Dissociable roles of the posterior parietal and the prefrontal cortex in manipulation and monitoring processes

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Numerous functional neuroimaging studies reported increased activity in the middorsolateral prefrontal cortex (MDLFC) and the posterior parietal cortex (PPC) during the performance of working memory tasks. However, the role of the PPC in working memory is not understood and, although there is strong evidence that the MDLFC is involved in the monitoring of information in working memory, it is also often stated that it is involved in the manipulation of such information. This event-related functional magnetic resonance imaging study compared brain activity during the performance of working memory trials in which either monitoring or manipulation of information was required. The results show that the PPC is centrally involved in manipulation processes, whereas activation of the MDLFC is related to the monitoring of the information that is being manipulated. This study provides dissociation of activation in these two regions and, thus, succeeds in further specifying their relative contribution to working memory.

fMRI | middorsolateral prefrontal cortex | intraparietal sulcus region | working memory

Although it is now clear that both the MDLFC and the PPC play an important role in working memory (1–6), the relative contribution of these two regions is not well understood. For instance, it is often stated that the MDLFC is involved in a variety of high-order cognitive processes such as the monitoring (1, 2, 7, 8) and manipulation (6, 9–11) of information in working memory, but the relation between these two processes needs clarification. Monitoring, as a functional role of the MDLFC, was defined as the process of keeping track of the current status of events in relation to other events in working memory (7, 10). Manipulation (i.e., the rearrangement) of items of information in working memory, which can operationally be defined as the reordering or transformation of these items, necessarily involves the monitoring of the information that is being manipulated in working memory (i.e., keeping track of the status of each item in relation to other items as they are being rearranged). Monitoring, however, can also be tested in working memory tasks that do not involve rearrangement of items (8, 12). The suggestion that the monitoring of events in working memory is the critical contribution of the MDLFC to cognitive control was first made by Petrides (8, 12) on the basis of studies demonstrating that lesions limited to this cortical region in monkeys impair severely performance on working memory tasks that require monitoring of items without involving any manipulation of those items. For instance, monkeys with MDLFC lesions are impaired on a working memory task in which a random subset of stimuli from an expected set is presented (e.g., two visual objects from a familiar set of three), and the animals simply have to monitor the stimuli that occurred so that they can decide, on the test trial, which one of the three stimuli has not been presented (see ref. 12, experiments 2 and 3). Thus, although the current standard view of the MDLFC is that it is centrally involved in a variety of cognitive processes, including the manipulation and the monitoring of information in working memory (e.g., ref. 6, 9–11), it remains to be determined whether the increased activity observed in this region in working memory tasks requiring manipulation is due to the manipulation of the items *per se* or the inevitable increase in the monitoring demands that accompany such manipulation.

The role of the PPC in working memory remains unclear. It is widely thought that the PPC serves as a buffer for verbal and spatial information, the left PPC being more critical for verbal information (5, 13–15) and the right being more involved with spatial information (14, 15). Although this may be true, it is necessary to ask the question whether the PPC is additionally involved in some specific operation on the information being held there. This question is of interest, because we also know that posterior cortical lesions involving the parietal cortex result in severe impairments in mental rotation (16, 17) and in calculation (18, 19), and functional neuroimaging studies have also repeatedly shown increased activity in the PPC during the performance of both mental rotation (20–22) and arithmetical calculation (see ref. 23 for a review). Although mental rotation is traditionally viewed as an analogical process related to the gradual transformation of visual imagery and calculation is linked to arithmetic (i.e., cognitive domains not traditionally related to working memory), they provide the basis on which to pose the question whether the PPC may play a more general role on information held in it such as the manipulation (i.e., the rearrangement) of information in working memory.

On the basis of the above, we tested, in a functional MRI (fMRI) study, the hypothesis that the PPC may be more involved in the manipulation process than the MDLFC and that the MDLFC may be primarily involved in the monitoring of information in working memory and only secondarily in the manipulation of such information. To test this hypothesis, we designed an event-related fMRI study to compare brain activity changes due to the manipulation and the monitoring of events in working memory. Previous functional neuroimaging studies could not address this question, because they had not directly compared the cerebral activity related to the manipulation of mnemonic information to the activity related to the monitoring of such information.

Eleven right-handed normal human subjects (eight females and three males; mean age 25 years, range 22–30 years) participated in this study after providing informed written consent according to the institutional guidelines established by the Ethics Committee of the Montreal Neurological Hospital and Institute.

