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Verbal storage in a premotor–parietal network: evidence from fMRI-guided magnetic stimulation

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Abstract

Phonological rehearsal helps to keep selected information consciously in mind for further processing. This part of short-term storage takes place during the delay period of verbal working memory tasks and involves a frontoparietal network as functional magnetic resonance imaging (fMRI) studies have shown. The involved cortical areas can be further investigated by interfering with the local information processing using transcranial magnetic stimulation (TMS). On a single subject level, we identified predominantly left-sided premotor, prefrontal, and parietal areas active during the delay period of a verbal working memory task using event-related fMRI. In a pilot approach, TMS was neuronavigated to the individually active areas by using a stereotaxic device. Then, TMS was applied during the delay period of similar tasks as in fMRI. Error rates increased significantly upon stimulating left premotor cortex, but not upon parietal or prefrontal stimulation. The contribution of the premotor cortex to storage and rehearsal is discussed as an active top-down storage process within the frontoparietal network.

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Introduction

Short-term maintenance of recently acquired information is essential for relating this information to internal goals and to upcoming events for decision making and acting. This working memory process is necessary for higher cognitive functions, ranging from maintaining the beginning of sentences while reading or listening, to integrating complex multimodal information for planning and problem solving (Cohen et al., 1997). One strategy for performing verbal short-term maintenance is phonological rehearsal by using inner speech as a conscious and attention demanding process. Rehearsal and storage, as well as executive control, encoding, and retrieval (Baddeley, 1992, 2000; Smith and Jonides, 1997), are subroutines of verbal working memory.

The central nervous processing of these functions can be attributed to a frontoparietal network. Higher level executive control has been ascribed to prefrontal areas like the dorsolateral prefrontal cortex (DLPFC; Brodman areas [BA] 9, 46; Smith and Jonides, 1999; Fletcher and Henson, 2001). Rehearsal has been associated with premotor cortex (PMC; BA 6) and Broca's area (BA 44; Awh et al., 1996; Smith and Jonides, 1999; Fiez et al., 1996; Henson et al., 2000). Phonological storage has been found to involve parietal areas (Paulesu et al., 1993; Awh et al., 1996; Jonides et al., 1998). Verbal items are supposed to be processed predominantly left-sided, and visuospatial material predominantly right-sided (Smith and Jonides, 1999; Walter et al., 2003; Zurowski et al., 2002).

Transcranial magnetic stimulation (TMS) can be used to investigate cognitive functions and to prove hypotheses gained from fMRI findings (Walsh and Cowey, 2000). TMS applied over a cortical area has the property of interfering noninvasively with the local information processing by inducing neuronal depolarization. Stimulation can be applied

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during a certain task period in order to investigate the chronological involvement of the stimulated area. Previous studies have investigated DLPFC, but not PMC involvement in working memory using TMS (e.g., Grafman et al., 1994; Mottaghy et al., 2000; Mull and Seyal, 2001).

We studied cortical areas involved in the rehearsal process within a delayed match-to-sample verbal working memory task using fMRI and TMS. Using a neuronavigational device, the magnetic coil was guided individually to prefrontal, premotor, and parietal areas as identified on a single subject basis in prior fMRI. TMS was applied in the second half of the 6-s delay period of the task, assuming to mainly influence rehearsal. We hypothesized that TMS would interfere with the local information processing and disturb memory task performance.

Methods

Subjects

Nine healthy subjects took part in the study and gave written informed consent. The study was approved by the local ethics committee. Subjects were right-handed and did not have a history of neuropsychiatric disorder, epilepsy, brain injury or brain operations, or a cardiac pacemaker.

Sternberg item recognition task

The experimental trial for the fMRI scans consisted of presentation, delay, and retrieval periods in two different memory load conditions (one letter = L1, six letters = L6). Subjects were presented a 2×3 array of six letters. Only consonants were used to make formation of syllables unlikely. The subjects were instructed to remember the yellow letters, which were either one (L1) or all six (L6) of the set. The duration of the presentation of L1 and L6 was adjusted to the number of items. Given a baseline of 500 ms plus 500 ms for each letter, presentation resulted in 1000 ms for L1 and 3500 ms for L6. The presentation was followed by a blank screen with a fixation cross lasting 6000 ms (“delay”). In the following retrieval period of 1500 ms, subjects again saw a 2×3 array as a probe, consisting of red “#” signs and one yellow target letter. Subjects had to decide by pressing “yes” or “no” buttons whether this letter had been among the letters to be memorized. Twenty-one trials each of the L1 and the L6 condition were in one block, presented in random order. In the fMRI scanner, each subject performed two blocks resulting in a total of 84 trials. For TMS, the L6 condition was presented in a first approach; additionally we used a similar paradigm with seven instead of six letters to remember (Fig. 1) as outlined in the TMS methods section. The program for presentation was generated with ERTS (Experimental Run Time System; Beringer Software, Germany).

