

Distribution of Cortical Activation During Visuospatial *n*-Back Tasks as Revealed by Functional Magnetic Resonance Imaging

Human neuroimaging studies conducted during visuospatial working memory tasks have inconsistently detected activation in the prefrontal cortical areas depending presumably on the type of memory and control tasks employed. We used functional magnetic resonance imaging to study brain activation related to the performance of a visuospatial *n*-back task with different memory loads (0-back, 1-back and 2-back tasks). Comparison of the 2-back versus 0-back tasks revealed consistent, bilateral activation in the medial frontal gyrus (MFG), superior frontal sulcus and adjacent cortical tissue (SFS/SFG) in all subjects and in six out of seven subjects in the intraparietal sulcus (IPS). Activation was also detected in the inferior frontal gyrus, medially in the superior frontal gyrus, precentral gyrus, superior and inferior parietal lobuli, occipital visual association areas, anterior and posterior cingulate areas and in the insula. Comparison between the 1-back versus 0-back tasks revealed activation only in a few brain areas. Activation in the MFG, SFS/SFG and IPS appeared dependent on memory load. The results suggest that the performance of a visuospatial working memory task engages a network of distributed brain areas and that areas in the dorsal visual pathway are engaged in mnemonic processing of visuospatial information.

Introduction

The neuronal mechanisms of working memory, i.e. the temporary storage of information that is processed in a range of cognitive tasks (Baddley, 1986), have been extensively studied in non-human primates and more recently in humans. Evidence from animal lesion studies and electrophysiological single cell recordings in primates (for reviews see Goldman-Rakic, 1987; Fuster, 1989; Funahashi and Kubota, 1994) indicates that the dorsolateral prefrontal cortex (PFCdl) is a central area for neuronal processing of visuospatial working memory. Single neurons in and around the principal sulcus exhibit spatially selective delay-related changes in their firing rate and have been suggested to represent the neuronal substrate for working memory processing (e.g. Fuster and Alexander, 1971; Niki, 1974; Funahashi *et al.*, 1989; Carlson *et al.*, 1997). Memory-related neuronal activity has also been recorded in brain areas outside of the aforementioned prefrontal cortical areas, e.g. in the anterior temporal cortex (Miyashita and Chang, 1988), primary somatosensory cortex (Zhou and Fuster, 1996) and in the parietal cortex (Gnadt and Andersen, 1988; Koch and Fuster, 1989). However, these areas may have different roles in memory task performance. For instance, the delay-related single neuron activity in the posterior parietal cortex has been shown to be related to the type of movement being planned (Snyder *et al.*, 1997).

Several laboratories have employed event-related brain potential recordings, positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) to study the organization of visuospatial working memory processing in the human brain (e.g. Ruchkin *et al.*, 1992; Jonides *et al.*, 1993;

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McCarthy *et al.*, 1994, 1996; Rämä *et al.*, 1995, 1997; Smith *et al.*, 1995; Courtney *et al.*, 1996). These studies and some more recent investigations (Belger *et al.*, 1998; Courtney *et al.*, 1998) have not, however, yielded uniform results.

In humans, visuospatial working memory related brain activation has been detected in many frontal cortical areas (e.g. Jonides *et al.*, 1993; Smith *et al.*, 1995, 1996; McCarthy *et al.*, 1994, 1996; Courtney *et al.*, 1996, 1998; Belger *et al.*, 1998) but only in some of these studies was activation found in the middle frontal gyrus (MFG) (McCarthy *et al.*, 1994, 1996; Smith *et al.*, 1996; Belger *et al.*, 1998) in areas presumably corresponding to Brodmann's areas (BAs) 46 and 9 (Rajkowska and Goldman-Rakic, 1995). Other frontal areas that have been reported to be activated in this context include the superior frontal sulcus (SFS) and the superior frontal gyrus (SFG) (Courtney *et al.*, 1996, 1998), the premotor area (Jonides *et al.*, 1993; Smith *et al.*, 1995) and the inferior frontal gyrus (IFG) (Jonides *et al.*, 1993; Smith *et al.*, 1995, 1996). In studies in which even the more posterior parts of the brain were imaged, brain activation was detected in the intraparietal sulcus (IPS) or in other posterior parietal areas (Jonides *et al.*, 1993; Courtney *et al.*, 1996; Belger *et al.*, 1998) and in occipital visual areas (Jonides *et al.*, 1993; Courtney *et al.*, 1996; Smith *et al.*, 1995).

In addition to the relation of BA 46/9 to visuospatial mnemonic processing, activation in this cortical area in the human brain has also been associated with verbal working memory (Petrides *et al.*, 1993; Cohen *et al.*, 1994; Mellers *et al.*, 1995; Braver *et al.*, 1997), and object working memory processing (Courtney *et al.*, 1996, 1997; McCarthy *et al.*, 1996).

The outcome of functional brain imaging studies concerning visuospatial working memory mechanisms depend critically on the type of memory and control tasks used in the studies. Recently, an *n*-back task paradigm employing a sequential letter task with delays was employed in human neuroimaging studies (Smith *et al.*, 1996; Braver *et al.*, 1997; Cohen *et al.*, 1997). Since *n*-back tasks have no intertrial intervals they require continuous working memory processing and allow the comparison of the effects of different load levels (Braver *et al.*, 1997) on cortical activation patterns. Cohen *et al.* (1997) modified the *n*-back task by increasing the delay time; this allowed them to study the dynamics of brain activation during the different phases of the memory task.