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Abbreviations: IPS, intraparietal sulcus; MDLFC, middorsolateral prefrontal cortex; PPC, posterior parietal cortex; BOLD, blood oxygenation level dependent.

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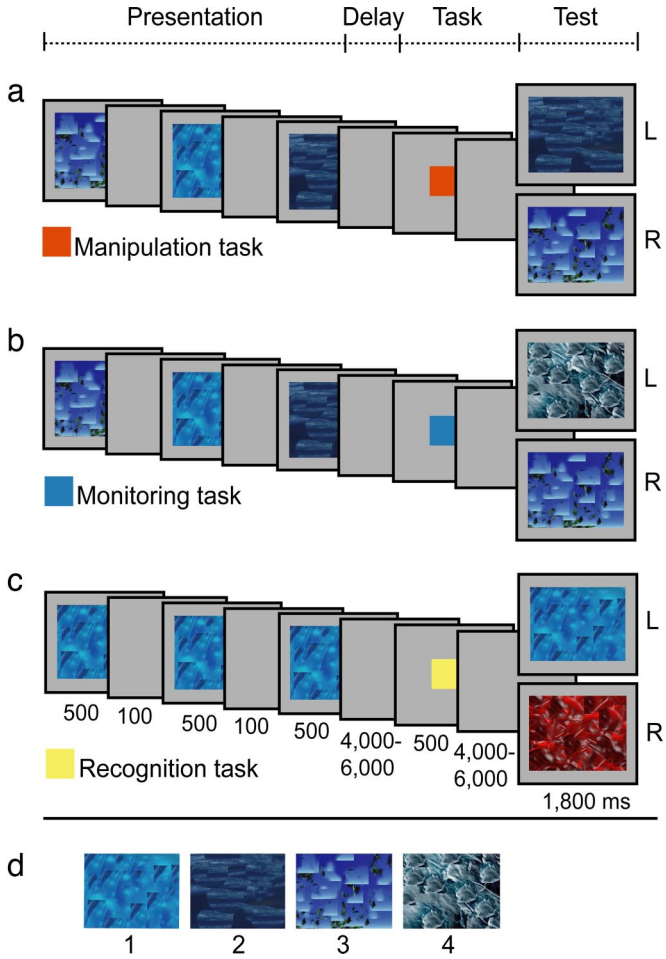

Fig. 1. Behavioral tasks. Schematic diagram of the manipulation (*a*), monitoring (*b*), and recognition control (*c*) trials. To perform the manipulation task, the subjects had memorized, before scanning, a fixed sequence of the four designs used during the experiment. The fixed sequence of the four abstract designs that the subjects had learned before scanning is shown in *d*. The number under each abstract design represents its position in the learned sequence that was essential for the performance of the different trials during scanning (see SI Fig. 5 and *SI Text* for details on the prescanning training session). These numbers are indicated here simply for the benefit of the reader and did not appear anywhere during the performance of the tasks. L, left response; R, right response.

The subjects were scanned while they performed a manipulation, a monitoring, and a recognition control task (Fig. 1 and see *Methods*). The same familiar set of four abstract designs was used for the three tasks, which shared a common sequence of events: a presentation phase, a delay phase, a task phase, and a test phase. During the presentation phase, the subjects viewed the information necessary to perform the task. A brief cue, which followed the presentation phase, instructed the subjects which task to perform. This task phase was the period of interest in this experiment. The response of the subjects during the test phase provided confirmation that the subjects had indeed performed the task required. During the presentation phase of the monitoring trials, three of the four abstract designs were selected randomly and presented one at a time on the screen. The subjects' task was to identify the design that was not presented on each trial. Note that, because the three items shown during the presentation phase of each trial were drawn randomly and repeatedly from the same set of four familiar designs (i.e., a different subset of three items was shown on each trial), there was considerable interference. Thus, the subjects had to track carefully which specific designs from the four familiar and repeatedly presented ones had been shown on the particular trial to identify the design from he target set that had not been shown. Because we wished the subjects to perform the monitoring task during the task phase, the subjects had been trained to watch passively the presentation of the three designs and to rerun in their mind, during the task phase, the three stimuli presented to find the one that had not been shown during the presentation phase of the current trial. At the end of the training and scanning sessions, all subjects reported that, after the cue and during the task phase, they had rerun in their mind the stimuli to identify the design that had not been presented in the current trial. This task had previously been shown to be a good measure of the monitoring function of the MDLFC in both functional neuroimaging with human subjects (1, 2) and monkey lesion studies (7, 8, 12). The presentation phase of the manipulation trials was identical to that of the monitoring trials, i.e., three of the four abstract designs were selected randomly and presented one at a time on the screen. However, during the task phase of the manipulation trials, the subjects had to reorder mentally the presented sequence on the basis of a fixed sequence that had been learned before scanning. Note that, in contrast, in the task phase of the monitoring trials, the subjects had simply to rerun the presented sequence of designs in their mind to find the stimulus that had not been shown. In the task phase of the recognition control trials, the subjects had to recall and visualize the one design that was presented during the presentation phase.

