CHAPTER 32

The causal role of the prefrontal cortex in episodic memory as demonstrated with rTMS

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1. Imaging episodic memory

Episodic Memory refers to the ability to memorize and recollect specific events in our lives. This memory system accumulates daily experiences to form the conscious story of our existence and its functioning requires the encoding and subsequent retrieval of information from long-term memory (for a review see Tulving 2002). As such, it plays an important role in many cognitive processes. In the last few years, many researchers have moved toward the investigation of its neural basis by means of neuroimaging techniques. Brain imaging studies in humans, performing an episodic memory task have shown a consistent engagement of lateral prefrontal areas during the encoding and retrieval of information. These data, point out that prefrontal cortex is not only active while subjects perform working memory tasks, as shown previously (Goldman-Rakic, 1996; Ungerleider et al., 1998; Fuster, 2001), but also in long-term episodic learning (see Fletcher and Henson, 2001). However, the causal

relationship between prefrontal cortex activations and episodic memory processes still needs to be established.

Quite unexpectedly, on the basis of findings in lesional patients, early investigations with positron emission tomography have also indicated a hemispheric functional asymmetry pattern during episodic memory tasks with verbal material. Namely the left prefrontal cortex appeared to be mostly involved in encoding processes, while a right prefrontal predominance was observed during retrieval. These findings led Tulving et al. (1994) to propose a general model of brain function subserving episodic memory, the hemispheric encoding retrieval asymmetry (HERA). According to the HERA model, the left prefrontal cortex plays a crucial role in encoding, whereas the right prefrontal cortex is involved in the retrieval of information from episodic memory. The HERA model, initially corroborated only for verbal tasks, was later proposed also for non-verbal material by Nyberg et al. in 1996.

In the last few years, a number of imaging studies have indicated that the hemispheric asymmetry pattern during episodic memory is not an absolute feature, but rather is influenced by several task-related and individual factors, such as the verbal or non-verbal nature of the stimulus, its novelty for the subjects, the difficulty of the task, the outcome of

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the memory process and the age of subjects (Wagner et al., 1998; Cabeza, 2002; Johnson et al., 2003).

A recent review by Cabeza and Nyberg (2000) conclude that in encoding conditions of verbal materials, prefrontal activation was often left lateralized. In contrast, for nonverbal stimuli a bilateral or right-lateralized activation is generally observed. Regarding the retrieval conditions, it has been shown that prefrontal activation is sometimes bilateral, although most of the studies point to a right-sided lateralization (Kelley et al., 1998; Wagner et al., 1998; McDermott et al., 1999; Golby et al., 2001). Kelley et al. (1998) investigated the involvement of dorsal frontal regions during the encoding of words, nameable line-drawn objects, and unfamiliar faces. Encoding of words produced left-lateralized dorsal frontal activation, whereas encoding of unfamiliar faces produced homologous right-lateralized activation. Encoding of nameable objects yielded bilateral dorsal frontal activation. Golby et al. (2001) found that, while verbal encoding resulted in left-lateralized activation of prefrontal cortex, abstract pattern encoding activated the right prefrontal cortex whereas scenes (indoor and outdoor) and unfamiliar faces resulted in approximately symmetrical activation in both regions. Wagner et al. (1998) found asymmetrical activation in the prefrontal cortex when directly comparing words and patterns during both encoding and retrieval. McDermott et al. (1999) found that words produced predominantly left-sided activation and faces produced predominantly right-sided activation during both encoding and retrieval. Thus, both the material and type of memory process may affect the lateralization of frontal activation during memory tasks (Fletcher and Henson, 2001).

The functional significance of right-lateralization during retrieval has been the subject of much debate. It has for example been interpreted as reflecting the adoption of a "retrieval mode" (Nyberg et al., 1995), the expenditure of "retrieval effort", the right (and left) prefrontal cortex being more active when retrieval is difficult (Schacter et al., 1996), and the engagement of "postretrieval" processing (Rugg et al., 1996). According to postretrieval hypothesis, right prefrontal activation reflects demands placed upon cognitive operations responsible for acting on the products of memory retrieval. These operations are thought to include the integration of retrieved information into a coherent episodic representation, and the monitoring of retrieved information for its relevance to task-related behavioral goals.