In the present study, we used fMRI (Kwong *et al.*, 1992) to detect brain areas activated in human subjects performing a visuospatial version of the *n*-back task with two load levels and a 0-level. We were particularly interested in visualizing the brain areas displaying visuospatial working memory related activation. The imaged volume in the present study included the whole cerebrum (excluding pons and cerebellum). Only the mnemonic requirements are varied and all other features of the *n*-back task (e.g. number of stimuli, number and type of responses) remain

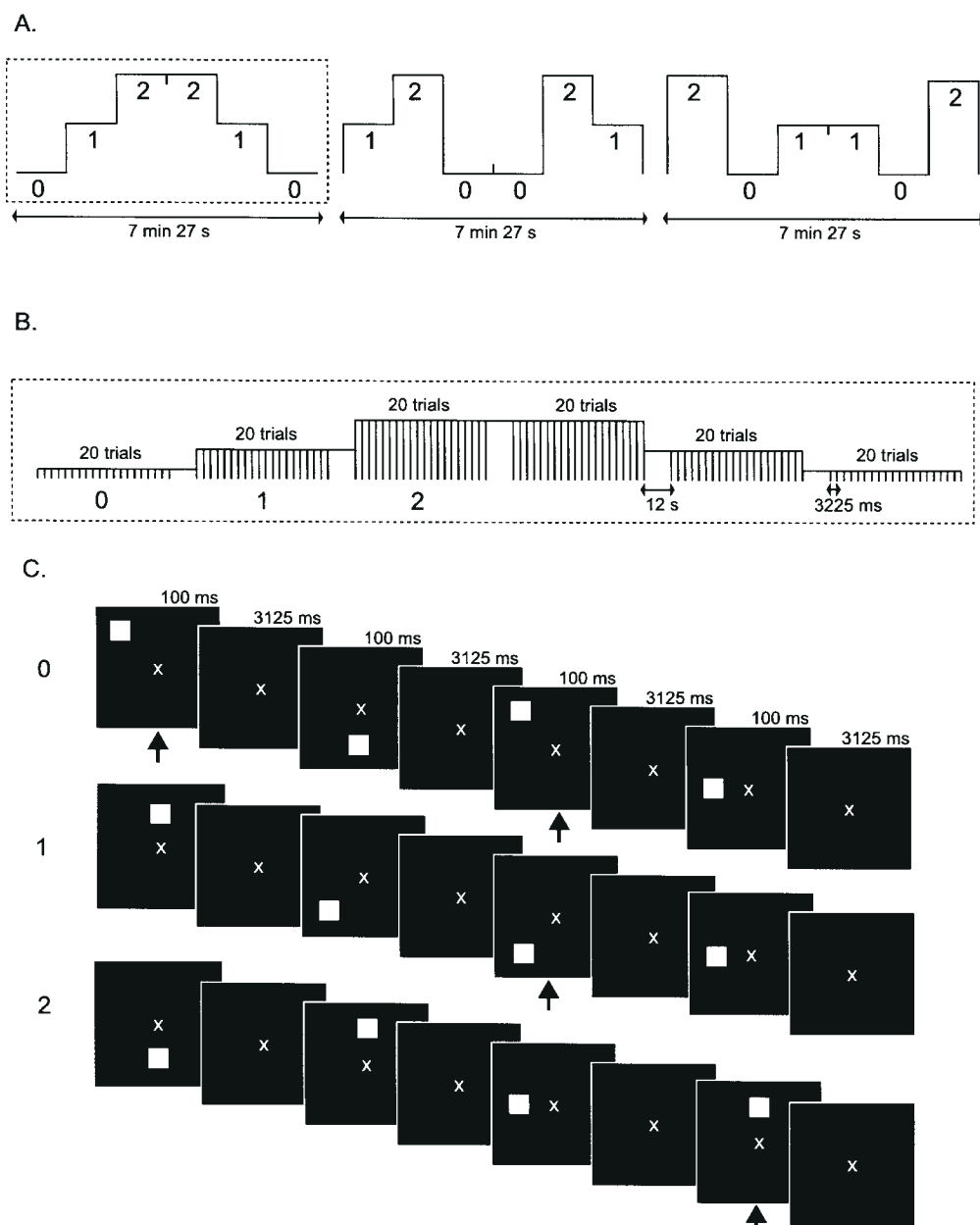


Figure 1. Illustration of the fMRI session of the visuospatial *n*-back task. (A) The temporal order of the 0-back, 1-back and 2-back memory tasks in each of the three consecutive experiments of the session. The tasks (0, 1 and 2) with different memory loads were presented in a counterbalanced order. (B) Acquisition of the 20 image sets during the performance of each task condition in the first experiment of the session. Each task consisted of 20 trials: 20 scans were taken during the performance of the 20 trials; 12 s refers to the intertask interval and 3225 ms to the duration of the delay period. (C) Illustration of four trials in the visuospatial 0-back, 1-back and 2-back tasks. In the 0-back task, the subject pressed the left button of the mouse whenever the stimulus was in the predetermined location (arrow). In the 1-back task the subject pressed the left button whenever the stimulus was in the same location as the previous one (arrow), and in the 2-back task whenever the stimulus was in the same location as that presented two back (arrow). In all other trials the subject pressed the right button. 100 ms refers to the duration of each stimulus and 3125 ms to the remaining delay period.

similar at the different load levels. Thus, this task paradigm should be adequate for studying working memory related neuronal processing, and the brain areas found to be activated when different load levels are compared should reflect only working memory related, load-dependent activation.

Materials and Methods

Subjects

Seven healthy right-handed subjects (four males, three females, age 17–23 years, mean 21.1) participated in the experiment. The subjects gave informed consent about their participation. Before the fMRI, the *n*-back

task was explained to the subjects and they were allowed to practice one block of 120 trials in which 20 trials of each task condition were presented twice in a counterbalanced order, as in the real experiment. The data files of the practice tasks, and thus the order of the presentation of the cues, were different from those used during the fMRI. The study protocol was approved by the ethical committee of the Department of Radiology at the Helsinki University Central Hospital.