Results

We first compared the signal obtained during the task phase of the manipulation and the monitoring trials (separately) with the signal obtained during the task phase of the recognition control trials to confirm the prediction from earlier work that there would be increased activity in both the MDLFC and the PPC in these two types of trial. These two comparisons yielded very similar patterns of cerebral activity. In both comparisons, increased activity was found in the MDLFC. The role of the MDLFC in monitoring has been consistently demonstrated in lesion (8, 12) and neuroimaging studies (1, 2, 10). The activity found in this region was bilateral but stronger in the right hemisphere, consistent with the use of nonverbal material, i.e., the abstract designs (2, 10). The comparison of the task phase of the manipulation and monitoring trials with that of the recognition control trials also yielded peaks of increased activity in the PPC and more specifically in the depth of the intraparietal sulcus (IPS) and in the superior parietal lobule bilaterally [see supporting information (SI) Tables 1 and 2 for the complete list of peaks of increased activity found in the comparison of the experimental tasks with the control task].

The above comparisons confirmed that the tasks used in the present study did indeed elicit the expected increased activity in both the MDLFC and PPC in working memory tasks requiring manipulation and monitoring. Fig. 2 illustrates the mean blood oxygenation level-dependent (BOLD) signal change in the monitoring and manipulation conditions relative to the control condition. A two-way analysis of variance of the BOLD signal change demonstrated a significant interaction [repeated-measures ANOVA, $F(1,20) = 13.76$, $P < 0.001$] between the two anatomical regions (IPS and MDLFC) and the two conditions (manipulation and monitoring). The monitoring signal was greater than the manipulation signal in the MDLFC region, whereas the manipulation signal was greater than the monitoring signal within the IPS region.

Another way of looking at this interaction is to carry out a direct comparison of the signal obtained during the task phase of the manipulation and monitoring trials. The manipulation minus monitoring comparison aimed at localizing activity spe-

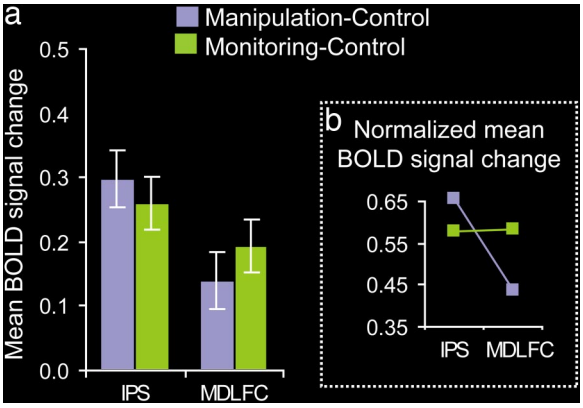

Fig. 2. Mean BOLD signal change within the IPS and the MDLFC in the comparison of the manipulation and monitoring conditions minus the control condition. The mean BOLD signal change in the left IPS was significantly greater in the manipulation condition in comparison with the monitoring condition. In contrast, the mean BOLD signal change within the MDLFC was significantly greater in the monitoring condition in comparison with the manipulation condition. The error bars illustrate the standard errors.

cific to the manipulation of information in working memory. The main peak of increased activity revealed by this comparison was observed in the depth of the IPS in the left hemisphere [$x = -38$, $y = -48$, $z = 48$, $t = 4.43$], in terms of both the spatial extent of the activity and its statistical significance (Fig. 3*a*). More specifically, the peak of the increased activity was located in the horizontal segment of the IPS region, close to the intersection with the ventral branch emerging from the IPS caudal to the postcentral sulcus. In addition to the increased activity observed in the region of the left IPS, cluster analyses revealed areas of increased activity in the right superior parietal lobule as well as in the left putamen (see SI Table 3). Importantly, as hypothesized, the manipulation minus monitoring comparison did not yield any significant increases of activity within the prefrontal cortex: no voxel within the lateral prefrontal cortex had a t value >2.5, i.e., all t values in the prefrontal cortex were clearly not significant.

