FUNCTIONAL MR IMAGING OF THE PREFRONTAL CORTEX: SPECIFIC ACTIVATION IN A WORKING MEMORY TASK

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Functional magnetic resonance imaging was used to identify cortical regions activated by a working memory task involving letter detection. Twenty four normal subjects were scanned with a conventional 1.5-T magnet while performing one of two tasks: In the activation task, subjects responded by pressing a button whenever any presented letter was the same as the second last in the sequence. In the control condition, subjects had to respond to a single predefined letter without memory update requirements. The activation task and the control condition were identical with regard to perceptual input and motor output. They were different only regarding the task demand. Movement artifacts were minimized in a two way strategy and eight subjects were excluded from further analysis. Functional MR data from the remaining 16 subjects were analyzed on the basis of anatomical regions-of-interest which were manually defined in each subject. The engagement of working memory produced significant activation in the dorsolateral prefrontal cortex (Brodman’s areas 9, 10, 46, and 47) in both hemispheres. Results demonstrate the applicability of the paradigm within a clinical MRI setup and corroborate previous findings of non-lateralized dorsolateral prefrontal activation during continuous context updating and active maintenance. © 1997 Elsevier Science Inc.

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INTRODUCTION

Working memory is the cognitive function of continuously updating and actively maintaining information "on-line" for the guidance of ensuing behavior.1,2 A well known example from everyday life is to look up a phone number and to keep it in mind until the number is dialed. Working memory is not restricted to the short term storage of numbers or words, but refers to the cross-temporal integration and manipulation of various kinds of information relevant to immediate action.3 Characteristic features of working memory are limited duration (seconds) and capacity (a few items). It is therefore often compared with a scratchpad or with the random access memory (RAM) of a computer. Working memory is crucial for a wide range of cognitive tasks including comprehension, learning, and reasoning. Just & Carpenter,4 for example, demonstrated the key role of working memory in sentence comprehension.

Electrophysiological studies in animals demonstrated that neuron populations in the prefrontal cortex play a crucial role in working memory.5,6,7 In a spatial working memory task, primates had to maintain the location of a briefly presented visual stimulus for several seconds before looking to the eccentric target (delayed response). In the prefrontal cortex, neurons were identified that showed elevated activity exclusively in the period between target offset and response. Moreover, elevated activity predicted correct responses of the animals, whereas the animal failed to reach the target when the neuron did not maintain its activation during the delay period.5

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Selective cooling of the dorsolateral prefrontal cortex in primates reversibly disabled working memory function regardless of the modality of the task. Whereas this finding is indicative of a supramodal organization of the frontal cortex,1,2 a dissociation between pattern-activated and spatial location-activated frontal neurons has been demonstrated.9

Several positron emission tomography (PET) studies in normal subjects addressed the localization of working memory.10,11 They confirmed the predicted localization in the prefrontal dorsolateral cortex, regardless of task modality. In addition to the classical spatial delayed response paradigm, other forms of working memory tasks were investigated. Smith et al.12 suggested a task-dependent lateralization in activation of the prefrontal cortex in that spatial working memory activates right prefrontal areas whereas object recognition activates left parts.

The technique of functional magnetic resonance imaging (fMRI) has recently been applied in activation studies addressing working memory. McCarthy et al.13 demonstrated bilateral prefrontal activation in a classical spatial working memory paradigm. With a simple letter paradigm, Cohen et al.14 found a bilateral activation pattern in an fMRI study. These data were confirmed by another study.15

Working memory tasks that reliably activate frontal cortical areas may have clinical applications in the evaluation of patients with frontal cortical deficits. In addition to neurological cases, frontal dysfunction has been implicated in psychiatric disorders such as schizophrenia16 and depression.17,18 Accordingly, working memory impairments were found in schizophrenic patients.19,20

The present study was designed with clinical applicability in mind and therefore had to meet several systematic and methodological requirements. First, the working memory paradigm developed by Gevins et al.21 and adapted to functional imaging by Cohen et al.14 was implemented within a conventional clinical MRI setup. The paradigm is simple and clearly interpretable, and it allows for the adjustment of difficulty (see below). Secondly, the headcoil used in most clinical setups should provide the RF field homogeneity needed to detect any lateralized activation. Thirdly, a motion correction algorithm was implemented and applied. And finally, quantitative analysis was based upon anatomically defined regions across subjects.

