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Activation of the Prefrontal Cortex in a Nonspatial Working Memory Task With Functional MRI

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Abstract: Functional magnetic resonance imaging (fMRI) was used to examine the pattern of activity of the prefrontal cortex during performance of subjects in a nonspatial working memory task. Subjects observed sequences of letters and responded whenever a letter repeated with exactly one nonidentical letter intervening. In a comparison task, subjects monitored similar sequences of letters for any occurrence of a single, prespecified target letter. Functional scanning was performed using a newly developed spiral scan image acquisition technique that provides high-resolution, multislice scanning at approximately five times the rate usually possible on conventional equipment (an average of one image per second). Using these methods, activation of the middle and inferior frontal gyri was reliably observed within individual subjects during performance of the working memory task relative to the comparison task. Effect sizes (2–4%) closely approximated those that have been observed within primary sensory and motor cortices using similar fMRI techniques. Furthermore, activation increased and decreased with a time course that was highly consistent with the task manipulations. These findings corroborate the results of positron emission tomography studies, which suggest that the prefrontal cortex is engaged by tasks that rely on working memory. Furthermore, they demonstrate the applicability of newly developed fMRI techniques using conventional scanners to study the associative cortex in individual subjects.

Key words: neuroimaging, magnetic resonance imaging, topography, spiral scanning, cognitive neuroscience, CPT

INTRODUCTION

The prefrontal cortex (PFC) is one of the areas of the human brain that is most significantly expanded, relative to other animals. General consensus exists that the PFC is centrally involved in higher cognitive activities such as planning, problem solving, and language. However, despite this consensus, relatively little is known about the specific processes subserved by the PFC that contribute to these cognitive activities or its functional organization. Theorists in the past have attributed many general functions to the frontal lobes such as attention [Ferrier, 1886], abstract intelligence [Hitzig, 1874], and synthesis of percepts [Bianchi, 1922]. In recent years, more specific hypotheses have begun to emerge, including the possibility that the PFC is centrally involved in working memory. Working memory has been defined as "... the temporary maintenance and manipulation of information"

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[Baddeley, 1992]. Neurophysiological, neuropsychological, and neuroimaging research have all been used to support the idea that the PFC contributes importantly to this function.

It has been known, for over 20 years, that populations of neurons in the PFC have patterns of activity that strongly suggest their involvement in the temporary maintenance of information [Fuster and Alexander, 1971; Kubota and Niki, 1971]. For example, electrophysiological and lesion studies [Barone and Joseph, 1989; Goldman-Rakic, 1987] have demonstrated that an area of the dorsolateral prefrontal cortex, in and around the principal sulcus in the monkey, is involved in the maintenance of spatial information. Cells have been identified that remain active during delays in which the subject must actively, and internally, maintain a representation of the target, but not when the target is marked by an external cue during the delay. Other lesion studies suggest that the dorsolateral frontal cortex also supports the maintenance of other types of information [e.g., serial order and conditional association, Petrides, 1991]. Evidence also exists that information may be organized topographically within the PFC. For example, localized lesions in areas supporting spatial information appear to disturb memory for specific locations in a highly topographic manner [Funahashi et al., 1989]. In addition, Wilson et al. [1993] have recently reported that different areas support memory for spatial and pattern information.

Neuropsychological studies of patients with damage to the frontal cortex have provided strong support for the idea that the PFC plays an important role in human working memory [Damasio, 1985; Petrides and Milner, 1982; Stuss et al., in press; Shimamura et al., 1990]. This idea is also supported by a number of recent studies using positron emission tomography (PET) that have shown activation of this region during a variety of cognitively demanding tasks, all of which can be thought to involve working memory. Thus, tasks that involve short-term memory for digits [Grasby et al., 1993], letters [Paulesu et al., 1993; Sergent et al., 1992], words [Becker et al., 1993], abstract shapes [Petrides et al., 1993a], and faces [Haxby et al., 1993] all activate anterior regions of the frontal cortex.

Similarly, tasks in which subjects must generate words that belong to a particular category [Frith et al., 1991] or random sequences of numbers [Petrides et al., 1993b] also activate the prefrontal cortex. All of these tasks can be thought to involve components of working memory, in one way or another. For example, short-term memory tasks require that subjects maintain the to-be-remembered materials on-line during an experimentally imposed delay. Word and random number generation tasks require that subjects keep prior responses in mind to avoid repeating them. Thus, these findings support the idea that regions of the PFC become activated during tasks that rely on working memory.

Interestingly, however, most of these tasks seem to activate similar regions of the PFC, despite the fact that different types of information are involved. Thus, studies involving memory for letters, digits, words, shapes, and faces have been reported to produce activation of Brodmann's area 46. This does not support the idea that the PFC is organized topographically by information type. Furthermore, the one PET study to examine memory for spatial information [Jonides et al., 1993] produced activation of Brodmann's area 47, which is ventral to area 46, that is, activation in a spatial memory task appeared to activate a region ventral to the region most commonly activated by tasks involving memory for objects, such as letters, digits, words, and faces.[1] This is inconsistent with the finding of Wilson et al. [1993], in nonhuman primates, that spatial information is represented dorsally relative to object information. One possible interpretation of this finding, however, is that the imaging methods used to date have not provided sufficient spatial resolution to differentiate meaningfully between functionally distinct regions of the PFC. These studies have used between-subject averaging of data, which may obscure subtle differences in the areas of activation produced by different types of stimuli.

