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The functional neuroanatomy of human working memory revisited Evidence from 3-T fMRI studies using classical domain-specific interference tasks

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Abstract

In the present event-related functional magnetic resonance imaging study, the neural implementation of human working memory was reinvestigated using a factorial design with verbal and visuospatial item-recognition tasks each performed under single-task conditions, under articulatory suppression, and under visuospatial suppression. This approach allowed to differentiate between brain systems subserving domain-specific working memory processes and possible neural correlates of more “central” executive or storage functions. The results of this study indicate (1) a domain-specific functional-neuroanatomical organization of verbal and visuospatial working memory, (2) a dual architecture of verbal working memory in contrast to a unitary macroscopic architecture of visuospatial working memory, (3) possible neural correlates for a domain-unspecific “episodic buffer” in contrast to a failure to find brain areas attributable to a “central executive,” and (4) competition for neuronal processing resources as the causal principle for the occurrence of domain-specific interference in working memory. © 2003 Elsevier Science (USA). All rights reserved.

Introduction

Working memory refers to a cognitive system that enables temporary maintenance and further processing of information in the brain. During the last decade, the functional neuroanatomy of human working memory has already been extensively investigated by numerous functional neuroimaging studies. Following the influential three-component model provided by Baddeley and Hitch (1974), most of these studies assessed merely one of the proposed working memory components, i.e., either the phonological loop, the visuospatial scratch pad, or the central executive, in isolation (e.g., Jonides et al., 1993; Paulesu et al., 1993; D’Esposito et al., 1995; Courtney et al., 1996, 1998; Haxby et al., 2000). Different brain systems were found to underlie verbal and visuospatial working memory. So far, only four neuroimaging studies directly compared the neural corre-

lates of verbal and visuospatial working memory in human subjects, thereby yielding inconsistent results. One of these investigations confirmed the dissociation suggested by the numerous studies concerned with a single working memory component (Smith et al., 1996), whereas the other three failed to find such functional-neuroanatomical differences (D’Esposito et al., 1998; Nystrom et al., 2000; Zurovski et al., 2002). Initially, the dissociation between verbal and visuospatial working memory had been established by purely behavioral studies using the so-called dual task approach. In these studies, working memory tasks were performed in combination with other tasks that selectively interfered in a domain-specific way with the primary working memory task (e.g., Baddeley et al., 1975, 1984). Interestingly, this important methodological approach had been overlooked by neuroscientists for a long time.

Only recently two neuroimaging studies have used this fruitful approach to gain further insight into the neural implementation of working memory processes in the human brain. In the first of these studies, articulatory suppression was used to investigate the neural correlates of verbal working memory in humans. Using silent articulatory suppres-

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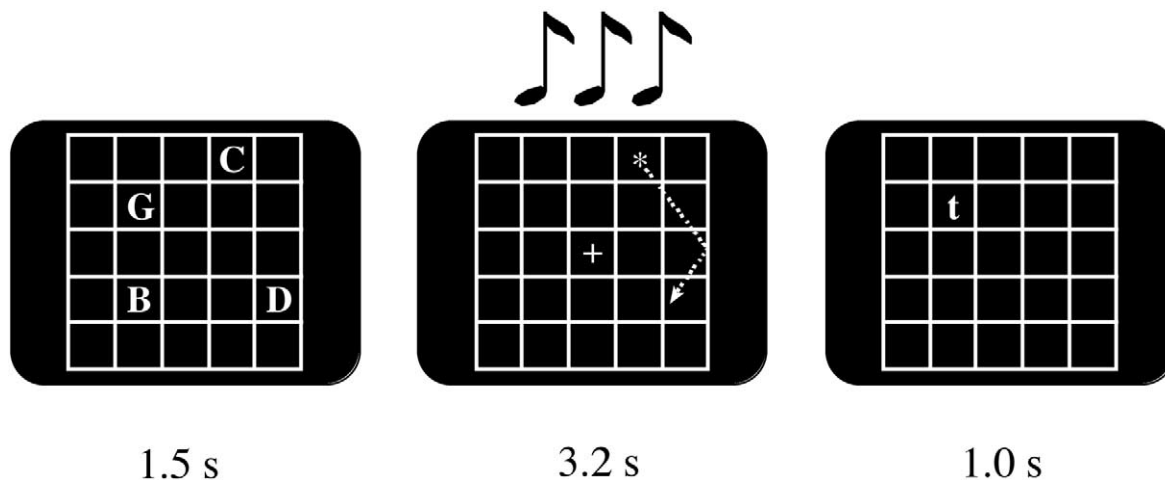


Fig. 1. Experimental design. Using this stimulus material for each of nine possible task combinations, the subjects performed either a verbal item-recognition task, a visuospatial item-recognition task, or a nonmnemonic control task (letter case judgment). During the delay interval, subjects had to either merely fixate the fixation cross in the center of the matrix (single-task condition), to perform, in addition, articulatory suppression by repeatedly subvocalizing “one, two, three, four, one, two, three, four,” and so on to 4-kHz tones that were presented throughout this interval, or to perform visuospatial suppression by following with the eyes the little star that quickly moved across the screen. See Materials and Methods for details.

sion during functional magnetic resonance imaging (fMRI) it was possible to dissociate the “classical” brain areas of the articulatory loop that are involved in explicit verbal rehearsal, from a second network of anterior prefrontal and inferior parietal brain regions that presumably underlie an alternative, nonarticulatory mechanism for maintaining phonological representations, i.e., phonological storage (Gruber, 2001). The second study confirmed that these latter prefrontal and parietal activations did not result from a possible switch to visual memory strategies, but were associated more specifically with phonological working memory under articulatory suppression. Although both phonological and visual working memory processes activated similar prefronto-parietal networks, they were found to be differentially distributed along the same neuroanatomical structures. In particular, while the phonological task variant again yielded strong activations along the anterior intermediate frontal sulcus and in the inferior parietal lobule, working memory for visual letter forms or colours preferentially activated more posterior prefrontal regions along the intermediate and superior frontal sulci as well as the superior parietal lobule (Gruber and von Cramon, 2001).

However, from these two studies cited here it could not be excluded that the activations under articulatory suppression may represent the recruitment of more “central” memory resources, i.e., resources that are not specific to the phonological domain, but which can be generally used when secondary tasks interfere with predominant verbal or visual memory strategies in a domain-specific way. Therefore, the aim of the present event-related fMRI study was to clarify which of the activations observed during verbal working memory performance under articulatory suppression are indeed re-

lated to domain-specific, i.e., phonological, memory processes, and which of these activations underlie more central executive or storage functions. For this purpose, we used a fully crossed design with a verbal and a visuospatial working memory task, each performed under single-task conditions, under articulatory suppression, and under visuospatial suppression (see Fig. 1). We hypothesized that if the activations of the anterior part of the middle frontal gyrus/intermediate frontal sulcus and of the inferior parietal lobule were related more generally to any kind of domain-specific interference in working memory, then these activations should also occur when a visuospatial working memory task is performed under visuospatial suppression. By contrast, those brain regions, that would only be activated during the verbal working memory task under interfering conditions, but not by the visuospatial working memory task under similar conditions of domain-specific interference, could be attributed more specifically to domain-specific processes of phonological working memory.

Materials and methods

Subjects

Thirteen consistent right-handers according to the Edinburgh Inventory (Oldfield, 1971) participated in this study (8 men and 5 women; mean age, 24.9 ± 3.5 years). The project was approved by the regional ethics committee, and all subjects gave written informed consent prior to the experiment. All subjects were pretrained to perform the

experimental tasks at high accuracy levels (see behavioral data in the Results section).

fMRI data acquisition

Imaging was performed on a 3-T MRI scanner (Bruker Medspec 30/100, Bruker BioSpin MRI GmbH, Ettlingen, Germany) with a standard birdcage head coil. Sixteen axial slices (voxel size $3 \times 3 \times 5 \text{ mm}^3$, distance factor 0.2) were positioned in parallel to the AC-PC plane, covering the entire brain. Prior to the functional scans, anatomical MDEFT (modified driven equilibrium Fourier transform pulse sequence) slices and EPI-T1 (echo-planar imaging, T1-weighted) slices were obtained. These measurements were followed by three runs of a single-shot, gradient EPI sequence (TR 2 s, TE 30 ms, flip angle 90° , field of view 192 mm, 64×64 matrix) each acquiring a total of 556 image volumes. Functional imaging was synchronized with stimulus presentation by means of ERTS (Experimental Run Time System, Version 3.11, BeriSoft Cooperation, Frankfurt am Main, Germany). In a separate session, a high-resolution structural scan (3D MDEFT) was obtained for each subject.

