Functions of the left superior frontal gyrus in humans: a lesion study

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The superior frontal gyrus (SFG) is thought to contribute to higher cognitive functions and particularly to working memory (WM), although the nature of its involvement remains a matter of debate. To resolve this issue, methodological tools such as lesion studies are needed to complement the functional imaging approach. We have conducted the first lesion study to investigate the role of the SFG in WM and address the following questions: do lesions of the SFG impair WM and, if so, what is the nature of the WM impairment? To answer these questions, we compared the performance of eight patients with a left prefrontal lesion restricted to the SFG with that of a group of 11 healthy control subjects and two groups of patients with focal brain lesions [prefrontal lesions sparing the SFG (n = 5) and right parietal lesions (n = 4)] in a series of WM tasks. The WM tasks (derived from the classical n-back paradigm) allowed us to study the impact of the SFG lesions on domain (verbal, spatial, face) and complexity (1-, 2- and 3-back) processing within WM. As expected, patients with a left SFG lesion exhibited a WM deficit when compared with all control groups, and the impairment increased with the complexity of the tasks. This complexity effect was significantly more marked for the spatial domain. Voxel-to-voxel mapping of each subject’s performance showed that the lateral and posterior portion of the SFG (mostly Brodmann area 8, rostral to the frontal eye field) was the subregion that contributed the most to the WM impairment. These data led us to conclude that (i) the lateral and posterior portion of the left SFG is a key component of the neural network of WM; (ii) the participation of this region in WM is triggered by the highest level of executive processing; (iii) the left SFG is also involved in spatially oriented processing. Our findings support a hybrid model of the anatomical and functional organization of the lateral SFG for WM, according to which this region is involved in higher levels of WM processing (monitoring and manipulation) but remains oriented towards spatial cognition, although the domain specificity is not exclusive and is overridden by an increase in executive demand, regardless of the domain being processed. From a clinical perspective, this study provides new information on the impact of left SFG lesions on cognition that will be of use to neurologists and neurosurgeons.

Keywords: prefrontal cortex; working memory; cognitive functions; human; neuropsychology

Abbreviations: CI = confidence interval; FEF = frontal eye field; MMSE = Mini-Mental State Examination; PFC = prefrontal cortex; SEM = standard error of measurement; SFG = superior frontal gyrus; WM = working memory


Introduction

Many studies in humans and monkeys have demonstrated the key role of the lateral prefrontal cortex (PFC) in decoupling perception from action by creating a temporal buffer that allows voluntary behaviours to be generated on the basis of internal guidance (Luria, 1980; Goldman-Rakic, 1987; Fuster, 1997). Working memory (WM) is a set of fundamental processes that take place within this temporal buffer to guide voluntary or goal-directed behaviours...
(Goldman-Rakic, 1987). These fundamental processes include the short-term maintenance of relevant information, the mental manipulation of this information and the mental organization of the forthcoming sequence of actions (Baddeley, 1996; Goldman-Rakic, 1987; Baddeley, 1998). Although a large body of evidence indicates that the lateral PFC is essential for WM, its anatomical and functional organization for WM is still a matter of debate (Goldman-Rakic, 1987; Fuster, 1997; Owen, 1997; Duncan and Owen, 2000; Postle et al., 2000; Miller and Cohen, 2001; Johnson et al., 2003; Curtis and D'Esposito, 2004; Petrides, 2005). What are the critical subregions for WM within the lateral PFC and what is the nature of the processing for WM performed by these subregions? Most studies have focused on the anatomical and functional organization of the 'mid-dorsolateral' region [Brodmann (BA) 9/46] within the middle frontal gyrus, and the ventrolateral aspect (BA 44, 45, 47) (Owen et al., 1996, Smith and Jonides, 1999; Levy and Goldman-Rakic, 2000; Wagner et al., 2001), leaving apart from discussion the superior frontal gyrus (SFG). The purpose of the present study is to determine the role of the SFG in executive functions and especially in WM. The SFG is generally considered to encompass the lateral and the superior portion of area 9, the whole of area 8 (Brodmann, 1909) or only its superior portion (Sarkissov et al., 1955; Petrides and Pandya, 1999), and, more caudally, the lateral part of area 6, although differences exist between the different cytoarchitectonic maps available in humans (Brodmann, 1909; Sarkissov et al., 1955; Petrides and Pandya, 1999, 2002). Several functional studies have indicated that the lateral SFG is activated in WM paradigms (Courtney et al., 1998; Postle et al., 2000; Rowe et al., 2000; Leung et al., 2002; Johnson et al., 2003). However, the precise role of the SFG and its anatomical and functional organization for WM remains to be clarified. Is the SFG critical for the mental manipulation and monitoring of information, regardless of the domain being processed, as suggested by the 'two-stage' model of functional organization of the PFC (Owen et al., 1996; Petrides, 2003)? Or, on the contrary, is the SFG specialized in one domain of information, notably spatial WM (Courtney et al., 1998; Haxby et al., 2000)? What are the subregions of the SFG along the rostral-caudal (BA 9, BA 8 or BA 6) and lateral-medial axes that contribute the most to WM and for what type of processing within WM?

To answer these questions about the functional role of the SFG in WM, we used the anatomical–clinical correlation method, which is complementary to functional imaging studies in that it gives the functional weight of a given region to the cognitive process studied, as measured by the residual performance obtained at a distance of several months after the focal destruction of the said region. A group of patients, all presenting with a lesion restricted to the left SFG, performed a WM paradigm that allowed us to investigate, in a cross-modal analysis, two different dimensions: the level of processing (by progressively increasing task difficulty) and the domain of the information being processed (by using different types of material: verbal, spatial, faces). Several hypotheses were postulated according to the models under debate: (i) if the deficit observed is domain-dependent, then the left SFG lesion may induce a deficit restricted to one domain (most likely spatial, according to the available literature, regardless of the level of complexity). In this case, the lesion should spare face processing (which would suffer in the event of a ventrolateral lesion and/or a right-sided lesion) and verbal (which would suffer from a left ventrolateral lesion); (ii) if the deficit is processing-dependent, a left SFG lesion will produce a greater deficit when the executive demand increases in WM, regardless of the domain being processed; (iii) if the deficit is more complex (e.g. an interaction between location, domain and complexity) it could correspond to a 'hybrid' model relying on a given domain but only above or beyond a given threshold of cognitive demand or for a specific type of processing.

