Prefrontal Cortex Asymmetry for Memory Encoding of Words and Abstract Shapes

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Previous work suggested a differential contribution of prefrontal cortex (PFC) to successful encoding depending on the stimulus material. Here, we tested the hypothesis that encoding of words preferentially involves the left PFC, while encoding of nonverbal items (abstract shapes) relies on the right PFC. We used an experimental design that evaluated encoding of both words and abstract shapes in the same healthy volunteers. A transient virtual lesion of the left or the right PFC was elicited with transcranial magnetic stimulation (TMS) while subjects memorized verbal and nonverbal items. We found that encoding of verbal material was disrupted by left PFC stimulation, whereas encoding of nonverbal material was disrupted by right PFC stimulation. These results demonstrate a functionally relevant lateralization of prefrontal contribution for verbal and nonverbal memory encoding.

Introduction

Episodic memory (explicit memory for recently experienced events) depends upon a number of circumscribed, interconnected brain regions, including the medial temporal lobe and the prefrontal cortex (PFC) (Milner and Petrides, 1984; Cohen *et al.*, 1985; Tulving *et al.*, 1994; Wagner *et al.*, 1999; Golby *et al.*, 2001; Otten and Rugg, 2001; Rugg *et al.*, 2002; Johnson *et al.*, 2003). Previous lesion studies proposed a link between material-specific lateralization and encoding for both medial temporal lobe and PFC (Riege *et al.*, 1980; Whitehouse, 1981; Milner and Petrides, 1984; Cohen *et al.*, 1985; Squire, 1992; Cohen, 1993; Schacter and Tulving, 1994). However, while medial temporal lesions critically impair memory formation (Squire, 1992; Cohen, 1993; Schacter and Tulving, 1994), the impact of prefrontal lesions is less clear (for a review see Buckner *et al.*, 1999). Additionally, lesion studies could not distinguish between brain regions that play a role in encoding as opposed to retrieval of memories (Otten and Rugg, 2001; Johnson *et al.*, 2003).

Functional imaging studies consistently demonstrated prefrontal activation during memory encoding, but yielded heterogeneous results on the issue of lateralization and intrahemispheric location. Prefrontal lateralization during encoding may depend on the material presented (Brewer *et al.*, 1998; Wagner *et al.*, 1998, 1999; Kirchhoff *et al.*, 2000) as well as on the stage of memory processing studied (encoding versus retrieval; Tulving *et al.*, 1994; Smith and Jonides, 1999; Haxby *et al.*, 2000). Within the left PFC, an anterior–posterior gradient has been proposed for encoding of words that rely on semantic versus phonological processing (Fiez, 1997; Poldrack *et al.*, 1999; Devlin *et al.*, 2003). Imaging studies that directly compared encoding of verbal and nonverbal items raised the hypothesis that the 'verbalizability' of the item to remember determines the neural substrate underlying the encoding process (Kelley *et al.*, 1998; Golby *et al.*, 2001; Otten and Rugg, 2001; Johnson *et al.*, 2003).
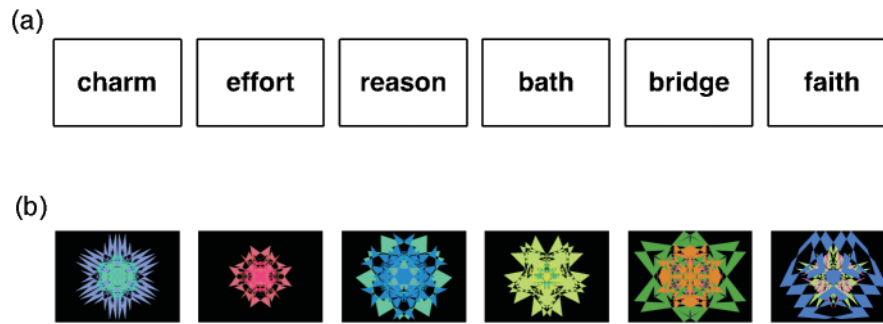
However, activation of a brain area in association with performance of a memory task does not prove a causal link (Wagner *et al.*, 1999; Fletcher and Henson, 2001; Rugg *et al.*, 2002). One way to evaluate the functional contribution of a particular brain region to a specific function is transcranial magnetic stimulation (TMS) (Hallett, 2000; Pascual-Leone *et al.*, 2000). This technique allows probing encoding processes in intact humans while activity in specific brain regions is disrupted ('virtual lesion'). TMS reports of memory encoding showed disparate results: right (Epstein *et al.*, 2002) and left (Rossi *et al.*, 2001) prefrontal involvement with presentation of pictorial items, and left (Kohler *et al.*, 2004) and bilateral (Sandrini *et al.*, 2003) prefrontal involvement with presentation of words. None of these studies directly compared verbal and nonverbal stimuli. Taken together, these reports indicate that the specific role of the PFC in encoding of information is still controversial.

Here, we studied the effects of a 'virtual lesion' of left and right PFC on encoding of both words and abstract shapes in the same group of healthy volunteers. In particular, if constructing a novel representation of a word or a nonverbal abstract stimulus differentially depends on the integrity of left or right PFC, disrupting these areas should negatively influence recognition performance.
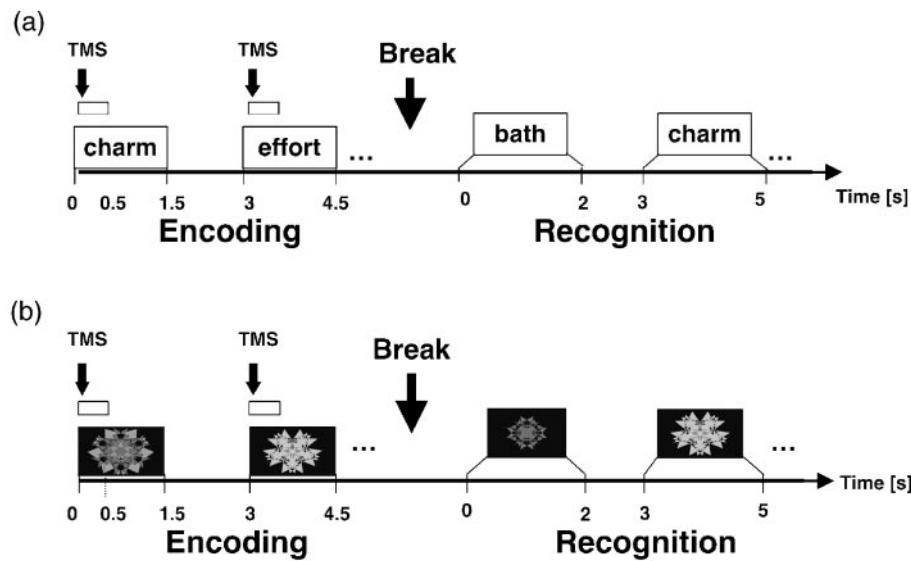
Materials and Methods

Participants

Fifteen neurologically intact native speakers of English (nine female), 22–35 years old (average 28), naive to the experimental hypotheses, gave their written informed consent for the study. The protocol was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board and by the Food and Drug Administration. All subjects were right-handed (mean handedness score (Oldfield, 1971) ± SD: 95% ± 8.3).

