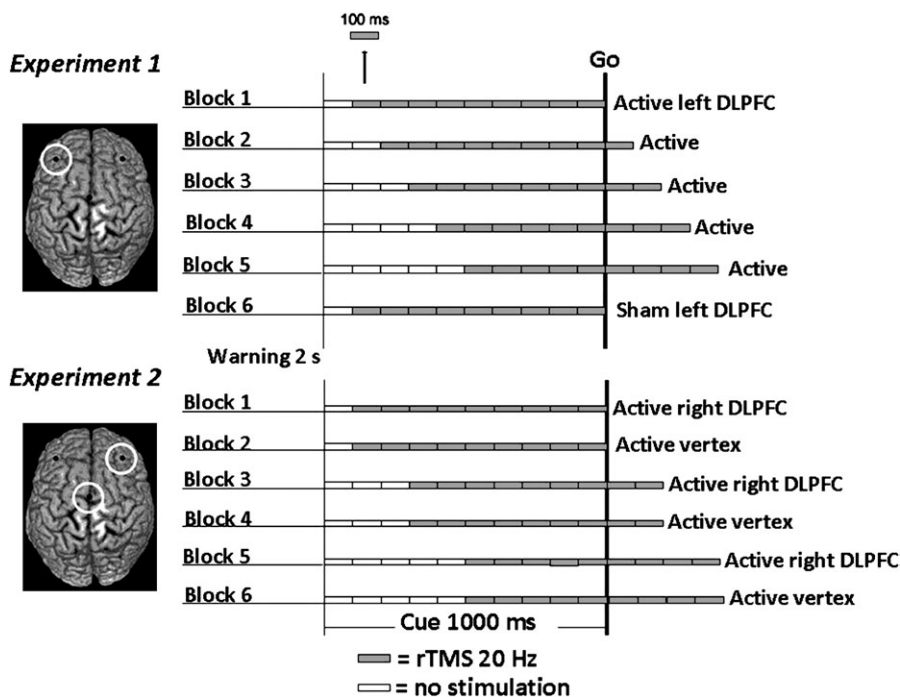

Figure 2. Schematic representation of the 2 experiments. Experiment 1: rTMS is delivered on the left DLPFC, corresponding to the superior frontal gyrus/Brodmann area 9. Each of the 6 blocks of encoding has a different delay of rTMS (filled rectangles, each rectangle is 100 ms) from the cue presentation (i.e., 100, 200, 300, 400, and 500 ms). The length of the rTMS application is always 900 ms. Experiment 2: same organization as above. In this case, the right DLPFC or the vertex were stimulated with delays of 100, 300, and 500 ms. Left and right DLPFCs were identified using the SofTaxic optic navigator (EMS Medical, Bologna, Italy).

The effect of the order of presentation and images sets across subjects was not significant, although the number of subjects/conditions did not allow a complete randomization. The computation of discrimination (d') and criterion (C) allowed to relate retrieval differences to the variability across encoding conditions rather than to subjective or block-to-block differences in the general willingness to categorize any image as already seen (Table 1, Fig. 3).

Experiment 1

The experiment 1 was based on the active or sham stimulation of the left DLPFC. Hits significantly changed across encoding conditions ($F_{5,70} = 13.7$, $P < 0.001$). Sidak's correction highlighted a distinctive drop of recognition accuracy for images encoded when real rTMS was delivered with a delay of 500 ms compared with all other conditions (vs. real rTMS at all other delays, $P < 0.001$, and vs. 100 ms delayed sham stimulation, $P = 0.008$). No other pairwise comparisons of Hits reached significance. Similar to Hits, d' significantly varied across blocks ($F_{5,70} = 10.9$, $P < 0.001$): all significant corrected pairwise comparisons showed significantly lower values for the

500 ms delayed real stimulation block compared with all other conditions of real stimulation (vs. 100 delay, $P < 0.001$; vs. 200 delay, $P < 0.001$; vs. 300 delay, $P = 0.009$; vs. 400 delay, $P = 0.002$). The absence of difference with the sham stimulation block appeared to derive from a tendency for a better discrimination of targets encoded under real rTMS at shortest delays (i.e., delay <400 ms).