To see whether there was greater activity in the MDLFC during monitoring relative to manipulation, the monitoring minus manipulation comparison was carried out. The only significant increase in activity revealed from this comparison was located within the MDLFC ($x = 21, y = 40, z = 26, t = 3.64$) (Fig. 3*b*). The activity observed in the MDLFC during the monitoring of abstract designs in working memory was therefore greater than the activity related to the manipulation of the same designs. This finding is consistent with the hypothesis tested, namely that the MDLFC is primarily involved in the monitoring of information in working memory, and that the increase in activity during manipulation reflects the inevitable monitoring of the manipulated information. No significant increase in activity was observed in the parietal lobe in the monitoring minus manipulation comparison and, within the region of the IPS, no voxel had a t value >2.3, i.e., all voxels were clearly not significant.

It is important to note here that the monitoring and manipulation tasks were carefully matched in difficulty both in terms of overall performance levels (mean success rate 97.0%, range 89.4–100%, for the manipulation condition and 95.9%, range 87.9–100%, for the monitoring condition; paired samples t test, $t_{10} = 1.44$, $P > 0.18$) and reaction times (mean reaction time 680 ms, range 331–1,782 ms for the manipulation condition and 705 ms, range 331–1,632 ms, for the monitoring condition; paired samples t test, $t_{10} = 1.06$, $P > 0.31$).

It is also important to mention that the increased activity in the left IPS and right MDLFC was observed during the task phase

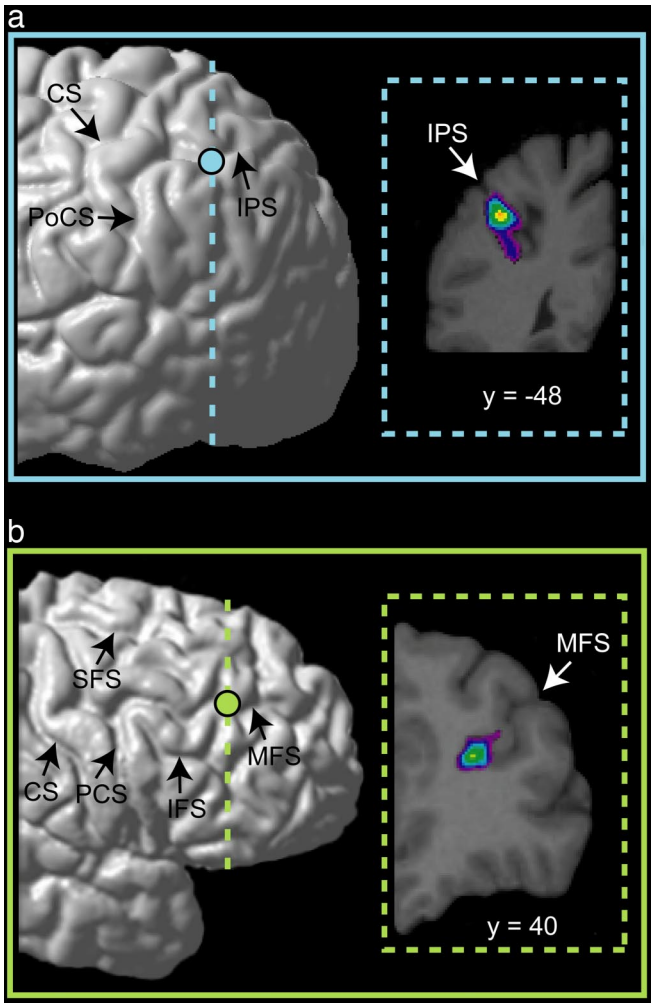

Fig. 3. Activity in the manipulation minus monitoring and in the monitoring minus manipulation comparisons. Cortical surface renderings in standard stereotaxic space of a subject's brain are shown on the left. (*a*) Increased activity in the left IPS obtained from the manipulation minus monitoring comparison. The vertical blue line on the left hemisphere cortical surface rendering indicates the anteroposterior level of the coronal section illustrated on the right. (*b*) Increased activity in the right MDLFC obtained from the monitoring minus manipulation comparison. The vertical green line on the right hemisphere cortical surface rendering indicates the anteroposterior level of the coronal section illustrated on the right side. CS, central sulcus; PoCS, postcentral sulcus; PCS, precentral sulcus; SFS, superior frontal sulcus; IFS, inferior frontal sulcus; MFS, middle frontal sulcus.