Recently, advances in magnetic resonance imaging (MRI) have provided an alternative method for detecting brain activity that may be capable of significantly higher spatial resolution [Bandetti et al., 1992; Kwong, et al., 1992; Ogawa et al., 1992; Schneider et al., 1993]. This method, often referred to as the *deoxy* or *BOLD* technique (for blood oxygenation level detection), relies on the observation that when hemoglobin becomes oxygenated, it exhibits changes in its magnetic susceptibility and that this can be detected in measurements of the transverse relaxation rate [Thulborn et al., 1982]. Thus, areas of increased oxygenation should produce a stronger T2* magnetic resonance (MR) signal than areas of lesser oxygenation. PET studies

[1]It is possible that subjects may have been able to rely on configural information rather than spatial location to perform the task used by Jonides et al. [1993]. However, these investigators were recently able to replicate this result using a better controlled task that did not permit this possibility (personal communication).

have indicated that, at least within primary sensory and motor areas, local brain activity leads to increases in perfusion that are associated with a paradoxical *increase* in oxygenation [Raichle, 1988]. Thus, these areas should also produce a stronger MR signal than less activated areas. A large number of studies, both in animals [e.g., Ogawa et al., 1990; Turner et al., 1991] and in humans [e.g., Kwong et al., 1992], have now reported results that are consistent with these assumptions. Most of these studies have used specialized apparatus [echo-planar (EPI) equipment and/or high-field scanners].

However, studies using conventional scanners have begun to produce similar results [Constable et al., 1993; Frahm et al., 1993; Schneider et al., 1993]. For example, we recently reported an fMRI study of the topographic organization of the visual cortex [Schneider et al., 1993]. By presenting stimuli selectively to different areas of the visual field, we were able to delineate regions of activity within the cuneate and lingual gyri that corresponded appropriately to what is known about the functional anatomy of the visual cortex—in some cases distinguishing functionally between areas of activation that were separated by as little as 1 mm.

The purpose of the study we report here was to explore the use of these techniques for examining the functional topography of the frontal cortex. To date, fMRI has been used primarily to study activation in sensory and motor areas [Bandetti et al., 1992; Blamire et al., 1993; Kim et al., 1993; Kwong et al., 1992; Ogawa et al., 1992; Schneider et al., 1993; Turner et al., 1993b]. Only a small number of studies have examined frontal activation. Most of these have used versions of a word generation task [Hinke, Hu, Stillman, and Ugurbil, 1993; McCarthy et al., 1993a; Rueckert et al., 1993], replicating PET findings of activation in areas 47 and 10 [Petersen et al., 1989]. To our knowledge, only one preliminary study has directly addressed working memory function [McCarthy et al., 1993b]. In this study, activation of a relatively dorsal region of the PFC (Brodmann's areas 9 and 46) was observed during performance of a spatial working memory task. As yet, there have been no studies of working memory using nonspatial stimuli or conventional scanning equipment. We report here a study of prefrontal cortex activation during performance of a nonspatial working memory task using fMRI. Scanning was performed using a conventional MRI scanner, and permitted the identification of activity within specific cortical gyri of individual subjects.

MATERIALS AND METHODS

Cognitive tasks

Twelve right-handed subjects were studied (seven males and five females), ranging in age from 20 to 29 yr. Subjects were scanned while they performed a working memory task and a control task. In both tasks, subjects observed random sequences of letters appearing one at a time in the center of a visual display and were instructed to respond by pressing a button on a hand-held fiberoptic response box whenever a target appeared (see below). Stimuli were presented for 500 ms, with an interstimulus interval of 1,000 ms. Stimulus presentation was controlled by a Macintosh IIci computer, using PsyScope software [Cohen et al., 1993a], and rear-projected onto a display screen using a high-luminance overhead projector and an LCD panel connected to the computer [for details, see Cohen et al., 1993b].

In the control task, a target was any occurrence of the letter "X." In the memory task, targets were any letter that repeated with exactly one intervening nonidentical letter (e.g., A-F-A, but not A-A or A-Q-G-A). Target frequency (1/7) and the frequency of repeated letters were matched in the two tasks. Thus, the only differences between the tasks were the appearance of the letter "X" in the control but not the memory task, and the instructions given to subjects. Both the control and memory tasks required that subjects monitor sequences of letters presented visually one at a time, encode each letter, evaluate its identity, and respond to a target by pressing a button. However, the memory task had the additional requirement that the subject keep in mind both the identity and order of the two previous letters, and continuously update this mental record as the sequence progressed. These operations are central to the concept of working memory, as it has been defined in cognitive psychology [Baddeley, 1986; Just and Carpenter, 1992], and our task is similar to others that have been used to study working memory [e.g., Gevins and Cutillo, 1993].