The distribution of False Alarms across conditions weakly deviated from chance ($F_{5,70} = 3.5$, $P = 0.019$); however, this stems from smaller and, crucially, differently distributed differences: lower False Alarms in the 200 ms delayed stimulation block (vs. sham stimulation block, $P = 0.030$; vs. 100 and 500 ms delayed real stimulation block, $P = 0.019$ and $P = 0.001$).

Accordingly, focusing on the real stimulation blocks, the delay of stimulation showed a robust inverse correlation with the correct retrieval of encoded images ($r = 0.686$, $P < 0.001$ for Hits; $r = 0.668$, $P < 0.001$ for d'; $r = 0.202$, $P = 0.18$ for False Alarms).

Experiment 2

The experiment 2 addressed the laterality and temporal specificity of rTMS behavioral effects. Active stimulation was applied on the right DLPFC and on a control site (vertex), not involved in memory processes. None of the measures varied across conditions (Hits: $F_{5,60} = 0.61$, $P = 0.63$; False Alarms: $F_{5,60} = 2.10$, $P = 0.09$; d': $F_{5,60} = 1.76$ $P = 0.18$; and C: $F_{5,60} = 0.98$, $P = 0.42$). A general linear model for repeated measures aimed to assess the role of the 2 factors underlying the experimental conditions, namely site (vertex and right DLPFC) and delay of rTMS from cue onset (100, 300, and 500 ms), failed to account for a significant amount of the variance in the distribution of Hits and d'. Consistently, the absence of interaction between the factors pointed to the absence of any differential effect of the explored delays on the 2 site of stimulation for Hits and d'. Furthermore, no correlation emerged between delay and correct recognition of images encoded during stimulation on either site (right DLPFC: $r = 0.18$; vertex: $r = 0.02$). A weak negative correlation between delay and d' ($r = -0.39$, $P = 0.015$) was probably sustained by a correlation between delay and False Alarms ($r = -0.40$, $P = 0.010$), as it disappeared controlling

Table 1

Percentages of Hits, False Alarms, and measures of signal detection (d' and C) for the different encoding conditions of the 2 experiments

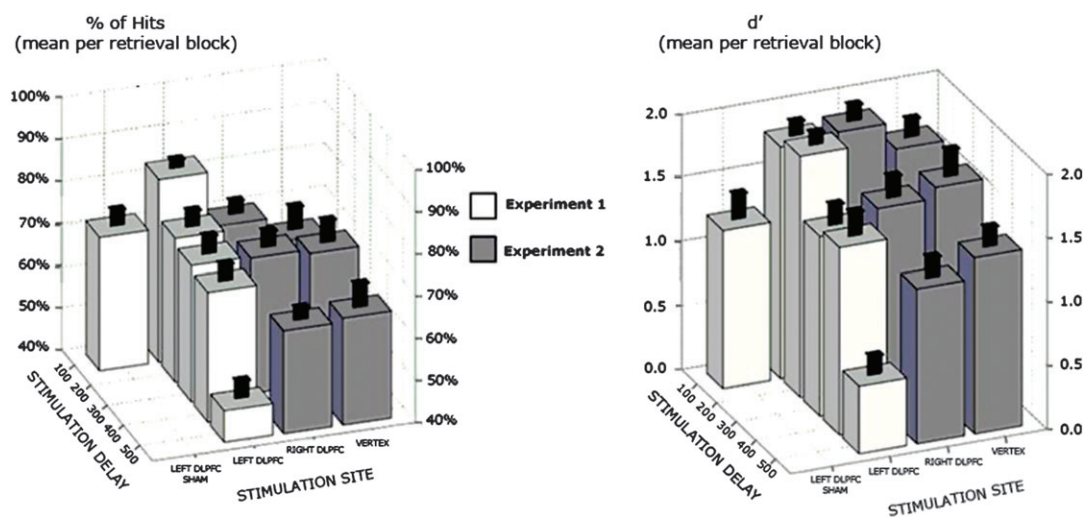| Stimulation site	Stimulation delay	n	Hits (mean % ± SD)	False Alarms (mean % ± SD)	d' (mean ± D)	C (mean ± SD)
Experiment 1						
Left DLPFC	100 sham	15	72 (±16)	29 (±19)	1.24 (±0.82)	0.00 (±0.34)
	100	15	83 (±9)	22 (±14)	1.82 (±0.47)	−0.09 (±0.30)
	200	15	74 (±16)	11 (±12)	1.89 (±0.61)	0.23 (±0.35)
	300	15	73 (±18)	24 (±16)	1.41 (±0.67)	0.06 (±0.40)
	400	15	71 (±17)	21 (±19)	1.47 (±0.78)	0.14 (±0.39)
	500	15	48 (±18)	29 (±16)	0.53 (±0.62)	0.33 (±0.38)
Right DLPFC	100	13	70 (±13)	8 (±8)	1.86 (±0.49)	0.36 (±0.22)
	300	13	72 (±15)	19 (±17)	1.55 (±0.64)	0.14 (±0.40)
	500	13	64 (±11)	22 (±14)	1.21 (±0.62)	0.21 (±0.25)
Experiment 2						
VERTEX	100	13	64 (±22)	10 (±10)	1.64 (±0.58)	0.40 (±0.42)
	300	13	71 (±20)	16 (±16)	1.64 (±0.79)	0.19 (±0.39)
	500	13	65 (±21)	18 (±16)	1.38 (±0.58)	0.24 (±0.49)

