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Enhancing analogic reasoning with rTMS over the left prefrontal cortex

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CME

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Article abstract—The authors utilized repetitive transcranial magnetic stimulation (rTMS) in 16 normal volunteers to investigate the role of the left dorsolateral prefrontal cortex (PFC) in analogic reasoning. rTMS over the left and right PFC, over the left motor cortex, and sham stimulation over the left PFC were administered during memory and analogic reasoning conditions. rTMS over the left PFC led to a significant reduction in response times only in the analogy condition without affecting accuracy. These results indicate that the left PFC is relevant for analogic reasoning and that rTMS applied to the PFC can speed up solution time.

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Analogic reasoning occurs when a person tries to determine the similarity between different stimuli, scenes, or events. The ability to establish analogies rapidly is biologically important in learning, problem solving, and as a survival tool in adverse environments. To successfully solve a problem by analogy, one has to find specific characteristics of the current problem and construct and match a useful analog to it.[1,2] Recent neuroimaging studies demonstrated the activation of the left dorsolateral prefrontal cortex (PFC) in analogic reasoning processes.[2] It is unknown, however, if this activation reflects a biologically relevant process that contributes to the analogic reasoning task, or if the PFC is incidentally activated by other cortical systems. Here, we used repetitive transcranial magnetic stimulation (rTMS) to address this question. rTMS applied to motor[3] and language cortical regions[4] can facilitate task performance. We demonstrated that rTMS applied to the left PFC accelerated analogic reasoning, indicating the functionally relevant role of this region in this cognitive process.

Methods. Sixteen healthy, right-handed, normal volunteers (five women, mean age ± SE, 37.3 ± 2.0 years) were shown two sets of pictures of colored geometric shapes presented in match-to-sample (literal) and analogy conditions on a computer screen. Analogous trials included pictures that did not share similar geometric shapes but had the same system of abstract visuospatial relations (figure 1). For each condition, four blocks of 16 randomly ordered trials were used. Individual trials consisted of either the sequential or simultaneous presentation of two pictures. The sequential version of the task was used to control for the effect of working memory process. Sequential trials included a source picture (3-s display), a fixation cross (100-ms display), a target picture (3-s display), and another fixation cross (intertrial delay, 1 second). Simultaneous trials contained both a source and a target picture (4-s display), followed by a fixation cross (intertrial delay, 1 second). Subjects judged whether the presented pictures were analogous (analogy condition) or identical (literal condition), and responded by pressing a key on a computer keyboard using the right index and middle fingers. Response times (RT) and error rates were measured.

In separate sessions (with at least 1 day in between), focal rTMS (10% below motor threshold, three trains of 10-s duration and 5-Hz frequency) was performed during the tasks using a Magstim Rapid stimulator (Magstim Company, UK, figure 8–shaped coil with each wing 10 cm in diameter and oriented parallel to midline). To measure the motor threshold, the optimum stimulation point to induce motor-evoked potentials in the contralateral first dorsal interosseous muscle was determined. Subjects were then asked to spread their fingers and the maximum stimulation intensity that did not induce any visible muscle twitch was defined as the motor threshold for the given hemisphere. This was checked at the beginning of each session and the stimulus intensity was adjusted. To comply with the generally accepted safety regulations for rTMS,[5] trains were timed to cover the first, middle, and the last 10 seconds of each block. Magnetic stimuli were applied over the left and right PFC (6 cm anterior and 1cm lateral from the hand area of the motor cortex[6]), and over the left motor cortex (hand area). Additionally, sham stim-

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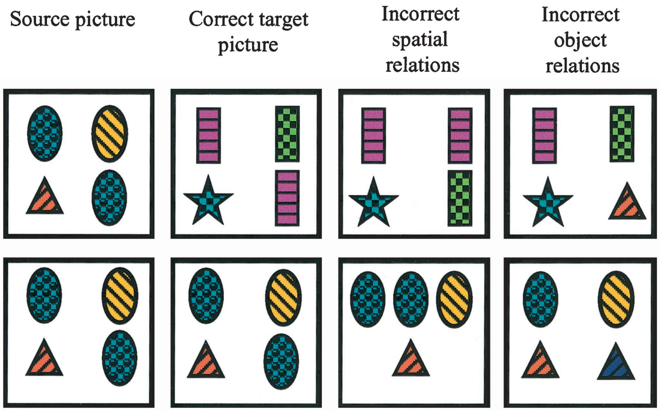

Figure 1. Examples of correct and incorrect trials for the analogy (top row) and the literal condition (bottom row).