fMRI protocol

A 1,5 Tesla Magnetom VISION MRI scanner (Siemens, Erlangen, Germany) was used to acquire T1 structural images (MPRAGE, $1 \times 1 \times 1$ mm isotropic voxels) and T2-weighted echoplanar imaging in axial orientation (matrix: 64×64 , 3.6 by 3.6 mm pixels, TE = 50 ms, TR = 2011 ms, 21 slices per volume covering the whole cortex, slice thickness 3 mm, distance factor 0.8, two sessions with 312 volume images each). The scanner was synchronized with the presentation of the trials. The onset of the trials was jittered in time with intertrial intervals between 1100 and 3550 ms. Within the scanner, stimuli were presented by means of LCD video goggles (Resonance Technologies, California).

Data were analyzed using the BrainVoyager Software (BrainInnovation, The Netherlands). Preprocessing consisted of a slice scan time correction, coregistration of the functional images with the corresponding individual structural T1 volume, motion correction applying the least square method, and high-pass filtering of the time series across each session with a cutoff for frequency components below three cycles within the time series. No smoothing was administered for individual analyses of single subject data. Voxel-wise analysis was performed using a general linear model for autocorrelated observations. BOLD signal changes were analyzed event-related for the delay period of the task by testing with covariates that modeled the expected BOLD signal response in the event of an increase in neural activity. Individual and group analyses were performed. To assess delay period related activity we determined a contrast of the delay covariates of the L6 and the L1 condition, L1 serving as control.

Selection of sites for magnetic stimulation

Based on the single subject analyses we determined activation sites for stimulation in each subject. In single subjects analysis, voxels of which effects survived P values of $P < 0.05$ in an F test were accepted when found in clusters of at least 50 voxels (Table 1). In the case of higher significant activities, the region for stimulation was selected according to more conservative analysis adjusting the threshold up to $P < 0.0001$ (Table 1). Within an activated voxel cluster, the coordinate of the maximally activated voxel was identified, referring to the Talairach system after morphing the brain into Talairach space. The anatomical locations of the activities were verified according to the Talairach atlas (Talairach and Tournoux, 1988). For the first TMS sessions using the L6 task, we selected the stimulation sites according to individually highest significance levels within frontal or parietal cortex, resulting, for instance, in inferior parietal and temporoparietal stimulation sites within the group of parietal stimulations. For the additional L7 task, we focused the selection of the stimulation sites for better comparison purposes onto the individual activations

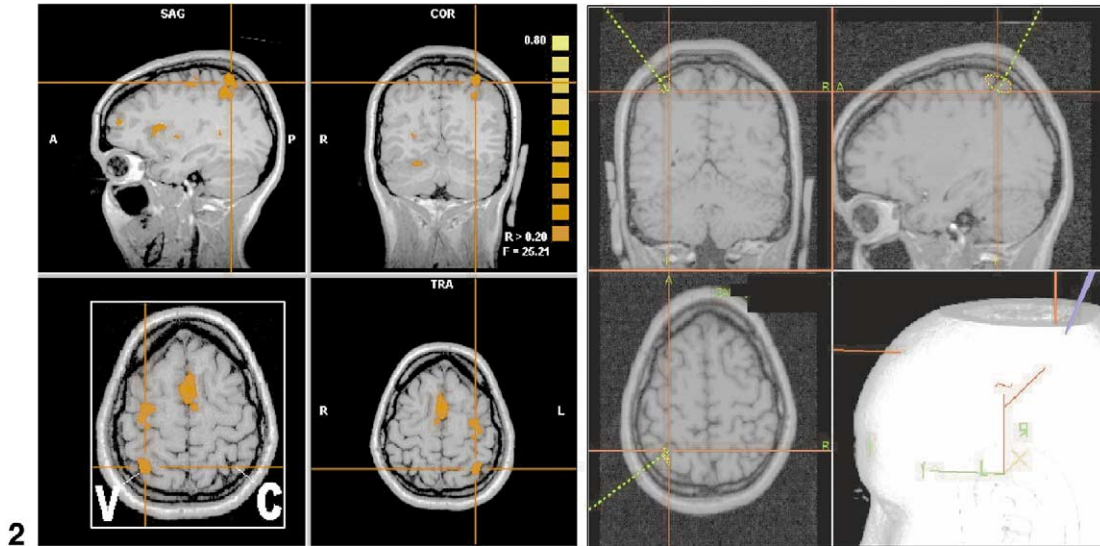
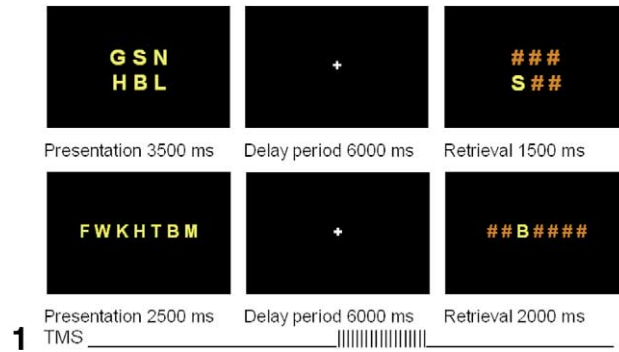