The Visuospatial *n*-Back Task

fMRI was conducted during the performance of a visuospatial *n*-back task with three load levels (Fig. 1). The visual stimuli were white squares ($1.8^\circ \times 2.3^\circ$ of visual angle) presented randomly in one of eight possible spatial

locations on a dark screen with a fixation cross in the middle of it. The visual stimuli were delivered onto a semitransparent screen subtending approximately $16^\circ \times 23^\circ$ of visual angle. The subjects viewed the stimuli through a mirror positioned on the head-coil. The distance of the subject's eyes from the mirror was ~8–12 cm. The locations of the stimuli were distributed around the center of the screen and subtended a visual angle of $5\text{--}7.5^\circ$ from the fixation cross. The presentation of the stimuli was controlled by a computer program (Neuro Scan, Inc.) which also triggered the MR image acquisition and collected behavioral data consisting of information concerning responses (correct, incorrect, misses) and reaction times. The stimuli were presented for 100 ms with an interval of 3225 ms (delay period). During this delay period only the central fixation cross was visible on the screen. The subject responded after each stimulus by pressing with the right index or middle finger the left or right button respectively of a mouse with fiberoptic connections to the computer. In the *0-back task*, the subject was instructed to press with the right index finger the left button whenever the stimulus was in a predetermined location (Fig. 1C). When the stimulus occurred in any other location the subject was instructed to press with the right middle finger the right button. In the *1-back task*, the subject pressed the left button whenever the stimulus occurred in the same location as the previous one. If the stimulus was in any other location the subject was instructed to press the right button. In the *2-back task*, the subject was instructed to press the left button whenever the stimulus was in the same location as the one presented two back. If in any other location, the subject was instructed to press the right button. At each load level ~33% of the trials were 'match' trials and required a left button press. Subjects were instructed to blink normally but to maintain visual fixation of the central cross throughout the task performance and to move their eyes only during the intertask interval.

Each task condition (0-back, 1-back and 2-back) consisted of 20 trials. The acquisition of a set of 16 transaxial slices was started simultaneously with the presentation of the cue. Thus 20 image sets of 16 slices were obtained during the performance of one task condition (Fig. 1B). During one experiment, each task condition was presented twice in a counterbalanced order. Thus, during one experiment a time series of 120 sets of 16 axial slices was acquired. The type of task to be started (whether 0-back, 1-back or 2-back) was indicated at the beginning of each task condition with a figure consisting of one, two or three white crosses presented on the screen. One cross signified the 0-back task, two crosses the 1-back task and three crosses the 2-back condition. The duration of the instruction figure was 1 s followed by a 1 s interval before the task started. At the end of each task condition there was a 10 s interval during which the screen remained blank. This intertask interval was introduced to allow a recovery time for the cerebral blood flow from the effects of the previous task. The duration of one trial was 3225 ms and the duration of each *n*-back task was thus 64.5 s (20×3225 ms). One experiment of 120 scans including the five 12 s intertask intervals lasted 7 min 27 s. The experiment was run three times during the same imaging session, and thus the data consisted of three blocks of 120 scans, each one of them representing the brain activation during the performance of the different memory task loads presented in a counterbalanced order: I, 0-1-2-2-1-0; II, 1-2-0-0-2-1; III, 2-0-1-1-0-2 (Fig. 1A).

After the fMRI, the subjects were asked to fill in a questionnaire and evaluate the level of difficulty of the different task conditions using a five-point scale (1 = very easy, 2 = easy, 3 = rather difficult, 4 = difficult, 5 = very difficult) and to describe whether they had used any strategies in their performance.

Functional MR Imaging

All MR images were acquired with a Siemens Vision (Erlangen, Germany) 1.5 T scanner equipped with EPI capability. The head of the subject was stabilized with a moldable vacuum cushion to minimize effects of movement during imaging. fMRI measurements were performed using a gradient-echo EPI sequence (16 axial slice planes with a thickness of 5 mm each, 0.5 mm gap between slices, field of view 256 mm, 64×64 matrix size, $T_E = 76$ ms, $T_R = 3225$ ms, flip angle 90°). The slices of the functional image set extended from the superior edge of the brain down to the basal parts of the cerebrum. The slices were parallel to a line from the base of the occipital lobe to the base of the frontal lobe in midline

sagittal localizer image. We also acquired a T_1 -weighted 3D-MPRAGE structural image set (180 sagittal slice planes with thickness of 1 mm without gap, field of view 256 mm, 256×256 matrix size, $T_R = 9.7$ ms, $T_E = 4$ ms, $T_1 = 20$ ms, flip angle 10°). A pixel-by-pixel two-tailed Kolmogorov-Smirnov test – a non-parametric analysis that does not contain *a priori* assumptions about the underlying distributions of the data – was performed between images belonging to different task conditions (2-back versus 0-back task, 1-back versus 0-back task, and 2-back versus 1-back task). Both tails of the Kolmogorov-Smirnov test were inspected to discriminate activation from inhibition. The first two volumes of the 16 slices from the beginning of each task condition were excluded from analysis, allowing hemodynamic responses to stabilize. Voxels with *P*-values equal or less than 10^{-6} (corresponding *P*-value < 0.01 after Bonferroni correction for 10 000 voxels which roughly corresponds to the total number of brain voxels in the imaged volume) were considered to show a statistically significant signal change. The brain areas with voxels reaching the aforementioned statistical significance level were considered statistically significant activation areas. Statistical parameter maps were co-registered with the three-dimensional structural image sets using location and orientation information in the image file headers and nearest neighbor interpolation. This allowed the reconstruction of the coronal, transaxial and sagittal slices containing both the structural and functional information. Both the statistical parameter maps and structural image sets were transformed into Talairach space (Talairach and Tournoux, 1988). Registration and interpolation were performed using Matlab (Mathworks Inc., USA), statistical analysis using XDS (Timothy L. Davis, USA) and Talairach transformations using MEDx (Sensor Systems Inc., USA) software. The Talairach coordinates of the significantly activated voxels were determined. The anatomical location and the corresponding Brodmann's area of the significantly activated brain areas (two or more significantly activated voxels) were determined by using the Talairach coordinates of the center of the maximum activation, and by finding the corresponding area in the Talairach and Tournoux brain atlas (1988) and comparing this location with the anatomical brain atlas of Damasio (1995). The number of significantly activated voxels was counted in each hemisphere in the areas which were activated in all subjects. The voxels were counted from the image sets which were in the Talairach space. An activation was considered bilateral when significantly activated voxels were detected in corresponding anatomical locations in both hemispheres after the anatomical locations had been determined as explained above.

Statistical analyses

The reaction times in the 0-back, 1-back and 2-back tasks were analyzed using repeated measures of analysis of variance (ANOVA). If task had a significant effect on the reaction times ($P < 0.05$), a *post hoc* analysis was performed using the Bonferroni multiple comparisons test. The number of incorrect responses and the subjective evaluation points of task difficulty were analyzed using Friedman's non-parametric repeated-measures test; if there was a significant task effect on the number of mistakes or on the evaluation points ($P < 0.05$) a *post hoc* analysis was performed with Dunn's multiple comparison test. The number of significantly activated voxels was counted for the activation foci which were bilaterally activated and compared between the two hemispheres using the Wilcoxon matched-pairs signed-ranks test.