Experimental design

A fully crossed, 3×3 factorial design was employed with factors consisting of short-term memory demands in the verbal or in the visuospatial domain, on one hand, and factors consisting of domain-specific interference tasks, i.e., either silent articulatory suppression or visuospatial suppression, on the other. Overall, the experiment contained nine different task combinations that were performed on identical stimulus material (see Fig. 1).

Before each trial a visual cue instructed the subjects which task combination they had to perform next. This cue lasted for 2 s, and then a 5×5 matrix appeared on the screen. For 1.5 s, four squares of this matrix were filled by four letters that were randomly taken out of a set of eight (in German) phonologically similar letters (B, C, D, E, G, P, T, and W). Upon this stimulus material the subjects had to perform either a verbal working memory task (i.e., remembering the four letters independent of their location), a visuospatial working memory task (i.e., remembering the four squares that were filled by the letters independent of the letters themselves), or a letter case judgment task, that was matched for visual, motor, and unspecific cognitive processing, but that did not impose any specific short-term memory demands. To avoid the possibility of two or more adjacent squares being encoded as a single item in the visuospatial working memory tasks, constraints were imposed on selection of the target squares; i.e., no two adjacent squares could be filled by letters.

The target presentation was followed by a 3.2-s delay interval during which the matrix remained on the screen. During this delay there were again three possible task con-

ditions. First, the subjects had to merely fixate the fixation cross in the center of the matrix. Second, they had to perform, in addition, articulatory suppression by repeatedly subvocalizing “one, two, three, four, one, two, three, four,” and so on to 4-kHz tones that were presented throughout this interval with a stimulus-onset asynchrony (SOA) of 300 ms. This secondary task had already been proven to (selectively) interfere with verbal working memory in two prior studies (Gruber, 2001; Gruber and von Cramon, 2001). Third and alternatively, visuospatial suppression had to be conducted by following with the eyes a little star that quickly moved across the screen. Both tracking tasks and eye movements have been shown to effectively interfere with visuospatial, but not with verbal working memory (e.g., see Baddeley and Lieberman, 1980; Baddeley, 1986; Morris, 1989). Furthermore, since it has been proposed that visuospatial rehearsal (as an active component of visuospatial working memory analogous to verbal rehearsal) may be accomplished by means of focal shifts of spatial selective attention to memorized locations (Awh et al., 1999; see, also, Awh and Jonides, 2001) and since it has been shown that overt and covert attentional shifts are subserved by the same network of areas (with overt shifts producing even stronger activation in this network as covert shifts of visuospatial attention; see Beauchamp et al., 2001), the eye tracking task used in the present experiment appears to be perfectly suited to prevent the subjects from using visuospatial rehearsal and, in this sense, to interfere with this visuospatial working memory process.

In the response phase that followed the delay interval, a single letter was presented for 1 s in one of the squares of the matrix. In the verbal working memory trials, the subjects had to decide whether this probe matched one of the target letters. In the visuospatial working memory conditions, the subjects had to judge whether the same square had been filled during target presentation. In the control task devoid of short-term memory demands, subjects had to indicate whether the single letter was uppercase or lowercase. Responses were given by left/right button presses with the index/middle finger of the right hand. The matching proportion was pseudorandomized to 50% in each condition.

After each trial there was an additional fixation interval of 2.3-s duration before the next cue appeared on the screen. Thus, the total trial length was 10 s and the interval between the delay periods of the trials was 6.8 s.

In the verbal working tasks, the subjects were explicitly instructed to rehearse the letters both in the single-task and in the noninterfering dual-task condition (i.e., under visuospatial suppression), and not to use visual memory strategies during articulatory suppression. To preclude a pure visual-matching strategy in this latter task condition, letter case was systematically changed between the targets and the probe (see Fig. 1, for an example). Concerning the visuospatial working memory tasks, the subjects were instructed to perform visuospatial rehearsal, i.e., repetitive attentional shifts to the memorized locations, in both the single-task

Table 1
Mean performance rates in the different working memory tasks in dependence of the secondary task component^a

Primary task	Secondary task		
	None	Articulatory suppression	Visuospatial suppression
Verbal working memory			
Mean percentage correct	95.1%	77.9% ($P < 0.001$)	89.2% ($P = 0.002$)
Mean reaction time	1086 ms	1234 ms ($P = 0.004$)	1089 ms ($P = 0.867$)
Visuospatial working memory			
Mean percentage correct	91.1%	86.5% ($P = 0.174$)	80.7% ($P = 0.019$)
Mean reaction time	955 ms	909 ms ($P = 0.103$)	1132 ms ($P = 0.002$)

^a The statistical values given in parentheses relate to the behavioral effects of articulatory and visuospatial suppression on verbal and visuospatial working memory task performance.

and the noninterfering dual-task condition (i.e., under articulatory suppression). In the variant with visuospatial suppression, they were told to remember the four target squares by memorizing the overall spatial pattern that was build by these squares.

Data analysis

The fMRI data were analyzed using the software package LIPSIA (Lohmann et al., 2001). First, the functional images were corrected for motion artifacts. Then a correction for slice-time acquisition differences was performed by using a sinc interpolation algorithm. Afterward, for each subject the 2D MDEFT and EPI-T1 slices geometrically aligned with the functional slices were coregistered with the high-resolution 3D reference T1 data set. Rotational and translational parameters computed for this registration were stored in an individual transformation matrix. For single-subject analyses, this matrix was directly applied to the functional data resulting in a coregistration with the individual 3D anatomical data set. On the other hand, to prepare statistical group analyses each individual transformation matrix was also scaled to the standard Talairach brain size ($x = 135$, $y = 175$, $z = 120$ mm; (Talairach and Tournoux, 1998) by linear scaling. The resulting normalized transformation matrix was then applied to the individual fMRI data to normalize the functional data sets to the standard stereotactic space. Slice gaps were scaled by using a trilinear interpolation, generating output data with a spatial resolution of 3 mm^3 . Finally, the data sets were spatially smoothed using Gaussian filter kernels with a σ of 1 and 0.5 (for group and single-subject analyses, respectively).

The statistical evaluation was based on a least-squares estimation using the general linear model for serially autocorrelated observations (e.g., Worsley and Friston, 1995). For single-subject analyses a design matrix was generated with a synthetic hemodynamic response function and a response delay of 6 s (Friston et al., 1998). To test for differential activation during the delay intervals of the different tasks, these intervals of 3.2-s duration were modeled as two events occurring at the beginning and in the middle of the delay interval. This resulted in a good approximation

of the synthetic hemodynamic response function to a hemodynamic response evoked by constant activation throughout this epoch. The model equation, including the observation data, the design matrix, and the error term, was convolved with a Gaussian kernel of dispersion of 4-s FWHM. A high-pass filter was applied to correct for low-frequency signal fluctuations. The increased temporal autocorrelation caused by filtering was taken into account by adjustments of the degrees of freedom (Worsley and Friston, 1995). The contrasts between the different task combinations were calculated using t statistics. Subsequently, the t values were converted to Z scores. Group analyses were performed on the normalized functional data in two different ways, first, by use of a one-sample t test at corresponding voxels of individual Z maps across subjects (Bosch, 2000), and second, by random effects analyses that were performed on single-subject contrast images obtained in first-level analyses (Holmes and Friston, 1998). Results are reported for brain activations that reached a voxelwise significance level of $P < 0.001$, uncorrected, in the random effects analyses. In addition, the results of these group analyses were confirmed in individual analyses, which allowed more precise neuroanatomical identification of the brain structures activated in this study.

Results

Behavioral data

As expected, both error rates and reaction times ascertained during fMRI indicated a significant reduction of verbal working memory performance during silent articulatory suppression and of visuospatial working memory performance under visuospatial suppression (see Table 1). There was also a significant influence of visuospatial suppression on (increasing) error rates in the verbal memory task; however, this effect was substantially smaller than the effect of articulatory suppression and, in contrast to the latter, it was not accompanied by a parallel increase in reaction times.

