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Testing the model of caudo-rostral organization of cognitive control in the human with frontal lesions

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ABSTRACT

The *cascade model* of cognitive control, mostly relying on functional neuroimaging studies, stipulates that the lateral frontal cortex (LFC) is organized as a cascade of executive processes involving three levels of cognitive control, implemented in distinct LFC areas from the premotor to the anterior prefrontal regions. The present experiment tested this model in patients with LFC lesions and studied the hierarchy of executive functions along the caudo-rostral axis, i.e. the respective roles of the different LFC areas in the control of behavior. Voxel-based lesion-symptom mapping and region of interest group analyses were conducted in 32 patients with focal LFC lesions who performed cognitive tasks assessing the cascade model. We first showed that three different LFC areas along the caudo-rostral axis subserved three distinct control levels, whose integrity is necessary for adaptive behavior. Second, we found that prefrontal cognitive control has an asymmetric organization: higher control processes involving more anterior prefrontal regions rely on the integrity of lower control processes in more posterior regions, while lower control processes can operate irrespective of the integrity of higher control processes. Altogether, these findings support a caudo-rostral cascade of executive processes from premotor to anterior prefrontal regions.

Introduction

The lateral frontal cortex (LFC) is a pivotal structure in the neural network involved in the inhibition of reflex or automatic actions and the elaboration or control of goal-directed behaviors. The question of its functional architecture is central, as it holds the key to understanding the functional architecture of cognition in general. Several models of the anatomical and functional organization of the LFC have been proposed and debated. There is a general agreement on two key ideas underlying these models. First, that the LFC is essential for temporal control: it serves as a temporal buffer between past events and future actions, allowing behaviors that follow internal goals to occur (Fuster, 2001; Goldman-Rakic, 1987; Petrides, 2005). Second, that the LFC exerts "top-down" cognitive control that modulates processes associated with the posterior regions on the basis of internal plans and goals (Miller and Cohen, 2001; Passingham, 1993; Shallice, 1988). Koechlin et al. (2003) have proposed a functional model combining these two critical dimensions of cognitive control, based on Shannon's theory of information (Berlyne, 1957). The novelty of this model lies in the fractioning of cognitive control itself: executive functions can be subdivided into hierarchical control levels depending on the amount of information required for action selection and on the temporal frame in which the stimulus occurs. This modular model involves three nested levels of processing, implemented in three different areas organized along the caudo-rostral axis of the LFC. The posterior LFC (the lateral premotor cortex/BA 6) subserves *sensory* control, i.e., it is involved in selecting appropriate behavioral response to stimuli based on stored sensorimotor associations. A caudal portion of the lateral prefrontal cortex (BA 9/44/45) is the neural substrate for *contextual* control, involved in selecting appropriate sensorimotor representations in the premotor cortex according to the immediate context; a more rostral portion of the lateral prefrontal cortex (BA 46) subserves *episodic* control, involved in selecting relevant caudal prefrontal representations according to the temporal episode in

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which the person is acting, i.e. according to temporally remote events. The implementation of this cognitive architecture within the LFC is supported by evidence from functional magnetic resonance imaging (fMRI) studies in healthy human subjects (Braver et al., 2003; Koechlin et al., 2003). It is interesting to note that after Koechlin's model, Badre and colleagues have also proposed a caudo-rostral model of functional organization of the LFC, based on fMRI and lesion studies (Badre and D'Esposito, 2007; Badre et al., 2009). This model matched Koechlin's one in terms of anatomical segregation along the caudo-rostral axis of the LFC, but it differed in the functions associated with each of the defined subregions (see Discussion).

This cascade model of cognitive control may modify our view of the functional organization of prefrontal cortex and may also modify our interpretation of the clinical signs observed in patients with prefrontal damages. However, to which extent this model may predict the behavioral deficits in patients with frontal lesions remains unknown. Indeed, functional neuroimaging and physiological measurements in intact systems only confirm the engagement of a brain region by a cognitive process but not its necessity for this process. This raises the issue regarding the causal hierarchy and the integration processes within this network. In particular, can higher control levels implemented in more anterior prefrontal regions operate irrespective of the integrity of lower control levels and more posterior prefrontal regions? To address this question, we tested the cascade model of cognitive control in a large cohort of patients with stable focal frontal lesions. Indeed, lesion studies, i.e. the study of deficits associated with damage to a specific brain region, may provide convincing evidence for the critical role of a brain region in certain cognitive processes and/or the control of a specific behavior (Rorden and Karnath, 2004; Sarter et al., 1996).

