

## When thoughts become action: An fMRI paradigm to study volitional brain activity in non-communicative brain injured patients

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The assessment of voluntary behavior in non-communicative brain injured patients is often challenging due to the existence of profound motor impairment. In the absence of a full understanding of the neural correlates of consciousness, even a normal activation in response to passive sensory stimulation cannot be considered as proof of the presence of awareness in these patients. In contrast, predicted activation in response to the instruction to perform a mental imagery task would provide evidence of voluntary task-dependent brain activity, and hence of consciousness, in non-communicative patients. However, no data yet exist to indicate which imagery instructions would yield reliable single subject activation. The aim of the present study was to establish such a paradigm in healthy volunteers. Two exploratory experiments evaluated the reproducibility of individual brain activation elicited by four distinct mental imagery tasks. The two most robust mental imagery tasks were found to be spatial navigation and motor imagery. In a third experiment, where these two tasks were directly compared, differentiation of each task from one another and from rest periods was assessed blindly using a priori criteria and was correct for every volunteer. The spatial navigation and motor imagery tasks described here permit the identification of volitional brain activation at the single subject level, without a motor response. Volunteer as well as patient data [Owen, A. M., Coleman, M.R., Boly, M., Davis, M.H., Laureys, S., Pickard J.D., 2006. Detecting awareness in the vegetative state. *Science* 313, 1402] strongly suggest that this paradigm may provide a method for assessing the presence of volitional brain activity, and thus of consciousness, in non-communicative brain-injured patients.

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### Introduction

Improvements in medical practice have led to an increasing number of patients surviving acute brain injury. Survivors of severe traumatic or hypoxic–ischemic brain damage classically go through distinct clinical stages before partially or fully recovering consciousness. Coma is defined as ‘unarousable unresponsiveness’. After some days or weeks comatose patients may eventually open their eyes. When this return to ‘wakefulness’ is accompanied by reflexive motor activity only, devoid of any voluntary interaction with the environment, the condition is called a vegetative state (The Multi-Society Task Force on PVS, 1994). The vegetative state may be a transition to further recovery. Limited but reproducible signs of self- or environment-awareness characterize the minimally conscious state (MCS) (Giacino et al., 2002). Functional communication indicates the next boundary – emergence from MCS – in the course of recovery (Laureys et al., 2005).

There currently exists no method for acquiring an objective physical measure of conscious awareness in either a patient or a healthy volunteer. Its estimation in patients requires expert clinical interpretation of voluntary versus reflexive behaviors, necessarily relying on ‘motor responsiveness’ (Majerus et al., 2005). Indeed, the only method that any of us can use to demonstrate our awareness to others is through some form of motor activity—speech, facial expression, eye-tracking, limb movement, shrugging shoulders, nodding-shaking the head, etc. (Majerus et al., 2005). Therefore, clinical assessment is limited in the extent to which ‘internal awareness’ can be established in a patient who lacks the motor function to demonstrate this awareness (Giacino and Zasler, 1995). These difficulties may partly explain the high frequency of misdiagnosis (up to 43%) among non-communicative brain injured patients (Tresch et al., 1991; Childs et al., 1993; Andrews et al., 1996). A recent study of 42 locked-in syndrome patients (fully conscious but completely paralyzed) found a mean diagnosis delay

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of 2.5 months (78.1 days) from the time the patient suffered the stroke or traumatic brain injury (Leon-Carrion et al., 2002). Some fully aware but non-communicative patients sometimes even stay misdiagnosed (as being in a vegetative state) for periods as long as 4 years (Leon-Carrion et al., 2002).

Several brain imaging studies have shown relatively normal patterns of brain activation in response to complex sensory stimulation in some non-communicative patients, mainly responding to the clinical criteria of minimally conscious state (Bekinschtein et al., 2004; Boly et al., 2004; Laureys et al., 2004; Owen et al., 2005; Schiff et al., 2005). However, in the absence of a full understanding of the neural correlates of consciousness, even a near-to-normal activation in response to passive sensory stimulation cannot be considered as a proof of the presence of awareness in these patients. Instead, all that can be inferred is that a specific brain region is, to some degree, still able to process the relevant sensory stimuli. Our hypothesis is that functional imaging could be a tool for assessing certain forms of volitional brain activity without requiring any motor output from the volunteers. Our reasoning was that a predictable activation in response to the instruction to perform a mental imagery task would provide evidence of consciousness in non-communicative patients. However, no data yet exist to indicate which imagery tasks would be most suitable in this context, and in addition, which tasks are likely to yield reliable results in individual subjects. Indeed, the reliability of the results obtained in individual volunteers rather than across a group is crucial for any clinical application where interpretation will take place on a single subject basis. The aim of the present study was to validate this approach in healthy volunteers.

The experimental procedure took place in three steps. Two exploratory experiments searched for appropriate mental imagery tasks that elicited in individual healthy volunteers robust brain activation in task-specific areas (as previously reported in the neuroimaging literature). A third experiment compared the two most reproducible tasks to one another and tested whether a blind analysis could differentiate each task from one another and from rest periods in each volunteer.

## Methods

### Volunteers

The two exploratory experiments were performed at the Wolfson Brain Imaging Centre (WBIC), Addenbrookes Hospital, University of Cambridge, UK. The third experiment was performed at the Cyclotron Research Center (CRC), University of Liège, Belgium. Twelve volunteers participated in each experiment (whole group mean age  $24 \pm 4$ , 12 males). Volunteers gave their written informed consent to participate in the study. None of the volunteers declared any history of neurological or psychiatric disease. Volunteers were paid for their participation in the experiment. The Cambridge Local Research Ethics Committee and the Ethics Committee of the University of Liège approved the study.

### Choice of the tasks

Four mental imagery tasks were studied and standard instructions were given to volunteers for conducting each task:

- (1) Spatial navigation (around subject's home) (Curran et al., 2004): the volunteers were asked to imagine visiting all the

rooms of their house, starting from the front door. They were instructed to mentally inspect the rooms and notice all the details as they looked around, rather than concentrating on walking. If they had mentally toured the entire house before the next instruction, they had to mentally go back in the same manner towards the front door.

- (2) Sub-vocal rehearsal/auditory imagery (of a familiar tune) (Curran et al., 2004): the volunteers were asked to sing a familiar song in their head (for standardization purpose we chose the song 'jingle bells'). They were instructed to project their voice in their head and imagine singing very loudly, as if they were on a stage, without mouthing the words or moving any part of their body.
- (3) Motor imagery: imagery of complex movements has been shown to elicit stronger activation than imagery of simple ones (Kutzt-Buschbeck et al., 2003). We asked volunteers to imagine playing tennis, concentrating on hitting the ball very hard, as if they were on a court during a competition. This mental imagery task was chosen because it was relatively easy to imagine, without needing previous training.
- (4) Visual imagery of faces: the volunteers were asked to imagine faces of familiar relatives, focusing attention on the features of one particular face (nose, eyes, mouth, etc.), and to switch to another face as soon as they felt it necessary for the maintenance of their attention.

### Experimental paradigm

The mental imagery tasks were organized in single session block design paradigms. Standard summarized auditory instructions to perform a specific task (e.g. "play tennis") were given every 30 s. For rest periods, the auditory instruction was 'now please, just relax'. Volunteers kept their eyes closed during the experiment.