MATERIALS AND METHODS

General Setup

Presentation of visual stimuli as well as response measurements were controlled by a microcomputer (Apple Macintosh LC II, Apple Computer GmbH, München, Germany) placed outside the scanning room. A video-projector (Sharp Vision XG 3800E, Sharp, Japan) projected the stimuli into the scanning room onto a translucent screen. A mirror was connected to the headcoil of the scanner and allowed subjects to view the stimuli from within the scanner, obtaining a visual field of approximately 24° in the horizontal and 12° in the vertical direction. Stimuli were set up vertically and horizontally flipped to compensate for back-projection and mirror effects. Subjects responded to the stimuli by pressing a button on a little box placed comfortably under the right index finger. As demonstrated in a previous study,22 an ordinary unprotected wire connecting the button box with the computer did not cause any detectable error signal in MRI. The subjects’ responses were stored online by the microcomputer and were monitored by the experimentators in order to control the general performance of the subjects.

Subjects

Twenty four healthy subjects (12 male, 12 female, average age 28.1 ± 3.5 years) were recruited from the Heidelberg area. They had no history of neurological or psychiatric disorder and gave informed consent to participation in the MR study prior to the investigation, after the aims of the study and the experimental procedures had been fully explained to them. The Edinburgh Inventory23 was applied to score the handedness. Immediately before starting the experiment, the subjects were informed about the timing of the scanning procedures and task sequence (see below). They were trained by running at least one block of each experimental condition.

Experimental Design

The stimuli consisted of all consonants of the alphabet, excluding Q (because of its similarity to O) as well as X, Y, and Z (because of their rare frequency in the German language). Vowels were excluded because they are generally more present in the German language, resulting in a psychometric imbalance. Characters were displayed in 24 point Geneva font.

An experimental block consisted of a sequence of 121 consonants. Each letter was presented for 0.5 s on the translucent screen followed by a black screen for 2.5 s, resulting in a new stimulus letter every 3 s. Occurrence of the different consonants was balanced. Subjects had to scan the sequences and to react by pressing the button only under a definite condition (go-no-go paradigm). Two different instructions were given (Fig. 1). In the control condition (C), subjects had only to detect one definite consonant (the letter “S”), occurring 17 times per block. This condition does not require memory updating during task performance. In the activation task (A), subjects had to analyze the sequence of consonants.
Fig. 1. Example of a stimulus sequence presented to the subjects. In the control condition, subjects were instructed to indicate whenever the letter ‘‘S’’ appeared by pressing the button. In the working memory activation task, subjects had to respond whenever the letter presented was identical to the one presented second last in the sequence (‘‘G’’ in our example). Note that the stimulus sequences were identical in both the control condition and the activation task. Only the instructions given to the subject and the ensuing cognitive processes were different.

continuously. Every time the consonant stimulus was identical to the stimulus that had been presented before the previous stimulus (the second last in the sequence), subjects had to respond. For example in the sequence ‘‘D-G-S-G-D-D’’, the second ‘‘G’’ is the target in the activation task. It occurred 17 times per block (1/7 of all stimuli). In other words, each letter had to be compared with the letter two positions back. This task (two-back condition) requires repetitive working memory updating.

The sequence contained repeated characters. They did not only serve as distractors but were also controlled for position and frequency such that they formed a ‘‘one-back’’ task with 17 events. This condition was not used in the experiments presented in this study. It was implemented, however, to serve as a fall-back paradigm for further clinical investigations with patients unable to perform the two-back task.

Each block of 121 stimuli lasted 363 s. To avoid learning effects by repetition of the same block, three different blocks were set up in a pseudorandomized manner using custom software (MacLab 2.0).24 Each block was presented either forwards or backwards. In total, each subject had to view and act upon six blocks, beginning with the control condition and followed by the first activation task (two-back), resulting in the scheme: C-A-C-A-C-A. At the beginning of each block, the current instruction was presented as a short sentence on the screen.