Results

Behavioral Performance

The mean and SEM reaction times for the three task conditions are illustrated in Figure 2A. ANOVA revealed a significant effect of load on the reaction times [$F(2,6) = 30.32$, $P < 0.0001$]. A *post hoc* analysis showed that both the 1-back and 2-back tasks had significantly longer reaction times than the 0-back task (1- versus 0-back task, $t = 3.36$, $P < 0.05$; 2-back task versus 0-back task, $t = 7.76$, $P < 0.001$) and that the 2-back task had longer reaction times than the 1-back task ($t = 4.401$, $P < 0.001$). The subjects made very few incorrect responses in all task conditions. The

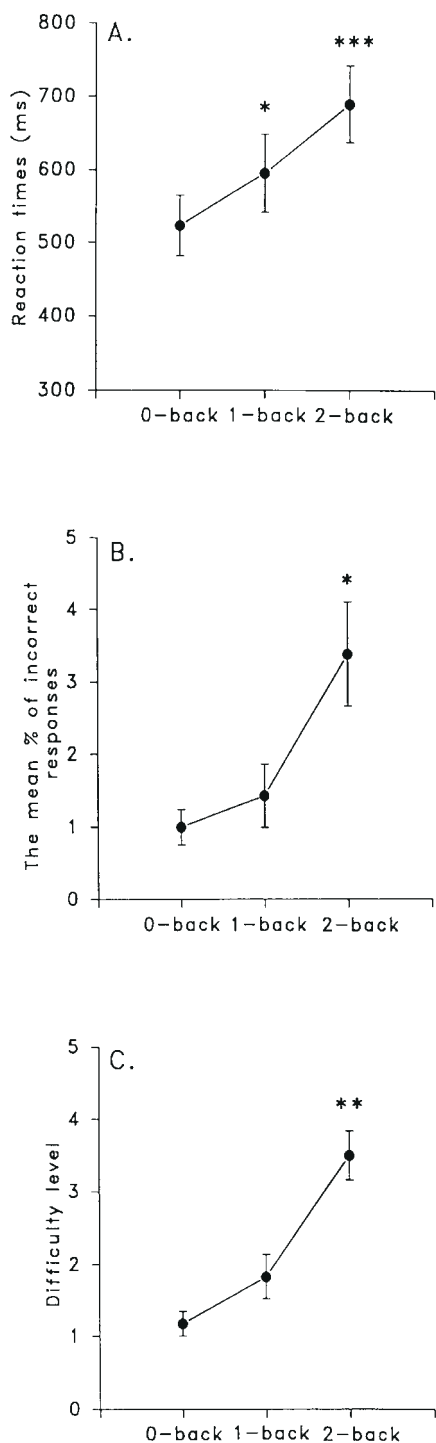


Figure 2. (A) The mean reaction times in the 0-back, 1-back and 2-back tasks. (B) The mean percentages of incorrect responses in each task condition with different memory loads. (C) The mean of the scores given by the subjects in the evaluation of the difficulty level of the three task conditions. Vertical bars indicate SEMs. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.)

mean percentages and SEMs of incorrect responses for the three different tasks are illustrated in Figure 2B. ANOVA showed, however, that there was a significant task effect on the number of incorrect responses ($F = 9.36$, $P < 0.005$). The subjects made significantly more mistakes in the 2-back than in the 0-back task ($P < 0.05$), whereas the differences in the number of mistakes

between the 1-back and the 0-back tasks as well as between the 2-back and the 1-back tasks were not statistically significant.

Subjective Evaluation of Task Difficulty

Data of the subjective evaluation of the task performance were available for six subjects. On a five-point scale all these subjects evaluated the 0-back task as either very easy ($n = 5$) or easy ($n = 1$). Five subjects evaluated the 1-back task as very easy or easy and one subject as rather difficult. The 2-back task was evaluated as either easy ($n = 1$), rather difficult ($n = 1$) or difficult ($n = 4$). No subject described the 2-back task as very difficult. The subjects did not report having used verbal or other types of strategies. They expressed, for example, that they had kept the location in mind or attended to the location. Figure 2C illustrates the means and SEMs of the subjective evaluation points. There was a significant task effect on the subjective evaluation of the difficulty level ($F = 11.27$, $P < 0.0001$). The 2-back task was evaluated as being more difficult than the 0-back task ($P < 0.01$). There was no statistically significant difference between the evaluation of the 1-back and 0-back tasks.

fMRI Results

2-Back versus 0-Back Task Comparison

Table 1 presents the brain regions showing significant signal intensity changes in the comparison between the 2-back and 0-back tasks. Bilateral activation in the middle frontal gyrus (MFG) was found in all subjects (Fig. 3). According to the Talairach and Tournoux (1988) map this area includes portions of BA 46 and 9. Another area in the prefrontal cortex was also consistently activated bilaterally in all subjects. This activation was located in the superior frontal sulcus (SFS) or in the adjacent superior frontal gyrus (SFG) (Fig. 4). This region is labelled SFS/SFG in the present study and includes parts of BAs 6 and 8. In the 2-back versus 0-back comparison, another area in the SFG was also bilaterally activated in three subjects and in the left hemisphere in four. This area is more medial to the aforementioned SFS/SFG and is labelled SFG/FGd (Fig. 4) and presumably also corresponds to BAs 6 and 8. In five subjects activation was also detected in the inferior frontal gyrus (IFG), near or in the inferior frontal sulcus (IFS). This activation is labelled IFG/IFS and corresponds to BAs 45 and 47. In five subjects activation was detected in the frontal polar (FPole) cortex, corresponding to BA 10. In five subjects activation was detected in the precentral gyrus (PreCG), corresponding to BA 6. In the parietal cortex, an area in or adjacent to the intraparietal sulcus (IPS) was bilaterally activated in six subjects and unilaterally in one (Fig. 5). The Brodmann's areas corresponding to this region presumably include portions of areas 40 and 7. Significant activation was also detected in other posterior parietal areas, including the precuneus (six subjects), the superior parietal lobule (BA 7) (four subjects), and the inferior parietal lobule including the angular gyrus and the supra-marginal gyrus (BAs 39 and 40) (six subjects). In all but one subject, activation was found in the occipital visual association areas. The activation was located in the lateral occipital gyrus (LOG), and in the fusiform and lingual gyrus (FG and LG respectively), corresponding to BAs 18 and 19. These areas are shown together in Tables 1 and 2 and labelled LOG/FG/LG. Less consistently, activation was detected in the insula (frontal operculum). In all subjects activation was also detected in subareas of the cingulate cortex in the 2-back versus 0-back task comparison. Bilateral activation in the anterior cingulate cortex