Table 1 summarizes the experimental paradigm for the three experiments. During the first session, volunteers were asked to alternate between (a) imagining moving around the rooms of their home, (b) sub-vocal rehearsal (imagine singing jingle bells) and (c) rest periods. Each instruction was repeated seven times with a period of 30 s between instructions. In the second experiment, volunteers alternated between (a) imagining playing tennis (motor imagery), (b) face imagination and (c) rest. Given previous evidence indicating face imagination elicits weaker cerebral activation than the other tasks (see O'Craven and Kanwisher, 2000a), each instruction was repeated ten times in the second experiment. Again instructions were given every 30 s.

The two most robust mental imagery tasks from experiments 1 and 2 were found to be spatial navigation and motor imagery. The

Table 1  
Experimental design

Stages	Aim of the experiment	Task 1	Task 2
Experiment 1	Find reproducible single-subject activation	Spatial navigation	Subvocal rehearsal
Experiment 2	Find reproducible single-subject activation	Motor imagery (tennis)	Imagining faces
Experiment 3	Test possibility of blinded discrimination of each task versus rest	Spatial navigation	Motor imagery (tennis)

third experiment aimed to test whether a blinded observer could differentiate between these two tasks and rest. Therefore, volunteers alternated between 30-s periods of spatial navigation imagination, motor imagery and rest in a pseudo-randomized order chosen by a computer, without any direct feedback to the experimenter. We then sought to determine, by means of our statistical parametric analysis, which period corresponded to rest, or to a particular mental imagery task in each individual volunteer. This was achieved using predefined criteria, differentiating each state from one another using the most reliable differential activations obtained in the first two experiments (see data analysis paragraph). The same auditory instructions used in experiments 1 and 2 were given at the beginning of each 30-s block and each condition was repeated seven times. At the beginning of the fMRI acquisition, the stimulus PC randomly selected a particular task presentation order from a set of predefined possible sequences. All of these sequences resulted in an identical design matrix for the analysis, with the tasks randomly assigned between the 3 first columns of this matrix. The corresponding randomly selected task sequence was saved for each volunteer in a separate file. These results files were only consulted at the end of all data analyses, when predictions had been made about the order in which different tasks were performed in each volunteer.

#### Data acquisition

In the first and second experiments, a 3T Bruker system (S300, Bruker Medical, Ettlingen, Germany) at the WBIC was used to acquire echo-planar functional images (TR=1100 ms, TE=27.5 ms, 21 interleaved axial slices oriented  $\sim 10^\circ$  from the AC–PC transverse plan, 4 mm thickness, 1 mm inter-slice skip, 200 mm FOV,  $64 \times 64$  matrix, 1 session of 582 volumes acquisition). Volunteers were lying down in the scanner in front of a mirror box that allowed them to see a projector screen. Head movements were minimized by using a vacuum cushion. Eighteen additional volumes were collected and discarded at the beginning of each session to allow for T1 equilibration. High resolution T1 weighted MR scans were also acquired during the same session.

In the third experiment, data were acquired on a 3 T head-only MRI scanner (Allegra, Siemens Medical Systems, Erlangen, Germany) at Liège using a T2\* sensitive gradient echo (EPI) sequence (TR=2130 ms, TE=40 ms, FA  $90^\circ$ , matrix size  $64 \times 64 \times 32$ ; voxel size:  $3.4 \times 3.4 \times 3$  mm<sup>3</sup>). Thirty-two contiguous 3-mm thick transverse slices were acquired, covering the whole brain. Anatomical images were obtained by using a T1-weighted 3D MP-RAGE sequence (TR 1960 ms, TE 4.43 ms, TI 1100 ms, FOV  $230 \times 173$  cm<sup>2</sup>, matrix size  $256 \times 256 \times 176$ , voxel size:  $0.9 \times 0.9 \times 0.9$  mm) for each subject. A standard head coil was used in the data acquisition. In all sessions, the first four volumes were discarded to account for magnetic saturation effects. Volunteers were lying down in the scanner in front of a mirror box that allowed them to see a projector screen. Volunteers kept their eyes closed during the experiment. Head movements were minimized by using a vacuum cushion. Three hundred functional volumes (mean duration 10 min) were obtained per subject. Before the fMRI session, the acoustic level of the auditory instructions was individually adjusted for optimal comfort during a sham fMRI acquisition.

#### Data analysis

Data were pre-processed and analyzed using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>). Data were first manually reoriented.

The mean image of the realigned scans were computed and used as the source image for spatial normalization of the data. Data were then spatially smoothed, using a 12-mm and an 8-mm FWHM Gaussian isotropic kernel for data acquired from the WBIC and CRC scanners respectively. The difference in smoothing kernel reflects different acquisition parameters on the WBIC and CRC scanners (i.e., spatial resolution of raw functional images). The time series in each voxel were high pass-filtered to 1/128 Hz to remove low-frequency noise, corrected for temporal auto-correlation using a AR(1)+white noise model, and scaled to a grand mean of 100 across voxels and scans in each session.

For the two exploratory experiments, single subject fixed-effect analyzes were performed in each subject. Two types of events were defined for each session: corresponding to the two mental imagery task periods of 30 s duration. Events for each of these regressors were modeled by convolving onset times with a canonical hemodynamic response function. Parameters of each regressor were estimated using the general linear model, with movement parameters

Table 2  
Areas activated in the different imagery tasks compared to rest

Brain areas	Side	x	y	z	Z value	p value
<i>Songs &gt; rest</i>						
Pre-SMA		0	10	62	4.55	0.001
Dorsal premotor cortex		-50	2	56	4.15	0.001
		58	-2	46	5.00	0.012*
Superior temporal <sup>o</sup>		-58	4	-18	3.28	0.011
<i>Spatial navigation &gt; rest</i>						
Pre-SMA <sup>o</sup>		-2	16	56	4.13	0.001
		2	16	56	3.98	0.002
Dorsal premotor cortex <sup>o</sup>		-36	2	50	4.11	0.001
		38	4	60	3.57	0.005
Parahippocampal cortex <sup>o</sup>		28	-28	-30	3.43	0.008
		-28	-32	-28	3.27	0.012
Retrosplenial cortex <sup>o</sup>		14	-54	4	4.24	0.001
		-10	-58	2	4.30	0.001
Occipito-parietal junction <sup>o</sup>		28	-68	16	3.88	0.002
		-26	-74	26	4.37	<0.001
Precuneus		-20	-74	44	3.75	0.003
		20	-74	44	3.10	0.018
		-18	-70	54	3.74	0.003
		14	-68	58	3.74	0.003
<i>Tennis &gt; rest</i>						
Pre-SMA		10	4	64	5.74	0.001*
Dorsal premotor cortex		-36	-2	50	4.07	0.002
		38	0	50	4.29	0.001
SMA <sup>o</sup>		0	-4	64	4.37	0.001
Inferior parietal lobule <sup>o</sup>		-66	-46	30	3.97	0.002
		54	-40	34	3.94	0.002
<i>Faces &gt; rest</i>						
Pre-SMA		0	12	58	4.70	0.043*
Dorsal premotor cortex		-34	0	54	3.89	0.002
		34	2	42	4.98	0.016*
Fusiform gyrus		46	-46	-22	3.02	0.025
Intraparietal sulcus		28	-50	34	5.01	0.015*
Occipital cortex <sup>o</sup>		32	-70	30	4.85	0.026*
Inferior Frontal Cortex		40	34	8	4.91	0.021*

