THE ROLE OF THE DORSOLATERAL PREFRONTAL CORTEX IN RETRIEVAL FROM LONG-TERM MEMORY DEPENDS ON STRATEGIES: A REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION STUDY

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Abstract—The ability to associate a name to a face is a crucially relevant task in daily life. In this study, we investigated the neuronal basis of face-name retrieval in young subjects using repetitive transcranial magnetic stimulation (rTMS) over the left or right dorsolateral prefrontal cortex (DLPFC). The experimental task was composed of two study phases: an encoding phase and a retrieval phase. During the encoding phase, subjects saw a face (familiar or unfamiliar) followed by a name. During the retrieval phase, they saw the face together with two names and had to choose the name that was correctly associated with the face. rTMS was delivered only during retrieval. In addition, we evaluated the use of memory strategies during the task. Accordingly, subjects were subdivided into two groups: strategy users (SU) and no-strategy users (NSU). No rTMS effects were present for familiar face-name pairs, probably due to a ceiling effect. However, for unfamiliar face-name pairs, the different use of memory strategies resulted in different rTMS effects. The SU group showed a selective interference effect after right DLPFC stimulation, whereas the NSU group showed an effect after left DLPFC stimulation. Importantly, DLPFC involvement for encoding and retrieval during memory retrieval was limited to verbal materials in its original proposal, the model was later extended to nonverbal materials by Nyberg and co-workers (Nyberg et al., 1996; Habib et al., 2003). Nevertheless, this is not a clear-cut result, and several studies suggest that the type of material, rather than the nature of the process, accounts for the lateralization (Kelley et al., 1998; Wagner et al., 1998). Accordingly, recent repetitive transcranial magnetic stimulation (rTMS) studies have shown that episodic encoding of verbal (Rami et al., 2003; Floel et al., 2004; Kohler et al., 2004) or verbalizable (Rossi et al., 2001) material critically depends on the left or bilateral (Sandrini et al., 2003) PFC, whereas encoding of non-verbalizable material (Epstein et al., 2002) depends on the right dorsolateral PFC (DLPFC). Several studies have also evaluated the role of the DLPFC in the retrieval phase (Sandrini et al., 2003; Rossi et al., 2001) and have reported right DLPFC involvement for verbal or verbalizable stimuli. Furthermore, Sandrini and co-workers (Sandrini et al., 2003) also addressed the role of DLPFC on semantically related or unrelated word pairs to assess the effect of stimulus novelty on the same experimental paradigm (see also Miniussi et al., 2003). Importantly, DLPFC involvement was shown only for unrelated word pairs, suggesting that DLPFC would be engaged for encoding and retrieval only during the elaboration of novel material (Miniussi et al., 2003; Sandrini et al., 2003). Overall, these results strongly indicate that the nature of the material to be remembered interacts highly with the encoding-retrieval DLPFC asymmetry and that the role of DLPFC is mainly evident in the processing of novel stimuli. Recent studies have also emphasized the role of memory strategies in influencing cerebral activity during episodic retrieval (Kondo et al., 2005; Raposo et al., 2009). Since DLPFC constitutes a specialized region for the monitoring of self-ordered and external-ordered responses (Petrides, 1995, 2005), these regions would be more engaged during paradigms that require retrieval strategies.

Key words: cognition, retrieval, face-name pairs, memory strategies, DLPFC, TMS.

In order to correctly remember, both good encoding and successful retrieval of the information are crucial. The relevance of these two different processes in episodic memory is now well established (see also Nyberg et al., 1996; Cabeza et al., 2003). Functional imaging studies have provided evidence for hemispheric asymmetry in memory encoding and retrieval, as suggested by the Hemispheric Encoding Retrieval Asymmetry (HERA) model (Tulving et al., 1994). According to this model, the left prefrontal cortex (PFC) is involved in the encoding of novel events, whereas the right PFC is involved in the retrieval of information from episodic memory. Although the HERA model was limited to verbal materials in its original proposal, the model was later extended to nonverbal materials by Nyberg and co-workers (Nyberg et al., 1996; Habib et al., 2003).