On the whole, differences in task demand, stimulus type, cognitive strategy and overall difficulty of these experiments places limits on what we can conclude from this analysis. Moreover, the activation of these brain circuits recruited during different tasks does not show that there are functional consequences of these activations in terms of playing a crucial role in a given task (i.e. lack of causality).

This widely acknowledged limitation of neuroimaging studies in establishing a critical role beyond greater precision in mapping a process (Price and Friston, 1999) suggests that the HERA model should also endorse using other sources of information. Repetitive TMS can be directly used to test the prediction of the HERA model, that is neural activity of prefrontal cortex during an episodic memory task is asymmetric. So the first aim of the present study was to better clarify the role of the DLPFC(s) during encoding and retrieval memory process using TMS technique. The second aim was to evaluate possible changes in the hemispheric pattern of lateralization related to the verbal or non-verbal nature of the material and to its novelty.

Despite the increasing interest for TMS, a technique that is seen as one of the most useful research tools to "interact directly" with brain activity (Helmuth, 2001; Chicurel, 2002), its application to the investigation of episodic long-term memory is still limited. The first mention of an induction of a free recall deficit induced by rTMS dates back to 1994, when Grafman et al. (1994) investigated whether they could selectively interfere with an immediate recall task of verbal information, depending on the site and timing of TMS. Recall was consistently significantly diminished only after left mid-temporal and bilateral dorsofrontal rTMS. However, limitations of this study were the lack of a sham-controlled condition and the several scalp sites stimulated during the memory task, a factor that

makes it hard to disentangle whether the decremental effect on the memory performance was actually due to the stimulation of a specific region or to the summation of the effects of several rTMS trains sequentially applied to several scalp positions along the whole task.

We performed two recognition memory experiments with pictures and word pairs; the implementation of the same experimental design for both types of memoranda allows to better disentangle the role of the attributes of the presented material on the functional lateralization of PFC involvements, by measuring individual behavioral performances, during episodic memory tasks.

2. Visual episodic memory studied with rTMS

The first study showed that using an interference approach, it was possible to obtain an asymmetric performance pattern, during encoding and retrieval, consistent with the HERA model. Moreover, in the same experiment we were able to induce interference (i.e. worsen the performance) only in subjects who were unfamiliar with the material used. This effect suggests that the prefrontal cortex takes part actively in encoding and retrieval process only with novel material. In the second experiment, additional evidences are presented using verbal material underlying the asymmetrical role of prefrontal cortex in episodic memory of novel information.

A total of eighteen subjects aged 22–41 years free from family history of epilepsy or other neurological disorders participated in this study (these data are partially reported in Rossi et al., 2001). They were right-handed, with a mean Edinburgh Handedness Inventory score of 91.1%. For this, and all the other experiments, informed consent was obtained, and the local ethics committee approved the protocols. Thirteen of the subjects were naïve to experiments with rTMS and were blinded to the aims of the study, except that it was designed "to investigate memory". The other five subjects were extremely familiar with TMS recordings as well as with the pictures of the task, due to picture scanning operation, preparation and assistance during the experimental task. However, their degree of familiarity with memoranda was not specifically scored.

The subjects sat in front of a computer monitor in a dimly illuminated room. During the encoding phase the subjects were asked to classify a set of pictures as indoor or outdoor (six encoding blocks, each one containing eight indoor and eight outdoor images). One hour later, six paired retrieval blocks were again presented, each one containing 16 pictures, eight of which being novel indoor pictures (distractors) and eight indoor pictures presented in the previous phase (tests). In this second part they were ask to press a button to differentiate between "test" and "distractor" pictures. The six encoding/retrieval blocks were labeled according to the type (active or sham) and the side (left/right) of the rTMS applied on dorsolateral prefrontal areas (see Table 1). The course of the experiment can be found in Fig. 1. Trains of rTMS (20 Hz, 500 ms) were delivered at 10% below individual resting motor threshold, immediately after each picture presentation over the left or right DLPFC.[1]