of the manipulation and monitoring trials. This can clearly be observed in Fig. 4, which shows the time course of the BOLD signal during the different phases of the three trial types in a representative subject. Note that, within the IPS region, the signal increase related to the manipulation is occurring during the task phase and is greater than the signal due to the monitoring and control conditions (Fig. 4*a*). Within the MDLFC region, the signal increase is also occurring during the task phase and is greater in the monitoring condition compared with the manipulation and control conditions (Fig. 4*b*). These results suggest that the subjects performed the tasks during the task phase of the manipulation and monitoring trials, as instructed and as confirmed by them during debriefing after the training and scanning sessions.

Finally, a functional connectivity analysis allowed us to determine how the two regions of interest (IPS and MDLFC) interacted with each other and with other cortical and subcor-

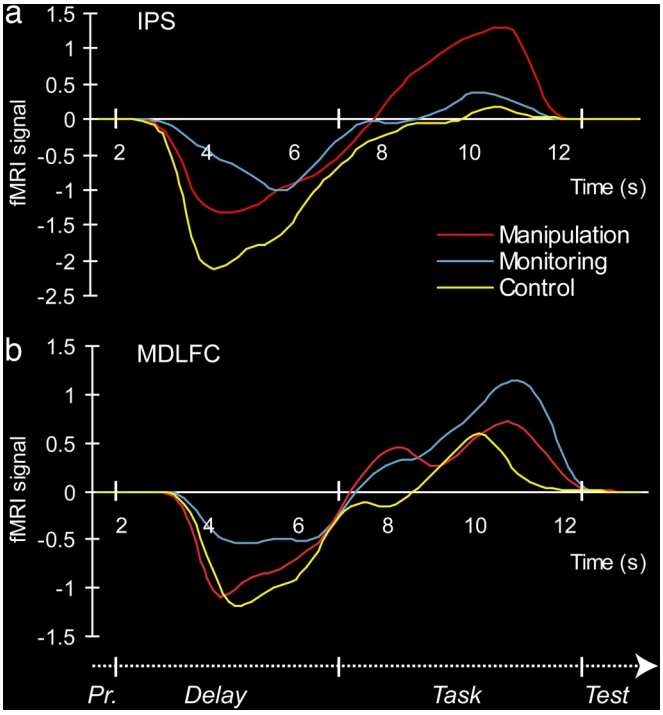

Fig. 4. Trial-averaged time courses of the BOLD signal in the manipulation, monitoring, and control trials in IPS (*a*) and MDLFC (*b*). The BOLD signal is time-locked to the beginning of the trials. Pr., presentation phase.

tical structures during the performance of the manipulation and monitoring tasks. During the task phase of the manipulation as compared with the task phase of the control trials, the left IPS region exhibited significant increase in functional connectivity with the MDLFC (bilaterally), the left supplementary motor area, the premotor cortex (bilaterally), the putamen (bilaterally), and the IPS region of the right hemisphere (see SI Table 4). In the task phase of the monitoring trials as compared with the task phase of the control trials, there was a significant increase in functional connectivity of the right MDLFC region with the right supplementary motor area, the premotor cortex (bilaterally), the putamen and caudate nuclei (bilaterally), the IPS region (bilaterally), and the MDLFC in the left hemisphere (see SI Table 5). These results demonstrate the broader functional circuit engaged in interaction with the regions of interest (IPS and MDLFC) during the manipulation and monitoring of information in working memory. Interestingly, functional connectivity in the task phases of the manipulation and monitoring trials when these were compared with each other revealed that the left IPS region interacted significantly more with the right MDLFC during manipulation than during monitoring (manipulation minus monitoring comparison, seed voxels: peaks of increased activity in the left IPS region, interaction with MDLFC in the right hemisphere ($x = 55, y = 40, z = 17, t = 3.55$); monitoring minus manipulation comparison, seed voxels: peaks of increased activity in the region of the right MDLFC, no significant interaction with the left IPS region ($x = -38, y = -48, z = 48, t = -1.64$)). This finding is consistent with the present hypothesis on the additional contribution of the IPS region in the manipulation of information in working memory.