Figure 1. Example stimuli from the word (*a*) and picture (*b*) session. Words for the different stimulation conditions were matched for word length, frequency, and ratio of abstract to concrete meanings. Pictures were abstract shapes selected to encourage spatial processing and discourage verbal encoding strategies (Miyashita *et al.*, 1991).

Figure 2. Experimental paradigm for words (*a*) and pictures (*b*). Words and pictures were tested in separate sessions. In each session, subjects were instructed to memorize 108 words or pictures for a later recognition test. TMS was applied to right PFC, left PFC, and in a sham condition synchronously with the onset of viewing each word or picture during the encoding period. A short break separated the encoding and recognition parts of the session. During recognition, subjects were shown 108 words or pictures already seen during encoding and 108 words or pictures that were new. The instruction was to identify each word or picture as 'well remembered', 'familiar' or 'new' (Wagner *et al.*, 1998). See Supplementary Material for a color version of this figure.

Overall Study Design

Each subject participated in two separate sessions: one for word encoding and recognition and one for picture encoding and recognition. Words were balanced for length, familiarity, and concreteness ratings (Kucera and Francis, 1967) (Fig. 1*a*). Picture stimuli were generated by the same fractal algorithm as trial-unique probes to restrict verbal identifications and to encourage encoding on the basis of internal spatial organization of the items (Miyashita, 1988; Miyashita *et al.*, 1991) (Fig. 1*b*). In each block, subjects were instructed to memorize words or pictures carefully for a subsequent memory recognition test. In each of the sessions, encoding was followed by a recognition test in which subjects were instructed to press one of three buttons as quickly and accurately as possible to characterize the presented items as: 'well-remembered' (high-confidence studied), 'familiar' (low-confidence studied), or new (Wagner *et al.*, 1998). Repetitive transcranial magnetic stimulation (rTMS) trains were applied only during the encoding process (Fig. 2*a*,*b*).

Experimental Set-up

Each session (words or pictures) comprised two parts: encoding and recognition. During encoding, words or pictures were presented for 1500 ms each, with inter-item presentation intervals of 1500 ms (Fig.

2*a*,*b*). In the encoding period (presentation of 108 words or pictures), the TMS coil was tangentially positioned over left PFC, right PFC, or perpendicularly to the scalp surface, with one of the wings touching the scalp over Fz (international 10–20 EEG system) in a sham condition (Lisanby *et al.*, 2001) (36 trials for each coil position). For Sham, the scalp contact and discharging noise were similar to active stimulation, but the induced magnetic field did not activate cortical neurons. In 27 of the 36 trials for each position, an rTMS train of 500 ms, starting at the onset of viewing of the word or picture, was delivered. In nine of the 36 trials, no rTMS was delivered as an additional control. Stimulated and not-stimulated trials were randomly intermixed. Trials without rTMS were later averaged across coil positions. For each scalp position, items were presented in one block for words and in six blocks for pictures. A short break (15 min for word session and 1 min for picture session) separated encoding from recognition. During recognition, words or pictures were presented for 2000 ms, with inter-item presentation intervals of 1000 ms.

Stimulus Material

The number of blocks per stimulus type (see above) was designed to render comparable recognition rates in a preliminary study (corrected recognition rate, mean ± SE: 63 ± 4.2% for words and 61 ± 3.8% for pictures; hit rate, mean ± SE: 74 ± 4.1% for words and 76 ± 3.9%). Order

of word and picture tasks and order of stimulation sites were randomized across subjects.

Words and pictures were presented visually on a 17-inch screen connected to a personal computer equipped with SuperLab Pro software (Cedrus Corporation, San Pedro, CA). Subjects sat comfortably in a chair 50 cm away from the monitor. Subjects viewed 216 English nouns (Times New Roman, font size 150, half concrete, half abstract; half of them during encoding, all of them during recognition testing) selected from the Psycholinguistic Database (http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm). Word lengths ranged from 3 to 11 letters, with a Kucera–Francis written frequency from 50 to 60 000 (Kucera and Francis, 1967). Half of the words had an abstract meaning; the other half, a concrete meaning (concreteness ratings: <400, examples: words 1–3; >400, examples: words 4–6). Instructions encouraged a verbal encoding strategy ('find associations'). Under these conditions, there were no significant differences in baseline recognition accuracy for concrete versus abstract words (concrete: 74.6 ± 17.3%; abstract: 72.6 ± 15.9%), consistent with a previous report (Schwanenflugel et al., 1992). Subjects also viewed 216 pictures (half of them during encoding, all of them during recognition testing) generated by computer, following the algorithm described by Miyashita and colleagues (Miyashita et al., 1991). Instructions encouraged a nonverbal encoding strategy ('remember them as shapes or icons').

Transcranial Magnetic Stimulation

We determined stimulation positions using a frameless, MRI-guided, stereotactic system for coil positioning. Initially, T_1-weighted MRI in each subject was obtained using a 1.5 T scanner and a standard head-coil, fast spoiled gradient-recalled at steady-state images, repetition time = 11.2 ms, echo time = 2.1 ms, inversion time = 300 ms, flip angle = 30°, field of view = 24 cm, 256 × 256 matrix, 124 slices, voxel size = 0.94 × 0.94 × 1.5 mm, GE, Milwaukee, WI, USA. Subjects lay supine on a scanner bed. Foam cushions and elastic tape were used to minimize head motion. The MRI data were later fed to a Macintosh computer.

Preceding stimulation, left and right prefrontal targets (BA 45/47, overlying the left anterior and ventral extent of the inferior frontal gyrus) were identified in axial, sagittal, and 3-D views of each individual MRI. The target site for stimulation was the boundary between the pars triangularis and pars opercularis of the left inferior PFC (Devlin et al., 2003). They were then projected over each subject's scalp surface, and frameless stereotaxy (Brainsight, Rogue Research, Inc., Montreal, Canada, http://www.rogue-research.com) was used to position the center of the coil (junction of the wings) over this site in each individual with the handle parallel to the mid-sagittal line and pointing backwards.

Parameters of TMS and Recording Procedures

rTMS was applied using a Magstim Rapid stimulator (Magstim Co., Whitland, south west Wales, UK) with a focal figure-of-eight coil (dual 70 mm coil). Short 20 Hz rTMS trains at 90% motor-threshold (MT) intensity were delivered for 500 ms in synchrony with the onset of each word or picture during the encoding part of each session. For MT determination, electromyographic responses were recorded with surface electrodes positioned on the skin overlying the right and left first dorsal interosseous muscle (FDI). MT was defined as the minimal intensity of the stimulator output capable of evoking a motor-evoked potential greater than 50 μV with 50% probability (Rossini et al., 1994).

Motor thresholds were (mean ± SD) 54.9 ± 7.0% (range between 42% and 74% for the right hand) and 55.1 ± 7.4% (range between 42% and 74% for the left hand, NS). rTMS trains were applied at 90% of individual motor thresholds.

Sub-threshold rTMS did not lead to overt eye-blinking in any subject.