ulation that elicited auditory and cutaneous sensations similar to those of brain stimulation was delivered with the coil tilted 45° away from the scalp. Preliminary studies showed a training effect on the subjects' performance. Therefore, only those subjects who had a counterbalanced order of sham and target stimulations (e.g., left PFC-sham and sham-left PFC) were included in the final analysis. This led to different numbers of subjects for different stimulus locations (left PFC versus sham, n = 8; right PFC versus sham, n = 12; left motor cortex versus sham, n = 14). Wilcoxon's signed-rank test was used to compare RT and the rank sum test was used to compare error rates during left and right PFC and motor cortex stimulation with results obtained during sham stimulation. Significance level was set to 0.0025 to account for multiple comparisons.

Results. rTMS over the left PFC led to significantly reduced RT in the analogy condition, compared with sham stimulation for both sequential and simultaneous trials ($p < 0.000001$; figure 2). In the literal condition, rTMS over the left PFC did not affect RT. Stimulation over the right PFC induced no significant changes in RT for either condition. Left motor cortex stimulation, similar to previous studies,[7,8] induced a nonspecific, condition-independent reduction in RT with one exception (the effect did not reach significance for simultaneous trials in the literal condition, $p = 0.003$).

Error rates ranged across all conditions between 8 and 22% and were unaffected by rTMS ($p > 0.3$ for all conditions).

Discussion. Repetitive subthreshold TMS over the left PFC led to a significant reduction in RT during analogic reasoning without affecting the error rates. Theoretically, this enhancement in analogic reasoning can be due to direct facilitation of the stimulated area (left PFC) itself or brain areas synaptically connected to it. The speed-up effect in the analogy condition was present for both simultaneous and sequential analogous picture presentations. Thus, changes in working memory capacity cannot account for the reduction in analogous reasoning RT. Because no RT changes could be detected following right PFC stimulation, a nonspecific facilitation of cognitive processing (e.g., due to intersensory facilitation) is an unlikely explanation for our results. Acceleration of analogic reasoning through a stimulus spread from the stimulation site over the left PFC to the motor cortex cannot explain our results, because in this case one would expect a nonspecific effect for both (analogy and literal) conditions, similar to the results following left motor cortex stimulation.

Although in our control (sham) condition the coil was tilted 45° away from the scalp, it has been shown that the TMS pulse can still affect the cortex.[9] Thus, we cannot rule out changes in prefrontal cortex activity following sham stimulation. However, because effects following stimulation over other cortical areas were measured against sham stimulation, this would not change our results. The mechanisms underlying this facilitation remain unclear at the current time. Changes in synaptic excitability (e.g., post-tetanic facilitation) have been proposed to be responsible for the increase in motor cortex excitability following rTMS at 5 Hz,[10] but direct evidence is still lacking.

This study shows, for the first time, that low-intensity rTMS over the left PFC can facilitate a form of analogic reasoning, implying that the left frontal cortex is functionally relevant for performing this cognitive process. The specific cognitive process affected by rTMS in this study may involve processes required for the selection of candidate source-target arguments leading to a decisive source-target binding. Patients with left PFC brain lesions have deficits in formal reasoning.[1] Although our study involved only normal subjects and not subjects with brain injury, the facilitation of response time in analogic reasoning with rTMS raises a question of a future therapeutic effect of this technique in neurorehabilitation.

