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Prefrontal cortex fMRI signal changes are correlated with working memory load

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WE investigated whether a nonspatial working memory (WM) task would activate dorsolateral prefrontal cortex (DLPFC) and whether activation would be correlated with WM load. Using functional magnetic resonance imaging we measured regional brain signal changes in 12 normal subjects performing a continuous performance, choice reaction time task that requires WM. A high WM load condition was compared with a non-WM choice reaction time control condition (WM effect) and a low WM load condition (load effect). Significant changes in signal intensity occurred in the DLPFC, frontal motor regions and the intraparietal sulcus (IPS) in both comparisons. These findings support the role of DLPFC and IPS in WM and suggest that signal changes in DLPFC correlate with WM load.

Key words: Functional MRI; Intraparietal sulcus; Prefrontal cortex; Working memory

Introduction

Working memory (WM) is a cognitive psychological construct that refers to the process of actively holding information 'on-line' and manipulating it in the service of guiding behavior.[1] It is hypothesized to be a temporary store whose contents are continually updated, scanned and manipulated in response to immediate information processing demands. WM is a critical component of normal cognition and is impaired in individuals with neuropsychiatric diseases such as schizophrenia.[2] The anatomical components of the hypothetical neural network underlying WM are not yet well established, but the dorsolateral prefrontal cortex (DLPFC) is thought to play a critical role on the basis of converging lines of evidence from non-human primates and from neuroimaging studies of humans.[3,4] Depending on the nature of the task, the type of material held on-line, and the mode of presentation, different subregions of the DLPFC are believed to maintain a temporary representation of the stimulus through control over reciprocally connected brain regions.[5] Preliminary work in humans suggests that activation of DLPFC and other regions varies with WM load (the amount of information being held on-line).[6] We conducted a study to determine whether a non-spatial WM task would lead to task-related signal changes in the DLPFC as assessed by functional magnetic resonance imaging (fMRI) and whether fMRI signal changes would be correlated with WM load.

We employed a modified version of the Sternberg Item Recognition Paradigm (SIRP)[7] to examine task-related differences in cerebral activity using local variations in blood oxygenation level-dependent (BOLD) contrast as measured by fMRI to provide an indirect measure of regional cerebral perfusion. The SIRP is a continuous performance, choice reaction time task that involves WM. The task requires subjects to memorize a set of digits (targets). They are then presented with single digits and must respond by indicating whether the digit presented is a target (a member of the memorized set) or a foil (not a member of the memorized set). Accurate responses are predicated upon a temporarily stored representation of the targets that must be maintained in WM for the duration of the trial. Sternberg has demonstrated that a linear relationship exists between the number of targets and reaction time (RT), the time needed to indicate whether a presented digit is a target or a foil.[7] We examined regional signal changes in a WM task *vs* a non-WM task by comparing the WM paradigm with a choice RT control condition that minimized WM demands. We also investigated the effect of WM load on regional signal changes by manipulating the number of targets and comparing a high WM load condition with a low WM load condition.

Materials and Methods

Subjects: Twelve normal right-handed male volunteers ranging in age from 25–43 years (mean 34.5 ± 5 years), with no history of psychiatric or neurological disease, were recruited from the hospital staff. Determination of right-handedness was based on a laterality score of ≥ 70 (mean 95.83 ± 8.21) on the Edinburgh Handedness Inventory.[8] Subjects gave informed consent and the experimental protocol was approved by the Committee on Clinical Investigations at Beth Israel Hospital.

Tasks: Experimental tasks were controlled by a Macintosh PowerBook 180c using Macintosh stimulus presentation software (MacStim®). Prior to scanning, subjects practised until their performance indicated that they understood the tasks. They were instructed to respond as quickly and accurately as possible. Stimuli were rear-projected on a screen at the end of the patient gurney. Subjects lay supine in the scanner and viewed the screen through a mirror positioned on the head coil. Subjects responded with fiberoptic thumb triggers in either hand. The triggers were attached to the PowerBook mouse port so that response RT and side (right or left) were recorded. Following scanning, they were asked about the strategies they used to perform the tasks.

In the high WM load condition (5T), subjects were presented with five target digits to remember. This was followed by stimulus trials during which they responded to individual digits that appeared on the screen by pressing with the right thumb (R) if the digit was a target and the left thumb (L) if it was a foil. The low WM load condition (2T) was identical to the 5T condition except that there were only two target digits to remember. In the non-WM control condition (Arrows) subjects responded to the display of arrows pointing right or left by pressing the corresponding trigger.

