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# The Influence of Low-frequency Left Prefrontal Repetitive Transcranial Magnetic Stimulation on Memory for Words but Not for Faces

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## Summary

Brain imaging studies suggest localization of verbal working memory in the left dorsolateral prefrontal cortex (DLPFC) while face processing and memory is localized in the inferior temporal cortex and other brain areas. The goal of this study was to assess the effect of left DLPFC low-frequency repetitive transcranial magnetic stimulation (rTMS) on verbal recall and face recognition. The study revealed a significant decrease of free recall in word encoding under rTMS (110 % of motor threshold, 0.9 Hz) in comparison with sham stimulation ($p=0.03$), while no significant difference was found with facial memory tests. Our findings support the essential role of the left DLPFC in word but not facial memory and confirm the content specific arrangement of cortical areas involved in semantic memory. As a non-invasive tool, rTMS is useful for cognitive brain mapping and the functional localization of the category specific memory system.

**Key words**

Face memory • Verbal memory • Repetitive transcranial magnetic stimulation • rTMS

## Introduction

Transcranial magnetic stimulation (TMS) is a newly developing, non-invasive method that induces functional changes in a relatively small area of the human cerebral cortex. The principle of TMS is derived from the Faraday's flux-cutting law. Short electric current transits in the coil produce a temporary magnetic field. This field passes over the medium, i.e. cranium and is turned back into an electric field, which induces transmembrane potentials and leads to the depolarization of neuron membranes (Barker *et al.* 1985).

TMS is used to affect different cognitive functions by inducing artificial cortical lesions and thus it can provide insight into cortical connectivity and localization. TMS, applied in cognitive brain mapping, is used as single pulse (spTMS), or rapid-rate pulse (up to 50 Hz) called repetitive TMS (rTMS). The spTMS applied in specific synchronization with the cognitive process can disrupt it and produce a so-called virtual lesion lasting for up to one second. The effect of rTMS depends on the power of the magnetic field, the



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localization of the stimuli and the frequency. High-frequency rTMS (>1 Hz) increases the cortical excitability and results in the long-term enhancement of synaptic transfer. Conversely, low-frequency rTMS (≤1 Hz) inhibits the cortical excitability and leads to weakening of the transfer at the synapses (Chen *et al.* 1997, Pascual-Leone *et al.* 1994, Wassermann and Lisanby 2001, Romero *et al.* 2002). In comparison with spTMS, the rTMS method allows an increase or decrease of cortical activity for the entire duration of the stimulation or longer.

Currently, TMS has been used in various experiments to study memory encoding and retrieval (for review Mull and Seyal 2001, Grafman and Wasserman 1999, Pascual-Leone and Hallett 1994) and its results correspond with the data from neuroimaging studies.

The investigation of structure-function relationships by means of functional neuroimaging brought evidence for the vital role of the frontal cortex in semantic memory. The anatomical specialization of semantic memory for different types of stored information (words, faces, animals) has been proposed (Fletcher and Henson 2000, Kelley *et al.* 1998). The cortical information-modality specialization is a challenging concept in brain mapping and theory of information processing. A review of human functional imaging studies indicates that verbal memory tasks activate foremost the left dorsolateral prefrontal cortex, while face encoding and consolidation involves the basal frontotemporal cortex (Fletcher and Henson 2000, Cabeza and Nyberg 2000).

The primary goal of our study was to evaluate the effect of low-frequency rTMS localized on the DLPFC (the dominant hemisphere) on the encoding of semantic memory for faces and words. With regard to the cortical inhibitory effect of low-frequency rTMS and the cortical specialization for different types of memory we tested the following hypothesis: low-frequency rTMS on left DLPFC in comparison with sham (inactive) stimulation decreases the memory encoding of verbal but not face information.

## Methods

*Subjects*

The study was a sham-controlled trial in which all participants completed two memory test examinations. Ten right-handed volunteers (aged 23.8±2.3 years, mean ± SD), five males (24.4±3.2) and five females (23.2±1.1), carefully screened for neurological, psychiatric, or physical illness or head injury were involved into the study. All subjects had no previous history of and were not taking any medication. Motor thresholds, measured in percent of Magstim output, were 54.8±8.51 % for the whole group (59±12.4 % for males and 51.2±2.5 % for females). Mean education level in our group was 16.8±1.2 years (16.6±1.1 for males and 17.0±1.4 for females). The Institutional Ethics Committee approved the study and an informed consent form was signed by each subject.

*Cognitive testing*

The tests were conducted under randomized assignment to sham or experimental rTMS. The inter-testing interval within the sham and experimental condition was at least one week, with each session occurring approximately at the same daytime.

