

The neural substrate of orientation short-term memory and resistance to distractor items

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Abstract

We used Positron Emission Tomography to map the neural substrate of human short-term memory for orientation, defined as retaining a single orientation in memory over a long delay, by comparing a successive discrimination task with a 6-s delay to the same task with a brief 0.3 s delay and to an identification control task. Short-term memory engaged the superior parietal lobe bilaterally, the middle occipital gyrus bilaterally and the left dorsolateral prefrontal cortex. In addition, we studied the resistance to a distractor item by comparing the successive discrimination task with long delay, with and without an intervening distractor stimulus. This manipulative process engaged left ventral premotor cortex and left dorsolateral prefrontal cortex. The activation of left dorsolateral prefrontal cortex is interpreted as reflecting co-ordination between task components. These results, combined with those of two previous studies using an identical reduction strategy, underscore the functional heterogeneity in the prefrontal cortex during short-term and working memory.

Introduction

Over the last decade, the neural substrate of human visual short-term and working memory has received the increasing interest of researchers using neuro-imaging techniques and several types of simple and complex visual stimuli presented in a range of task paradigms (for review, see Owen, 1997; D'Esposito *et al.*, 1998). In primates, elementary stimulus attributes have been used with success in investigations into the link between neuronal properties and behavioural performance. For example, Fuster (1981) used simple coloured symbols to investigate visual short-term memory, Newsome & Pare (1988) used dynamic random dot displays in the study of visual motion processing, while Treue & Maunsell (1999) used simple pairs of moving dots in the study of visual attention effects on motion processing. Likewise, our studies of the neural substrate of successive discrimination (temporal same different task, TSD), have successfully used orientation of a grating in monkey inferotemporal (IT) cortex single-cell recordings (Vogels & Orban, 1994) and IT lesion studies (Vogels *et al.*, 1997). Moreover, an approach in which both nonhuman and human primates are studied in parallel using similar stimuli and tasks is extremely powerful, as it allows one to relate single-cell properties derived from the animal models directly to the human imaging results. Indeed, by using the TSD task with orientation as the visual attribute, Orban *et al.*, (1997) have identified human right middle fusiform gyrus as the potential homologue area of monkey IT cortex. The involvement of right fusiform cortex in TSD has been confirmed for other attributes such as direction of motion (Cornette *et al.*, 1998).

Using orientation as attribute, we recently conducted two imaging studies in humans (Cornette *et al.*, 2001a, b), to investigate the neural substrate of the short-term and working memory continuum for orientation, with visual input and performance levels equated across all tasks. 'Ultra-short-term memory' is defined as the capacity to retain a single item over a delay interval of 300 ms, without manipulative operations, which represents one extreme of the spectrum. 'Working memory' (WM) lies at the opposite end of the spectrum and includes maintenance (i.e. storage and rehearsal of multiple items), whether or not accompanied by nonmnemonic manipulative operations. Storage and rehearsal of a single item in 'short-term memory' (STM) is situated in-between the two extremes of the spectrum. STM covers a nondistracted delay interval, generally a few seconds in duration, without manipulative operations.

In the first study, we observed a clear dissociation between TSD and the orientation 2back task, which represent the two extremes of the STM/WM spectrum (Cornette *et al.*, 2001a). While ultra-short-term orientation memory engaged a large expanse of right occipitotemporal cortex, WM for orientation involved left dorsolateral prefrontal cortex (DLPFC), left superior frontal sulcus (SFS) and left supramarginal gyrus. The observed dissociation between the activity patterns involved in ultra-short-term memory and WM for orientation could be due to one or more of the following factors: (i) manipulative operations in a 2back task, such as the continuous updating of stored items, which is intertwined with assigning a temporal order to these items, and inhibiting the responses to irrelevant or distractor items (for review, see Smith & Jonides, 1999); (ii) different numbers of items to be stored and rehearsed (a single item in the TSD task vs. two items in the 2back task) and finally (iii) the duration of the delay. The second study (Cornette *et al.*, 2001b) therefore investigated the neural substrate of orientation updating and identified a medial SFS region (SFSm) as being instrumental in that

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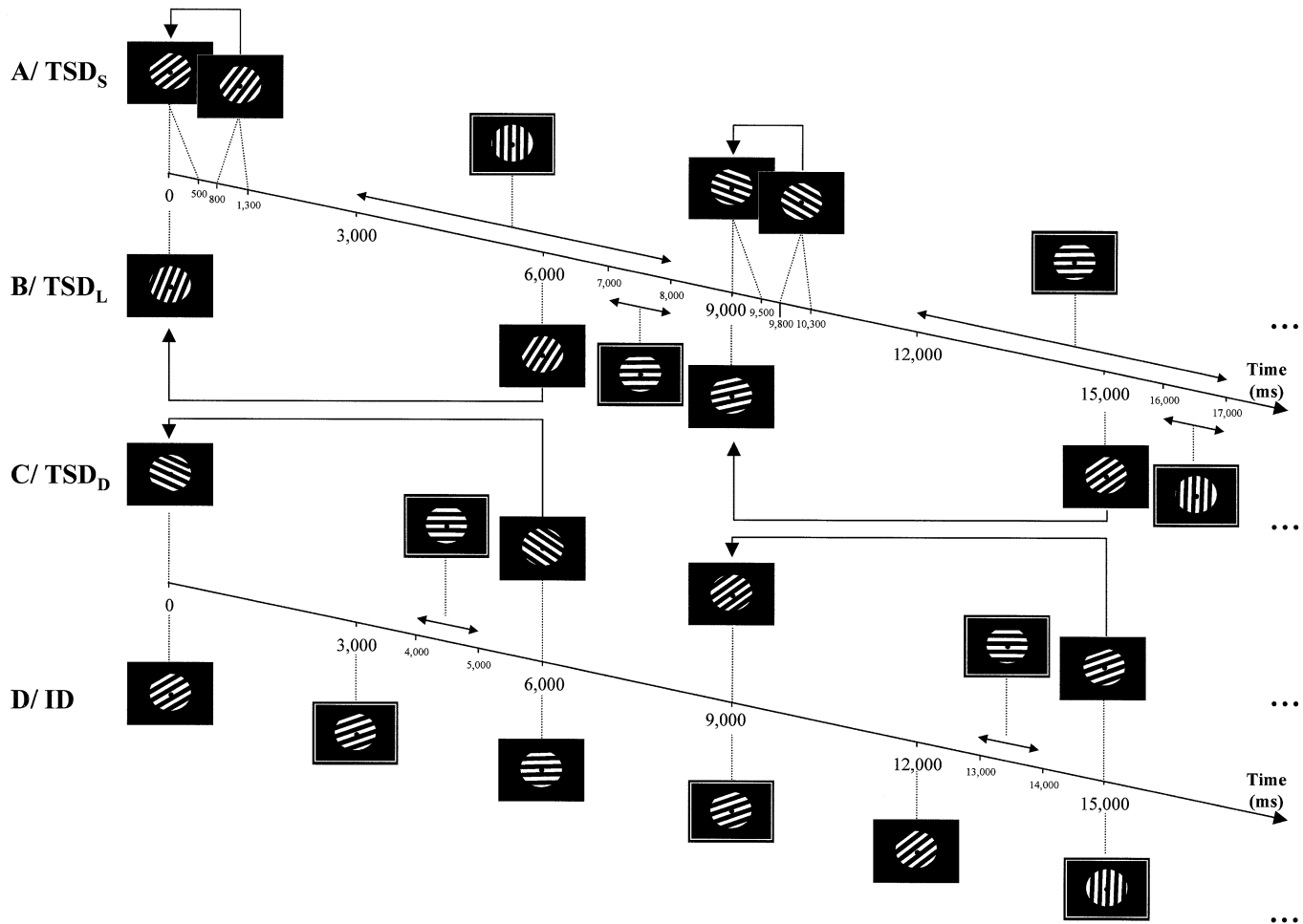