Each task was run in 60-s blocks, during which scans were acquired. Subjects were instructed not to vocalize or "subvocalize" stimuli in either of the tasks, but to "do the task in their heads." All 12 subjects performed at least ten blocks of each task, with blocks alternating between tasks. There was a 30–40 s delay between blocks, during which the subject rested and the scanner downloaded data. Four of the subjects also performed an equal number of blocks using their left hand to examine the effects that laterality of motor

response might have on area of activation. The order of response hand was counterbalanced across these four subjects.

Scanning procedures

Scans were performed at six contiguous slice locations in the prefrontal cortex of the 12 volunteer subjects (Fig. 1A).[2] Functional images were acquired using multislice, high-speed spiral scanning [Ahn et al., 1986; Meyer et al., 1992; Noll et al., 1993] techniques on a conventional 1.5-T GE Signa whole-body scanner. Two 5-inch surface coils, mounted parallel to one another in a sagittal orientation on each side of the head, were used to maximize signal to noise. (There was some asymmetry in the signal associated with each coil; however, this was a random factor across subjects and was not found to be a significant factor in statistical analyses.) Subjects' heads were restrained using a vacuum-compressed surgical pillow. Functional scans were 7 mm thick, with 128 × 128 pixels (1.88 × 1.88 mm) in plane, acquired at six contiguous locations in an oblique coronal plane [approximately 60 deg relative to the anterior commissure-posterior commissure (AC-PC) line], with the center of the posteriormost slice aligned with the posterior margin of the genu of the corpus callosum. Structural images were obtained at these locations before functional scanning, using a standard T1-weighted sequence. Functional images were acquired using a 10-interleave spiral scan pulse sequence with a TR of 600 ms, a gradient echo TE of 35 ms, flip angle of 45 deg, and a field of view of 24 cm. No shimming procedures or specialized hardware were used. A set of images from all six slice locations was obtained every 6 s. Ten sets were obtained during each 60-s task block, for ten blocks in each task, providing 100 scans at each slice location in each task.

To our knowledge, this is the first time spiral scanning techniques have been applied to the study of the association cortex. Previous fMRI reports [e.g., McCarthy et al., 1993b] have used EPI instruments, which permit very rapid image acquisitions but are costly and, to date, relatively scarce; or conventional scanners with 2D Fourier acquisition [Kumar et al., 1975] sequences, which are limited in their rate of image acquisition. These approaches have proved useful for demonstrating activation of primary sensory and motor cortex, whose anatomic localization was already quite well established. Spiral scan pulse sequences provide significant benefits when studying the less well-established topography of higher cognition, by allowing both rapid multislice acquisition and high resolution.

[2]Informed consent was obtained from subjects in accordance with a protocol approved by the University of Pittsburgh Institutional Review Board.

Analysis

Image processing

Each set of 200 functional images acquired at a given plane location was scaled to a common mean (to reduce the effects of global signal drift or other forms of scanner instability) and registered in-plane using a simple sum squared error reduction algorithm. Mean normalization was performed as follows: First, the mean pixel value was computed for one image in the set, to act as a reference. The same computation was then performed for each other image in the set, and the value of each pixel in a given image scaled by the ratio reference mean/image mean. Image registration was then performed on the set of mean-normalized images. This involved a simple test procedure, in which each image was shifted in all combinations of 0, 1, or 2 pixels in each of four directions (25 cases) and then compared with a common image used as the reference. Comparisons were made using the mean squared difference between pixels in the two images, and the shift was chosen that produced the smallest difference.

Statistical subtractions and anatomic localization

Statistical subtraction procedures were applied to the functional scans (memory-control) for each subject separately. Areas of significant activation at each scan location were identified by performing pixel-wise t tests between images acquired during the control and memory tasks using a split-halves method, as follows. For each slice location, the first 50 scans acquired during the control task were compared with the first 50 acquired during the memory task using a standard pixel-wise t test. The same procedure was applied to the second set of 50 images in each condition. Areas were then identified that had five or more contiguous pixels with t values of 2.0 or greater ($P < 0.025$, one-tailed) in *both* comparisons.[3] The likelihood that

[3]In accord with our interest in areas of increased activation during performance of the memory vs. the control task, and the corresponding choice of a one-tailed t test, only areas with significant positive t values were chosen for further analysis. We should note, however, that areas with significant negative t values were also observed and are subject to further analysis.

an individual pixel would be considered active by this method, due solely to chance, is 0.000625 (0.025 × 0.025). Given 16,384 pixels/image, one expects about ten such "active" pixels per slice. This procedure has also been used successfully in a study of visual cortex [Schneider et al., 1994]. Furthermore, Monte Carlo simulations indicate that these spuriously active pixels form contiguous clusters of five or more pixels with a probability of <0.00025/slice. Thus, with 12 subjects and six slices per subject, the probability of a type I error for our entire study was <0.02 ($12 \times 6 \times 0.00025$; a full description of the Monte Carlo simulations showing the distribution of different size clusters as a function of individual pixel alpha level and image dimension is in preparation).