Active and sham memory testing had two parts: the word memory (recall) test and the face recognition memory test. Both subtests were in two equivalent versions (verified previously on a large sample of 101 subjects) to avoid the influence of learning in the second (re-) testing. The subtests were administered in random order with a half hour interval between the two. All tests were administered on a computer, which was placed at eye level 1 m in front of the subjects while the rTMS was applied. The word-memory test explored verbal memory by presenting a series of 25 target real words, with 4 to 6 letters per word (for example: rose, mother, table) in white sans-serif font on a black screen in Czech. An interstimulus interval (frequency) was 4.5 s (word presentation for 3 s then 1.5 s of blank screen). Immediately after this encoding period (and rTMS) the subjects were asked to recall the words, which they viewed during the presentation and the number of correct words was counted as the result. The face recognition test investigated memory for faces by consecutively presenting 25 target photographs of young Caucasian male faces in identical apparel on a monitor with the same interstimulus interval as in the word test. After the presentation the participants were tested for recognition by being prompted to choose the already presented face from its pair (a same-sized, but novel face), which were side by side on the screen and the exposure time was done by the click for next pair.

*Repetitive transcranial magnetic stimulation (rTMS)*

The rTMS application for each subtest started

one minute before the test began and continued throughout the acquisition phase (192 magnetic pulses per one subtest). A high-speed Magstim Super Rapid Stimulator (Magstim, Whitland, UK) with a continuous air cooling figure-of-eight coil and a 70 mm diameter span for each wing was used for the rTMS administration. Motor threshold (MT) for each participant was measured with an EMG Neurosign 400 at the beginning of the first session. The intensity of the motor threshold was established by the lowest strength needed to elicit five motor evoked potentials within 10 trials. The left DLPFC stimulation site was defined as the region 5 cm rostral in the same sagittal plane as the optimal site for MT production in the right abductor pollicis brevis (Rossini 1994).

The active stimulation condition was defined as low-frequency rTMS with a stimulation intensity that was 110 % of motor threshold. The frequency of rTMS was 0.9 Hz over DLPFC (192 magnetic pulses per one subtest). This stimulation procedure was within safety guidelines (Wasserman 1998). The sham stimulation was defined with a coil diverted by 90 degrees and a stimulation intensity of 50 % of output of stimulator with the same frequency, duration and position as in the active rTMS. This method of sham stimulation was established as adequate in the previous studies (Loo *et al.* 2000). Immediately following the word or face stimuli presentation the rTMS was finished and free recall of words or recognition of faces was evaluated. The investigator responsible for test presentation was blind to the rTMS condition.

*Statistical analysis*

Due to the sample size and non-normal distribution (Kolmogorov-Smirnov test) we used the non-parametric Wilcoxon matched pairs test for within subject comparison based on 10 differences in the sham and active rTMS conditions in both the face-recognition and the word-recall subtests. Regarding the a priori hypothesis that low frequency would decrease the memory recall we used one-tailed p values (confidence interval, C.I. = 95 %).

## Results

In our sample we did not find any significant difference between results of recognition of faces in the sham (median 22.50, C.I. 95 % = 24.0 - 25.11) and active (median 22.50, C.I. 95 % = 20.42 - 23.58) stimulation conditions (sum of signed ranks, W´= –2.0, p>0.5, Fig. 1.). In the free recall of words we found significant worsening under active (median 11.00, C.I. 95 % = 9.11 - 13.89) rTMS in comparison with sham conditions (median 13.00, C.I. 95 % = 11.78 -16.02) (sum of signed ranks, W = –18.0, p = 0.03, Fig. 1.).

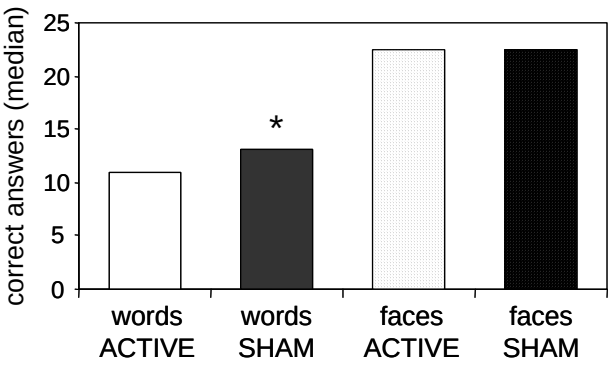


**Fig. 1.** The influence of low-frequency 0.9 Hz rTMS (ACTIVE) in comparison with control rTMS (SHAM) on memory for words and faces. The active 0.9 Hz rTMS during encoding decreased word recall (Wilcoxon matched pairs test, $p \leq 0{,}05$, marked by *) but not face recognition (p = n.s.).