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[1] Relatively to the cerebral site of stimulation a common problem of most TMS studies regards the location of the stimulating coil with respect to the anatomy of the targeted cortex, in the single subject. In this regard recently developed neuro-navigated TMS systems seem to be promising tool (Herwig et al. 2001; Fernandez et al., 2002) but not always the subjects' MRIs are available. In this study left and right DLPFCs were stimulated by placing the anterior end of the junction of the two coil wings on F3 or F4 (10-20 international EEG system). F3 and F4 locations on the subject's scalp were automatically identified using SofTaxic Navigator system, on the basis of digitised skull landmarks (nasion, inion and two pre-auricular points) and about 40 scalp points (Fastrak Polhemus digitiser). Although individual radiological head images (i.e. magnetic resonance images – MRIs) were not available, Talairach coordinates of cortical sites underlying F3 and F4 locations were automatically estimated by the SofTaxic Navigator Stereotaxic Navigator System (E.M.S. Italy. www.emsmedical.net), on the basis of an MRI-constructed stereotaxic template (accuracy of ± 1 cm, Talairach space) (Talairach and Tournoux, 1988). This method represents a good compromise among the localization accuracy, the high economical demands of neuro-navigation devices, and the availability of the single subject MRI.

TABLE 1.   Experimental blocks.

Label	Description
Baseline	Absence of stimulation in encoding and in retrieval
Sham	rTMS* applied on left DLPFC in encoding and right DLPFC in retrieval
R-Enc	Right rTMS in encoding, applied on the DLPFC; no stimulation in retrieval
L-Enc	Left rTMS in encoding, applied on the DLPFC; no stimulation in retrieval
R-Ret	No stimulation in encoding; right rTMS, applied on the DLPFC, in retrieval
L-Ret	No stimulation in encoding; left rTMS, applied on the DLPFC, in retrieval

* The coil was handled perpendicular to the scalp surface, by using the same intensity of stimulation (10% below the individual resting motor threshold) of the other conditions.
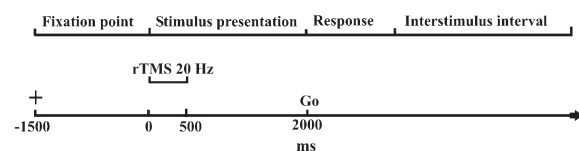

Fig. 1.   Time course of the experimental conditions with respect to visual and rTMS stimulation. Subjects fixated a small cross at centre of the screen, which preceded images for 2,000 ms, and monitored for the appearance of target stimuli. In the encoding phase subjects had to classify stimuli in relation to a category by a choice response. One hour later, in the retrieval phase, they had to recognize stimuli previously presented (tests) among new stimuli (distractors). The stimuli were present on the monitor for 2,000 ms. Trains of rTMS (500 ms, 20 Hz, 10% subthreshold) were delivered simultaneously with the visual stimulus presentation for 500 ms to the left or right DLPFC, when required by the experimental design.

Behavioral findings of this study in the group of 13 naïve subjects directly demonstrated that the prefrontal cortex was actively participating both to encoding and episodic retrieval, and basically reproduced what could be predicted on the basis the neuroimaging-derived HERA model. Indeed, the highest number of recognition errors was induced in the R-Ret block (42%), when the right DLPFC was stimulated during retrieval (Fig. 2a). This suggested that the disrupting effect of rTMS was direct, since it took place immediately after the stimulation period and lasted at least 1.5 s, that is the time in which the picture was displayed on the monitor without concurring rTMS. Such right-sided prevalence of the

PFC during episodic retrieval is in line with most of neuroimaging findings (Fletcher and Henson, 2001). A less expected finding, given the material presented, was a left functional prevalence during the encoding phase. Indeed, the probability to correctly remember the encoded information was significantly lower (versus sham and baseline blocks) when the left DLPFC had been stimulated during the encoding. Given the material used (essentially a visuospatial stimulus) a right side functional prevalence could be expected (see, for example, Kirkhoff et al., 2000), although individual strategies of stimulus verbalization could not be excluded. Nevertheless, this finding might reflect a less efficient encoding (more "shallow" processing) and/or to a faster decay of the information due to the concomitant interference of the rTMS.