FIG. 1. Schematic representation of stimulus timing in the four tasks: TSD_S task (A), TSD_L task (B), TSD_D task (C) and ID task (D). Duration of stimulus presentation is 500 ms in all conditions. White rectangles outlining gratings refer to the simple identification task. The arrows parallel to the time axis indicate the time interval during which the simple identification task can randomly occur (5000 ms interval for the TSD_S task and 1000 ms interval for the TSD_L task). Other arrows point to the stimulus with which a grating has to be compared. Orientations are shown within both 10–80° and 100–170° ranges. Orientations in the TSD_S task are 40–48°, 93°, 156–148°, 3° ($\delta = 8^\circ$). Orientations in the TSD_L task are 74–64°, 3°, 17–27°, 89° ($\delta = 10^\circ$). Orientations in the TSD_D task are 158°, 3°, 144°, 40°, 178°, 26° ($\delta = 14^\circ$). Orientations in the ID task are 36°, 28°, 3°, 28°, 36°, 88° ($\delta = 8^\circ$). Notice that although the temporal spacing of stimuli among tasks is different, the number of stimuli per minute equals 20 in all tasks.

manipulative operation. In addition, the study identified a distributed frontoparietal network involved in the maintenance of multiple orientations, consisting of left and right lateral superior frontal sulcus (SFSI), bilateral VLPFC, bilateral precuneus and right superior parietal lobe (SPL).

To complete the picture, the current study was designed to address the following two remaining issues, using the same strategy as in Cornette *et al.*, (2001a, b). The first aim was to investigate the neural substrate involved in the storage of a single orientation item over a long delay, as in our previous studies we investigated the storage of three and six items or of a single item for a very brief period. Several imaging studies have already used STM task paradigms, in which subjects have to store and rehearse a single stimulus. These have indicated that the delay duration between two stimuli to compare might have a significant impact on the activity pattern observed. For instance, Haxby *et al.*, (1995), using a face as stimulus and a delayed-(non)match-to-sample task design, parametrically increased the delay interval from 1 s up to 21 s. They observed an involvement of left inferior temporal, inferior parietal, middle and inferior frontal

regions during longer delays, while a negative correlation with longer intervals was found in posterior occipitotemporal regions. Other groups, also using a delayed-(non)match-to-sample task design, compared a long (15 s) to a short (5 s) delay interval, using a complex stimulus pattern (Elliott & Dolan, 1999). Significant activity in anterior temporal and ventrolateral PFC (VLPFC) regions was observed only during longer delays, while medial parietal cortex was involved during short delays. From these studies, which used rather complex stimuli, one cannot predict which region will be recruited during storage and rehearsal of a more elementary attribute, such as orientation, using longer delays. Hence, we decided to lengthen the delay interval during a TSD task from 0.3 s (short delay, TSD_S task) to 6 s (long delay, TSD_L task), similar to the delay interval used in the orientation 2back task (Cornette *et al.*, 2001a). The TSD_S task involves only storage of a single item, taxing ultra-short-term memory, while the TSD_L task involves rehearsal in addition to single item storage, taxing orientation STM. We were interested in seeing whether (part of the) activity pattern involved in the orientation 2back study (Cornette *et al.*, 2001a) would be

similarly recruited during successive discrimination using a 6-s delay, but now involving storage of a single stimulus and in the absence of any manipulative operations.

The second aim was to investigate the neural substrate of resistance to distractor items during storage and rehearsal, a manipulative operation demanded by many of our previously used orientation STM/WM tasks. Short-term and working memory are crucial for reducing distraction by maintaining the prioritization of relevant information (de Fockert *et al.*, 2001). During a 2back orientation task (Cornette *et al.*, 2001a), the temporal comparison between each new probe stimulus and the stimulus shown two trials back is continuously hampered by the presence in memory of the item, shown one trial previously. Although insertion of distraction into an STM task only temporarily interferes with storage and rehearsal operations, it has been suggested that such interference may include several DLPFC-supported operations, such as shifting attention among different components of a task (Rogers & Monsell, 1995), selection among competing responses (Thompson-Schill *et al.*, 1997) or gating of behaviourally irrelevant stimuli (Chao & Knight, 1995). The latter component does not apply in the current context, as in an orientation 2back task each distractor item is actively processed and stored, and thus highly significant. In addition to these executive operations, insertion of a distractor item may induce a more intense refreshing or rehearsal of stored information (Johnson, 1992). However, a recent review of the neuropsychological delayed-response literature indicated that not all DLPFC-lesioned patients demonstrate impaired performance when a delay period was filled with a distractor (D'Esposito & Postle, 1999). It may be that differences in the site of DLPFC-lesion in patients explain a great deal of variance reported in such studies. It may also be that DLPFC contribution becomes important only when subjects need to actively process the distractor item during delayed response tasks. Hence, here we investigate the impact of disrupting a successive orientation discrimination task (i.e. TSD_D, 6 s delay with distractor interspersed). We explicitly asked the subjects to identify the orientation of a distractor grating with the same spatial frequency as the test gratings, as it has been shown that the highest level of interference is obtained when the same visual attribute is to be processed in both test and distractor gratings (Magnussen *et al.*, 1991).

Methods

Subjects

As in our previous study (Cornette *et al.*, 2001b), nine volunteers (mean age 23.5 years, range 17–32) were involved in the current experiment. All subjects were male, right-handed, had normal vision and a normal brain structure as visualized with MRI. There was no history of neurological/psychiatric complaints, pathology or drug abuse. Prior to the PET-session, subjects thoroughly practised all tasks in two, 1.5-h sessions. The study was approved by the Ethical Committee of the Medical School, Katholieke Universiteit Leuven and written informed consent was obtained from all subjects.