SD, standard deviation.

Figure 3. Percentages of Hits and d' for each retrieval block of the 2 experiments. Mean values are shown divided according to the delay of rTMS in encoding with respect to the cue presentation and to the site of stimulation (bars show standard error of the means).

for False Alarms ($r = -0.19$, $P = 0.26$). The distribution of False Alarms investigated by general linear modeling points to a weak overall effect of stimulation delay but fails to provide evidences for an effect of the site of stimulation or of any interaction between the 2 factors.

Discussion

The main result of this study is the link between the drop of the accuracy in retrieval and the timing of rTMS interference on the left DLPFC at encoding. Such a worsening took place when stimulation was applied at 500 ms poststimulus onset and persisted for 400 ms following the disappearance of the image from the screen (see Fig. 1).

In the first place, this effect confirms the functional necessary role of the left DLPFC (Rossi et al. 2001, 2004, 2006; Sandrini et al. 2003; Floel et al. 2004) in encoding operations, a role that remains operational throughout the entire life span (Rossi et al. 2004), in agreement with the hemispheric encoding–retrieval asymmetries model introduced by Tulving in the mid nineties (Tulving et al. 1994) and later revised (see Habib et al. 2003). Additionally, the critical timing of left DLPFC rTMS in encoding provides evidence against the assumption that rTMS-induced decreased memory performance might be simply due to the subjective discomfort of the prefrontal stimulation, as previously suggested (Abler et al. 2005).

Furthermore, the current study allowed to address in a novel way the temporal dynamics of the PFC engagement in building up a successful memory trace. In previous studies investigating episodic encoding by rTMS, stimulation interference coincided with the presentation of the memorandum and ended before, or just at, its disappearance from the screen (Rossi et al. 2001, 2004, 2006; Devlin et al. 2003; Rami et al. 2003; Sandrini et al. 2003; Floel et al. 2004; Kohler et al. 2004; Turriziani et al. 2008; Feurra et al. 2010). Therefore, such an approach did not allow to disentangle chronometric details related to the processes of temporal maintenance of the episodic trace and their subsequent consolidation for long-term memory use. In other words, rTMS produced interference only in the frame of the sensory register system (Baddeley 2003) that in most cases concerns a well-defined temporal stage lasting around 200–300 ms by which an incoming stimulus is analyzed at perceptual level (low-level processes) (Atkinson and Shiffrin 1971).

