

Research Report

Double dissociation in neural correlates of visual working memory: A PET study

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Accepted 8 September 2005

Available online 20 October 2005

Abstract

Using positron emission tomography (PET), we investigated the organisation of spatial versus object-based visual working memory in 11 normal human subjects. The paradigm involved a conditional colour-response association task embedded within two visual working memory tasks. The subject had to remember a position (spatial) or shape (object-based) and then use this to recover the colour of the matching element for the conditional association. Activation of the nucleus accumbens and the anterior cingulate cortex was observed during the conditional associative task, indicating a possible role of these limbic structures in associative memory. When the 2 memory tasks were contrasted, we observed activation of 2 distinct cortical networks: (1) The spatial task activated a dorsal stream network distributed in the right hemisphere in the parieto-occipital cortex and the dorsal prefrontal cortex, and (2) The non spatial task activated a ventral stream network distributed in the left hemisphere in the temporo-occipital cortex, the ventral prefrontal cortex and the striatum. These results support the existence of a domain-specific dissociation with dorsal and ventral cortical systems involved respectively in spatial and non spatial working memory functions.

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Theme: Neural basis of behavior

Topic: Learning and memory: systems and functions—animals

Keywords: Associative memory; Object; PET; Spatial; Working memory

1. Introduction

Visual working memory allows the temporary storage and manipulation of visual information that is no longer available in the environment and that will be subsequently used for behavioural or cognitive purposes. The prefrontal cortex has been largely considered as the main candidate supporting different aspects of executive functions including visual working memory [24]. However, while a number of studies [3,14–16,43,45,46,50,51,53,55,57,70] investigated the neural mechanisms and substrates involved in different

components of working memory, there is still no consensus concerning the functional framework characterizing the prefrontal organisation of visual working memory. Indeed, evidence has been provided both in monkey and in human of two distinct two-stage prefrontal models of working memory. One is based on the remembered visual modalities ([33] for Review) and the other on the executive processes ([44,51] for Review).

In the context of the first model, using oculomotor delayed response tasks in monkey, sustained unit activity has been described in lateral prefrontal cortex during the delay period corresponding to the storage of the visual information [22]. In analogy to the segregated organisation of posterior visual pathways, Wilson et al. [70] identified in primate prefrontal cortex a similar dissociation into object (“what”)

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and spatial (“where”) memory domains. These authors proposed a theory in favor of a modality-specific model of the prefrontal processes with a ventral region supporting object memory and a dorsal region location memory. In man, a similar prefrontal pattern subtending spatial and non-spatial visual working memory has been suggested by neuro-imaging studies [3,14–16,64]. Accordingly, these authors localized in the superior prefrontal cortex an area specific for spatial information maintenance, and in the ventral prefrontal cortex a region that stores information related to faces. Behavioural deficits consecutive to prefrontal lesions are suggestive of an informational segregation of visual working memory organisation in monkey and in man [10,23,38,49]. In case of dorsal prefrontal lesion in man, a specific impairment of visuo-spatial working memory was found with preservation of verbal and shape working memory [10]. Moreover, using prefrontal cortex stimulation by rTMS in man, Mottaghy et al. [40] report the same prefrontal distribution of 2 functional ventral and dorsal prefrontal regions differently involved in an informational specificity of visual working memory.

In contrast to the modality specific model, several neuro-imaging studies in human argue in favor of a prefrontal segregation depending not on the visual modality but on the executive function processed during the visual working memory [43,45,46,50,52,53]. Thus, while evidence is convincing that the prefrontal cortex is crucial in visual working memory, the literature is therefore controversial about the functional segregation of the different prefrontal regions involved in visual working memory. Such a conflicting literature can have different methodological grounds. One is the diversity of the experimental tasks used, as some are based on more elementary designs [3,14] than others requiring high memory load and/or several executive functions [45,52,53,55]. A second is the neuro-imaging method and the image analysis employed, including the types of contrast either between the memory and the control tasks or between the two memory tasks.

In the present study, we investigated the anatomical organisation of visual working memory by using a modified delayed-match-to-sample paradigm combined with a conditional associative memory task. The paradigm involved a conditional colour-response association task embedded within two visual working memory tasks. In the working memory component, the subject had to remember either a position (spatial) or shape (object-based) cue, and then match this remembered cue with a corresponding colored stimulus in order to extract its color. This colour was then used to determine the correct response based on the learned colour-response association. This dual paradigm allows a reliable comparison between the two types of visual working memory in order to identify their neuronal substrates. The cerebral activation was measured by positron emission tomography (PET) and the cerebral activation responsible for the visual information memory process was extracted by direct comparison between the

two memory tasks, the association task, and simple motor tasks. Specifically, we performed contrasts between conditions of a simple motor response task (MOT), the colour-response association task (AM), and the complete spatial working memory (SPA) and non-spatial working memory (NSPA) tasks.

2. Methods

2.1. Subjects

A group of eleven right-handed volunteers, healthy subjects [6 males and 5 females, mean age = 53; sd = 6.7; range = 45–62] participated in this study. All the subjects were screened on the basis of a normal medical examination, no history of neurological and psychiatric disorders and no alcohol or drug abuse. Prior to PET evaluation, they gave their informed consent to participate in this research previously approved by the Research Ethics Committee (CCPRB L. Berard, Proposal No 02/045).

2.2. Task paradigm

The paradigm consisted of a motor task (MOT), a conditional associative learning task (AM) and two visual working memory tasks (WM) (Fig. 1).

In the motor task (MOT), the subject fixated a visual fixation point (white square) located at the center of the display. After a 500 msec fixation of the central point, 2 visual targets (white squares, view angle = 1.2 deg) were presented at an eccentric location, 10 deg right and left from the center. On each trial, the brightness of one of the 2 targets was randomly changed and the subject was instructed to move the handle of a joystick to the side of the brightest one. If the motor response was correct i.e. to the side of the brightest target, this target became larger, indicating that the movement was correct. Then the screen cleared until the next trial and the subject's hand returned to the rest position of the joystick (central position).

In the conditional associative learning task (AM), the subject had to associate the colour of a central cue to the direction of a joystick movement as shown in Fig. 1. As in the previous task, each trial started with a central fixation point followed by 2 simultaneous eccentric visual targets; then, a coloured central fixation cue (red or blue; view angle = 1.2 deg) appeared at the same location as the previous fixation point. The subject had to learn by trial and error the association between the cue colour and the movement direction. If the response was correct (i.e. to the side of the correct target), this target changed into the colour of the cue. If the response was incorrect, the screen was cleared. The association rule for the 2 colours used remained identical over the successive experimental sessions (red-left, blue-right).

