To investigate brain mechanisms of sound location memory, we studied the distribution of brain activation with functional magnetic resonance imaging (fMRI) in subjects performing an audiospatial n-back task with three memory load levels. Working memory processing of audiospatial information activated areas in the superior, middle and inferior frontal gyri, and in the posterior parietal and middle temporal cortices. In a control experiment, fMRI during audio- and visuospatial 2-back task performances revealed only few differentially activated subregions between the two tasks. These results demonstrate that working memory processing of auditory locations involves a distributed network of brain areas and suggest that mnemonic processing of audio- and visuospatial information is directed along a common neural pathway in the posterior parietal and prefrontal cortices.

Introduction

The neuronal mechanisms of sound localization in mammals, which is based on interaural time delay, filtering effects of the pinna and intensity differences of the sound, have been studied extensively (Aitkin et al., 1984). Binaural neurons carrying information essential for sound localization are found in the auditory pathway from the superior olive onwards (Goldberg and Brown, 1968; Brugge and Merzenich, 1973). Lesions in the primary auditory cortex impair sound localization ability (Neff et al., 1956; Heffner and Heffner, 1990), and neurons in the primate posterior parietal (Leinonen et al., 1980; Linden et al., 1999) and prefrontal (Azuma and Suzuki, 1984; Vaadia et al., 1986) cortices respond spatially selectively to auditory stimuli, suggesting that a distributed network of cortical areas participates in conscious perception of auditory locations. Recent neuroimaging studies indicate that auditory spatial processing involves prefrontal and posterior parietal cortical areas also in the human brain (Bushara et al., 1999; Weeks et al., 1999).

Despite the evolutionary importance of keeping a sound location in mind for a short period of time and adjusting behavior accordingly, there are only a few reports on the neurophysiological mechanisms of working memory processing of auditory locations. Research concerning spatial working memory both in experimental animals and humans has focused on the visual system, and the results indicate the involvement of areas in the dorsal visual pathway — including areas in the dorsolateral prefrontal cortex — in working memory processing of visual locations (Goldman-Rakic, 1987; Fuster, 1989; Courtney et al., 1996, 1998; McCarthy et al., 1996; Belger et al., 1998; Carlson et al., 1998; Chafee and Goldman-Rakic, 1998). In studies on auditory working memory, the emphasis has been in mnemonic processing of sound content but not location (Kauffman et al., 1992; Zatorre et al., 1994; Chao and Knight, 1996, 1998; Stevens et al., 1998). In the few studies in which working memory processing of sound location has been investigated, it has been demonstrated that neurons in the posterior parietal cortex respond spatially selectively during the delay period of auditory localization tasks (Mazzoni et al., 1996; Linden et al., 1999). Also, the anterior archistriatum in the barn owl, an area that may be analogous to the primate frontal cortex, has been shown to be essential for audiospatial working memory (Knudsen and Knudsen, 1996). In humans, slow delay-related potentials have been recorded during the performance of auditory working memory tasks over the frontal and parietal recording sites (Barcelo et al., 1997; Rämi et al., 2000), suggesting that subareas in these cortical regions may participate in audiospatial working memory processing.

In the present work, we aimed to determine which brain areas are involved in audiospatial working memory processing. For this purpose, the distribution of cortical activation during temporary storage of auditory locations was studied using functional magnetic resonance imaging (fMRI) (Kwong et al., 1992). Healthy young subjects were imaged while they performed an audiospatial version of an n-back working memory task. In the n-back task paradigm, memory load is modulated in a parametric manner by changing the instructions while maintaining all other features of the task (number of stimuli, number and type of responses) constant (Cohen et al., 1997; Carlson et al., 1998). Performance at all n-back task load levels requires continuous updating and recalling of the memorized information, and therefore load level dependent image signal changes reflect changes in attention and working memory related neuronal activation.