Fig. 1. Modified Sternberg verbal working memory task: Upper row display of the six letter load condition (L6), lower row load 7 condition (L7), with the different periods following each other and their duration in milliseconds. TMS was applied during the second half of the delay period for 3000 ms (vertical signs).
 Fig. 2. Neuronavigation according to fMRI data. Left: Presentation of the analysis in BrainVoyager in the different axes according to which the decisions about the stimulation sites were made. The framed image in the lower left edge is the same as the lower right image but mirrored to neurological convention in order to resemble the screen presentation of the navigational device. The “V” indicates the site of verum stimulation above the active area, and “C” indicates the mirrored control stimulation. Right: Surgical Tool Navigator (STN) screen of the same subject while stimulating above the yellow marking according to the individual fMRI result in the parietal cortex corresponding to “V”. The dotted green line runs perpendicular through the midpoint of the coil and therefore represents the coils’ peak magnetic field.

within distinct anatomical areas like the region of the intraparietal sulcus or the premotor cortex (Fig. 3). Sites were chosen for stimulation only if the activation was not bilaterally symmetrical. Relevant contralateral activity was ex-

cluded by decreasing the significance threshold to $P = 0.05$. In the rare case of contralateral activity, the significance level should differ by a factor of 100, and the stimulated activity should have a multiple of voxels. The stimulation

Table 1
 Individual fMRI data of the regions selected for L7 stimulation

Subject #	1	2	3	4	5	6
Tal. coord. PMC	-47/0/25	-55/-9/25	-42/10/41	-55/9/28	-57/-2/24	-47/-1/40
Brodman areas	BA 6/44	BA 6/4	BA 6/9	BA 6/44	BA 6	BA 6/8/9
Sign. level $P <$	0.0005	0.0001	0.05	0.0001	0.0001	0.0001
Parietal	-30/-53/58	-50/-48/46	-55/-49/32	-48/-31/53	-35/-55/43	-30/-54/54
	BA 7	BA 7	BA 40	BA 40	BA 7	BA 7
	0.0001	0.005	0.05	0.001	0.0001	0.0001

Note. Individual fMRI results selected as sites for the premotor and parietal stimulation during the seven letter task (L7) in the six subjects: Talairach coordinates (x, y, z) of the maximally activated voxel, Brodman areas (BA) covered by the corresponding cluster, and significance levels (P values) in fMRI activity according to which stimulation sites were selected.