Functional imaging data

To reveal memory-related activations for the different task combinations, we contrasted both the verbal and the visuospatial working memory tasks each under all three possible secondary task conditions (i.e., under single-task conditions, under articulatory suppression, and under visuospatial suppression) with the corresponding nonmnemonic control task combinations (i.e., letter case judgment under single-task conditions, under articulatory suppression, and under visuospatial suppression). Thus, these control tasks were not only matched for general visual, motor, and cognitive processing, but also for the secondary task component. Overall, these statistical comparisons revealed that the verbal and the visuospatial working memory tasks activated very different cortical networks (compare Figs. 2 and 3, see also Fig. 4 for a direct statistical comparison). Complete lists of these activations are given in Table 2 for verbal working memory, in Table 3 for visuospatial working memory, as well as in Table 4 for the significant differences between these domain-specific activation patterns. Like in previous experiments (Gruber, 2001; Gruber and von Cramon, 2001), the effects of the interference tasks on these different cortical networks involved in human working memory were determined by interaction contrasts (e.g. [verbal working memory plus articulatory suppression task versus nonmnemonic control task plus articulatory suppression task] versus [verbal working memory without suppression task versus nonmnemonic control task without suppression task]), and they will be reported separately for each memory domain in the following sections.

Verbal rehearsal that was used in verbal working memory task performance both under single-task and under noninterfering dual-task conditions (i.e., under visuospatial suppression), elicited activations in multiple, predominantly left-sided frontal and parietal brain regions (including Broca's area and the left precentral gyrus), in the cerebellum and in the head of the caudate nucleus (Table 2, parts A and C, left column; Fig. 2a). While visuospatial suppression did not lead to a significant modulation of this memory-related activation pattern, we replicated our previous finding that articulatory suppression has two differential effects on brain activation associated with verbal working memory (Gruber, 2001). First, it significantly reduced (and eliminated) memory-related activity in the left precentral gyrus, which is part of the network subserving verbal rehearsal (Table 2, part A, second and third column; Fig. 2b and c). It is important to note that the left precentral gyrus was also found to be activated by silent articulations themselves (i.e., by the dual-task component that interfered with verbal rehearsal), when these subvocalizations were performed outside the memory tasks (Table 2, part A, right column; Fig. 2d). Second, specifically under the conditions of articulatory suppression, verbal working memory produced additional brain activations in a bilateral frontoparietal network including the cortex along the anterior part of the intermediate

frontal sulcus, the inferior parietal lobule, and the anterior cingulate cortex (Table 2, part B; Fig. 2b and c). By contrast, this network of brain regions was not active when the verbal memory task was performed by intensive rehearsal (see Table 2, part B, left column; Fig. 2a).

On the other hand, activations associated with "visuospatial rehearsal," i.e., visuospatial working memory both under single-task conditions and under noninterfering dual-task conditions (i.e., under articulatory suppression) were observed in a different bilateral prefrontoparietal network including the cortices along posterior parts of the superior frontal sulcus and along the intraparietal sulcus, along precentral, intraoccipital, and occipitotemporal sulci, in the cerebellum and right-sided in parts of the middle frontal gyrus, inferior parietal lobule, and inferior temporal gyrus (Table 3, parts A–C, left column; Fig. 3a). In contrast to its effects in the domain of verbal working memory, articulatory suppression had no effect on these activations associated with visuospatial working memory. By contrast, some of these activated areas were modulated by visuospatial suppression in a similar way as activity in the precentral gyrus (during verbal working memory) was modulated by articulatory suppression. Bilaterally in the cerebellum and along the occipitotemporal sulci, activity related to visuospatial working memory was eliminated by visuospatial suppression (Table 3, part B, second and third column). In addition, activation related to visuospatial working memory was significantly reduced by visuospatial suppression in multiple other brain areas. These brain areas included almost the entire network, which was activated by visuospatial working memory under single-task and noninterfering dual-task conditions (see Table 3, part A, third column; Fig. 3c). While this suppression of brain activation related to visuospatial working memory mirrored corresponding effects of articulatory suppression on activation related to verbal working memory in the left precentral gyrus, the second differential effect of articulatory suppression in the verbal domain (i.e., the occurrence of a network of additional activations; see Fig. 2c) had no counterpart in the visuospatial domain (see Fig. 3c). Furthermore, like in the verbal domain, there were also some regions that were activated by visuospatial working memory irrespective of the secondary task condition and the memory strategy used, and that did not show any significant changes of memory-related activity in response to domain-specific interference (Table 3, Part C). Finally, the visuospatial suppression (i.e., eye tracking) task itself activated many of the brain regions that were also activated by visuospatial working memory, and additionally the visual cortex and the superior part of the left precentral sulcus (Table 3, right-most column).

Overall, verbal working memory and visuospatial working memory under the various secondary task conditions produced activation in very different brain areas. There were only a few regions that were active during working memory tasks in both informational domains. For example, the left precentral gyrus was activated by visuospatial work-

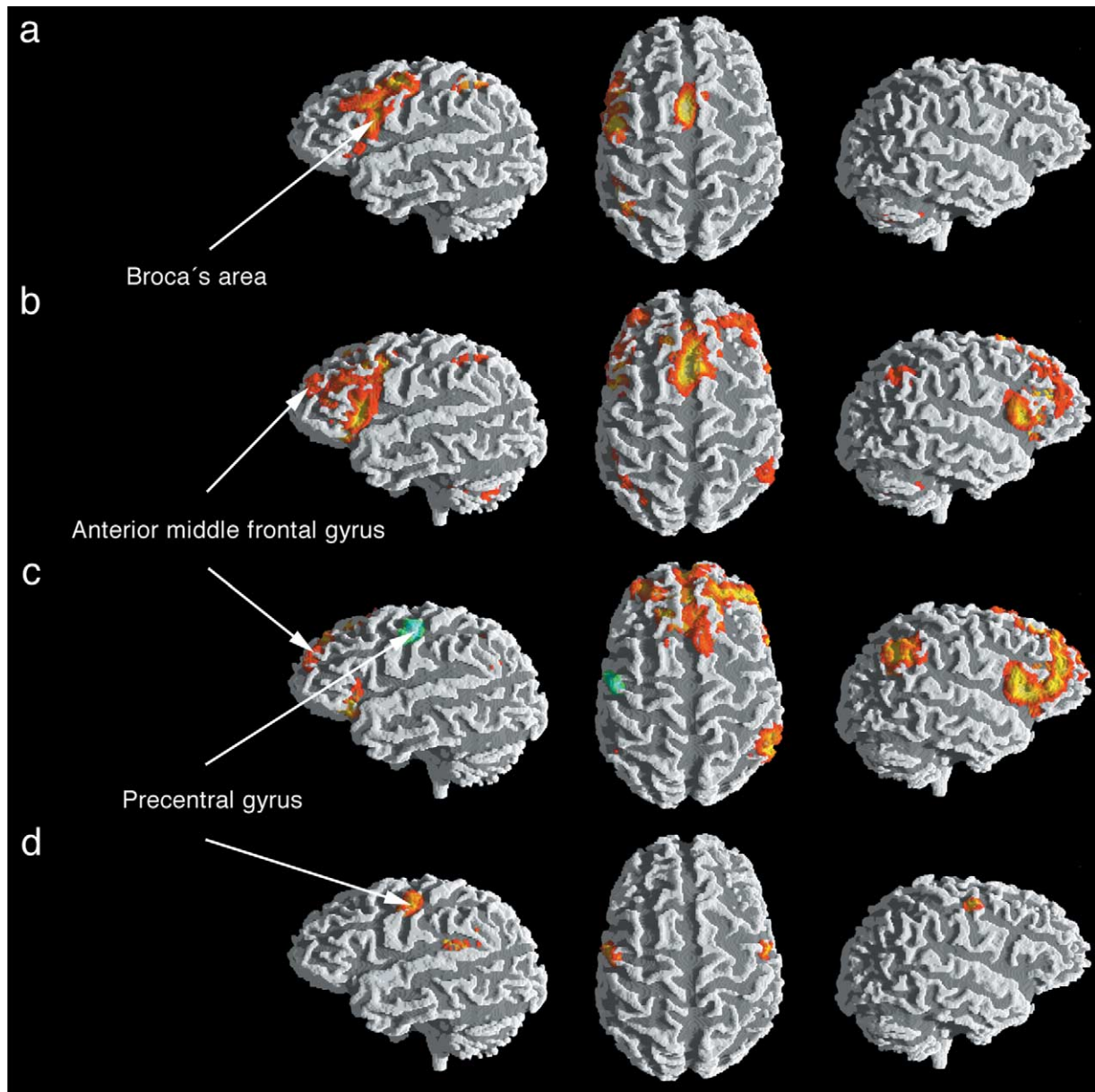


Fig. 2. Group-averaged brain activations (viewed from left, top, and right) associated with (a) verbal rehearsal, (b) phonological working memory under conditions of articulatory suppression, i.e., nonarticulatory maintenance of phonological information, and (d) silent articulations. (c) The modulatory effects of articulatory suppression on these memory-related activations are depicted. Significant increases of memory-related activation under articulatory suppression are indicated in yellow and red, and significant decreases in blue and green. See Table 2 for Z values and spatial coordinates of the activation maxima.

ing memory under each task condition as well as by verbal rehearsal, but not by nonarticulatory maintenance of phonological information during articulatory suppression (Table 2, part A and Table 3, part A). The deep

frontal opercular cortex was active during all memory tasks, and its activity related to verbal working memory was even enhanced by articulatory suppression (Table 2, part C, note the third column, and Table 3, part C).