Human lesion studies focusing on spatial selective attention have not yielded uniform results (Farah et al., 1989; Pincet al., 1989; Soroker et al., 1999). However, because there is a close behavioral relationship between sound localization ability and visual orientation to the sound, we predicted that partially the same brain areas that have been shown to be involved in visuospatial working memory processing may also be activated in mnemonic processing of auditory locations. This hypothesis was also feasible in the light of the recent information about perceptual processing of visual and auditory locations in the human brain (Bushara et al., 1999; Weeks et al., 1999).

A particular problem in fMRI studies of auditory functions is the strong background noise induced by the gradient coils during imaging. This background noise can interfere with the delivery of auditory stimuli to the subjects and may also affect the study of other sensory systems and cognitive functions (Elliott et al., 1999). In the present study, the difficulties related to the background noise were reduced by interleaving stimulus presentation with image acquisition (Fig. 1C). This design allowed the subjects to listen to the tones without interference from the noise produced by image acquisition.
Materials and Methods

**Functional Magnetic Resonance Imaging**

Ten right-handed, healthy subjects (five females, aged 20–30 years, mean 25) were imaged while they performed an audiospatial version of an n-back working memory task with three load levels (1-, 2- and 3-back tasks) (Fig. 1A,B). MR images were acquired with a Siemens Vision (Erlangen, Germany) 1.5 T scanner. The head of the subject was stabilized with a vacuum cushion to minimize motion artifacts during imaging. In the beginning of each MR-imaging session a structural image set of the subject’s head was acquired using a $T_1$-weighted three-dimensional MPRAGE sequence (180 sagittal slice planes with thickness of 1 mm, no gap, field of view 256 mm, $256 \times 256$ matrix size, $T_E = 4$ ms, $T_I = 20$ ms, flip angle 10°). After this, fMRI measurements were performed using a gradient-echo EPI sequence (16 transaxial slice planes with a thickness of 5 mm each, 0.5 mm gap between slices, field of view $256 \times 64$ matrix size, $T_E = 70$ ms, $T_R = 3000$ 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. After motion correction (AIR 3.0) (Woods et al., 1998), a voxelwise two-tailed $t$-test was performed between images belonging to different task conditions (3-back versus 1-back task and 2-back versus 1-back task). The first two volumes of the 16 slices from the beginning of each task condition were excluded from analysis to ensure the stability of the hemodynamic responses. Therefore, the total number of functional MR images in the statistical analysis was 108 volumes ($18 \times 6$) per task condition (1-, 2- and 3-back tasks), resulting in 324 volumes per subject. Statistical parameter maps were calculated and voxels with $P$-values equal or less than $10^{-7}$ (corresponding $P$-value $< 0.001$ after Bonferroni correction for 10 000 voxels roughly corresponding to the total number of brain voxels in the imaged volume) were considered to show a significant signal change. Statistical parameter maps were co-registered with the three-dimensional structural image sets using location and orientation information in the image file headers. The Talairach coordinates of the center of the significantly activated brain areas (the positive tail of the $t$-test) were determined, or the mean of the center coordinates if the activation consisted of multiple voxel clusters within the same anatomical region. The anatomical location of the significantly activated brain areas and their corresponding Brodmann’s areas were determined using anatomical brain atlases (Talairach and Tournoux, 1988; Damasio, 1995). Image analysis was performed using MEDx (Sensor Systems Inc., Sterling, VA, USA) software. The study protocol was approved by the ethical committee of the Department of Radiology at the Helsinki University Central Hospital.