## Discussion

In our study we used low-frequency rTMS to inhibit the cortical activity during memory encoding. The inhibitory effect of low-frequency rTMS is hypothetically attributed to the transsynaptic activation of GABAergic inhibitory interneurons, the recurrent inhibition of the targeted neurons through axonal collaterals (Pascual-Leone *et al.* 1994, 1998), and long-term depression phenomenon (Chen *et al.* 1997) or "disfacilitation" by interference within the rTMS frequency and axonal inputs with specific firing rate (Romero *et al.* 2002). Although the inhibitory mechanism of low-frequency rTMS is not fully elucidated, it produces a temporally distinct decrease of cortical activity useful for evaluating the role of a specific cortical area involved in cognition.

The negative results of low-frequency rTMS on face recognition are in accordance with the neuroimaging studies. It was shown that the fusiform gyrus shows a greater response to faces than to other stimuli (Puce *et al.* 1995, 1996, Kanwisher *et al.* 1996, 1997). Memory encoding of faces activates the left inferior temporal cortex and bilateral mediotemporal cortex and other regions distributed in the left and right dorsolateral as orbitofrontal and premotor cortex (Kelly *et al.* 1996, Haxby *et al.* 1996, 2000ab). In the face learning task, the

sensory information is processed in a series of areas of cortex including the unimodal association visual areas in the inferotemporal cortex specifically concerned with face recognition and is also conveyed to the hippocampus and the remainder of the mediotemporal lobe (Martin *et al.* 1996). Additionally, studies involving cortical lesions support the importance of the temporal and parietal cortex for the memory involved in face matching (Ojemann *et al.* 1992, Sergent *et al.* 1992). The role of prefrontal cortex in face encoding and recognition is less understood and hemisphere lateralization seems to be strongly dependent on the materials being encoded. Encoding of unfamiliar faces produced right-dorsal frontal activation, whereas encoding of words produced left-lateralized homologous activation (Kelley *et al.* 1998). Some studies have found that the encoding of faces also activates left prefrontal cortex (Haxby *et al.* 1996). Our findings support the evidence that (in contrast to word encoding) left DLPFC specialization does not play an essential role in face encoding and recognition and that different brain areas (such as inferotemporal, mediotemporal, parietal or right frontal) are more responsible for this function.

Neuroimaging studies focused on verbal free memory recall tasks have demonstrated that the left dorsolateral frontal cortical areas (area 45, 46 and 9) are involved in the encoding and recall of verbal information, in addition to contributing to speech (Nyberg *et al.* 1996, Kelley *et al.* 1998, Cabeza and Nyberg, 2000, Kim *et al.* 1999, Paulesu *et al.* 1993). Our finding of decreased word encoding with 0.9 Hz rTMS over the left DLPFC are in concordance with these neuroimaging studies and also with the TMS "virtual" lesion trials supporting the role of the left DLPFC in verbal memory function (Ferbert *et al.* 1991, Mull and Seyal 2001, Grafman and Wassermann 1994).

Our study has some methodological limitations. The comparison of recognition of faces with the free-recall task for words in this study cannot be taken as fully equivalent. However the combination of these paradigms is a way to balance the difficulty of both subtests and to keep the same rTMS duration for interference with memory and the same interstimulus interval (4.5 s) for face and word presentation during the encoding. Based on our preliminary experiment the word recognition procedure similar to the face recognition was rejected for its simplicity within the 2-min rTMS paradigm. Nevertheless, due to the control (sham) condition and the within subject design it is possible to compare the influence of rTMS on the memory for faces and words, albeit the word recall was more difficult as indicated by the lower number of correct answers when compared to face recognition.

Some of the inconsistency with previous studies could result from the lack of synchronization of the stimuli and the target objects as was established in the spTMS studies. Our study was based on the rTMS design which, in contrast to the spTMS, creates the spatially demarcated period of decreased cortical activity during task performance. It was presumed that stimulation at regular intervals throughout the presentation of the target stimuli was sufficient to reveal deficits, if indeed the left DLPFC was involved in the processing of either type of the test objects. The synchronization of the TMS pulses and presentation of the target stimuli may contribute to a more reliable effect of TMS on time convey interval and sequence of memory encoding.

Our results support the theories of specialization of the implicated cortical network and the role of left DLPFC in verbal memory encoding but not in face encoding and recognition. As a non-invasive tool, rTMS is useful for cognitive brain mapping and the functional localization of the category specific memory system. These results appear to be of potential value in the future detection of memory deficits associated with the pathology of specific diseases.

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