Fig. 3. Group-averaged brain activations associated with (a) visuospatial working memory as performed by overt shifts of visuospatial attention, i.e., “visuospatial rehearsal,” (b) visuospatial working memory under conditions of visuospatial suppression, and (d) tracked eye movements. (c) The modulatory effects of visuospatial suppression on these memory-related activations are depicted. There were only significant decreases of memory-related activation under visuospatial suppression. These are indicated in blue and green. See Table 3 for Z values and spatial coordinates of the activation maxima.

Fig. 4. Domain specificity of verbal and visuospatial working memory. Depicted are the results from direct statistical comparisons between the two memory-related activation patterns shown in Fig. 2a and 3a (a: verbal > visuospatial working memory; b: visuospatial > verbal working memory). See also Table 4 for Z values and spatial coordinates of the activation maxima.

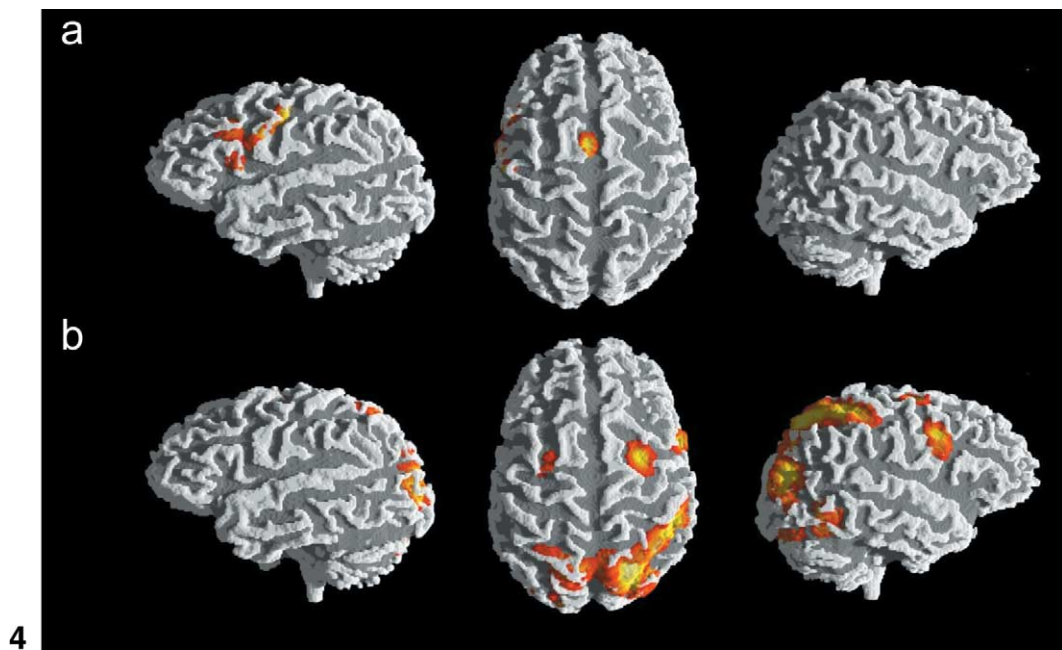
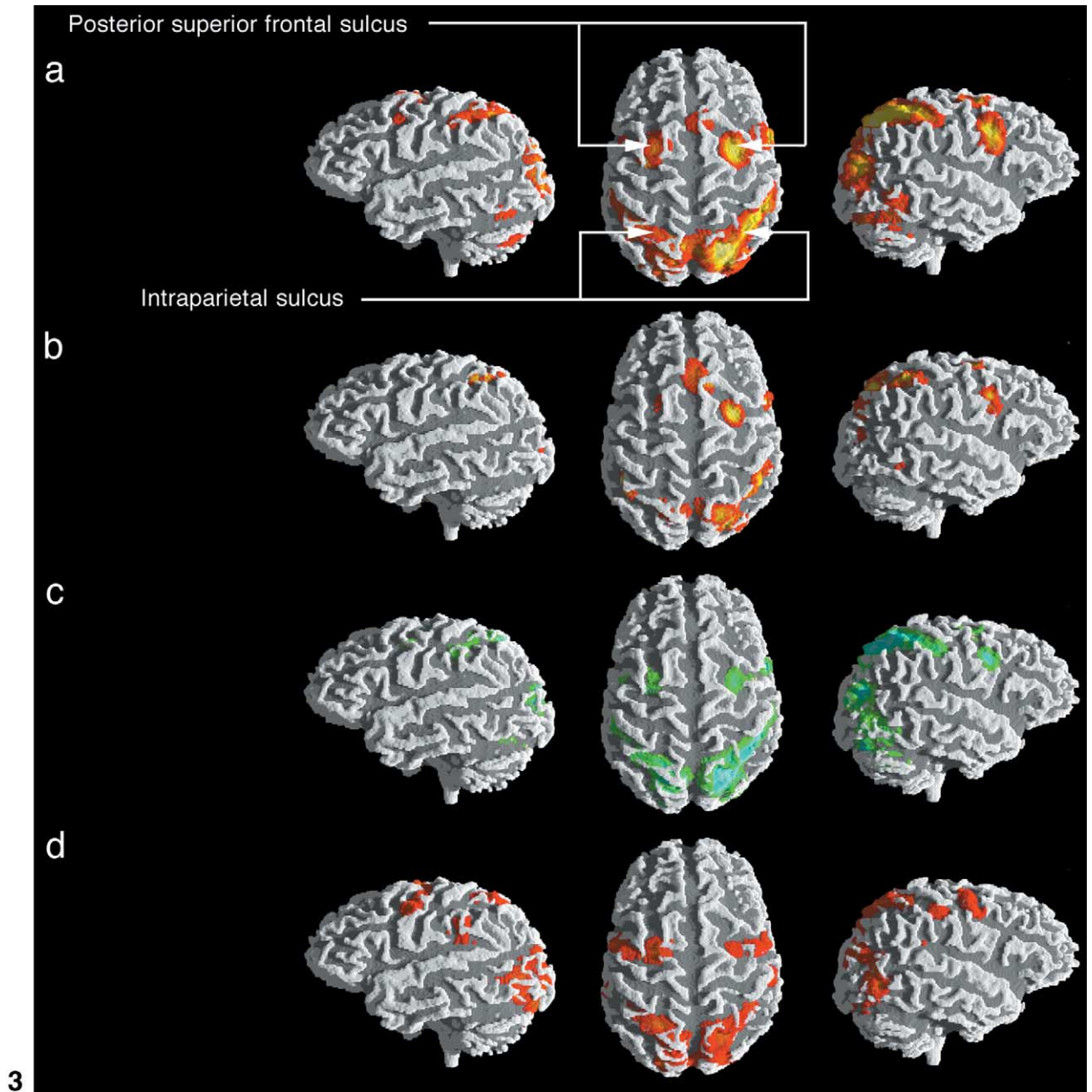


Table 2
Brain regions showing significant activation related to the domain of verbal (phonological) working memory^a