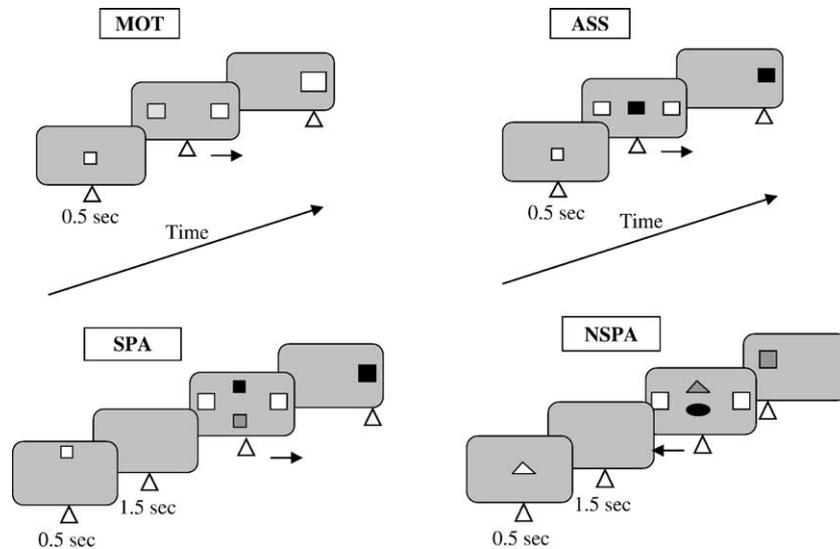


Fig. 1. Representation of the activation paradigm with a motor (MOT), a conditional associative learning (AM), a spatial (SPA) and a non spatial (NSPA) task. The arrow indicates the hand movement. (MOT), the subject has to move the hand to the brightened target. (AM), the subject has to associate the colour of a central cue to the direction of the hand movement. (SPA) the subject has to extract the colour of one of the 2 central cues at the position of the previously seen memory cue, (NSPA) the subject has to extract the colour of one of the 2 central cues matching the shape of a previously seen memory cue, and then use the extracted colour to retrieve the associated movement.

In the working memory tasks (WM), each trial started with a single white memory cue presented for 500 msec followed by a 1500 msec delay, then 2 coloured cues and the eccentric visual targets serving as a go signal were displayed for 1000 msec. One of the 2 coloured cues that matches the characteristic (position or shape) of the memory cue was then processed based on its colour.

2.2.1. Spatial working memory task (SPA)

For each trial, the initial memory cue (white square) could be in 2 different positions along the vertical central axis of the display (“up” or “down”). As shown in Fig. 1, when the two coloured cues were presented, the subject was required to extract the colour of the cue that matched the position of the previous memory cue, and to use this colour to retrieve the associated movement based on the learned colour-direction rule.

2.2.2. Non-spatial working memory task (NSPA)

The initial memory cue presented at the centre of the screen could have 2 different shapes (triangle or circle). When the two coloured cues were presented, the subject had to extract the colour of the cue that matched the shape of the initial memory cue, and to use this colour to retrieve the associated movement based on the learned colour-direction rule.

Prior to the scanning procedure, each subject was trained until she/he performed each task with no errors. During PET scanning, motor responses and reaction times were recorded for each trial. For each task, the trials were randomized over the 1 minute scan period. Each task (MOT, AM, SPA, NSPA) was repeated 3 times, corresponding to 12 PET scan acquisitions. The

order of the tasks was randomized and balanced over the subjects.

2.3. Scanning procedure

PET scanning was realized in the Neurology Hospital Imaging Center (CERMEP, Lyon, France) on a CTI HR+ Siemens tomograph (CTI/ Siemens, Knoxville, TN). A transmission scan was performed using rotating rod sources of ^{68}Ge . For each emission scan, an intravenous brachial bolus injection of 333 MBq of [^{15}O]H $_2\text{O}$ tracer was realized. The PET scanning started when the brain radioactivity count reached a threshold value of 400% of a 40s preliminary scan measure estimating the basal level of activity. Then, the scan continued for a period of 1 min. The radiation counts followed a linear relation to the regional cerebral blood flow (rCBF) changes. The subject initiated the task 25 sec prior the scanning onset to avoid any novelty effect on the rCBF measurement. A 10 minutes rest interval was applied between each emission scan to assure a reliable blood radioactivity decrease. The PET images were reconstructed by 3D filtered back projection (Hanning filter; cut-off frequency: 0.5 cycles/pixel) leading to 63 slices of 128 × 128 pixels format matrix yielding approximately 2 mm cubic voxels.

Head movements were prevented by a thermoplastic mask that was molded to the subject’s head and fixed to the scanner bed. The head position was checked throughout the PET examination using a laser alignment with reference points. During PET scanning, visual stimuli were presented by videoprojector on a translucent screen behind the scanning bay. The subject viewed the screen via a mirror fixed inside the camera and located at 20 cm of the subject’s head. The motor response was measured through a joystick

that the subject held in the right hand. The experimental procedure and data collection were monitored on PC computer using CORTEX software (NIH, Bethesda, USA).

2.4. Data analysis

2.4.1. Image analysis

Using CAPP software, the original emission scans in ECAT7 file format were converted to ANALYZE file format that were then processed in MATLAB 5.3 (Math Works, Natick, MA, USA) using the Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, MRC Cyclotron Unit, London, UK). The 12 individual PET scans were aligned to the first scan to correct for possible head movements and then normalized into the standard stereotactic space provided in SPM. The normalized images were smoothed with an isotropic Gaussian kernel (full width half maximum 14 mm for all directions) in order to allow for inter-individual gyrus variation and to improve the signal to noise ratio. rCBF changes were statistically analysed for all voxels exceeding 80% of the mean value of the scan with an analysis of variance with 4 task and 11 subject factors. Individual voxel values were adjusted by proportional scaling on the scan mean to account for injected dose effect. A post-hoc Student *t* test was used to compare the different tasks using the following contrasts: AM-MOT; SPA-AM; NSPA-AM; SPA-NSPA; NSPA-SPA. The WM tasks contrasted to the AM task (SPA-AM; NSPA-AM) displayed the cerebral activation related to the working memory processes while the between WM tasks contrasts displayed the cerebral activation related to the specific visual information memory process. Coordinates of the cerebral activation foci obtained with SPM were transformed into Talairach coordinates [68] using the following formula [5]:

$$X' = 0.88X - 0.8$$

$$Y' = 0.97Y - 3.32$$

$$Z' = 0.05Y + 0.88Z - 0.44.$$

The significance level was established for each cerebral activation pixel at $P < 0.0005$, uncorrected for multiple comparisons ($z > 3.291$). To verify these hypothesis, we performed a statistical analysis on regions of interest (ROI) delineated on the basis of the “limiting fissures” according to the human brain parcellation model developed by Rademacher et al. [59]. Twelve ROIs in each hemisphere were determined: –in the occipital region, the occipital lobe (OP) corresponding to BA areas 17,18, the occipito-lateral gyri, superior (OLs) and inferior (OLi) corresponding to BA areas 18,19 and the cuneus (CN) corresponding to BA areas 17,18,19, –in the temporal region, the temporo-occipital fusiform gyrus (TOF) corresponding to BA area 37, the temporal gyri including the middle (TO2) and the inferior (TO3) parts of BA area 37, –in the angular gyrus (AG) corresponding to BA area 39, –in the precentral gyrus (PRG)

corresponding to BA areas 4,6 and –in the frontal lobe, the superior (F1), middle (F2) and inferior (F3) gyri. The superior frontal gyrus (F1) included BA areas 6,8,9 and overlapped the dorsal prefrontal regions defined by Courtney et al. [16] to be specifically activated during spatial working memory. The middle frontal gyrus F2 included BA areas 6,8,9,46 and overlapped the dorso-lateral prefrontal cortex largely involved in visual working memory, especially in manipulation processes. Finally, the inferior frontal gyrus (F3) corresponded to BA areas 44,45, involving the ventro-lateral prefrontal cortex (VLPFC). Using the image analysis software ACTIVIS (CNRS-INSERM, Lyon, France), each ROI was drawn on the corresponding MNI canonical images, then transformed into mask templates that were then applied to our previously described contrasts for statistical analysis in SPM99 using “small volume correction”.

2.4.2. Behavioural analysis

Motor responses were analysed using CORTVIEW software and the percentage of errors and the reaction time were provided in each condition.

3. Results

3.1. Behavioral data

3.1.1. Percentage of errors

While no statistically significant difference was found between the 2 movement directions (side effect $F(1,10) = 0.39$; $P > 0.05$), the percentage of errors differed significantly between the tasks (main task effect $F(3,30) = 6.17$; $P < 0.01$). This effect was mainly related to the significant difference (post hoc comparison $P < 0.05$) between the NSPA (3%) task and MOT (0%) and AM (0.2%) tasks. No significant differences were found between the 2 memory SPA (1%) and NSPA (3%) tasks, not between SPA, MOT and AM tasks (post hoc comparison $P < 0.05$).

3.1.2. Reaction times

The mean reaction time (RT) was significantly different between the tasks (main task effect $F(3,30) = 81.56$; $P < 0.001$). While no statistically significant difference was found between MOT (556 msec) and AM (597msec) tasks (post hoc comparison $P > 0.05$), RT was significantly longer in the NSPA (854 msec) and SPA (671 msec) tasks as compared to MOT, AM (post hoc comparison $P < 0.05$). A significant RT difference was also found between NSPA and SPA tasks (post hoc comparison $P < 0.05$).

3.2. Imaging data

3.2.1. Activation due to associative memory

Significant rCBF changes were observed during the visual associative memory task (AM) relative to the motor task (MOT) caudally and bilaterally in the fusiform gyrus

and rostrally in the left anterior cingulate gyrus and in the right nucleus accumbens. In the fusiform gyrus, the activation foci were located in the Brodman area 20 in 2 different zones depending on the cerebral hemisphere, more medial on the left (Talairach coordinates: -43, -5, -32; $P < 0.001$) than on the right (Talairach coordinates: 38, -28, -25, $P = 0.003$). Only in the left cingulate cortex, we detected at a significant level of $P = 0.001$, a small activated focus located at the rostral end of the Brodman area 25. Interestingly, the nucleus accumbens was slightly activated ($P = 0.002$) in the right hemisphere.

3.2.2. Activation due to visual working memory process

3.2.2.1. Spatial working memory related cerebral activation

Spatial working memory task vs. Associative memory task. As shown in Table 1, the contrast SPA minus AM revealed significant rCBF changes ($P < 0.0005$) in different brain regions 1) bilaterally in the posterior cortex, including the inferior parietal (BA 40) and occipital gyri (BA 19) spreading to the cuneus and the precuneus (BA 7); 2) in the right prefrontal cortex, located in the midfrontal gyrus (BA area 9); 3) in the premotor cortex where two patches of activation were observed in the left hemisphere along the depth of the precentral sulcus at the limit with the midfrontal gyrus (BA 6-4), and in the depth of the precentral gyrus (BA 6-44) and 4) in the left anterior insula, as a focus bordering rostrally the putamen.

Spatial working memory task vs. Non Spatial working memory task. As compared to the previous contrast, the SPA minus NSPA analysis revealed a more restricted

network of activated cerebral structures specific to the visual spatial working memory modality. Interestingly this network of activation mainly involved the dorsal occipito-parieto- prefrontal cortical pathways of the right hemisphere. As shown in Table 1, a significant amount of activation ($P < 0.0005$) was observed (1) caudally (Fig. 2A), at the limit between the right occipital gyrus and the inferior parietal lobe, in the angular gyrus (BA areas 39-19) and bilaterally in the cunei and (2) rostrally (Fig. 3A), in the depth of the right midfrontal gyrus spreading from Talairach coordinates [33, 18, 34] to [40, 32, 44] (BA area 8-9, peak of activation in area 9 see Table 1).