Table 1

Brain areas and their mean Talairach coordinates in which significantly activated voxels were detected in the comparison between 2-back versus 0-back visuospatial memory tasks. The results are shown for each subject and both hemispheres (R/L)

Area	BA	Talairach coordinates			1	2	3	4	5	6	7
		x	y	z	R/L	R/L	R/L	R/L	R/L	R/L	R/L
MFG	46/9	38	23	31	×	×	×	×	×	×	×
		-37	32	32	×	×	×	×	×	×	×
SFS/SFG	6/8	18	3	58	×	×	×	×	×	×	×
		-23	14	51	×	×	×	×	×	×	×
SFG/FGd	6/8	2	10	54	-×	-×	×	-×	×	-×	×
		-9	10	55							
IFG/IFS	45/47	37	14	29	--	-×	×	×	×	×	--
		-43	17	27							
Fpole	10	34	53	10	--	-×	×	×	×	×	--
		-26	49	11							
PreCG	6	37	-6	49	--	-×	×	×	×	×	--
		-44	-4	40							
PreCun	7	3	-68	46	×	×	-×	×	×	×	--
		-4	-64	45							
SPL	7	8	-58	65	-×	--	-×	--	×	×	--
		-13	-63	57							
	40/7	29	-59	45	×	×	×	×	×	×	-×
		-35	-58	45							
SMG/AG	40/39	41	-51	33	×	×	×	--	×	×	-×
		-45	-54	40							
LOG/FG/LG	18/19	25	-74	27	--	×	×	×	×	×	×
		-22	-75	22							
CingC											
Anterior	24/32	2	14	40	-×	×	×	×	-×	×	×
		-3	11	44							
Posterior	23/31	6	-51	29	-×	-×	×	--	-×	-×	×
		-5	-50	23							
Insula	Fr.Op.	34	17	3	-×	×	×	×	--	--	--
		-36	11	6							

MFG, medial frontal gyrus; SFS/SFG, superior frontal sulcus/superior frontal gyrus; SFG/FGd, superior frontal gyrus/dorsal frontal gyrus; IFG/IFS, inferior frontal gyrus/inferior frontal sulcus; Fpole, frontal pole; PreCG, precentral gyrus; PreCun, precuneus; SPL, superior parietal lobule; IPS, intraparietal sulcus; IPS, intraparietal sulcus; SMG/AG, supramarginal gyrus/angular gyrus; LOG/FG/LG, lateral occipital gyrus/fusiformgyrus/lingualgyrus; CingC, cingulate cortex.

(BA 24/32) was detected in three subjects and a unilateral activation in four subjects. In one subject bilateral activation was found in the posterior cingulate cortex (BA 23/31), whereas the activation was unilateral in five subjects.

Lateralization of Activity in the 2-Back versus 0-Back Task Comparison

The number of significantly activated voxels in the IPS was greater in the right than left hemisphere in the 2-back versus 0-back comparison [$t(7) = 26.5$, $P < 0.05$] (Fig. 6). In MFG and SFS/SFG, in which consistent, bilateral activation was detected, the difference between the number of significantly activated voxels in the two hemispheres did not reach significance [MFG: $t(6) = 1.00$, $P > 0.05$; SFS/SFG: $t(7) = 13.00$, $P > 0.05$] (Fig. 6).

1-Back versus 0-Back Task Comparison

The comparison between the 1-back and 0-back tasks resulted in the detection of significant activation only in a few brain areas listed in Table 2. There was a strong effect of load on all those cortical areas which were consistently activated in all subjects in the 2-back versus 0-back task comparison (areas MFG, SFS/SFG and IPS). There was no significant activation in any of the subjects in the MFG. In one subject activation was detected in the SFS/SFG bilaterally and in two subjects unilaterally on the left side in the SFG/FGd. Activation in the Fpole was detected unilaterally in four subjects. In the IFG/IFS, activation was detected unilaterally in the left hemisphere in two subjects. No

Table 2

Brain areas and their mean Talairach coordinates in which significantly activated voxels were detected in the comparison between 1-back versus 0-back visuospatial memory tasks. The results are shown for each subject and both hemispheres (R/L)

Area	BA	Talairach coordinates			1	2	3	4	5	6	7
		x	y	z	R/L	R/L	R/L	R/L	R/L	R/L	R/L
MFG	46/9				--	--	--	--	--	--	--
SFS/SFG	6/8	14	4	56	--	--	--	--	--	×	×
		-32	-4	62							
SFG/FGd	6/8	-8	-5	55	--	--	--	-×	--	-×	--
IFG/IFS	45/47	-38	34	-7	--	--	-×	--	--	-×	--
Fpole	10	12	50	-8	×	-×	-×	--	--	-×	--
		-26	54	3							
PreCG	6				--	--	--	--	--	--	--
PreCun	7	2	-52	54	--	--	--	--	-×	×	--
		-7	-57	54							
SPL	7	18	-66	56	-×	--	--	--	--	×	×
		-15	-63	42							
IPS	40/7	-31	-59	43	--	--	--	-×	--	-×	--
SMG/AG	40/39	-55	-44	51	--	--	--	--	--	-×	--
LOG/FG/LG	18/19	27	-82	-2	--	--	×	×	×	-×	--
		-14	-79	11							
CingC											
Anterior	24/32	8	32	-4	--	--	×	--	--	-×	--
		-8	52	-2							
Posterior	23/31	-8	-62	28	-×	--	--	--	--	--	--
Insula	Fr.Op.				--	--	--	--	--	--	--

Legend as Table 1.