Results of group analysis in WBIC volunteers, thresholded at FWE (\*) or SVC corrected  $p$  value < 0.05. <sup>o</sup> Areas significantly more activated in the present task compared to the paired mental imagery modality.

in the 3 directions of motion and 3 degrees of rotation included as confounds, and one covariate representing the mean session effect. Linear contrasts were then used to obtain subject-specific estimates for each of the effects of interest, and to search for areas specifically more activated in each mental imagery task compared to the other one. The contrast images containing these estimates for each voxel were then smoothed at 8 mm FWHM Gaussian kernel (Peigneux et al., 2006). This second smoothing procedure was performed to increase inter-subject averaging at the group level, taking into account inter-individual anatomical variability. As parameters estimation, contrasts and smoothing are all linear operations, smoothing at the second level permits the overall smoothing kernel

to increase in a linear manner. This improves statistical power at the group level while allowing spatially accurate results at the first level. As Gaussian smoothing adds in quadrature, the effective smoothing at the second level was 14.4 mm. The smoothed contrast images were then entered into the second stage of analysis treating volunteers as random effects, using one-sample *t*-tests across the twelve volunteers. Given our a priori hypotheses, all results were thresholded using Gaussian random field theory (Worsley et al., 1996) at uncorrected  $p < 0.001$ , then 10-mm radius sphere small volume corrected (SVC)  $p$  value  $< 0.05$  on previously documented coordinates (from spatial navigation mental imagery (Ghaem et al., 1997a; Mellet et al., 2000b; Ino et al., 2002), motor imagery (Lotze

Table 3  
Individual results in each mental imagery task for WBIC volunteers

Individual subject number	1	2	3	4	5	6	7	8	9	10	11	12	Total	Peak coordinates (x, y, z; mean ± SD)
<i>Spatial navigation &gt; rest</i>														
Pre-SMA	+	+	+	+	+	+	+	+	+	+	+	+	12/12	2±5, 15±4, 58±5
Dorsal premotor cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	31±5, 6±3, 59±4 -30±3, 3±5, 55±4
Precuneus	+	+	+	+	+	+	+	+	+	+	+	+	12/12	-20±4, -73±4, 51±4
Retrosplenial cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	14±4, -59±4, 8±5
Parahippocampal cortex	+	+	-	+	+	+	+	+	+	+	+	+	11/12	30±3, -37±6, -27±6 -30±3, -37±2, -25±6
<i>Songs &gt; rest</i>														
Pre-SMA	+	+	+	+	+	+	+	+	+	+	+	+	12/12	2±3, 9±5, 63±5
Dorsal premotor cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	54±3, -1±6, 46±4 -51±5, 2±4, 52±5
Superior temporal	+	-	-	+	+	-	-	-	-	-	-	-	3/12	-60±1, 4±0, -20±2
<i>Spatial navigation &gt; songs</i>														
Precuneus	+	+	+	+	+	+	+	+	+	+	+	+	12/12	-19±4, -73±4, 51±4
Retrosplenial cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	14±3, -59±2, 9±5
Parahippocampal cortex	+	+	-	+	+	+	+	+	+	+	+	+	11/12	31±3, -37±6, -25±5 -31±4, -36±3, -23±3
<i>Songs &gt; spatial navigation</i>														
Superior temporal	-	-	-	-	+	-	-	-	-	-	-	-	1/12	-62, 2, -20
<i>Tennis &gt; rest</i>														
Pre-SMA	+	+	+	+	+	+	+	+	+	+	+	+	12/12	8±7, 5±3, 64±6
Dorsal premotor cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	31±5, -2±5, 54±3 -33±6, -1±4, 53±4
SMA	+	+	+	+	+	+	+	+	+	+	+	+	12/12	3±5, -1±5, 63±4
Inferior parietal lobule	+	+	+	+	+	+	+	+	+	+	+	+	12/12	56±7, -39±5, 34±5 -64±3, -46±4, 27±5
<i>Faces &gt; rest</i>														
Pre-SMA	+	+	+	+	+	+	+	+	+	+	+	+	12/12	2±3, 12±5, 57±6
Dorsal premotor cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	37±5, 2±5, 43±6 -35±5, -1±4, 57±5
Right fusiform gyrus	+	+	-	+	+	+	+	+	+	+	+	+	11/12	48±3, -47±5, -25±5
<i>Tennis &gt; faces</i>														
SMA	+	+	+	+	+	+	+	+	+	+	+	+	12/12	5±6, -3±4, 64±3
Inferior parietal lobule	+	+	+	+	+	+	+	+	+	+	+	+	12/12	59±3, -40±4, 36±5 -63±3, -45±5, 31±7
<i>Faces &gt; tennis</i>														
Right fusiform gyrus	+	+	+	+	+	+	+	+	+	+	+	+	12/12	45±6, -47±6, -23±4

Results thresholded at SVC corrected  $p$  value  $< 0.05$ . The last column shows peak coordinates of activation for each area of interest in individual volunteers (group mean ± standard deviation).

Table 4  
Areas commonly activated in all mental imagery tasks versus rest

Brain areas	Side	x	y	z	Z value	p value
Pre-Supplementary motor area		4	10	60	5.72	<0.001*
Dorsal premotor cortex	L	-44	0	54	4.38	0.028*
	R	46	0	56	3.15	0.011

Results are thresholded at FWE corrected  $p$  value < 0.05 whole brain\* or 10-mm radius sphere SVC. PMd: dorsal premotor cortex.

et al., 1999; Jenkins et al., 2000; Naito et al., 2002; Kuitzbuschbeck et al., 2003), faces perception/imagination (O'Craven and Kanwisher, 2000a; Ishai et al., 2002; Rossion et al., 2003), auditory imagery/speech-related (Halpern, 2001; Price et al., 2005), neuroimaging studies). We finally performed a conjunction random effects analysis searching for brain activation common to all 4 mental imagery tasks versus rest. As different subjects were used in experiments 1 and 2, this conjunction between the 4 tasks could not be made at the individual level. Individual contrasts of each task versus rest were thus entered separately into a second-level design matrix, and a conservative conjunction approach was used to define which region was systematically activated in any of the four tasks compared to rest. As we had here no strong a priori hypothesis, the resultant statistical map was thresholded at whole volume FWE-corrected  $p$  value < 0.05. In other words, areas had to be significant at FWE-corrected  $p$  < 0.05 in each and every task versus rest contrast to be considered significant at the conjunction level.

Single subject analyses assessed the reliability of individual brain activation for each task versus rest and versus the other experimental task, in the areas found to be significant for these contrasts at the group analysis level. In order to test the inter-subject spatial variability, a cross-validated analysis was performed. For each contrast, individual results were masked by the corresponding RFX analysis results (thresholded at uncorrected  $p$  value < 0.001) from the remaining 11 other volunteers of the same group. Results were thresholded at uncorrected  $p$  < 0.005, before a 10-mm radius sphere small volume correction (SVC)  $p$  value < 0.05 was applied around group analyses peak coordinates.