Data Analysis

Data on word and picture sessions were analyzed separately and expressed as mean ± SE. Probability of a hit ($P_{hits, well remembered}$), ($P_{hits, well remembered + familiar}$), and probability of a false alarm ($P_{false alarms, well-remembered}$), ($P_{false alarms, well-remembered + familiar}$) were

calculated for L-TMS, R-TMS, and Sham. From these data, hit rate ($P_{hits, well-remembered}$), corrected recognition rate ($P_{hits, well remembered}$ − $P_{false alarms, well-remembered}$), discrimination measure d', and reaction time (reaction time of well-remembered hits) were calculated. Discrimination measure d' is derived from signal detection theory, which reflects the subject's ability to distinguish between test and distractor items: $d' = \Phi^{-1}(P_{hit}) - \Phi^{-1}(P_{fa})$, with P_{hit} = hit rate ($_{well remembered}$), P_{fa} = false alarm rate ($_{false alarms, well-remembered}$) and Φ^{-1} = inverse cumulative distribution function for the standard normal distribution (Snodgrass and Corwin, 1988).

Repeated-measure ANOVAs ($ANOVA_{RM}$) with repeated measures STIMULATION SITE (L-TMS, R-TMS and Sham) and the factor STIMULUS TYPE (words/abstract shapes) were used to analyze hit rate and corrected recognition rate. Hit rate during unstimulated trials was 73.6 ± 16.2% for words and 76.1 ± 13.6% for pictures, similar to levels during Sham stimulation, and was not included in the ANOVA. Paired *t*-tests, corrected for multiple comparisons of dependent observations (Bonferroni) were used for *post hoc* comparisons.

Results

Outcome measures were hit rate, corrected recognition rate, discrimination measure d', and reaction time, including 'well-remembered' items only, and calculated separately for words and pictures as a function of stimulation site.

Hit Rate (HR), Corrected Recognition Rate (CRR), Discrimination Measure d′

$ANOVA_{RM}$ revealed a significant interaction of STIMULATION SITE by STIMULUS TYPE [for CRR: $F(2,56) = 18.3$, $P < 0.0001$; for HR: $F(2,56) = 14.9$, $P < 0.0001$; for d': $F(2,56) = 17.7$, $P < 0.0001$].

Post hoc testing revealed that recognition performance for words was significantly affected by stimulation site: corrected recognition rate (Fig. 3a), hit rate (Fig. 3b), and d' for words after L-TMS were worse than after R-TMS or Sham (CRR: L-TMS versus R-TMS, $P < 0.001$, L-TMS versus Sham, $P < 0.01$; HR: L-TMS versus R-TMS, $P < 0.01$; L-TMS versus Sham, $P < 0.001$; d': L-TMS versus R-TMS, $P < 0.001$; L-TMS versus Sham, $P < 0.001$). These results point to a left lateralization effect of encoding processing for words.
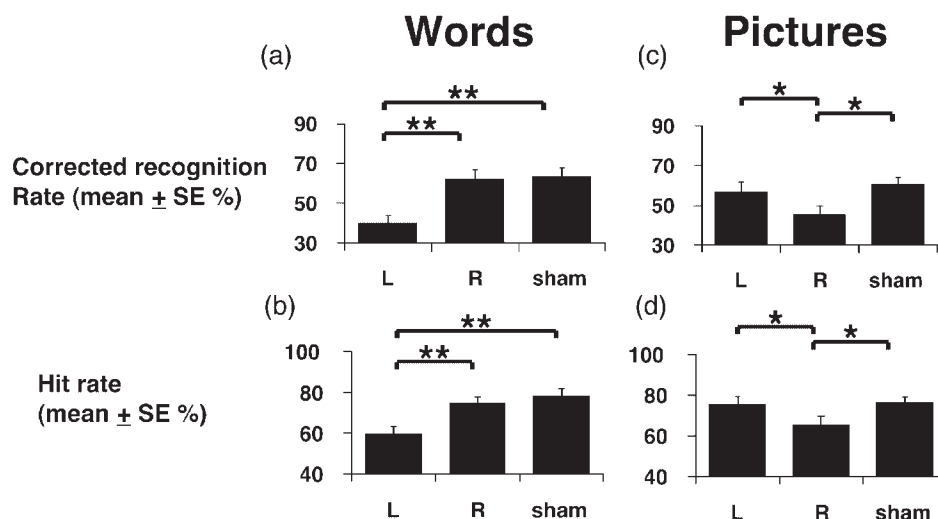
For abstract shapes (Fig. 3c,d), *post hoc* testing revealed that corrected recognition rate (Fig. 3c), hit rate (Fig. 3d), and d' after R-TMS were worse than after L-TMS and Sham (for CRR: R-TMS versus L-TMS, $P < 0.02$, R-TMS versus Sham, $P < 0.01$; for HR: R-TMS versus L-TMS, $P < 0.05$, R-TMS versus Sham, $P < 0.01$, for d': R-TMS versus L-TMS, $P < 0.03$; R-TMS versus Sham, $P < 0.001$), indicating a robust right lateralization effect of encoding abstract pictures that could not be easily verbalized.

Table 1 provides the complete list of hit rates and false alarm rates for words and pictures, separately for 'well-remembered' items and 'well-remembered + familiar' items.

Reaction Time

For reaction times, there was no significant interaction of STIMULATION SITE with STIMULUS TYPE: $F(2,56) = 32.5$, $P = 0.09$, and no significant main effect of STIMULATION SITE or STIMULUS TYPE, suggesting that the results on corrected recognition rate, hit rate, and d' cannot be explained by a speed–accuracy trade-off.

The results on hit rate, corrected recognition rate, and d' cannot be attributed to a prior performance gradient between the words and pictures, since there was no difference between them in baseline performance: hit rate and reaction times did not differ significantly between words and shapes when

Figure 3. Recognition memory for words and pictures. Disruption of PFC activity with TMS differentially interfered with encoding of words (a, b) and pictures (c, d). Left PFC stimulation disrupted corrected recognition rate (a) and hit rate (b) for words more than right PFC stimulation (all Ps < 0.01) and Sham (all Ps < 0.01). Right PFC stimulation disrupted corrected recognition rate (c) and hit rate (d) for pictures more than left PFC stimulation (all Ps < 0.05) and Sham (all Ps < 0.01). Data reported as means ± SE; significance values corrected for multiple comparisons. L = left PFC stimulation, R = right PFC stimulation, sham = sham stimulation. *$P < 0.05$, **$P < 0.01$.

Table 1

Hit rate and false alarm rates for words and pictures. Values are means ± SE

	Stimulation site		
	Left PFC	Right PFC	Sham
Words, hit rate$_{well\ remembered}$	59.7 ± 3.5	74.5 ± 3.1	78.3 ± 3.5
Words, false alarm rate$_{well\ remembered}$	19.9 ± 2.1	12.6 ± 2.0	14.9 ± 1.9
Words, hit rate$_{well\ remembered\ +\ familiar}$	71.0 ± 3.3	81.2 ± 2.9	82.1 ± 4.2
Words, false alarm rate$_{well\ remembered\ +\ familiar}$	26.0 ± 2.1	20.1 ± 2.6	22.2 ± 3.3
Pictures, hit rate$_{well\ remembered}$	75.5 ± 3.7	65.3 ± 4.3	76.2 ± 3.1
Pictures, false alarm rate$_{well\ remembered}$	18.7 ± 2.0	20.0 ± 2.1	15.5 ± 1.9
Pictures, hit rate$_{well\ remembered\ +\ familiar}$	82.9 ± 3.3	68.3 ± 3.9	84.1 ± 2.7
Pictures, false alarm rate$_{well\ remembered\ +\ familiar}$	26.1 ± 1.9	27.2 ± 2.1	24.1 ± 2.1

Hit rates (P_{hits}) and false alarm rates ($P_{false\ positive}$) for 'well remembered' (high confidence studied) items, and 'well-remembered + familiar' (high confidence studied plus low confidence studied) items. Left PFC: stimulation over left PFC; right PFC: stimulation over right PFC; sham: sham stimulation.

comparing the No-TMS or Sham conditions, indicating comparable difficulty for both tasks (*t*-test words versus pictures for No TMS, hit rate: $P = 0.77$, reaction times: $P = 0.30$; *t*-test words versus pictures for Sham, hit rate: $P = 0.64$, reaction times: $P = 0.76$).