**Material and methods**

**General design**

We studied the performance of a group of eight patients with a left SFG lesion ('SFG group') with the same aetiology and three groups of control subjects [11 normal control subjects ('normal control group'), five patients presenting with a prefrontal PFC lesion sparing the SFG ('PFC non-SFG group') and four patients with a right parietal lesion ('parietal group')] in a customized version of the n-back paradigm, varying in terms of complexity (mental manipulation and allocation of attention resources) and domain (spatial items, faces and letters). Subjects were required to perform nine WM tasks: 1-, 2- and 3-back tasks for each type of material, that is, spatial items, face and letter stimuli. In addition, voxel-based mapping of the cognitive performance was performed, indicating which sub-area(s) within the SFG seemed to contribute the most to the presumed cognitive deficit. The ethics committee for biomedical research of the Pitie-Salpetriere Hospital approved the study, and informed consent was obtained from control subjects and patients before their inclusion in the study.

**Patients and control subjects**

**SFG group**

Eight patients, five females and three males, ranging in age from 29 to 54 years (mean age: 42.50 ± 9.44 years), with a focal lesion in the left SFG were recruited from the Neurosurgery Department of Pitie-Salpetriere Hospital (Paris, France) (Table 1 and Fig. 1). None of the patients had a prior history of neurological disease, psychiatric disorder or substance abuse and all were able to understand and perform the tasks. All patients had undergone left-sided frontal lobe excision for low-grade gliomas (WHO grade II). Lesion volume ranged from 11 860 to 41 725 mm³ (mean volume: 22 509.57 ± 4 506.75 mm³). Before surgery, hemispheric dominance was determined using functional MRI coupled with a language testing procedure (see Lehericy et al., 2000 for further details). The left hemisphere was dominant for language functions in all patients. There was no language or motor deficit at the time of surgery. The topography of the tumour was accurately analysed...
on a preoperative MRI. All patients underwent surgery under local anaesthesia so that functional cortical and subcortical mapping could be carried out preoperatively, using direct brain stimulations as already described (Duffau et al., 1999, 2002). Sensorimotor (movement and/or paraesthesia) and language (counting and naming tasks) functions were tested throughout the resection procedure in order to avoid removing pathways involved in these functions. Clinical outcome (sensorimotor and cognitive) was assessed systematically by a neuropsychologist and a neurologist, both during the postoperative stage and 3 months after surgery. All the patients included in the study were tested at least 6 months after resection (time from surgery ranging from 8 to 36 months). At the

### Table 1 Main characteristics of the studied populations

<table>
<thead>
<tr>
<th></th>
<th>Normal control group (n = 11) mean (SD)</th>
<th>Parietal group (n = 4) mean (SD)</th>
<th>PFC non-SFG group (n = 5) mean (SD)</th>
<th>SFG group (n = 8) mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>47.8 (16.8)</td>
<td>52.7 (3.2)</td>
<td>43.6 (3.8)</td>
<td>42.5 (9.4)</td>
</tr>
<tr>
<td>Education (year)</td>
<td>14.5 (2.7)</td>
<td>13.0 (2.8)</td>
<td>13.6 (4.7)</td>
<td>11.8 (3.6)</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>77.3 (60.7)</td>
<td>/</td>
<td>52.7 (64.1)</td>
<td>86.2 (20.2)</td>
</tr>
<tr>
<td>MMSE</td>
<td>30 (0.0)</td>
<td>28.7 (1.9)*</td>
<td>28.2 (1.3)*</td>
<td>28.4 (2.3)*</td>
</tr>
<tr>
<td>Category fluency</td>
<td>22.2 (5.3)</td>
<td>/</td>
<td>16.6 (4.1)</td>
<td>12.8 (4.7)*</td>
</tr>
<tr>
<td>Letter-based fluency</td>
<td>14.8 (4.8)</td>
<td>/</td>
<td>8.0 (4.2)</td>
<td>7.1 (2.5)*</td>
</tr>
<tr>
<td>WCST (criteria)</td>
<td>3.7 (1.4)</td>
<td>5.4 (0.6)</td>
<td>5.2 (1.8)</td>
<td>3.9 (1.8)</td>
</tr>
</tbody>
</table>

SD = standard deviation; MMSE = Mini-Mental State Evaluation; WCST = Wisconsin Card Sorting Test. *P ≤ 0.05 when compared with the normal control group.

Fig. 1 Lesion diagrams of each patient from the SFG group and 3D brain lesion mapping on a normalized brain. (A) An axial, coronal and sagittal slice plane in each of the eight patients at Talairach coordinates −25, 10, 45 showing the estimated extent of cortical and subcortical excision. The left SFG was involved in all patients. (B) 3D brain mapping of the eight lesions superimposed on a normalized brain.
of time of inclusion in the study, none of the patients presented sensorimotor or language impairments. All patients underwent an MRI at inclusion. Brain lesions were mapped by 110 axial contiguous inversion recovery three-dimensional (3D) fast SPGR images (1.5 mm thick; 400 ms; in-plane resolution: 0.94 mm²; MR scanner: General Electrics, 1.5 T). As the surgical removal of the lesions produced well-delineated borders with the adjacent brain tissue, the boundaries of the lesions were easy to define and this simplified the subsequent segmentation of the lesions. A computerized system (Volume Analysis; Voxtool 3.03: General Electrics Medical Systems) was used to reconstruct each patient’s brain and the lesion in a 3D space. This allowed us to identify all major sulci and gyri in 3D as well as 2D images, analyse the involvement of specific cortical areas and measure the volume of the brain and the lesion in each case. The lesions were analysed in terms of sulci and gyri, and were designated by the corresponding Brodmann cytoarchitectonic area. All MRI were analysed by two raters blind to the experimental results. The left SFG was involved in all patients (Fig. 1A). Patients 2, 3, 5 and 7 had sustained additional removal of part of the middle frontal gyrus. On the medial surface, the excision extended down to the cingulate gyrus in Patients 3 and 6, and to the callosal sulcus in Patient 6 (Fig. 1A).