**Auditory n-Back Tasks**

The stimulus was a sinusoidal tone ($2250$ Hz, duration 100 ms, interstimulus interval 3000 ms) presented through plastic tubes inserted into the earcanals through hearing protector plugs (EarTips, Nicolet Biomedical Inc., Madison, WI, USA). Tones were presented binaurally with an interaural intensity difference of $11$ dB to mimic the right and left locations and with an equal intensity to mimic the middle location. Before the imaging was started the subjects were presented with a set of test tones interleaved with fMRI gradient pulse noise to ensure proper sound location perception. The background noise level in the magnet during image acquisition was $\sim 95$ dB SPL (measured with Precision Sound Level Meter Type 2203, Bruel & Kjaer, Naerum, Denmark) without attenuation produced by the earplugs, and $\sim 60$ dB SPL when measured through the earplugs. The subjects responded after each stimulus by pressing with the right index or middle finger the left or right button, respectively, on a response pad. In the 1-back task the subject was instructed to press the left button whenever the stimulus was in the same location (left, middle...
or right) as the previous one and, when in any other location, the right button. In the 2-back task the subject pressed the left button when the stimulus was in the same location as the one two trials back, and in the 3-back task when in the same location as the one three trials back. For all other stimuli, the subject pressed the right button. Before the fMRI the subjects were allowed to practice the tasks until they felt comfortable performing them. Each task condition (1-, 2- and 3-back) consisted of 20 trials. Twenty image sets of 16 slices were obtained during the performance of one task condition. The acquisition of a set of 16 transaxial slices was triggered 75 ms after the end of each auditory stimulus. In one experiment, a time series of 120 sets of 16 transaxial slices was acquired and each task condition was presented twice in a counterbalanced order. At the end of each task condition there was a 10 s interval during which the screen remained blank. At the beginning of each task condition an instruction figure (one, two or three white bars for 1-, 2- and 3-back tasks respectively) was displayed on the screen for 2 s to indicate which memory task was about to start. The experiment was run three times during the same imaging session. Thus, the data consisted of 20 trials.

The auditory stimuli were the same as described above and the visual stimulus was a white square (visual angle 1.8° × 2.3°) presented in one of three possible locations (left, top-middle and right) on a screen. The visual stimulus and the visuospatial 2-back task have been described elsewhere (Carlson et al., 1998). Both stimulus types (auditory and visual) were presented simultaneously. In both modalities, the locations were presented in a random order, and thus the visual and auditory locations were different in two of the three of the trials. A figure at the beginning of each task condition instructed the subject of the modality to attend. The subjects were again instructed to fixate the central cross on the screen throughout the imaging. Both the auditory and visual tasks consisted of five sets of 20 trials presented in a counterbalanced order. Altogether 100 trials of both tasks were performed. At the end of the experiment the subjects filled a questionnaire evaluating the level of difficulty of the tasks (1 = very easy, 2 = easy, 3 = rather difficult, 4 = difficult, 5 = very difficult) and described whether they had used any strategies in their performance. The presentation of the stimuli, triggering of the MR image acquisition and collection of the behavioral data (correct/incorrect responses and reaction times) were controlled by a computer program (Stim, Neuro Scan, Inc., Sterling, VA, USA).

Audio- and Visuospatial 2-Back Tasks of the Control Experiment

The auditory stimuli were the same as described above and the visual stimulus was a white square (visual angle 1.8° × 2.3°) presented in one of three possible locations (left, top-middle and right) on a screen. The visual stimulus and the visuospatial 2-back task have been described elsewhere (Carlson et al., 1998). Both stimulus types (auditory and visual) were presented simultaneously. In both modalities, the locations were presented in a random order, and thus the visual and auditory locations were different in two of the three of the trials. A figure at the beginning of each task condition instructed the subject of the modality to attend. The subjects were again instructed to fixate the central cross on the screen throughout the imaging. Both the auditory and visual tasks consisted of five sets of 20 trials presented in a counterbalanced order. Altogether 100 trials of both tasks were performed. At the end of the experiment the subjects filled a questionnaire evaluating the level of difficulty of the tasks and describing the strategies they had used. A voxelwise two-tailed t-test was performed between images belonging to auditory 2-back and visual 2-back tasks. This comparison should reflect differences in mnemonic processing of auditory and visual locations. Otherwise, the image analysis was performed as described above for the main experiment of this study.