The area (in number of pixels) of each region of activation identified as described above was computed and its mean and peak t values were also computed. These regions were then overlaid on the corresponding structural images, to identify their exact locations, and assigned to one of the five anatomic structure categories listed in Table I. Assignment of regions of activity to structures was performed independently by two raters, using a standard magnetic resonance imaging brain atlas as a reference [Duvernoy, 1991].

Interrater reliability on this procedure was >0.9, and a consensus rating was performed on those areas for which the individual ratings did not agree. Only regions that lay over gray matter, and not over vessels identifiable in the structural images, were categorized. The regions that satisfied this criterion were presumed to be associated with capillaries or sufficiently small vessels as to reflect effects localized to the structure with which they were identified. A small number of activated regions overlaid more than one structure; these were assigned to a category based on the structure over which their most active pixels lay. In some images, there were also large areas of significant differences along the rim of the cortex, usually unilaterally; these were believed to be related to motion artifact and were excluded from analysis [as per Kim et al., 1993].

Quantitative analysis of the anatomic distribution

This was performed by conducting analyses of variance (across subjects) examining the number, size, and significance of regions of activation within the anatomic structures and hemispheres listed in Table I.

Time series

Finally, the mean MR signal for each anatomic structure was plotted as a function of time (Fig. 2). Specifically, plots were generated by first computing the mean value of the pixels associated with each region of activity at each time point (i.e., scan) for each subject. These means were then averaged for all of the regions within each anatomic category, to generate a mean value for regions of activity within each structure at that time point for each subject. These were then re-expressed as a percent difference from the mean of such values across all time points (i.e., all 200 scans). Finally, the percent difference values at each time point for each structure were averaged across subjects and plotted as a function of time. Each point in Figure 2 reflects the average signal over 6 s of scanning. Shaded areas indicate blocks of the memory task, and white areas the control task.

RESULTS

As shown in Table I, greatest activation was observed in the middle and inferior frontal gyri. Although some subjects showed greater activation than others, 11 of 12 subjects showed significant activation in at least one of these two structures, 7 of 12 showed activation in both, and 7 showed bilateral activation of one or both of these structures. Most of the regions in the middle frontal gyrus fell within Brodmann's area 46 (59%), with a fewer number in areas 9 (19%) and 10 (19%); most of the regions in the inferior frontal gyrus fell within Brodmann's area 45 (40%), with the remainder distributed among areas 10 (23%), 44 (14%), 46 (14%), and 47 (8%) [Talairach and Tournoux, 1988]. In addition, 11 subjects showed lesser activation of one or more additional structures. An analysis of variance (ANOVA), with structure and hemisphere as factors and number of regions as the dependent measure, showed only a significant main effect of structure ($F = 8.1$, $P < 0.001$), providing no evidence for lateralization.[4] Post hoc comparisons (pairwise t tests of all structures, using a Tukey-Kramer correction for multiple comparisons) were conducted to explore the main effect of structure. A significantly greater number of particles were observed in the middle frontal ($P < 0.002$) and inferior frontal ($P < 0.05$) gyri than all other structures, except for the comparison between

[4]ANOVAs using region area and average t value produced similar results. We observed a tendency, overall, for greater activation on the left. We believe this was due to the surface coils used to improve signal-to-noise ratio. The use of these coils introduced an inescapable asymmetry in signal sensitivity, which, for a number of our subjects, was biased strongly toward the left. When we reanalyzed the subset of our subjects ($n = 7$) for whom coil sensitivity was better balanced (slightly greater on the right), this tendency toward left lateralization was no longer observed.