Stimulus characteristics

Stimulus characteristics were a static square wave grating (4° in diameter, mean luminance 23.1 Cd/m², contrast 90%, cycle width 1.3°), presented in the central visual field, with a red central fixation point. Only orientations between 10 and 80°, and between 100 and 170° were used, i.e. no vertical or horizontal orientations were shown to avoid verbal and semantic encoding. Phase was randomised between trials and noise was superimposed on the edges of the bars to

prevent subjects from using any cues other than orientation. The stimuli were displayed on a high-resolution colour screen (Philips Brilliance 2120, horizontal width 380 mm, vertical height 285 mm, resolution 800 × 600 pixels, refresh rate 78 Hz noninterlaced), hosted by a 486 TIGA workstation. The monitor was mounted above the scanner bed at an angle of 52° relative to the horizontal. Subjects viewed the stimuli binocularly in a dimly lit room (0.07 Cd/m²) from a fixed distance of 114 cm. Stimuli were presented for 500 ms at a rate of 20 stimuli/min in all tasks. Thus, the stimuli and rate of presentation were the same as those of Cornette *et al.*, (2001a, b). No auditory feedback was provided during the two 1.5-h training sessions or PET-acquisition. Accuracy of fixation was monitored with electro-oculographical recordings.

Task configuration

Tasks were adapted from previous studies (Orban *et al.*, 1997; Cornette *et al.*, 2001a, b) and included successive discrimination (temporal same different, TSD task) with a short delay (TSD_S task), TSD with a nondistracted long delay (TSD_L task), TSD with distractor during the long delay interval (TSD_D task) and an identification task (ID) (Fig. 1). All tasks lasted 150 s. To keep the stimulus presentation rate identical to that of our previous studies (20 stim/min) despite the addition of the distractor gratings, the number of TSD trials was reduced to one every 9 s (i.e. ~7 trials/min), compared to 10 trials/min in our previous studies. In each TSD task, two types of judgements were made. First, the subjects were asked to press the right key for two identical successively presented oblique orientations, bridging a 0.3-s (TSD_S task) or 6 s (TSD_L and TSD_D tasks) delay interval, or left for two different successively presented orientations, within 600 ms after the onset of each second stimulus presentation. Second, subjects in the same trial performed a simple identification of a nearly horizontal (i.e. varying between 3 and 8°; press right) or nearly vertical (i.e. varying between 82 and 87°; press left) orientation. In the TSD_S and TSD_L tasks, subjects performed the identification upon completion of a successive discrimination, i.e. outside the delay interval (see Fig. 1), whereas, in the TSD_D task, subjects identified the orientation of the distractor grating within the 6 s delay interval. Hence, the only difference between TSD_D and TSD_L tasks relates to the interference with orientation storage and rehearsal operations. To prevent any interference with the encoding of the first stimulus presented in each discrimination trial, the distractor item was shown within a 1-s random interval occupying the second half of each 6 s delay interval. In all TSD tasks, the orientation of the gratings to be discriminated differed by an angle, δ .

In order to match the identification control task (ID) with the TSD experimental tasks, subjects performed the simple, or coarse, identification task during the ID task at a rate of 1 per 3 items (i.e. once each 9 s), and the standard, or fine, identification for the other 2 of the 3 gratings. Subjects were presented with either oblique orientations that were tilted $-\delta/2$ (press right) or $+\delta/2$ (press left) degrees from an internal reference orientation (i.e. fine identification judgement), or with nearly horizontal (press right) or vertical (press left) orientations (i.e. coarse identification judgement). A different reference orientation was used in each replication. Subjects pressed right or left keys, depending on the orientation, within 600 ms. The parameter, δ , was used to equate task performance and was individually adapted using the results of the second training session as a guide. All the conditions were matched for the number of left and right motor responses prepared and executed.

In order to equalize the visual input among all tasks and subjects, the stimulus presentations during the TSD tasks were programmed to

include as many orientations as possible within both ranges and to distribute them equally among all subjects (Kolmogorov–Smirnov test for distribution matching). Also, all 27 reference orientations used in the ID tasks were chosen so as to cover the two orientation ranges as homogeneously as possible among subjects, taking into account each subject's orientation threshold.

Training sessions

During practice, the difference δ was gradually decreased for each task, as soon as performance reached a steady level of 80–85% correct for a given difference. The δ at which each subject reached 82% correct at the end of the second training session was then used in the corresponding condition of the PET-study.

Statistical analysis of behavioural data

Task performance during PET-sessions, expressed as percent correct responses, was normalized to Z scores (CSS software) and analysed with analysis of variance (ANOVA). The number of tasks was included as a repetitive factor within each subject. The mean reaction times were calculated as the average of the latencies of all trials in which subjects responded within the response window.

Data acquisition

Brain activity was monitored as the relative change in regional cerebral blood flow (rCBF) using the H215O method (Fox *et al.*, 1986). All measurements were performed in 3D mode with a Siemens-CTI Ecat Exact HR+ (Brix *et al.*, 1997). Subjects were not allowed to speak during the procedure and had been instructed not to think of anything in particular, apart from concentrating on the stimulus and the task. The room was kept as quiet as possible. The head was immobilized with a foam headholder (Smither Medical Products, Akron, Ohio, USA). Each subject had a catheter inserted into the left brachial vein for tracer administration. Accuracy of fixation was monitored with electro-oculographical recordings (EOG), using contact electrodes placed on the outer ocular canthi and a reference electrode placed between the eyes. Before each experiment, the EOG was calibrated for fixation and for horizontally visually guided saccades of 2 and 4° amplitude. A transmission scan was taken (⁶⁸Ge rod sources) to correct for attenuation. The start of each task coincided with the intravenous injection of 300 MBq H₂¹⁵O (half-life, 123 s) over 12 s. Each subject performed all four tasks three times, with a 10 min interval between two successive injections. Different orientations were used in the replications. This yielded 12 emission scans per subject and 27 emission scans per task, similar to our previous study (Cornette *et al.*, 2001b). The order in which tasks were presented was randomised both within and between subjects. Data acquisition (60 s) began as soon as the intracranial radioactivity count rate rose sharply, i.e. usually about 40 s after injection. Total duration of each task performed was 150 s. The attenuation-corrected data were reconstructed using the reproject algorithm (Kinahan & Rogers, 1989) resulting in 63 planes (plane separation, 2.425 mm). The integrated radioactivity counts were used as a measure of rCBF.

Data analysis

Analysis was performed on Sun SPARC computers (Sun Microsystems, Mountain View, CA) with the Statistical Parametric Mapping software (SPM, Wellcome Department of Cognitive Neurology, London, UK), implemented in MATLAB (Mathworks Inc Sherborn MA, USA). Both our previous orientation working memory studies (Cornette *et al.*, 2001a, b) have been analysed with SPM96. Optimal comparison of the current results with our previous studies required the use of a similar template. We therefore decided to

analyse the current set of data using SPM96, as applied in both our previous studies.