Statistical Analysis of Behavioral Parameters

The reaction times, the number of incorrect responses and the subjective evaluations of difficulty levels in the 1-, 2- and 3-back tasks were analyzed statistically using an analysis of variance for repeated measures (ANOVA); if there was a significant task effect ($P < 0.05$), a paired parametric $t$-test (reaction times) or a paired nonparametric Wilcoxon signed-rank test (incorrect responses, subjective difficulty levels) was used.

Lateralization of Activations

To study the lateralization of detected cerebral activations, the number of significantly activated voxels was individually counted and compared between selected regions of interests (ROIs) in Talairach calibrated brain volumes. The compared ROIs included the left and right frontal areas [number of all significantly activated voxels within a rectangular box with corner coordinates in the Talairach system (–60,70,66)–(–10,4,–20)] and (60,70,66)–(10,4,–20) with the sides parallel to the Talairach coordinate axis]; the left and right parietal areas [number of all significantly activated voxels within a rectangular box with corner Talairach coordinates (–64,–36,24)–(–12,–94,66) and (64,–36,24)–(–12,–94,66) with the sides parallel to the Talairach coordinate axes]. The percentages of significantly activated voxels in each ROI of the total number of significantly activated voxels in the corresponding ROIs in both hemispheres were counted and compared between the hemispheres using the Wilcoxon matched-pairs signed-ranks test.

Results

Behavioral Performance

An increase in mnemonic load had a significant effect on the number of incorrect responses ($Fr = 15.80, P < 0.0001$), reaction times (RTs) [$Fr(2,9) = 25.99, P < 0.0001$] and subjective evaluation of the difficulty of the tasks ($Fr = 20.00, P < 0.0001$). The subjects made significantly more incorrect responses during the 3-back than the 1-back task ($P < 0.005$) and during the 3-back than the 2-back task ($P < 0.005$) (Fig. 2A). The RTs were longer in the 2-back ($t(9) = 5.00, P < 0.0001$) and 3-back ($t(9) = 5.67, P < 0.0001$) tasks than in the 1-back task and in the 3-back task than in the 2-back task ($t(9) = 3.90, P < 0.005$) (Fig. 2B). The subjects considered the 2-back and 3-back tasks significantly more difficult to perform than the 1-back task ($P < 0.005$) and the 3-back task more difficult than the 2-back task ($P < 0.005$) (Fig. 2C). In the 1-back and 2-back tasks half of the subjects and in the 3-back task six subjects reported using a verbal strategy. In addition, one subject in the 2-back and one in the 3-back task reported using a combination of verbal and visual strategies. Visual strategy alone was used by two subjects in the 1- and 3-back tasks, and by three in the 2-back task.
Table 1

BRAIN AREAS AND THEIR MEAN TALAIRACH COORDINATES IN WHICH ACTIVATION WAS DETECTED IN AT LEAST HALF OF THE SUBJECTS IN THE COMPARISON BETWEEN 3-BACK AND 1-BACK TASKS AND ACTIVATIONS IN THESE AREAS IN THE 2-BACK VERSUS 1-BACK TASK COMPARISON