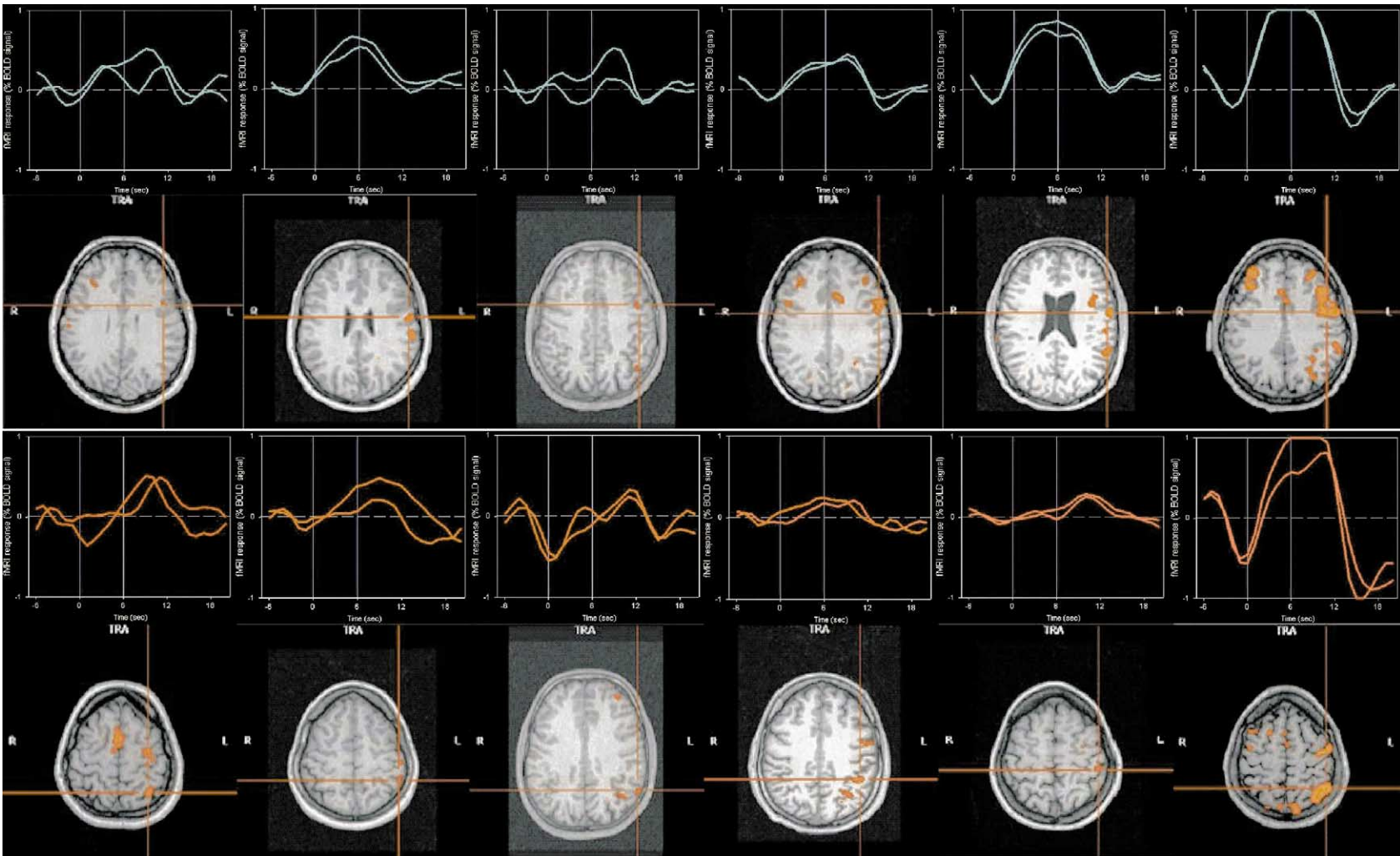


Fig. 3. Individual fMRI results selected as stimulation sites: Premotor and parietal stimulation sites during the L7 task of the six individual subjects (from right to left) as mentioned in Table 1. In the upper row, the time courses (in seconds, x axis) of the fMRI BOLD signal change of the activity (in percent, y axis) in the premotor areas selected for stimulation are presented. The time between 0 and 6 seconds on the y axes represent the delay period. The two curves reflect the signal change in the two fMRI trial blocks of the premotor activity. In the second row, the plots with the premotor activity in the transversal axis are shown ($F = 25$), with the stimulated region indicated by the cross hair. In the third and fourth row, the plots of the parietal activity in the six subjects stimulated in the L7 tasks are shown.

sites had to be accessible to TMS, meaning that the cortex was within the range of the magnetic field without causing unbearable discomfort.

Neuronavigation

A neuronavigational system (Surgical Tool Navigator, Zeiss Oberkochen) was adapted to navigate the coil to the individually determined cortical regions. Based on optically tracked frameless stereotaxy, head fixation was avoided. The method is described in detail in Herwig et al. (2001, 2002). In brief, the system enables monitoring of the position of the coil in real time on a computer screen in relation to the brain which is visualized as structural T1 MRI (voxel $1 \times 1 \times 1$ mm).

The transformation of the fMRI results onto the structural MRI for neuronavigation was performed by marking the anatomical region of the fMRI cluster (Fig. 2a) within the structural MRI (Fig. 2b) using the markaton tool of the navigational software (STP4, Zeiss-Leibinger, Germany). The coil, displayed on the screen by a dotted green line running perpendicular through its midpoint, was then guided to the center of the marking visible on the screen, so that the cortical area active in fMRI was within the magnetic field during TMS (Herwig et al., 2002).

Magnetic stimulation

Subjects were seated in a comfortable chair. Magnetic stimulation was applied with a MagPro Stimulator (Dantec/Medtronic) using a figure-8-coil (MC-B70). Motor threshold (MT) was determined as lowest stimulation intensity for evoking at least three MEPs in six stimulations of at least 50 μ V recorded by a surface EMG (Keypoint Portable, Medtronic) from the relaxed right M. abductor pollicis brevis (Rossini et al., 1994). Stimulation parameters were 110% of individual MT, one train with 15 Hz for 3 s (45 stimuli). The intertrain interval was >15 s considering safety criteria (Wassermann, 1998). Before beginning the task, subjects received a test stimulation to get familiar with stimulation conditions and side effects. The coil was stereotactically guided to the cortical areas individually identified in prior fMRI and held tangentially to the skull with the handle pointing in an anterior–caudal direction whereby the LEDs on the coil were best detectable by the navigators cameras. Stimulation was applied in the second half of the 6 s delay period, triggered by the ERTS program, because stimulation of the whole delay period would have been outside the safety criteria, and because a major effect of interference with pure rehearsal (assuming a finished encoding) was expected for the period directly prior to recall when ultrashort term sensory memory was assumed mostly to be faded (Gazzaniga et al., 1998).