For the third experiment, single subjects fixed-effect analyses were first performed in each subject, using the blinded design matrix described above (each column randomly assigned to condition a, b and c). Linear contrasts were then used to obtain subject-specific estimates for each of the effects of interest, and for the areas specifically more activated in each task compared to the 2 other ones. For individual data interpretation, we used predefined decision criteria taken directly from the main differential activations obtained in experiments 1 and 2. Therefore,

the results were thresholded at uncorrected  $p$  value < 0.005, then 10-mm radius spheres SVC  $p$  value < 0.05 were constructed around a priori coordinates extracted from the statistical peaks of the corresponding contrasts in the group analyses of experiments 1 and 2. Criteria for the performance of a mental imagery task versus rest were the presence of pre-SMA and dorsal premotor cortex activation (as these were the most reliable activations differentiating any mental imagery task from rest, see Table 2). Once rest period determination had been performed, we re-ran fixed-effect analyses implicitly modeling baseline, in order to facilitate data interpretation. We then sought to differentiate spatial navigation imagination from tennis imagery periods using a similar procedure to that used to separate tasks from rest periods. Determination criteria distinguishing spatial navigation from motor imagery periods were the presence of high activation respectively in parieto-occipital, retrosplenial and parahippocampal areas for the spatial task, and high supplementary motor and inferior parietal lobule cortices activation for the motor task. The anatomical location of these areas was defined using small volume correction analysis on a priori coordinates extracted from peak statistical results in corresponding contrasts of the group analyses performed in the first two experiments. In particular, the location of pre-SMA and SMA clusters were differentiated along the medial convexity according to their position anterior and posterior to the VAC line, respectively. For second level analysis purposes, Liège's volunteers contrast images were re-smoothed by means of a 6-mm FWHM Gaussian kernel (Peigneux et al., 2006). As Gaussian smoothing adds in quadrature, the effective smoothing at the second level analysis stage was here 10 mm. Finally, conjunction analyses were performed between the data sets acquired in the both centers for the spatial navigation imagination and motor imagery versus rest contrasts. Second level random effects analyses were performed, separating the two centers volunteers in two corresponding groups. Three separate design matrices were computed, one for spatial navigation versus rest contrast, one for motor imagery versus rest contrast, and one directly comparing spatial navigation and motor imagery versus rest contrasts to one another. Results were thresholded at FWE whole brain or 10-mm radius sphere SVC  $p$  value < 0.05 as reported for previous group analyses.

## Results

### Experiment 1

Spatial navigation (imagine moving around the rooms of your home) activated the bilateral precuneus/parieto-occipital junction

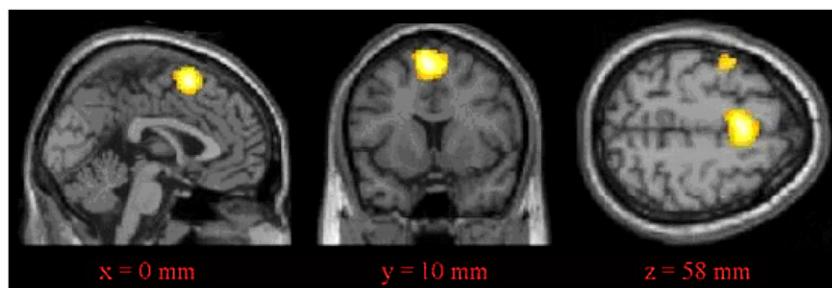


Fig. 1. Group results showing activation of pre-SMA and dorsal premotor cortex is common to all active tasks compared to rest. For display, results are thresholded at uncorrected  $p$  value < 0.001 and rendered on a canonical single subject T1 MR image.

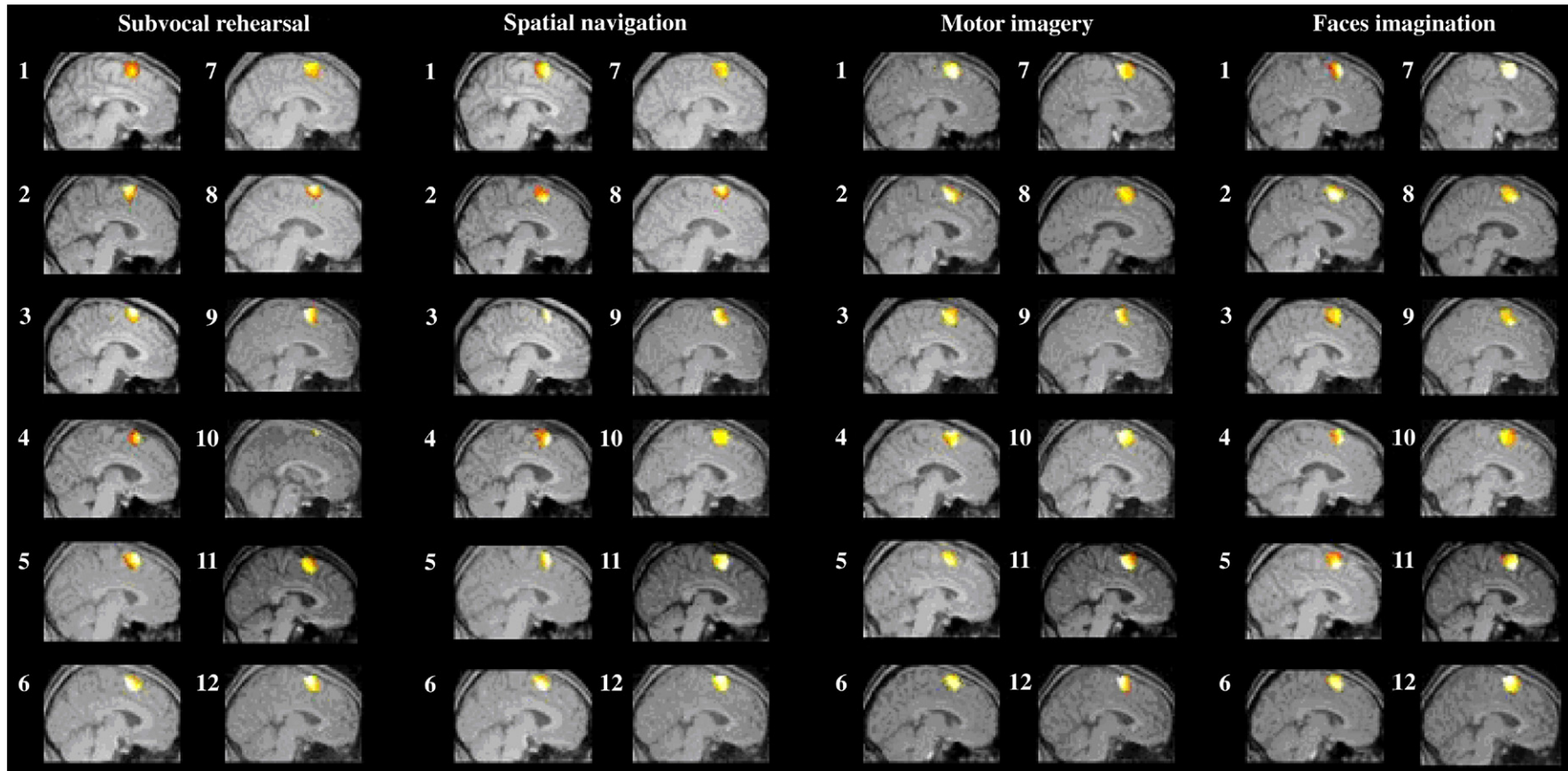


Fig. 2. pre-SMA activation was found in all volunteers for each mental imagery task compared to baseline. Transverse sections at  $x=4$  mm except subject 10, for sub-vocal rehearsal ( $x=0$  mm) and subject 8, for spatial navigation ( $x=10$  mm). Results displayed on individual normalized T1 image, thresholded at uncorrected  $p<0.001$  and masked by the group RFX analysis results thresholded at  $p<0.001$ .

and retrosplenial cortex in all volunteers, and parahippocampal cortex in 11/12 volunteers, both compared to rest and to sub-vocal rehearsal.