**Control groups**

The SFG group was first compared with a group of 11 normal control subjects. Groups were matched for age, gender and level of education (Table 1). None of the subjects had a past history of neurological or psychiatric illness or took psychotropic drugs. Two lesion control groups were then included in order to verify the specificity of the pattern of behavioural performances of the SFG group, that is, that the performance observed in the SFG group was not only due to the general effect of a brain lesion, regardless of its location, volume and aetiology. Therefore, two different groups of patients with a focal lesion were included in this study. A first group was composed of five patients with a lesion affecting the PFC but sparing the SFG ('PFC non-SFG group'), with the same aetiology as the SFG group (i.e. removal of a low grade glioma). These control patients underwent a surgical procedure similar to that described for the SFG group. The mean time from surgery to the testing procedure in the PFC non-SFG patients included in the study was 17.5 ± 14.62 months—a delay not statistically different from that of the SFG group. At the time of inclusion in the study, none of the patients presented sensorimotor or language impairments. The location and extent of the lesion are represented in Fig. 2A. Lesions were located in middle and/or inferior frontal gyri and/or the insula. In four cases, lesions were right-sided. Patient 1 has a lesion that also encompassed the right frontal pole; lesion in Patient 5 included the temporal pole. Lesion volume ranged from 3042 to 41 934 mm³ (mean volume: 22 488 ± 8835.16 mm³).

A second group of lesion control patients was composed of four patients with a right parietal lesion due in all cases to an ischaemic stroke affecting the posterior territory of the right middle cerebral artery (parietal group). These patients were recruited from the stroke centre (Pr. Y. Samson) at la Salpetrière hospital. The mean time from the onset of the stroke to the testing procedure in the parietal group was 6.00 ± 1.41 months—a delay significantly shorter than that of the SFG group. At the time of inclusion in the study, none of the parietal patients presented sensorimotor or language impairments. The location, extent of the lesion are represented in Fig. 2B. None of these lesions affected the frontal lobe. Lesion volume ranged from 12 508 to 37 041 mm³ (mean volume: 24 775.00 ± 5505.51 mm³).

The SFG, PFC non-SFG and parietal groups were not statistically different for age, level of education (Table 1) as well as for the mean volume of lesions.

**Cognitive tasks**

**WM paradigm**

Tasks were based on the n-back procedure (Cohen et al., 1994), in which the subject has to indicate whether a visual stimulus...
functions of the superior frontal gyrus (Fig. 3). This procedure requires the relevant information to be maintained and updated in WM. Two dimensions were explored: (i) the level of mental manipulation (‘complexity’) within WM, with three different levels: 1-back (maintenance of one item of information in WM in the interval between the cue and target stimuli), 2- and 3-back (interposition of one or two ‘distractors’, respectively, between the cue and target stimuli, each ‘distractor’ becoming the cue for the next trial); (ii) the nature of the stimuli being processed (‘domain’), with three different materials: different locations of squares on a matrix of several squares (the ‘spatial n-back’ task), different pre-selected men’s faces (the ‘face n-back’ task) and different pre-selected letters (the ‘letter n-back’ task). In the spatial n-back task, the visual stimulus was a blue square presented pseudo-randomly in one of six possible locations on a dark screen (the six squares were pseudo-randomly distributed on the screen in order to cover central, lateral and vertical aspects of spatial attention; see Fig. 3 for examples). In the face n-back task, the stimulus was a man’s face among eight possible faces. These faces were chosen from Warrington’s Recognition Memory Test for Faces (Warrington, 1996). In the letter n-back task the stimulus was a capital letter among seven possible letters selected for their frequency of occurrence. Faces and letters were presented in a central position on the screen. The n-back procedure followed a factorial design, crossing the two dimensions (complexity and domain processing) and yielding a total of nine task conditions.

A pilot study involving 23 healthy controls (9 males, 14 females; mean age: 50.7 ± 8.0; mean educational level: 13.8 ± 3.2 years) was designed to determine the number of stimuli in each domain that produces matched performances (i.e. no significant difference between spatial, face and letter tasks at each step of the n-back task). In contrast, for each domain, an increased level of complexity significantly decreased performance, giving a parametric effect [performance on the 1-back > 2-back > 3-back; P < 0.0001, one-way ANOVA (analysis of variance)]. There was no interaction between complexity and domain.

All tasks were computerized and started at a ‘go signal’ triggered by one of us (F.D.B.), who stood behind the subject throughout the testing procedure. Participants were seated in front of a personal computer screen. Each of the nine WM tasks consisted of three blocks of 15 responses to cue/target stimuli (16, 17 and 18 stimuli per session). All patients were given a training block of trials for each of the nine WM tasks (Fig. 3). A maximal score for each task was 45 (15 trials · 3 blocks). In order to avoid a bias favouring or affecting the performances in one given domain, tasks were pseudo-randomly ordered for each subject according to the domain (spatial, face and letter), such that there was no block composed of only one domain and that the domain of the first and last trials of each session varied from one subject to another. Each stimulus was presented on the screen for 3000 ms. The subject had 3 s in which to answer ‘same’ or ‘different’. After a 1000 ms inter-stimulus interval, a new stimulus appeared on the screen.

presented on the screen (the ‘target’ stimulus) is similar to or different from a previously presented stimulus (the ‘cue’ stimulus) (Fig. 3). This procedure requires the relevant information to be maintained and updated in WM. Two dimensions were explored: (i) the level of mental manipulation (‘complexity’) within WM, with three different levels: 1-back (maintenance of one item of information in WM in the interval between the cue and target stimuli), 2- and 3-back (interposition of one or two ‘distractors’, respectively, between the cue and target stimuli, each ‘distractor’ becoming the cue for the next trial); (ii) the nature of the stimuli being processed (‘domain’), with three different materials: different locations of squares on a matrix of several squares (the ‘spatial n-back’ task), different pre-selected men’s faces (the ‘face n-back’ task) and different pre-selected letters (the ‘letter n-back’ task). In the spatial n-back task, the visual stimulus was a blue square presented pseudo-randomly in one of six possible locations on a dark screen (the six squares were pseudo-randomly distributed on the screen in order to cover central, lateral and vertical aspects of spatial attention; see Fig. 3 for examples). In the face n-back task, the stimulus was a man’s face among eight possible faces. These faces were chosen from Warrington’s Recognition Memory Test for Faces (Warrington, 1996). In the letter n-back task the stimulus was a capital letter among seven possible letters selected for their frequency of occurrence. Faces and letters were presented in a central position on the screen. The n-back procedure followed a factorial design, crossing the two dimensions (complexity and domain processing) and yielding a total of nine task conditions.

