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Delay-related cerebral activity and motor preparation

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ABSTRACT

Flexible goal-oriented behavior requires the ability to carry information across temporal delays. This ability is associated with sustained neural firing. In cognitive terms, this ability has often been associated with the maintenance of sensory material online, as during short-term memory tasks, or with the retention of a motor code, as during movement preparation tasks. The general issue addressed in this paper is whether short-term storage of sensory information and preparation of motor responses rely on different anatomical substrates.

We used functional magnetic resonance imaging (fMRI) to measure sustained and time-varying delay-related cerebral activity evoked during performance of a delay non-match to sample (DNMS) task, where task contingencies rather than explicit instructions ensured that either sensory or motor representations were used to cross the delay period on each trial. This approach allowed us to distinguish sensory from motor characteristics of delay-related activity evoked by task contingencies, rather than differences in the control of short-term storage driven by verbal instructions.

Holding sensory material online evoked both sustained and time-varying delay-related activity in prefrontal regions, whereas movement preparation evoked delay-related responses in precentral areas. Intraparietal cortex was sensitive to the presence of memoranda, but indifferent to the type of information that was retained in memory. Our findings indicate that short-term storage of sensory information and preparation of motor responses rely on partially segregated cerebral circuits. In the frontal lobe, these circuits are organized along a rostro-caudal dimension, corresponding to the sensory or motor nature of the stored material.

1. Introduction

Adaptive behavior requires the ability to make decisions, avoiding stereotyped reactions to an environmental impulse (Glimcher, 2003). For instance, it can be beneficial, following a sensory instruction, to delay a response until it is appropriate. Under these circumstances, the brain needs to bridge a temporal gap between perception and action. In neural terms, this ability relies on the maintenance of information through internally generated sustained activity (Fuster and Alexander, 1971; Goldman-Rakic, 1987; Vogels et al., 2005). These neural patterns can support different cognitive processes, from the storage of sensory information for prospective behavior (Rainer et al., 1999) to sustained preparation of motor

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responses (Wise and Mauritz, 1985), and abstract rules (Wallis et al., 2001). Empirical tests of models of working memory have focused on the temporary storage of visuospatial and verbal materials, neglecting movement representations as a relevant informational code (Baddeley, 1992; Smith and Jonides, 1999). Here we test whether the neural implementation of short-term storage of sensory information and the preparation of motor responses involve different anatomical substrates.

Some authors have argued against such a dissociation, since the neural system involved in carrying sensory information over temporal gaps could also be involved in generating motor plans (Constantinidis et al., 2001). According to this perspective, sensory features of an instruction are maintained online and there is no commitment to a specific response until its execution. However, motor preparatory mechanisms do not need to maintain a sensory instruction online once the response is selected. Accordingly, other authors have suggested a different interpretation of sustained activity, in which mnemonic and preparatory activities are conceptually and neuronally distinct phenomena (Fuster, 2000). This dissociation has been probed in previous studies, suggesting a dissociation between retention of spatial location and the planning of eye movements in the oculo-motor system (Curtis et al., 2004), and between the retention of spatial locations and manual movement planning (Simon et al., 2002).

Here we have tested the dissociation between sensory and motor codes along a novel dimension. We explore the domain of arbitrary stimulus–response mappings, i.e., flexible learned mappings that transcend the stereotypical performance of spatially congruent sensorimotor associations (Wise and Murray, 2000; Toni et al., 2001). A large body of work on selection and preparation of actions has focused on this type of mappings, pointing to the involvement of the left parietal and left dorsal premotor cortices in the transformation of sensory material into motor responses (Rushworth et al., 2003; Toni et al., 1999). However, given the massively recursive computational architecture of these parieto-frontal circuits (Burnod et al., 1999; Johnson et al., 1996), it remains unclear under which conditions these regions work as distinct modules, as their anatomical features would suggest (Passingham et al., 2002), and whether the sensorimotor gradients found in the premotor cortex (Picard and Strick, 2001; Chouinard and Paus, 2006; Johnson et al., 1996) also apply during online maintenance.

We have tested whether short-term storage of sensory and motor information rely on spatially segregated cerebral structures. We have exploited a novel task in which participants could cross temporal delays interposed between instructions and responses by using either sensory or motor codes (Toni et al., 2002). In previous studies on this issue, participants were verbally instructed to use a particular spatial code to solve a given task (Curtis et al., 2004; D'Esposito et al., 2000; Leung et al., 2002; Simon et al., 2002). However, this approach remains sensitive to differences in the control of short-term storage driven by verbal instructions (Sakai and Passingham, 2003). In this study, we avoid this potential confound by assessing differences in delay-related activity evoked by task contingencies, i.e., participants were driven to use either a sensory or a motor code to cross a temporal delay by exploiting particular combinations of procedurally learned stimulus–response mappings.

Participants solved a DNMS task between two ''sample'' visual patterns and a ''test'' pattern, separated by a time delay. The task involved a comparison of their shape (Fig. 1). We influenced the type of information carried over the delay period by manipulating the relevance of the shape of the test cue for correct performance. Using fMRI, we measured sustained and time-varying delay-related cerebral activity evoked during task performance. This experimental design allowed us to distinguish delay-related activity from transient stimulus- and motor-related effects; and sensory from motor characteristics of delay-related activity, independently from spatial attention.

2. Methods

2.1. *Participants*

We studied nine right-handed volunteers (two females, age range 19–27 years), with normal or corrected-to-normal vision. Participants gave informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem, Nijmegen, Netherlands), and were paid €30 for their participation. Data from two additional participants were discarded because their behavioral data indicated that they failed to engage in motor preparation.

2.2. *Experimental setup*

During the scanning session, participants lay supine in the scanner. Head-movements were minimized by an adjustable padded head-holder. Visual stimuli covered a visual angle of approximately 6° and were projected onto a mirror above the participants' heads. Motor responses were recorded via an MR-compatible keypad (MRI Devices, Waukesha, WI), positioned on the right side of the participants' abdomen. Stimulus presentation and response collection were controlled by a PC running Presentation .81 (Neurobehavioral Systems, San Francisco, CA).

2.3. *Behavioral procedures*

To ensure optimal task performance during the scanning sessions, participants were trained extensively beforehand. In total, there were four training sessions and one scanning session occurring over three consecutive days. In the first training session (day 1), participants learned, by trial and error, to perform a visuomotor associative task (160 trials) relating four shapes to two movements of their right hand (Fig. 1A). Two shapes instructed the flexion of the index finger; the other two shapes instructed the flexion of the middle finger. During each trial, one of the four shapes [instruction cue (IC), 300 msec] was visually presented. A variable delay (.5–2.5 sec in steps of .5 sec) was followed by a tone [trigger cue (TC), 1000 Hz, 300 msec]. The TC informed the participants to deliver the motor response specified by the IC. On each trial, immediately after the movement, a visual feedback stimulus (a green 'V' or a red 'X') was presented (200 msec), informing the participants whether the movement was correct or not.