Realignment and spatial normalization

The scans from each subject were realigned using the first scan as a reference. The six parameters of this rigid body transformation were estimated using a least-squares approach. Images were subsequently stereotactically transformed to a standard template in the Talairach space (Talairach & Tournoux, 1988). The normalizing spatial transformation matches each scan (in a least-squares sense) to a reference or template image that already conforms to the standard space. The procedure involves a 12-parameter affine (linear) and quadratic (nonlinear) three-dimensional transformation, followed by a two-dimensional piece-wise (transverse slices) nonlinear matching, using a set of smooth basic functions that allows for normalization at a finer anatomical scale (Friston *et al.*, 1995a). Finally, images were smoothed with an isotropic Gaussian kernel of 16 mm full width at half maximal (FWHM). The final image smoothness estimates (FWHM) were $x = 14.9$ mm, $y = 17.0$ mm, $z = 19.2$ mm.

Statistical analysis

Statistical parametric maps (SPMs) are spatially extended statistical processes used to characterize regionally specific effects in imaging data, by combining the general linear model (to create the statistical map of SPM) and the theory of Gaussian fields (to make statistical inferences about regional effects) (Friston *et al.*, 1991; Worsley *et al.*, 1992; Friston *et al.*, 1994). The statistical analysis can be regarded as an ANCOVA, as the design matrix includes global brain activity as a covariate of no interest fixed at 50 mL/(dL.min) (Friston *et al.*, 1995b). The condition, subject and covariate effects are estimated according to the general linear model at each voxel. To test hypotheses about regionally specific condition effects, the estimates were compared using linear contrasts. The resulting set of voxel values for each contrast constitutes a statistical parametric map of the t-statistic SPM(t). The SPM(t) values were then transformed to the unit normal distribution [SPM(Z)]. Activations reaching $P_{\text{corr}} < 0.05$ (corrected for multiple comparisons) for peak height (i.e. $Z \geq 4.44$) were considered significant. Regions significant at $P_{\text{uncorr}} < 0.001$ (uncorrected for multiple comparisons) for height (i.e. $Z \geq 3.09$) were considered equally significant only if based upon an *a priori* hypothesis. Other activation sites significant at $P_{\text{uncorr}} < 0.001$ for height were added for descriptive purpose.

MRI template

Each subject also underwent a high-resolution magnetic resonance imaging (MRI) scan of the brain (1.5 Tesla magnet, Siemens VISION). Acquisition parameters were: repetition time, 10 ms; echo time, 4 ms; flip angle, 8°; field of view, 256 mm; acquisition matrix, 256 × 256. The 3D volume had a thickness of 160 mm, partitioned into 128 sagittal slices. MRI images of each subject were registered to the corresponding PET images using the Multi-modality Image Registration algorithm based on Information Theory (MIRIT, Maes *et al.*, 1997). The same transformations into the standard space as those that were used for the PET images were applied to the resampled (and registered) MRI images. An average ($n = 14$) MRI image in the standard space was constructed and the thresholded parametric maps were projected onto MRI sections for visualization.

Planned analysis

To characterize the impact of delay duration on the storage of a single item, we first investigated the subtraction (TSD_L-TSD_S) and its

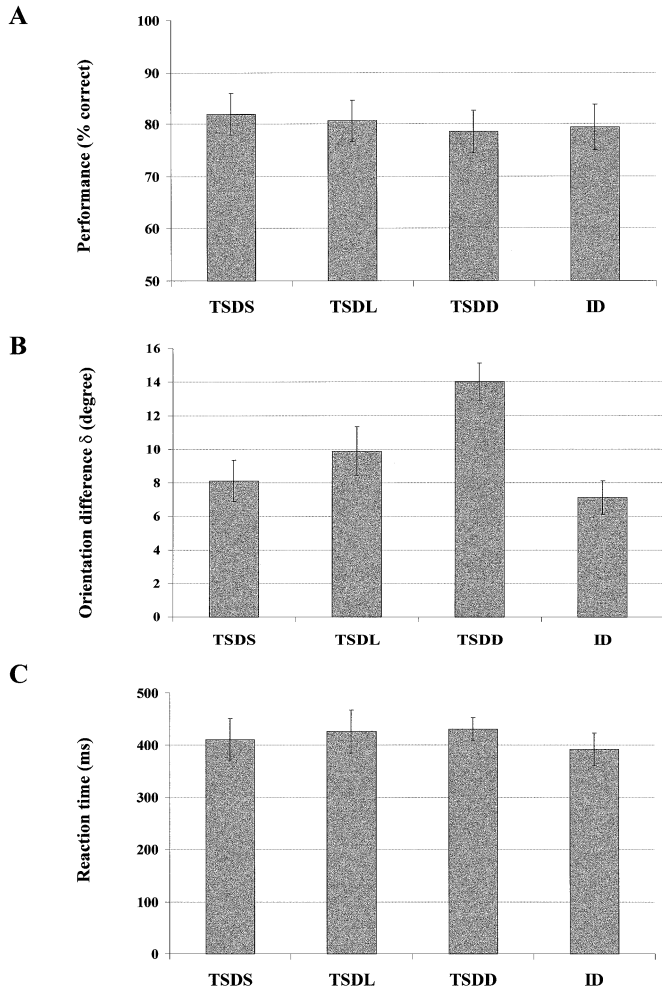


FIG. 2. Psychophysical data. Bar-charts showing for each task: (A) performance expressed as mean correct responses; (B) mean orientation difference δ ; (C) mean reaction times. Error bars indicate SEM.

inverse. To test whether the mnemonic components of orientation STM and ultra-short-term memory engaged separate cortical regions, we then tested all regions resulting from the subtraction ($TSD_L - ID$), i.e. the subtraction isolating the mnemonic components involved in TSD_L , for their significance in ($TSD_L - TSD_S$). Similarly, all regions resulting from the subtraction ($TSD_S - ID$), i.e. the subtraction isolating the mnemonic component involved in TSD_S , were tested for their significance in ($TSD_S - TSD_L$). Regions were considered specifically related to either orientation STM or ultra-short-term memory, if they reached $P_{uncorr} < 0.001$ ($Z\text{-score} \geq 3.09$) in both the simple subtraction isolating a memory type and the direct comparison between TSD_S and TSD_L . This procedure (Haxby *et al.*, 1994; Cornette *et al.*, 2001a) avoids including regions which reach significance in the direct comparisons of orientation ultra-short-term and STM mnemonic components simply because of deactivation in the second element of these comparisons.

To characterize the impact of resistance to a distractor item, we first investigated the subtraction ($TSD_D - TSD_L$). We then investigated which voxels reached $P_{corr} < 0.05$ in the conjunction of the two orthogonal contrasts $[(TSD_L + TSD_D) - 2ID]$ & $(TSD_D - TSD_L)$.

Results

Visual stimulation during PET scanning

Group analysis ($n = 9$) revealed that the visual input, i.e. the distributions of the orientations presented in both the 10–80 and 100–170° ranges, was similar among the various tasks. No significant differences were found between the distributions in any of these four tasks (Kolmogorov–Smirnov, $P > 0.5$).