Table 3

Brain areas and their mean Talairach coordinates in which significantly activated voxels were detected in the comparison between 2-back versus 1-back visuospatial memory tasks. The results are shown for each subject and both hemispheres (R/L)

Area	BA	Talairach coordinates			1	2	3	4	5	6	7
		x	y	z	R/L	R/L	R/L	R/L	R/L	R/L	R/L
MFG	46/9	40	34	21	--	-×	--	--	-×	×	×
		-34	40	32							
SFS/SFG	6/8	24	12	50	-×	×	--	×	×	×	×
		-26	7	51							
SFG/FGd	6/8	11	10	56	-×	--	-×	×	-×	×	--
		-11	23	53							
IFG/IFS	45/47	53	24	5	--	-×	-×	--	-×	×	--
		-50	18	24							
Fpole	10	12	54	1	--	×	×	--	--	×	×
		-13	56	17							
PreCG	6	50	0	46	--	--	-×	×	-×	-×	--
		-36	-8	50							
PreCun	7	8	-61	45	--	--	×	-×	×	×	-×
		-8	-59	53							
SPL	7	24	-59	51	--	--	×	--	-×	×	--
		-19	-61	55							
IPS	40/7	29	-57	36	--	×	-×	--	-×	×	-×
		-37	-60	38							
SMG/AG	40/39	42	-48	37	×	-×	×	×	-×	-×	×
		-43	-55	34							
LOG/FG/LG	18/19	34	-77	12	--	--	×	×	-×	×	×
		-27	-79	23							
CingC											
Anterior	24/32	5	29	25	×	--	-×	--	--	×	-×
		-4	5	43							
Posterior	23/31				--	--	--	--	--	--	--
Insula	Fr.Op.	28	12	10	-×	--	--	--	-×	×	--
		-44	13	1							

Legend as Table 1.

statistically significant activation was found in the PreCG in any of the subjects. In two subjects there was unilateral activation in the IPS on the left side. In four subjects activation was detected

in the occipital visual association areas LOG/FG/LG. No activation was found in the insula in any of the subjects. Activation was detected in two subjects in the anterior cingulate and in one subject in the posterior cingulate cortex.

2-Back versus 1-Back Task Comparison

In the 2-back versus 1-back comparison (Table 3) the activation in the MFG, SFS/SFG and IPS was less consistent than in the 2-back versus 0-back comparison. Significant activation in the MFG was detected bilaterally in two and unilaterally in another two subjects. In the SFS/SFG, activation was detected bilaterally in four subjects and unilaterally in two. In the IPS, significant activation was detected bilaterally in one and unilaterally in three subjects. In the other cortical areas listed in Table 3 significant activation was also detected less consistently than in the 2-back versus 0-back comparison, but more often than in the 1-back versus 0-back comparison.

Discussion

fMRI of subjects performing a visuospatial version of the *n*-back working memory task with different load levels showed bilateral, load-dependent activation in the MFG, SFS/SFG and IPS (bilateral in six out of seven subjects). Significant activation in the 2-back versus 0-back task comparison was also detected in several other cortical areas, including the IFG/IFS, PreCG, inferior and superior parietal lobuli, occipital visual association areas, and subareas of the cingulate cortex.

The *n*-back task paradigm has earlier been used in fMRI and PET studies to investigate the relationship between the organization of brain activation and working memory processing (Smith *et al.*, 1996; Braver *et al.*, 1997; Cohen *et al.*, 1997). These studies employed a sequential letter *n*-back task that required phonological processing. Smith *et al.* (1996) used a visuospatial version of the letter *n*-back task in a PET study in which the subjects were required to memorize locations of letters presented on a visual display. In the present study, we adapted the *n*-back task paradigm and designed a non-phonological visuospatial version of it. In the *n*-back task, the memory load can be modulated by maintaining the number of visual stimuli and the demands for motor programming similar between the tasks. The mnemonic load is modulated by changing the instruction given to the subject. Therefore, when the pattern of significantly activated areas in the different tasks is compared (2-back versus 0-back, 1-back versus 0-back, and 2-back versus 1-back), the influence of the visual stimulation *per se* and that of the motor performance is abolished and the activated brain areas reflect neuronal processing related to the load differences of the tasks.

The reaction times increased linearly from the 0-back to 2-back task (Fig. 2A). This finding indicates that the cognitive demands of the tasks were different. This phenomenon, originally described by Sternberg (1966), implies that the

reaction times in short-term memory tasks vary according to the number of items that are kept in mind. Although the subjects made significantly more incorrect responses in the high-load memory task (2-back task) than in the 0-back task, the number of errors was small also in the 2-back task. The subjects performed >95% of the trials correctly at all task levels (Fig. 2B). Thus, the activation areas seen in the 2-back versus 0-back task comparison cannot be thought to result from the effects of incorrect responses on working memory related neuronal processing. This is important, because in electrophysiological studies it has been demonstrated that the firing patterns of single neurons recorded in the PFCdl in monkeys performing visuospatial working memory tasks are affected by distractive stimulation and by incorrect responses (Fuster, 1973; Funahashi *et al.*, 1989). Difficulty factors are inherent in all working memory tasks and may not be dissociable from the working memory process. Thus, whether the load-dependent increase of activity found during the visuospatial task performance was due to increased working memory processing or to, for example, greater mental effort required in the 2-back than 1-back task performance cannot be resolved with the paradigm used in our study. This question was addressed by Barch *et al.* (1997), who studied the contribution of working memory processing and processes related to task difficulty on the activation detected in different brain areas. They found that regions in the left dorsolateral prefrontal, left inferior frontal and left parietal cortex showed greater activation in tasks with long delays than in tasks with short delays, whereas activation in the anterior cingulate and right inferior frontal cortex was related to task difficulty rather than mnemonic processing.

Frontal Areas

The present results revealed memory load dependent bilateral activation in the MFG (BA 46/9). Although several neuroimaging studies have detected activation in this area during visuospatial working memory task performance (McCarthy *et al.*, 1994, 1996; Belger *et al.*, 1998), there are also contradicting results (Jonides *et al.*, 1993; Smith *et al.*, 1995, cf. exp. 2; Courtney *et al.*, 1996), and the specific role of this area in visuospatial working memory processing has recently been questioned (Courtney *et al.*, 1998; Rushworth and Owen, 1998). There may be various causes for the discrepancy in the results of human neuroimaging studies. These include differences in the methodology, e.g. the extent of the brain volumes studied, the statistical criteria employed, and the nature of the memory and control tasks.