Furthermore, TMS effects did not differ significantly between abstract and concrete words [ANOVA$_{RM}$ for words only, with WORD CLASS (abstract, concrete) as within-subject factor, showed no significant effect of WORD CLASS ($P = 0.64$ for hit rate, $P = 0.79$ for corrected recognition rate]. Therefore, data were pooled over abstract and concrete words.

Discussion

Verbal and nonverbal processes participate in encoding of episodic memory (Kelley *et al.*, 1998; Golby *et al.*, 2001). Encoding of pictures, for example, may be implemented through nonverbal and through verbal strategies (Kelley *et al.*, 1998; Golby *et al.*, 2001; Otten and Rugg, 2001; Johnson *et al.*,

2003). In this way, a subject presented with the picture of a tree to memorize could later recall the item by its physical features or by recollection of the word 'tree'. Therefore, even when the task is to memorize the picture of a tree, its high 'verbalizability' could make the encoding process rely predominantly on verbal processing (Kelley *et al.*, 1998).

The PFC is consistently activated in functional imaging studies in association with performance of memory tasks (see reviews by Buckner *et al.*, 1999; Wagner *et al.*, 1999; Fletcher and Henson, 2001; Rugg *et al.*, 2002). Neuroimaging and lesion studies proposed that the PFC contribution to memory encoding differs depending on the 'verbalizability' of the stimulus material (Kelley *et al.*, 1998; Golby *et al.*, 2001; Otten and Rugg, 2001; Johnson *et al.*, 2003). However, a cause–effect link between PFC activation and encoding has not been demonstrated (Wagner *et al.*, 1999; Fletcher and Henson, 2001; Rugg *et al.*, 2002). We evaluated the consequences of transient disruption of activity of PFC on encoding of both verbal and nonverbal items in a balanced experimental design using TMS. Both stimulus types were structured to differ maximally in 'verbalizability,' and examined encoding of both stimulus types in the same subjects. Abstract shapes were selected to minimize natural verbal labels or associations and to encourage encoding on the basis of internal spatial features of the items (Miyashita, 1988; Miyashita *et al.*, 1991). They were all generated by the same fractal algorithm and exhibited similar pattern complexity (Miyashita *et al.*, 1991). On the other hand, in the word encoding task, subjects were encouraged to find semantic associations during encoding, and to avoid using imagery strategies. A prestudy was conducted to identify groups of items that rendered similar recognition rates for both stimulus types. As a consequence, only items that were recognized with high confidence (well-remembered and not just familiar) were included in the analysis (Brewer *et al.*, 1998; Wagner *et al.*, 1998; Dobbins *et al.*, 2003). The similar success rates documented in our study for encoding of abstract and concrete words is consistent with the view that subjects utilized predominantly semantic encoding strategies and did

not rely on imagery of objects represented by the words (Schwanenflugel *et al.*, 1992).

The main finding of the present study was that right PFC stimulation disrupted encoding of abstract shapes while left PFC stimulation disrupted encoding of words.

These results are consistent with a recent TMS study that found the left inferior PFC to be involved in encoding of words (albeit with a facilitating effect, most likely due to differences in stimulation parameters and coil type) (Kohler *et al.*, 2004) and with the report of left-lateralization for semantic processing in the left inferior PFC (Devlin *et al.*, 2003). In addition to semantic processing, it is likely that words were processed along a phonological dimension (Van Orden *et al.*, 1988; Price *et al.*, 1996), both strategies contributing to encoding success in the left inferior PFC, in spatially overlapping regions (Devlin *et al.*, 2003). Therefore, we present experimental evidence for the proposal that activity in left PFC is crucial to encoding of verbal items.

Our results also shed light on two contradictory reports regarding the encoding lateralization of pictorial items. In one, picture encoding was disrupted by left PFC stimulation (Rossi *et al.*, 2001) and in the other by right PFC stimulation (Epstein *et al.*, 2002). However, the pictures presented by Rossi *et al.* (Rossi *et al.*, 2001) were highly verbalizable landscapes that could easily be remembered using verbal strategies, while activity in right PFC has a role in encoding of non-verbalizable items [abstract shapes in our study and unfamiliar abstract patterns in the study by Epstein *et al.* (2002). These findings are consistent with the proposal of differentiated neural substrates within the PFC depending on stimulus features (Goldman-Rakic, 1995).

TMS was applied to the antero-ventral inferior prefrontal gyrus (BA 45/47), using a frameless stereotactic technique and the individual subjects' MRI (Paus, 1999). Stereotactically guided focal coil placement here allowed a more accurate placement in relation to previous TMS studies (Rossi *et al.*, 2001; Epstein *et al.*, 2002; Sandrini *et al.*, 2003), and evaluation of the effects of focal reversible inactivation of BA 45/47 on memory encoding in relation to lesion studies and to reports of intracarotid anesthesia of a complete hemisphere (Kelley *et al.*, 2002).

While stimulation was focal and of relatively low intensity, it is conceivable that direct disruption of activity in area BA 45/47 trans-synaptically influenced other components of the network (Paus, 1999; Chouinard *et al.*, 2003) involved in memory encoding such as ipsilateral frontal (Goldman-Rakic, 1995; Smith and Jonides, 1999; Baddeley, 2001) [e.g. affecting working memory processes (see Baddeley, 1986)], and medial temporal structures (Squire and Zola-Morgan, 1991). Neural substrates connecting these regions exist, and the medial temporal lobe may bind together the outcomes of information processed in frontal cortical regions to form lasting memory traces (Cohen *et al.*, 1985; Squire and Zola-Morgan, 1991; Wagner *et al.*, 1999; Rugg *et al.*, 2002). Prefrontal TMS may disrupt the crucial input from frontal regions into medial temporal lobe structures (Buckner *et al.*, 1999) in the healthy brain, thereby deteriorating encoding success. The finding that patients with chronic frontal lobe lesions often perform well on simple recognition memory tasks (Milner *et al.*, 1985; Schacter and Tulving, 1994) indicates that other brain areas may be capable of taking over the function of PFC in the injured brain (Buckner *et al.*, 1999; Kelley *et al.*, 2002). An interesting question for future investigation will be to determine which brain regions underlie successful memory formation after lesions of the PFC.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oupjournals.org/

Notes

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Prefrontal Cortex Asymmetry for Memory Encoding of Words and Abstract Shapes

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Previous work suggested a differential contribution of prefrontal cortex (PFC) to successful encoding depending on the stimulus material. Here, we tested the hypothesis that encoding of words preferentially involves the left PFC, while encoding of nonverbal items (abstract shapes) relies on the right PFC. We used an experimental design that evaluated encoding of both words and abstract shapes in the same healthy volunteers. A transient virtual lesion of the left or the right PFC was elicited with transcranial magnetic stimulation (TMS) while subjects memorized verbal and nonverbal items. We found that encoding of verbal material was disrupted by left PFC stimulation, whereas encoding of nonverbal material was disrupted by right PFC stimulation. These results demonstrate a functionally relevant lateralization of prefrontal contribution for verbal and nonverbal memory encoding.