Task performance during PET scanning

Performance among all four tasks averaged between 78 and 82% correct during PET-acquisition and did not significantly differ among tasks (repeated measures ANOVA $F_{(6,48)} = 1.05$; $P > 0.4$; Fig. 2A). No additional learning occurred during PET-acquisition, as accuracy in all tasks was similar to that at the end of the second training session. Performance levels were equalized by systematically adjusting δ (repeated measures ANOVA $F_{(6,48)} = 264$; $P < 10^{-6}$; Fig. 2B). The value of δ was significantly larger in the TSD_D task than in the TSD_L task (Scheffé test, $P < 10^{-6}$, Fig. 2B), indicating that distractor stimuli in the TSD_D task successfully interfered with the active storage and rehearsal of orientation. In contrast with our previous study (Cornette *et al.*, 2001b), current reaction times were similar among tasks (repeated measures ANOVA $F_{(6,48)} = 1.51$; $P > 0.19$; Fig. 2C). Hence, differences in computational demands between the four tasks are reflected primarily in the value of δ .

Subjects maintained fixation well during both experiments. In all participating subjects, the electro-oculographical recordings were virtually identical to the fixation trace of the calibration during PET scanning. The number of saccades was insignificant in all conditions.

The impact of delay duration on orientation storage and rehearsal

The subtraction ($TSD_L - TSD_S$) characterizes the impact of delay duration on the storage of a single item (Table 1, column A). Three regions in left and right SPL (BA 7) were significant at $P_{corr} < 0.05$: left dorsal intraparietal sulcus lateral (DIPSL), left dorsal IPS medial (DIPSM) and right dorsal IPS medial/lateral (DIPSM/L). Their activity profile, i.e. the adjusted rCBF plotted for all tasks (Fig. 3A), indicates that these regions are engaged during a 6-s delay, with the presence of a distractor item having no significant impact. Note also that all three regions are to some extent involved in the orientation ID task, as shown previously by Faillenot *et al.*, (2001). Other regions significant at $P_{uncorr} < 0.001$ were located in left dorsolateral prefrontal cortex (DLPFC or BA 9/46 and also BA 9), right callosomarginal sulcus (BA 24), left precentral gyrus (BA 6), left and right middle occipital gyrus (MOG, i.e. the upper bank of the transverse occipital sulcus, BA 18) and right inferolateral part of the cerebellum.

The opposite subtraction ($TSD_S - TSD_L$) involved ($P_{uncorr} < 0.001$) several regions in anterior temporal cortex, i.e. right middle temporal (BA 39 and 21) and left superior temporal (BA 22) gyrus (Table 1, column B). In addition, activations were observed in right posterior lingual (BA 18), cingulate (BA 32), right superior (BA 8 and 10) and inferior (BA 47) frontal gyri.

We next tested whether the mnemonic components of orientation STM and ultra-short-term memory engaged separate cortical regions. All regions resulting from the subtraction ($TSD_L - TSD_S$) were tested for their significance in ($TSD_L - ID$). Regions specifically related to orientation STM (Table 1, column A, asterisk, $P_{uncorr} < 0.001$) were left DLPFC, the three regions in SPL and bilateral MOG. We then tested all regions resulting from the subtraction ($TSD_S - TSD_L$) for their significance in ($TSD_S - ID$).

TABLE 1. Orientation storage

Brain Region	(A) TSD _L – TSD _S				(B) TSD _S – TSD _L			
	Coordinates (mm)				Coordinates (mm)			
	x	y	z	Z score	x	y	z	Z score
Frontal								
L middle frontal gyrus, BA 9/46 (DLPFC)	–34	26	32	3.73*	–	–	–	–
L middle frontal gyrus, BA 9 (DLPFC)	–52	30	34	3.14*	–	–	–	–
R callosomarginal sulcus, BA 24	20	–12	44	3.65	–	–	–	–
L precentral gyrus, BA 6	–20	–8	66	3.32	–	–	–	–
R superior frontal gyrus, BA 8	–	–	–	–	12	46	40	4.00
Cingulate gyrus, BA 32	–	–	–	–	6	32	16	3.48
R inferior frontal gyrus, BA 47	–	–	–	–	36	32	–2	3.48
R superior frontal gyrus, BA 10	–	–	–	–	14	60	20	3.39
Parietal								
L superior parietal lobe, BA 7 (DIPSL)	–32	–52	62	5.71†*	–	–	–	–
L superior parietal lobe, BA 7 (DIPSM)	–16	–64	60	5.45†*	–	–	–	–
R superior parietal lobe, BA 7 (DIPSM/L)	26	–64	56	4.72†*	–	–	–	–
Occipital								
L middle occipital gyrus, BA 18 (MOG)	–32	–90	16	4.33*	–	–	–	–
R middle occipital gyrus, BA 18 (MOG)	30	–82	8	4.23*	–	–	–	–
L posterior lingual gyrus, BA 18	–	–	–	–	–24	–84	–22	3.56
Temporal								
R middle temporal gyrus, BA 39	–	–	–	–	46	–62	24	4.13
R middle temporal gyrus, BA 21	–	–	–	–	72	–16	–10	3.23*
L superior temporal gyrus, BA 22	–	–	–	–	–58	–42	20	4.11
Cerebellum								
R inferolateral Cerebellum	40	–38	–36	3.84	–	–	–	–

x, *y*, *z* are the Talairach coordinates of the local maxima (in millimetres); *x* = 0 at the midline (+/–, right/left-sided); *y* = 0 at the anterior commissure (+/–, anterior/posterior); *z* = 0 at the anterior-posterior commissure level (+/–, superior/inferior). L, left; R, right; BA, Brodmann Area; TSD_S, temporal same different task with 0.3 s delay interval; TSD_L, temporal same different task with nondistracted 6 s delay interval; ID, identification task. Z score designates the level of significance: all figures, activation significant at $P_{\text{uncorr}} < 0.001$ (Z-score ≥ 3.09) for peak height; †activation significant at $P_{\text{corr}} < 0.05$ (Z-score ≥ 4.44) for peak height; *regions significant at $P_{\text{uncorr}} < 0.001$ in both (TSD_L – TSD_S) and (TSD_L – ID) (column A) and in both [TSD_S – TSD_L] and [TSD_S – ID] (column B).

Only one region was specifically related to ultra-short-term memory (Table 1, column B, asterisk, $P_{\text{uncorr}} < 0.001$), i.e. the right middle temporal gyrus (BA 21). Hence, the neural substrate involved in orientation STM is clearly dissociated from that involved in orientation ultra-short-term memory.