<table>
<thead>
<tr>
<th>Area</th>
<th>BA</th>
<th>3-back versus 1-back Talairach</th>
<th>2-back versus 1-back Talairach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFG/FGd</td>
<td>6/8</td>
<td>R 4,15,51 + + + + + + + + + + + 4,19,49 + + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 4,18,58 + + + + + + + + + + + 3,71,51 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFG/SFS</td>
<td>6/8</td>
<td>R 24,7,51 + + + + + + + + + + 22,2,57 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 23,8,54 + + + + + + + + + + + 23,8,54 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFG</td>
<td>9/46</td>
<td>R 40,32,30 + + + + + + + + + + + 39,32,33 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 41,35,35 + + + + + + + + + + + 41,25,33 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFG</td>
<td>6/8</td>
<td>R 38,13,50 + + + + + + + + + + 35,11,47 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 35,15,46 + + + + + + + + + + + 37,15,46 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFG/IFS</td>
<td>44/45</td>
<td>R 45,18,19 + + + + + + + + + + + 40,21,15 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 44,18,19 + + + + + + + + + + + 44,21,17 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fpole</td>
<td>10</td>
<td>R 30,51,4 + + + + + + + + + + 21,52,4 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 34,22,11 + + + + + + + + + + + 24,54,1 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreCG</td>
<td>4/6</td>
<td>R 41,37,6 + + + + + + + + + + 41,6,40 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 41,41,4 + + + + + + + + + + + 39,40,4 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPL</td>
<td>7</td>
<td>R 23,67,50 + + + + + + + + + + + 19,57,54 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 23,67,46 + + + + + + + + + + + 21,64,49 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPS</td>
<td>7/40</td>
<td>R 35,54,1 + + + + + + + + + + + 31,51,4 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 35,50,44 + + + + + + + + + + + 36,51,44 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMG</td>
<td>40</td>
<td>R 42,49,40 + + + + + + + + + + + 40,51,41 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 47,49,41 + + + + + + + + + + + 39,56,42 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreCun</td>
<td>7</td>
<td>R 6,42,24 + + + + + + + + + + 5,59,49 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 6,46,51 + + + + + + + + + + + 6,64,48 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTG/STS</td>
<td>21/37</td>
<td>R 51,45,1 + + + + + + + + + + 49,41,3 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 50,51,7 + + + + + + + + + + + 48,52,5 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITG</td>
<td>20/37</td>
<td>R 42,63,5 + + + + + + + + + + 46,55,11 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 46,55,8 + + + + + + + + + + + 46,55,11 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>24/32</td>
<td>R 7,16,29 + + + + + + + + + + 8,30,23 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 4,16,35 + + + + + + + + + + + 5,21,30 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>23/31</td>
<td>R 5,42,33 + + + + + + + + + + 8,44,34 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 2,44,25 + + + + + + + + + + + 3,44,25 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>34/17,11</td>
<td>R 34,17,11 + + + + + + + + + + 37,4,4 + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L 33,17,7 + + + + + + + + + + + 36,9,5 + + + + + + + +</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The occurrences and laterality of activation are shown individually. BA, Brodmann's area; R, right; L, left.

Parietal Cortical Areas

Areas in the supramarginal gyrus in the inferior parietal lobule (SMG, BA 40) and the adjacent intraparietal sulcus (IPS, BAs 46/48) were activated in all subjects (Fig. 3B, E, H). Activation was also found bilaterally in the inferior frontal gyrus and sulcus (IFG/IFS, BAs 44/45) in all but one subject. In all subjects activated voxels were detected in the frontopolar cortex (Fpole) (BAs 11/12) (Fig. 3E, F) and in seven subjects in an area in the precentral gyrus (PreCG, BAs 4/6).

Prefrontal Cortical Areas

A cortical area in the superior frontal gyrus and adjacent sulcus (SFG/SFS), and an area medially in the SFG (SFG/FGd), corresponding to Brodmann's areas (BAs) 6/8, was activated in all subjects (Fig. 3A, H). In the middle frontal gyrus (MFG), bilateral activation was found in an area corresponding to BAs 46/9 in all but one subject (Fig. 3B, C). Another more posterior area in the MFG (BAs 6/8) was bilaterally activated in all subjects (Fig. 3B, E, F, H). Activation was also found bilaterally in the inferior frontal gyrus and sulcus (IFG/IFS, BAs 44/45) in all but one subject. In all subjects activated voxels were detected in the frontopolar cortex (Fpole) (BAs 11/12) (Fig. 3E, F) and in seven subjects in an area in the precentral gyrus (PreCG, BAs 4/6).
than in the left hemisphere (Figs. 3A, 4B, D). The number of significantly activated voxels was differentially distributed bilaterally in the insula in six subjects and on the left side in one subject. In addition, in less than five subjects, activation was found in the lateral and medial occipital gyri, the fusiform gyrus and cuneus (BAs 18/19).