Discussion

The present study compared the activation within the MDLFC and the PPC in a monitoring and a manipulation task that were carefully matched in terms of type of stimulus material (the same abstract visual images were used in both tasks) and difficulty (both in terms of overall performance levels and reaction times). The results demonstrated that, within the MDLFC (Fig. 3*b*), the activity observed during the monitoring of the abstract visual designs in working memory was greater than the activity related to the manipulation of the same designs (Fig. 2). This finding is consistent with the hypothesis that the MDLFC is primarily involved in the monitoring of information in working memory and that the increase in activity during manipulation reflects the inevitable monitoring of the manipulated information. In sharp contrast, there was greater activity in the depth of the IPS in the left hemisphere (Fig. 3*a*), in the right superior parietal lobule, and in the putamen during the manipulation process. It is important to emphasize here that the present study examined the contribution of the PPC to the reordering of a sequence of abstract designs and was not designed to examine whether this region would also be involved in the storage of such information.

Several functional imaging studies have reported increased activity in the region of the right superior parietal lobule (20) and, interestingly, also in the left IPS during mental rotation (i.e., the mental transformation of perceptual stimuli) (20, 24). Alivisatos and Petrides (20) and Petrides *et al.* (24) found peaks of increased activity located in the same region of the left IPS in two different studies exploring the neural correlates of mental rotation of alphanumeric characters and abstract spatial stimuli, respectively. We suggest that, although the cognitive domain of mental rotation (i.e., the analogical transformation of mental imagery) is totally different from the reordering of visual stimuli in working memory that was studied here, these two processes may both be conceived, fundamentally, as the manipulation (i.e., the rearrangement) of stimulus information and this may be a basic contribution of the PPC.

Similarly, increased activity in the region of the left IPS has been frequently observed in functional imaging studies during mental arithmetic (see ref. 23). Dehaene *et al.* (23), who reviewed a number of functional neuroimaging studies, reported an average peak of increased activity located in the horizontal segment of the IPS (coordinates: $x = -44, y = -48, z = 47$) in nine studies exploring the neural correlates of quantity processing. This area of increased activity corresponds to the one observed in the manipulation minus monitoring comparison in the present study. Importantly, Dehaene *et al.* (23) noted that the intraparietal activity observed in these studies was independent of the modality of input and increases with the amount or duration of quantity that is being processed. We believe that this finding (again from a totally different cognitive domain, namely that of arithmetic) is consistent with the results of our study in which reordering of visual stimuli was required in working memory and showed that the left intraparietal region is centrally involved in the manipulation of information in working memory.

In yet another cognitive domain, Bor *et al.* (25) investigated, with fMRI, activity related to the presentation of structured sequences of spatial moves which permit perceptual chunking. It is of considerable interest that the structured sequences yielded greater activity within the PPC at sites very similar to the ones observed here. Furthermore, within the prefrontal cortex, the activity related to the encoding of structured sequences was located within the ventrolateral prefrontal region and not within the MDLFC, where the monitoring peaks were located in the present study. It would be expected that the monitoring demands of structured sequences would be comparable to those of unstructured sequences, and therefore one would not see increased activity in the MDLFC from such a comparison. The activation results from this study of perceptual reorganization originating from the structuring of spatial moves are concordant with the conclusions of the present study.

The present study succeeds in dissociating the roles of the MDLFC and PPC components of the frontoparietal network in working memory. It demonstrates that the MDLFC is primarily

involved in the monitoring of information in working memory, whereas the PPC is primarily involved in the manipulation of that information. Furthermore, it is shown that the IPS region, working in tandem with various brain regions including the superior parietal lobule and the putamen, is centrally involved in the manipulation of information in working memory. Finally, the present findings confirm that the monitoring of events in working memory is the critical and specific contribution of the MDLFC to cognitive control, and that the observation of increased activity in the MDLFC in numerous functional neuroimaging studies using manipulation tasks was probably because the manipulation of items of information in working memory necessarily involves the monitoring of the information that is being manipulated. These findings are consistent with the fact that patients with lesions involving the MDLFC can still perform tasks requiring the mental transformation of visual stimuli, such as mental rotation tasks (26) or tasks involving the manipulation of numbers in elementary arithmetical operations (27), although they are severely impaired on working memory tasks involving monitoring (28). The present study clarified understanding of the neuronal bases of higher-order cognitive functions by demonstrating the relative contribution of the MDLFC and the PPC to working memory.