Nevertheless, this is not a clear-cut result, and several studies suggest that the type of material, rather than the nature of the process, accounts for the lateralization (Kelley et al., 1998; Wagner et al., 1998). Accordingly, recent repetitive transcranial magnetic stimulation (rTMS) studies have shown that episodic encoding of verbal (Rami et al., 2003; Floel et al., 2004; Kohler et al., 2004) or verbalizable (Rossi et al., 2001) material critically depends on the left or bilateral (Sandrini et al., 2003) PFC, whereas encoding of non-verbalizable material (Epstein et al., 2002) depends on the right dorsolateral PFC (DLPFC). Several studies have also evaluated the role of the DLPFC in the retrieval phase (Sandrini et al., 2003; Rossi et al., 2001) and have reported right DLPFC involvement for verbal or verbalizable stimuli.

Furthermore, Sandrini and co-workers (Sandrini et al., 2003) also addressed the role of DLPFC on semantically related or unrelated word pairs to assess the effect of stimulus novelty on the same experimental paradigm (see also Miniussi et al., 2003). Importantly, DLPFC involvement was shown only for unrelated word pairs, suggesting that DLPFC would be engaged for encoding and retrieval only during the elaboration of novel material (Miniussi et al., 2003; Sandrini et al., 2003). Overall, these results strongly indicate that the nature of the material to be remembered interacts highly with the encoding-retrieval DLPFC asymmetry and that the role of DLPFC is mainly evident in the processing of novel stimuli.

Recent studies have also emphasized the role of memory strategies in influencing cerebral activity during episodic retrieval (Kondo et al., 2005; Raposo et al., 2009). Since DLPFC constitutes a specialized region for the monitoring of self-ordered and external-ordered responses (Petrides, 1995, 2005), these regions would be more engaged during paradigms that require retrieval strategies.
Following the "production-monitoring hypothesis," the right PFC is more involved in monitoring and verification, whereas the left PFC is more involved in semantically guided information production (Cabeza et al., 2003). Accordingly, the effect of retrieval strategies would predominantly affect the activation patterns of the right DLPFC, such that higher strategies would induce higher right DLPFC activation during retrieval. Concerning poor strategy users, a recent fMRI study (Kompus et al., 2009) that investigated the flexibility of memory retrieval suggested that, during memory retrieval, early processes determine if the task can be solved by the default system. In case that this is not possible a dynamic shift to cognitive control processes, guiding retrieval from episodic memory, is engaged. Starting from this hypothesis, we can speculate a reduced right DLPFC involvement in poor strategy users. To the best of our knowledge, however, no published rTMS study has evaluated the role of DLPFC on memory strategies. In the present study, we investigate the functional asymmetry of DLPFC during the retrieval of face-name pairs using an rTMS paradigm.

Namely, we wanted to evaluate the influence of subjective retrieval strategies on such asymmetry of DLPFC measured by rTMS, and to define the retrieval strategies employed by the subjects we used a semi-structured questionnaire.

Moreover, we used both familiar and unfamiliar pairs in order to evaluate rTMS induced effects both on trials involving episodic memory (i.e., unfamiliar pairs) and on trials in which episodic memory would be less crucial since they have been already learned (i.e., familiar pairs).

We hypothesized that, if the right DLPFC is crucial for episodic memory retrieval due to its relevance in monitoring (Shallice et al., 1994; Henson et al., 1999; Shallice, 2006), then right DLPFC involvement would be seen in subjects who use more retrieval strategies, which require higher monitoring processes. On the other hand, the right DLPFC should be less involved in subjects who do not use retrieval strategies.

**EXPERIMENTAL PROCEDURES**

**Participants**

Fourteen healthy volunteers (six males, eight females) aged between 19 and 35 years (mean age = 28 ± 7) with no contraindications to rTMS participated in the experiment. All of the subjects were right-handed [Edinburgh Handedness Inventory = 94 ± 8; (Oldfield, 1971)], had normal or corrected-to-normal vision and were native Italian speakers. All participants gave informed consent and the experimental protocol was approved by the Ethics Committee of IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy.