Sub-vocal rehearsal (imagine singing jingle bells) produced activation of the left superior temporal gyrus only in 3/12 volunteers.

Group activations for each task compared to rest are shown in Table 2. Individual results for each task are reported in Table 3.

### Experiment 2

Motor imagery (imagine playing tennis) specifically activated bilateral SMA and inferior parietal lobule in all volunteers compared to rest and to imagining faces (see Table 3). Imagination of faces elicited right fusiform gyrus activation in 11/12 volunteers, but with lower spatial extent and greater inter-subject variability.

### Activation common to all tasks (experiments 1 and 2)

Group brain activations common to all tasks versus rest were found in bilateral pre-SMA and dorsal premotor cortex (Table 4, Fig. 1). Pre-supplementary motor area (pre-SMA) and dorsal premotor cortex activation was found in every subject for each of the 4 mental imagery tasks compared to rest (Table 3, Fig. 2).

On the basis of the results of Experiments 1 and 2, spatial navigation and motor imagery were selected as being the most robust paradigms for blind testing in Experiment 3.

### Experiment 3

In the third experiment, blinded differentiation of rest, spatial navigation and motor imagery tasks was made with 100% accuracy in each and every subject. Individual results of this experiment are reported in Table 5. Spatial navigation imagery elicited robust parahippocampal, retrosplenial and parieto-occipital cortices activation in every volunteer, both compared to rest and to the motor imagery task (Fig. 3). Motor imagery activated SMA in 12/12 volunteers and inferior parietal lobule in 11/12 volunteers (Fig. 4). Supplementary motor area activation in the motor imagery period was greater than that induced by spatial navigation task in all but one subject (Fig. 4 reporting Liège's data, subject 7). This subject showed pre-SMA activation for the two active task periods, spatial navigation-specific activation in only one of the two active task conditions, and a tendency to greater SMA activation in the second task, allowing unequivocal identification of the task periods.

Taking into account the results from both Cambridge and Liège, we found pre-SMA and dorsal premotor activation during the performance of a task versus rest in all volunteers tested, regardless of the nature of the task. Spatial navigation imagery activated the precuneus/parieto-occipital junction in 24/24 volunteers, retrosplenial cortex in 24/24 volunteers and parahippocampal gyrus in 23/24 volunteers. Motor imagery elicited supplementary motor area activation in 24/24 volunteers and inferior parietal lobule activation in 23/24 volunteers.

Table 5  
Individual results for each mental imagery task in Liège's volunteers

Individual subject number	1	2	3	4	5	6	7	8	9	10	11	12	Total	Peak coordinates (x, y, z; mean±SD)
<i>Spatial navigation &gt; rest</i>														
Pre-SMA	+	+	+	+	+	+	+	+	+	+	+	+	12/12	5±6, 10±3, 54±4
Dorsal premotor cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	34±4, 2±4, 54±4 -22±4, 3±4, 53±4
Precuneus	+	+	+	+	+	+	+	+	+	+	+	+	12/12	-13±5, -68±3, 57±4
Retrosplenial cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	-12±11, -55±3, 13±3
Parahippocampal cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	31±4, -39±4, -14±14 -30±3, -39±1, -17±1
<i>Spatial navigation &gt; tennis</i>														
Precuneus	+	+	+	+	+	+	+	+	+	+	+	+	12/12	-16±13, -74±5, 50±4
Retrosplenial cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	-14±3, -56±3, 13±5
Parahippocampal cortex	+	+	+	+	+	+	+	+	+	+	+	+	11/12	30±3, -40±3, -15±4 -29±3, -42±3, -13±4
<i>Tennis &gt; rest</i>														
Pre-SMA	+	+	+	+	+	+	+	+	+	+	+	+	12/12	7±3, 7±5, 55±6
Dorsal premotor cortex	+	+	+	+	+	+	+	+	+	+	+	+	12/12	27±4, -5±4, 61±6 -27±6, -7±5, 49±3
SMA	+	+	+	+	+	+	+	+	+	+	+	+	12/12	-8±5, -2±4, 68±3
Inferior parietal lobule	+	+	+	-	+	+	+	+	+	+	+	+	11/12	58±4, -34±4, 29±3 -60±5, -40±4, 30±4
<i>Tennis &gt; spatial navigation</i>														
SMA	+	+	+	+	+	+	-	+	+	+	+	+	11/12	-5±6, -4±3, 64±5
Inferior parietal lobule	+	+	+	-	+	+	+	+	+	+	+	+	11/12	60±5, -35±12, 28±5 -54±4, -40±11, 28±6

Results thresholded at SVC corrected  $p$  value < 0.05. The last column shows peak coordinates of activation for each area of interest in individual volunteers (group mean ± standard deviation).