Region	Statistical effects (Z value)			
	Verbal rehearsal	Phonological storage	Effects of articulatory suppression on memory-related activations	Silent articulations
(A) Memory-related activation only in the absence of articulatory suppression				
L precentral gyrus/sulcus	3.94 (−41 6 38)	n.s.	−3.3 (−47 −5 40)	3.57 (−41 12 39)
(B) Memory-related activation only under articulatory suppression				
L intermediate frontal sulcus (BA 46/10)	n.s.	4.48 (−26 51 22)	4.12 (−23 49 25)	n.s.
R intermediate frontal sulcus (BA 46/10)	n.s.	4.80 (40 46 12)	4.63 (25 54 21)	n.s.
L inferior parietal lobule (supramarginal gyrus)	n.s.	3.15 (−50 −41 30)	3.68 (−50 −54 30)	n.s.
R inferior parietal lobule	n.s.	4.10 (52 −49 35)	4.27 (49 −38 30)	n.s.
L anterior cingulate sulcus	n.s.	4.06 (−5 35 20)	4.25 (−14 27 24)	n.s.
R anterior cingulate sulcus	n.s.	4.59 (13 3 35)	5.05 (1 35 34)	n.s.
R ascending branch of the Sylvian fissure	n.s.	4.26 (52 14 7)	4.05 (52 16 4)	n.s.
R inferior frontal sulcus (posterior part)	n.s.	3.86 (37 9 28)	n.s.	n.s.
Anterior frontomedial cortex	n.s.	3.14 (7 64 11)	3.93 (4 64 11)	n.s.
(C) Common memory-related activations (independent of articulatory suppression or, in part, enhanced by articulatory suppression)				
L inferior frontal gyrus (dorsal opercular part)	4.45 (−56 13 19)	3.23 (−56 13 19)	n.s.	n.s.
L ascending branch of the Sylvian fissure	4.40 (−53 14 10)	n.s.	n.s.	
L inferior frontal sulcus (posterior part)	3.33 (−41 10 31)	4.22 (−41 7 31)	n.s.	n.s.
L intraparietal sulcus	3.87 (−41 −35 46)	4.55 (−38 −37 35)	n.s.	n.s.
R intraparietal sulcus	3.55 (31 −45 43)	4.49 (37 −40 36)	n.s.	n.s.
L cerebellum	3.77 (−32 −58 −14)	4.28 (−38 −57 −23)	n.s.	n.s.
R cerebellum	3.82 (31 −55 −15)	3.85 (37 −53 −18)	n.s.	n.s.
L head of caudate nucleus	4.33 (−11 16 4)	4.62 (−14 15 −1)	n.s.	n.s.
R head of caudate nucleus	4.04 (7 23 8)	3.85 (10 20 8)	n.s.	n.s.
R middle frontal gyrus (middle third)	3.07 (37 42 24)	3.96 (40 45 23)	n.s.	n.s.
Pre-supplementary motor area	3.83 (−2 13 45)	4.33 (1 14 47)	n.s.	3.62 (−2 9 54)
L deep frontal opercular cortex	4.57 (−29 31 0)	4.50 (−23 20 6)	4.19 (−32 18 0)	n.s.
R deep frontal opercular cortex	3.69 (31 31 3)	4.34 (34 23 8)	4.21 (40 27 −3)	n.s.
L inferior frontal sulcus (middle third)	3.20 (−41 32 18)	4.53 (−41 28 15)	3.57 (−41 27 13)	n.s.

^a The values given in parentheses are the Talairach coordinates of the activation maxima. BA, Brodmann's area; n.s., not significant; L, left; R, right.

Furthermore, the right middle frontal gyrus and the pre-supplementary motor area (pre-SMA) were activated during all memory conditions without any modulating effects of articulatory or visuospatial suppression (Table 2, part C, and Table 3, part C). Finally, the cortex along the intraparietal sulcus and the cerebellum, which were activated by verbal working memory without a significant modulation due to articulatory suppression, showed a reduction or even an elimination of activation related to visuospatial working memory due to visuospatial suppression (Table 1, part C, and Table 2, parts A and B, note the third column). Important to note, this gross and partial regional overlap of activation due to both verbal and visuospatial working memory does not exclude that a functional dissociation may also exist within these brain regions on a finer neuroanatomical scale.

With respect to the effects of domain-specific interference on brain systems involved in verbal and visuospatial working memory, Figs. 2c and 3c nicely illustrate that these effects were very different for the two domains. This finding was corroborated by direct statistical comparisons between these two domain-specific interference effects that are documented in Table 4. Candidate regions

for domain-specific interference effects could be determined by searching for common activations evoked by the respective primary and secondary tasks, i.e., verbal rehearsal and silent articulations, on one hand, and visuospatial working memory (rehearsal) and tracked eye movements, on the other. These regions comprised the left precentral gyrus for the articulatory suppression effect (compare Fig. 2a and d) and almost the complete network subserving visuospatial memory for the visuospatial suppression effect (compare Fig. 3a and d). Memory-related activity in all these regions was significantly reduced during suppression conditions (Figs. 2c and 3c). Conversely, additional memory-related activations during interfering conditions occurred in a bilateral network comprising the cortex along the anterior parts of the intermediate frontal sulcus and the inferior parietal lobule (Fig. 2c). Most notably, none of these areas were activated by interference in the visuospatial domain (see Fig. 3c), which means that they were specific to the domain of verbal working memory (see, also, Table 4 for the confirmatory direct statistical contrast between the two domain-specific interference effects).

Table 3
Brain regions showing significant activation related to the domain of visuospatial working memory^a

Region	Statistical effects (Z value)			
	Visuospatial rehearsal	Visual pattern storage	Effects of visuospatial suppression on memory-related activations	Eye tracking
(A) Common memory-related activations both in the presence and in the absence of visuospatial suppression, with significant reduction of activity due to visuospatial suppression				
L superior frontal sulcus (posterior part)	3.90 (−26 0 39)	4.03 (−20 8 49)	−3.0 (−23 −5 40)	3.20 (−23 6 52)
R superior frontal sulcus (posterior part)	5.14 (25 3 41)	5.71 (19 12 51)	−3.8 (25 0 42)	3.87 (22 3 41)
L intraparietal sulcus (anterior/middle part)	5.09 (−32 −41 45)	4.56 (−35 −40 47)	−3.6 (−32 −38 44)	2.96 (−32 −35 44)
R intraparietal sulcus (anterior/middle part)	4.50 (28 −49 52)	4.55 (31 −43 48)	−4.2 (31 −38 44)	3.66 (31 −36 41)
L intraparietal sulcus (posterior part)	3.87 (−17 −66 44)	4.81 (−14 −46 49)	−3.0 (−20 −62 49)	3.44 (−23 −46 51)
R intraparietal sulcus (posterior part)	4.54 (19 −55 51)	4.46 (13 −62 49)	−4.2 (19 −55 51)	3.70 (22 −51 53)
L intra-occipital sulcus	4.62 (−26 −70 28)	3.52 (−26 −70 25)	−3.6 (−29 −73 26)	4.23 (−23 −72 28)
R intra-occipital sulcus	5.33 (34 −72 28)	5.52 (34 −72 31)	−4.6 (31 −73 26)	4.13 (31 −67 27)
L precentral sulcus	3.57 (−44 5 35)	3.11 (−47 8 34)	−3.3 (−41 8 37)	3.80 (−47 8 37)
R precentral sulcus/inferior frontal sulcus	4.60 (46 9 25)	4.12 (43 9 25)	−3.8 (49 8 23)	4.11 (52 7 31)
R posterior inferior temporal gyrus	4.19 (49 −55 0)	3.12 (49 −52 −1)	−3.5 (46 −55 0)	4.10 (37 −66 4)
(B) Memory-related activation only in the absence of visuospatial suppression, i.e., elimination of memory-related activity due to visuospatial suppression				
L lateral occipitotemporal sulcus	3.98 (−47 −64 −1)	n.s.	−3.1 (−38 −68 −3)	2.63 (−50 −64 −1)
L cerebellum	4.47 (−23 −61 −13)	n.s.	−3.0 (−29 −63 −10)	3.83 (−32 −52 −15)
R medial occipitotemporal sulcus/cerebellum	4.00 (31 −68 3)	n.s.	−4.7 (31 −68 −6)	3.50 (28 −63 −10)
Cerebellar vermis	4.16 (−2 −71 −17)	n.s.	−4.0 (−2 −69 −23)	3.33 (7 −66 −21)
(C) Common memory-related activations (independent of visuospatial suppression)				
R middle frontal gyrus (middle third)	3.38 (43 40 16)	4.30 (40 41 18)	n.s.	n.s.
Pre-supplementary motor area	3.68 (4 22 43)	4.17 (−2 33 35)	n.s.	n.s.
L deep frontal opercular cortex	3.97 (−29 26 4)	3.88 (−26 24 0)	n.s.	n.s.
R deep frontal opercular cortex	3.82 (28 28 4)	3.65 (31 24 0)	n.s.	n.s.
R inferior parietal lobule	2.79 (52 −42 39)	3.50 (49 −42 39)	n.s.	n.s.
(D) Additional activations during eye tracking				
L visual cortex	n.s.	n.s.	n.s.	5.37 (−5 −72 5)
R visual cortex	n.s.	n.s.	n.s.	5.32 (4 −71 8)
L superior precentral sulcus	n.s.	n.s.	n.s.	3.44 (−41 −1 45)

^a The values given in parentheses are the Talairach coordinates of the activation maxima. BA, Brodmann's area; n.s., not significant; L, left; R, right.