Keywords: episodic memory, frontal cortex, nonverbal, transcranial magnetic stimulation, verbal

Introduction

Episodic memory (explicit memory for recently experienced events) depends upon a number of circumscribed, interconnected brain regions, including the medial temporal lobe and the prefrontal cortex (PFC) (Milner and Petrides, 1984; Cohen *et al.*, 1985; Tulving *et al.*, 1994; Wagner *et al.*, 1999; Golby *et al.*, 2001; Otten and Rugg, 2001; Rugg *et al.*, 2002; Johnson *et al.*, 2003). Previous lesion studies proposed a link between material-specific lateralization and encoding for both medial temporal lobe and PFC (Riege *et al.*, 1980; Whitehouse, 1981; Milner and Petrides, 1984; Cohen *et al.*, 1985; Squire, 1992; Cohen, 1993; Schacter and Tulving, 1994). However, while medial temporal lesions critically impair memory formation (Squire, 1992; Cohen, 1993; Schacter and Tulving, 1994), the impact of prefrontal lesions is less clear (for a review see Buckner *et al.*, 1999). Additionally, lesion studies could not distinguish between brain regions that play a role in encoding as opposed to retrieval of memories (Otten and Rugg, 2001; Johnson *et al.*, 2003).

Functional imaging studies consistently demonstrated prefrontal activation during memory encoding, but yielded heterogeneous results on the issue of lateralization and intrahemispheric location. Prefrontal lateralization during encoding may depend on the material presented (Brewer *et al.*, 1998; Wagner *et al.*, 1998, 1999; Kirchhoff *et al.*, 2000) as well as on the stage of memory processing studied (encoding versus retrieval; Tulving *et al.*, 1994; Smith and Jonides, 1999; Haxby

et al., 2000). Within the left PFC, an anterior–posterior gradient has been proposed for encoding of words that rely on semantic versus phonological processing (Fiez, 1997; Poldrack *et al.*, 1999; Devlin *et al.*, 2003). Imaging studies that directly compared encoding of verbal and nonverbal items raised the hypothesis that the 'verbalizability' of the item to remember determines the neural substrate underlying the encoding process (Kelley *et al.*, 1998; Golby *et al.*, 2001; Otten and Rugg, 2001; Johnson *et al.*, 2003).
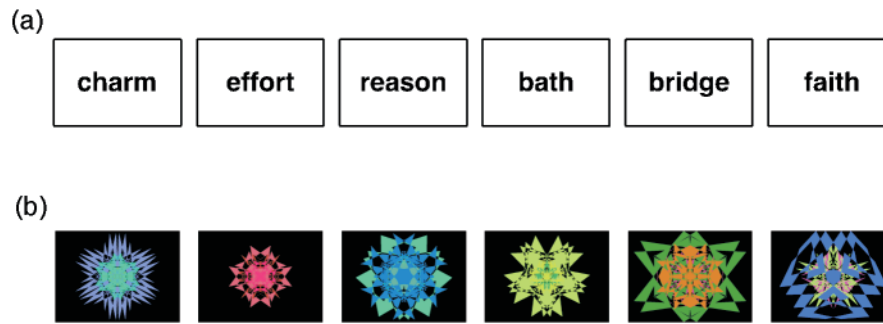
However, activation of a brain area in association with performance of a memory task does not prove a causal link (Wagner *et al.*, 1999; Fletcher and Henson, 2001; Rugg *et al.*, 2002). One way to evaluate the functional contribution of a particular brain region to a specific function is transcranial magnetic stimulation (TMS) (Hallett, 2000; Pascual-Leone *et al.*, 2000). This technique allows probing encoding processes in intact humans while activity in specific brain regions is disrupted ('virtual lesion'). TMS reports of memory encoding showed disparate results: right (Epstein *et al.*, 2002) and left (Rossi *et al.*, 2001) prefrontal involvement with presentation of pictorial items, and left (Kohler *et al.*, 2004) and bilateral (Sandrini *et al.*, 2003) prefrontal involvement with presentation of words. None of these studies directly compared verbal and nonverbal stimuli. Taken together, these reports indicate that the specific role of the PFC in encoding of information is still controversial.

Here, we studied the effects of a 'virtual lesion' of left and right PFC on encoding of both words and abstract shapes in the same group of healthy volunteers. In particular, if constructing a novel representation of a word or a nonverbal abstract stimulus differentially depends on the integrity of left or right PFC, disrupting these areas should negatively influence recognition performance.
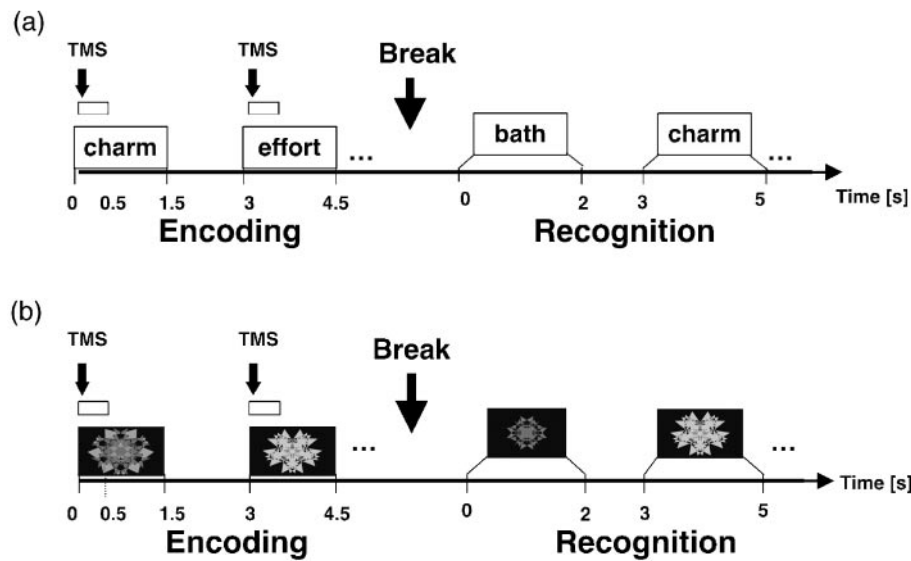
Materials and Methods

Participants

Fifteen neurologically intact native speakers of English (nine female), 22–35 years old (average 28), naive to the experimental hypotheses, gave their written informed consent for the study. The protocol was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board and by the Food and Drug Administration. All subjects were right-handed (mean handedness score (Oldfield, 1971) ± SD: 95% ± 8.3).