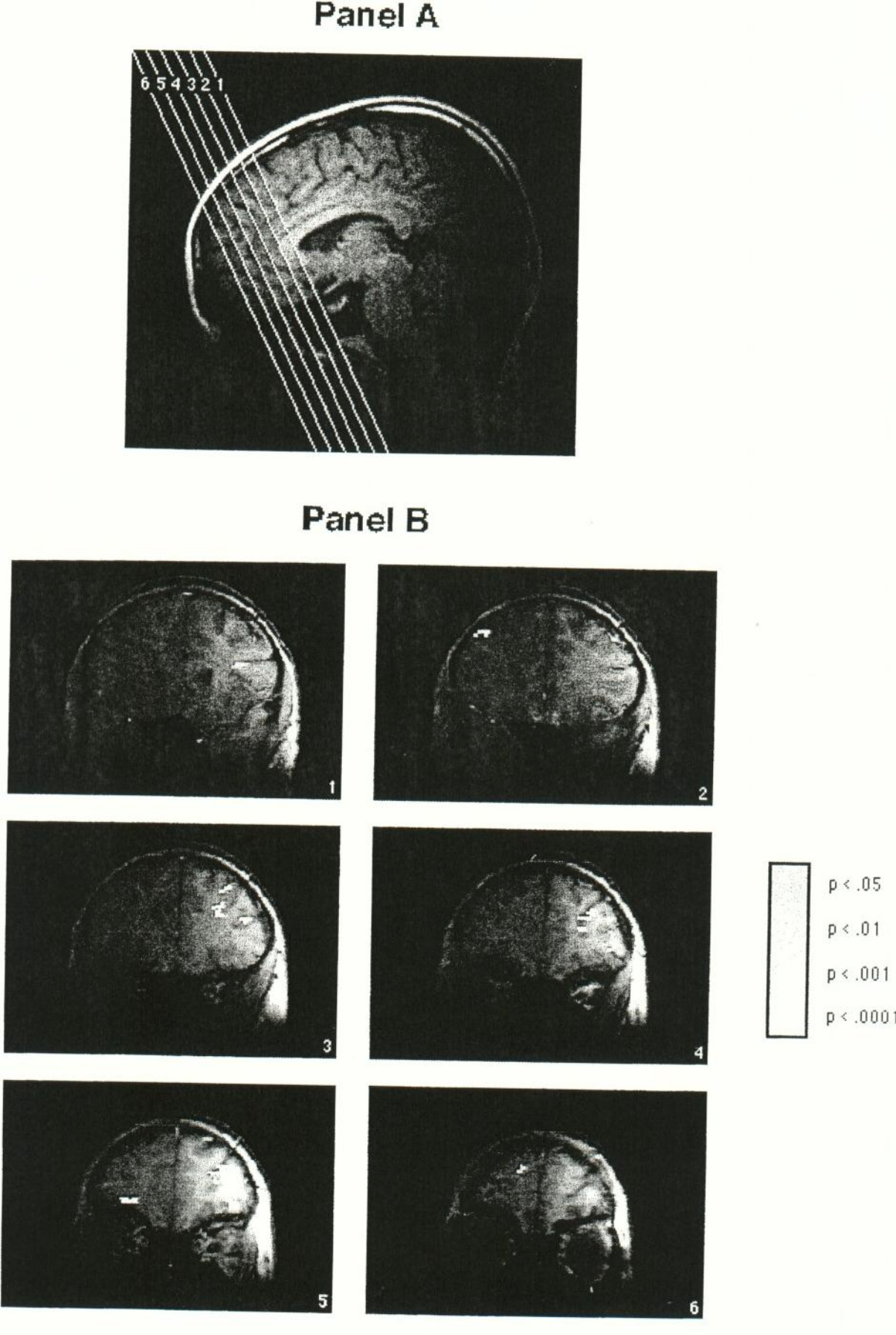

Figure 1

TABLE I. Statistics for areas of activation*

Structure	No. of subjects	Location (x, y, z)	*N*	Area (mm^2)	% diff	Mean *t*	Peak *t*
SFG	—	—	—	—		—	—
	4	17, 49, 25 (R)	4	29	1.8	3.3	4.1
MFG	7	29, 38, 20 (L)	19	107	2.1	3.8	6.3
	6	31, 42, 22 (R)	13	100	1.8	3.6	5.9
IFG	7	36, 33, 13 (L)	31	214	1.3	4.0	7.2
	7	39, 39, 14 (R)	17	64	1.8	3.6	5.6
Cingulate	1	3, 39, 13 (L)	2	39	1.1	4.0	7.4
	2	3, 22, 15 (R)	2	19	3.8	4.5	6.9
Orbital	4	24, 27, −11 (L)	6	60	1.4	3.9	5.0
	2	26, 41, −11 (R)	3	47	2.7	4.3	5.4

* Statistics are reported for areas of activation in the superior frontal gyrus (SFG), middle frontal gyrus (MFG), inferior frontal gyrus (IFG), orbital gyri (Orbital, primarily posterior and lateral gyri), and anterior cingulate (Cingulate). For each structure, the following data are reported: the number of subjects showing activation in that structure in the left and right hemispheres; the mean of the x (left–right), y (anterior–posterior), and z (superior–inferior) coordinates for regions of activation relative to the anterior commissure (which was identified in a midsagittal image for the corresponding subject); the total number of regions of activation identified across subjects (*N*); total region area, computed first within subjects, and then averaged across subjects; percent change in signal intensity weighted by region area (% diff) and averaged across subjects; mean region *t* values weighted by area and averaged across subjects; peak region *t* values averaged across subjects. Note: averages are across only those subjects showing activation in the corresponding structure.

middle frontal gyrus and orbital structures, which only approached significance ($P < 0.15$). No other comparisons approached significance. Finally, separate ANOVAs were conducted on the four subjects who performed the additional set of trials with their nondominant hand. These revealed, once again, a main effect of structure (with a distribution across structures similar to the main study), but no significant effects of hemisphere, response hand, or interactions between these.

The signal value in the activated areas exhibited highly regular patterns of change, increasing abruptly at the start of each memory task (Fig. 2). In most cases, the signal reached or approached its maximum value within 6 s (first scan) of the start of the memory block. This is consistent with previously reported observations that maximum MR response typically occurs within 3–6 s of task onset [Belliveau et al., 1992; Blamire et al., 1993; Frahm et al., 1993).

Figure 1.

A: Midsagittal T1-weighted image, indicating the location and plane of functional scans. **B:** Set of activation images for one subject with the areas of activation that were analyzed overlaid on the corresponding structural images. The left of the image corresponds to the subject's right.