**Stimuli**

Each stimulus consisted of a grey-scale face associated with a proper name. Faces were downloaded from an electronic dataset on the web and processed by Adobe Photoshop 5.0 (http://www.adobe.com). The photographs portraying familiar faces were of well-known politicians, movie stars and other celebrities, whereas the unfamiliar faces were "common" people and were chosen for their resemblance to the images of familiar people for values of brightness, contrast and other perceptual features. We conducted a pilot study with a set of 80 familiar faces and 80 unfamiliar faces to verify and define the experimental set of pictures. Pictures printed on A4 format paper were presented to thirty young adults (age = 25 ± 4) who were asked to correctly name the famous people. We considered only pictures generating a percentage of correct responses above 90%. A final set of 50 familiar faces and 50 unfamiliar faces was identified (50 males, 50 females). These pictures were scaled to 210 × 263 pixels and presented on a computer screen (subtending a visual angle of 3.15° × 4°). With respect to names, each familiar face was associated with its name (name and surname shown in Arial font at a font size of 24), while a set of 50 (25 male, 25 female) unfamiliar proper names was generated and randomly assigned to the unfamiliar faces.

**Procedure**

*rTMS procedure.* rTMS was applied using a Magstim super Rapid magnetic stimulator (50 Hz—biphasic, four booster modules) and a figure-eight coil (custom double 70 mm; Magstim Company Limited, Whitland, UK). Before the experiment, the active motor excitability stimulation threshold was established for each subject. This criterion was defined as the lowest stimulation intensity over the primary motor cortex that resulted in a visible contraction in the right hand, as agreed upon by two experimenters, in at least five out of ten consecutive stimulations. The stimulation intensity used during the experiment was set at 90% of each subject's threshold. The mean stimulation intensity was 49% (min. 43%, max. 57%) of the maximum of the stimulator output.

We applied rTMS only during the retrieval phase. Retrieval included three blocks corresponding to three stimulation sites: the left DLPFC, the right DLPFC and the sham. The stimulation site order was counterbalanced across participants. To stimulate the DLPFC, we placed the junction of the two coil wings above these locations. The stimulation site for the sham condition was on the vertex (Cz), but the coil was held perpendicular to the scalp, which ensured that no effective magnetic stimulation reached the brain during the sham condition. The stimulation sites were chosen from previous literature. In similar rTMS studies the same areas were targeted (Rossi et al., 2001, 2004; Sandrini et al., 2003). To localize these sites, Talairach coordinates of the cortical sites underlying coil locations were estimated for each participant by the SofTaxic Evolution Navigator system (E.M.S., Bologna, Italy). This frameless stereotaxic neuronavigational system consists of a graphic user interface and a 3D optical digitizer (NDI, Polaris Vicra) with three location items. One of these items was placed solidly on the subject’s head to rule out any inaccuracy due to head movements. The second item was accurately positioned on the TMS coil to measure its position (X, Y and Z Cartesian coordinates) and orientation. The third item is part of a stylus that was used to register craniometric landmarks on the subject's head. Furthermore, the SofTaxic Navigator system permits the computation of an estimated volume of magnetic resonance images (MRI) of the subject's head to guide the TMS coil positioning. The estimated MRI images are automatically calculated by means of a warping procedure, through the operation of a generic MRI volume (template) on the basis of a set of points digitized from the subject's scalp. The accuracy of this procedure has been evaluated on 28 healthy adults (mean age 35 years) having own MRIs used as gold standard. In this evaluation, the TMS stimulation brain site was localized using both own and estimated MRIs, while the position of the TMS coil was kept fixed onto the subject's scalp. The results indicate a mean error of 2.11 mm, with a standard deviation of 2.04 mm, lower than TMS spatial resolution (unpublished data). Based on these estimated MRIs, we located the left or right DLPFC [i.e., middle frontal gyrus (Talairach coordinates X = ±35, Y = 24, Z = 48)] in each subject. The stimulation coil was supported and fixed in place by a mechanical arm.
During the experiment, rTMS was delivered starting 100 ms after the trial onset using a train of eight pulses with a frequency of 10 Hz, which lasted a total of 700 ms. The participants tolerated rTMS well and did not report any adverse effects.