ROI Analysis. Using the Rademacher’s model [59] of ROI outlining, we identified 2 small bilateral occipital patches triggered during the spatial WM task (as compared to the non spatial WM task): in the occipital poles (OP) and in the cunei (CN), on the right at a P corrected < 0.01 (Talairach coordinates: 10, -93, 18 and 1, -92, 18) and on the left at a p corrected < 0.05 (Talairach coordinates: -10, -95, 9 and -8, -89, 20) corresponding to BA areas 17 and 18. More rostrally, 4 ROIs of the occipito-parietal cortex were significantly activated forming a large cluster from Talairach coordinates [27, -69, 10] to [41, -88, 36] (1) in the right superior occipital lobe (OLs) (P corrected < 0.0001) corresponding to the associative visual area 19 (Talairach coordinates: 33, -79, 26) along with the right angular gyrus (AG) (P corrected < 0.0001) and finally (2) as a small lateral extent (P corrected < 0.01) in the inferior occipital lobe (OLi) along with the middle temporal gyrus (TO2) ($P < 0.0001$) (Talairach coordinates: 36, -75, 15 and 33, -79, 24). In the prefrontal gyrus, a small significant patch of activation was localized in the right middle prefrontal gyrus (F2) (P corrected = 0.006) dorsally at the limit of Brodmann areas 8 and 9 (Talairach coordinates: 34, 20, 39). In contrast, no significant suprathreshold cluster could be detected in other occipital and prefrontal ROIs during the spatial working memory condition.

3.2.2.2. Non spatial working memory related cerebral activation

Non Spatial working memory task vs. Associative Learning task. By analysing the contrast SPA minus AM conditions (Table 2), we observed several cortical regions significantly activated during the non-spatial working memory process. A large activation patch was found bilaterally in the posterior cortex, including an activation of the precuneus (BA area 7), the cuneus (BA area 17) and the occipital gyrus (BA areas 18-19) spreading ventrally into the fusiform and lingual gyri (BA 17-18-37). Rostrally, the cerebral activation was limited to the left hemisphere in the ventral prefrontal cortex, located in the inferior frontal gyrus (BA 45-46) and in the premotor cortex as a large focus in the ventral precentral gyrus (BA 44-6).

Table 1
Steretaxic coordinates and Z score for the significant activation foci during spatial working memory

Region	Brodmann area	Talairach coordinates			Z score
		x	y	z	
<i>Spatial > association</i>					
Left inferior parietal gyrus	40	-29	-61	39	6.81
Right inferior parietal gyrus	40	27	-63	42	4.72
Right occipital gyrus	19	31	-81	25	6.78
Left cuneus	19	-10	-77	31	6.65
Right precuneus	7	4	-72	45	6.64
Left fusiform gyrus	19	-52	-73	-11	4.06
Left precentral gyrus	6/4	-27	1	47	4.97
	44/6	-36	1	28	4.05
Right midfrontal gyrus	9	34	28	33	3.65
Insula		-25	14	2	3.35
<i>Spatial > non spatial</i>					
Right superior occipital gyrus	19	33	-79	24	5.35
Right cuneus	19	6	-93	18	4.48
Left cuneus	19	-11	-89	16	4.08
Right midfrontal gyrus	9	34	20	39	3.53

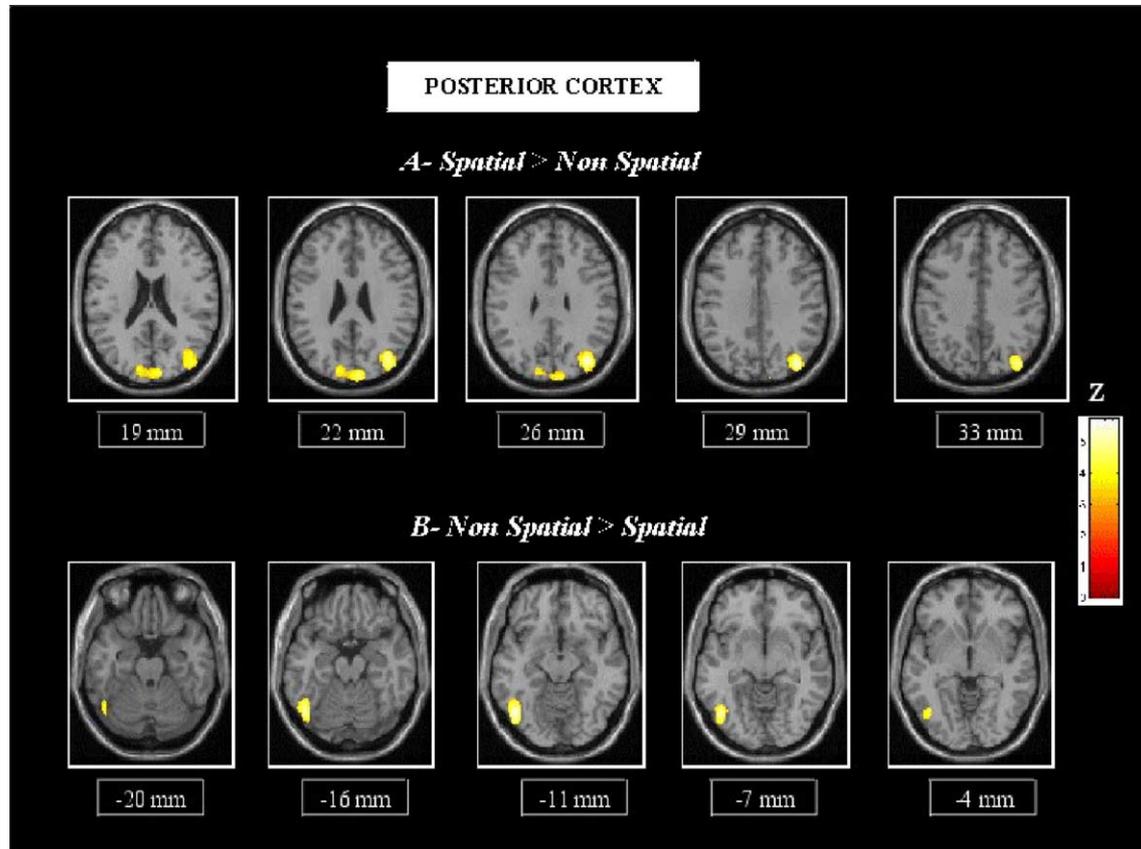


Fig. 2. Localisation of the significant ($P < 0.0005$) rCBF changes in the posterior cortex (occipital and fusiform gyri and cuneus) (A) during the spatial as compared to the non spatial working memory task and (B) during the non spatial versus the spatial working memory task represented on coronal sections overlaid on the normalized MNI image. The levels of the coronal sections are indicated in Talairach's coordinates [68]. The right hemisphere is shown on the right and the left hemisphere on the left.