Notably, in the sub-group of subjects who were familiar with pictures, the effects of the rTMS on the performance were almost lacking (Fig. 2b). An analyses of variance with training as between-subjects factor and condition as within-subjects factor, showed a significant training by condition interaction $[F = 4.59;\ p < 0.00]$, arising from a different effect of the rTMS in naïve and trained subjects: in fact, there was no behavioural interference of rTMS on trained subjects for any site of stimulation $[F = 2.08;\ p = 0.11]$, whereas clear modulation was detected in subjects naïve to the stimuli. As expected, the factor of training was also significant as main effect, because errors were significantly lower in trained than naïve subjects $[F = 23.57;\ p < 0.00]$.

Pictures Task

Naïve

Trained

Word-pairs Task

Unrelated

Related

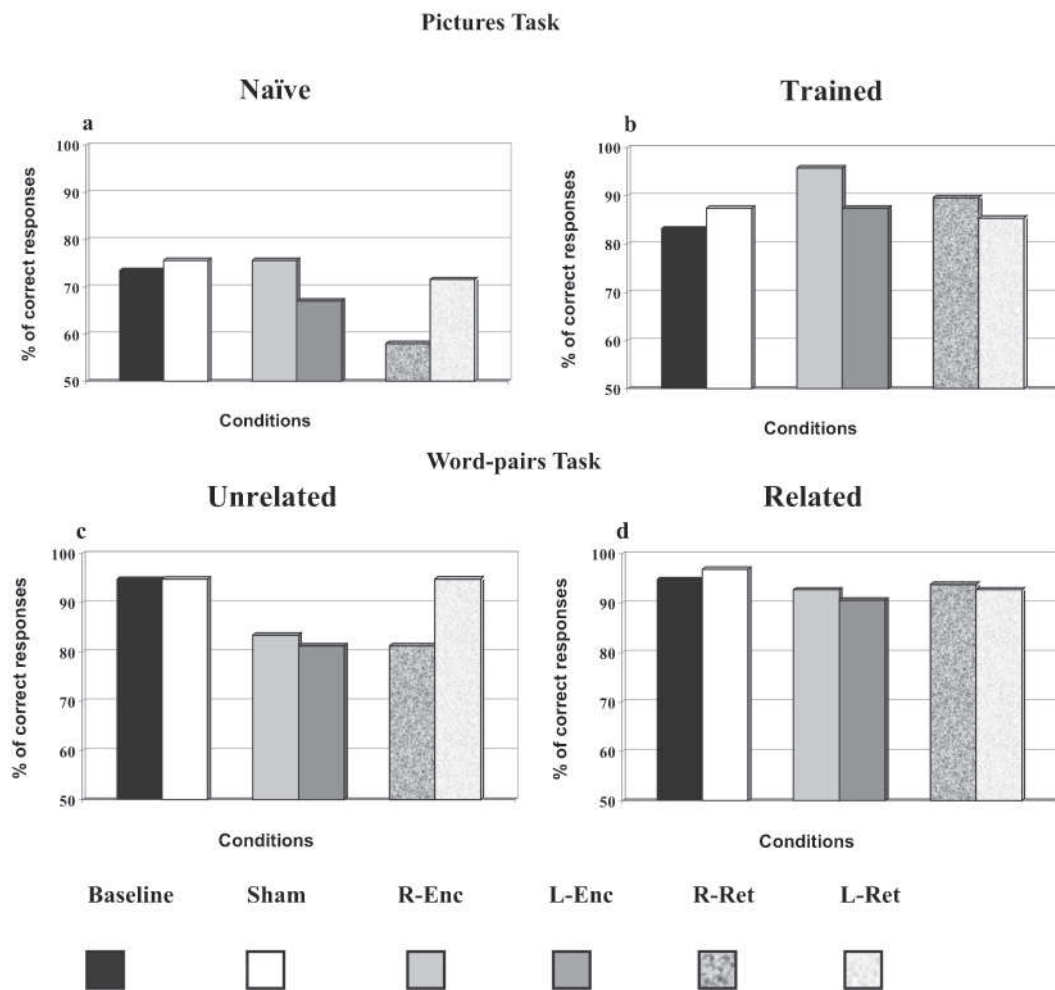| Baseline | Sham | R-Enc | L-Enc | R-Ret | L-Ret |

Fig. 2. Results of picture and word recognition experiments. The graphs show percentages of correct detection of target stimuli in the retrieval phase for the six conditions divided by type of material. In the following experiments (a) recognition of picture in the naïve group (b) recognition of picture in the trained group (c) recognition of unrelated word-pairs (d) recognition of related word-pairs.