We applied “verum” stimulations above the areas active in fMRI, and “control” stimulations above the mirrored

locations (same coordinates in y , z axes, x reversed) on the other hemisphere (Fig. 2a). Additionally, in some subjects, one block of sham stimulation was performed with the coil held in midline 5 cm above the vertex, without touching the skull. Sham stimulations were for technical reasons not complete in the L7 task and not considered for the analysis.

Initially, for the TMS trials, the same L6 paradigm as in the MRI session was used. The L1 condition had served as control in fMRI and was therefore not performed with TMS. L6 above prefrontal and parietal cortex did not produce sufficient errors (false answers given within the retrieval period) in order to reveal a possible interference of TMS. Hence, a follow-up TMS trial was generated consisting of seven letters (L7). They were presented for 2500 ms and arranged in line to rule out grouping effects, in order to render the task more difficult (Fig. 1 lower-row). The retrieval period was extended to 2000 ms, because it was found that 1500 ms resulted in invalid trials due to delayed responses. All other conditions remained the same in both L6 and L7 TMS task, included using the prior fMRI results for navigation, assuming that principally the same cortical regions were involved (Braver et al., 1997). In our first L6 TMS trials, stimulation of DLPFC activities had turned out to be uncomfortable, leading to possibly painful sensations, to twitching of the eyes and trembling of the lower jaws in most of the subjects. We considered this discomfort to be a potential source of biasing results. Therefore we ceased DLPFC stimulation with the L7 task. The parietal cortex and the prominent and regular premotor cortical activity sites in six subjects had been selected for the L7 task. The selected areas were investigated with two blocks (42 single runs) in the L6 condition and with one block (21 runs) in the L7 condition. The sequence of the stimulation locations (right and left parietal, right and left frontal, sham) was pseudorandomized in order to rule out effects of learning/fatiguing or habituation.

Statistical analysis

Reaction times and error rates of each single run were recorded with ERTS. Wrong answers given within the required time were counted as errors. Forty-two single runs for L6 and 21 runs for L7 were analyzed for each stimulation location. In order to test an effect of stimulation on task performance, a repeated measures multivariate analysis of variance (MANOVA) was applied, considering error rate and reaction time as dependent variables, and stimulation condition (verum and control) and stimulated region (frontal, parietal) as categorical factors (using Statistica 5.5, Statsoft, Tulsa, OK, USA). When a dependence of the variables to stimulation condition was detected, further analysis was performed with Students’ paired t test, one-tailed according to the hypothesis.

Results and discussion

fMRI results and selection of stimulation sites

The fMRI data of eight of the nine subjects (age 23–33, mean 26; four females) were included (artifacts in one subject). The rate of errors in the scanner during the L6 task was 3.2%. The mean reaction time of correct answers was 907 ms (± 156 ms). fMRI data were analyzed event-related for the delay period on a single subject basis. Prominent activities were detected in prefrontal, premotor, and parietal regions, some bilaterally but predominantly left-sided (Table 1 and Fig. 3). Activities accessible to TMS in one subject were bilaterally symmetrical, and therefore the subject had to be excluded from TMS.

The subjects showed activity in anterior and/or dorsolateral prefrontal regions which covered overall Brodmann areas (BA) 8, 9, 10, 44, 45, and 46. We found activity in the region of the inferior parietal sulcus and/or the inferior parietal lobe (BA 7/40), and temporoparietally. All subjects had activity in the premotor cortex (PMC; BA 6), partly combined with adjacent Broca's area (BA 44) activity. The activated areas were left lateralized in all but one subject.

For L6 stimulation, the DLPFC (BA 9) in five subjects (four left and one right sided) and the border to BA 6 in one subject were chosen, as well as the most prominent activations in the inferior parietal areas of four subjects and temporoparietally in two subjects. One subject refused L6 stimulation. In the subsequent L7 task, the activity present in the left PMC of six subjects was targeted (Fig. 3, first two rows), and in the same six subjects the inferior parietal activity (one of the eight subjects refused, one had symmetrical activation) (Fig. 3, lower rows).

In the individual analysis, further activity was found in the anterior cingulate, in supplementary motor regions, in the primary motor cortex, in the temporosupramarginal region, and in occipital cortex. These activities were not considered for stimulation, and hence are not reported in detail here.

The group analysis, which was not used for the selection of the stimulation sites, showed most prominent activity in BA 6 covering the premotor cortex on the anterior edge of lateral precentral gyrus (Fig. 4 and Table 2).

The fMRI results demonstrate the involvement of a predominantly left lateralized prefrontal–premotor–parietal network in rehearsal of verbal working memory. It is in accordance to previous reports of working memory areas identified by neuroimaging (Jonides et al., 1998; Postle et al., 1999; Smith and Jonides, 1999; Henson et al., 2000).