Non Spatial working memory task vs. Spatial working memory task. (Table 2) The pattern of activation due to the non spatial visual working memory modality represented a network restricted to the left hemisphere and distributed between the temporo-occipital cortex, the premotor and the ventral prefrontal cortex. In the posterior cortex (Fig. 2B), a significant activation occurred in the mid-occipital gyrus (BA 19) that stretched to the inferior occipital (BA 18) and the fusiform gyri (BA 37). Rostrally, (Fig. 3B), the cortical activation formed 2 main patches, one in the inferior frontal gyrus (BA 45-46) and the other, in the premotor cortex located in the precentral gyrus (BA 6/4). Interestingly, as illustrated in Fig. 4, a significant focus of activation ($P < 0.001$) was found also in the caudal and ventral extremity of the left caudate nucleus (Talairach coordinates: $-10, -5, 12$).

ROI Analysis. In the non spatial WM condition (as compared to the spatial WM condition), significant rCBF increases were found in 3 ROIs of the left occipito-temporal cortex: (1) in the inferior occipital lobe (OLi), corresponding to BA areas 18,19 (P corrected < 0.001) (Talairach coordinates: $-39, -73, -11$) (2) in the inferior temporal lobe (TO3) along with (3) the temporo-occipital fusiform gyrus

(TOF) (P corrected < 0.001) corresponding to posterior BA area 37 (Talairach coordinates: $-39, -71, -14$ and $-41, -69, -16$). The prefrontal activation related to the non spatial working memory condition was significantly (P corrected < 0.01) established as a small patch extending in the left inferior frontal gyrus (F3) from Talairach coordinates $[-31, 22, 18]$ to $[-39, 32, 14]$ at the junction of BA areas 45 and 46 (Talairach coordinates: $-38, 24, 17$). Finally, a less significant activation (P corrected = 0.09; uncorrected $P < 0.001$) was detected in the precentral gyrus (PRG) corresponding to BA area 6 (Talairach coordinates: $-48, -5, 21$). No supra-threshold clusters were observed in the non spatial working memory condition in the other posterior and anterior ROIs.

4. Discussion

As it is illustrated in Fig. 5, the main finding of this study is the demonstration of a topographic dissociation between spatial and non spatial visual working memory. The spatial working memory task activated a dorsal pathway distributed between the parieto-occipital and the dorsal prefrontal cortex predominantly in the right cerebral hemisphere. In contrast, the non spatial working memory task activated a

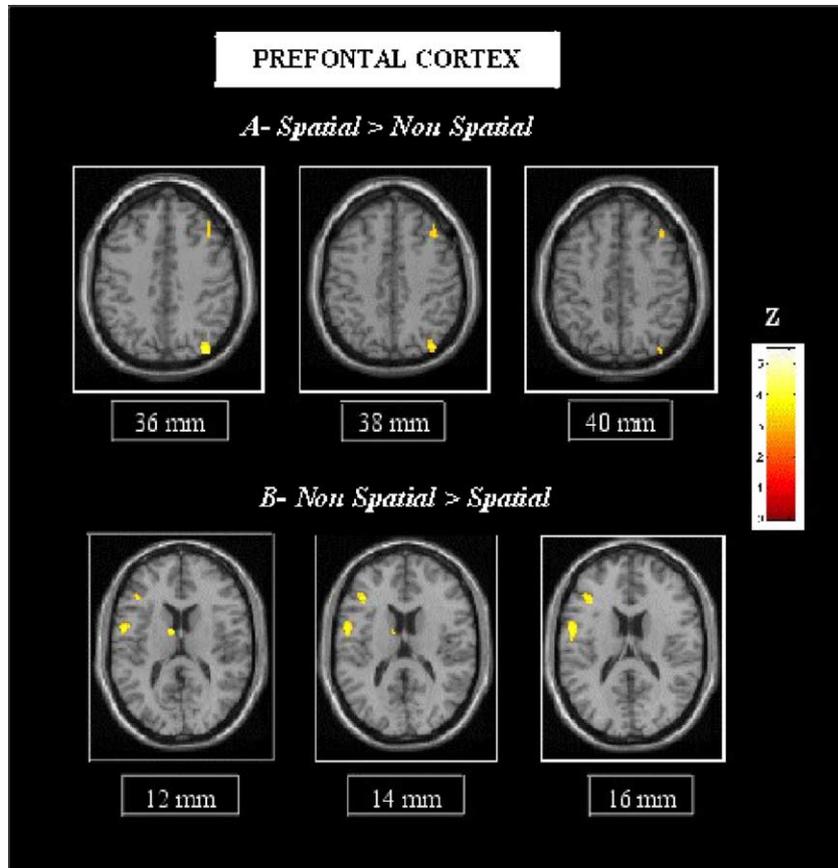


Fig. 3. Localisation of the significant ($P < 0.0005$) rCBF changes in the prefrontal cortex (A) during the spatial versus the non spatial and (B) during the non spatial versus the spatial working memory task represented on coronal sections overlaid on the normalized MNI image. The levels of the coronal sections are indicated in Talairach's coordinates [68]. The right hemisphere is shown on the right and the left hemisphere on the left.

ventral pathway distributed between the temporo-occipital cortex and the ventral prefrontal cortex along with a precentral cortical area and the striatum, predominantly in the left cerebral hemisphere. During the associative memory task, a cerebral activation was observed in the infero-temporal cortex and the basal forebrain including the nucleus accumbens and the anterior cingulate cortex.

4.1. Activation in limbic structures during associative memory

The colour-movement associative task yielded a cerebral activation, principally located in the basal forebrain structures, the anterior cingulate cortex and the nucleus accumbens. Though this activation appears to be modest, there is a functional correspondance between associative learning and the activated sites. Indeed, evidence has been provided that the anterior cingulate cortex and the nucleus accumbens are involved in conditional associative learning as Pavlovian behaviour [48,61]. The nucleus accumbens in interaction with the basolateral amygdala could mediate the effects of conditioned reinforcement by way of a dopamine transmission [20,61]. In consequence, the activation of the nucleus accumbens as observed in our current study, could reflect a consolidation of learnt colour-response associations

through trials. In the context of Pavlovian positive reinforcement, the anterior cingulate cortex, as largely connected with all sensory cortices, could be more implicated in the integration of stimuli association than in the reinforcement per se. Likewise, single unit recording during a delayed conditional discrimination task demonstrated that neurons of the anterior cingulate cortex in monkey are activated exclusively in relation to conditional visual cues and selection of the appropriate movement to produce [31]. In agreement with these different observations, the activation of the anterior cingulate cortex and the nucleus accumbens observed in our current study during the associative memory task could reflect the neural substrates of the learnt visuo-motor associative processes. In order to confirm such a functional interpretation, further investigations related to the mechanisms of associative memory are required.