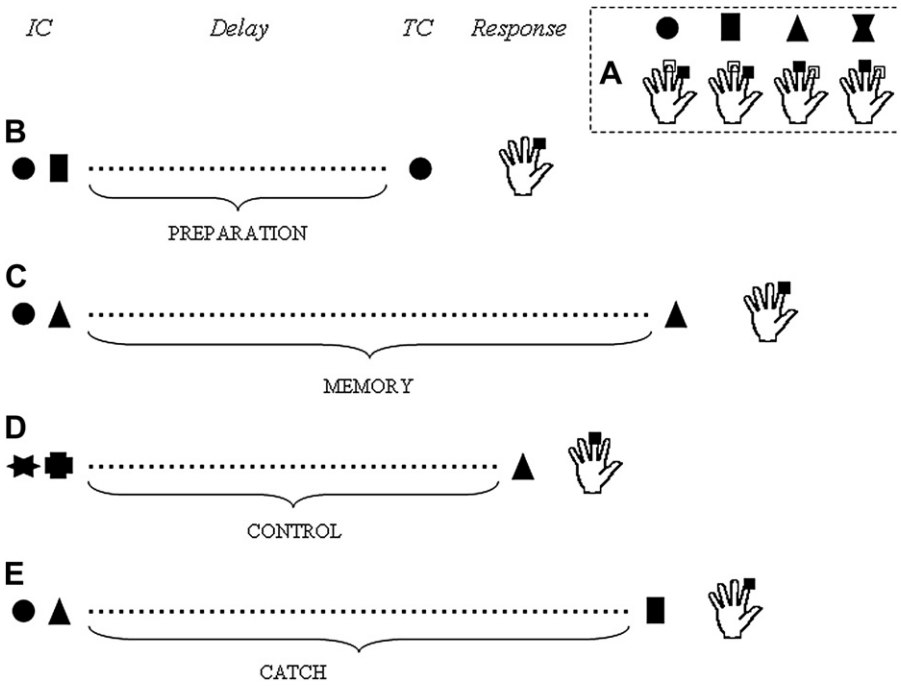

Fig. 1 – Diagram of the experimental task. (A) Stimulus–response associations. Each of four visual stimuli was associated with one of two different movements. (B–E) DNMS task. Two of the four stimuli were briefly presented (sample, 300 msec). A variable delay (delay, 1–21 sec) was followed by the brief presentation of one of the four stimuli (test, 300 msec). Participants were instructed to press the finger specified by the non-matching shape between the set of three shapes presented in that trial (IC and TC). IC and TC shapes were paired as to evoke (B) movement preparatory activity (PREPARATION – in these trials the pattern configuration allowed the participants to prepare the correct response immediately after the presentation of the sample); (C) maintenance of sensory items (MEMORY – in these trials the pattern configuration required the participants to compare the shape of the test and sample stimuli); or (D) no memory load (CONTROL – in these trials the correct response was fully specified by the test stimulus). During the pre-scanning training phase, CATCH trials were also presented (E), to prevent the use of alternative strategies during MEMORY trials.

In the second training session (day 1), participants learned, by trial and error, to perform a DNMS task (Toni et al., 2002) (450 trials). Two ''sample'' shapes (IC) out of a set of six (Fig. 1) were visually presented for 500 msec. The set of IC shapes was constituted by the four shapes used in first training session (i.e., shapes associated with a particular finger movement) and by two novel shapes not associated with any movement. A variable delay (1–5 sec in steps of 1 sec during the first 200 trials; 1–21 sec in steps of 5 sec during the subsequent 250 trials) was followed by the presentation (300 msec) of a ''test'' shape (TC) out of the same set of four shapes used in the first training session. To solve the DNMS task, the participants were required to press the finger specified by the non-matching shape among the set of three presented shapes (two sample stimuli and one test stimulus). In most trials, the test shape matched one of the two sample stimuli. When this was not the case (see below), the participants were required to press the finger specified by the test shape. The response was to be provided as quickly as possible after the presentation of the TC. The presence of an RT cut-off (range: 2000–700 msec, decreasing every 50 trials) forced participants to emphasize response speed. On each trial, immediately after the movement, a visual feedback stimulus (a green 'V' or a red 'X') was presented (200 msec), informing the participants whether the movement was correct or not. When participants responded after the RT cut-off, a message ('too late') appeared on the screen.

The critical experimental manipulation embedded in the DNMS task was the following. An IC was composed by a pair of shapes that could have instructed (i) the same movement; (ii) different movements; (iii) no movement (Fig. 1B–D). When the two sample shapes instructed the same movement (Fig. 1B), then the test shape invariably matched one of the two instruction stimuli. It follows that the correct response was completely specified by the instruction shapes. In these trials (PREPARATION trials, 30% of trials), the participants could have selected the response after the presentation of the IC, and therefore could hold the movement ready during the delay. Therefore, delay-related responses evoked during these trials can be taken to include the effects of carrying motor material over a temporal gap.

When the two sample shapes instructed different movements, then the test shape could have matched (70%) or not one of the two sample stimuli. It follows that the correct response was specified by the comparison between sample and test shapes. In these trials (MEMORY trials, Fig. 1C, 30% of trials), the participants needed to wait until the presentation of the test shape to be able to compare the sensory

characteristics of test and sample stimuli and select the appropriate response. In those trials in which the test shape did not match either of the two sample stimuli (30% of trials where the pair of shapes instructed different movements), the participant applied the rule that required them to press the finger specified by the test shape (see above). These were CATCH trials (Fig. 1E). Their presence allowed us to probe whether the participants were solving the MEMORY trials by applying an alternative strategy to the one detailed above. Namely, during MEMORY trials, the participants could have simply opted for performing the movement that was not instructed by the TC. This alternative strategy did not require the participants to hold the IC shapes online, but it relied on the TC being invariably matched to one of the two sample stimuli. Thus, if the participants used this alternative strategy, they would have been unable to perform the CATCH trials correctly. Therefore, delay-related responses evoked during MEMORY trials can be taken to include the effects of carrying sensory material over a temporal gap.

When the two sample shapes instructed no movement (Fig. 1D), then the test shape did not match any of the two sample stimuli, since the TC was drawn from the set of four shapes previously associated with a specific movement. It follows that the correct response was completely specified by the test shape alone. In these trials (CONTROL trials, 30% of trials), the participants needed to wait until the presentation of the TC to select the appropriate response, and the sample shapes did not need to be compared with the TC in order to solve the task. Therefore, delay-related responses evoked during these trials can be taken to reflect effects not specifically associated with carrying sensory or motor material over a temporal gap.

On the third training session (day 2), participants were further trained on the DNMS task for 250 trials, with delays varying between 1 and 21 sec (in steps of 5 sec). For the last 200 trials, participants performed the task without visual feedback.

The fourth training session (day 3) took place just before the start of the scanning session. Participants practiced the DNMS task for 50 trials before entering the MR scanner and for 50 trials inside the scanner just before scanning. Afterwards, the scanning session started and participants performed the task for 120 trials. During the scanning session, the delay between IC and TC varied between 1 and 21 sec (uniform distribution), and the inter-trial interval varied between 1 and 13 sec (uniform distribution). Feedback, including 'too late' feedback, was not provided. Furthermore, unknown to the participants, there were no CATCH trials during the scanning session. CATCH trials were removed in order to keep the length of the scanning session to a minimum. A total of 120 trials, distributed evenly across the MEMORY, PREPARATION, and CONTROL conditions, were presented. The experimental session lasted for approximately 40 min per participant, resulting in a total of 900–1100 functional images per participant.

These settings optimized the ability of our DNMS task to induce participants to bridge temporal delays interposed between instructions and responses by using either sensory or motor codes. By the same token, it should be emphasized that our task cannot be compared to the trial-unique DNMS tasks used to assess item recognition (Kowalska et al., 1991; Suzuki et al., 1993).