Before the fMRI studies were run, the experimental paradigm was tested in the psychological laboratory in order to control the level of difficulty of both tasks. Healthy subjects were able to perform the two-back task, but they consistently reported that is was more difficult and needed more effort than the control condition. When subjects were run with the same sequence but asked to respond to repeated characters (‘‘one-back’’ condition), the task was reported to be rather easy. We also tested a ‘‘three-back’’ version of the paradigm, i.e., identical letters were to be detected three positions back with two letters in between. This task was so difficult that the error rates increased to 50–90%. Because of the nature of the paradigm (go-no-go) and because subjects scored rather badly in the three-back condition, the three-back activation condition was thought to be hardly comparable to the control condition and hence not used.

**Imaging Protocol**

Images were generated on a 1.5-Tesla whole-body MRI system equipped with a conventional gradient system (Magnetom 63 SP®, Siemens AG, Erlangen, Germany). For imaging of cortical regions, we used the standard circular-polarized headcoil for RF transmission and detection at 63.64 MHz. Head fixation was accomplished by bi-temporal cushions and by an additional tape across the subjects’ forehead.

The shape and the total integral of the free induction decay (FID) signal was optimized by careful magnet shimming in each subject (ΔB0/ΔBzz ≤ 0.15 ppm). In order to localize the planes of interest, we first acquired 19 sagittal T1-weighted spin-echo images (repetition time, TR = 600 ms; echo time, TE = 15 ms; matrix size, MA = 256 × 128; field-of-view, FOV = 300 mm; slice thickness, TH = 5 mm; slice distance, SD = 0.5 mm; number of excitations, NEX = 1). Then on the mid-sagittal slice, we identified the commissura anterior (AC) as well as the commissura posterior (PC) and defined the bicomissural plane according to Talairach & Tournaeu.25 Eight adjacent slices (FOV = 200 mm, TH = 5 mm, SD = 0 mm) were planned perpendicular to the bicomissural plane with the first slice placed 8 mm posterior to the frontal pole (Fig. 2). For each plane under investigation, T1-weighted spin-echo images (TR = 600 ms, TE = 15 ms, MA = 256 × 256, NEX = 4) were acquired from planes identical to those used for functional imaging.

During the presentation of the visual stimuli, a series
of strongly $T_2^*$-weighted images was generated using an optimized first-order flow-rephased FLASH pulse sequence at high spatial resolution (TR = 480 ms, TE = 40 ms, flip angle, $\alpha = 40^\circ$, MA = 128 x 128, NEX = 2). After data acquisition, the matrix size was interpolated to $256 \times 256$ picture elements by zero-filling in the phase-encoding and read-out direction. The complete scanning time was about 70 min for each subject.

**Behavioral Data Analysis**

Response accuracy was calculated using standard procedures from signal detection theory. The sensitivity index $d'$ describes the response accuracy of a subject independent of response biases. For each condition (activation and control), relative hit rates ($HR = \text{correct responses divided by the number of all target trials}$) and relative false positive rates ($FPR = \text{false positive responses divided by the number of all non-target trials}$) from all three experimental blocks were computed. Z-scores of hit rates and false positive rates were calculated. Perfect hit rates ($HR = 1$) and no false positive responses ($FPR = 0$) were corrected to $2^{-1/6}$ and to $1-2^{-1/6}$, respectively, with $s = \text{number of possible hit rates}$ and $n = \text{number of possible false positives (noise trials)}$. Then the sensitivity index $d'$ was calculated by subtracting the z-scores of the FPR from the z-scores of the HR ($d' = z(\text{HR}) - z(\text{FPR})$).

**Image data analysis**

MR images were analyzed on a DEC 3000/400 AXP workstation (Digital Equipment Corporation, Maynard, USA) using custom software.

**Motion quantitation and correction.** Image artifacts due to head movement were quantitated by calculating the mean coefficient of variance of all pixels in a selected brain slice over the $T_2^*$-weighted MR images in the activation task ("movement coefficient"). In the next step, a matching algorithm was employed to minimize the mismatch between the $T_2^*$-weighted images in the entire fMRI series by translating (in steps of one quarter of a pixel) and rotating (in steps of 0.3°) each image with respect to a reference image (generally the first image in each series). This algorithm based on a two-dimensional affine image transformation maximized the image congruency over the
entire fMRI series and minimized the movement artifacts (Fig. 3).