4.2. Activation of common cortical areas during visual working memory

As compared to the associative memory task, the visual working memory tasks elicited cerebral activation in large networks spreading from the posterior cortex to the premotor and prefrontal cortices. Among these sites, some were common to both spatial and non spatial components of

Table 2
Steretaxic coordinates and Z score for the significant activation foci during non spatial working memory

Region	Brodmann area	Talairach coordinates			Z score
		x	y	z	
<i>Non spatial > association</i>					
Left fusiform gyrus	37	-41	-73	-18	7.14
Right fusiform gyrus		41	-75	-25	4.98
Left occipital gyrus	19	-25	-63	35	6.73
Right midoccipital gyrus	18/19	29	-94	7	6
Left cuneus	17	-3	-96	0	4.62
Right precuneus	7	6	-69	45	4.81
Left precentral gyrus	44/6	-39	0	26	4.99
Left inferior frontal gyrus	46/45	-36	22	20	4.04
		-43	41	16	3.9
<i>Non spatial > spatial</i>					
Left fusiform gyrus	37	-41	-69	-16	5.13
Left inferior occipital gyrus	18	-22	-91	-1	3.56
Left inferior frontal gyrus	45/46	-34	24	17	3.74
Left posterior ventral caudate nucleus		-8	-5	12	3.78
Left precentral gyrus	6/4	-48	-5	21	4.12

visual working memory. In the posterior cortical regions, rCBF changes were observed in striate and extrastriate visual cortex, including the cuneus and the mid-occipital gyrus (BA areas 17, 18, 19). This activation is coherent with the general visual processes elicited in our mnemonic tasks, including visual cue encoding, visual recognition, object and space perception [4,29,30,69]. The precuneus including the medial parietal cortex of BA area 7 was largely active in our visual working memory tasks. Interestingly, this region has been implicated in visual imagery and visual imagery occurring during memory retrieval ([37] for Review). Thus, the precuneus recruitment in the medial parietal region might reflect the retrieval component of the memorized visual features of the cue (position or shape) combined with the associative visual feature (colour).

Finally, another common site was found in the ventral precentral gyrus (BA areas 6/44) corresponding to the premotor cortex, typically involved in preparatory motor mechanisms. Such a precentral activation constitutes a recurrent finding in visual working memory studies independently of the sensory modality studied [11,14,19,26,52,53,65–67]. Interestingly, the ventral premotor cortex has been implicated in the selection of appropriate movement [18], in memorizing manipulable objects [27] and in attention shifting [12]. Alternatively, in accordance with its role in attentional shifting, the ventral premotor cortex might mediate rehearsal in maintenance processes of visual working memory as suggested by several studies [16,32,65]. Indeed, these 2 cognitive functions, visual attention and working memory, share common processing and neural substrates, including the parietal, prefrontal and premotor cortex [1,12,13,65]. In our task the attention was likely shifted to the visual field location of the memory cue that induces a rehearsal in the visual processing linked to working memory.

4.3. Activation of dissociated neural networks during visual working memory

Based on the comparison between memory tasks, we identified 2 occipito-frontal networks dissociated on the basis of the visual mnemonic modalities. The spatial working memory component activated 2 main cortical regions distributed along the right dorsal stream i.e. the occipito-parietal cortex including the extrastriate visual areas 18/19 and 39 and the dorsal prefrontal cortex including the BA area 9 up to the junction of areas 8 and 9. In contrast, when working memory was elicited by using a visual form discrimination cue, the rCBF changes were distributed principally in the left hemisphere along a ventral stream of occipito-temporo-prefrontal pathways including the ventral premotor cortex (BA area 6) and the inferior prefrontal cortex (area BA 45/46). Interestingly, the storage of the non spatial visual information activated a subcortical site localized in the ventral and the caudal extremity of the caudate nucleus.

4.3.1. Prefrontal cortical sites

Our results related to prefrontal activation are in accordance with previous studies demonstrating the existence of segregated prefrontal areas involved in visual working memory in monkey [70] and in man [3,14,36,64]. By single unit activity recordings in monkey, Goldman-Rakic's group proposed a domain specific memory organisation by which ventral and dorsal regions of the prefrontal cortex would respectively support object and space working memory [33,42,70]. In man, a similar prefrontal dissociation has been suggested by Courtney et al. [14] using either the features or the location of faces as the visual stimuli to be memorized. While our findings and Courtney's converge to a same locus of the non spatial working memory in the ventral prefrontal cortex, there are some dissimilarities regarding the dorsal prefrontal site involved in spatial working memory. In previous neuroimaging studies in man, evidence has commonly been provided for mid-frontal cortical activation of BA areas 9 and 46 during spatial working memory [2,19,35,45,52,53,57]. Likewise, our spatial task triggered a well distinguished focus with a peak of activation in the BA area 9 at the border of the area 8. Our site of activation in dorsolateral prefrontal area 9 (Talairach coordinates: 34, 20, 39) was close to that identified by Petrides et al. [52] (Talairach coordinates: 32, 32, 36) and Owen et al. [45] (Talairach coordinates: 39, 25, 36). As we could not find overlap between our spatial working memory area and Courtney's (more caudal in BA area 8/6 of the superior frontal sulcus), the question remains open whether or not these 2 sites localized in the mid-dorsolateral prefrontal cortex or just posterior to it, respectively area 9 and area 8, are parts of the same working memory module associated to the maintenance of information related to location or spatial relations?