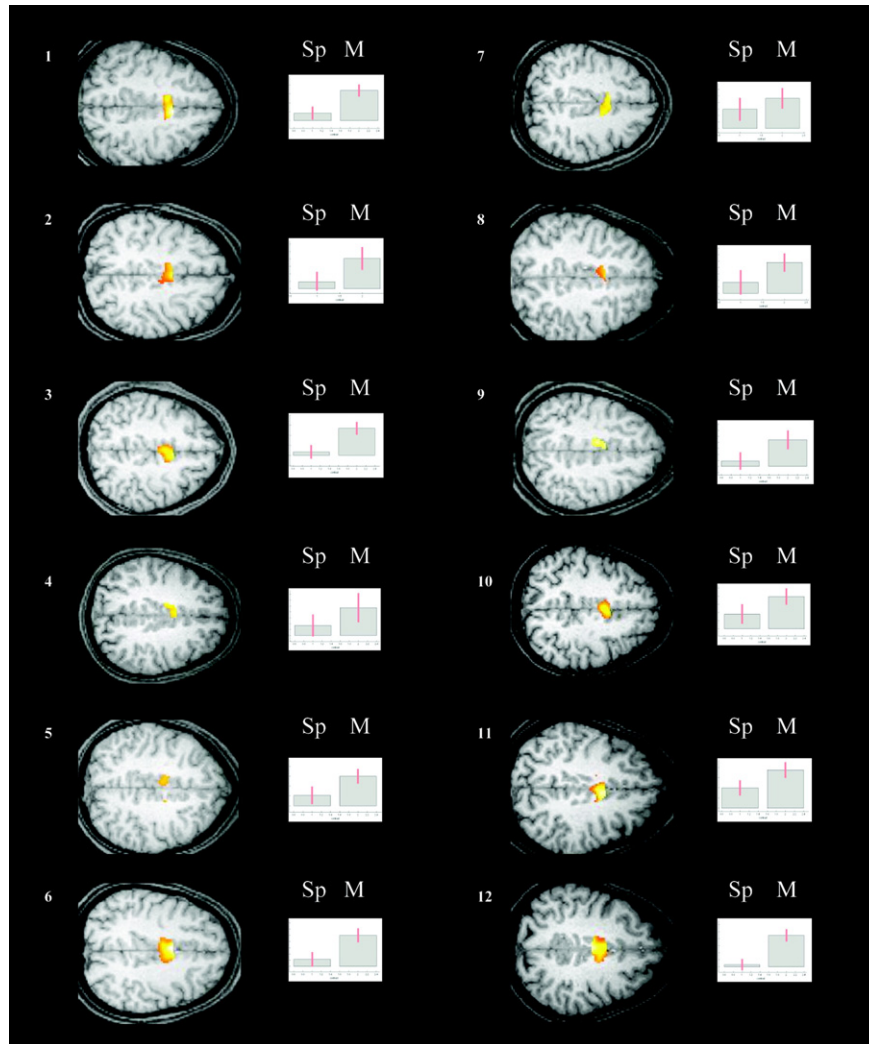


Fig. 3. Example of individual results for motor imagery task versus rest for Liège's volunteers. Transverse sections at  $z=62$  mm. Results thresholded at uncorrected  $p$  value  $<0.001$ , masked inclusively by the group results at  $p < 0.001$  (tennis versus spatial navigation contrast). For each volunteer, the level of activation in this area (plot on the right, mean parameters estimate) was greater for the motor task (M) than for the spatial navigation imagination task (Sp).

#### Multi-centric conjunction analysis

Multi-centric random affects analysis results (second level conjunction analysis between WBIC and CRC volunteers) are reported in Table 6. They confirm a specific involvement of the bilateral precuneus/parieto-occipital junction, retrosplenial and parahippocampal cortices in the spatial navigation imagination task, and the SMA and bilateral inferior parietal lobule in motor imagery performance (Fig. 5).

#### Discussion

##### Modality-specific activations

A number of studies have suggested that mental imagery engages many of the same cognitive and neural mechanisms that are involved in perception (Kosslyn et al., 1995; O'Craven and Kanwisher, 2000a) or action (Jeannerod and Frak, 1999). In the visual domain, O'Craven et al. (O'Craven and Kanwisher, 2000a)

have shown that context-specific neural activity in extrastriate visual cortex can be created by voluntary imagination even when no visual stimulus is presented at all. Studies using binocular rivalry have shown that activation of specific extrastriate areas is related more to the content of current awareness than to the nature of the retinal stimulus presented (Tong et al., 1998). In several other mental imagery modalities, EEG studies designed to set up brain-computer interfaces have reported that the functional patterns due to pairs of cognitive tasks can be reliably differentiated (Curran et al., 2004) for spatial navigation, auditory and motor imagery domains). We postulated that even if in response to instructions, the subjects used mental representations that differed significantly from one another (e.g. number of rooms, size of rooms, detail in each room etc, in the case of spatial navigation), a particular mental imagery task is likely to have led to brain activity in regions involved in the generic characteristics of the task (e.g. spatial navigation or the motor component in imagery). The instruction to perform a particular category of task may result in consistent brain activity in areas involved in general



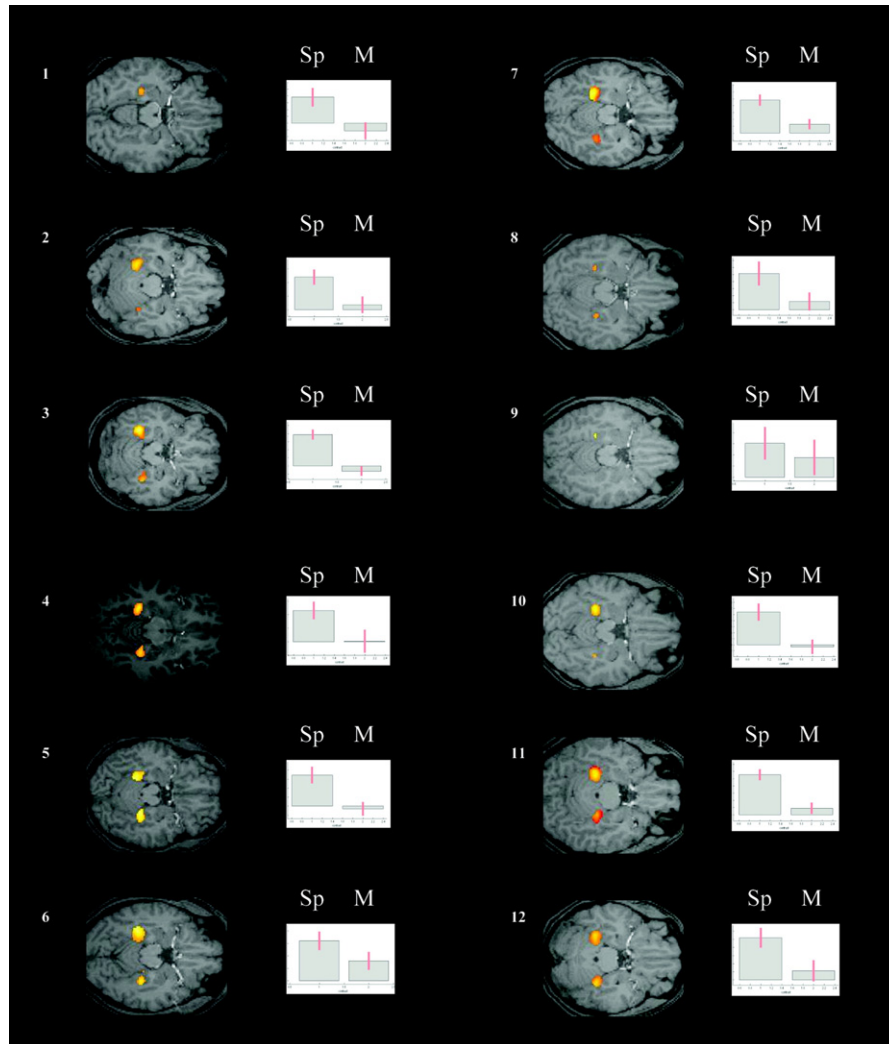


Fig. 4. Example of individual results for spatial navigation imagery task versus rest for Liège's volunteers. Transverse sections at  $z=-12$  mm, except for subjects 8 and 9 ( $z=-14$  mm). Results thresholded at uncorrected  $p$  value  $<0.001$ , masked inclusively by the group results at  $p<0.001$  (tennis versus spatial navigation contrast). For each volunteer, the level of activation of left parahippocampal gyrus (plot on the right, mean parameters estimate) was greater for the spatial task (Sp) than for the motor imagery task (M).

and common brain mechanisms generating the task, despite the individual variability in imagery details during performance of the task.