Conditions were presented repeatedly in a counterbalanced order. Each run of a condition lasted 64 s and included a 10 s pause at the beginning for instructional prompts and presentation of targets during which no scanning took place. Each run consisted of 20 stimulus trials of either digits or arrows. For half the trials, the correct response was a R response and for the other half, a L response. Each trial lasted 2750 ms including a random interstimulus interval which ranged from 150 to 1000 ms. The number of repetitions of the three conditions was either five (seven subjects, total experiment time 16 min) or seven (five subjects, total experiment time 22 min 24 s). One subject participated twice, with five and seven repetitions, to examine the effect of adding runs on regional signal changes (only the initial experiment was included in the group results).

Performance measures of RT and response accuracy were subject to repeated measures analyses of variance. RTs from incorrect trials were excluded. Subjects given five and seven repetitions were combined for comparisons of accuracy and RT between conditions. They were analyzed separately for comparisons of RT between runs, within conditions and of RT for R *vs* L responses within conditions. A statistic was considered to be significant if its exact two-tailed probability value was ≤ 0.05.

Imaging: Images were obtained with a whole-body 1.5-T Siemens Medical System Magnetom MR modified for echo-planar imaging (Erlangen, Germany). A circularly polarized head coil was used for excitation/receiving. Tape and cushioning minimized head motion. A three-dimensional magnetization prepared, rapid acquisition gradient echo (MPRAGE) pulse sequence was acquired for anatomical localization (1.25 × 1.25 × 2.0 mm voxel size). Functional images were acquired for each condition with a gradient-echo, echo-planar imaging pulse sequence (TE: 64 ms, TR: 2.16 s, 25 acquisitions, 240 mm FOV) with eight contiguous 8 mm axial slices that covered most of the frontal lobes (3.75 × 1.875 × 8.0 mm voxel size).

The first three acquisitions of each run were eliminated to attain steady state magnetization. Raw T2* weighted images were smoothed with a Gaussian

Table 1. Regions that consistently showed significant task-related signal changes in the 5T *vs* Arrows (A) and 5T *vs* 2T comparisons

	DLPFC			SMA			Premotor			Motor			IPS		
	R	L	B	R	L	B	R	L	B	R	L	B	R	L	B
5T *vs* A	4	0	7	1	7	4	0	6	6	0	6	6	2	4	6
5T *vs*2T	4	0	5	1	6	2	0	9	0	1	3	3	1	2	4

Numbers indicate subjects who showed signal changes in each region divided by laterality: unilateral right (R), unilateral left (L) and bilateral (B). DLPFC, dorsolateral prefontal cortex; SMA, supplementary motor area; IPS, intraparietal sulcus.

filter (element size: 5). Regions with task-related signal changes were detected using cross-correlation analyses comparing voxel intensities to an idealized boxcar waveform.[9] A Bonferroni-corrected significance level of $p < 7.63 \times 10E\text{-}8$ ($p < 0.01/131{,}072$) the denominator is based on the number of voxels per image (16 384) multiplied by the number of slices (8) was used to identify voxels with significant positive task-related changes. Comparisons of signal intensity during the high WM load *vs* the low WM load conditions (5T *vs* 2T) and the high WM load *vs* the control conditions (5T *vs* Arrows) were performed. Colorized functional images were co-registered with the anatomical images. Regions with significant voxels were identified with reference to standard atlases. The DLPFC was defined as the middle frontal gyrus and bordering superior and inferior frontal sulci which presumably include portions of Brodmann's Areas 9 and 46.[10]