DISCUSSION

The results of this study indicate that it is possible to use fMRI to study the activity of the frontal cortex during performance of a working memory task and that it is possible to do so using conventional MRI scanners. Specifically, the results corroborate findings from PET studies that areas of the prefrontal cortex are activated during the performance of a task that relies on working memory. Below, we address a number of technical and conceptual issues that are relevant to these results.

Effect size

There has been considerable interest in the magnitude of the signal observed in different cortical regions using neuroimaging techniques that depend on changes in blood flow. Typically, these are expressed as a percentage difference in the mean signal for a given region between the activated and control conditions. PET studies have reported a substantial disparity in effect sizes between primary sensory and motor areas (>15%) and association areas (<10%) [Raichle, 1989]. The magnitude of the signal change that we observed ranged from 1.1 to 3.8% across areas (average of 2.0%). This is close to the values that have been

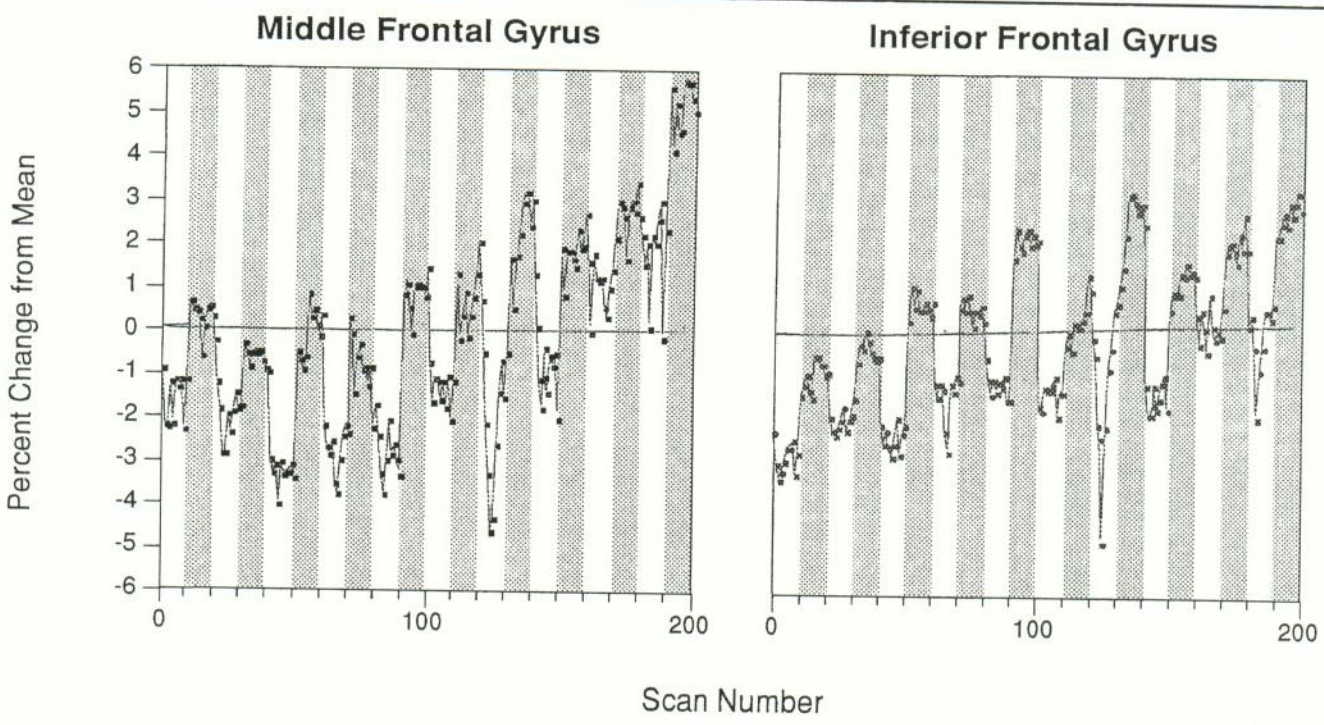

Figure 2.
Plots of the average MR signal across time, as a percent difference from the mean, in the activated areas of middle and inferior frontal gyri. See text for details of analysis.

observed in the visual cortex [1.8–3.3%—Frahm et al., 1993; Kwong et al., 1992; Schneider et al., 1993] and the motor cortex [4.3%—Bandetti et al., 1992] using fMRI. This finding suggests that the size of changes in association areas may be more similar to primary sensory and motor areas than has previously been thought.

Two factors may have contributed to the current results. First, improved spatial resolution and within-subject averaging may be more important in association areas, where functional anatomy may be more variable across subjects. This hypothesis is supported by the variability of activation location, even within prefrontal cortex, observed in our study. Second, our task required that subjects maintain working memory representations *continuously* throughout the full duration of each block, that is, subjects had to maintain at least two stimuli in memory at all times. This contrasts with tasks used in previous neuroimaging studies of working memory, which allowed subjects to "unload" working memory after each response [e.g., Paulesu et al., 1993]. The continuous demands placed on working memory in our task may be more similar to the conditions used to produce activation in sensory and motor areas, in which stimuli or motor activity are sustained continuously throughout each block.