Task procedure. Subjects were seated in a dimly lit room facing a computer monitor placed at a distance of 100 cm from them. The stimuli were presented using Presentation software (Version 9.90, http://www.neurobs.com) running on a personal computer with a 17-inch screen. After establishing stimulation thresholds and before starting the experiment, subjects completed a practice run that involved two familiar and two unfamiliar faces. The experimental procedure was structured with an encoding phase followed by a retrieval phase. Both the encoding and the retrieval phases were comprised of three separate blocks of 32 (16 familiar) trials each. Gender and familiarity of the stimuli were counterbalanced and randomized across blocks.

Encoding phase. During the encoding phase, subjects were presented with a face (1000 ms), followed by the corresponding proper name (1000 ms). The proper name was followed by a fixation point that was displayed until the response. The response was followed by an inter-trial interval of 6000 ms. For each trial subjects were requested to indicate if a male or a female was presented, pressing one of two buttons of a response-box, using both hands (for half the subjects, the left button was matched with female, and the right one was matched with male). During this phase, subjects were also requested to associate the proper name to the presented face. The encoding phase was followed by a 10 min delay before the beginning of the retrieval phase (Fig. 1).

Retrieval phase. During the retrieval phase, each trial involved a previously-seen face that was presented in the middle of the screen and two names displayed below the face, one on the right side and one on the left side. The two presented names included the proper name, which had been associated with that face during the encoding phase (target), and an “incorrect” proper name (distracter), which had been displayed with a different face during the encoding phase. Foils were always drawn from the same face-name pairs category (i.e., familiar or unfamiliar) of the correct choice. Subjects were instructed to press the right or left button of the button box as soon as possible, according to the position of the name (right or left) that they selected. The position of the correct name was counterbalanced across trials within blocks.

In both the encoding and retrieval periods, the accuracy and reaction times were collected.

Performance analysis. Statistical analyses were performed using Statistica (version 6) software (http://www.statsoft.com). The sphericity assumption was checked using Mauchly’s test (Mauchly, 1940), and Huynh–Feldt’s correction (Huynh and Feldt, 1976) was adopted, if necessary, for the degrees of freedom. First, a T-test was conducted between the performances acquired during sham stimulation in the two groups, comparing the baseline performance of the two groups. Then, a repeated measure ANOVA was performed for each dependent variable, which were reaction time and accuracy. Each ANOVA featured three sites of stimulation (left DLPFC, right DLPFC or sham, within subjects), familiarity (familiar or unfamiliar, within subjects) and group (Strategy Users—SU or No-Strategy Users—NSU, between subjects) as factors.

Strategy questionnaire. To classify participants on the basis of their memory approach, the subjects were asked to answer a brief questionnaire at the end of the experiment to evaluate their strategy utilization. They were asked to say if they used any strategy solving the task and in that case, they had to rate if they had used each of six possible retrieval strategies to study face-name pairs. Three of these strategies represented an associative strategy (“linking a feature of the face to the name,” “linking the initial of the name/surname to the face,” “linking the age of the person depicted by the face to the name”), while the others regarded only the name or only the face (“repeating the name to yourself,” “using mental imagery to fix the face,” “associating the name to a familiar person that remembers the face”). The strategy endorsement report (involving the selection from a list of possible strategies that could have been employed on the memory task) is a form of questionnaire that frequently is used in order to assess retrieval strategies, especially in the case of individuals that could have difficulties in eliciting mnemonics (Rankin et al., 1984; Dunlosky and Hertzog, 1998, 2001). The list of retrieval strategies was based on the literature and on participants’ reports of strategy use during pilot testing. In particular, we verified if the subject used any strategy and we investigated if that strategy was related to a link between the face and the name or to a different (probably less useful) strategy. As a questionnaire, it is a guided subject’ self-report, but being a semi-structured one is a reliable measure to test subjective retrieval strategies (see Kirchhoff and Buckner, 2006).

RESULTS

Strategy questionnaire

Four out of the fourteen subjects reported not using any strategy during the task, while the remaining ten participants reported using an associative (i.e., relational) strategy to link the face and name. Accordingly, the subjects...
were divided into two groups: a strategy users group (SU, \(n=10\)) and a no-strategy users group (NSU, \(n=4\)).

**Reaction time analysis**

The analysis of reaction times did not show any significant statistical differences.