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Additional neuropsychological tests
All subjects underwent several neuropsychological tests including the Mini-Mental Status Test (Folstein et al., 1975), the Frontal Assessment Battery (FAB, Dubois et al., 2000), the Modified version of the Wisconsin Card Sorting Test (WCST) (Nelson, 1976), two verbal fluency tasks (letter and category) (Cardebat et al., 1990) and the Trail Making test (Spreen and Strauss, 1998) (Table 1). The statistical differences in the Mini-Mental State Examination (MMSE) between normal control and the different groups of patients were unlikely due to a global cognitive deterioration in the lesion groups (mean MMSE ranging between 28.2 and 28.7) but rather to the absence of variability of performance in the normal control group (MMSE = 30 ± 0.00) and the existence of a mild dysexecutive syndrome in the groups of patients (Table 1).
performances for each task on two different types of map. The first for each overlapped voxel. We were thus able to represent mean scores on a given cognitive task were allocated to each voxel of to remove any subregions with fewer than three overlaps. In sum, patients with a lesion including that voxel. A threshold was applied each voxel was reassigned according to the average score of the individual patient’s normalized MRI was superimposed, and defined in the normalized brain. For each WM task, the patient’s areas from biasing the transformation (Brett brains from computing the cost function, thereby preventing these lesion-induced registration errors, spatial normalization was included in the lesion (Ashburner and Friston, 1999). To reduce Neurology; www.fil.ion.ucl.ac.uk/spm), enabling us to obtain the SPM99 software package (Wellcome Department of Cognitive neuroimaging analysis was performed on superimposed slides of the observed impairment. The method of voxel-based lesion mapping used in this study has already been described elsewhere (Kinkingnehun et al, 2004) and only the main steps will be presented here. Spatial normalization was performed using the SPM99 software package (Wellcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk/spm), enabling us to obtain the Talairach coordinates (Talairach and Tournoux, 1988) of any voxel included in the lesion (Ashburner and Friston, 1999). To reduce lesion-induced registration errors, spatial normalization was performed using a mask that excluded the damaged areas of the brains from computing the cost function, thereby preventing these areas from biasing the transformation (Brett et al., 2001). After normalization, the brain lesion was segmented and its borders were defined in the normalized brain. For each WM task, the patient’s score was assigned to each voxel in the lesioned area. Subsequently, the individual patient’s normalized MRI was superimposed, and each voxel was reassigned according to the average score of the patients with a lesion including that voxel. A threshold was applied to remove any subregions with fewer than three overlaps. In sum, scores on a given cognitive task were allocated to each voxel of the patient’s lesion, enabling us to calculate a mean score ± SEM for each overlapped voxel. We were thus able to represent mean performances for each task on two different types of map. The first type of map, using a colour scale, represented voxel-to-voxel mapping of mean performance for voxels including at least three overlaps. The second type of map represented the 95% confidence interval (CI) for each performance map (i.e. it indicated the absolute range of performance in patients who could be accepted for each voxel with a 5% statistical risk of error). The lower the CI value the higher is the degree of confidence. These two types of map were provided for each of the nine WM tasks.

### Data analyses

#### Group comparisons

We analysed the proportion of correct answers in each condition (number of correct responses/total number of responses = X/45). We performed within-group and between-group ANOVAs: (i) in the within-group analyses we studied the effects of complexity and domain and any interaction between these two factors; (ii) in the between-group analyses, all groups were compared together to assess the group effect and its influence on complexity, domain and first- and second-order interaction between factors; for significant factors or interactions, post hoc comparisons were made with paired Fisher tests. P-values  < 0.05 were considered statistically significant. Statistical analyses were performed using Statistica 6.0 software (Statsoft, Tulsa, USA). Results were expressed as mean performance (mean number of correct responses) ± standard error of measurement (SEM).

#### Clinical–neuroimaging analysis

In addition to the comparison of the WM performance of the SFG group with that of all other groups, a voxel-based clinical–neuroimaging analysis was performed on superimposed slides of brains in order to determine which voxels contributed the most to the observed impairment. The method of voxel-based lesion mapping used in this study has already been described elsewhere (Kinkingnehun et al., 2004) and only the main steps will be presented here. Spatial normalization was performed using the SPM99 software package (Wellcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk/spm), enabling us to obtain the Talairach coordinates (Talairach and Tournoux, 1988) of any voxel included in the lesion (Ashburner and Friston, 1999). To reduce lesion-induced registration errors, spatial normalization was performed using a mask that excluded the damaged areas of the brains from computing the cost function, thereby preventing these areas from biasing the transformation (Brett et al., 2001). After normalization, the brain lesion was segmented and its borders were defined in the normalized brain. For each WM task, the patient’s score was assigned to each voxel in the lesioned area. Subsequently, the individual patient’s normalized MRI was superimposed, and each voxel was reassigned according to the average score of the patients with a lesion including that voxel. A threshold was applied to remove any subregions with fewer than three overlaps. In sum, scores on a given cognitive task were allocated to each voxel of the patient’s lesion, enabling us to calculate a mean score ± SEM for each overlapped voxel. We were thus able to represent mean performances for each task on two different types of map. The first

### Results

#### Normal control group

A within-group ANOVA (1-, 2-, 3-back and three categories of stimuli) showed an effect of complexity \[F(2, 20) = 46.60;\ P < 0.0001\], with an increase in the number of errors with complexity [1-back differed from 2-back \(P < 0.0001\)] and 3-back \(P < 0.0001\), 2-back differed from 3-back \(P < 0.0001\)] (Table 2; Fig. 4). There was also an effect of domain \[F(2, 20) = 3.64;\ P = 0.044\]. Performances in the face n-back task (1- + 2- + 3-back: 38.03 ± 1.60) were lower than those in the spatial (1- + 2- + 3-back: 40.06 ± 1.21; \(P = 0.038\)) and letter (1- + 2- + 3-back: 40.27 ± 1.07; \(P = 0.023\)) tasks. There was no interaction by complexity and domain.