2.4. *Experimental timing*

During the scanning session, the length of the delay period varied across trials between 1 and 21 sec (uniform distribution). The inter-trial interval varied between 1 and 13 sec (uniform distribution). The delay period lengths and inter-trials intervals, and the randomization of trials over the session were determined separately for each participant. The onset of trials was randomized with respect to volume acquisition.

The experimental timing and the wide range of delays enabled us to characterize the evoked hemodynamic responses (EHR) at a finer temporal resolution than the actual TR (Josephs et al., 1997) and allowed us to characterize the blood oxygen level dependent (BOLD) responses to independent components (Toni et al., 1999; Mars et al., 2005, 2007) aligned with the IC, with the TC, and extending over the delay period. This model distinguishes between responses that are comparable in duration across trials (i.e., IC- or TC-related response) and responses that vary according to the delay length (i.e., sustained delay-related activity). Therefore, this approach can effectively distinguish between these two types of responses even if the IC-related responses are not transient but extend some seconds into the delay period. The extensive range of delays ensured that the participants were ready to respond at any time after the presentation of the IC (Toni et al., 2002). The pseudorandom presentation of different trial types ensured that the participants could not anticipate the order of the conditions.

2.5. *Behavioral analysis*

Mean response times (RTs) and error rates (ERs) measured during the scanning session were analyzed separately and considered as dependent variables in a 3×5 repeated measures analysis of variance (ANOVA) with main effects of TRIAL TYPE (three levels: MEMORY, PREPARATION, and CONTROL) and DELAY LENGTH (five levels, arising from the subdivision of the instructed delays into bins of equal duration). Participants were considered as a random factor. The alpha-level was set at $p = .05$, univariate approach, Huynh–Feldt corrected.

2.6. *Image acquisition*

Images were acquired using a 3 T Trio scanner (Siemens, Erlangen, Germany). BOLD sensitive functional images were acquired using a single shot gradient echo-planar imaging (EPI) sequence (TR/TE 2.430 sec/40 msec, 33 transversal slices, ascending acquisition, voxel size $3.5 \times 3.5 \times 3.5$ mm). Following the experimental session, structural images were acquired using a MP-RAGE sequence (TR/TE/TI 2.3 sec/3.93 msec/1100 msec, voxel size $1 \times 1 \times 1$ mm).

2.7. *Image analysis*

Functional data were pre-processed and analyzed using SPM2 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). The first five volumes of each participant's data set were discarded to allow for T1 equilibration. The image timeseries were spatially realigned using a sinc interpolation algorithm that estimates rigid body transformations (translations,

rotations) by minimizing head-movements between each image and the reference image. The timeseries for each voxel were realigned temporally to the time of acquisition of the middle slice. Subsequently, images were normalized onto a custom MNI-aligned EPI template (based on 28 male brains acquired on the Siemens Trio scanner at the F.C. Donders Centre) using both linear and 16 nonlinear transformations and resampled at an isotropic voxel size of 2 mm. Finally, the normalized images were spatially smoothed using an isotropic 8 mm full-width-at-half-maximum Gaussian kernel. Each participant's structural image was spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997) and spatially normalized by using the same transformation matrix applied to the functional images.

The fMRI timeseries were analyzed using an event-related approach in the context of the General Linear Model. Analysis of the imaging data considered main effects of trial type and trial Epoch [10 levels: IC, MEMORY-DELAY$_{SUST}$, PREPARATION-DELAY$_{SUST}$, CONTROL-DELAY$_{SUST}$, MEMORY-DELAY$_{RAMP}$, PREPARATION-DELAY$_{RAMP}$, CONTROL-DELAY$_{RAMP}$, MEMORY-TC, PREPARATION-TC, CONTROL-TC]. IC- and TC-related effects were modelled as delta functions. Delay-related activities were modelled as (i) square-waves time locked to the onset/offset of the corresponding IC/TC and extending over the delay period (DELAY$_{SUST}$ component); and as (ii) triangular-waves time locked to the onset/offset of the corresponding IC/TC and ramping-up over the delay period (DELAY$_{RAMP}$ component). Delay-related activity was thus defined by a time interval rather than by a specific time point, and we accounted for both sustained and (linearly) time-varying activity occurring over the delay period. Each of these functions was then convolved with a canonical hemodynamic response function (Friston et al., 1995b), and down-sampled at each scan in order to generate regressors modelling the main effects described above.

Separate covariates including trials with incorrect or missing responses, corrective responses, trial-by-trial variations in RT, head-related movements (as estimated by the spatial realignment procedure) and a constant term over scans were also considered in the model. Furthermore, we also included terms describing the average white-matter intensity and cerebral–spinal fluid intensity as extracted from the EPI timeseries following a standard segmentation procedure. These regressors were meant to capture scan-by-scan variations in global signals unconfounded by task-related BOLD changes. Data were high-pass filtered (cut-off 500 sec) to remove low frequency confounds, such as scanner drifts. Temporal autocorrelation was modelled as an AR(1) process.

2.8. Statistical inference

The statistical significance of the estimated EHR was assessed using *t*-statistics in the context of a multiple regression analysis. The null hypothesis was that the variance explained by a given regressor was consistent with the residual error, once the variance explained by the other components of the model was accounted for. Linear compounds (contrasts) were used to determine the effects associated with each task component, generating *t*-values for each voxel in the image, i.e., statistical parametric maps (SPMs) of *t*-values.

In the current study, the focus is on activity elicited during the delay period in each of the three experimental conditions described above (PREPARATION, MEMORY, and CONTROL). Having taken confounding factors such as IC-, TC-, and movement-related activity in separate regressors (see above), we focused our contrasts on the regressors capturing delay-related activity.

We isolated both differential delay-related responses (indicated by ">") and common delay-related responses (indicated by "∩") (Nichols et al., 2005). Futhermore, we assessed both sustained delay-period activity and activity showing increasing activity (captured in the DELAY$_{SUST}$ and DELAY$_{RAMP}$ regressors, respectively). This time-varying activity was also taken into account following reports of increasing memory-related activity in the dorsolateral prefrontal cortex with increasing load (Narayanan et al., 2005) and increasing preparatory activity, as indexed by cortico-muscular coherence, with increasing response probability (Schoffelen et al., 2005). Considering these earlier studies, we only tested for increasing time-varying activity, although in principle our statistical model is unbiased with respect to the direction of the effect.

We assessed the spatial distribution of the following effects:

(a) We isolated sustained delay-related responses showing stronger activity during the MEMORY trials than during the PREPARATION and CONTROL trials, ensuring that this differential activity was driven by relative increases during the MEMORY trials rather than decreases during the PREPARATION and CONTROL trials. These constraints were implemented in the following contrast: (MEMORY-DELAY$_{SUST}$ > PREPARATION-DELAY$_{SUST}$) ∩ (MEMORY-DELAY$_{SUST}$ > CONTROL-DELAY$_{SUST}$), masked by (PREPARATION-DELAY$_{SUST}$ > 0 ∩ CONTROL-DELAY$_{SUST}$ > 0).