In the current study, spatial navigation imagery activated bilateral parahippocampal gyri, retrosplenial and parieto-occipital cortices, both contrasted to rest and to other mental imagery modalities. Studies of spatial navigation imagery have shown consistent activation of parahippocampal gyrus (Ghaem et al., 1997b; Mellet et al., 2000b; O'Craven and Kanwisher, 2000a; Ino et al., 2002). Retrosplenial posterior cingulate cortex activation has been consistently reported in previous neuroimaging studies involving topographic tasks (Aguirre et al., 1996; Aguirre and D'Esposito, 1997; Maguire et al., 1998). Occipito-parietal regions (precuneus and cuneus) (Mellet et al., 1996, 1998, 2000a,b) and bilateral angular gyri/occipital cortex junctions (Aguirre et al., 1996; Maguire et al., 1997; Ino et al., 2002) have also been reported to be activated during mental navigation in a number of previous studies.

Several brain imaging studies have reported SMA involvement in motor imagery (Decety et al., 1990; Grafton et al., 1996; Roth et al., 1996; Lotze et al., 1999; Romero et al., 2000; Boecker et al., 2002; Naito et al., 2002; Nair et al., 2003). Activation of SMA, caudal to the VCA line, has been observed primarily in relation to aspects of movement (Picard and Strick, 2001). However, conditions affecting the motor system usually leave the ability to generate motor imagery intact, especially when lesions are located in primary motor cortex (Jeannerod and Frak, 1999). Paraplegics patients have preserved and even greater SMA activation in mental imagery tasks than normal controls (Alkadhi et al., 2005). Inferior parietal lobule has been involved in a number of motor imagery neuroimaging studies (Decety, 1996; Grafton et al., 1996; Ball et al., 1999; Boecker et al., 2002; Malouin et al., 2003).

In the current study, imagining faces activated fusiform gyrus at the group level and in 11/12 volunteers tested. The fusiform gyrus has been specifically implicated in visual processing (Kanwisher et al., 1997) and imagination (O'Craven and Kanwisher, 2000b) of

Table 6

Results of the multicentric conjunction analysis for spatial navigation and tennis tasks compared to rest and to one another

Brain areas	Side	x	y	z	Z value	p value
<i>Tennis &gt; rest</i>						
Pre-supplementary motor area		10	6	54	Inf	<0.001*
		-10	10	50	7.15	<0.001*
Dorsal premotor cortex		24	-4	60	Inf	<0.001*
		-26	-10	42	6.00	<0.001*
		52	4	38	5.85	<0.001*
		-44	0	50	4.95	0.013*
SMA		-8	0	62	Inf	<0.001*
Basal ganglia		30	4	-2	6.92	<0.001*
		-20	-6	-2	5.80	<0.001*
Inferior parietal lobule		54	-32	32	5.25	0.003*
		-62	-44	32	5.16	0.005*
Intraparietal sulcus		34	-38	44	6.39	<0.001*
		36	-44	34	6.04	<0.001*
Cerebellum		-26	-52	-46	5.73	<0.001*
Insula		48	8	4	6.07	<0.001*
Occipito-temporal junction		-50	-60	8	6.47	<0.001*
		46	-68	16	5.46	0.001*
Brainstem		14	-10	-8	5.00	0.010*
		16	-2	-6	4.93	0.014*
Inferior frontal gyrus		56	10	10	5.38	0.002*
		-50	12	0	5.06	0.008*
Middle frontal gyrus		-62	10	26	4.93	0.014*
<i>Spatial navigation &gt; rest</i>						
Pre-supplementary motor area		10	8	56	6.60	<0.001*
		-12	6	58	6.10	<0.001*
Dorsal premotor cortex		38	6	52	7.54	<0.001*
		-20	8	50	7.44	<0.001*
Parahippocampal cortex		32	-38	-24	6.10	<0.001*
		34	-46	-14	5.47	0.001*
		22	-48	-4	5.30	0.002*
		-26	-34	-24	6.07	<0.001*
Retrosplenial cortex		-12	-54	6	7.35	<0.001*
		12	-54	6	6.69	<0.001*
Occipito-parietal junction		-22	-62	16	6.32	<0.001*
		-38	-84	30	6.02	<0.001*
		20	-68	48	5.92	<0.001*
		32	-74	24	5.81	<0.001*
Precuneus		-14	-66	54	5.82	<0.001*
		8	-52	56	4.75	0.024*
Intraparietal sulcus		36	-42	40	6.64	<0.001*
Anterior cingulate cortex		-14	22	32	5.21	0.003*
Brainstem		-4	-22	-42	5.25	<0.001*
Cerebellum		-12	-42	-32	5.04	0.007*
		14	-24	-40	4.73	0.026*
<i>Tennis &gt; spatial navigation</i>						
SMA		-8	-2	62	5.39	0.001*
		12	-6	60	4.76	0.021*
Inferior parietal lobule		-56	-42	32	4.86	0.021*
		-48	-62	8	4.65	0.033*
		60	-36	34	4.14	<0.001
		56	-70	8	3.93	0.003
Basal ganglia		-26	0	4	3.38	0.015
		26	-2	-4	3.31	0.018
<i>Spatial navigation &gt; tennis</i>						
Parahippocampal cortex		-24	-38	-12	5.97	<0.001*
		-24	-36	-18	5.86	<0.001*
		-24	-48	-10	5.50	0.001*

Table 6 (continued)

Brain areas	Side	x	y	z	Z value	p value
<i>Spatial navigation &gt; tennis</i>						
Parahippocampal cortex		30	-42	-14	5.94	<0.001*
		34	-34	-24	5.80	<0.001*
Retrosplenial cortex		-12	-54	8	6.94	<0.001*
		12	-54	8	6.93	<0.001*
Occipito-parietal junction		-24	-64	24	5.44	0.001*
		-34	-86	38	5.27	0.002*
		-24	-78	42	5.19	0.003*
		26	-70	34	4.93	0.024*
Precuneus		-18	-76	46	4.29	0.001
		20	-68	50	3.91	0.003

Results thresholded at FWE (\*) or SVC corrected  $p$  value < 0.05.

faces, especially in the right hemisphere (Ishai et al., 2002). However, compared to the two tasks previously discussed, activation of fusiform gyrus while imagining faces was both more restricted in spatial extent and more variable in location. At the group level, sub-vocal rehearsal activated left superior temporal cortex in language-related areas (Price et al., 2005). However, both tasks were also found to produce less reproducible activation at the individual level than imagining spatial navigation and motor imagery. This was the rationale for us to select the two latter tasks for the third experiment.