The comparison between the 2-back and 1-back tasks showed activation in the same cortical areas as in the 3-back and 1-back task comparison, but less consistently (Table 1).

### Comparison between Audiospatial and Visuospatial Working Memory Areas

Since several of the prefrontal and parietal cortical areas that were activated in the present study during audiospatial working memory task performance — the PreCun, IPS, SPL, IPL, FGd, SFG/SFS and MFG — were also activated in our earlier study concerning working memory processing of visual locations (Carlson et al., 1998), a control experiment was conducted to investigate whether the same subareas process both audio- and visuospatial mnemonemic information. Eight right-handed, healthy subjects (age 21–28 years, mean 24 years, five females) participated in the study. Functional MRI was conducted while they performed an audio- and visuospatial 2-back task (Fig. 4A). The auditory stimuli in the 2-back task paradigm were the same as those used in the main experiment and the visual stimuli have been described elsewhere (Carlson et al., 1998).

Analysis of the behavioral performance revealed that the auditory 2-back task was more difficult. The reaction times were longer (F(1,4) = 5.14, P < 0.005) and the number of incorrect responses higher (P < 0.05) in the auditory than visual 2-back task. The auditory task was also subjectively evaluated more difficult than the visual task (P < 0.01) (Fig. 4B–D).

In Table 2, brain areas that were differentially activated between the audio- and the visuospatial tasks are listed. There were only two areas, IFG/IFS and Fpole, that were differentially activated in the comparison between the auditory and visual tasks in four or more subjects. In both areas the signal was more pronounced in the auditory task as compared with the visual task. No differential activation was detected in four subjects in the subareas of the MFG and in five in the SFG or SFS. There was no differential activation in any subject in the FGd. Most subjects had no differentially activated areas in the SPL, IPS, SMG or PreCun. In only one subject were differentially activated regions detected in both the visual and auditory tasks in the SPL and in another subject in the SMG.

Few small, differentially activated locations were detected in three subjects in the temporal and in four in the occipital cortex. No areas were activated differentially in the cingular cortex or in the insula.

### Discussion

By employing fMRI in subjects performing an audiospatial n-back task or a visuospatial and audiospatial 2-back task, we demonstrated that working memory processing of auditory locations activates a network of distributed cortical areas in the posterior parietal and prefrontal cortices, and that these areas overlap with areas engaged in visuospatial working memory processing. The results suggest that both auditory and visual spatial information is directed along a partially common neural network involving brain areas in the posterior parietal and
prefrontal cortices which have been suggested to be part of the dorsal spatial cortical pathway.

**The Significance of the Activated Brain Areas to Working Memory Processing of Auditory Locations**

An area in the MFG corresponding to BAs 46/9, which in non-human primate studies has been found to be predominantly specialized in visuospatial working memory processing (Goldman-Rakic, 1987; Fuster, 1989), was load-dependently activated during audiospatial n-back tasks. In neuroimaging studies on humans this area has been reported to be activated during spatial and nonspatial visual and verbal working memory tasks (Courtney *et al.*, 1996; McCarthy *et al.*, 1996; Smith *et al.*, 1996; Jonides *et al.*, 1997; Belger *et al.*, 1998; Carlson *et al.*, 1998). In the present study, activation of the MFG (BAs 46/9) cannot be explained merely by an auditory–visual transformation strategy since only three subjects reported having used a visual strategy during the task performances. It is more likely that activation in the MFG was related to mnemonic processing of auditory locations or to some other feature in the auditory tasks which changed systematically when memory load was increased, e.g. the level of attention.