**Accuracy analysis**

First, the T-test conducted comparing the performance in sham condition of the two groups did not indicate any difference in the baseline performance of the two groups (familiar: \(T_{12} = -1.69, P=0.12\); unfamiliar: \(T_{12} = 0.29, P=0.78\)).

Moreover, an ANOVA on accuracy values revealed a significant effect on familiarity, such that accuracy was higher for familiar items (99% of correct responses, \(\pm 1\)) than for unfamiliar items (63%\(\pm 10\)) \((F_{1,12} = 135.4; P=0.001\)). The interaction between the main factors, which were the site of stimulation, familiarity and group, was significant \((F_{2,24} = 12.57; P=0.0001\)). Post-hoc analyses (Bonferroni) showed significant differences according to the site of stimulation and group only for unfamiliar face-name pairs. Specifically, SU participants showed a decrease in their performance after stimulation of the right DLPFC (52%\(\pm 9\)) when compared to sham (68%\(\pm 12\); \(P=0.0002\)) and left DLPFC (66%\(\pm 9\); \(P=0.001\)) stimulation. In NSU participants, however, performance decreased after stimulation of the left DLPFC (50%\(\pm 22\)) when compared to sham (70%\(\pm 14\); \(P=0.002\)) and right DLPFC (72%\(\pm 18\); \(P=0.0009\)) stimulation (Fig. 2). In other words, left DLPFC stimulation decreased performance in the NSU participants, while right DLPFC stimulation decreased performance in the SU participants.

**DISCUSSION**

Our study investigated the role of DLPFC during retrieval in a face-name association task. Both familiar and unfamiliar pairs were used, but rTMS interference effects were present only for unfamiliar items. The identification of famous people is known to be more related to posterior areas, such as the temporal pole and anterolateral temporal cortex (Sugiura et al., 2006, 2009). Consequently, different possible explanation could account for the lack of effects for these stimuli. First, it is possible that we did not really interfere with the recognition of a famous name and its association with a face, since these brain areas were not stimulated. Moreover, the role of DLPFC might be evident only for novel stimuli, as previously suggested (Miniussi et al., 2003; Sandrini et al., 2003). Another possible explanation is that no learning was required with famous stimuli and DLPFC might be not important for retrieval of over learned information, being relevant only for episodic memory trials (i.e., unfamiliar trials). Furthermore, a simpler and probable hypothesis is that the lack of effects on familiar trials could be due to a ceiling effect. Familiar stimuli induce a performance near the 100% and rTMS effects on accuracy at this level are difficult to obtain.

Consequently, we cannot draw specific hypothesis about familiar face-name pairs.

In our experiment, interesting results were shown for unfamiliar pairs. Since episodic memory performance could be influenced by individual strategies (Kondo et al., 2005; Raposo et al., 2009), we evaluated the individual memory approaches used to solve the task. There were differences among the individuals with regard to strategy use, and the overall group was divided into two subgroups according to the presence or absence of reported strategies. The use or lack of memory strategies resulted in different rTMS effects during retrieval. The SU group showed a selective interference effect only after right DLPFC stimulation, while interference in the NSU group was only present after left DLPFC stimulation. Importantly, the overall performance of the two groups was similar, which highlighted the fact that, even if they solved the task in different ways, they had the same final success rate. According to the HERA model, the functional involvement of right DLPFC during retrieval was expected, as was found in SU group. In contrast, this model did not predict the involvement of the left DLPFC, as was found in the NSU group.

In previous studies, Hofer and colleagues (2007) evaluated the correct recognition of unfamiliar faces using fMRI and found a significant activation in the left DLPFC and left
parietal cortex. Similar results have also been reported by other researchers investigating the retrieval of both newly learned faces (Clark et al., 1998; Leube et al., 2003) and verbal stimuli (Rugg et al., 2002). Frontal activation in studies using verbal stimuli is predominant in the left PFC, but face-name pairs could induce some different results because of the association of both verbal (name) and visual (face) stimuli. It is indeed a challenge to show how the brain is able to integrate distinct neural representations. This integration has been defined the “binding problem” (Damasio, 1989), in which interactions between different brain regions are necessary to provide a correct association. The visual-face association has already been investigated by several studies during encoding (e.g., Leveroni et al., 2000), but only few studies investigated this issue during retrieval (Campanella et al., 2001). Campanella et al. (2001) identified a network of three areas distributed in the left hemisphere that are active both in name-face versus face-face and face-name versus name-name comparisons. This activation was considered to be the locus of the integration of visual face and name representations. These three regions were localized in the left PFC (including the inferior frontal gyrus and the medial frontal gyrus) and in the left supramarginal gyrus of the inferior parietal lobe. Therefore, considering our results, the use of associated verbal and visual materials might account only for the left DLPFC involvement during retrieval in NSU group in which there was no involvement of right DLPFC probably because of the absence of monitoring strategy.