In the present study, comparison between the 1-back and 0-back tasks did not reveal significant activation in the MFG in any of the subjects. This result may have several reasons. Although the reaction times in the 1-back task were longer than in the 0-back task, there were no significant differences in the numbers of incorrect responses or in the subjective evaluation of the difficulty level between the two tasks. The 0-back and the 1-back tasks were similar in all other respects, except that in the

Figure 3. Two coronal slices illustrating bilateral brain activation in the MFG in subject 6 in the 2-back versus 0-back task comparison. The horizontal lines in the middle figure indicate coronal slice levels, and the color of the line refers to the color of the frame in which the coronal slice is presented. The right hemisphere is shown on the left in each image.

Figure 4. An axial (a), two coronal (b,d) and a sagittal (2) slice illustrating brain activation in the SFS/SFG and SFG/FGd in subject 1 in the 2-back versus 0-back task comparison. The horizontal lines in the axial brain figure (a) indicate the level of the coronal slices which are presented in the frames with the corresponding colors. The right hemisphere is shown on the left in the axial and coronal slices.

Figure 5. A coronal (a) and a sagittal (b) slice illustrating bilateral brain activation in the IPS in subject 1 in the 2-back versus 0-back task comparison. The number of significantly activated voxels in the right IPS was larger than in the left IPS. The right hemisphere is on the left in the coronal slice.

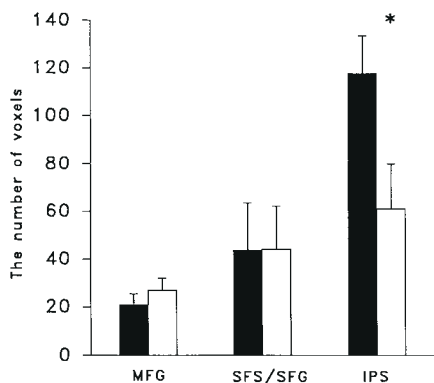


Figure 6. The figure illustrates the mean number of voxels in all seven subjects which were significantly activated in the MFG, SFS/SFG and IPS in the right (black columns) and in left hemispheres (white columns). The vertical bars indicate SEMs. The number of significantly activated voxels was larger in the right than left IPS, whereas the difference did not reach significance in the other brain areas.

0-back task the subjects matched the location of each new stimulus with the location that had already been indicated to the subject at the beginning of the experiment, whereas in the 1-back task the match was made with the location of the previous stimulus. Thus, in the 0-back and 1-back tasks (as well as in the 2-back task) information needed to be updated on every trial and the correct response could not be predicted from the previous response. In the 0-back task, however, the reference (the predetermined location) remained the same, whereas in the 1-back task (and in the 2-back task) it, too, was updated on each trial. The finding that only few significantly activated brain areas were found in the 1-back versus 0-back comparison indicates that the tasks, however, required similar levels of activation in the neuronal networks engaged in visuospatial processing. On the other hand, the threshold for significantly activated voxels in the present study was relatively conservative (voxels with P -values equal or less than 10^{-6} , corresponding to P -value < 0.01 after Bonferroni correction). Thus, some brain areas with weaker but perhaps biologically significant activation foci might have remained undetected. It is also noteworthy that had we employed only the 1-back and 0-back tasks in this study, we would not have detected activation in the MFG and other critical areas. Therefore, the type of tasks used as the test and control tasks is critical for the outcome of the results.

In a PET study, Smith *et al.* (1996) employed a spatial version of a sequential letter 3-back task and found bilateral activation – though more in the right than left hemisphere – in the MFG (BA 46), premotor and parietal areas (BAs 40 and 7). Earlier, the same group had not found activation in the MFG during visuospatial memory task performance (Jonides *et al.*, 1993) or had found weak but statistically non-significant activation in the MFG in the right hemisphere (Smith *et al.*, 1995). The authors pointed out that one likely cause for detecting activation in the areas in which they had not earlier observed it was the continuous nature of the n -back task in which working memory is uninterruptedly loaded with a new item requiring reorganization of the contents of the memory buffer. The results of the present study are in line with the study by Smith *et al.* (1996), indicating that the n -back task type is especially suitable for revealing working memory related brain activation.

The MFG has also been shown to be activated in verbal working memory tasks (e.g. Petrides *et al.*, 1993; Mellers *et al.*, 1995; Smith *et al.*, 1996; Braver *et al.*, 1997; Cohen *et al.*, 1997), object visual working memory tasks (Courtney *et al.*, 1996,

1997) and in the early stage of learning (Sakai *et al.*, 1998). In studies, in which visuospatial working memory related activation in the MFG was found, activation was either in the right MFG or bilateral but stronger in the right hemisphere, but not bilateral and similar in both hemispheres as in the present study.

In all subjects imaged in the present study, an area located in or adjacent to the SFS (SFS/SFG) was bilaterally activated in the 2-back versus 0-back comparison. Activation of this area was dependent on the memory load because the comparison between the 1-back and 0-back tasks revealed activation in SFS/SFG in one subject only. Activation in the corresponding cortical area has been previously found in neuroimaging studies using visuospatial working memory tasks (Courtney *et al.*, 1996, 1998). An area in the SFS, but not in the MFG, was suggested to be specifically activated in subjects performing a visuospatial working memory task (Courtney *et al.*, 1998), suggesting that the human cortical area specialized in visuospatial working memory processing is located superiorly and posteriorly to the respective areas described in the monkey (Ungerleider *et al.*, 1998). In the present study, the finding that there was activation in the SFS/SFG is in line with these earlier studies, suggesting that this cortical area participates in visuospatial working memory processing. However, an area in the MFG was also consistently, bilaterally and load-dependently activated in all subjects.