Very recently, a paper by Machizawa et al. (2010) addressed the issue of the temporal dynamics of encoding by TMS. However, that study and the current one are not directly comparable since they differ in terms of target region (i.e., VLPFC vs. DLPFC), type of TMS protocol (double-pulse TMS vs. repetitive TMS), material to be remembered (i.e., verbal vs. visuospatial), and accuracy results. In the paper of Machizawa et al. (2010), the subjects' memory performance was reduced only in comparison with the improvement induced by TMS on the vertex.

Here, rTMS interference took place in a late stage of encoding processes, which starts to engage working memory (WM) operations (Baddeley 2000). At this elaboration stage, integration between perceptual and cognitive information takes place, in the frame of an interplay between bottom–up and top–down processes (Bar et al. 2006). Indeed, a close inspection of Figure 3 suggests that the drop of accuracy induced by rTMS interference, as indexed by both Hits rate and d', is not an "all or nothing" phenomenon occurring at a fixed

time delay from the presentation of the memorandum. Instead, it is a progressively increasing effect, reaching significance when the rTMS in encoding is applied 500 ms poststimulus onset and lasting for an additional 400 ms after its offset. This finding provides direct evidence that the impairment of memory performance at retrieval is not due to the direct interference with perceptual stimulus analysis at encoding (Rossi et al. 2001), but rather with later postperceptual executive processes required for stimulus maintenance. In this sense, the use of relatively long trains of rTMS shifted at different time during and after stimulus presentation, as those adopted in the current study, may represent a better probe than a single (Kahn et al. 2005) or a double TMS pulse (Machizawa et al. 2010) to fully appreciate the reliance of the stimulated region in the complex temporal dynamics of episodic encoding. Indeed, if a cognitive task is impaired by online TMS due to the induced random neural noise (Harris et al. 2008), then a relatively long train of rTMS is more likely to be effective in this sense than a single or a double pulse. This hypothesis is supported by the impact of the TMS on accuracy data in the current paper compared with the results of the 2 other studies reported above (Kahn et al. 2005; Machizawa et al. 2010). There is an extensive evidence for a crucial role of DLPFC in WM operations (Petrides 2000). Moreover, the human DLPFC, as a part of a parietal–frontal network, is engaged at the delay phase of a spatial WM task (Koch et al. 2005). Other experimental studies suggest that during the delay phase of a visuospatial WM task, neurons in the monkey DLPFC fire in conjunction with those of the posterior parietal cortex (Chafee and Goldman-Rakic 1998) and that this mechanism is essential for short-term memory formation (Fuster 1995).

In visuospatial WM tasks the recruitment of PFC is critical in a time window of about 600 ms from the presentation of the visual stimulus (Oliveri et al. 2001; Mottaghy et al. 2002). Similarly, the recruitment of DLPFC during the recollection stage in a recognition memory task takes place critically in a period from 300 to 600 ms after visual stimulus presentation (Turriziani et al. 2008).

The complex relationship between WM and the formation of long-term memory traces has been addressed in the influential cognitive model introduced by Baddeley (2000) proposing the concept of the "episodic buffer." This is conceived as a distributed limited-capacity system responsible for multi-modal integration and information binding. It provides a temporary storage of the WM trace (i.e., after the image offset) required for the access to the long-term episodic system (Baddeley 2000). This system is capacity constrained and could thus be particularly susceptible to the random neural noise induced by rTMS interference.

A limitation of the current study is that only temporal dynamics of visuospatial encoding have been investigated, leaving unaddressed other fundamental questions related to the function of the left and right DLPFC within the networks of episodic memory. These include the relationship between deep and shallow encoding, as well as the distinction between familiarity and recollection processes. We preferred to adopt a step-by-step strategy, by addressing chronometry on a previously standardized set of memoranda. Work in progress is devoted to investigate how contextual manipulation (deep and shallow encoding) of the episodic memory trace differently engage the DLPFCs (Innocenti et al., unpublished data).