Although fMRI data were gained using the L6 task, it is in our view justifiable to use these results for targeting TMS in the L7 task, because the fMRI analysis was designed to reveal pure rehearsal activity in the delay period. This activity is expected to be mainly similar for six or seven letters concerning the involved areas (Braver et al., 1997).

Behavioral data during TMS

In six subjects, the left-sided regions active in the single subjects' fMRI in premotor and parietal cortex were stimulated using the L7 task. This resulted for both areas in higher error rates (PMC 14.3%, parietal 14.3%) as compared to stimulation of the mirrored control site (PMC 9.5%, parietal 9.5%). This difference was significant for stimulation of the PMC (Students' *t* test, one-tailed $P = 0.02$, Fig. 5), not for parietal stimulation ($P = 0.14$). The reaction times did not differ comparing verum (PMC mean 815 ± 103 ms, parietal 835 ± 119 ms) and control (PMC 824 ± 126 ms, parietal 828 ± 104 ms).

The prefrontal and parietal stimulation using the L6 task did not show differences in error rates and reaction times comparing verum and control. Subjective discomfort of premotor "verum" and "control" stimulation was comparable, so that the difference in error rates can hardly be attributed to side effects. Serious side effects were not observed.

Notably, the applied TMS protocol did not lead to different task performance comparing verum and control when stimulating prefrontal areas using the L6 task, and parietal areas in both tasks. We selected relatively high stimulation parameters concerning the combination of intensity, frequency, and train duration, while even lower parameters have been suitable to interfere with working memory processes (Grafman et al., 1994; Mottaghy et al., 2000; Mull and Seyal, 2001; Oliveri et al., 2001; Kessels et al., 2000; Rossi et al., 2001). The use of neuronavigation enabled the spatially precise stimulation of the individually preselected DLPFC and parietal areas. Thus, an explanation for the lack of interference may be a nonessential involvement of these areas in the rehearsal period when applying the L6 task.

Premotor cortex

In fMRI, the most consistently and intensely activated region was the left PMC. Higher error rates upon premotor TMS in the second half of the task's delay period support the hypothesis of an involvement of the left premotor cortex in rehearsal. Considering the small number of subjects, the data are in line with fMRI studies showing premotor and Broca's areas to host the process of verbal rehearsal (Henson et al., 2000). Rehearsal involves inner speech which engages mainly Broca's area (McGuire et al., 1996; Fiez et al., 1996; Shergill et al., 2001) and which has been related to conscious thinking processes (Tulving, 1987; Siegrist, 1995). Rehearsal within the memory process can be regarded in the frame of a premotor–parietal interaction. PMC (and Broca's area) may project an inner speech based representation of the remembered items in a continuous top-down process to parietal areas. Thereby, parietal activity, corresponding to the activity induced by prior perception of the items to memorize, may be held online in order to bias later recognition of the probe. This processing may occur