With the non spatial working memory task, the prefrontal cortex was recruited in the inferior frontal gyrus

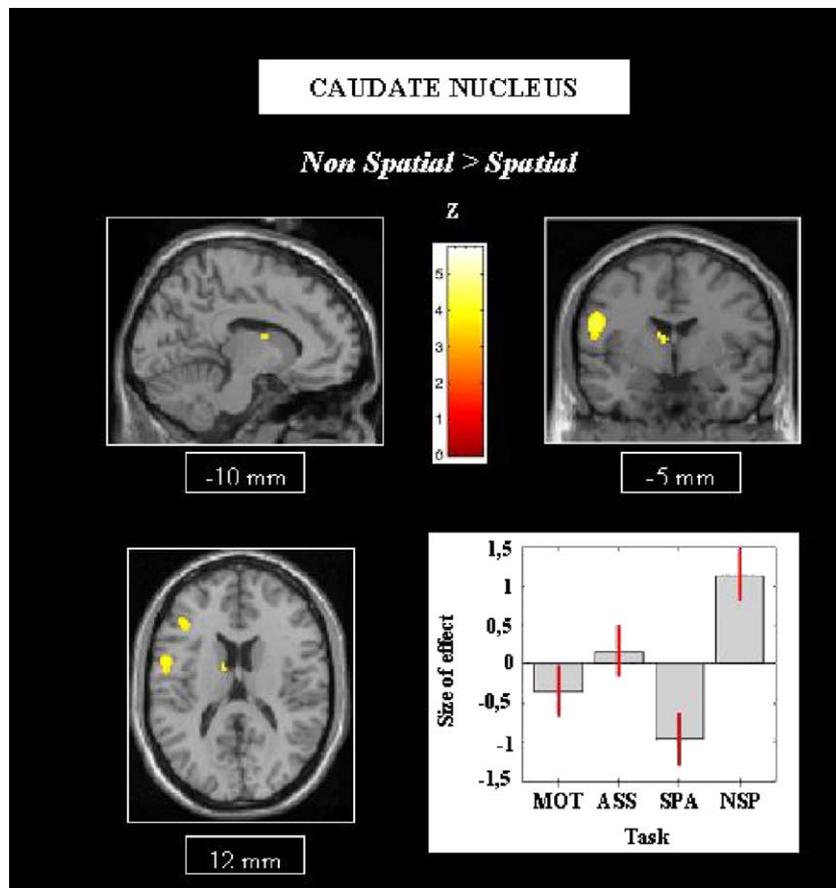


Fig. 4. Three orthogonal views of the rCBF changes ($P < 0.0005$) localised in the caudal extremity of the left caudate nucleus during the non-spatial (NSPA) versus spatial (SPA) working memory task. Plot is the mean effect value over subject of the tasks regressors. At this location, the effect is opposite and significantly different between NSPA and SPA tasks whereas it is moderated in the two other tasks.

at the junction of BA areas 45/46 in a region similar to the region identified by Courtney et al. [15] to develop sustained activity during facial images working memory. Taken together, this study and the current one converge to the idea of the existence in the human brain of well segregated dorsal and ventral prefrontal systems respectively involved in visuo-spatial and visual-feratural working memory. Accordingly, a recent study using rTMS provided evidence for such a visual modality specificity of prefrontal working memory organisation in man [40]. In contrast, Postle et al. [55,57] failed to find dissociated prefrontal activity when comparing “what” and “where” visual working memory. These authors suggested that domain-specific visual working memory might be mediated by posterior cortex. More recently, by single unit recording in the prefrontal cortex in monkey, Rao et al. [60] demonstrated that single prefrontal neurons are able to process both what and where information through interconnections between dorsolateral and ventrolateral prefrontal cortices. Likewise, using human neuroimaging, Sala et al. [64] suggested that the mechanisms for the maintenance of house identity information are distributed and overlapping with those that maintain spatial location information, while the mechanisms for maintenance of face identity information are

relatively more independent. These last works are suggestive of a more graded pattern in the cortical organisation of visual working memory.

4.3.2. Striatum site

Moreover, by direct memory task comparisons, we found a specific activation in the caudal part of the left caudate nucleus. The caudate nucleus has been described as a node in the neural cortico-striatal network subserving visual working memory in monkey and man [34,56]. Interestingly, Levy et al. [34] provide evidence in monkey of a functional and topographical gradient in the caudate nucleus organisation by which its rostral part (head of the caudate nucleus) more connected to the dorsolateral prefrontal cortex might be also preferentially engaged in spatial working memory and its caudal part (body and tail of the caudate nucleus), closely connected to the infero-temporal cortex, might be more engaged in the non spatial aspects of working memory. Accordingly, using a similar working memory paradigm, we demonstrated specific disorders in mild Parkinson patients OFF-dopamine only during the non spatial component, as compared to the spatial component, of our visual working memory task [39]. Such a dissociation of the striatal function between