Discussion

In this event-related fMRI study, we investigated the neural correlates of both verbal and visuospatial working memory processes by using a completely crossed factorial design with classical domain-specific interference tasks, i.e., articulatory and visuospatial suppression. This approach permitted a proper differentiation of brain systems that underlie several working memory components. With respect to verbal working memory, these working memory components comprise verbal rehearsal and nonarticulatory maintenance of phonological information (i.e., phonological storage during articulatory suppression). In the visuospatial domain, on one hand, we assessed a component of visuospatial working memory that consists of shifts of attention to the locations to be remembered and that has been proposed to represent a visuospatial rehearsal strategy analogous to verbal rehearsal (e.g., Awh and Jonides, 1998; Awh et al., 1999). On the other hand, we also looked for the neural correlates of an alternative component of visuospatial

working memory that subjects have to rely on when they cannot direct attention toward the memorized locations, i.e., under conditions of visuospatial suppression. Furthermore, we identified brain areas that subservise memory maintenance in a more general way, i.e., independent of both the informational domain and the exact strategy used. Such brain regions could contribute to the function of the episodic buffer, an additional hypothetical component that Baddeley has recently introduced into his model of working memory (Baddeley, 2000). Finally, we also attempted to determine candidate brain regions for central executive functions by searching for activations that are generally evoked by domain-specific interference both in the verbal and in the visuospatial domain of working memory.

Domain specificity of verbal and visuospatial working memory

With regard to the functional-neuroanatomical organization of verbal and visuospatial working memory in the

Table 4

Domain-specificity of the effects of memory task performance and of domain-specific interference in verbal versus visuospatial working memory^a

Region	Statistical effects (Z value)			
	Memory task performance		Domain-specific interference	
	Verbal rehearsal vs. visuospatial rehearsal	Visuospatial rehearsal vs. verbal rehearsal	Domain-specific effects of articulatory suppression vs. domain-specific effects of visuospatial suppression	Domain-specific effects of visuospatial suppression vs. domain-specific effects of articulatory suppression
(1A) Verbal memory-related activation only in the absence of articulatory suppression				
L precentral gyrus/sulcus	3.51 (−47 −4 33)	n.s.	n.s.	n.s.
(1B) Verbal memory-related activation only under articulatory suppression				
L intermediate frontal sulcus (BA 46/10)	n.s.	n.s.	3.61 (−20 44 17)	n.s.
R intermediate frontal sulcus (BA 46/10)	n.s.	n.s.	3.59 (40 49 13)	n.s.
L inferior parietal lobule (supramarginal gyrus)	n.s.	n.s.	2.74 (−44 −51 29)	n.s.
R inferior parietal lobule	n.s.	n.s.	4.25 (46 −36 29)	n.s.
L anterior cingulate sulcus	n.s.	n.s.	3.39 (−11 36 22)	n.s.
R anterior cingulate sulcus	n.s.	n.s.	3.27 (10 35 31)	n.s.
R ascending branch of the Sylvian fissure	n.s.	n.s.	3.98 (49 13 18)	n.s.
Frontomedial cortex	n.s.	n.s.	3.79 (−2 55 12)	n.s.
(1C) Common verbal memory-related activations (independent of articulatory suppression or, in part, enhanced by articulatory suppression)				
L inferior frontal gyrus (dorsal opercular part)	3.33 (−50 15 24)	n.s.	n.s.	n.s.
L ascending branch of the Sylvian fissure	3.38 (−44 23 7)	n.s.	n.s.	n.s.
L inferior frontal sulcus (posterior part)	3.33 (−50 15 24)	n.s.	n.s.	n.s.
R cerebellum	3.76 (19 −52 −13)	n.s.	n.s.	n.s.
L head of caudate nucleus	4.24 (−17 11 7)	n.s.	n.s.	n.s.
Pre-supplementary motor area	3.27 (−5 12 53)	n.s.	n.s.	n.s.
L deep frontal opercular cortex	3.84 (−35 31 3)	n.s.	3.80 (−41 21 −3)	n.s.
R deep frontal opercular cortex	n.s.	n.s.	4.74 (40 27 −1)	n.s.
L inferior frontal sulcus (middle third)	4.10 (−38 36 10)	n.s.	3.20 (−37 39 10)	n.s.
(2A) Common visuospatial memory-related activations both in the presence and in the absence of visuospatial suppression, with significant reduction of activity due to visuospatial suppression				
L superior frontal sulcus (posterior part)	n.s.	4.02 (−23 6 51)	n.s.	−4.2 (−23 −2 39)
R superior frontal sulcus (posterior part)	n.s.	4.56 (22 6 54)	n.s.	−3.6 (22 3 40)
L intraparietal sulcus (anterior/middle part)	n.s.	3.39 (−38 −33 51)	n.s.	−3.9 (−26 −40 47)
R intraparietal sulcus (anterior/middle part)	n.s.	4.72 (37 −36 52)	n.s.	−4.6 (34 −32 45)
L intraparietal sulcus (posterior part)	n.s.	3.65 (−14 −65 46)	n.s.	−3.8 (−20 −49 52)
R intraparietal sulcus (posterior part)	n.s.	4.89 (19 −55 50)	n.s.	−3.9 (19 −55 53)
L intra-occipital sulcus	n.s.	4.45 (−23 −70 25)	n.s.	−4.8 (−23 −66 29)
R intra-occipital sulcus	n.s.	5.54 (31 −73 28)	n.s.	−4.2 (25 −78 18)
L precentral sulcus	n.s.	n.s.	n.s.	−3.8 (−35 2 35)
R precentral sulcus/inferior frontal sulcus	n.s.	4.44 (46 9 25)	n.s.	−3.9 (46 6 28)
R posterior inferior temporal gyrus	n.s.	4.50 (49 −55 −1)	n.s.	−3.2 (46 −57 4)
(2B) Visuospatial memory-related activation only in the absence of visuospatial suppression, i.e. elimination of memory-related activity due to visuospatial suppression				
L. lateral occipitotemporal sulcus	n.s.	3.19 (−38 −57 2)	n.s.	−3.2 (−41 −60 2)
L. cerebellum	n.s.	3.09 (−29 −64 −13)	n.s.	−3.8 (−23 −72 −9)
R medial occipitotemporal sulcus/cerebellum	n.s.	4.99 (37 −58 0)	n.s.	−3.8 (34 −54 1)
Cerebellar vermis	n.s.	3.84 (−2 −71 −18)	n.s.	−4.0 (−5 −72 −23)
(2C) Common visuospatial memory-related activations (independent of visuospatial suppression)				
R middle frontal gyrus (middle third)	n.s.	2.91 (43 46 14)	n.s.	n.s.

^a Data in the sections 1A–C and 2A–C can be related to Tables 2 and 3, respectively.

human brain, we replicated previous findings showing that these two components are represented by different domain-specific cortical networks (e.g., Jonides et al., 1993; Paulesu et al., 1993; Courtney et al., 1996, 1998; Smith et al., 1996; Haxby et al., 2000). While verbal rehearsal elicited activa-

tion in a left-lateralized network including premotor and parietal brain regions, visuospatial working memory activated a bilateral brain system including the cortices along posterior parts of the superior frontal sulcus and along the intraparietal sulcus (compare Figs. 2a and 3a; see Fig. 4).

Prior to this study, four functional imaging studies have compared verbal and visuospatial working memory within the same subjects. Two of them were positron emission tomography (PET) studies (Smith et al., 1996; Zurowski et al., 2002) and the other two were fMRI studies that, in contrast to the event-related design used in the present study, used a blocked design (D'Esposito et al., 1998; Nystrom et al., 2000). Only one of these studies was based on an item-recognition task (Smith et al., 1996). In line with data from both behavioral and neuropsychological studies (as reviewed by Jonides et al., 1996), this study demonstrated a dissociation of verbal and visuospatial working memory that is very similar to the results presented here. By contrast, all other studies investigated working memory functions using *n*-back tasks, and these studies failed to find clear evidence for a dissociation between brain systems devoted to verbal and visuospatial working memory (D'Esposito et al., 1998; Nystrom et al., 2000; Zurowski et al., 2002). This suggests that the inconsistencies of the results of these previous studies may crucially depend on differences between item-recognition and *n*-back tasks. Thereby, it is important to note that the usage of item-recognition tasks is much more appropriate to test for the pure maintenance of information in working memory, because *n*-back tasks are heterogeneous tasks that engage several additional cognitive processes (like memory for serial order, sequencing, and updating of the contents of working memory) and that, for this reason, do not allow a selective testing of maintenance functions in working memory. The present findings confirm the previous observation of a double dissociation between the neural correlates of verbal and visuospatial working memory (Smith et al., 1996), and they suggest that this functional-neuroanatomical dissociation can be obscured by additional processes that are recruited by *n*-back tasks (beyond pure maintenance of information in working memory) and/or by control tasks that may cause rehearsal and storage-related activation to be subtracted out (Fiez, 2001).