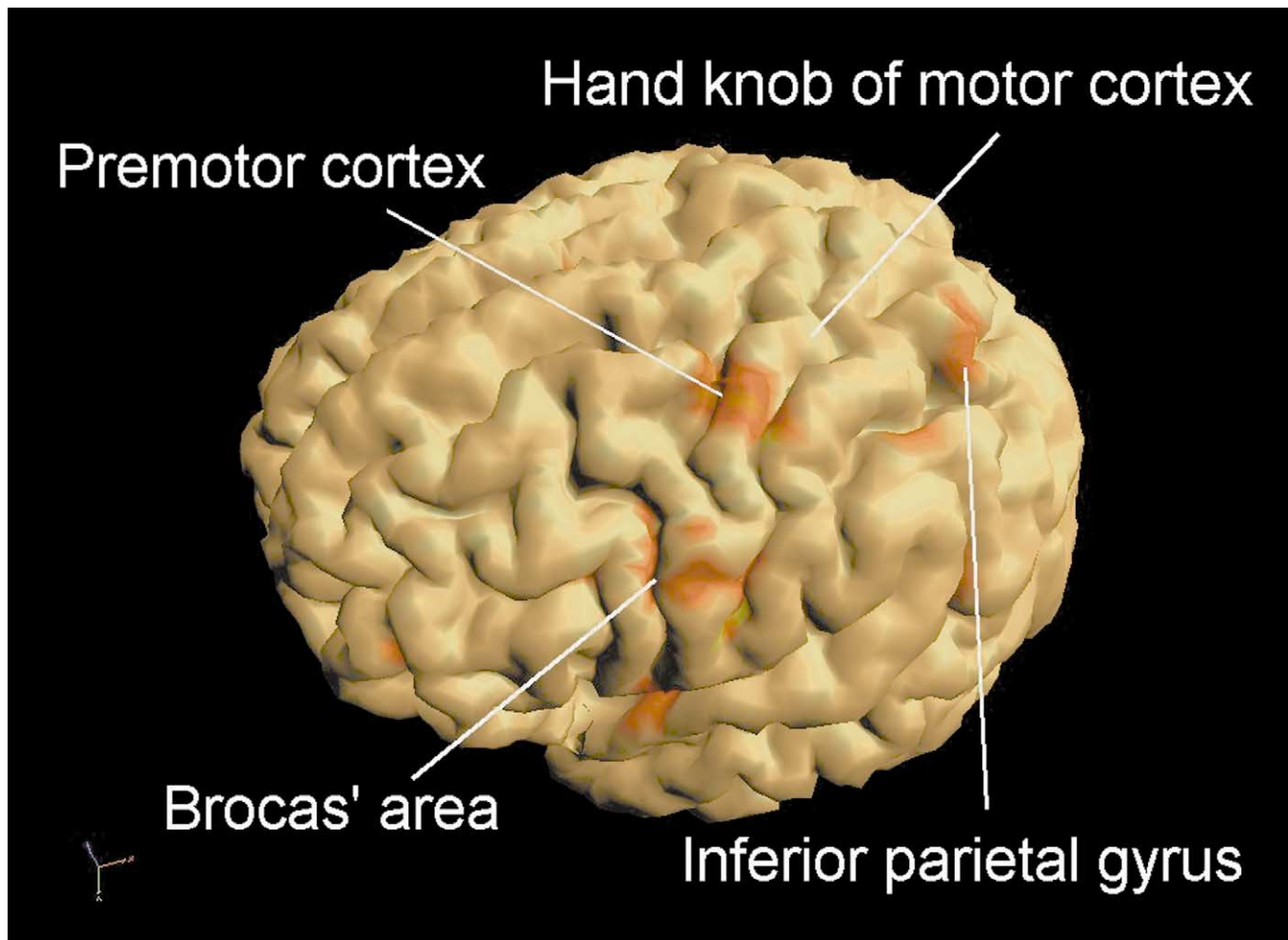


Fig. 4. Surface-rendered and Talairach-size-morphed individual brain with indicated regions of BOLD activity in the group analysis during the delay period of the working memory task ($n = 6$, $P < 0.0001$; see Table 2; contrast: L6 vs L1).

together with a bottom-up information flow during encoding and retrieval, unless on the executive level a decision about matching is made and action is initiated. Disturbing the rehearsal process by premotor stimulation may lead to loss of this top-down information, resulting in a higher error rate. An additional influence of the premotor targeted stimulation on the adjacent Broca's cortex cannot be totally excluded.

One interpretation of the observed premotor disturbance might be a disturbed preparation for the upcoming response movement. Yet, this would not explain a parametric load dependency of premotor and Broca's area activity (Cohen et al., 1997; Braver et al., 1997). This interpretation is further ruled out by our fMRI findings contrasting high load and one letter load condition, both requiring motor preparation.

Parietal cortex

According to the working memory model of Baddeley (1992), a subvocal rehearsal process refreshes the phonological buffer for short-term maintenance of phonological

information. The buffer for phonological storage has been ascribed to posterior and inferior parietal areas (Jonides et al., 1998). Parietal activity has further been attributed to the recognition subtask within working memory (Becker et al., 1999). The combination of rehearsal and recognition involves a frontoparietal interaction including also PMC (Jonides et al., 1998; Chein and Fiez, 2001). We may argue that phonological storage or buffering in parietal areas means top-down activation of internal representations of the perceived and encoded items, in order to selectively attend and recognize the anticipated target items by decoding visual input. Hence, the term storage may be misleading, because the memorized items are not stored like books on a shelf, but their experience-shaped neural network representation for perception is biased for recognition. It seems to be efficient to use existing internal representations for working memory, indicated, for instance, by better memory performance of familiar material.

The lacking TMS effect may be explained by the continuous top-down update, providing the information in parietal areas in the moment of required recognition. This may

Table 2
fMRI data of the group analysis

Cortex area	Hemisphere	Tal. coord.	No. of voxels
MFG, BA 9/10	Left	−36/44/18	1674
MFG, BA 9/46	Left	−41/20/31	1175
MFG, BA 9/46	Right	34/38/35	517
IFG/Ins., BA 45	Right	32/16/11	1789
PMC, BA 6/44	Left	−46/2/29	6465
PMC, BA 6/4	Left	−35/−8/57	2815
GC/SMA, BA 32/6	Bilat.	1/10/48	3015
GPO, BA 39/40	Left	−51/−10/24	1016
STG, BA 22	Left	−52/−44/18	1827
I/MTG, BA 37	Left	−42/−51/−2	4259
IPS, 7/40	Left	−37/−54/56	1471
IPS, 7/40	Left	−28/−55/35	602
IPS, 7/40	Left	−48/−38/48	90

Note. Activated regions in the group analysis during the delay period of the working memory task ($P < 0.0001$, contrast: load with six letters vs load with one letter). The coordinates of the strongest activated voxel within an area are given, as well as the Brodman areas (BA) covered by the whole extension of the activities. MFG, middle frontal gyrus; IFG/Ins., inferior frontal gyrus/insula; PMC, premotor cortex; GC/SMA, gyrus cinguli/supplementary motor area; GPO, parietooccipital area; STG, superior temporal gyrus; I/MTG, inferior/middle temporal gyrus; IPS, area around intraparietal sulcus.

compensate the parietal TMS during the delay period, which cannot “delete” a store that is continuously filled again. However, a technical reason for nondisturbance may be due to the fact that in some cases, activation was found not to be at the cortical surface but deeper in brain such as in the inferior parietal sulcus (Fig. 3). These activities may not have been accessible by the electromagnetic field because of its limited range.