Thus, these two different functional asymmetry patterns found in the two different groups that were reported in our work could be explained, which then suggested that the use or lack of memory strategies could lead to the preferential functional involvement of one of two memory systems: episodic memory retrieval or semantic memory retrieval processing. The right lateralization of activity described in the HERA model has been suggested to be primarily driven by retrieval mode activations (Lepage, 2004), whereas left DLPFC activity during episodic retrieval reflects semantic operations (Fletcher et al., 1996; Cabeza et al., 1997, 2003). However, this explanation fails to account for the pattern of results observed in the present study. Burgess and Shallice (Burgess and Shallice, 1996) have suggested that right and left prefrontal cortex may be differentially involved in different aspects of episodic memory. Nevertheless participant in our study performed the same episodic memory task. A possible explanation of the differential involvement of left and right DLPFC in the two groups is that selective interference effect during DLPFC stimulation, observed in this study, was related to different aspects of episodic remembering. The NSU group might have engaged a systematic process in order to perform the same task without retrieval strategies. According to Nolde et al. (1998) heuristic processes are sufficient when retrieval tasks are relatively simple, whereas systematic retrieval processes are needed when retrieval tasks require complex operations, such as self cueing or deliberate analysis of retrieved information. In other words when a retrieval task is difficult and accuracy is important, systematic processes are engaged in order to monitor and evaluate the retrieval information (Johnson and Raye, 1998). In our study, poor retrieval strategies users might have used a systematic process to solve the task with the same accuracy of the other group since retrieval strategies did not help them.

Retrieving the names of familiar persons is a seemingly effortless process, whereas correctly naming persons met only once may involve effortful memory search to evoke the contextual details from the past encounter. One way of conceptualizing this learning-related reorganization is in terms of episodic and semantic memory processes (Tulving, 2002). Starting from this hypothesis, the authors of an fMRI study (Kompus et al., 2009) used a task similar to our, to investigate the flexibility of memory retrieval. They compared high and low familiar items finding a left DLPFC involvement for high familiar pairs and a right DLPFC involvement for unfamiliar ones. The authors suggested that, during memory retrieval, early processes determine if the task can be solved by a default system, and, if not, there is a dynamic shift to cognitive control processes that guide retrieval from episodic memory. In our study we cannot draw any conclusion about familiar stimuli (see above) but this hypothesis fits with differential involvement of DLPFC in the two groups. Thus, there would be left frontal activation in the case that systematic processes are used and right frontal activation in the case that cognitive control/episodic retrieval processes are used.

**CONCLUSION**

The present work highlights that episodic retrieval of associated stimuli leads to the differential involvement of DLPFCs (and also probably of other cortical areas), depending on the individual retrieval strategies. Nevertheless the meaning of the involvement of left DLPFC in this approach need a better understanding and further studies are required. However, this study might indicate that there is a selective specialization of the right DLPFC in the monitoring phase of retrieval. This monitoring phase might be crucial in the frame of a specific memory strategy to determine the correct response but not under other conditions, such as the use of the semantic system. Even if other mechanisms associated with retrieval strategies could be responsible of the right rTMS effect obtained, monitoring processes (including checking functions) seem to be the best candidates explaining the overall present resulting effects. Even if there are few studies contrasting different prefrontal processes involved in strategy selection, realization and checking, it is generally stated that the control of monitoring processes is lateralized to the right dorsolateral regions by comparison with other processes (for a revision see Shallice, 2006). Moreover, these results suggest that, to better evaluate the engagement of differential areas in memory tasks, recording individual retrieval strategies might be crucial.

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