#### Patients

##### SFG group

In this group, as in control subjects, there was a complexity effect \[F(2, 14) = 64.82;\ P < 10^{-6}\] with an increase in the number of errors with complexity [1-back differed from 2-back \(P = 0.0003\) and 3-back \(P < 0.0001\), 2-back differed from 3-back \(P = 0.00012\)] (Table 2; Fig. 4). There was a tendency for an effect of domain but it did not reach significance \[F(2, 14) = 2.97;\ P = 0.08\]. However, there was a significant interaction between complexity and domain \[F(4, 28) = 2.94;\ P = 0.038\]. Post hoc analyses revealed that performances in the spatial 3-back task were significantly lower than those in the face 3-back task \(P = 0.002\) and the letter 3-back task \(P = 0.0005\), whereas none of the other comparisons showed any significant differences.

No significant correlation was found between lesion volume and performance for each domain (\(r\) ranging from 0.09 to 0.55) and each level of complexity (\(r\) ranging from

### Table 2

Subjects’ performance in the n-back tasks

<table>
<thead>
<tr>
<th>Group</th>
<th>Spatial 1-back</th>
<th>Spatial 2-back</th>
<th>Spatial 3-back</th>
<th>Face 1-back</th>
<th>Face 2-back</th>
<th>Face 3-back</th>
<th>Letter 1-back</th>
<th>Letter 2-back</th>
<th>Letter 3-back</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>44.54 (0.20)</td>
<td>43.27 (1.86)</td>
<td>32.36 (2.27)</td>
<td>44.27 (0.30)</td>
<td>39.82 (1.51)</td>
<td>30.00 (2.20)</td>
<td>44.09 (0.36)</td>
<td>42.18 (1.43)</td>
<td>34.54 (2.08)</td>
</tr>
<tr>
<td>PFC non-SFG</td>
<td>44.40 (0.40)</td>
<td>40.20 (1.59)</td>
<td>31.60 (3.98)</td>
<td>43.40 (0.67)</td>
<td>39.80 (1.50)</td>
<td>32.60 (1.77)</td>
<td>44.20 (0.37)</td>
<td>41.20 (0.97)</td>
<td>35.40 (2.62)</td>
</tr>
<tr>
<td>Parietal</td>
<td>43.75 (0.63)</td>
<td>41.50 (1.71)</td>
<td>33.75 (3.70)</td>
<td>43.25 (0.63)</td>
<td>41.25 (1.89)</td>
<td>35.00 (1.47)</td>
<td>44.00 (0.41)</td>
<td>39.25 (2.13)</td>
<td>35.75 (3.50)</td>
</tr>
<tr>
<td>SFG group</td>
<td>44.12 (0.24)</td>
<td>35.00 (2.18)</td>
<td>20.12 (2.66)</td>
<td>44.12 (0.35)</td>
<td>37.87 (1.77)</td>
<td>26.75 (2.59)</td>
<td>44.00 (0.43)</td>
<td>35.25 (1.68)</td>
<td>27.75 (2.43)</td>
</tr>
</tbody>
</table>

Results are expressed as the mean number of correct responses ± SEM. The maximum score for each task is 45 correct responses.
0.09 to 0.64) or between the delay from surgery to the testing procedure for each domain (r ranging from 0.38 to 0.57) and each level of complexity (r ranging from 0.44 to 0.53).

**PFC non-SFG group**
There was a complexity effect \( F(2, 8) = 15.64; P = 0.002 \) (Table 2). Unlike with the SFG group and the normal control group, performances between the 1- and 2-back were not statistically different, whereas the performances in the 3-back were lower than those in the 1- and 2-back tasks (\( P = 0.0006 \) and 0.006, respectively). There was no domain effect and no interaction between domain and complexity.

**Parietal group**
There was a complexity effect \( F(2, 6) = 20.52; P = 0.002 \) (Table 2). However, unlike with the SFG group and the normal control group, performances between the 1- and 2-back were not statistically different. The performances in the 3-back were lower than those in the 1- and 2-back tasks (\( P = 0.0008 \) and 0.006, respectively). There was no domain effect and no interaction between domain and complexity.

**SFG group compared with each of the other groups**
**SFG group compared with the normal control group**
Statistical analyses demonstrated a group effect \( F(1, 17) = 8.63; P = 0.0091 \): mean global performance of the SFG group in the n-back tasks was inferior to that of the normal control group (SFG group: 34.46 ± 1.35; normal control group: 39.45 ± 1.15) (Table 2 and Fig. 4).

There was no effect of domain \( F(2, 34) = 1.56; P = \) not significant (NS)). However, there was an interaction between
groups and domain \[ F(2, 34) = 5.35; P = 0.009 \]. Post hoc analyses indicated that performances in the SFG group were significantly lower than those of the control group in the spatial task (SFG group: 33.08 ± 1.42; normal control group: 40.06 ± 1.21; \( P = 0.016 \)) but not in the letter (SFG group: 35.67 ± 1.26; normal control group: 40.27 ± 1.07; \( P = \text{NS} \)) and face (SFG group: 36.25 ± 1.36; normal control group: 38.03 ± 1.16; \( P = \text{NS} \)) n-back tasks (Fig. 4A).

A complexity effect was observed \[ F(2, 34) = 113.50; P < 10^{-6} \]. Performances in the 3-back < 2-back < 1-back in both groups]. There was also an interaction between groups and complexity \[ F(2, 34) = 6.39, P = 0.004 \]: Post hoc analyses revealed that performances of SFG patients were lower than those of the normal control group in the 2-back (\( P = 0.04 \)) and 3-back (\( P = 0.01 \)) tasks but were not different from those of the normal control group for the 1-back task (\( P = 0.93 \) (Fig. 4B)).

An interaction was observed between domain and complexity \[ F(4, 68) = 3.21; P = 0.018 \]. This interaction resulted mainly from significantly lower performances in the spatial 3-back task as compared with other 3-back tasks and in particular with the letter 3-back task (\( P = 0.0003 \)), whereas there was no significant difference between spatial, face and letter conditions at the 1- and 2-back levels. The within-group analysis for the SFG group showed a significant interaction between modality and complexity, resulting from significantly lower performances in the spatial 3-back task as compared with the face and letter 3-back tasks. In contrast, in the within-group analysis of the normal control group, no interaction was found between complexity and modality, and between the spatial, face and letter 3-back tasks (Fig. 4C).