Functional-neuroanatomical architecture of verbal working memory

Besides this confirmation of a domain-specific functional organization of verbal and visuospatial working memory, our data replicate further previous results (Gruber, 2001) that demonstrated a dual architecture of verbal working memory in the human brain; i.e., nonarticulatory maintenance of phonological information produced activation in a different network of brain regions compared to verbal rehearsal (compare Fig. 2a and b). This network comprised the cortex along anterior parts of the intermediate frontal sulcus/middle frontal gyrus, the inferior parietal lobule, and the anterior cingulate cortex. No such dual architecture was found for the visuospatial domain, where visuospatial working memory performed under visuospatial suppression activated the same brain areas that were also active when the

task was performed by overt shifts of visuospatial attention, a strategy that has been proposed to represent visuospatial rehearsal (Awh and Jonides, 1998; Awh et al., 1999; see Fig. 3a and 3b). These differential findings of a dual architecture of verbal and a (on the macroscopic level) unitary architecture of visuospatial working memory provide clear evidence that the anterior prefrontal and inferior parietal brain areas, which were activated during nonarticulatory maintenance of phonological information under articulatory suppression, supported working memory task performance in a domain-specific way. Since these areas were not active during visuospatial working memory under comparable conditions of domain-specific interference, activity in these areas cannot be accounted for by central executive processes or by central memory resources like the episodic buffer, a component that Baddeley has recently added into his model of working memory (Baddeley, 2000). Instead, our results suggest that this bilateral prefrontal-parietal network subserves phonological storage, whenever the speech-based rehearsal mechanism is not available or not sufficient to solve the memory task by itself.

Functional-neuroanatomical architecture of visuospatial working memory

There is a current debate of whether visuospatial working memory (in close analogy to verbal working memory) can be subdivided into “active” rehearsal and “passive” storage components (see, for example, Logie, 1995; Vecchi et al., 1995; Bruyer and Scailquin, 1998; Washburn and Astur, 1998). A recent neuroimaging study (Awh et al., 1999) as well as previous behavioral studies (Smyth and Scholey, 1994; Smyth, 1996; Awh and Jonides, 1998) suggest that visuospatial working memory is supported by focal shifts of spatial selective attention, which may form the basis of a visuospatial rehearsal mechanism (Awh and Jonides, 2001). Convergent evidence for this claim comes from repeated observations that visuospatial working memory and visuospatial attention recruit similar networks of brain regions (LaBar et al., 1999; Pollmann and von Cramon, 2000). In the present study, we did not find evidence for a functional-neuroanatomical dissociation of active rehearsal and passive storage mechanisms in visuospatial working memory. Visuospatial working memory activated identical brain areas independent of whether the task was performed by overt shifts of visuospatial attention, i.e., “visuospatial rehearsal,” or whether this strategy was not applicable, i.e., under visuospatial suppression (see Fig. 3a and b). Moreover, most of these brain areas were also activated by mere eye movements during the tracking task (Fig. 3d), which is consistent with the previous finding of overlapping brain systems for visuospatial working memory and saccadic behavior (Postle et al., 2000). However, when the (identical) eye tracking task was combined with visuospatial working memory demands, we found significantly enhanced activation in these brain areas (compared to

the eye tracking task performed alone; Fig. 3b), thus confirming the additional functional role of these areas for visuospatial working memory per se. Finally, it must be noted that, although the two different strategies of visuospatial working memory tested for in this experiment relied on the same network of brain regions (at least on a macroscopic neuroanatomical level), this result still leaves open the possibility that the neural implementation of these working memory processes may differ on a finer grained neuroanatomical level and/or in terms of the functional interactions between different parts of this network.

Brain regions attributable to central memory or executive functions

Recently, a further central/amodal storage component has been proposed to complement the functional architecture of working memory (Baddeley, 2000). In the present study, candidate regions for this hypothetical “episodic buffer” were searched for by looking for brain regions exhibiting memory-related activation irrespective of both the informational domain and the exact memory strategy used. Such activation was found in the right middle frontal gyrus and the pre-SMA as well as bilaterally in the deep frontal opercular cortex and the cortex along anterior and middle parts of the intraparietal sulcus (compare Table 2, part C, and Table 3, part C). By contrast, we did not observe any activations occurring as a general consequence of interference both in the verbal and in the visuospatial domain (compare Figs. 2c and 3c). This result is in line with the data from previous studies, which also failed to find brain areas whose activity could be connected with the so-called central executive (Klingberg, 1998; Adcock et al., 2000; Bunge et al., 2000, 2001).

Neural correlates of interference effects

The similar behavioral effects of articulatory and visuospatial suppression were found to have very different neuroimaging correlates (Figs. 2c and 3c). On one hand, the left precentral gyrus was activated by both the articulatory suppression task (i.e., silent articulations) and by verbal rehearsal (Table 2, part A). This was the only brain region in which activity being related to verbal working memory was eliminated by articulatory suppression (Fig. 2c). Hence, this brain area may be regarded as the primary locus of domain-specific interference in verbal working memory evoked by articulatory suppression. On the other hand, the network of brain regions activated by visuospatial working memory overlapped almost completely with the brain areas activated by the visuospatial suppression (i.e., eye tracking) task (compare Fig. 3a and d), and activity being related to visuospatial working memory was significantly reduced or even disappeared in these regions as a consequence of visuospatial suppression (Fig. 3c). That means that the domain-specific effect of visuospatial suppression was distributed over several brain areas, whereas the effect of articulatory

suppression in the verbal domain was focused on only one brain region. In contrast to these results concerning domain-specific interference effects, we did not find any neural correlates of the partial crossed interference effects observed in the behavioral data, which means that there was no effect of articulatory suppression on brain activation related to visuospatial working memory, nor was there an effect of visuospatial suppression on brain activation associated with verbal working memory. This result highlights the specificity of the domain-specific interference effects observed in the neuroimaging data presented here. On the other hand, it points out that, in part, performance reductions may also represent less specific effects, the possible neurophysiological basis of which may not be detectable by fMRI. Taken together, these findings confirm and further specify previous results suggesting that interference between two tasks may be caused by the fact that the two tasks recruit one or more of the same brain areas (Klingberg and Roland, 1997; Klingberg, 1998).

Conclusion

To sum up, the present study gives rise to the following conclusions that are compatible with the broader literature: (1) Verbal and visuospatial working memory are represented in the human brain by different domain-specific cortical networks. (2) There is a dual architecture of verbal working memory that is represented by two (at least partly) dissociable systems, a left-lateralized premotor-parietal network underlying verbal rehearsal and a bilateral anterior-prefrontal/inferior-parietal network subserving nonarticulatory maintenance of phonological information. (3) By contrast, no clear evidence could be found for a neuroanatomical dissociation of different components of visuospatial working memory; i.e., on the macroscopic level, visuospatial working memory relies on only one (bilateral) brain system including the cortices along posterior parts of the superior frontal sulcus and along the entire intraparietal sulcus. (4) Some brain regions appear to be activated during both verbal and visuospatial working memory tasks, i.e., activity of these brain areas could be attributed to a hypothetical (central) episodic buffer. (5) No evidence could be found for the existence of a brain region generally involved in the resolution of domain-specific interference in working memory, a function generally ascribed to the central executive. (6) It is suggested that domain-specific interference in verbal as well as in visuospatial working memory is caused by the fact that both the memory and the interference tasks demand activation of one or more of the same brain regions. (7) Possible loci for such a neurophysiological interference mechanism to occur comprised the left precentral gyrus for articulatory suppression and almost the complete network subserving visuospatial working memory for visuospatial suppression. (8) Through detection of these neural correlates, domain-specific interference effects in working mem-

ory can be distinguished from other, more general deteriorations of memory performance.