The impact of a distractor item during successive orientation discrimination

Upon initial consideration, the involvement of left DLPFC in the subtraction (TSD_L – TSD_S) is rather unexpected, as we reported previously that DLPFC is involved predominantly in complex task co-ordination and less so in orientation maintenance (Cornette *et al.*, 2001b). However, the TSD_L task also involves a continuous switching between nondistracted successive orientation discrimination and identification (Fig. 1), requiring careful task co-ordination from the participating subjects. This should apply even more for the TSD_D task. We therefore first investigated the subtraction [(TSD_L+TSD_D) – 2ID], which yielded four significant regions ($P_{\text{corr}} < 0.05$, Fig. 4): left MOG (–34, –88, 12), left DIPSM (–20, –64, 54), right DIPSM/L (32, –64, 60) and left DLPFC (–40, 30, 22). The functional profile of left DLPFC (Fig. 3B) clearly indicates its higher activity level during the orientation TSD_D task. Subsequently, we specifically investigated the impact of a distractor item, testing the significance of all voxels yielded by the subtraction [(TSD_L+TSD_D) – 2ID] in the subtraction (TSD_D – TSD_L). Interestingly, this conjunction analysis yielded only one significant ($P_{\text{corr}} 0.05$) region involved in the combat of a distractor item, i.e. the

ventral premotor region (VPREM, BA 6/44, Table 2). Its functional profile clearly demonstrates the impact of a distractor item (Fig. 3C). Other regions significant at $P_{\text{uncorr}} < 0.001$ were located in left DLPFC (BA 9/46), bilateral SPL (BA 7), right MOG (BA 18) and left posterior fusiform gyrus (BA 18).

Discussion

We characterized the impact of delay duration on the storage of a single item, comparing two successive orientation discrimination tasks with a different delay interval. Short-term memory, involving a long 6 s delay interval, engaged a frontoparietooccipital network, i.e. left DLPFC (BA 9/46), bilateral superior parietal lobe (SPL, BA 7) and bilateral middle occipital gyrus (MOG, BA 18), whereas, ultra-short memory, involving only a 0.3-s interval, recruited mainly anterior temporal regions. In addition, we characterized the neural substrate underlying resistance to a distractor item, which involved a ventral premotor region (VPREM, BA 6/44) and left DLPFC.

Design issues

The use of multiple, closely spaced orientations, different for each 150-s run, made it impossible for subjects to use verbal labels, as confirmed by debriefing the subjects. In addition, the presentation of oblique orientations in the central visual field and the use of phase randomization excluded the contribution of vestibular, visual pos-

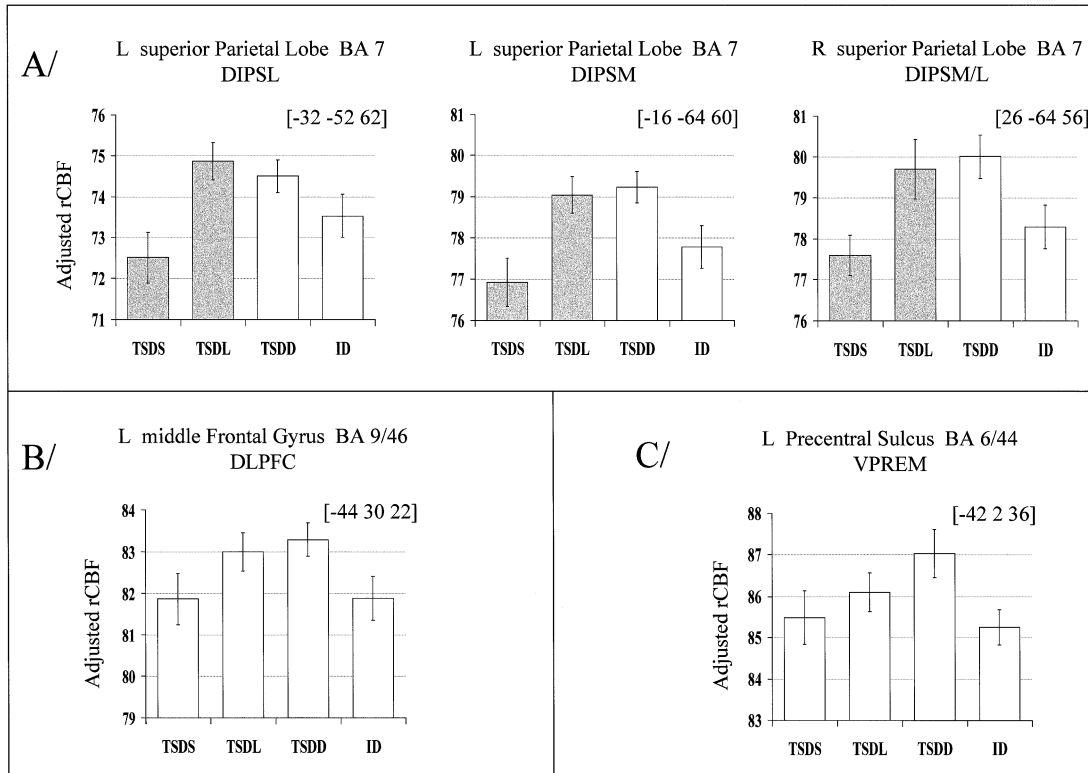


FIG. 3. Functional profiles. (A) Functional profiles of three regions corresponding to the subtraction ($TSD_L - TSD_S$): left DIPSL, left DIPSM and right DIPSM/L. The adjusted rCBF (vertical axis) is plotted for four different conditions (horizontal axis, from left to right: TSD_S , TSD_L , TSD_D and ID tasks). Vertical bars indicate SEM. (B) Functional profile of left DLPFC resulting from the subtraction $[(TSD_L + TSD_D) - 2ID]$. (C) Functional profile of left VPREM resulting from the conjunction between $[(TSD_L + TSD_D) - 2ID]$ and $(TSD_D - TSD_L)$.

itional and rotational cues. Our study therefore differs substantially from other recent neuroimaging studies targeting the neural substrate of STM. First, a recent fMRI (Greenlee *et al.*, 1998) and PET-study (Della-Maggiore *et al.*, 2000) similarly involved a successive discrimination task using sine wave gratings. However, subjects needed to discriminate between gratings differing in spatial frequency. In addition, multiple distractors were used by Greenlee *et al.*, 1998 and gratings were presented at different locations on the screen in the PET study (Della-Maggiore *et al.*, 2000). Unlike the latter report, our study found no significant hippocampal activity, which may be due to the absence of a spatial STM component during our central stimulus presentation (for review, see Kessels *et al.*, 2001). Second, using fMRI, Petit *et al.*, (1998) demonstrated the role of the medial wall structures in visual delayed discrimination tasks. Again, we did not identify any differential activity in medial wall structures, which may be related to the stimuli used (faces vs. simple gratings), the presence of a spatial STM component or the specific task design (multiple items vs. a single item).