**SFG group compared with the groups of lesion control patients**

As compared with the PFC non-SFG group, statistical analyses demonstrated an interaction between groups and complexity (\( F = 5.031; P = 0.016 \)). Post hoc analyses revealed that in the 3-back task, performance of SFG patients (24.87 ± 1.95) was lower than that of the PFC non-SFG group (33.20 ± 2.46; \( P = 0.04 \)). There was no interaction between groups and domain and between groups, domain and complexity.

When compared with the right parietal group, a significant interaction between groups and complexity was observed (\( F = 7.76; P = 0.003 \)). Post hoc analyses revealed that in the 3-back task performances of SFG patients were lower than those of the PFC non-SFG group (34.83 ± 2.66; \( P = 0.027 \)). There was no interaction between groups and domain and between groups, domain and complexity.

**Comparisons between the normal control and the PFC non-SFG and the parietal groups**

No significant difference was observed between each group of subjects for age and the level of education. No difference for the mean volume of the lesion was detected between the PFC non-SFG and the parietal groups.

Neither group effect nor significant interaction between groups and complexity, groups and domain and between groups, domain and complexity was observed for the comparisons between the normal control and the parietal groups and between the normal control and the PFC non-SFG groups.

**Voxel-based mapping**

Maps were constructed in order to determine which subregions within the common lesioned area contributed the most to the deficits observed in the n-back tasks (Table 3; Fig. 5). An area localized in the lateral and posterior portion of the SFG [BA 8, rostral to the frontal eye field (FEF), according to data from functional imaging studies (Paus, 1996); Talairach coordinates of the epicentre: −25; 10; 45] was associated with the decreased performance of patients in spatial 3-back tasks (Fig. 5B). Indeed, for the voxel located at the epicentre of this area (−25; 10; 45), the mean performance was 17.4/45, which was far less than −2 SD of the mean of the performance of the control group (32.36 ± 2.27), for a CI = 3.58, indicating that there was a 95% probability that the performance for this voxel ranged

### Table 3 Voxel-based mapping: clinical–neuroimaging dissociation within the left SFG

<table>
<thead>
<tr>
<th>Region of interest score (95% CI)</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Spatial n-back</th>
<th>Verbal n-back</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-back</td>
<td>2-back</td>
</tr>
<tr>
<td>Superior frontal sulcus</td>
<td>−25</td>
<td>10</td>
<td>45</td>
<td>43.8 (5.39)</td>
<td>31.25 (4.75)</td>
</tr>
<tr>
<td>Pre-SMA</td>
<td>−10</td>
<td>15</td>
<td>54</td>
<td>44.3 (5.43)</td>
<td>38.3 (5.08)</td>
</tr>
</tbody>
</table>

The table illustrates the patterns of performance in the spatial and verbal n-back tasks of two prototypical voxels located in the centre of two different subregions within the left SFG. One voxel is located in the superior frontal sulcus (BA 8) and another one in the medial PFC (pre-SMA). \( x, y, z \) represent Talairach coordinates. Performance is expressed as the mean number of correct responses for each of these two voxels. Figures in parentheses are the 95% CI for each result (i.e. the range of performance that can be accepted for each voxel with a 5% statistical risk of error). The results shown in bold illustrate the clinical–neuroimaging dissociation between lesions of the lateral and the mesial SFG. Lateral SFG lesions contribute to the deficit but not those of the mesial SFG. It may be noted that the results for the face n-back tasks, although showing a slightly smaller deficit than the two other domains, followed a similar pattern of dissociation to the verbal and spatial n-back tasks.
between 20.98 and 13.82 (Table 3). In contrast, there was an area in the medial SFG [pre-supplementary motor area (pre-SMA), epicentre: /C0 -10, 15, 54] in which performance in the spatial 3-back was within the range of the mean performance of the control group (performances = 30/45 with a CI = 89.41), indicating that there was a 95% probability that the performance for this voxel ranged between 34.41 and 25.59. These data suggest that voxels in this subregion contributed less to the deficit than the lateral and posterior portion of the SFG (Fig. 5B, Table 3).

**Discussion**

This is the first study on the effect of a unilateral (left) and homogeneous lesion of the SFG on WM when compared with groups of patients with brain damages sparing the SFG and with normal control subjects matched for age, gender and level of education. Our findings can be summarized and interpreted as follows. (i) Patients with an SFG lesion were globally impaired in WM tasks. Taken in conjunction with the fact that the impairment was still present months to years after the removal of the lesioned area, this result indicates that the SFG is a key component of the WM network. (ii) The significant group–complexity interaction was mostly due to the differences between controls and patients in the 2- and 3-back tasks. This indicates that the deficit is above all dependent on the level of executive processing within WM, suggesting a major involvement of this region in response to an increase in executive demand in WM. (iii) Although the deficit affected all domains (spatial, face and letter) in the tasks that involved higher levels of executive demand (i.e. the 2- and 3-back tasks), the most...
severe impairment occurred in the spatial 3-back task. This suggests that the SFG combines two aspects of WM processing, a domain-oriented involvement (in spatial WM) that is overridden by a complexity-oriented involvement. (iv) The results of the voxel-based mapping of performance evidenced an anatomical-functional dissociation within the SFG: the lateral and posterior SFG (BA 8, rostral to the FEF) contributed the most to the impairment in WM, whereas lesions to the medial aspect of the SFG were not associated with the WM deficit in this group of patients. This suggests that, in humans, the subregion involved in WM within the lateral and posterior SFG (mostly 8 but also caudal 9 and rostral 6) could share a functional homology with the principal sulcus of the macaque monkey, which has been specifically implicated in spatial WM. However, in contrast to findings in the monkey, the aforementioned subregion within the left SFG was also involved in other modalities and was only triggered for the highest executive demand in WM processing.