The maximal error rate during encoding was present in the Baseline block (16.7%) without rTMS stimulation, in other words rTMS did not interfered with subjects performance suggesting that the functional specialization of the left and right DLPFC in encoding and retrieval, respectively, likely occurs mainly when new material has to be used. This supports the idea that the prefrontal cortex decrease its competence to subserve encoding and retrieval of information, once they are previously stored. Moreover, these data are compatible with reports of progressively reduced frontal activation with task repetition (Petersen et al., 1996), and may be related to the requirement of more elaborate information processing during encoding of novel information, as well as to the different retrieval demands of the non-practiced task (Rugg and Wilding, 2000).

3. Verbal episodic memory studied with rTMS

In the second study (Sandrini et al., 2003), we tested the functional DLPFC asymmetries in a verbal episodic memory task, in order to confirm with the rTMS approach the HERA model in the verbal domain and to verify the observation that only novel material engages the prefrontal cortex during encoding and retrieval. Twelve healthy young Italian-speaking subjects, aged between 20 and 34 years, were tested using the same experimental design as in previous experiment (Fig. 1 and Table 1). In the current setting, pairs of Italian nouns with high imagery content replaced complex pictures. For each block of the six encoding phase blocks, 16 word pairs (eight semantically related and eight unrelated) were randomly presented on the monitor, with two inter-trial intervals (7,000 or 8,000 ms). During the encoding phase the subjects were asked to classify word pairs as highly associated (e.g. bread-butter, garlic-onion), or non-associated (cow-table), according to norms collected for this experiment. One hour later, they were presented with the first word of each pair, and a choice between the second and a novel word (distractor). Events of the retrieval and encoding phases occurred with the same timing (see Fig. 1). Subjects were instructed to press the left or right key according to the position of the word which had been seen previously. The correct responses during the encoding and retrieval phases were evenly distributed across left and right button presses (eight each), thus avoiding rules effects.

Both left and right DLPFC rTMS interfered with the encoding phase, only to semantically unrelated word pairs (Fig. 2c), therefore, suggesting a specific role of DLPFC(s) only when novel information had to be memorized. Such bilateral reliance on DLPFCs for encoding process was somewhat unexpected, since most of previous neuroimaging literature pointed to a left-lateralization, at least for verbal materials (see Fletcher and Henson, 2001). We therefore speculated that the current task might have required participants to perform a deep manipulation, in agreement with the predictions of the "dual-coding theory". According to it, processing of abstract nouns would rely almost exclusively on left-sided verbal code representations, whereas concrete nouns additionally would access a second image-based processing system in the right hemisphere (Paivio, 1986). The involvement of the right DLPFC during encoding (that is, increased errors induced by right rTMS) of word pairs of high imagery content could parallel this strategy. Therefore, bilateral DLPFC involvement might result from the combined engagement of verbal as well as non-verbal strategies in the context of episodic encoding. Comparison with our previous study indicates that only the retrieval effect is largely material-independent; during encoding, both hemispheres are engaged, with a relative contribution modulated by the nature of the material. The prefrontal contribution to episodic memory is crucial only in the case of "novel" information, such as unusual word combinations.