(b) We isolated sustained delay-related responses showing stronger activity during the PREPARATION trials than during the MEMORY and CONTROL trials, ensuring that this differential activity was driven by relative increases during the PREPARATION trials rather than decreases during the MEMORY and CONTROL trials. These constraints were implemented in the following contrast: (PREPARATION-DELAY$_{SUST}$ > MEMORY-DELAY$_{SUST}$) ∩ (PREPARATION-DELAY$_{SUST}$ > CONTROL-DELAY$_{SUST}$), masked by (PREPARATION-DELAY$_{SUST}$ > 0 ∩ CONTROL-DELAY$_{SUST}$ > 0).

(c) We isolated sustained delay-related responses showing common differential activity during MEMORY and PREPARATION trials as compared to the CONTROL trials. These constraints were implemented in the following contrast: (MEMORY-DELAY$_{SUST}$ > CONTROL-DELAY$_{SUST}$) ∩ (PREPARATION-DELAY$_{SUST}$ > CONTROL-DELAY$_{SUST}$).

(d) We isolated time-increasing delay-related responses evoked during the MEMORY trials as compared to the PREPARATION trials, ensuring that this differential activity was driven by relative increases during the MEMORY trials rather than decreases during the PREPARATION trials. These constraints were implemented in the following contrast: (MEMORY-DELAY$_{RAMP}$ > PREPARATION-DELAY$_{RAMP}$), masked by (MEMORY-DELAY$_{RAMP}$ > 0).

(e) We isolated time-increasing delay-related responses evoked during the PREPARATION trials as compared to the MEMORY trials, ensuring that this differential activity was driven by relative increases during the PREPARATION trials rather

than decreases during the MEMORY trials. These constraints were implemented in the following contrast: (PREPARATION-DELAY$_{RAMP}$ > MEMORY-DELAY$_{RAMP}$), masked by (PREPARATION-DELAY$_{RAMP}$ > 0).

Gaussian field theory allowed us to make inferences corrected for the number of non-independent comparisons (Friston et al., 1995b). The effective degrees of freedom of the error term took into account the temporal autocorrelation of the data (Friston et al., 1995a).

We used a fixed-effects analysis to asses the effects of our experimental manipulations at the group level. Our experiment was not designed to make inferences at the population level but rather to assess the cerebral dissociability of two distinct cognitive processes. Hence, our results speak only to the question of whether the processes of retaining stimulus or motor codes can be dissociated at the cerebral level and do not make any claims on the size of these effects in the human population. The statistical inferences adopted a cluster-level threshold of $p < .05$, corrected for multiple comparisons over the whole brain using the family-wise error correction (Friston et al., 1996). Cluster-level statistics considers the spatial extent of activity laying above a given intensity threshold. In this study the intensity threshold was set at a conservative $t = 4$ (conservative in the context of cluster-level statistics, Friston et al., 1994). This allowed us to maximize the anatomical specificity of the inferences (high intensity threshold) while preserving the increased power of cluster-level statistics. Tables 1 and 2 report the corresponding intensity level *t*-values.

To ensure the reliability of our effects we assessed the presence of the effects in each participants. This was done by determining for each participant whether the relevant standardized beta weight reliably exceeded the noise levels for this effect. This procedure, although different from the current practice of performing random-effects analyses, is a valid method for describing the reliability of the effect across a group (Rosnow and Rosenthal, 1989).

For areas displaying time-varying delay-related activity, we plotted the BOLD signal time course during the scanning session for each condition separately. In particular, we calculated the inter-subject average and standard error of the peak BOLD response for each of 10 consecutive and equally spaced time bins along the delay period.

2.9. *Anatomical inference*

Anatomical details of significant signal changes were obtained by superimposing the SPMs on the structural images of each subject in MNI coordinates. The atlas of Duvernoy (Duvernoy et al., 1991) was used to identify relevant anatomical landmarks. When applicable, Brodmann areas (BAs) were assigned on the basis of the SPM Anatomy Toolbox (Eickhoff et al., 2005), i.e., the anatomical position of our significant clusters and local maxima was formally tested against published three-dimensional probabilistic cytoarchitectonic maps.

3. Results

3.1. *Behavioral performance*

Fig. 2 illustrates the mean error rates (ERs) and RTs as a function of delay during the three trial types, obtained during the scanning session. The data indicate that our design was successful in inducing participants to bridge the delay period between IC and TC by using different mental representations. Participants were faster and made fewer errors during the PREPARATION trials than during the CONTROL and MEMORY trials (main effect of TRIAL TYPE – ER: $F(2,16) = 22.929$, $p < .001$; RT: $F(2,16) = 48.76$, $p < .001$). Also, there was a significant main effect of delay on error rate ($F(4,32) = 4.371$, $p = .006$). Crucially, delay length differentially affected the PREPARATION and the MEMORY trials (TRIAL TYPE × DELAY LENGTH interaction – ER: $F(8,64) = 3.26$, $p = .004$). Post-hoc comparisons revealed that during MEMORY, but not during PREPARATION or CONTROL, the error rate increased as a function of the delay interposed between the IC and the TC ($p < .003$). This indicates that the mental representations used to bridge the temporal gap between IC and TC during the MEMORY trials were more labile than those used during the PREPARATION trials. Because Fig. 2 shows a strong trend on RT, we assessed the modulation of RT by delay in each condition, using a linear regression for each participant. Participant's beta weights were tested at the second level using a one-tailed *t*-test. This post-hoc analysis revealed shortening in RT with increasing delay length in both PREPARATION ($p = .044$) and CONTROL ($p = .007$) conditions, but not in the MEMORY condition.

Table 1 – Differential delay-related sustained activity

Anatomical region	Stereotactic coordinates			*t*-value	Cluster size	Occurrence
(memory$_{sust}$ > preparation$_{sust}$) ∩ (memory$_{sust}$ > control$_{sust}$) (masked incl. by preparation$_{sust}$ > 0 ∩ control$_{sust}$ > 0)						
Mesial superior frontal gyrus	−6	8	52	6.82	172	8/9
Superior frontal sulcus	−28	−6	70	6.49	162	9/9
(preparation$_{sust}$ > memory$_{sust}$) ∩ (preparation$_{sust}$ > control$_{sust}$) (masked incl. by preparation$_{sust}$ > 0 ∩ control$_{sust}$ > 0)						
Mesial superior frontal gyrus	−6	−12	54	11.59	602	8/9
Central sulcus/precentral gyrus	−36	−26	48	6.11	247	7/9
memory$_{sust}$ > control$_{sust}$ ∩ preparation$_{sust}$ > control$_{sust}$						
Intraparietal sulcus	−44	−52	54	6.42	584	7/9
Putamen	−26	6	−12	4.52	41	7/9

Table 2 – Differential delay-related time-varying activity

Anatomical region	Stereotactic coordinates			t-value	Cluster size	Occurrence
$MEMORY_{RAMP} > PREPARATION_{RAMP}$ (masked incl. by $MEMORY_{RAMP} > 0$)						
Middle frontal gyrus	−40	62	−2	4.57	43	6/9
$PREPARATION_{RAMP} > MEMORY_{RAMP}$ (masked incl. by $PREPARATION_{RAMP} > 0$)						
Precentral gyrus	−52	2	46	5.50	41	8/9

A paired-samples t-test was performed on the RT of correct MEMORY and CATCH trials measured during the third training session (last 200 trials) in order to ensure that participants were retaining sensory information during the MEMORY trials (see Section 2.3). Note that, apart from the presence of CATCH trials, the task procedures used during this training session were identical to those used during the scanning session. RTs evoked during the MEMORY and CATCH trials did not differ ($t(8) = 1.057$, n.s.), indicating that in both conditions participants used a similar strategy to solve the task (Toni et al., 2002).