The impact of delay duration

We reported previously a functional segregation between ultra-short-term memory for orientation, that engaged right occipitotemporal cortex, and working memory for orientation, that engaged left inferior parietal cortex, DLPFC and SFS (Cornette *et al.*, 2001a). The current demonstration of right anterior temporal cortex recruitment during ultra-short-term orientation memory (Table 1), using a different group of subjects, corresponds well with these results. In addition, here we increased the delay in the successive orientation discrimination task from 0.3 to

6 s, prompting subjects to rehearse the presented visual attribute, in addition to simply storing it. The impact of delay duration was obvious: activation was no longer observed in inferotemporal cortex, but, instead, was shifted to bilateral MOG, bilateral SPL and left DLPFC.

The current results are in agreement with single-cell results. Cells at early processing stages in the visual system respond primarily to very simple attributes of the two-dimensional retinal image, such as the orientations of edges (e.g. Hubel & Wiesel, 1959), whereas neurons in later processing stages respond to increasingly complex aspects of the retinal image, such as faces (e.g. Perrett *et al.*, 1985; Desimone, 1991) or complex motion types (Saito *et al.*, 1986; Lagae *et al.*, 1994). Neurons in anterior IT preferentially process more complex stimulus features than simple bars (Miyashita & Chang, 1988; Tanaka *et al.*, 1991), and also exhibit delay activity significantly more frequently than posterior IT neurons (Fuster, 1990; Mikami, 1995). Thus, one would expect human temporal cortex to be active in delayed match-to-sample tasks involving complex stimuli, as has been observed by Elliot & Dolan (1999). On the other hand, anterior IT neurons have been reported to display delay activity in the TSD_S task (Vogels & Orban, 1994). Thus, although the effect of delay in orientation successive discrimination has not been tested in the single-cells, our results are consistent with the known single-cell results. It has also been reported that neurons in the posterior intraparietal sulcus can be tuned for orientation (Sakata & Taira, 1994) and that posterior parietal neurons are capable of bridging delay period activity (e.g. Andersen *et al.*, 1987; Quintana & Fuster, 1992; Constantinidis & Steinmetz, 1996).

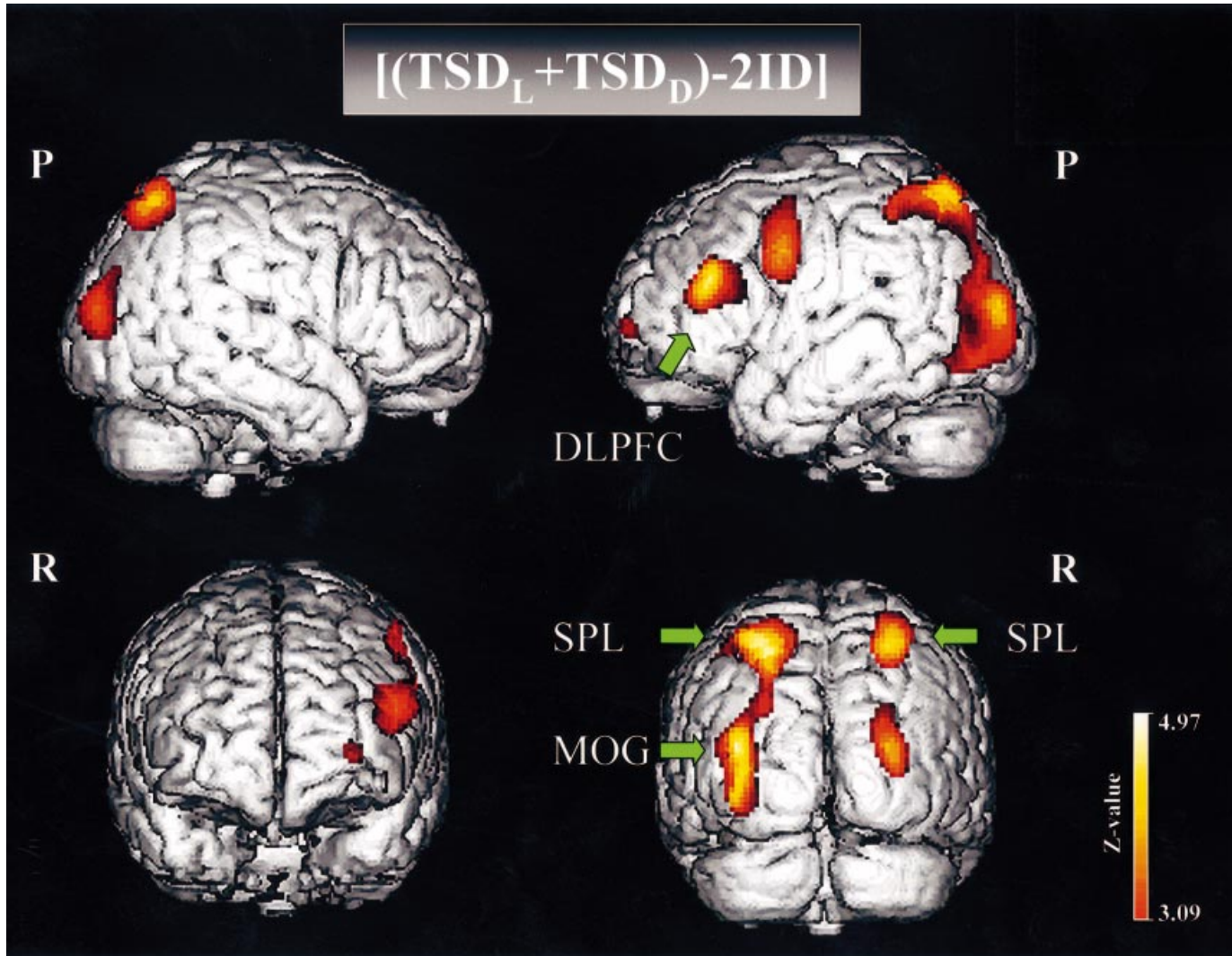


FIG. 4. Rendered images of $[(TSD_L + TSD_D) - 2ID]$. Statistical parametric maps showing the regions differentially active in $[(TSD_L + TSD_D) - 2ID]$, superimposed on a rendered brain. The rendered brain is that of SPM96, in order to ensure optimal comparison of the current results with our previous orientation working memory studies (Cornette *et al.*, 2001a, b). Colour scale of significance is indicated. Regions significant at $P_{\text{corr}} < 0.05$ are: left DLPFC ($-40, 30, 22$), left MOG ($-34, -88, 12$), left DIPSM ($-20, -64, 54$) and right DIPSM/L ($32, -64, 60$). P, Posterior; R, Right hemisphere.

Neuroimaging studies using simple visual stimuli in STM tasks have reported an activity pattern strikingly similar to the pattern we observed in orientation STM. For example, in a recent event-related fMRI study of subjects' expectations regarding the direction of motion, using a simple visual stimulus (array of 50 dots) and a similar delay duration (~ 5 s), storage occurred predominantly in occipitotemporal and parietal regions (Shulman *et al.*, 1999). Baker *et al.*, (1996) reported activation of mediolateral parietal and extrastriate visual cortex during active representation of spatial location in a delayed response task using simple symbols and a delay of 45 s. Zarahn *et al.*, (1999) reported functional changes in right SPL when using a retention delay of 12 s in a spatial discrimination between a simple target and probe vernier stimulus.