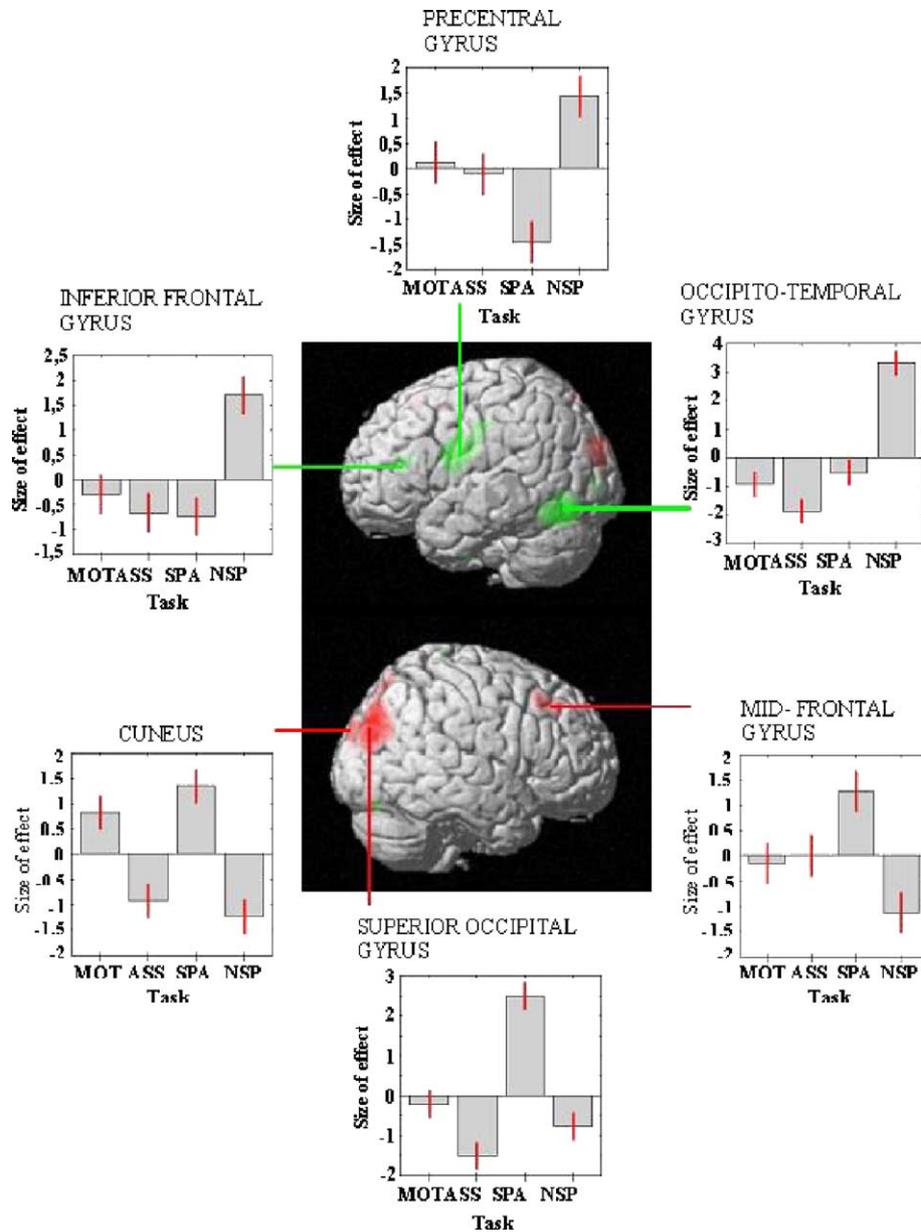


Fig. 5. Distribution of the activation foci obtained in the non-spatial (NSPA) and in the spatial (SPA) working memory tasks rendered on the surface of three-dimensional MNI MRI templates. Green are positive Z-score in SPA minus NSPA contrast and red are positive Z-score in the NSPA versus SPA contrast. For each cluster, the mean value of the regression effect is plotted for each task. Note the opposite pattern of activation effect in the NSPA versus SPA tasks, especially in the mid-frontal and the inferior frontal gyri.

spatial and non spatial working memory is also clearly reflected in our current neuro-imaging data showing a predominant activation of the tail of caudate nucleus during the non spatial working memory task. While our 2 visual working memory tasks were similar in terms of complexity and difficulty, the more distributed cortical and subcortical network activated in non spatial working memory suggests more extended mnemonic processes for object than for space recognition and memorisation. Accordingly, we found corresponding differences in motor performance (response time) between the 2 memory tasks.

4.4. Activation of dissociated prefrontal areas and non memory processes

On the basis of our mid-aged population, it could be argued that the observed segregated organisation of the visual working memory is related to an age effect. In this context, it is noteworthy that older subjects tend to demonstrate a reduction both in the segregation and hemispheric lateralisation of working memory [6–9,25,28,47,62,63]. This indicates that the presence of such dissociations observed in the current study on middle aged subjects is not related to age effects.

Another potential concern raises the possibility that the activation of the prefrontal areas partly reflects eye movements and/or verbal rehearsal that could be differently elicited in the spatial and non spatial tasks. While the principal frontal region involved in eye movement generation is localized in the dorsal prefrontal cortex, its activation observed during our tasks cannot be accounted for by ocular saccades alone, for several reasons. First, area 9 in the dorsolateral prefrontal cortex which was activated during our spatial memory task has been implicated in spatial memory processes (maintenance, manipulation, decision) rather than in eye movements generation (see [54] for Review). Second, in contrast, the Frontal Eye Field (FEF) characterized as the prefrontal oculomotor center (saccadic and pursuit eye movements) is localized in human more posteriorly in the Brodman areas 6 and 8 at the intersection between the precentral sulcus and the superior prefrontal sulcus well dissociated from the prefrontal regions activated in the current study.

It is noteworthy that the precentral cortex activation limited to the ventral part of the precentral cortex (area 6/44), was observed in both working memory tasks when contrasted with the association task. As we noted above, the precentral cortex activated in our tasks could be responsible for motor preparation, attention shifting or more likely for verbal rehearsal. Indeed, the posterior part of the left inferior prefrontal cortex is part of a neural network that supports phonological working memory and verbal rehearsal [17,41]. Interestingly, this premotor rCBF change is predominant during the non spatial task and thus might mediate a verbal rehearsal of visual form memorization that is likely less required than during the visuo-spatial memorization. However, this site is clearly distinct from the inferior prefrontal site at the BA 45/46 boundary activated in our non spatial working memory task.

4.5. Methodological issues of cognitive subtraction

The use of subtraction to analyse activation differences across conditions must be evaluated with a certain degree of caution, particularly with respect to a logic of “pure insertion” [21,58,71]. Pure insertion assumes that comparison of activation and baseline tasks only reflect the cognitive component added in the activation task, leaving unchanged the implementation of components shared by activation and baseline tasks. A number of studies have revealed that this pure insertion logic is flawed, and that processes involved in baseline tasks are often modulated by the cognitive component added in the activation task [21,58,71]. Zarahn et al. [71] thus documented such limitations in a study in which a delay was added to a perceptual task in order to study working memory. They observed regions active in the Delay-NonDelay contrasts that did not display increases in signal uniquely attributable to the delay. In this context, it is thus possible that our SPA-AM (and NSPA-AM) activation is dependent on the

interaction of AM with the SPA task (and NSPA task, respectively). Given this limitation, these subtractions must be considered to reflect the activity of spatial and non-spatial working memory and associative memory, compared to associative memory alone. Importantly, the contrasts that represent the focus of our study directly compare SPA and NSPA working memory and thus fall outside of the strict cognitive subtraction domain, in that there is no presumed additive relation between the SPA and NSPA conditions. That is, one is not a subtask or baseline for the other, and thus the loss of information about interaction between the two tasks is not an issue.

4.6. Conclusions

In conclusion, by using combined associative and working memory tasks, we demonstrated in man a dissociation of spatial and non spatial visual working memory organisation. The object location related mnemonic processes recruited a dorsal network predominantly distributed in the right hemisphere between occipito-parietal and dorsal prefrontal cortex. In contrast, object feature related memory triggered a ventral cortical and sub-cortical network predominantly distributed in the left hemisphere including the occipito-temporal, premotor and ventral prefrontal cortices and the caudate nucleus. The spatial and non-spatial working memory tasks we employed followed an identical protocol logic, and thus did not significantly differ with respect to employment of executive function. This suggests that the observed dissociations in cortical activation are due to differences in visual modality processing, rather than differences in recruitment of executive function.

Acknowledgments

The authors thank Dr. Marc Janier for participant recruitment, Veronique Berthier, Martine Lionet and Christine Vighi for participant monitoring during scanning and the personnel at the Brain Imaging Center (CERMEP) for technical assistance. This work has been funded by a CNRS grant (Cognition et Traitement de l'Information) and by LAFMI project.

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