Detection of activated areas. For the detection of activated cortical areas, the significance of differences in MR signal enhancement in the activation task compared to the control condition was tested by applying the non-parametric Wilcoxon rank sum test for different median values\textsuperscript{32} on a pixel-by-pixel basis. We specifically tested for positive signal differences since the stimulus-induced MR signal changes were positive due to the known neurophysiological functioning and the BOLD MR contrast mechanism.\textsuperscript{33-35} The significance level was set to $p = 0.05$ in the one-tailed test.

Reduction of type-I errors. In order to remove signal contamination due to stochastic noise in isolated pixels, the calculated fMRI activation maps were further filtered using the following continuity criterion: At least five additional significant pixels had to be in a $3 \times 3$ grid around an examined activated pixel. It has been shown by Monte-Carlo simulations and with experimental data that such a cluster criterion provides considerable protection against type-I errors.\textsuperscript{36,37} Due to the lower effective $p$ value, the specificity in the fMRI activation maps was considerably improved.

Construction of fMRI maps. In picture elements with significantly increased signal strength, the relative signal difference $\Delta S = (S - S_0)/S_0$ was computed where $S$ denotes the mean value in the activation task and $S_0$ the corresponding value in the control condition. The relative signal difference $\Delta S$ was quantitated on a scale from 1% to 4%, color-coded in steps of 1%, and overlaid onto the corresponding anatomical $T_1$-weighted spin-echo images.

Activation profiles. Selected regions-of-interest (ROIs) were manually delineated on the fMRI activation maps to assess the time-course of the MR signal intensity and to allow a comparison of the changes in activation strength with the behavioral data. In the selected ROIs, the mean signal intensity was calculated at each time point of the fMRI series and normalized to the average signal intensity of the control condition ($=100\%$) in the same region.

Quantification of cortical activation. Six anatomical regions were defined in both hemispheres according to the Talairach & Tournoux\textsuperscript{25} brain atlas: Superior frontal gyrus (GFs), middle frontal gyrus (GFi), inferior frontal gyrus (GFi), orbital gyri (GO), cingulate gyrus (GC), and medial frontal gyrus (GFme). For each subject and each of the eight adjacent slices, these regions were manually delineated on the $T_1$-weighted images (Fig. 4). Then the number of all voxels as well as the number of significantly activated voxels were calculated for each region in each slice by use of custom developed software.\textsuperscript{38} The corresponding regions on adjacent slices were aggregated and transformed into the volume of the anatomically defined cortical area (volume of one voxel $= 0.5 \cdot (20/256)^2$ ml). Then the ratio of the number of activated voxels to the total number of voxels was calculated for each of the 12 regions for each subject (relative activation volume).
Fig. 4. **Top**, delineation of the anatomical regions. GFs: superior frontal gyrus, GFmi: middle frontal gyrus, GFi: inferior frontal gyrus, GO: orbital gyri, GC: cingulate gyrus, GFme: medial frontal gyrus. Note that maximally five of the anatomically defined frontal regions appear in a coronal slice of the frontal lobe, but not all six regions simultaneously. Due to the sickle-like form of the GC and the GFi, both were scanned in the 5 to 6 posterior orientated coronal slices (**top left**). In the 2 or 3 anterior slices (**top right**), neither the GC nor the GFi was touched, but the GFme could be delineated. **Bottom**: Volumes of the anatomical regions delineated manually for each subject and each slice and then aggregated from adjacent slices. Mean values and SD are given separately for the left and the right hemisphere. There was no significant difference in the corresponding volumes of both hemispheres.