3.2. *Imaging data: sustained delay-related activity*

The following section describes the SPMs associated with sustained delay-period activity. Significant differential delay-related responses are listed in Table 1.

First, we isolated sustained delay-related responses showing stronger activity during the MEMORY trials than during the PREPARATION and CONTROL trials, ensuring that this differential activity was driven by relative increases during the MEMORY trials rather than decreases during the PREPARATION and CONTROL trials [i.e., $(MEMORY\text{-}DELAY_{SUST} > PREPARATION\text{-}DELAY_{SUST}) \cap (MEMORY\text{-}DELAY_{SUST} > CONTROL\text{-}DELAY_{SUST})$, masked by $(PREPARATION\text{-}DELAY_{SUST} > 0 \cap CONTROL\text{-}DELAY_{SUST} > 0)$]. This contrast revealed two significant clusters of activity (Fig. 3, in green). One cluster (local maximum at −6, 8, 52) was located along the mesial aspects of the superior frontal gyrus, within the 50% probabilistic boundary of cytoarchitectonically defined BA6, and encroaching into the pre-SMA (Picard and Strick, 1996). A second cluster (local maximum at −28, −6, 70) was located along the caudal superior frontal sulcus, at the border between BA6 and BA8 (Eickhoff et al., 2005).

Second, we isolated sustained delay-related responses showing stronger activity during the PREPARATION trials than during the MEMORY and CONTROL trials, ensuring that this differential activity was driven by relative increases during the PREPARATION trials rather than decreases during the MEMORY and CONTROL trials [i.e., $(PREPARATION\text{-}DELAY_{SUST} > MEMORY\text{-}DELAY_{SUST}) \cap (PREPARATION\text{-}DELAY_{SUST} > CONTROL\text{-}DELAY_{SUST})$, masked by $(PREPARATION\text{-}DELAY_{SUST} > 0 \cap CONTROL\text{-}DELAY_{SUST} > 0)$]. This contrast revealed two significant clusters of activity (Fig. 3, in red), contiguous but distinct and caudal to the MEMORY clusters described above. One cluster (local maximum at −6, −12, 54) was located along the mesial aspects of the superior frontal gyrus, within the 100% probabilistic boundary of cytoarchitectonically defined BA6 (Eickhoff et al., 2005), and encroaching into the SMA (Picard and Strick, 1996). A second cluster (local maximum at −36, −26, 48) was located along the central sulcus extending onto the precentral gyrus. Probabilistic cytoarchtectonic maps (Eickhoff et al., 2005) place this cluster at the border between BA3, BA4 and BA6.

Third, we isolated sustained delay-related responses showing common differential activity during MEMORY and

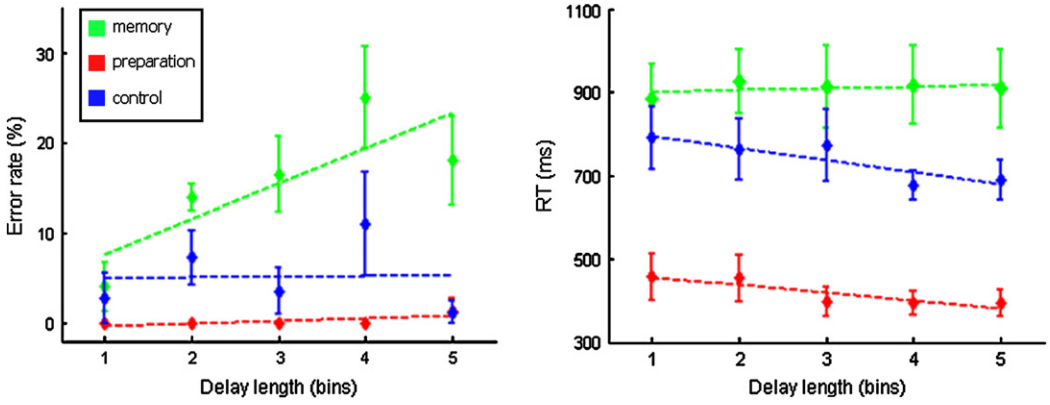

Fig. 2 – Behavioral results. Error percentages (A) and reaction times on correct trials (B) in the PREPARATION (red), MEMORY (green), and CONTROL (blue) conditions as a function of delay length, obtained during the scanning session. Dashed lines indicate linear regression curves between group-averaged data and instructed delays; error bars indicate ±SEM. During MEMORY trials, but not during PREPARATION or CONTROL trials, accuracy decreased as a function of delay length, indicating that participants used different mental representations to cross the instructed delay in the different conditions. During PREPARATION trials, performance was faster than during CONTROL trials, indicating that the participants prepared the response specified by the sample whenever possible.

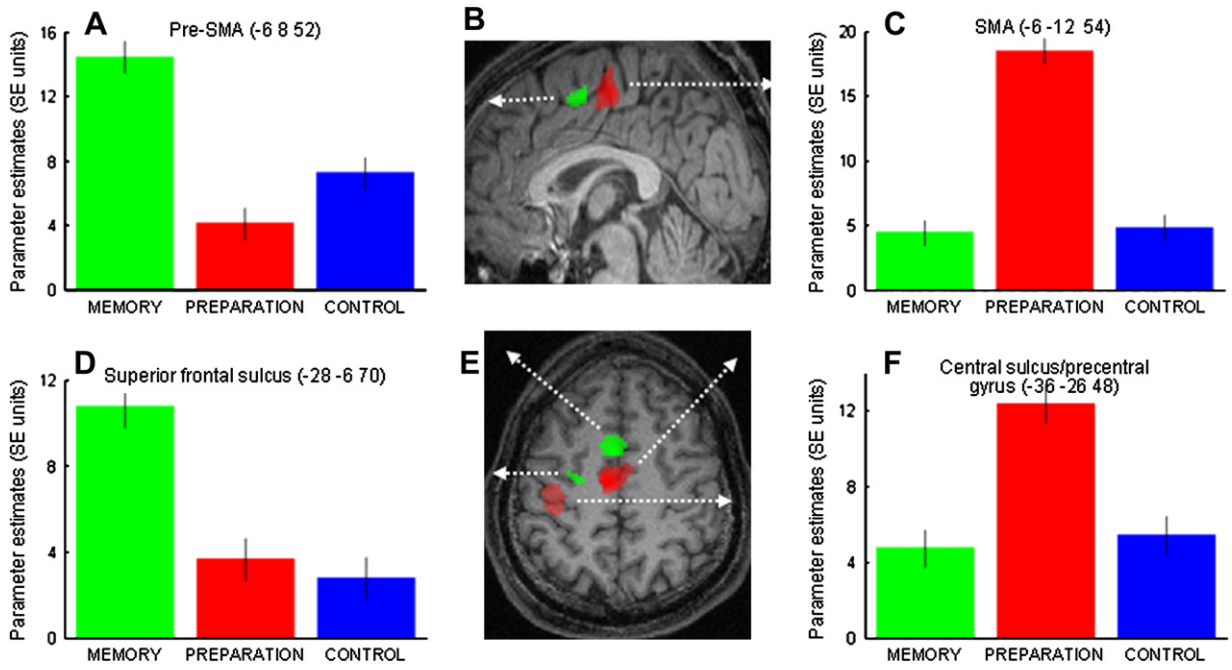

Fig. 3 – Imaging results. Differential delay-related sustained activity. Anatomical location [panels (B) and (E); SPM{t}s of the contrasts detailed in Table 1, overlaid on spatially normalized anatomical sections of one participant] and effect sizes [panels (A), (C), (D), and (F); parameter estimates of multiple regression in SEM units] of regions modulated by the task contingencies during the delay period. Regions with stronger sustained activity during delay periods of either MEMORY trials (in green) or PREPARATION trials (in red) are shown on sagittal (B) and transverse (E) anatomical sections. Clusters of delay-related activity supporting task performance during PREPARATION trials were distributed along the caudal precentral cortex (precentral gyrus, SMA-proper), whereas MEMORY trials evoked activity along the caudal prefrontal cortex (BA6/BA8 and pre-SMA).