**Power of the lesion study in humans**

The anatomical and functional organization of the lateral PFC for WM is still a matter of debate (Levy and Goldman-Rakic, 2000; Owen et al., 2000; Miller and Cohen, 2001; Johnson et al., 2003; Koechlin et al., 2003; Curtis and D’Esposito, 2004; Petrides, 2005) for several reasons. Among them, at least two are directly related to the choice of experimental method. (i) Although the general principles of the anatomical and functional organization of the PFC can be inferred from lesion and single-cell recording studies in macaque monkeys (for a review, see Petrides, 2005), the precise localization of functions cannot be directly transposed to humans because of interspecies macroscopic anatomical differences (Petrides and Pandya, 1999) due to the considerable difference in size between the human and monkey PFC (Fuster, 1997). (ii) In humans, functional imaging (PET scan and fMRI) cannot show whether one given region of a network is critical (i.e. the cognitive process cannot be implemented without this region) or accessory (i.e. it may contribute but the cognitive process can be partially or fully functional without it). Therefore, lesion studies in humans are particularly useful to complement experimental studies in animals and functional imaging studies (Rorden and Karnath, 2004), although, in this particular study, some limitations should be pointed out: (i) lesions tend not to be conveniently localized in cytoarchitectonically distinct areas; (ii) voxel-to-voxel mapping of several patients’ lesions can only provide useful information for areas where at least three lesions overlap.

In this study, these shortcomings have been by-passed by restricting our study to a small, well-defined area that seems to be critical for the processes under evaluation, namely the SFG, a region considered essential to WM (Petrides, 2005). Our methodological approach has several advantages: the group of SFG patients was homogeneous in terms of the location of the lesion (Fig. 1) and the underlying mechanism responsible for lesion (i.e. the surgical removal of a low-grade glioma). Furthermore, the boundaries between the lesioned areas and non-lesioned brain tissues were clear-cut, allowing precise segmentation of the lesions that were subsequently used for voxel-to-voxel mapping. All patients were tested >6 months after surgery. Consequently, any residual WM deficit would indicate that the functional reorganization of the neural network for WM was unable to compensate for the removal of the SFG. Interestingly, no correlation was found between WM performance and time from surgery or lesion size, suggesting that the level of performance in these patients was directly related to the location of the lesion. The inclusion of two other groups of patients with a focal lesion served as control for several parameters: the fact that these patients performed like controls indicates that the effect observed in the SFG group was not a non-specific effect, only due to a brain lesion, but rather related to the specific location of the lesions. The normal performances of the two lesion control groups also indicated that the deficit in the 3-back tasks observed in the SFG group was not due to a ’mass effect’ as the mean volume of the lesion in this group was not superior to that of the two other groups of patients. It is also noteworthy that the deficit could not be related to the specific aetiology of the lesion, since neither the group of control patients with a brain removal for a low-grade glioma or the group of control patients with an ischaemic lesion were impaired. However, one should keep in mind the three following limitations in terms of interpretation of these results. (i) Our study does not provide information on other regions involved in WM functions, and the interpretation of our results must therefore be limited to the functions of the SFG. (ii) One may interpret the absence of deficit in the 1-back task in all the groups of subjects tested as a ’ceiling effect’. Alternatively, it is also possible that none of the lesions was located in areas that can elicit such a deficit. Another explanation can be that unilateral lesions, even located in the WM network, are not sufficient to induce an impairment affecting the maintenance of one item in short-term memory. Following this idea, fMRI studies showed bilateral activation during the 1-back task in the lateral premotor (BA 6) and posterior parietal (intraparietal sulcus; BA 7) cortices (for a review, see Owen et al., 2005). (iii) It is not possible to determine, from our study, the weight of the white matter involvement in the deficit. However, it is likely that the subcortical extension of the lesions contributed to the impairment by disconnecting several functional subregions involved in WM (between areas included in the SFG lesion, between the SFG region and other PFC regions or between retro-rolandic areas and the SFG).

**Left SFG involvement in WM**

At a general level, our results are in agreement with numerous functional imaging studies using various...
experiment paradigms to demonstrate the activation of foci in the SFG in WM (Awh et al., 1995; Braver et al., 1997; Postle et al., 2000; Corneille et al., 2001). A recent meta-analysis of 24 articles regarding the n-back paradigm in functional imaging studies in normal subjects indicates regular foci of activation in the SFG within a more diffuse network (Owen et al., 2005). The deficit observed in our study not only supports the functional imaging data but also indicates that the foci of activation within the SFG play a critical role in the processes required for the n-back tasks.

Voxel-to-voxel mapping showed that the subregion that contributes the most to the WM deficit was located in the lateral, inferior and posterior portion of the SFG, encompassing most of BA 8 and caudal portion of BA 9. Two lines of evidence suggest that this lesioned area is rostral to the FEF. (i) According to functional imaging studies, the FEF is reportedly located on the anterior bank of the junction between the superior frontal sulcus and the precentral sulcus (Paus, 1996; Courtney et al., 1997; Luna et al., 1998; Lobel et al., 2001), ~15–20 mm caudal to the subregion that contributes the most to the deficit. (ii) If the lesion site affected the FEF—an area that participates in the control of saccadic eye movements and where eye movements can be elicited by electrical stimulation (Paus, 1996)—then one would also expect the deficit to occur in the spatial 1-back task that requires control or triggering of eye movements at exactly the same level as in the 3-back task. Furthermore, the deficit resulted from a more subtle dysfunction where complexity and domain interacted, suggesting that the incriminated area was rather involved in cognitive than in motor control.

The area involved in this study is usually activated in n-back studies, particularly when the load and complexity increase, as in the 2- and 3-back tasks (Cohen et al., 1997; Carlson et al., 1998; Callicott et al., 1999). Whereas most of the functional studies have emphasized the essential role in WM of the region located in the upper portion of the middle frontal gyrus, immediately beyond the lower bank of the superior frontal sulcus (i.e. the ‘mid-dorsolateral’ PFC or area 9/46 according to the current taxonomy) (for a review, see Owen, 2005; Petrides, 2000), our study showed that the area lying in the upper bank of the posterior superior frontal sulcus also plays an important role. Furthermore, the voxel-to-voxel mapping also indicated, with a high degree of confidence, that the voxels located in the medial part of the left SFG did not significantly contribute to the observed deficits (see Fig. 4 and Table 3), which is in agreement with functional imaging data indicating that the medial portion of the left SFG does not belong to the neural network of WM.