Figure 1. Example stimuli from the word (*a*) and picture (*b*) session. Words for the different stimulation conditions were matched for word length, frequency, and ratio of abstract to concrete meanings. Pictures were abstract shapes selected to encourage spatial processing and discourage verbal encoding strategies (Miyashita *et al.*, 1991).

Figure 2. Experimental paradigm for words (*a*) and pictures (*b*). Words and pictures were tested in separate sessions. In each session, subjects were instructed to memorize 108 words or pictures for a later recognition test. TMS was applied to right PFC, left PFC, and in a sham condition synchronously with the onset of viewing each word or picture during the encoding period. A short break separated the encoding and recognition parts of the session. During recognition, subjects were shown 108 words or pictures already seen during encoding and 108 words or pictures that were new. The instruction was to identify each word or picture as 'well remembered', 'familiar' or 'new' (Wagner *et al.*, 1998). See Supplementary Material for a color version of this figure.

Overall Study Design

Each subject participated in two separate sessions: one for word encoding and recognition and one for picture encoding and recognition. Words were balanced for length, familiarity, and concreteness ratings (Kucera and Francis, 1967) (Fig. 1*a*). Picture stimuli were generated by the same fractal algorithm as trial-unique probes to restrict verbal identifications and to encourage encoding on the basis of internal spatial organization of the items (Miyashita, 1988; Miyashita *et al.*, 1991) (Fig. 1*b*). In each block, subjects were instructed to memorize words or pictures carefully for a subsequent memory recognition test. In each of the sessions, encoding was followed by a recognition test in which subjects were instructed to press one of three buttons as quickly and accurately as possible to characterize the presented items as: 'well-remembered' (high-confidence studied), 'familiar' (low-confidence studied), or new (Wagner *et al.*, 1998). Repetitive transcranial magnetic stimulation (rTMS) trains were applied only during the encoding process (Fig. 2*a*,*b*).

Experimental Set-up

Each session (words or pictures) comprised two parts: encoding and recognition. During encoding, words or pictures were presented for 1500 ms each, with inter-item presentation intervals of 1500 ms (Fig. 2*a*,*b*). In the encoding period (presentation of 108 words or pictures), the TMS coil was tangentially positioned over left PFC, right PFC, or perpendicularly to the scalp surface, with one of the wings touching the scalp over Fz (international 10–20 EEG system) in a sham condition (Lisanby *et al.*, 2001) (36 trials for each coil position). For Sham, the scalp contact and discharging noise were similar to active stimulation, but the induced magnetic field did not activate cortical neurons. In 27 of the 36 trials for each position, an rTMS train of 500 ms, starting at the onset of viewing of the word or picture, was delivered. In nine of the 36 trials, no rTMS was delivered as an additional control. Stimulated and not-stimulated trials were randomly intermixed. Trials without rTMS were later averaged across coil positions. For each scalp position, items were presented in one block for words and in six blocks for pictures. A short break (15 min for word session and 1 min for picture session) separated encoding from recognition. During recognition, words or pictures were presented for 2000 ms, with inter-item presentation intervals of 1000 ms.

Stimulus Material

The number of blocks per stimulus type (see above) was designed to render comparable recognition rates in a preliminary study (corrected recognition rate, mean ± SE: 63 ± 4.2% for words and 61 ± 3.8% for pictures; hit rate, mean ± SE: 74 ± 4.1% for words and 76 ± 3.9%). Order

of word and picture tasks and order of stimulation sites were randomized across subjects.

Words and pictures were presented visually on a 17-inch screen connected to a personal computer equipped with SuperLab Pro software (Cedrus Corporation, San Pedro, CA). Subjects sat comfortably in a chair 50 cm away from the monitor. Subjects viewed 216 English nouns (Times New Roman, font size 150, half concrete, half abstract; half of them during encoding, all of them during recognition testing) selected from the Psycholinguistic Database (http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm). Word lengths ranged from 3 to 11 letters, with a Kucera–Francis written frequency from 50 to 60 000 (Kucera and Francis, 1967). Half of the words had an abstract meaning; the other half, a concrete meaning (concreteness ratings: <400, examples: words 1–3; >400, examples: words 4–6). Instructions encouraged a verbal encoding strategy ('find associations'). Under these conditions, there were no significant differences in baseline recognition accuracy for concrete versus abstract words (concrete: 74.6 ± 17.3%; abstract: 72.6 ± 15.9%), consistent with a previous report (Schwanenflugel et al., 1992). Subjects also viewed 216 pictures (half of them during encoding, all of them during recognition testing) generated by computer, following the algorithm described by Miyashita and colleagues (Miyashita et al., 1991). Instructions encouraged a nonverbal encoding strategy ('remember them as shapes or icons').

Transcranial Magnetic Stimulation

We determined stimulation positions using a frameless, MRI-guided, stereotactic system for coil positioning. Initially, T_1-weighted MRI in each subject was obtained using a 1.5 T scanner and a standard head-coil, fast spoiled gradient-recalled at steady-state images, repetition time = 11.2 ms, echo time = 2.1 ms, inversion time = 300 ms, flip angle = 30°, field of view = 24 cm, 256 × 256 matrix, 124 slices, voxel size = 0.94 × 0.94 × 1.5 mm, GE, Milwaukee, WI, USA. Subjects lay supine on a scanner bed. Foam cushions and elastic tape were used to minimize head motion. The MRI data were later fed to a Macintosh computer.

Preceding stimulation, left and right prefrontal targets (BA 45/47, overlying the left anterior and ventral extent of the inferior frontal gyrus) were identified in axial, sagittal, and 3-D views of each individual MRI. The target site for stimulation was the boundary between the pars triangularis and pars opercularis of the left inferior PFC (Devlin et al., 2003). They were then projected over each subject's scalp surface, and frameless stereotaxy (Brainsight, Rogue Research, Inc., Montreal, Canada, http://www.rogue-research.com) was used to position the center of the coil (junction of the wings) over this site in each individual with the handle parallel to the mid-sagittal line and pointing backwards.

Parameters of TMS and Recording Procedures

rTMS was applied using a Magstim Rapid stimulator (Magstim Co., Whitland, south west Wales, UK) with a focal figure-of-eight coil (dual 70 mm coil). Short 20 Hz rTMS trains at 90% motor-threshold (MT) intensity were delivered for 500 ms in synchrony with the onset of each word or picture during the encoding part of each session. For MT determination, electromyographic responses were recorded with surface electrodes positioned on the skin overlying the right and left first dorsal interosseous muscle (FDI). MT was defined as the minimal intensity of the stimulator output capable of evoking a motor-evoked potential greater than 50 μV with 50% probability (Rossini et al., 1994).

Motor thresholds were (mean ± SD) 54.9 ± 7.0% (range between 42% and 74% for the right hand) and 55.1 ± 7.4% (range between 42% and 74% for the left hand, NS). rTMS trains were applied at 90% of individual motor thresholds.

Sub-threshold rTMS did not lead to overt eye-blinking in any subject.