Sources of artifact

As we noted above, in a number of images we observed large areas of artifact overlying the cortical rim, which we attributed to task-related movements. This raises the possibility that other regions of "activation" may also have been related to movement. Although this may be the case, we do not believe that this significantly influences our results, for several reasons. First, these areas were observed in only a subset of subjects (six), whereas regions of activation overlying the inferior and/or middle frontal gyri were observed consistently across subjects. Furthermore, it seems unlikely that movement could account for the specific regional distribution of activation observed in our study (significantly greater activation of inferior and middle frontal gyri as compared with the superior frontal, orbital, and cingulate gyri). Finally, studies of sensory [Schneider et al., 1993] and motor [Kim et al., 1993] cortices have also revealed areas of activation at the rim of the cortex and have used similar procedures for eliminating them from analysis. These have produced results that conform extremely well to what is known about the functional anatomy of these regions from direct electrophysiological examination in nonhuman primates. There does not appear to be any reason

to believe that circumstances should be different in the association cortex.

Another potential concern surrounds the possibility that areas of activation reflect changes in the oxygenation state of large draining vessels, which may serve regions anatomically removed from the areas in which effects are observed. As noted, we attempted to minimize this possibility by excluding from analysis areas of activation that lay over vessels identifiable within the structural scan. Our reasoning was that by eliminating areas of activation associated with vessels large enough to be observed, remaining areas would most likely be associated with vessels small enough to serve relatively local regions. This assumption seems warranted, relative to the spatial resolution at which we analyzed our data, which was at the level of the cortical gyri. We should also note that the magnitude of our effect sizes (2–4%) was in the range that others, using high-field systems [Menon et al., 1993] have reported for small vessels and capillaries (<6%), and not in the range reported for larger vessels (e.g., >6%). Of course, as finer grained studies of cortical topography are attempted, this issue will become increasingly important, and methods to address it will need to be developed. This may include more reliable detection of vessels using magnetic resonance angiography [Dumoulin et al., 1989] and techniques to suppress the venous signal, such as spin-echo methods [Turner et al., 1993a] and the use of T2-weighted/driven equilibrium preparation pulses [Menon et al., 1993].

Working memory and effort

The experimental task we used was designed to maximize demands on working memory. Subjects had to remember both the identity and order of the two previously presented stimuli at all times and continuously update this mental record with each subsequently presented stimulus. As noted earlier, these demands correspond closely to the functions of working memory as these have been defined within the cognitive psychological literature. The comparison task that we used was designed to control for as many of the nonworking memory related processes as possible. Thus, it shared with the memory task the need to attend to the visual display, encode and identify each stimulus, compare this to a target kept in memory, and respond to targets with the same frequency as in the memory task. Although the control task did require that subjects keep the target in memory, we assumed that the demands to do this for a single letter that remained constant across all control blocks would be trivial.[5] We interpret the activation observed within the prefrontal cortex, therefore, to be related to the differences in working memory demands between the two tasks.

It might be argued, however, that differences in working memory demands were confounded by differences in difficulty between the two tasks, and therefore in the effort required to perform them. From this view, frontal activation might be related to mental effort, rather than working memory per se. In fact, this is a confound that is present in every study of working memory that has been performed to date. Indeed, the early theories of working memory associated this directly with the idea of effort, arguing specifically that effortful, attention-requiring processes rely on the central capacity of working memory [e.g., Kahneman, 1973]. The relationship between working memory and effort is a long-standing question within the psychological literature and is beyond the scope of this discussion. We would like to point out, however, that by assuming that the mechanisms underlying working memory rely on the prefrontal cortex, it may now be possible, using neuroimaging techniques, to test the idea that effort is directly related to working memory. If the latter is true, then all effortful tasks should activate the prefrontal cortex. Given an appropriately operationalized definition of effort (e.g., limitations of capacity under dual-task conditions), it should be possible to test such claims. Conversely, if "effort" is not directly related to working memory function—that is, it is reflective of some other process or mechanism that is often confounded with working memory function—then it should be possible to dissociate effort from prefrontal activation. In other words, it should be possible to produce activation of the prefrontal cortex in some noneffortful tasks and to design effortful tasks that do not produce activation of the prefrontal cortex.