**RESULTS**

**Behavioral Data**

Subjects responded more accurately in the control condition than in the activation task (Table I). The mean sensitivity index $d'$ was $4.46 \pm 0.67$ in the control condition and $3.82 \pm 0.59$ in the activation task (paired $t$-test, two-tailed: $t(23) = 4.51, p < 0.001$). After the exclusion of eight subjects because of movement artifacts (see below), the remaining 16 subjects showed a similar significant difference in sensitivity scores $d'$ between control and activation runs with a mean $d'$ of
4.51 ± 0.67 in the control condition and a mean d’ of 3.75 ± 0.65 in the activation task (t(15) = 4.77, p < 0.001). These subjects were all right-handed, with a mean handedness score of +85.8%.

The d’ values for the three consecutive blocks of the entire experiment were calculated and no significant changes were found. This indicates that there was no habituation in performance of the working memory task during the experimental session.

Image Data

Movement artifacts. Movement coefficients, calculated as mean coefficient of variance of all brain pixels in the activation task throughout the experiment, were in a range from 1.80% to 4.73%, with a mean of 2.82% ± 0.69% (Table 1). Reduction of the coefficients due to the matching algorithm was effective to a significant degree (2.27% ± 0.57%, paired t-test, two-tailed: t(23) = 6.71, p < 0.001; for an example, see Fig. 3). However, the algorithm was not equally effective in all data sets. Therefore, we set a movement coefficient calculated on the matched data of above 2.5% as a criterion for the exclusion of a subject from further analysis. Because of this criterion, eight subjects were excluded due to movement artifacts. The remaining 16 subjects had a mean movement coefficient of 2.56% ± 0.54% in the uncorrected data which was reduced to 1.98% ± 0.26% with movement correction (t(15) = 5.17, p < 0.001). From these subjects, functional MR data were further evaluated.

Anatomical data. The mean volumes of the anatomically defined regions are displayed in Fig. 4. There was no significant asymmetry comparing the corresponding regions of both hemispheres (paired t-test, two-tailed: t(95) = 0.925, p = 0.36).

Activation data. In all 16 subjects, the activation task produced a significant increase in signal intensity in at least two frontal regions. As illustrated in Fig. 5, the relative signal increase ranged from 1% to 4% in most cases. Activation profiles from four corresponding ROIs in adjacent slices are shown in Fig. 6. Cortical activation was most pronounced in the middle and inferior frontal gyri (GFr m and GFr f) as well as in the cingulate gyrus (GC) in both hemispheres. These regions correspond to Brodmann’s areas 9, 10, 46, and 47. A two-way ANOVA with hemisphere and region as intra-subject factors revealed a significant main effect for region (F(1/75) = 5.54, p < 0.001). There were no other significant main effects as well as no significant interactions (i.e. no lateralization). Post-hoc comparisons (Fisher-LSD tests) demonstrated that the orbital gyrus (GO) were activated to a smaller degree than the other frontal areas. Similarly, the medial frontal gyrus (GFe m) was less active than the middle and inferior frontal gyrus (Fig. 7).

DISCUSSION

Cortical activation induced by a working memory task was studied using a conventional MR scanner equipped with additional hard- and software for fMRI of higher cognitive functions. Twenty four healthy subjects performed a letter recognition task designed to yield both a control and a working memory condition. The engagement of working memory caused non-lateralized significant cortical activation in Brodmann’s areas 9, 10, 46, and 47. The study touches on a number of methodological and systematic issues of importance in fMRI in general and the study of working memory in particular.

The traditional approach in functional activation studies was to adapt a clinically established neuropsychological or experimental psychological paradigm to the imaging setting. Therefore, activation studies addressing the frontal cortex and working memory involved paradigms such as the Wisconsin Card Sorting Test (WCST) as well as the Tower of Hanoi Test (TH).16 In these complex activation tasks, a well defined control condition is lacking. Most of the imaging studies used a nonspecific resting condition as a control. As higher cognitive functions require sensory input and motor output in addition to the task in question, such a comparison between task and rest for the generation of activation images is not desirable.22 For these reasons, we used a
Fig. 5. Activation maps from a single subject in eight adjacent slices covering the prefrontal cortex. Significant increase of fMRI signal intensity in the working memory task compared to the control condition is color-coded and overlaid onto anatomical $T_1$-weighted spin-echo images.