At first sight, the involvement of left DLPFC in orientation short-term memory was somewhat unexpected, as we had previously reported that DLPFC is involved predominantly in complex task co-ordination and less so in orientation maintenance (Cornette *et al.*, 2001b). However, the contradiction is only apparent as subjects continuously alternated between two different discriminations (suc-

cessive discrimination and identification) in TSD_L , requiring careful task co-ordination. The need for task co-ordination increased as the interval, in which the grating to be identified could occur, shortened, i.e. in TSD_L and TSD_D (Fig. 2). Although slightly different from the original described dual-task component (i.e. concurrent execution of two tasks, D'Esposito *et al.*, 1995), several recent neuroimaging studies provide converging evidence that any task involving several cognitive components, and hence careful co-ordination of task execution, may yield DLPFC activation. For example, Rowe *et al.*, (2000) reported DLPFC involvement during a 'selection' task and not during maintenance. The selection task itself involved the concurrent execution of multiple cognitive components. Pochon *et al.*, (2001) reported that DLPFC was recruited only when a forthcoming sequential action based on visuospatial information stored in STM was needed.

The impact of distractor items

The current study demonstrates that a region located anterior to the lower part of the left precentral sulcus, i.e. VPREM, is significantly

TABLE 2. Resistance to distractors

Brain Region	Coordinates			[(TSD _L + TSD _D) - 2ID] & (TSD _D - TSD _L)
	x	y	z	
Frontal				
L precentral sulcus, BA 6/44 (VPREM)	-42	2	36	4.48 [†]
L middle frontal gyrus, BA 9/46 (DLPFC)	-44	26	24	3.59
Parietal				
R superior parietal lobe, BA 7 (DIPSL)	34	-68	60	4.00
L superior parietal lobe, BA 7 (DIPSM)	-16	-66	54	3.92
	-22	-74	40	3.49
L superior parietal lobe, BA 7	-46	-42	46	3.37
Occipital				
R middle occipital gyrus, BA 18 (MOG)	28	-86	18	4.39
L posterior fusiform gyrus, BA 18	-28	-78	-6	3.85

See Table 1 for abbreviations and conventions. TSD_D, temporal same different task with distracted 6 s delay interval.

involved when a distractor item interferes with the storage process during a successive orientation discrimination task. This region (-44, 2, 36) is located in the most posterior part of the middle frontal gyrus (BA 6/44), close to the inferior frontal sulcus and clearly differs from the higher located precentral sulcus region involved during a nondistracted orientation discrimination task [(-20, -8, 66), Table 1]. VPREM is also clearly located anterior to the frontal eye fields, based on published co-ordinates (for review, see Paus, 1996; Petit *et al.*, 1997). Furthermore, it closely matches a left precentral focus involved in our previous study using the orientation 2back task (-42, -4, 46), $P_{\text{uncorr}} < 0.001$ (Table 1, Cornette *et al.*, 2001a). It also closely matches the VPREM region commonly observed in functional imaging studies of calculus, as described by Pesenti *et al.*, (2000), (Talairach co-ordinate, -46, -2, 38) and Zago *et al.*, (2001), (Talairach co-ordinate, -40, 0, 36). Indeed, several calculus operations involve resistance to distracting information.

In addition, DLPFC (BA 9/46), located more anterior in the middle frontal gyrus than VPREM, was also involved in the distracted orientation discrimination task, and, hence, points towards a functional heterogeneity within the middle frontal gyrus. As indicated previously, at least two DLPFC-supported executive operations are recruited when subjects are asked to actively process the distractor items, i.e. shifting attention among different components of a task (Rogers & Monsell, 1995) and selection among competing responses (Thompson-Schill *et al.*, 1997). It may well be that different executive operations recruit different subregions within the middle frontal gyrus. Klingberg *et al.*, (1997), using an alternated delayed-match-to-sample task similarly observed activation in a frontal region (-43, 2, 34), closely matching VPREM involved in the TSD_D task. Indeed, it is highly likely that the alternated delayed-match-to-sample task evokes shifting of attention among different task components, similarly evoked by the interference with short-term storage.

Functional heterogeneity in the prefrontal cortex becomes strikingly apparent when we group all relevant foci from the current study and from our two previous studies (Cornette *et al.*, 2001a, b). At least four different regions are significantly involved during various aspects of orientation STM/WM, even when visual input and task performance were similar across all tasks, i.e. SFS, VLPFC, VPREM and DLPFC. We tested the functional segregation of the current short-term orientation memory network from our previously described orientation STM/WM networks. To that end, we tested the differential activity of the left SFSm region (-16, 2, 56), activated

during orientation WM (Cornette *et al.*, 2001b), and the left VLPFC region (-42, 36, -24), activated during orientation maintenance for multiple items (Cornette *et al.*, 2001b) in the subtractions (TSD_L - TSD_S), [(TSD_L+TSD_D) - 2ID] and the conjunction [(TSD_L+TSD_D) - 2ID] & (TSD_D - TSD_L). All Z-scores obtained were < 2, for both regions and their right homologues, indicating a clear functional segregation between the networks described. On the other hand, bilateral SPL is engaged by different types of orientation STM/WM tasks.

Overall, our data fully support the concept of functional heterogeneity within prefrontal cortex (Petrides, 1994; Fuster, 1997): distinct regions in the prefrontal cortex are involved in different aspects of orientation short-term and working memory. This contrasts with the relatively homogeneous recruitment of parietal cortex during these tasks. The use of a simple attribute in both nonhuman and human primates, while maintaining identical visual input across the different tasks and groups of human subjects studied, combined with a careful equalization of task performances, has proved to be an extremely powerful tool to investigate the complex functional organization of the prefrontal cortex.

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Abbreviations

ANOVA, analysis of variance; BA, brodmann area; DIPSL/M, dorsal intraparietal sulcus lateral/medial; DLPFC, dorsolateral prefrontal cortex; EOG, electrooculogram; FWHM, full width at half maximal; ID, identification; IT, inferotemporal; MRI, magnetic resonance imaging; PET, positron emission tomography rCBF; regional, cerebral blood flow; SFSm, superior frontal sulcus, medial part; SFSl, superior frontal sulcus, lateral part; SPL,

superior parietal lobe; SPM, statistical parametric mapping; STM, short-term memory; TSD_D, temporal same different task with distracted long delay interval; TSD_L, temporal same different task with nondistracted long delay interval; TSD_S, temporal same different task with nondistracted short delay interval; VLPMC, ventrolateral prefrontal cortex; VPREM, ventral premotor region; WM, working memory.

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