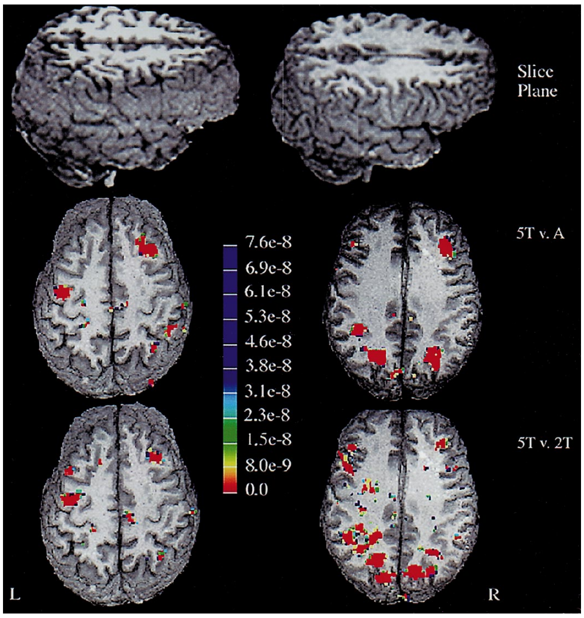

FIG. 1. Brain slices of two representative subjects illustrating significant task-related signal changes in the DLPFC in the 5T *vs* Arrows and 5T *vs* 2T comparisons.

Results

Performance: All subjects performed the tasks accurately (95–99.98% correct responses). There were no significant differences in number of errors between conditions ($F(2,11) = 1.97$, $p > 0.10$). Mean RT increased significantly as a function of condition from Arrows to 2T to 5T as indicated by a planned linear contrast ($F(1,11) = 205.31$, $p = 0.0001$). There was no main effects of runs on RT for runs in any of the three conditions (i.e. RTs did not change as a function of repetition: there was neither a fatigue nor practice effect). While there was no main effect for side of response (R *vs* L) on RT in the Arrows condition ($F(1,6) = 0.645$, $p = 0.4585$ for five repetitions, $F(1,4) = 0.001$, $p = 0.9738$ for seven repetitions) in both the 5T and 2T conditions, R responses (to targets) were significantly faster than L responses (to foils) (5T: $F(1,6) = 33.158$, $p = 0.0012$ for five repetitions, $F(1,4) = 43.417$, $p = 0.0027$ for seven repetitions; 2T: $F(1,6) = 9.790$, $p = 0.0352$ for five repetitions, $F(1,4) = 55.320$, $p = 0.0007$ for seven repetitions).

Subjective strategy: Ten subjects reported that they repeated the targets continuously to themselves (covert verbal rehearsal) for the 5T condition. Two subjects reported using both covert verbal rehearsal and visual imagery. Subjects had difficulty describing their strategies in the 2T and Arrows conditions.

Regional signal change: The subject who participated twice showed overlapping regions of signal change in five *vs* seven runs. Since there were no changes in RT as a function of repetition and the pattern of regional signal change was not affected by the number of repetitions, data from subjects with five and seven runs was considered together. Table 1 presents the regions that consistently showed significant signal intensity changes in the two comparisons, 5T *vs* Arrows and 5T *vs* 2T, and the number of subjects in whom these changes were observed. Consistency was defined as regional signal changes observed in eight or more subjects in either comparison. This pattern of signal change was observed in both comparisons, though in the 5T *vs* 2T comparison regional signal changes were observed in fewer subjects. Figure 1 shows horizontal slices in two representative subjects demonstrating overlapping regions of DLPFC signal changes in both comparisons.

Discussion

While there was some individual variability in both the pattern and lateralization of findings across subjects, several regions in the frontal and parietal lobes consistently showed significant task-related fMRI signal changes. These were: the DLPFC, the supplementary motor area (SMA), lateral premotor and primary motor cortex and the intraparietal sulcus (IPS). The DLPFC and the IPS are densely interconnected and may be components of a distributed neural network for WM.[3] The unique contributions of each component are still speculative. Signal changes in the DLPFC may reflect its role in maintaining information in WM.[11] The IPS may play a role in directed attention and visuo-motor integration which contribute to the selection of an appropriate motor response to behaviorally relevant visual cues.[3] Premotor cortex, SMA and primary motor cortex signal changes are consistent with their role in planning, generating and executing motor responses.

The DLPFC was preferentially activated on the right. None of the subjects showed unilateral left DLPFC signal changes and four showed unilateral right DLPFC signal changes. With one exception, in all of the cases of bilateral DLPFC signal changes, there was a greater spatial extent of signal changes on the right. The right-sided predominance of DLPFC signal changes was not anticipated given that materials were verbal (digits) and that subjects reported that they used covert verbal rehearsal to maintain the digits on-line. It is consistent, however, with previous neuroimaging studies of spatial WM tasks.[12,13] Non-spatial WM tasks for non-verbal materials (e.g. abstract designs, shapes) have activated either predominantly right[14] or bilateral DLPFC.[13] A WM task for verbal materials (digits) also produced bilateral DLPFC signal changes.[4] In addition to reflecting the nature of the materials held on-line, the laterality of DLPFC signal changes may reflect task demands including the deployment of attentional resources. The right DLPFC is thought to play an asymmetric role in sustaining attention to sensory input.[15]