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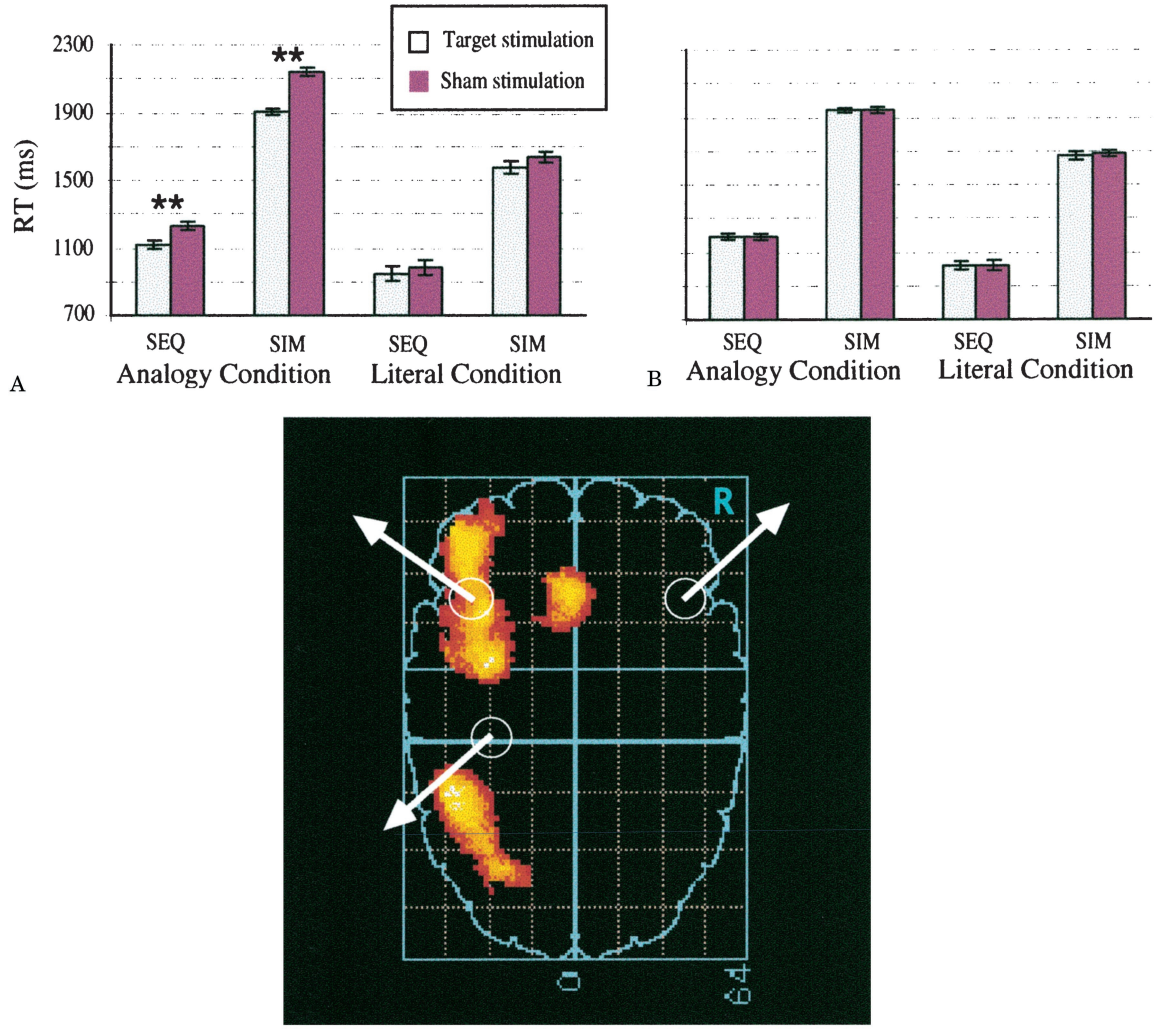

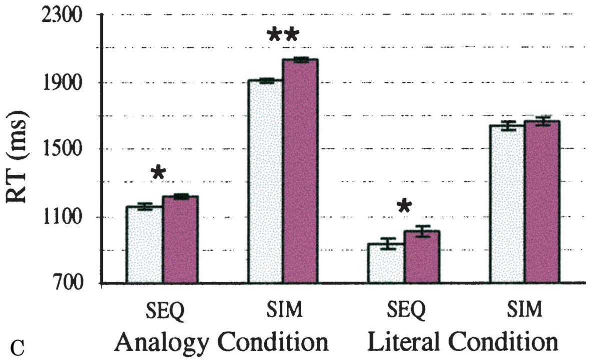

Figure 2. Brain activation in PET and reaction times. PET results published by Wharton et al.[2] *(modified) show brain regions activated in association with analogy–literal comparisons in the left hemisphere (middle frontal gyrus, Brodmann's area [BA] 6, inferior frontal gyrus, BA 10, 44, 45, 46, the superior parietal lobule, BA 7, 40, and the superior occipital region, BA 19). Based on these results, the stimulated regions were chosen for the TMS study (white circles). (A, B, and C) Bar graphs display reaction times (RT; mean ± SE) for different stimulation sites: (A) left prefrontal cortex (PFC); (B) right PFC; (C) left motor cortex compared with sham stimulation under different conditions (analogy and literal conditions with sequential [SEQ] and simultaneous [SIM] picture presentation). Stimulation over the left PFC led to significantly reduced RT in the analogy conditions. Left motor cortex stimulation led to RT reduction in both literal and analogy conditions.* $^{*}p < 0.0025$; $^{**}p < 0.000001$.

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