Regions of activation

Our findings support the idea that the prefrontal cortex becomes engaged when recently presented information must be represented and actively maintained to perform a task. In our task, this involved remembering the identity and sequence of letters and

[5]It is even possible that, over the large number of trials with this consistent target, subjects learned to automate this task. There is extensive evidence for this possibility in the psychological literature [e.g., Shiffrin and Schneider, 1977]. If this was the case, then the control task would have relied even less or not at all on working memory.

produced the greatest activation of the middle and inferior frontal gyri. According to the standard stereotactic atlas that has been used in most neuroimaging studies [Talairach and Tournoux, 1988], this corresponds to Brodmann's areas 45 and 46.[6] This finding concurs with previous studies using PET, most of which have found activation in areas corresponding to Brodmann's area 46 in tasks that involve working memory for nonspatial information. Furthermore, the regions in which we observed maximal activity seem to have been somewhat ventral to the area observed by McCarthy et al. [1993b] in a spatial working memory task. They reported activation in regions corresponding to Brodmann's areas 46 and 9, the latter of which is both rostral and dorsal to areas 45 and 46. Thus, although our study does not directly answer the question of whether information is organized topographically within the prefrontal cortex, when it is considered along with the preliminary findings reported by McCarthy et al. [1993b], it provides suggestive evidence along these lines. Furthermore, and perhaps more importantly, our results suggest that future studies using fMRI may be able to address this question directly, using single-subject designs. We have shown that it is possible to localize regions of activity to specific cortical gyri within individual subjects using this technique. Combined with the capability of testing subjects in multiple conditions, it should be possible to perform within-subject comparisons of the regions activated by tasks in which the information that must be remembered is varied (e.g., letter identity vs. spatial location). Thus, this directly tests the hypothesis that different types of information are represented in different regions of the prefrontal cortex.

Our study did not provide evidence for lateralization of activation. This is in contrast with previous studies [e.g., Paulesu et al., 1993; Sergent et al., 1992] that have shown greater activation in the left than the right frontal cortex for the processing of letters. One reason for our negative finding may be the use of surface coils which, as we referred to earlier (see footnote 4), may have reduced our sensitivity to laterality effects. Current improvements in gradient coils (that increase sensitivity while keeping it homogeneous throughout the brain) should help answer this question. Alternatively, it may be that the areas of activity associated with letters are more anatomically variable (within a given region) in the right than in the left frontal cortex. This could account for the discrepancy between our findings, which used a within-subject design to localize activity, and previous PET studies that used between-subject methods to localize activity. Newer PET methods that permit single-subject designs and the application of between-subject averaging to fMRI data sets should help clarify this issue.

Finally, we should note that, in addition to the inferior and middle frontal gyri, our study also provides evidence of activation in other structures, including the anterior cingulate. Although we found significantly less activation of these structures this may reflect a sampling bias (smaller volumes in the locations scanned), rather than lesser involvement in task performance. Activation of the anterior cingulate, in particular, should not be surprising. This structure has been implicated in attentionally demanding tasks [Bench et al., 1993; Corbetta et al., 1991; Pardo et al., 1990], which may account for its activation in this study. We should note, however, that we did not observe significant activation of regions that have been reported in more explicit verbal processing tasks, such as the word generate task [McCarthy et al., 1993a; Petersen et al., 1989). For the most part, these areas (Brodmann's areas 47 and 10) are more anterior and inferior to the region in which we observed the greatest activation. This difference in localization may be relevant to a distinction between working memory vs. retrieval from long-term memory, or it may reflect a difference in the type of stimuli involved (words vs.

[6]Brodmann's areas form a classification scheme based on the cytoarchitectural characteristics of neocortical structures. It is often assumed that these have functional relevance, which is one reason why they have been used as a reference system for identifying and comparing areas of activation in functional neuroimaging studies. Another advantage of this scheme is that it provides a basis for cross-species comparisons, in which homologies may be greater between cytoarchitectural features than gross anatomy. We should note, however, that the use of Brodmann's areas as a scheme for localization in human neuroimaging studies poses some problems. First, it is not possible to identify directly the cytoarchitectural features of a region of activity in a living human subject. Rather, identification must be done with reference to a standard atlas, which assumes that the relationship between cytoarchitectural regions and structural anatomy is the same across subjects. In fact, this relationship may well show the same considerable degree of variability that is observed in cortical anatomy across subjects. In contrast, with high-resolution techniques such as MRI, it is possible to localize areas of functional activity reliably to specific anatomic structures (e.g., cortical gyri) within individual subjects. Although the functional relevance of anatomic structures remains to be established (at least within prefrontal cortex), this provides a verifiable, and seemingly more reliable, basis for between-subject comparisons. With these considerations in mind, we have reported our results with reference to both anatomic structures (cortical gyri) and standardized stereotactic coordinates and the corresponding Brodmann areas. The latter have been provided specifically to permit comparison with PET studies, most of which use this classification scheme.

letters). These are intriguing questions, and fMRI may provide a new method for answering them in the future.

CONCLUSIONS

The results of this study indicate that it is possible, using conventional MRI equipment in combination with rapid scanning procedures, to observe task-related changes of brain activity in association cortex. These changes can be localized to specific anatomic structures and follow a time course that closely tracks changes in the behavioral task. They also show response characteristics that are similar to those observed in the primary sensory and motor cortex (changes of 2–4% within 4–6 s of behavioral activation). Our findings corroborate findings from PET studies that tasks involving working memory engage the prefrontal cortex. In comparison to these studies, however, we were able to localize areas of activation to specific cortical gyri in individual subjects. Although our results do not answer the question of whether information is organized topographically by type within the human prefrontal cortex, they do suggest that fMRI may provide the means to do so in future studies.

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