Prefrontal cortex

While prefrontal areas were active in fMRI during our task, DLPFC stimulation did not disturb L6 task performance comparing verum and control. Prefrontal areas like DLPFC and ventrolateral PFC, interacting with distinct sub-functions on the executive level, may control and initiate the general process of working memory performance and hold the nonmaterial specific context and the rules to be considered online (Wagner et al., 2001; Fletcher and Henson, 2001; Newman et al., 2002). The DLPFC is more strongly activated in dual tasks (D’Esposito et al., 1995; Koechlin et al., 1999), when interfering tasks like “n”-back working memory paradigms are performed (Braver et al., 1997), or when distracting stimuli are to be managed (Sakai et al., 2002). The DLPFC may be less essentially involved in simple maintenance, but more in encoding and retrieval (Rypma and D’Esposito, 1999; D’Esposito et al., 1999b), and when manipulation of the items is required (D’Esposito et al., 1999a). However, an increasing DLPFC activity has been reported with increasingly longer maintenance periods (Barch et al., 1997). The prefrontal areas thus may not

represent the storage level of specific items to be memorized but may initiate and monitor the task by “delegating” former performance to next levels like the PMC. Hence, because no task interferences or conflicts had to be managed in our task, a low prefrontal involvement may account for the missing effect of DLPFC stimulation at the L6 level. There may also be well-functioning compensatory mechanisms of these regions by, for instance, recruiting the other hemisphere (Newman et al., 2002).

TMS in working memory studies

In contrast to our data, effects on task performance, particularly by DLPFC stimulation, have been reported by other authors using TMS to study verbal working memory. Encoding was reported to be disturbed by stimulating with 20 Hz for 500 ms beginning 250 ms after word presentation above left temporal cortex and left and right DLPFC (Grafman et al., 1994). Suprathreshold single pulse TMS during the encoding within a 3-back working memory task 400 ms after each letter presentation lead to an impairment of performance after left, not after right DLPFC stimulation (Mull and Seyal, 2001).

Repetitive TMS was applied with 4 Hz at 110% motor threshold continuously during a 2-back working memory task (Mottaghy et al., 2000). A higher error rate was observed when stimulating above right and above left DLPFC compared to stimulating above the vertex, or performing the task without stimulation. A delayed response task demonstrated an increased error rate when stimulating repetitively above left and right DLPFC during the delay period compared to a stimulation above motor cortex or without stimulation (Pascual-Leone and Hallett, 1994). However, both latter tasks did not consider possible influence of side effects of the much more uncomfortable DLPFC stimulation compared to their sham conditions. Our control condition

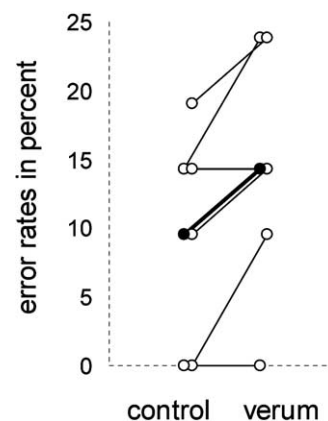


Fig. 5. Error rates during premotor stimulation: Individual error rates of the six different subjects (open dots) and the according mean (filled dots). “Verum” corresponds to the stimulation above left premotor cortex. “Control” means mirrored stimulation (inverse of x coordinate, same y , and z coordinate) above the right PMC.

involved a mirrored stimulation of the nonactive hemisphere in order to balance the influence of side effects, which are of considerable magnitude (Abler et al., in preparation). The n-back studies (Mottaghy et al., 2000; Mull and Seyal, 2001) showing interference effects when stimulating above the DLPFC, differ from our study, as n-back designs involve manipulation that recruits the DLPFC (D'Esposito et al., 1999a) and not solely maintenance as in our task. This may account for the different findings.

Conclusion

Our data add to the evidence for an interactive role of prefrontal, premotor, and parietal areas in rehearsal and storage during verbal working memory. Prefrontal areas such as the DLPFC may be involved on a general executive level and in encoding the task relevant material. The PMC appears to be centrally involved by providing phonological information to parietal areas. The concept of phonological storage can be viewed as a premotor mediated top-down activation of the internal representation of the memorized items in parietal areas for later recognition.

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