Fig. 6. Time-courses of relative fMRI signal intensity (normalized to 100% of the control condition) from activated areas in the right middle frontal gyrus (GFmi) measured independently in four adjacent slices (no. 2–5) of the subject shown in Fig. 5. The bars on the abscissa indicate the experimental condition (open, control condition; filled, activation task). Each value refers to one measurement with a duration of 120 s.
paradigm in which sensory input and motor output were identical in both the control and the activation condition. These conditions were different with respect to the cognitive component only, and hence, the subtraction image displayed activation caused by this component only.

In the present study, we presented a sequence of letters. Subjects had to react either on a single prespecified letter (control condition) or to react whenever a letter occurred that was identical to one presented two times before (activation task). This task activated working memory, because context relevant to behavior changed with every stimulus and had to be actualized in memory storage. All subjects reported that more effort was required to perform the activation task whereas the control condition was generally experienced as boring, involving only reflex-type responses that could be performed more or less automatically. The accuracy of target detection, i.e., the sensitivity index d', as an objective measure of task difficulty was significantly different between the activation task (more difficult) and the control condition.

In contrast to the WCST and the TH, which both involve complex perceptual, motor, cognitive and emotional components, the working memory task used in this study has only a single cognitive component. Because of its simplicity, the paradigm implies working memory function most clearly. It allows for the analysis of behavioral data (hit rates and error rates) within a signal detection theory framework, which enabled us to demonstrate the increased cognitive load of the working memory condition as well as the lack of habituation effects within the experimental runs.

With respect to the external validity of the task, it is noteworthy that it can directly be related to single cell recording data from primate studies, which demonstrate that neurons located in the dorsolateral prefrontal cortex are specifically active in the delay period of a similar working memory task. Accordingly, we found a task-specific activation of predominantly dorsolateral prefrontal cortical areas. This result is in line not only with the animal literature, but also with previous studies addressing the localization of working memory in humans. In particular, our data confirm the results of Cohen et al., who used the same paradigm with different scanning procedures and found a pattern of activation similar to our study. In contrast to Cohen et al., we used a conventional gradient-echo pulse sequence (not the advanced spiral MR technique) in combination with a head coil (Cohen et al. used two surface coils with a less homogeneous RF field).

The lack of laterality in the cortical representation of non-spatial working memory found by Cohen et al. was confirmed in this study. This confirmation is noteworthy since we used a head coil with a more homogeneous magnetic field and, hence, were able to generate data less prone to artifacts due to field inhomogeneity. Processing of letters, therefore, appears to be a function which is distributed not only within left frontal cortical areas but also right frontal areas. We cannot rule out laterality for more specialized functions of working memory, involving purely spatial or purely object representations.

A general advantage of fMRI is its capability to produce significant results in data obtained from single subjects. This calls for a different analysis strategy than is standard in the PET literature which relies on intersubject averaging. Steinmetz & Seitz clearly demonstrated the loss of relevant information, when activation data with inter-individual variability, in their example language processing, are averaged. As a consequence, the fMRI studies on working memory by Cohen et al. and by Mellers et al. described activation on a subject by subject basis. In our analysis, we went beyond the individual data level by manually defining anatomical regions for each individual and by averaging these preprocessed data. Using this technique, we were able to distinguish several frontal areas anatomically and to relate activation to well-defined cortical sites.

Because of the high spatial resolution of the MR technique, movement artifacts are an important problem in fMRI. We applied two different strategies for the control of movement related artifacts. We quantified the movement of each subject by calculating the coefficient of variance in all brain pixels measured in the activation task. Secondly, we used an algorithm to correct displacements and rotations in the two dimensions of the measured slices. Because this algorithm cannot account for
between-plane motion or pulsation artifacts, residual movement was quantified and subjects above a fixed movement coefficient were excluded from further analysis. This procedure excluded one third of the subjects but secured the quality of the activation data.43

In conclusion, working memory function can be studied with a conventional MRI system. A simple paradigm with no resting condition but an active control condition provides interpretable results, in particular when behavioral data are conjointly acquired and analyzed. From a clinical point of view, such working memory paradigms with their established neurophysiological context may provide useful for the study of several patient populations in neurology and psychiatry.

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