Activation in the more posterior part of the MFG and in subareas of the SFG (SFG/FGd and SFG/SFS), corresponding to BAs 6/8 and including areas of the supplementary motor and premotor cortex, was bilateral in most subjects (Fig. 2A B; Table 1). These areas have been reported to be activated in several earlier neuroimaging studies concerning working memory processing (Courtney *et al.*, 1996; McCarthy *et al.*, 1996; Smith *et al.*, 1996; Jonides *et al.*, 1997; Carlson *et al.*, 1998). Earlier, the premotor areas have been considered to have a role in preparation and sensory guidance of movements (Roland *et al.*, 1980; Wise, 1985), and in recalling and retrieving an appropriate response movement from memory on the basis of a sensory cue (Passingham, 1988, 1989). In the present study, activation in these areas cannot be explained only by preparatory motor activity, as the manual responses were similar at all three load levels, and movement-related activation is subtracted out when the different load levels are compared. The activation here in these areas may thus reflect neuronal activity related to mnemonic processing of auditory locations or to retrieval of the correct response movement from memory for each trial.

The activation detected in the IFG/IFS may have been related to the use of verbal strategies during the task performance, as indicated in the questionnaires by eight subjects. These areas have earlier been shown to be involved in, for example, visual working memory processing (Courtney *et al.*, 1996; McCarthy *et al.*, 1996), mnemonic processing of verbal material and subvocal rehearsal of phonological information during working memory task performance (Paulesu *et al.*, 1993; Smith *et al.*, 1996; Jonides *et al.*, 1997). Activation in the Fpole region was found in all subjects, suggesting involvement of this area in audiospatial working memory processing. This finding is in agreement with an earlier positron emission tomography study in which activity in Fpole was reported to be specifically related to mnemonic processing of auditory information (Petrides *et al.*, 1993).

The SMG and adjacent IPS were load-dependently activated in all subjects, with a more extensive activation in the right hemisphere. This is in line with human lesion studies indicating that right-sided posterior hemisphere lesions impair sound

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**Figure 4.** The control experiment. (A) The audio- and visuospatial 2-back tasks of the control experiment. Auditory and visual stimuli were presented simultaneously. Vertical arrows mark the match trials. The mean (B) percentages of incorrect responses, (C) reaction times and (D) scores of the subjective difficulty levels for the visual and auditory 2-back tasks. Vertical lines indicate SEMs. *P* < 0.05, **P** < 0.01, ***P** < 0.005.
localization and sound movement detection (Bisiach et al., 1984; Griffiths et al., 1996), and with recent neuroimaging studies which indicate that activation in the right parietal cortex is related to perception of spatial sound properties in humans (Griffiths et al., 1998; Bushara et al., 1999; Weeks et al., 1999). The present study demonstrates that not only perception but also working memory processing of spatial auditory information activates the posterior parietal cortex with a right-sided hemispheric predominance.

Functional MRI studies on sensory guided eye movements have detected activation in the precentral and paracentral sulci (frontal and supplementary eye fields respectively) and in the IPS and PreCun (Luna et al., 1998). In addition, memory-guided saccades activate the dorsolateral prefrontal and cingulate cortices (Luna and Sweeney, 1999). In the present study, the subjects were instructed to maintain fixation during memory trials but to blink normally. Since eye movements were not monitored it is not possible to know whether the subjects were able to maintain visual fixation throughout imaging. It is, however, highly unlikely that the subjects would have moved their eyes in a consistent manner during the tasks and that some of the observed brain activation would have been induced by eye movements. It is possible, however, that it was not equally easy to maintain visual fixation during the different n-back tasks and that some of the activity observed in the posterior parietal and prefrontal cortices was related to differences in maintaining eye movement control (visual fixation) rather than working memory processing of information.

Activation in the temporal cortical areas was detected less consistently than in the prefrontal and parietal areas. Lack of activation in the primary auditory areas is not surprising, because in the n-back task paradigm, activation related to auditory perception is subtracted out when data are analyzed. The finding that activation in the temporal lobe in most subjects was in the MTG is interesting in light of lesion studies suggesting that damage to the temporal auditory association cortex impairs short-term memory for tones (Zatorre and Samson, 1991). On the other hand, neuronal recordings in the human MTG have indicated that this area is involved in associative learning of word pairs (Ojemann and Schoenfield-McNeill, 1998). MTG activation in the present study supports the view that this cortical area has a role in complex cognitive processing, and suggests that it participates also in mnemonic processing of audiospatial information.