Methods

Experimental Design. The subjects were scanned while they performed manipulation, monitoring, and recognition control trials. Each scanning run was composed of 33 intermixed trials (i.e., manipulation, monitoring, and recognition trials) presented in a pseudorandom fashion. To perform these tasks, the subjects first had to familiarize themselves with a set of four abstract designs and, for the manipulation task, memorize a prescribed temporal sequence for them during a prescanning training session (see SI Fig. 5 and *SI Text* for a description of the prescanning training session). This set of familiar abstract designs was used for all three types of trial that shared a common sequence of events (Fig. 1). All trials started with a presentation phase, during which the information necessary to perform the task, namely a sequence of abstract designs, was shown. The presentation phase was followed, after a short delay (4,000–6,000 ms), by the task phase. The task phase was initiated with a brief cue (500 ms) instructing the subject which task to perform followed by a delay (4,000–6,000 ms), during which the subject was performing the required task. The subjects had been trained to start performing the appropriate task immediately after the presentation of the instruction cue. The trial ended with the test phase, during which the subjects provided an answer confirming they had indeed performed the required task. One abstract design was shown during the test phase, and the subjects had 1,800 ms to indicate their response by pressing the left button of a mouse when the design corresponded to the correct answer or the right button when it corresponded to an incorrect answer. Note that the subjects had been trained to make the decision during the task phase, so that during the test phase, they simply provided the answer in the short time they had to respond. It is also important to mention that we took great care to ensure the subjects performed the three tasks nonverbally (see *SI Text* for more details). The trials were separated by an intertrial interval (ITI), varying randomly between 8 and 10 s, during which they kept looking at a small cross in the center of the screen.

The monitoring trials were modeled on those of a monitoring working memory task that yielded a massive impairment in monkeys with MDLFC lesions (12) (Fig. 1*b*). In the presentation phase of the monitoring trials, three of the four abstract designs (selected randomly) were presented sequentially and, in the task phase, the subjects were instructed by means of a cue (a blue square) to find the one design that had not been presented on the current trial. During the test phase, one of the four designs was shown, and the subjects had to press the left button if that design had not occurred during the presentation phase and the right button if it had occurred. In this task, because on each trial a different set of three designs was drawn randomly from the familiar target set of four, there was considerable interference from trial to trial, and therefore the subjects had to track (i.e., monitor) carefully which ones of the target set had been presented and which one had not been presented. Because the subjects might have performed the monitoring during the presentation phase and then simply remembered the answer during the task phase, the subjects were instructed and trained during the prescanning session simply to look passively at the sequence presented and then, during the task phase, to rerun mentally the sequence to monitor which stimuli from the target set were presented and which one was not. There was no manipulation (i.e., rearranging) of the sequence to find the correct answer, as was the case in the manipulation task (see below).

The presentation phase of the manipulation trials was identical to that of the monitoring trials, i.e., again three of the four abstract designs were drawn randomly and presented sequentially (Fig. 1*a*). In the task phase of the manipulation trials, the cue (a red square) instructed the subjects to rearrange the sequence of the presented abstract designs according to a fixed order they had learned during the prescanning training session so that they would be able to select the design that would be second if the presented sequence was rearranged according to the learned order. For example, assume that A, B, C, D represent the four abstract designs in the learned fixed serial order. If C, A, D are sequentially shown during the presentation phase of the trial, the subject should rearrange mentally C, A, D into A, C, D (according to the previously learned order), to be able to find the correct stimulus for that trial, which is always the one that occupies the second position when rearranged according to the learned fixed order (C in this example). During the test phase of the manipulation trials, the subjects had to press the left button of the mouse if the design shown corresponded to a correct answer and to press the right button if it did not. Thus, in the task phase of the manipulation trials, the subjects had to reorder the presented sequence of designs to perform correctly on the test phase.

In the recognition control trials, one of the four abstract designs (selected randomly) was shown three times during the presentation phase (Fig. 1*c*). In the task phase, the cue (a yellow square) instructed the subjects to recall the design that was presented during the presentation phase and to visualize it. During the test phase, the subjects saw either the design shown during the presentation phase or an alternative one that was not part of the familiar set. The subjects had to press the left button if the design was the one presented during the presentation phase and the right button if it was the alternative one. The decision in the test phase was therefore based on the recognition of the design seen in the presentation phase and did not require the engagement of manipulation or monitoring processes.