**Nature of left SFG involvement in WM**

Patients with a left SFG lesion were impaired in the 2-back task, but above all in the 3-back task, as compared with controls (Fig. 4B). These data suggest that the lateral left SFG intervenes when executive demand in WM exceeds a certain threshold. This result is in line with the notion that areas located in the upper lateral PFC are involved in higher processes gathered under the concept of ‘monitoring and manipulation’ (Owen, 2000; Petrides, 2000) or ‘executive processing’ (Postle et al., 2000) within WM. Therefore, the left SFG is recruited by the specific cognitive processes necessary for the 3- and 2-back tasks that include the maintenance of two or three items in short-term memory, rehearsal and updating. In addition, the 2- and 3-back tasks, unlike the 1-back task, require the subjects to develop efficient strategies to improve performance in the course of successive trials (Rypma et al., 2002), such as the management of concurrent tasks and information to be used prospectively (the ‘branching’ hypothesis; Koechlin et al., 1999), the enhancement of the strength of memory, allowing resistance to interference (Sakai et al., 2002), the building of a temporal ordering of the mental representations or ‘chunking’ (linking and compression of items in memory) (Rypma and D’Esposito, 1999; Philips and Niki, 2002; Rypma et al., 2002), and so forth. Our study was not designed to determine which of these mechanisms might be particularly related to the functions of the SFG, and further studies are required to answer these questions.

In our study, the patients’ overall performance was lower in the spatial modality, largely due to the deficit in the spatial 3-back task. This result suggests that the lateral SFG, or at least the left SFG, is particularly involved in spatial WM. This first level of interpretation is in accordance with the findings of an fMRI study by Courtney et al. (1998) showing specific activation in spatial WM in a locus within the SFG (rostral to the FEF; Talairach coordinates: −31 ± 7; −7 ± 5; ± 46 ± 4) and located −10–15 mm caudally to the centre of the subregion that seemed to contribute the most to the WM deficit in our study. In line with Courtney et al.’s (1998) conclusion, one may hypothesize that in humans, unlike in monkeys, the regions involved in spatial cognition within the PFC (the spatial WM areas and the FEF) have been displaced to more superior and posterior regions within the lateral PFC. However, our data suggest that the main effect of the lesion of the left SFG is a complexity effect, regardless of the domain being processed. This interpretation is supported by the findings of an fMRI study by Nystrom et al. (2000) showing that, during n-back tasks, an area covering the focus of the lesions in our study is sensitive to load in WM but appears to be more activated in the spatial n-back than in the shapes n-back task. To conclude, the left SFG seems to be recruited above all when the executive demand in WM exceeds a certain threshold and is relatively oriented towards the spatial domain. Accordingly, one may speculate that other portions of the PFC are involved according to a similar general pattern but with a relative domain preference. If this were to be confirmed by similar data obtained in other PFC regions, it could modify the current view of the functional-anatomical architecture of the PFC for WM.
Implications for the understanding of the anatomical and functional organization of the WM neural network

How does this set of data fit with current models of the anatomical and functional organization of the PFC for WM? One debated issue is whether the lateral PFC is subdivided according to the nature of the cognitive processing or to the domain of the information being processed. The domain-specific model postulates an anatomical segregation within the PFC according to the domain being processed (for a review, see Goldman-Rakic, 1996). The domain-specific model is mainly derived from studies in the monkey, where anatomical studies, electrophysiological recordings of neurons and lesion experiments have identified in Walker’s area 46 and the principal sulcus an area specifically involved in spatial cognition and considered to be analogous to the human dorsolateral prefrontal cortex (DLPFC; BA 9/46). In humans, several data from functional imaging studies support the existence of ‘domain-related’ regions, such as a spatial area in the posterior SFG, close to the area found in our study (Courtney et al., 1998), a subvocal rehearsal component in Broca’s area for verbal WM (Paulesu et al., 1993), together with a relative hemispheric dominance depending upon the type of information being processed (Belger et al., 1998). However, several studies in humans have failed to demonstrate a domain-specific segregation within the DLPFC (Owen et al., 1998) but rather suggest an organization according to processing distinctions (Owen et al., 1996) or a holistic organization in which the lateral PFC is a global and flexible system for cognitive control, regardless of any distinctions in terms of processing or domain (Duncan and Owen, 2000; Miller and Cohen, 2001).

As already mentioned above, one of the explanations of the persistency of such a debate is that although the general functional architecture of the PFC can be inferred from studies in macaque monkeys, the precise localization of functions cannot be directly transposed to humans because of interspecies macroscopic anatomical differences due to the important increase in size of the most anterior portion of the PFC. Following this idea, any proposal of an anatomical or functional model of the lateral PFC in human should take into account not only the mid-dorsolateral region (9/46) but also other lateral PFC subregions, in particular those located in the most posterior portion of the PFC. Therefore, our data contribute to this debate by showing that in one of these posterior regions—the lateral and posterior SFG—there was a pattern of deficit that does not correspond to any of the proposed models of functional architecture of the PFC: at first sight, our data showing that a lesion to the left lateral and posterior SFG (in area 8 but not in FEF as delineated by functional imaging studies) was associated with a decreased performance in the spatial domain appear to be consistent with the ‘domain-specific’ model. However, the spatial involvement of the SFG was only relative in our study, the main effect observed being above all a complexity effect regardless of the domain being processed. In sum, the data reported in our study are consistent with the left lateral and posterior SFG being a hybrid area involved only up to a certain threshold of executive demand and relatively spatially oriented.

Conclusions

This study confirms the involvement of the SFG in the neural network dedicated to WM and extends our knowledge by showing that this area appears to be critical, since lesions produce a long-lasting and non-compensated WM deficit. These data are of importance for neurosurgeons who frequently remove lesions such as low-grade gliomas in the SFG. Our results should help them to provide more precise information on the expected cognitive sequelae following the removal of such lesions. The study also confirms that only the lateral (i.e. not the medial) aspect of the SFG belongs to the WM network. In addition, these data show that the lesion of the left SFG affects WM processing in its more executive functions with a relative domain specificity. Therefore, none of the current models of the functional organization of the PFC based only on segregation according to a distinction between domains or processing fully depicts the global architecture of the lateral PFC for cognition.

References

Functions of the superior frontal gyrus


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