fMRI signal changes in DLPFC were present in 11 of 12 subjects in the high load *vs* the 'no load' or control condition. They were still present, but in fewer subjects (9 of 12) in the high load *vs* low load conditions. We hypothesize that the significant task-related DLPFC signal increases in the high *vs* low WM load condition reflect the increase in WM load. With the exception of the number of target digits that subjects were required to represent in WM, all other aspects of the high and low WM conditions were identical. While it is true that the high WM load condition is a more difficult task than the low WM condition as reflected in the increased RT, performance was virtually error free and not different across conditions. We hypothesize that it is the process of interest (increased WM load) that is the basis of the increased difficulty, the increased RT and the increased signal changes. We speculate that the increased DLPFC signal changes in the high *vs* low WM load condition reflects the greater demands of comparing the presented stimulus to five rather than two target digits and of actively maintaining five rather than two targets on-line. This is in agreement with Sternberg's attribution of the linear increase in RT with each added target to the greater demands on a memory search process while other components of the task including stimulus decoding, response selection, and motor output remained constant.[7]

Although the motor responses required (R and L trigger presses) were identical across conditions, motor regions showed signal changes, including in primary motor cortex. This suggests that the motor components of the task are neither discrete nor easily separated from the cognitive components and that they may not 'subtract out', given a simpler control task with identical motor response demands. The increased signal in these areas with increased WM load may reflect a specific contribution required or a more general arousal of network components as WM demands increase.

Although all of our subjects were right-handed, there were no RT differences between R and L responses in the Arrows condition, suggesting that manual superiority in and of itself did not significantly affect RT. During 2T and 5T conditions, however, R responses were significantly faster. This may reflect that for targets, which required a R response, the comparison of the stimulus to the internal representation could be terminated when a match was found, unlike foils where the stimulus did not match and the search of the mental representation had to be exhaustive. However, this explanation runs contrary to evidence presented by Sternberg that RTs are not affected by the serial order of the targets, that responses occur considerably faster than would be possible if a self-terminating serial search strategy based on verbal rehearsal were used, and that the slopes for RT by number of targets were identical for probes and foils. He suggested that the task involves an exhaustive search and that regardless of self-report, the covertly rehearsed names are unlikely to be the only form in which the targets are represented and compared with the stimuli.[16] While rehearsal may be important to maintain targets on-line, the search and comparison of WM contents to presented stimuli may be independent of rehearsal and may rely on processes not accessible to conscious experience.

The decreased RT for R responses was accompanied by increased frequency and spatial extent of motor region signal changes on the left. Again, this is unlikely to reflect simple right manual superiority which was constant across conditions. It could be related to the faster RT for R responses (although the relationship between RT and signal intensity is likely complex since subjects showed increased signal intensity in motor regions in 5T *vs* 2T in spite of longer mean RTs). The asymmetry might also be related to the fact that R responses were used to signal target rather than foil detection. Targets may be more salient stimuli than foils and subjects may have pressed harder for R responses, especially with increased WM demands.

Conclusion

The current findings are consistent with previous studies in demonstrating DLPFC and IPS involvement in WM and suggest that signal changes in the DLPFC correlate with WM load. This study also introduces the SIRP as a promising paradigm in the study of the neuranatomical basis of WM. Future studies that manipulate material type and task demands may help to delineate the unique contributions to task performance of brain regions that exhibited task-related signal changes in this study. This paradigm should also be readily adaptable to the study of pathological conditions in which WM is deficient such as schizophrenia.

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General Summary
We measured regional brain activity using fMRI as normal subjects performed a task of working memory (WM). Working memory refers to the process of actively holding information 'on-line' in the mind and using that information to guide behaviour. When a WM task was compared with a non-WM control task the following brain regions showed increased activation: the dorsolateral prefrontal cortex (DLPFC), frontal motor regions and the intraparietal sulcus. The same regions showed increased activity when we compared a high load WM task (subjects hold five items in WM) with a low load WM task (subjects hold only two items in WM). Our findings add to the evidence that the DLPFC plays a role in maintaining information in WM and suggest that DLPFC activation increases as a function of WM load (the amount of information held on-line.