Thirty-two patients with LFC lesions and twenty-eight matched healthy participants were included in the study. All performed cognitive tasks testing the three levels of cognitive control (*episodic*, *contextual* and *sensory* control, see Fig. 1) as described in Koechlin et al. (2003). The tasks consisted of the presentation of series of colored visual stimuli (disks or letters) organized into blocks. Subjects made manual responses on the basis of an instruction cue that initiated each block. Task accuracy (percentage of correct answers) and Reaction Times were recorded in each condition and for each participant. All patients also underwent an anatomical T1-weighted MRI to map brain lesions.

We then analyzed the data following two different approaches. We first tested the hypothesis that *sensory*, *contextual* and *episodic* control levels involve segregated regions on a caudo-rostral axis in the LFC. For that purpose, we performed an analysis based on a cluster-by-cluster lesion–behavior mapping technique (Kinkingnehun et al., 2007). According to previous fMRI studies (Koechlin et al., 2003; Kouneiher et al., 2009), we expected that *sensory*, *contextual* and *episodic* deficits would be associated with focal damage to BA 6, BA 45 and BA 46, respectively.

Secondly, we addressed the question of the hierarchy of control between the different areas involved in this caudo-rostral organization by performing a group analysis that compares the performance of patients with lesions of the lateral premotor cortex (n = 11), caudal prefrontal cortex (n = 9) and rostral prefrontal cortex (n = 6) to the performance of 28 healthy controls. In this second study, we excluded patients with frontal lesions that did not involve the described regions of interest (i.e. BA 6, BA 44/45, or BA 46/47). In accordance with the hierarchical organization predicted by the cascade model described above, we expected that higher control processes involving more anterior prefrontal regions rely on the integrity of lower control processes in more posterior regions, whereas lower control processes can operate irrespective of the integrity of higher control processes.

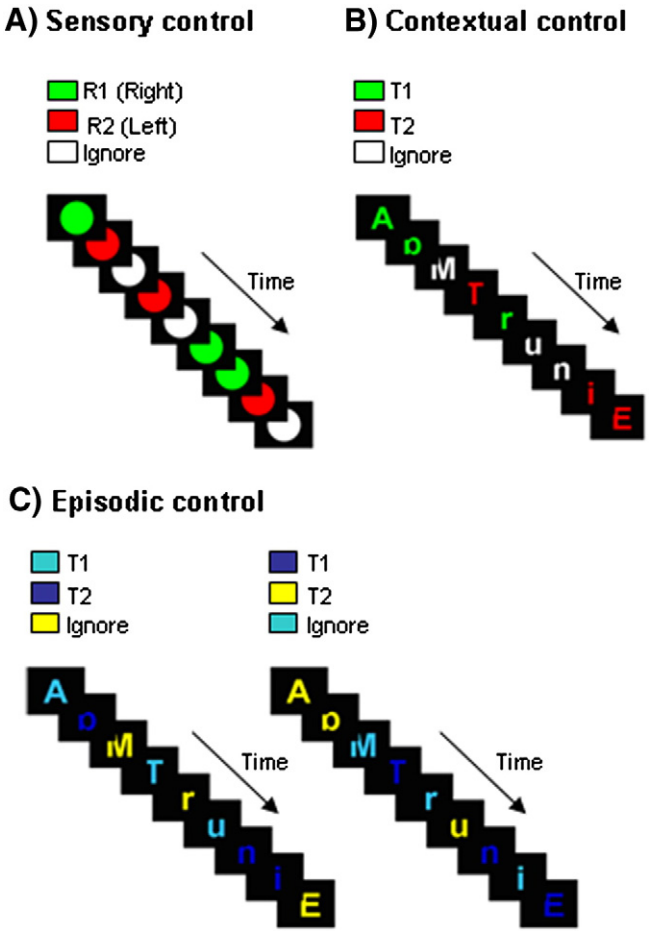

Fig. 1. Behavioral tasks. Participants performed the three tasks described in Koechlin et al. (2003) to assess the different levels of cognitive control. They had to provide a manual response to colored visual stimuli (disks or letters), on the basis of an instruction cue that initiated each block. (A) *Sensory* condition: participants had to press the right button when a green disk was presented on the screen (R1) and the left button when a red disk was presented (R2). They had to ignore white disks. (B) *Contextual* condition: participants had to make a letter discrimination using the right and left response buttons, the task being determined by the color of the letter ("*contextual* signal"). For green letters, participants had to perform a lower/upper case discrimination task (T1). For red letters, they had to perform a consonant/vowel discrimination task (T2). They had to ignore white letters. (C) *Episodic* condition: subjects performed the task as in the *contextual* condition except that association between the color and task varied according to the instruction cue. In one block, cyan letters were associated with T1, blue ones with T2 and yellow ones were ignored. In another block (initiated by another instruction cue) blue letters were associated with T1, yellow ones with T2 and cyan ones were ignored.