In summary, the present findings represent a first step to add a temporal dimension and an anatomical specificity to the episodic buffer model. The left but not the right DLPFC is engaged in a supervising role of the maintenance—or consolidation—of the information required for the formation of an effective long-term memory trace. The crucial timing of left DLPFC engagement for the maximal interference effect on memory formation processes occurs between 300 and 400 ms after stimulus disappearance, suggesting that in this time frame the left DLPFC is maintaining the integrated information that is required for its translation into an useful episodic trace.

Notes

Conflict of Interest: None declared.

References

Abler B, Walter H, Wunderlich A, Grothe J, Schonfeldt-Lecuona C, Spitzer M, Herwig U. 2005. Side effects of transcranial magnetic stimulation biased task performance in a cognitive neuroscience study. Brain Topogr. 17:193-196.

Atkinson RC, Shiffrin RM. 1971. The control of short-term memory. Sci Am. 225:82-90.

Babiloni C, Babiloni F, Carducci F, Cappa SF, Cincotti F, Del Percio C, Miniussi C, Moretti DV, Pasqualetti P, Rossi S, et al. 2004. Human cortical EEG rhythms during long-term episodic memory. A high-resolution EEG study of the HERA model. Neuroimage. 21:1576-1584.

Babiloni C, Vecchio F, Cola B, Babiloni F, Rossi S, Miniussi C, Rossini PM. 2006. Functional frontoparietal connectivity during encoding and retrieval processes follows the HERA model. A high-resolution EEG study. Brain Res Bull. 68:203-212.

Baddeley A. 2000. The episodic buffer: a new component of working memory? Trends Cogn Sci. 4:417-423.

Baddeley A. 2003. "Working memory: looking back and looking forward". Nat Rev Neurosci. 4(10):829-839.

Bar M, Kassam KS, Ghuman AS, Boshyan J, Schmidt AM, Dale AM, Hamalainen MS, Marinkovic K, Schacter DL, Rosen BR, et al. 2006. Top-down facilitation of visual recognition. Proc Natl Acad Sci. 103:449-454.

Campo P, Maestu F, Ortiz T, Capilla A, Santiuste M, Fernandez A, Amo C. 2005. Time modulated prefrontal and parietal activity during the maintenance of integrated information as revealed by magneto-encephalography. Cereb Cortex. 15:123-130.

Chafee MV, Goldman-Rakic PS. 1998. Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. J Neurophysiol. 79:2919-2940.

Devlin JT, Matthews PM, Rushworth MF. 2003. Semantic processing in the left inferior prefrontal cortex: a combined functional magnetic resonance imaging and transcranial magnetic stimulation study. J Cogn Neurosci. 15:71-84.

Fay S, Isingrini M, Ragot R, Pouthas V. 2005. The effect of encoding manipulation on word-stem cued recall: an event-related potential study. Brain Res Cogn Brain Res. 24:615-626.

Fernandez G, Brewer JB, Zhao Z, Glover GH, Gabrieli JD. 1999. Level of sustained entorhinal activity at study correlates with subsequent cued-recall performance: a functional magnetic resonance imaging study with high acquisition rate. Hippocampus. 9:35-44.

Feurra M, Fuggetta G, Rossi S, Walsh V. 2010. The role of the left inferior frontal gyrus in episodic encoding of faces. An interference study by repetitive transcranial magnetic stimulation. Cogn Neurosci. iFirst:1-8.

Fletcher PC, Henson RN. 2001. Frontal lobes and human memory: insights from functional neuroimaging. Brain. 124:849-881.

Floel A, Poeppel D, Buffalo EA, Braun A, Wu CW, Seo HJ, Stefan K, Knecht S, Cohen LG. 2004. Prefrontal cortex asymmetry for memory encoding of words and abstract shapes. Cereb Cortex. 14:404-409.

Fuster JM. 1995. Memory in the cortex of the primate. Biol Res. 28:59-72.

Habib R, Nyberg L, Tulving E. 2003. Hemispheric asymmetries of memory: the HERA model revisited. Trends Cogn Sci. 7:241-245.

Harris JA, Clifford CW, Miniussi C. 2008. The functional effect of transcranial magnetic stimulation: signal suppression or neural noise generation? J Cogn Neurosci. 20:734-740.