References

- Adcock, R.A., Constable, R.T., Gore, J.C., Goldman-Rakic, P.S., 2000. Functional neuroanatomy of executive processes involved in dual-task performance. *Proc. Natl. Acad. Sci. USA* 97, 3567–3572.
- Awh, E., Jonides, J., 1998. Spatial selective attention and spatial working memory, in: Parasuraman, R. (Ed.), *The Attentive Brain*, MIT Press, Cambridge, MA, pp. 353–380.
- Awh, E., Jonides, J., 2001. Overlapping mechanisms of attention and spatial working memory. *Trends Cogn. Sci* 5, 119–126.
- Awh, E., Jonides, J., Smith, E.E., Buxton, R.B., Frank, L.R., Love, T., Wong, E.C., Gmeindl, L., 1999. Rehearsal in spatial working memory: evidence from neuroimaging. *Psychol. Sci* 10, 433–437.
- Baddeley, A., 2000. The episodic buffer: a new component of working memory? *Trends Cogn. Sci* 4, 417–423.
- Baddeley, A., Lewis, V., Vallar, G., 1984. Exploring the articulatory loop. *O. J. Exp. Psychol. A* 36, 233–252.
- Baddeley, A.D., Grant, W., Wight, E., Thomson, N., 1975. Imagery and visual working memory, in: Rabbitt, P.M.A., Dornic, S. (Eds.), *Attention and Performance*, Academic Press, London, pp. 205–217.
- Baddeley, A.D., Hitch, G.J., 1974. Working memory, in: Bower, G. (Ed.), *Recent Advances in Learning and Motivation*, Academic Press, New York, pp. 47–90.
- Baddeley, A.D., Lieberman, K., 1980. Spatial working memory, in: Nickerson, R.S. (Ed.), *Attention and Performance*, Lawrence Erlbaum Associates Inc., Hillsdale, NJ, pp. 521–539.
- Baddeley, A.D., 1986. *Working Memory*, Oxford University Press, Oxford, UK.
- Beauchamp, M. S., Petit, L., Ellmore, T. M., Ingeholm, J., Haxby, J.V., 2001. A parametric fMRI study of overt and covert shifts of visuospatial attention. *Neuroimage* 14, 310–321.
- Bosch, V., 2000. Statistical analysis of multi-subject fMRI data: assessment of focal activations. *J. Magn. Reson. Imaging* 11, 61–64.
- Bruyer, R., Scailquin, J.C., 1998. The visuospatial sketchpad for mental images: testing the multicomponent model of working memory. *Acta Psychol* 98, 17–36.
- Bunge, S. A., Klingberg, T., Jacobsen, R. B., Gabrieli, J.D., 2000. A resource model of the neural basis of executive working memory. *Proc. Natl. Acad. Sci. USA* 97, 3573–3578.
- Bunge, S.A., Ochsner, K.N., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 2001. Prefrontal regions involved in keeping information in and out of mind. *Brain* 124, 2074–2086.
- Courtney, S.M., Petit, L., Maisog, J.M., Ungerleider, L.G., Haxby, J.V., 1998. An area specialized for spatial working memory in human frontal cortex. *Science* 279, 1347–1351.
- Courtney, S.M., Ungerleider, L.G., Keil, K., Haxby, J.V., 1996. Object and spatial visual working memory activate separate neural systems in human cortex. *Cereb. Cortex* 6, 39–49.
- D’Esposito, M., Aguirre, G.K., Zarahn, E., Ballard, D., Shin, R.K., Lease, J., 1998. Functional MRI studies of spatial and nonspatial working memory. *Brain Res. Cogn. Brain Res* 7, 1–13.
- D’Esposito, M., Detre, J.A., Alsop, D.C., Shin, R.K., Atlas, S., Grossman, M., 1995. The neural basis of the central executive system of working memory. *Nature* 378, 279–281.
- Fiez, J.A., 2001. Bridging the gap between neuroimaging and neuropsychology: using working memory as a case-study. *J. Clin. Exp. Neuropsychol* 23, 19–31.
- Friston, K.J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M.D., Turner, R., 1998. Event-related fMRI: characterizing differential responses. *Neuroimage* 7, 30–40.
- Gruber, O., 2001. Effects of domain-specific interference on brain activation associated with verbal working memory task performance. *Cereb. Cortex* 11, 1047–1055.
- Gruber, O., von Cramon, D.Y., 2001. Domain-specific distribution of working memory processes along human prefrontal and parietal cortices: a functional magnetic resonance imaging study. *Neurosci. Lett* 297, 29–32.
- Haxby, J.V., Petit, L., Ungerleider, L.G., Courtney, S.M., 2000. Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. *Neuroimage* 11, 380–391.
- Holmes, A.P., Friston, K.J., 1998. Generalisability, random effects and population inference [abstract]. *Neuroimage* 7, S754.
- Jonides, J., Reuter-Lorenz, P.A., Smith, E.E., Awh, E., Barnes, L.L., Drain, M., Glass, J., Lauber, E.J., Patalano, A.L., Schumacher, E.H., 1996. Verbal and visuospatial working memory in humans, in: Medin, D.L., (Ed.), *The Psychology of Learning and Motivation*, Academic Press, New York, pp. 43–88.
- Jonides, J., Smith, E.E., Koeppe, R.A., Awh, E., Minoshima, S., Mintun, M.A., 1993. Spatial working memory in humans as revealed by PET. *Nature* 363, 623–625.
- Klingberg, T., 1998. Concurrent performance of two working memory tasks: potential mechanisms of interference. *Cereb. Cortex* 8, 593–601.
- Klingberg, T., Roland, P.E., 1997. Interference between two concurrent tasks is associated with activation of overlapping fields in the cortex. *Brain Res. Cogn. Brain Res* 6, 1–8.
- LaBar, K.S., Gitelman, D.R., Parrish, T.B., Mesulam, M., 1999. Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *Neuroimage* 10, 695–704.
- Logie, R.H., 1995. *Visuo-spatial Working Memory*, Lawrence Erlbaum Associates Inc., Hillsdale, NJ.
- Lohmann, G., Muller, K., Bosch, V., Mentzel, H., Hessler, S., Chen, L., Zysset, S., von Cramon, D.Y., 2001. LIPSIA—a new software system for the evaluation of functional magnetic resonance images of the human brain. *Comput. Med. Imaging Graph* 25, 449–457.
- Morris, N., 1989. Spatial monitoring in visual working memory. *Br. J. Psychol* 80, 333–349.
- Nystrom, L.E., Braver, T.S., Sabb, F.W., Delgado, M.R., Noll, D.C., Cohen, J.D., 2000. Working memory for letters, shapes, and locations: fMRI evidence against stimulus-based regional organization in human prefrontal cortex. *Neuroimage* 11, 424–446.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia* 9, 97–113.
- Paulesu, E., Frith, C.D., Frackowiak, R.S., 1993. The neural correlates of the verbal component of working memory. *Nature* 362, 342–345.
- Pollmann, S., von Cramon, D.Y., 2000. Object working memory and visuospatial processing: functional neuroanatomy analyzed by event-related fMRI. *Exp. Brain Res* 133, 12–22.
- Postle, B.R., Berger, J.S., Taich, A.M., D’Esposito, M., 2000. Activity in human frontal cortex associated with spatial working memory and saccadic behavior. *J. Cogn. Neurosci* 12, 2–14.
- Smith, E.E., Jonides, J., Koeppe, R.A., 1996. Dissociating verbal and spatial working memory using PET. *Cereb. Cortex* 6, 11–20.
- Smyth, M.M., 1996. Interference with rehearsal in spatial working memory in the absence of eye movements. *Q. J. Exp. Psychol. A* 49, 940–949.
- Smyth, M.M., Scholey, K.A., 1994. Interference in immediate spatial memory. *Mem. Cognit* 22, 1–13.
- Talairach, J., Tournoux, P., 1988. *Co-planar stereotaxic Atlas of the Human Brain*. Thieme, Stuttgart.
- Vecchi, T., Monticellai, M.L., Cornoldi, C., 1995. Visuo-spatial working memory: structures and variables affecting a capacity measure. *Neuropsychologia* 33, 1549–1564.
- Washburn, D.A., Astur, R.S., 1998. Nonverbal working memory of humans and monkeys: rehearsal in the sketchpad? *Mem. Cognit* 26, 277–286.
- Worsley, K.J., Friston, K.J., 1995. Analysis of fMRI time-series revisited—again. *Neuroimage* 2, 173–181.
- Zurowski, B., Gostomzyk, J., Gron, G., Weller, R., Schirmer, H., Neumeier, B., Spitzer, M., Reske, S.N., Walter, H., 2002. Dissociating a common working memory network from different neural substrates of phonological and spatial stimulus processing. *Neuroimage* 15, 45–57.