Methods

This study was approved by institutional ethics committees for biomedical research (CCPPRB of the Pitié-Salpêtrière Hospital, Paris, France and Ethics Committee of the Salvador Hospital, Santiago, Chile). Subjects provided written informed consent before their inclusion in the study.

Participants

Thirty-two patients with focal frontal lesions were included in the study (mean age: 49.38 years [SD: 11.9]; years of formal education: 12.41 [SD: 3.58]; patients with right frontal lesions, n = 18, patients with left frontal lesions, n = 14). They were recruited from the Neurovascular and Neurosurgical Departments of La Pitié-Salpêtrière Hospital (Paris, France) and the Neurology Department of the Salvador Hospital (Santiago, Chile). They were selected based on the following criteria: (1) the presence of a single frontal focal lesion, excluding lesions extending to other lobes, and confirmed by an anatomical T1-weighted 3D MRI; (2) the absence of a prior history of neurological disease, psychiatric disorder or substance abuse; (3) the ability to understand and perform the tasks (in particular, patients did not exhibit

sensorimotor or instrumental impairments that could interfere with the performance of the cognitive tasks); (4) lesion acquired during adulthood and not due to an evolving disease. Only patients with sequelae from an ischemic or hemorrhagic stroke, removal of a low-grade glioma, or a focal traumatic brain injury without other associated lesions were included in the study; (5) consolidated lesions (patients were tested at least six months after the episode responsible for the frontal lesion). Here, it is important to note that no correlation was found between task performance and the time separating the occurrence of the lesion and the cognitive testing/imaging session. All patients who matched the above criteria were included, regardless of the location of the lesion within the frontal lobes or the pattern of cognitive deficit. The patients' motor abilities (muscle strength and motor sequencing) were tested at the bedside by a senior neurologist (C. A. or A S.). Hand motor sequencing was tested using Luria's motor series (Luria, 1966). None of the participants had even a slight motor impairment and all subjects were able to learn and correctly execute the Luria's motor sequences. Global cognitive ability was tested using the Mini Mental State Examination, MMSE (Folstein et al., 1975). A non-parametric Mann–Whitney U test showed no significant difference between the scores of patients and controls (Mann–Whitney $U = 117$, $p = 0.093$).

In order to statistically analyze the two different experimental approaches, we required normal values for each condition tested from a group of healthy subjects matched for age (t test for equality of means: $t = 1.66$, $p = 0.10$), and years of formal education ($t = 1.12$, $p = 0.27$). Thus, a group of 28 control subjects with no prior history of neurological or psychiatric disease was included (mean age: 44.57 years [SD: 9.99]; educational level: 13.96 years [SD: 3.57]).

Tasks and stimuli (Fig. 1)

Participants performed three tasks assessing the cascade model of cognitive control (*sensory*, *contextual* and *episodic* tasks) as described in Koechlin et al. (2003). The three tasks were virtually identical to those used in Koechlin et al. (2003), except that the overall arrangement of task conditions was simplified in order to make the protocol accessible to frontal patients. These simplifications prevented from quantitatively computing Shannon information across *sensory* control and *episodic* levels as in the Koechlin et al. (2003) study. However, the resulting behavioral protocol enabled the assessment of the causal involvement of prefrontal regions in every task and consequently in *sensory*, *contextual* and *episodic* control processes.

All tasks consisted of the presentation of series of colored visual stimuli (disks or letters), and required a manual response (pressing the left or right hand-held response button). The nature of the response varied according to the task. Participants were seated in front of a personal computer screen with their hands on the response pad. Tasks were organized into blocks. Each block included a series of 12 pseudo-randomized stimuli preceded by an instruction cue (corresponding to one of the three conditions). Each stimulus was presented on the screen for 4 s (this period was extended compared to the original tests, taking into account the possibility of longer Reaction Times for patients); participants were asked to respond during this period by pressing a button. There were 6 blocks of stimuli for each condition. The three different conditions were randomly distributed across the experimental session.

In the *sensory* condition, the stimuli were colored disks (green, red or white). Participants had to press the right button (R1) when a green disk was presented on the screen and the left button (R2) when a red disk was presented on the screen. On occasion, a white disk appeared on the screen (distracter), participants had to ignore it (i.e., no motor response was required).