4. Conclusions

By means of rTMS we were able to interfere transiently with ongoing tasks subserved by cortical networks involved in specific cognitive processes; this offers advantages for the investigation of the neurophysiological mechanisms underlying cognitive task performance. Perfusion-based neuroimaging techniques, such as functional magnetic resonance, are very useful to provide a spatially precise correlation of neural activity with a dependent variable, such as attention to a selected visual stimulus or behavioral performance in a given task. However, after this initial correlation TMS can be use as a direct test of the causal role of a given cerebral area in a task. In other words, we can verify if regions that are "functionally active" are also "functionally relevant", and in this instance, rather than asking whether activity is correlated with some dependent variable, TMS assess whether or not it is necessary for a specified task (Stewart et al., 2001).

The present findings of prefrontal cortical involvement during encoding and retrieval are consistent with data from animal studies (Goldman-Rakic, 1987, 1996) as well as neuropsychological investigations of brain-damaged patients (Warrington and Weiskrantz, 1982; Milner et al., 1985; Schacter, 1987), pointing

to an involvement of the prefrontal cortex in episodic memory. In addition, they consistently show that functional hemispheric asymmetries can be observed for encoding and retrieval processes. In line with this observation, prefrontal activations during episodic memory tasks have been demonstrated in numerous neuroimaging studies (for a review, see Cabeza and Nyberg, 2000). The number of TMS studies addressing episodic long-term memory in humans is still limited; however all of them converge in indicating that the PFC plays an important role in long-term episodic memory. These results, therefore, extend the concept that the prefrontal regions are mainly devoted to short-term and working memory processes. An important qualification is that the functional role of PFC appears to be limited to the memory processing of novel information.

Previous investigations on the effects of rTMS on memory are limited and focused mainly on verbal tasks: the recall of a 12-word list was impaired after rTMS of the left mid-temporal or dorsofrontal regions (Grafman et al., 1994). A more recent study by Epstein et al. (2002) used an associative memory task involving pairs of Kanji pictographs and unfamiliar abstract patterns. The authors found a significant impairment during recall only with TMS over right DLPFC. On the basis of theses results, the authors (Epstein et al., 2002) conclude that the right DLPFC is important in encoding mechanisms of non-verbal material. Some methodological factors, like the type of TMS protocol used, could account for partial discrepancies of these results with other findings on episodic memory in encoding (Rossi et al., 2001; Sandrini et al., 2003). An alternative hypothesis is that the functional relevance of the right DLPFC might be in relation to working memory processes required for the maintenance of paired associations until the recall phase.

The regions affected by rTMS in our study are probably the same as those engaged in working memory tasks (Callicott et al., 1999; Wagner, 1999; Fletcher et al., 2001). In the two-stage model of working memory, ventrolateral prefrontal regions are specialized for the maintenance and comparison of representations held in working memory, while dorsolateral areas are posited to subserve more complex or effortful monitoring and manipulation (Petrides, 1995). The operations of working memory and encoding/retrieval may in fact be closely linked, in the sense that prefrontal activation during learning and remembering might represent the contribution of working memory operations to episodic memory. A recent study by Ranganath et al. (2003) supports the view that the same regions are engaged by working memory and episodic memory, similar results were reported also by Nyberg et al. (2003). Notably, rTMS of the same prefrontal regions is able to impair behaviorally both working memory (Mottaghy et al., 2000, 2002) and episodic memory (Rossi et al., 2001). rTMS might transiently disable the processing contribution of DLPFC and adjacent structures to the circuitry of working memory, inducing a dramatic decrement of its role in the active manipulation of information (Fletcher and Henson, 2001).

To summarize, the important role of the right prefrontal areas in the retrieval of verbal and nonverbal material is confirmed by TMS. The causal role of prefrontal cortex in encoding is also supported by rTMS studies. Other variables, such as the type of process tested and individual strategies of memorization and retrieval may account for the inconsistent lateralisation of these encoding effects (Johnson et al., 2003). Therefore, lateralization differences among tasks may be due to the reliance on a mixture of verbal as well as nonverbal strategies in the context of episodic encoding (dual-coding). This interpretation is in line with findings that unfamiliar faces activated the right prefrontal cortex, whereas nameable famous faces activated bilateral prefrontal cortical areas (Kelley et al., 1998). Other variables, which should be taken into account, are those related to the experimental design, to the timing and parameters of TMS, and to the accuracy of coil positioning with respect to the underlying cortical anatomy.

Acknowledgments

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