#### Brain activation common to all tasks versus rest

In the current study, the results of the conjunction analysis of all tasks versus rest showed pre-SMA and premotor activation. Pre-SMA and rostral dorsal premotor cortex (PMd) activation was found during the performance of an active task versus rest in each and every volunteer studied, regardless of the nature of the task. In humans, the level of the anterior commissure (VCA line) (Talairach and Tournoux, 1988) marks the border between SMA proper and pre-SMA. A number of studies have reported pre-SMA activation in motor imagery (Deiber et al., 1998; Jenkins et al., 2000; Cunnington et al., 2002; Malouin et al., 2003) as well as in other mental imagery modalities (Paulesu et al., 1993; Ghaem et al., 1997a; Halpern and Zatorre, 1999; Mellet et al., 2000b; Halpern, 2001). Recent reviews suggest that it might be more appropriate to consider pre-SMA and rostral part of dorsal premotor cortex (PMd) as functional components of prefrontal cortex, rather than as proper premotor areas (Picard and Strick, 2001). Overall, neuroimaging studies leave no doubt that the pre-SMA is fundamentally different from the SMA. Activation of the SMA is observed primarily in relation to aspects of movement behavior. In contrast, pre-SMA activation is associated with cognitive aspects of a variety of tasks (Deiber et al., 1999; Lee et al., 1999; Gerardin et al., 2000; Jenkins et al., 2000; Crosson et al., 2001; Schubotz and von Cramon, 2001). The same functional dissociation is thought to exist within lateral premotor cortices, the rostral part being involved in cognitive processes, and the caudal part in motor tasks (Toni et al., 1999; Boussaoud, 2001). A contribution of PMd in motor imagery processes has been recently described (De Lange et al., 2005; De Lange et al., 2006). However, over a relatively large number of studies, activations related to higher-order processing have been reported in the rostral PMd (mean coordinates  $x=44$ ,  $y=5$ ,  $z=51$ ), an average of 19 mm anterior to movement-related activations in the precentral gyrus encompassing primary motor

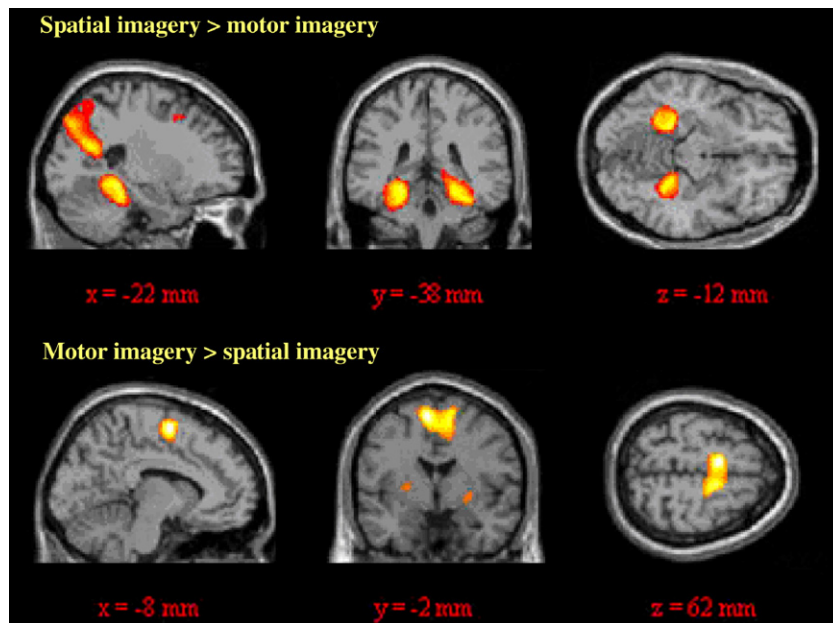


Fig. 5. Results of the multi-centric conjunction analysis for spatial navigation and tennis tasks compared to one another. For display, results are shown thresholded at uncorrected  $p$  value  $< 0.001$  on a canonical T1 template.

and caudal PMd cortices (latter mean coordinates  $x=37$ ,  $y=-14$ ,  $z=60$ ) (Picard and Strick, 2001).

Evidence has recently emerged about the role of pre-SMA in the endogenous generation of voluntary actions (Lau et al., 2004a, 2006) and volitional aspects of cognitive actions (Nachev et al., 2005). Pre-SMA has also been reported to be specifically involved in attention to intention (Lau et al., 2004b). A number of studies have also reported dorsal prefrontal cortex activity during the selection of willed actions (Deiber et al., 1991; Frith et al., 1991; Playford et al., 1992; Jahanshahi et al., 1995; Spence et al., 1998). During attention to intention, prefrontal cortex activity is specifically coupled with activity in pre-SMA (Lau et al., 2004b). Though our study did not investigate the neural mechanisms of volition itself, pre-SMA and dorsal premotor cortex activation in our volunteers during an active task compared to rest, regardless of the nature of the task, could be understood as reflecting a certain form of cognitive control, or the subject's intention to perform a task. Presence of additional task-specific regional brain activation would however be required for further interpretation.

#### *Searching for volitional brain activity in non-communicative brain injured patients*

Using spatial navigation and motor imagery tasks, we were able to identify consistent task-specific differential brain activation in individual healthy volunteers. Our data strongly suggest that this paradigm may provide a method for assessing the presence of volitional brain activity, and thus of consciousness, in non-communicative brain-injured patients. Indeed, positive findings in this paradigm cannot be interpreted here as a reflexive response to commands. The activation of task-related neural networks has to be actively maintained for 30 s, far longer after the end of the sparse instructions. In contrast, unconscious mental representations observed in many clinical and experimental contexts are fleeting,

lasting a few seconds or less (Greenwald et al., 1996; Naccache et al., 2005; Naccache, 2006). Moreover, the brain activity in response to auditory instructions is explicitly modeled as a regressor of no interest in our data analysis. Consequently, finding specific regional brain activation in response to the instruction to perform one of the mental imagery task presented here would confirm that a patient has understood the instructions and has voluntarily performed the task. This method has recently been used to detect pre-clinical voluntary brain activity in a traumatic non-communicative patient meeting the clinical criteria for vegetative state (Owen et al., 2006). Functional magnetic resonance imaging could thus be a supplementary tool in clinical situations to diagnose some patients who are aware but unable to produce an overt motor output to express understanding or communication.

Negative findings, however, would have to be very cautiously interpreted. Firstly, some supra-tentorial brain lesions could impair the patients' ability to perform one selected task, by causing e.g. apraxia or neglect. They could also lead to a certain amount of brain reorganization and plasticity, resulting potentially in the recruitment of other areas during the performance of a given cognitive task. These eventualities would lead to negative results independently of the patient's awareness or vigilance levels. The two mental imagery tasks selected here rely on spatially separate networks, giving us more chance to avoid brain lesions impairing both tasks performance at the same time. Secondly, maintaining mental imagery task for periods of 30 s is relatively attention demanding. Consciousness is not an all-or-none phenomenon but should rather be considered as a continuum (Majerus et al., 2005). Negative results must be cautiously interpreted in case of patients with severely altered level of vigilance, which could present only transient activity in response to the presentation of instructions. Finally, a defining feature of voluntary actions is that one can choose whether or not to execute them (Passingham, 1995). The success of any volitional evaluation is, in this context as in the clinical situation, dependent on a number of factors including the

desire or willingness (if the patient is aware) of the patient to respond (Majerus et al., 2005). It should also be emphasized that due to the frequency of false negatives reported across functional imaging investigations of healthy volunteers, that a negative result using this paradigm can never exclude the possibility that the patient retains awareness of self or environment.

In conclusion, the spatial navigation and complex motor imagery tasks described here permit the identification of volitional brain activation at the single subject level, without any overt motor response. Volunteers as well as patients data, strongly suggest that this paradigm may provide a method for assessing the presence of volitional brain activity, and thus of consciousness, in non-communicative brain-injured patients. Although the method described here represents a promising clinical tool we are not suggesting that it should replace existing clinical procedures i.e., the behavioural observation of a patient. In our view, this technique provides a valuable additional diagnostic tool in cases of patients with atypical presentation, leading to persisting doubts in clinical diagnosis.

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