Data Analysis

Data on word and picture sessions were analyzed separately and expressed as mean ± SE. Probability of a hit ($P_{hits, well remembered}$), ($P_{hits, well remembered + familiar}$), and probability of a false alarm ($P_{false alarms, well-remembered}$), ($P_{false alarms, well-remembered + familiar}$) were

calculated for L-TMS, R-TMS, and Sham. From these data, hit rate ($P_{hits, well-remembered}$), corrected recognition rate ($P_{hits, well remembered} - P_{false alarms, well-remembered}$), discrimination measure d', and reaction time (reaction time of well-remembered hits) were calculated. Discrimination measure d' is derived from signal detection theory, which reflects the subject's ability to distinguish between test and distractor items: $d' = \Phi^{-1}(P_{hit}) - \Phi^{-1}(P_{fa})$, with P_{hit} = hit rate ($_{well remembered}$), P_{fa} = false alarm rate ($_{false alarms, well-remembered}$) and Φ^{-1} = inverse cumulative distribution function for the standard normal distribution (Snodgrass and Corwin, 1988).

Repeated-measure ANOVAs (ANOVA$_{RM}$) with repeated measures STIMULATION SITE (L-TMS, R-TMS and Sham) and the factor STIMULUS TYPE (words/abstract shapes) were used to analyze hit rate and corrected recognition rate. Hit rate during unstimulated trials was 73.6 ± 16.2% for words and 76.1 ± 13.6% for pictures, similar to levels during Sham stimulation, and was not included in the ANOVA. Paired t-tests, corrected for multiple comparisons of dependent observations (Bonferroni) were used for post hoc comparisons.

Results

Outcome measures were hit rate, corrected recognition rate, discrimination measure d', and reaction time, including 'well-remembered' items only, and calculated separately for words and pictures as a function of stimulation site.

Hit Rate (HR), Corrected Recognition Rate (CRR), Discrimination Measure d'

ANOVA$_{RM}$ revealed a significant interaction of STIMULATION SITE by STIMULUS TYPE [for CRR: $F(2,56) = 18.3$, $P < 0.0001$; for HR: $F(2,56) = 14.9$, $P < 0.0001$; for d': $F(2,56) = 17.7$, $P < 0.0001$].

Post hoc testing revealed that recognition performance for words was significantly affected by stimulation site: corrected recognition rate (Fig. 3a), hit rate (Fig. 3b), and d' for words after L-TMS were worse than after R-TMS or Sham (CRR: L-TMS versus R-TMS, $P < 0.001$, L-TMS versus Sham, $P < 0.01$; HR: L-TMS versus R-TMS, $P < 0.01$; L-TMS versus Sham, $P < 0.001$; d': L-TMS versus R-TMS, $P < 0.001$; L-TMS versus Sham, $P < 0.001$). These results point to a left lateralization effect of encoding processing for words.
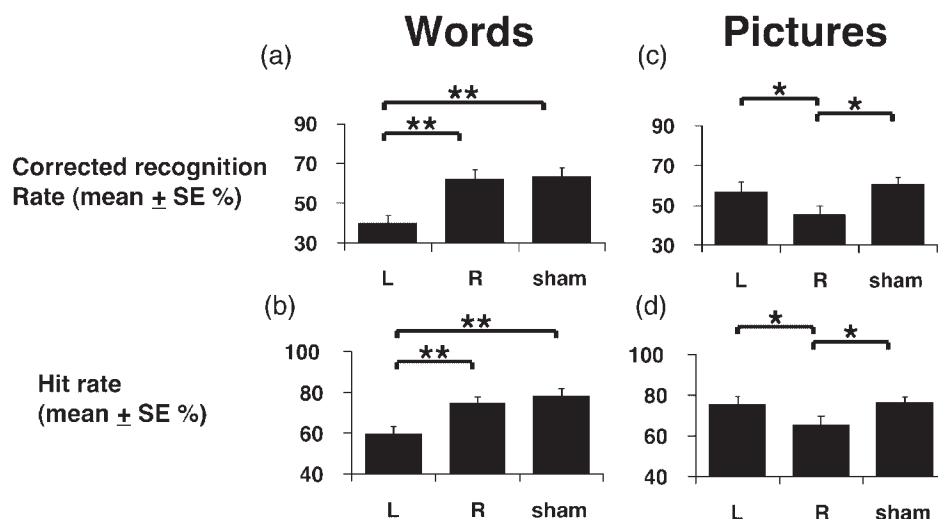
For abstract shapes (Fig. 3c,d), post hoc testing revealed that corrected recognition rate (Fig. 3c), hit rate (Fig. 3d), and d' after R-TMS were worse than after L-TMS and Sham (for CRR: R-TMS versus L-TMS, $P < 0.02$, R-TMS versus Sham, $P < 0.01$; for HR: R-TMS versus L-TMS, $P < 0.05$, R-TMS versus Sham, $P < 0.01$, for d': R-TMS versus L-TMS, $P < 0.03$; R-TMS versus Sham, $P < 0.001$), indicating a robust right lateralization effect of encoding abstract pictures that could not be easily verbalized.

Table 1 provides the complete list of hit rates and false alarm rates for words and pictures, separately for 'well-remembered' items and 'well-remembered + familiar' items.

Reaction Time

For reaction times, there was no significant interaction of STIMULATION SITE with STIMULUS TYPE: $F(2,56) = 32.5$, $P = 0.09$, and no significant main effect of STIMULATION SITE or STIMULUS TYPE, suggesting that the results on corrected recognition rate, hit rate, and d' cannot be explained by a speed–accuracy trade-off.

The results on hit rate, corrected recognition rate, and d' cannot be attributed to a prior performance gradient between the words and pictures, since there was no difference between them in baseline performance: hit rate and reaction times did not differ significantly between words and shapes when

Words

(a)

Corrected recognition Rate (mean ± SE %)

Pictures

(c)

(b)

Hit rate (mean ± SE %)

(d)

Figure 3. Recognition memory for words and pictures. Disruption of PFC activity with TMS differentially interfered with encoding of words (*a, b*) and pictures (*c, d*). Left PFC stimulation disrupted corrected recognition rate (*a*) and hit rate (*b*) for words more than right PFC stimulation (all $Ps < 0.01$) and Sham (all $Ps < 0.01$). Right PFC stimulation disrupted corrected recognition rate (*c*) and hit rate (*d*) for pictures more than left PFC stimulation (all $Ps < 0.05$) and Sham (all $Ps < 0.01$). Data reported as means ± SE; significance values corrected for multiple comparisons. L = left PFC stimulation, R = right PFC stimulation, sham = sham stimulation. *$P < 0.05$, **$P < 0.01$.