PREPARATION trials as compared to the CONTROL trials [i.e., (MEMORY-DELAY$_{SUST}$ > CONTROL-DELAY$_{SUST}$) ∩ (PREPARATION-DELAY$_{SUST}$ > CONTROL-DELAY$_{SUST}$)]. This contrast revealed two significant clusters of activity (Fig. 4). One cluster (local maximum at −44, −52, 54) was located along the intraparietal sulcus, posterior to the 20% probabilistic boundary of cytoarchitectonically defined BA2 (Eickhoff et al., 2005). A second cluster (local maximum at −26, 6, −12) was located in the middle third of the left putamen.

3.3. *Imaging data: time-varying delay-related activity*

The following section describes the SPMs associated with linearly time-varying delay-related activity, i.e., BOLD signals increasing during the delay length. Significant effects are listed in Table 2.

First, we isolated time-increasing delay-related responses evoked during the MEMORY trials as compared to the PREPARATION trials, ensuring that this differential activity was driven by relative increases during the MEMORY trials rather than decreases during the PREPARATION trials [i.e., (MEMORY-DELAY$_{RAMP}$ > PREPARATION-DELAY$_{RAMP}$), masked by (MEMORY-DELAY$_{RAMP}$ > 0)]. This contrast revealed a significant cluster of activity (Fig. 5A, in green, local maximum at −40, 62, −2), located on the middle frontal gyrus, anterior to cytoarchitectonically defined BA9/46 (Rajkowska and Goldman-Rakic, 1995), and thus in BA10.

Second, we isolated time-increasing delay-related responses evoked during the PREPARATION trials as compared to the MEMORY trials, ensuring that this differential activity was driven by relative increases during the PREPARATION trials rather than decreases during the MEMORY trials [i.e., (PREPARATION-DELAY$_{RAMP}$ > MEMORY-DELAY$_{RAMP}$), masked by (PREPARATION-DELAY$_{RAMP}$ > 0)]. This contrast revealed a significant cluster of activity (Fig. 5C, in red, local maximum at −52, 2, 46), located on the precentral gyrus, within the 70% probabilistic boundary of cytoarchitectonically defined BA6 (Eickhoff et al., 2005). Activity in this cluster increased with delay length during both PREPARATION and CONTROL trials, but was not modulated by delay length in the MEMORY condition.

4. Discussion

We measured the spatial distribution of delay-related cerebral activity evoked by holding online either sensory material or motor responses, while having accounted for and removed the effects of presenting the sensory material and providing the motor response. In medial and lateral frontal cortex, different clusters of delay-related activity supported task performance, according to the nature of the information retained during the instructed delay. Some regions showed sustained activity throughout the delay period, whereas in other regions activity increased as a function of delay length. In posterior

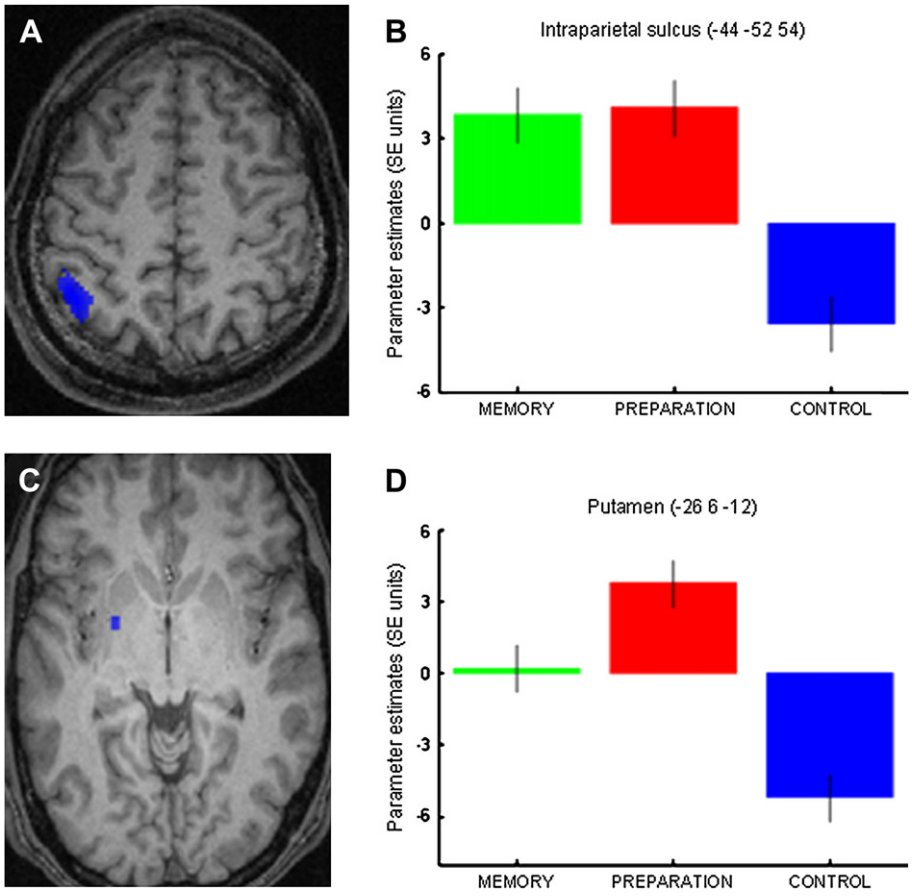

Fig. 4 – Imaging results. Common delay-related sustained activity. Anatomical location (A, C) and effect sizes (B, D) of the two clusters with stronger delay-related sustained activity during PREPARATION and MEMORY trials than during CONTROL trials. Other conventions as in Fig. 3.

parietal cortex, clusters with delay-related activity were indifferent to the type of information that was retained in memory. We infer that short-term storage of sensory information and preparation of motor responses rely on partially segregated cerebral circuits. In the following paragraphs, we discuss our findings and their implications for current models of working memory.

4.1. *Behavioral performance*

During scanning, participants solved the DNMS task at three different levels of proficiency (Fig. 2). Participants responded faster during the PREPARATION than during the CONTROL trials, indicating that in the former condition the participants were preparing to execute the movement specified by the sample cue. During both CONTROL and PREPARATION trials, performance became faster as a function of delay length, indicating that the participants took into account the increasing likelihood of providing a response as delay length increased. Crucially, during MEMORY trials, accuracy decreased as a function of delay length, whereas during PREPARATION trials, performance was homogeneously error-free across delay lengths (Fig. 2A). This indicates that the type of information retained during the MEMORY trials was more labile and of a different kind than that used during the PREPARATION trials.