In the *contextual* condition, the stimuli were colored letters (green, red or white). Participants had to make letter judgments, the task being determined by the color of the letter (the "*contextual* signal"). According to the color of the letter, participants had to perform either a lower/upper case (T1) or a vowel/consonant (T2) discrimination task on the letters, using the left and right response button. Green letters instructed the participants to perform the T1 task, while red letters instructed them to perform T2; white letters indicated that they had to ignore (I) the letter.

In the *episodic* condition, the *contextual* signal changed throughout. Stimuli were colored letters (blue, yellow and cyan). Within a given block, cyan letters were associated with T1, blue ones were associated with T2 and yellow ones were distracters. In another block (preceded by another instruction cue) blue letters were associated with T1, yellow ones were associated with T2 and cyan ones were distracters. Therefore, in this task, the response triggered by each color varied on a block-by-block basis.

In each condition "distracter" stimuli were included in order to faithfully reproduce the paradigm used in the fMRI study (Koechlin et al., 2003). In this paradigm, such stimuli were included for two different reasons: (1) so that the cognitive processing of colors would be the same in each condition, and (2) in order to force the subjects to pay the same level of visual attention in all conditions, even the most basic ones. These "distracter" stimuli had the same frequency in every condition (a third of the stimuli) and followed a randomized distribution.

The total duration of the session was 150 min. Prior to the experiment, each participant was given a practice session of 20 min (fixed training time). An investigator supervised the practice session to make sure that the tasks were fully understood before starting the experiment.

Lesion–behavior statistical mapping approach

The lesion–behavior mapping study was performed using a cluster-by-cluster lesion mapping method (AnaCOM: Anatomo-Clinical Overlapping Maps, see Kinkingnehun et al., 2007 for a full description of the method). This method consists of building statistical maps that indicate which clusters of voxels are responsible for the behavioral deficits in question. The advantage of such a method is that neither prior hypothesis regarding frontal areas responsible for deficits, nor patient groups pre-determined upon lesion sites or performances are required.

In brief, the patients' anatomical MRI scans were spatially normalized (according to the T1 Montreal Neurological Institute [MNI] Atlas). Each lesion was manually segmented and was used as a mask during the normalization procedure (Brett et al., 2001). The spatially normalized images were re-sliced with a final voxel size of $1.5 \times 1.5 \times 1.5$ mm^3. Brain lesions were then manually segmented on the normalized MRI in order to obtain a region of interest (ROI) image. This segmentation did not differentiate between gray and white matter. The score of the patient in the task of interest was then used to weight each voxel of each lesion; in other words, the score of each patient in a given task replaced each voxel value of the ROI while the rest of the image was set to zero, assuming that the brain lesion was responsible for the deficit. Following these steps, all patient ROIs ($n = 32$) were superimposed in normalized space, to build a "Maximum Overlap Map" (Fig. 2A). In this map, clusters (a group of contiguous voxels covered by the same lesion) were defined by the overlapping of segmented lesions. To build this map, we chose to switch all the patients' lesions to the left hemisphere in order to optimize the statistical power of the study by increasing the number of lesion overlaps. This choice was justified because there was no significant difference between the performance of patients with a right as opposed to a left frontal lesion. Indeed, we studied the effect of the side of the lesion on task accuracy. A repeated measures 2-by-3 ANOVA with lesion side (left-lesioned, $n = 14$ vs. right-lesioned, $n = 18$ patients) as a between-subjects and condition (*sensory*, *contextual* vs. *episodic*) as a within-subjects factor showed a significant main effect of condition ($F = 36.95$, $p < 0.01$), but there was neither a main effect of lesion side ($p = 0.984$) nor an interaction between the lesion side and condition ($p = 0.957$), indicating that behavioral impairments were independent of lesion side. This choice of lesion switching was also justified because fMRI activation in the Koechlin