Less consistent but significant activation in the 2-back versus 0-back comparison was observed in the SFG/FGd, IFS/IFG, in the frontal polar region and in the PreCG. All these areas have earlier been reported to be activated, to a variable degree, in visual working memory tasks. In a visual location working memory task, Belger *et al.* (1998) found activation in the medial aspect of the SFG. Visual shape working memory tasks have repeatedly been shown to activate the IFG, especially in the left hemisphere (Courtney *et al.*, 1996, 1997, 1998; McCarthy *et al.*, 1996) but significant activation in the IFG has also been detected in visuospatial memory tasks (Jonides *et al.*, 1993; Smith *et al.*, 1995; Belger *et al.*, 1998; Courtney *et al.*, 1998). PreCG activation was found in five subjects in the present study in the 2-back versus 0-back task comparison. This activation was also load-dependent because it was not found in any of the subjects in the 1-back versus 0-back task comparison. Activation in the corresponding cortical area has also been detected in some earlier studies that employed visuospatial working memory tasks (Jonides *et al.*, 1993; Smith *et al.*, 1995, 1996; Courtney *et al.*, 1998). Since the responses performed at each task level were the same, the activation detected in the PreCG cannot be considered to be related to movement preparation or execution, suggesting rather that the PreCG has a role in mnemonic processing.

Posterior Parietal and Occipital Association Areas

The activation in the IPS in the present study was load-dependent and greater in the right than left hemisphere in six out of seven subjects. This finding is in line with a recent study by Belger *et al.* (1998), which showed that in a location working memory task activation was greater in the right than in the left IPS. Belger *et al.* suggested that IPS activation was related to the processing of mnemonic spatial information, whereas activation of the inferior parietal area was related to the processing of spatial – not mnemonic – information. Activation in the IPS – as well as in the dorsal occipital and superior parietal cortex – has also been detected in a location matching but not in a face matching-to-sample task (Haxby *et al.*, 1994), suggesting that in the human brain – as in the monkey brain – there are two

functionally and anatomically specialized visual pathways. Other parietal areas, including the precuneus and areas in the superior and inferior parietal lobuli, also expressed significant activation in the 2-back versus 0-back comparison. There was a memory load effect on the activation in these areas (Table 2). The involvement of posterior parietal areas in the performance of visuospatial working memory tasks has previously been indicated in several neuroimaging studies (Jonides *et al.*, 1993; Smith *et al.*, 1995; Courtney *et al.*, 1996; Belger *et al.*, 1998), whereas the more posterior brain areas were not imaged in the studies by McCarthy *et al.* (1994, 1996). In a 2-deoxyglucose study, coactivation of the prefrontal and parietal cortex has also been demonstrated in monkeys performing spatial working memory tasks (Friedman and Goldman-Rakic, 1994). There is thus growing evidence suggesting that the posterior parietal regions, in addition to the prefrontal cortical areas, are engaged in spatial working memory processing. The load-dependent activation in the IPS found in the present study supports this suggestion.

In the 2-back versus 0-back task comparison activation was variably detected in the LOG, FG and LG in different subjects. In Tables 1 and 2 these areas were combined to signify occipital visual association areas. Significant bilateral activation in the LOG/FG/LG was detected in six subjects. In the 1-back versus 0-back comparison, significant activation in the occipital visual association areas was detected in two subjects, indicating that memory load affected activation also in these areas. Activation in the early visual areas has previously been detected during visual working memory tasks (Smith *et al.*, 1995; Courtney *et al.*, 1996; Belger *et al.*, 1998). Presumably, the above-mentioned posterior cortical areas (occipital visual association areas, precuneus, inferior and superior parietal lobuli, IPS) in the human brain are part of the proposed dorsal visual pathway (Mishkin *et al.*, 1983; Ungerleider *et al.*, 1998) specialized in visuospatial information processing. The results of the present study suggest that at least the IPS, but perhaps also the inferior parietal lobule, the precuneus and the occipital visual association areas, may have a role in mnemonic processing of visuospatial information.

The Cingulate Cortex

Subareas of the anterior cingulate cortex were activated in relation to the task performance in every subject in the 2-back versus 0-back comparison and only in two subjects in the 1-back versus 0-back comparison. Activation in the anterior cingulate cortex during working memory task performance has been reported in many studies (Smith *et al.*, 1995; McCarthy *et al.*, 1996; Courtney *et al.*, 1996). In addition to the relation of anterior cingulate cortex activity to task difficulty, suggested by Barch *et al.* (1997), the anterior cingulate has been shown to be activated in tasks requiring motor control (Paus *et al.*, 1993), attention (Posner *et al.*, 1988) and pain perception (Talbot *et al.*, 1991). The multiplicity of functions inferred to this cortical region requires that further studies be conducted to determine its role in different cognitive tasks. In the 2-back versus 0-back comparison significant activation was also detected in the posterior cingulate cortex in six subjects. The activation found in the posterior cingulate cortex was not as consistent between subjects, as, for example, in the MFG, SFS/SFG and IPS. In four subjects the activation was in the left and in one in the right hemisphere. In one subject the activation was bilateral. Changes in the level of activation in the posterior cingulate cortex have previously been detected in subjects performing various memory tasks (e.g. Moscovitch *et al.*, 1994; Swartz *et al.*, 1994;

Courtney *et al.*, 1996). In the present study, the posterior cingulate cortex was load-dependently activated during the memory task performance, suggesting that the activation is related to mnemonic processing. However, in some human imaging studies deactivation of the posterior cingulate cortex has also been found during performance of memory tasks (Moscovitch *et al.*, 1994; Courtney *et al.*, 1996). Thus, it is possible that changes in the metabolic activity in the posterior cingulate region do not reflect mnemonic processing but some other process related to the task performance such as changes in the behavioral state or level of attention.

Conclusions

The results of the present study indicate that in the human brain, visuospatial mnemonic information processing involves the activity of a network of spatially distributed cortical areas. Load-dependent activation was consistently found in the MFG, SFS/SFG and IPS in all subjects. Several other brain areas also expressed load-dependent activation in the visuospatial *n*-back tasks in more than half of the subjects. These areas included the IFG/IFS, SFG/FGd, PreCG, inferior parietal lobule, precuneus and occipital visual association areas. The intersubject consistency of the results, especially regarding the activation in the MFG, SFS/SFG and IPS, suggests that functional MR imaging during visuospatial *n*-back task performance may prove to be of diagnostic value in studying patients suffering from diseases that affect memory and attention.

Notes

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