4.2. *Sustained activity in precentral cortex*

We found sustained delay-related activity over the lateral and mesial aspects of the left precentral cortex. The pre-supplementary motor area (pre-SMA) and a caudal portion of the superior frontal gyrus (BA6/BA8; Fig. 3E, in green) showed strong sustained activity during the delay period of the MEMORY trials, but less so during PREPARATION and CONTROL trials. Since MEMORY and CONTROL trials had comparable movement selection requirements, the pre-SMA activity cannot reflect a generalized readiness to select a response (Petit et al., 1998). Rather, our results confirm that this region deals with rules that convert sensory material or intentions into the associated movements (Bunge, 2004; Hoshi and Tanji, 2004; Lau et al., 2004).

The cluster on the superior frontal gyrus falls in the same region (BA6/BA8) previously shown to be involved in holding visuospatial information online during a working memory task, both in humans (Rowe et al., 2000) and in macaques (Sawaguchi and Yamane, 1999), although the latter study obtained few measurements in BA8. This finding is important since it is not immediately compatible with domain-specific accounts of working memory (Levy and Goldman-Rakic, 2000; Smith and Jonides, 1999) that would predict a medio-lateral spatial segregation between regions supporting the online maintenance of identity and visuospatial features of a sensory

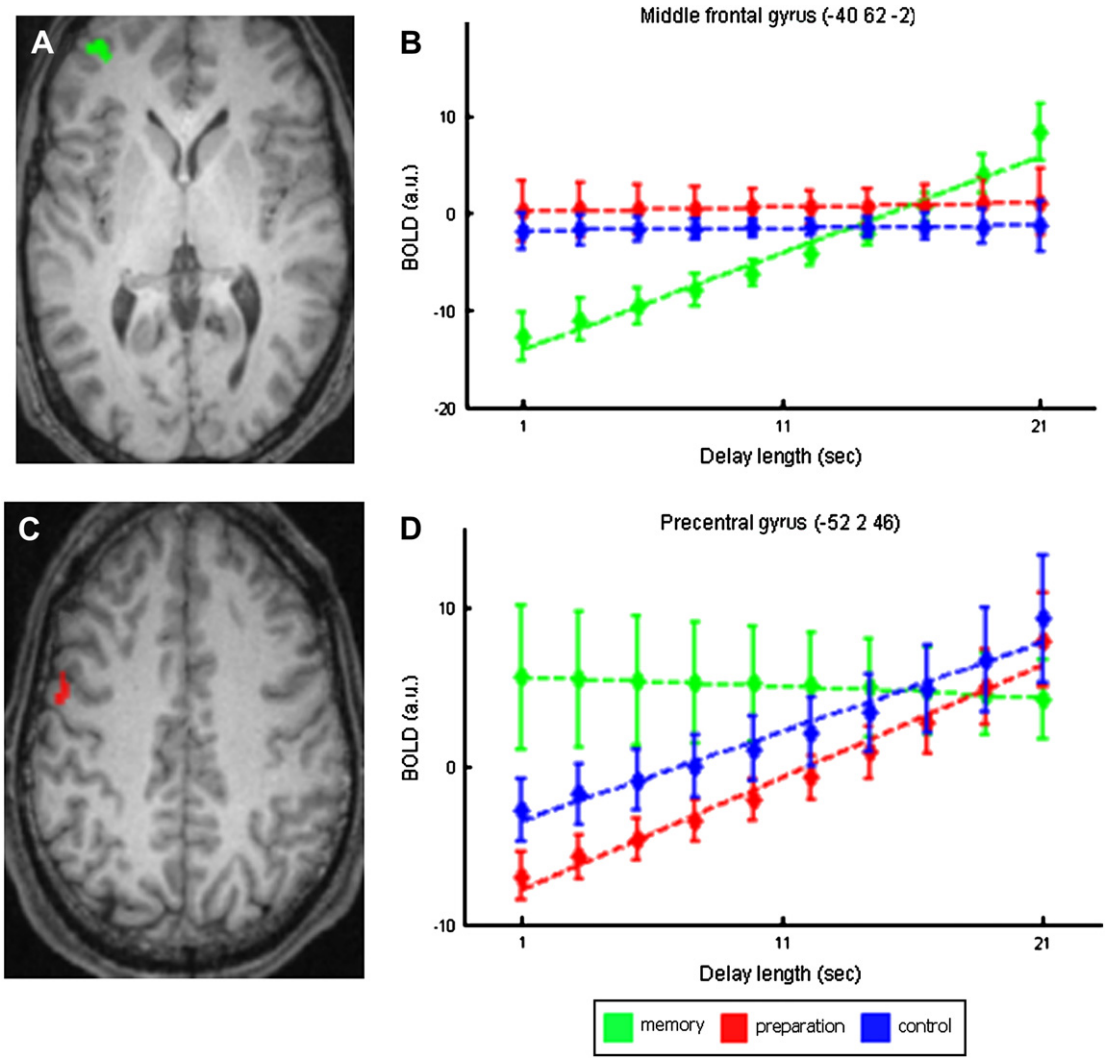

Fig. 5 – Differential delay-related time-varying activity. Anatomical location [panels (A) and (C); SPM{t}s of the contrasts detailed in Table 2] and effect sizes [panels (B) and (D)] of regions modulated by the task contingencies during the delay period. Regions with stronger time-varying activity during delay periods of either MEMORY trials (in green) or PREPARATION trials (in red) are shown on transverse anatomical sections. Delay-related activity increasing as a function of delay time during PREPARATION trials was found along the precentral gyrus (BA6), whereas MEMORY trials evoked activity along the middle frontal gyrus (BA10).

item. However, this between-studies inference will need to be further tested in a study directly comparing online maintenance of object- and spatial-related information.

In contrast to the MEMORY-related sustained activity found in pre-SMA and BA6/BA8, both SMA and lateral precentral gyrus (BA6; Fig. 3) were particularly active during the delay period of the PREPARATION trials. This finding illustrates how a substantial portion of the delay-related sustained activity that can be found in the caudal precentral gyrus is specifically related to the preparation of a motor response, over and above the effects of elapsing time (as indexed by the CONTROL trials) or holding sensory items online (as indexed by the MEMORY trials; Fig. 3F).

Overall, these results fit with the general partition of the precentral cortex into 'premotor' and 'pre-premotor' territories (Picard and Strick, 2001). Here we show that this anatomical distinction has a cognitive counterpart with respect to the nature of the material held online during a delay period. There was a clear rostro-caudal distribution of MEMORY- and PREPARATION-related effects (Fig. 3), indicating that the contributions of the frontal lobe to working memory could also be organized along a rostro-caudal dimension, corresponding to the sensory or motor nature of the stored material. This interpretation unifies previous distinctions made between motor preparation, visuospatial attention, and rule processing on the lateral surface (Simon et al., 2002; Bunge et al., 2003) and between motor preparation and processing of visuomotor rules on the mesial surface (Bunge, 2004; Hoshi and Tanji, 2004; Lau et al., 2004; Maier et al., 2002).