MRI Acquisition. Scanning was performed on a 1.5-T Siemens Sonata MRI Scanner (Siemens, Erlangen, Germany). After a high-resolution T1 anatomical scan (whole head, 1 mm^3 isotropic resolution), six runs of 217 images each (38 oblique T2* gradient echo planar images, voxel size = 3.4 × 3.4 × 3.4 mm, repetition time (TR) = 3.5 s, echo time (TE) = 45 ms, flip angle = 90°) sensitive to the BOLD signal were acquired (≈12 min each run). Visual stimuli were presented through a liquid-crystal display projector with a mirror system, and the responses of the subjects were recorded with a magnetic resonance-compatible optical computer mouse. Trials in which the subjects made an error were excluded from the analysis.

The above scanning parameters were dictated by behavioral constraints and the need to scan the whole brain and to provide

adequate statistical power for detection of intercondition contrasts. However, these scanning parameters, i.e., long repetition time, random delays within the trials, and the relatively long trials, are not optimal for obtaining the hemodynamic responses during the different phases of the trials. Thus, three subjects were rescanned with a modified scanning protocol to obtain optimal representation of the hemodynamic responses by improving the signal-to-noise ratio in reconstructed time series: a 500-ms repetition time echo planar sequence and constant time interval among all phases of the three types of trials (but random intertrial interval). This acquisition captured seven slices of 5-mm thickness (1-mm gap) and 3.13-mm in-plane spatial resolution.

Data Analysis. Images from all runs were first realigned with an AFNI image registration software using the third frame of the first run as reference (29) and then smoothed with a MINC blurring software (mincblur) using a 6-mm full-width half-maximum isotropic Gaussian kernel. Subsequently, all images were transformed into the Montreal Neurological Institute stereotaxic proportional system that is based on the Talairach and Tournoux (30) space, using in-house dedicated software (31). Functional and anatomical data were then merged to locate regions of significant activation.

The data analysis was performed with fmristat (ref. 32; available at www.math.mcgill.ca/keith/fmristat). The fMRI data were first converted to a percentage of the average signal intensity over all of the intracerebral voxels. The statistical analysis of the percentages was based on a univariate linear model with correlated errors. The paradigm was an event-related design with three events, corresponding to the task phase of each of the three tasks (manipulation, monitoring, and recognition control tasks) (see *Experimental Design*). The onset of these events was timed to coincide with the presentation of the cue in each trial, and their duration varied randomly between 4.5 and 6.5 s (the presentation of the cue and the following delay during which the subjects performed one of the three tasks). The hypothesis-testing two-tailed comparisons were based on the contrast between the coefficients of the task phase events for each of the three tasks: task phase of the manipulation trials minus task phase of the control recognition trials; task phase of the monitoring trials minus task phase of the control recognition trials; task phase of the manipulation trials minus task phase of the monitoring trials; and task phase of the monitoring trials minus task phase of the manipulation trials.

The resulting t statistic images were thresholded by using the minimum given by a Bonferroni correction and random field theory, taking into account the nonisotropic spatial correlation of the errors. For a single voxel in a directed search within predicted brain regions, the threshold for significance ($P < 0.05$) was set at $t = 4.072$. For a single voxel in an exploratory search involving all peaks within an estimated gray matter of 600 cm^3 covered by the slices, the threshold for reporting a peak as significant ($P < 0.05$) was $t = 4.570$ (33). Finally, a predicted cluster of voxels with a volume extent >110 mm^3 with a t value >3 was significant ($P < 0.05$) corrected for multiple comparisons using the method of Friston *et al.* (34).

We also examined the relative involvement of the IPS and MDLFC regions during the performance of the manipulation and monitoring tasks by calculating the mean percent of BOLD signal change in these regions during the task phase of the manipulation and monitoring trials in comparison with the task phase of the control trials. The mean BOLD signal change was calculated within a gray matter volume of a 10-mm^3 radius centered on the peaks of increase in activity located in the two regions of interest in each subject.

Functional connectivity analyses were performed to determine how neural activity at prechosen reference (i.e., seed) voxels correlates with all other voxels in the brain across time. To determine how functional connectivity is modulated by the performance of the manipulation and monitoring tasks, a variant of the psychophysiological interaction method proposed by Friston *et al.* (35) (see www.math.mcgill.ca/keith/fmristat) was performed for the IPS and MDLFC regions. The thresholds for significance were the same as for the linear univariate analysis presented above.

For the time-series analysis, hemodynamic response function shapes were determined by computing the finite impulse response associated with the onset of the event sequence corresponding to the presentation, delay, task, and test phases. This analysis was performed using NeuroLens (www.neurolens.org) (see *SI Text* for details on the analyses).

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