Table 1

Hit rate and false alarm rates for words and pictures. Values are means ± SE

	Stimulation site		
	Left PFC	Right PFC	Sham
Words, hit rate_well remembered	59.7 ± 3.5	74.5 ± 3.1	78.3 ± 3.5
Words, false alarm rate_well remembered	19.9 ± 2.1	12.6 ± 2.0	14.9 ± 1.9
Words, hit rate_well remembered + familiar	71.0 ± 3.3	81.2 ± 2.9	82.1 ± 4.2
Words, false alarm rate_well remembered + familiar	26.0 ± 2.1	20.1 ± 2.6	22.2 ± 3.3
Pictures, hit rate_well remembered	75.5 ± 3.7	65.3 ± 4.3	76.2 ± 3.1
Pictures, false alarm rate_well remembered	18.7 ± 2.0	20.0 ± 2.1	15.5 ± 1.9
Pictures, hit rate_well remembered + familiar	82.9 ± 3.3	68.3 ± 3.9	84.1 ± 2.7
Pictures, false alarm rate_well remembered + familiar	26.1 ± 1.9	27.2 ± 2.1	24.1 ± 2.1

Hit rates (P_{hits}) and false alarm rates ($P_{false positive}$) for 'well remembered' (high confidence studied) items, and 'well-remembered + familiar' (high confidence studied plus low confidence studied) items. Left PFC: stimulation over left PFC; right PFC: stimulation over right PFC; sham: sham stimulation.

comparing the No-TMS or Sham conditions, indicating comparable difficulty for both tasks (*t*-test words versus pictures for No TMS, hit rate: $P = 0.77$, reaction times: $P = 0.30$; *t*-test words versus pictures for Sham, hit rate: $P = 0.64$, reaction times: $P = 0.76$).

Furthermore, TMS effects did not differ significantly between abstract and concrete words [ANOVA_RM for words only, with WORD CLASS (abstract, concrete) as within-subject factor, showed no significant effect of WORD CLASS ($P = 0.64$ for hit rate, $P = 0.79$ for corrected recognition rate]. Therefore, data were pooled over abstract and concrete words.

Discussion

Verbal and nonverbal processes participate in encoding of episodic memory (Kelley *et al.*, 1998; Golby *et al.*, 2001). Encoding of pictures, for example, may be implemented through nonverbal and through verbal strategies (Kelley *et al.*, 1998; Golby *et al.*, 2001; Otten and Rugg, 2001; Johnson *et al.*,

2003). In this way, a subject presented with the picture of a tree to memorize could later recall the item by its physical features or by recollection of the word 'tree'. Therefore, even when the task is to memorize the picture of a tree, its high 'verbalizability' could make the encoding process rely predominantly on verbal processing (Kelley *et al.*, 1998).

The PFC is consistently activated in functional imaging studies in association with performance of memory tasks (see reviews by Buckner *et al.*, 1999; Wagner *et al.*, 1999; Fletcher and Henson, 2001; Rugg *et al.*, 2002). Neuroimaging and lesion studies proposed that the PFC contribution to memory encoding differs depending on the 'verbalizability' of the stimulus material (Kelley *et al.*, 1998; Golby *et al.*, 2001; Otten and Rugg, 2001; Johnson *et al.*, 2003). However, a cause–effect link between PFC activation and encoding has not been demonstrated (Wagner *et al.*, 1999; Fletcher and Henson, 2001; Rugg *et al.*, 2002). We evaluated the consequences of transient disruption of activity of PFC on encoding of both verbal and nonverbal items in a balanced experimental design using TMS. Both stimulus types were structured to differ maximally in 'verbalizability,' and examined encoding of both stimulus types in the same subjects. Abstract shapes were selected to minimize natural verbal labels or associations and to encourage encoding on the basis of internal spatial features of the items (Miyashita, 1988; Miyashita *et al.*, 1991). They were all generated by the same fractal algorithm and exhibited similar pattern complexity (Miyashita *et al.*, 1991). On the other hand, in the word encoding task, subjects were encouraged to find semantic associations during encoding, and to avoid using imagery strategies. A prestudy was conducted to identify groups of items that rendered similar recognition rates for both stimulus types. As a consequence, only items that were recognized with high confidence (well-remembered and not just familiar) were included in the analysis (Brewer *et al.*, 1998; Wagner *et al.*, 1998; Dobbins *et al.*, 2003). The similar success rates documented in our study for encoding of abstract and concrete words is consistent with the view that subjects utilized predominantly semantic encoding strategies and did

not rely on imagery of objects represented by the words (Schwanenflugel *et al.*, 1992).

The main finding of the present study was that right PFC stimulation disrupted encoding of abstract shapes while left PFC stimulation disrupted encoding of words.

These results are consistent with a recent TMS study that found the left inferior PFC to be involved in encoding of words (albeit with a facilitating effect, most likely due to differences in stimulation parameters and coil type) (Kohler *et al.*, 2004) and with the report of left-lateralization for semantic processing in the left inferior PFC (Devlin *et al.*, 2003). In addition to semantic processing, it is likely that words were processed along a phonological dimension (Van Orden *et al.*, 1988; Price *et al.*, 1996), both strategies contributing to encoding success in the left inferior PFC, in spatially overlapping regions (Devlin *et al.*, 2003). Therefore, we present experimental evidence for the proposal that activity in left PFC is crucial to encoding of verbal items.

Our results also shed light on two contradictory reports regarding the encoding lateralization of pictorial items. In one, picture encoding was disrupted by left PFC stimulation (Rossi *et al.*, 2001) and in the other by right PFC stimulation (Epstein *et al.*, 2002). However, the pictures presented by Rossi *et al.* (Rossi *et al.*, 2001) were highly verbalizable landscapes that could easily be remembered using verbal strategies, while activity in right PFC has a role in encoding of non-verbalizable items [abstract shapes in our study and unfamiliar abstract patterns in the study by Epstein *et al.* (2002). These findings are consistent with the proposal of differentiated neural substrates within the PFC depending on stimulus features (Goldman-Rakic, 1995).

TMS was applied to the antero-ventral inferior prefrontal gyrus (BA 45/47), using a frameless stereotactic technique and the individual subjects' MRI (Paus, 1999). Stereotactically guided focal coil placement here allowed a more accurate placement in relation to previous TMS studies (Rossi *et al.*, 2001; Epstein *et al.*, 2002; Sandrini *et al.*, 2003), and evaluation of the effects of focal reversible inactivation of BA 45/47 on memory encoding in relation to lesion studies and to reports of intracarotid anesthesia of a complete hemisphere (Kelley *et al.*, 2002).

While stimulation was focal and of relatively low intensity, it is conceivable that direct disruption of activity in area BA 45/47 trans-synaptically influenced other components of the network (Paus, 1999; Chouinard *et al.*, 2003) involved in memory encoding such as ipsilateral frontal (Goldman-Rakic, 1995; Smith and Jonides, 1999; Baddeley, 2001) [e.g. affecting working memory processes (see Baddeley, 1986)], and medial temporal structures (Squire and Zola-Morgan, 1991). Neural substrates connecting these regions exist, and the medial temporal lobe may bind together the outcomes of information processed in frontal cortical regions to form lasting memory traces (Cohen *et al.*, 1985; Squire and Zola-Morgan, 1991; Wagner *et al.*, 1999; Rugg *et al.*, 2002). Prefrontal TMS may disrupt the crucial input from frontal regions into medial temporal lobe structures (Buckner *et al.*, 1999) in the healthy brain, thereby deteriorating encoding success. The finding that patients with chronic frontal lobe lesions often perform well on simple recognition memory tasks (Milner *et al.*, 1985; Schacter and Tulving, 1994) indicates that other brain areas may be capable of taking over the function of PFC in the injured brain (Buckner *et al.*, 1999; Kelley *et al.*, 2002). An interesting question for future investigation will be to determine which brain regions underlie successful memory formation after lesions of the PFC.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oupjournals.org/

Notes

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