Kahn I, Pascual-Leone A, Theoret H, Fregni F, Clark D, Wagner AD. 2005. Transient disruption of ventrolateral prefrontal cortex during verbal encoding affects subsequent memory performance. J Neurophysiol. 94:688-698.

Koch G, Oliveri M, Torriero S, Carlesimo GA, Turriziani P, Caltagirone C. 2005. rTMS evidence of different delay and decision processes in a fronto-parietal neuronal network activated during spatial working memory. Neuroimage. 24:34-39.

Kohler S, Paus T, Buckner RL, Milner B. 2004. Effects of left inferior prefrontal stimulation on episodic memory formation: a two-stage fMRI-rTMS study. J Cogn Neurosci. 16:178-188.

Machizawa MG, Kalla R, Walsh V, Otten LJ. 2010. The time course of ventrolateral prefrontal cortex involvement in memory formation. J Neurophysiol. 103:1569-1579.

Mottaghy FM, Gangitano M, Sparing R, Krause BJ, Pascual-Leone A. 2002. Segregation of areas related to visual working memory in the prefrontal cortex revealed by rTMS. Cereb Cortex. 12:369-375.

Oliveri M, Turriziani P, Carlesimo GA, Koch G, Tomaiuolo F, Panella M, Caltagirone C. 2001. Parieto-frontal interactions in visual-object and visual-spatial working memory: evidence from transcranial magnetic stimulation. Cereb Cortex. 11:606-618.

Paller KA, Kutas M, Mayes AR. 1987. Neural correlates of encoding in an incidental learning paradigm. Electroencephalogr Clin Neurophysiol. 67:360-371.

Paller KA, Wagner AD. 2002. Observing the transformation of experience into memory. Trends Cogn Sci. 6:93-102.

Petrides M. 2000. Dissociable roles of mid-dorsolateral prefrontal and anterior inferotemporal cortex in visual working memory. J Neurosci. 20:7496-7503.

Rami L, Gironell A, Kulisevsky J, Garcia-Sanchez C, Berthier M, Estevez-Gonzalez A. 2003. Effects of repetitive transcranial magnetic stimulation on memory subtypes: a controlled study. Neuropsychologia. 41:1877-1883.

Rossi S, Cappa SF, Babiloni C, Pasqualetti P, Miniussi C, Carducci F, Babiloni F, Rossini PM. 2001. Prefrontal cortex in long-term memory: an "interference" approach using magnetic stimulation. Nat Neurosci. 4:948-952.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 120:2008-2039.

Rossi S, Miniussi C, Pasqualetti P, Babiloni C, Rossini PM, Cappa SF. 2004. Age-related functional changes of prefrontal cortex in long-term memory: a repetitive transcranial magnetic stimulation study. J Neurosci. 24:7939-7944.

Rossi S, Pasqualetti P, Zito G, Vecchio F, Cappa SF, Miniussi C, Babiloni C, Rossini PM. 2006. Prefrontal and parietal cortex in human episodic memory: an interference study by repetitive transcranial magnetic stimulation. Eur J Neurosci. 23:793-800.

Sandrini M, Cappa SF, Rossi S, Rossini PM, Miniussi C. 2003. The role of prefrontal cortex in verbal episodic memory: rTMS evidence. J Cogn Neurosci. 15:855-861.

Simons JS, Spiers HJ. 2003. Prefrontal and medial temporal lobe interactions in long-term memory. Nat Rev Neurosci. 4:637-648.

Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S. 1994. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proc Nat Acad Sci U S A. 91:2016-2020.

Turriziani P, Oliveri M, Salerno S, Costanzo F, Koch G, Caltagirone C, Carlesimo GA. 2008. Recognition memory and prefrontal cortex: dissociatin recollection and familiarity processes using rTMS. Behav Neurol. 19:23-27.

Wagner AD, Koutstaal W, Schacter DL. 1999. When encoding yields remembering: insights from event-related neuroimaging. Philos Trans R Soc Lond B Biol Sci. 354:1307-1324.

Wickens, Thomas D. 2002. Elementary signal detection theory. New York: Oxford University Press.