Overlap of Activated Areas Related to Audiospatial and Visuospatial Working Memory Processing

The control experiment aimed at detecting possible regional differences between activated cortical areas in audiospatial and visuospatial working memory processing. The auditory and visual 2-back tasks had a similar memory load as defined by the number of items to be memorized and the duration of time they were kept in mind. Their difficulty level, however, was different as measured by the reaction times, number of errors and subjective evaluation. This difference may be partly explained by the additional auditory distraction caused by the gradient noise of the MR imaging device. The decision to use the same memory load level — instead of two different memory loads and a similar level of difficulty between the tasks — was based on the aim of comparing working memory-related regional differences between the activated areas in the visual and auditory system. The analysis of the data revealed remarkably few differentially activated brain areas between the audiospatial and visuospatial tasks. This result suggests that working memory processing of audiospatial and visuospatial information engages a common neuronal network. The present results are partially contradictory with a recent PET study by Bushara et al. (Bushara et al. 1999). In their study, modality-specific subareas for auditory and visual spatial localization were identified in the superior parietal lobule, middle temporal and lateral prefrontal cortices. The contradictory results between these two studies concerning modality specificity may be partly due to differences in the experimental designs. Bushara et al. employed three different auditory and visual tasks. In the auditory tasks, in contrast to the present study, the subjects were instructed to keep their eyes closed, whereas in the visual tasks they were fixating a central light-emitting diode. In the control experiment of the present study, auditory and visual stimuli were presented simultaneously to give a similar amount of sensory stimulation in the tasks to be compared. This may have induced inadvertent attention to the unattended stimuli and may thus have contributed to the detected activation. While the present study attempted to match memory loads and to examine the mnemonic component of spatial information processing in the auditory and visual domains, the study by Bushara et al. employed more perceptually dependent tasks. Thus, it may be that perceptual processing of auditory and visual locations activates partially separable subareas in the parietal and prefrontal cortices, whereas the cortical areas participating in working memory processing of visual and auditory spatial information are common.

As in the main experiment, differential auditory activation in the IFG/IFS may be due to verbalization, which was used as a strategy in the performance of the auditory 2-back task by all subjects as compared to only two subjects in the visual task. The finding that the Fpole was differentially activated in the auditory task supports the suggestion that this area is related to mnemonic processing of auditory material.

The Neural Network of Working Memory Processing of Auditory Locations

Neuroanatomical and physiological studies on auditory information processing in the primate brain indicate that the auditory cortex can be divided into three subfields: the core, the belt and the parabelt (Kaas et al., 1999). The parabelt region is connected with several cortical association areas in the temporal, posterior parietal and prefrontal cortices. Electrophysiological recordings in the primate brain have demonstrated that subsets of single neurons in these target cortical areas fire in relation to various cognitive tasks requiring auditory processing (Vaadia et al., 1986; Mazzoni et al., 1996; Linden et al., 1999). A recent study on primes demonstrated that two separate pathways originating from the posterior and anterior nonprimary auditory cortices interconnect the temporal auditory areas with the dorsolateral, and rostral and ventral prefrontal areas respectively, suggesting that acoustic information processing is dissociated into anatomically — and perhaps also functionally — distinct subareas in the prefrontal cortex (Romanski et al., 1999). Less is known about the subdivisions and connections of the human auditory cortex. However, human lesion studies have suggested involvement of the right parietal and frontal lobes in auditory localization and the temporal lobe in spatial perception and pitch retention (Heilman and Valenstein, 1972; Bisiach et al., 1984; Zatorre and Samson, 1991; Griffiths et al., 1996).

The results of the present study suggest that mnemonic processing of auditory and visual locations utilizes the dorsally directed spatial pathway ending in the prefrontal cortex, and
that subareas in the posterior parietal and prefrontal cortices are supramodal, processing both visual and auditory spatial information.

Notes

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