4.3. *Sustained activity in the intraparietal sulcus*

Independent studies have shown that the posterior parietal cortex is involved in the maintenance of both sensory items (Rowe et al., 2000; Todd and Marois, 2004) and motor

intentions (Andersen and Buneo, 2002; Kalaska and Crammond, 1995; Thoenissen et al., 2002) over time intervals of seconds. Here we illustrate how the delay-related sustained activity evoked in this region is specifically related to the presence of memoranda, as evidenced by the relative decrease in activity in the CONTROL condition, whether these memoranda specify a motor response or not, as evidenced by the comparable responses during MEMORY and PREPARATION trials (Fig. 4B). These results appear consistent with the suggestion that this region contributes to the temporary storage of information (Jonides et al., 1998; Thoenissen et al., 2002), and more specifically storage in a format accessible to decision-making processes (Toth and Assad, 2002). However, our results do not exclude the possibility that MEMORY- and PREPARATION-related effects remain spatially segregated at a spatial scale below our resolution, i.e., that different neurons within the intraparietal sulcus exhibit sensory memory and motor preparatory activity, respectively (Quintana and Fuster, 1999).

Interestingly, the sustained activity during both memory and preparation trials was lateralized exclusively to the left hemisphere, both in frontal and parietal regions. Whereas a right lateralized activation is usually found in motor tasks guided by spatial rules and spatial attention (e.g., Toni et al., 2001), a left hemisphere dominance is commonly reported in tasks involving the learning and performance of arbitrary visuomotor associations (Schluter et al., 2001; Grol et al., 2006; Mars et al., 2007), as in the current task. The fact that the same left-hemispheric dominance is also present during the delay period of the MEMORY trials suggests that sensory information is maintained in a format accessible to the forthcoming type of sensorimotor transformation. In addition, it is possible that the left-hemispheric parietal dominance observed in this study could be partly driven by increased attention to time (Coull and Nobre, 1998), a reflection of the need to maintain motor or sensory items during the delay period of the PREPARATION and MEMORY trials.

4.4. *Sustained activity in the striatum*

In addition to the intraparietal response, the contrast testing for sustained activity during both the MEMORY and PREPARATION delays identified a significant cluster in the left putamen. However, as it can be seen in Fig. 4, this effect is mainly due to a decrease in the CONTROL condition, with sustained activity more prominent during the PREPARATION trials. This pattern of activity confirms involvement of the striatum in the performance of arbitrary visuomotor transformations (Boussaoud and Kermadi, 1997; Toni et al., 2001; Thoenissen et al., 2002), and more specifically the role of the posterior striatum (putamen) in the recall and retention of these mappings (Buch et al., 2006; Grol et al., 2006).

4.5. *Time-varying delay-related activity*

We found two regions which showed increasing activity with increasing delay length. A cluster along the middle third of the rostral precentral gyrus showed increasing activity during PREPARATION and CONTROL trials, but not during MEMORY trials (Fig. 5D). This time-varying precentral response appears to be related to the time-varying characteristics of the RT observed in the PREPARATION and CONTROL trials. Given that the cerebral effect (delay-related activity) precedes the behavioral effect (RT), it is plausible that this region might contribute to biasing a generic motor plan with contextual information generalized over trials, namely the conditional probability of providing a response at a given time, given that no response has been yet required (Schoffelen et al., 2005). Our results confirm that this temporal inference is not necessarily linked to the implementation of a specific motor plan (Coull et al., 2004), since behavioral and cerebral effects occur during both PREPARATION and CONTROL trials. On the other hand, the contributions of this precentral region appear to be embedded in a motor circuit, since there was no response (and no anticipatory behavior) when the incoming test stimulus was more than a simple motor instruction (MEMORY trials).

The anterior portion of the middle frontal gyrus (BA10) showed time-varying delay-related activity in the MEMORY trials only (Fig. 5A). This time-varying prefrontal response appears related to the time-varying characteristics of the error rate observed in the MEMORY trials (Fig. 2A). However, since the analysis was confined to correct trials only, our effect is not a trivial by-product of increasing error rate. Behaviorally, it has been shown that maintaining sensory information online requires additional resources as delay length increases (Ploner et al., 1998; White et al., 1994). Therefore, it is plausible that this prefrontal region might contribute to support activity in other cerebral structures more specifically involved in maintenance of the sensory items (Fig. 3D) only for the longer delays. This role appears to fit with previous reports suggesting that this region is not involved in allocating attentional resources per se (Koechlin et al., 1999), but rather it is involved in biasing cognitive operations performed by other cortical regions (Sakai and Passingham, 2003). Furthermore, our findings are in line with the suggestion that BA10 involvement requires more than the implementation of a single sensorimotor rule (Ramnani and Owen, 2004). Accordingly, this region contributed to those trials where a sensory item needed to be compared with similar items in memory, but not to PREPARATION and CONTROL trials.

4.6. *Interpretational issues*

Several interpretations suggested in the previous sections rely on the ability of the present task to evoke online maintenance of either sensory or motor material during the MEMORY and PREPARATION trials, respectively. However, it could be argued that, in the former condition, subjects might have maintained online both sensory items and their associated motor responses. We have addressed this issue in a related experiment using the same paradigm in conjunction with transcranial magnetic stimulation (van den Hurk et al., 2007), showing that, during the PREPARATION condition, there was an increase in corticospinal excitability of the muscle controlling the required response, and a decrease in excitability in muscles controlling the alternative response. In contrast, the MEMORY trials had no detectable effect on corticospinal excitability. These results suggest that participants did not solve the MEMORY trials by holding online two motor responses during the delay

period. Yet, it could be argued that, in principle, during the MEMORY trials the two potential motor responses could be held online while inhibiting them, with the pre-SMA possibly contributing to the latter phenomenon. However, then it becomes equally plausible that the same mechanisms described above for the MEMORY trials should operate during the CONTROL trials, and to a lesser degree during the PREPARATION trials (given that these trials involve only one response). This scenario would predict comparable responses in the MEMORY and CONTROL trials, and relatively reduced responses during the PREPARATION trials. This pattern does not fit with the fMRI responses found in this study (see Fig. 3). Taken together, these considerations suggest that a parsimonious interpretation of the present finding links the MEMORY and PREPARATION trials to the online maintenance of either sensory or motor material.

It should be noticed that, in this study, motor preparation refers to the specific preparation of a particular motor response (Wise and Mauritz, 1985). This can be contrasted with other studies, where motor preparation is used to label a combination of stimulus-, delay-, and response-related activities during trials in which subjects could not prepare in advance the correct response (Cavina-Pratesi et al., 2006). Previous studies have shown that, under these circumstance, cerebral activity is unlikely to be specifically related to the preparation of a movement, but rather to the anticipation of sensory events (Vaadia et al., 1988).

5. Conclusions

Our findings point to crucial differences in how prefrontal, precentral, and parietal regions contribute to the basic faculty of holding information online during a temporal gap between perception and action. The intraparietal cortex appears to be involved in online maintenance of sensory material with motor implications. Caudal precentral cortex appears to be involved in holding a movement online, provided that the movement can be fully specified in advance. Dorsal prefrontal cortex (border BA6/BA8) appears to be involved in the maintenance of sensory material and of the sensorimotor rules that allow for the selection of an appropriate response in the near future. Furthermore, both precentral (BA6) and prefrontal (BA10) regions reveal time-varying delay-related activity that is presumably involved in biasing sustained preparatory and mnemonic responses as a function of contextual information generalized over trials (i.e., the conditional probability of providing a response or selecting a rule, given that no response has been yet required).

In summary, these findings illustrate that the contributions of the frontal lobe to working memory are organized along a rostro-caudal dimension, corresponding to the sensory or motor nature of the stored material.

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