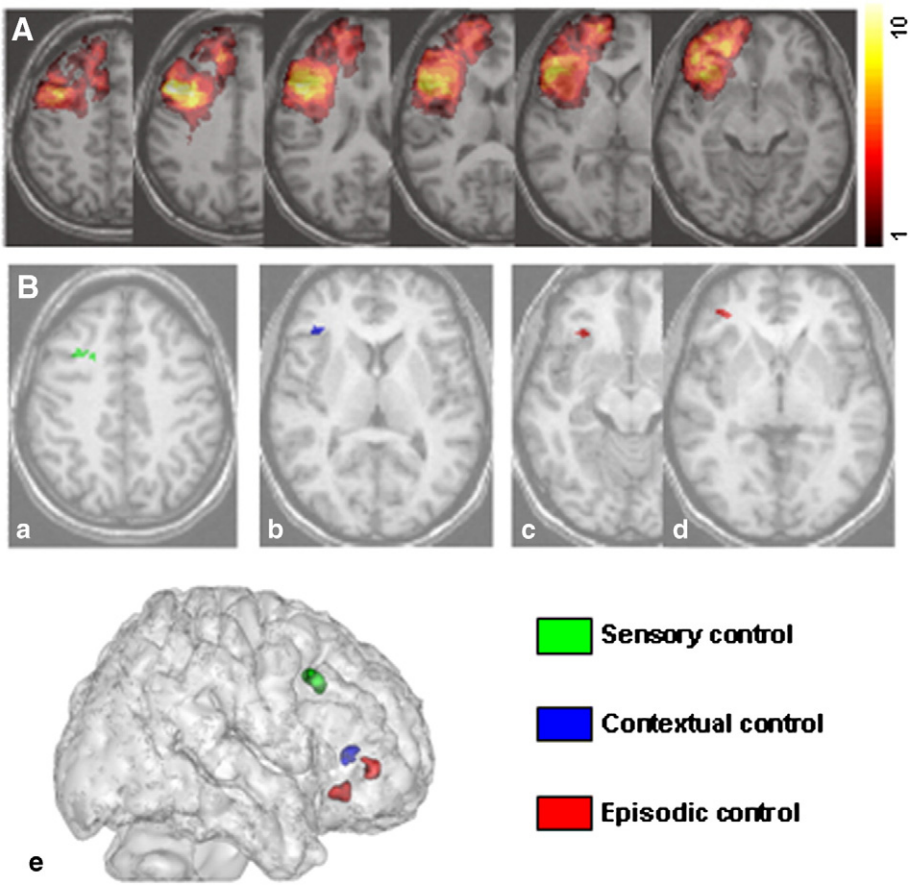

Fig. 2. Results of the lesion–behavior statistical mapping approach. (A) Overlap map of patients' lesions. Overlap map of patients' lesions (n = 32) superimposed on a normal brain (axial sections). The color code of each cluster of voxels indicates the number of patients whose lesion covers the cluster. Left and right lesions were both superimposed on the left hemisphere (see Methods). (B) Lesion–behavior statistical mapping results. Colored regions show areas significantly associated with a behavioral deficit (after a whole brain analysis, threshold $p = 0.05$, corrected for multiple comparisons; see Methods for details). Green (a, e), damaged area significantly associated with a deficit in the *sensory* condition (BA 6, Talairach coordinates of the epicenter: x = −20; y = 14; z = 51, $p = 0.0018$). Blue (b, e), damaged area significantly associated with a deficit in the *contextual* condition (BA 45, Talairach coordinates of the epicenter: x = −40; y = 35; z = 11, $p = 0.000061$). Red (c, d, e), damaged areas significantly associated with a deficit in the *episodic* condition (c: BA 47, Talairach coordinates of the epicenter: x = −35; y = 33; z = −12, $p = 0.0001$, d: BA 46, Talairach coordinates of the epicenter: x = −46; y = 45; z = 4, $p = 0.0004$).

et al.'s (2003) study was symmetric in the two hemispheres for the three tasks. Statistical analyses were performed with clusters that occurred in at least three lesions (Kinkingnehun et al., 2007). In these clusters, a non-parametric Kolmogorov–Smirnov test corrected for multiple comparisons (Holm's correction) was performed between the mean performance obtained for each voxel in patients and in healthy controls. Non parametric analyses were chosen because performance of patients and controls did not follow a Gaussian distribution. A $p < 0.05$, corrected for multiple comparisons over the entire brain was considered statistically significant. These analyses allowed statistical maps to be built for each condition (*sensory*, *contextual* and *episodic*), showing only regions that contributed significantly to deficits in that condition.

Group approach

All patients underwent an anatomical T1-weighted MRI where brain lesions were mapped by 110 axial contiguous inversion recovery three-dimensional (3D) fast SPGR images (1.5 mm thick; MR scanner: General Electrics, 1.5 T), see Supplementary Fig. 1. We precisely localized each patient's lesion using a Brodmann template (with MRIcro, http://www.sph.sc.edu/comd/rorden/mricro.html) superimposed on the normalized MRI of the patient. On the basis of the location of their frontal lesions on the anatomical MRI scans, patients were divided into three groups a priori defined and based on the main functional nodes of the cascade model. In the first group of patients (Fig. 3A), lesions affected the lateral premotor cortex (Brodmann area 6) and could extend to the surrounding prefrontal areas (n = 11). In the second group of patients (Fig. 3B), lesions affected a caudal portion of the lateral prefrontal cortex including Brodmann areas 44 and/or 45 (n = 9) and could extend to the surrounding prefrontal areas but spared the lateral premotor cortex. In the third group of patients (Fig. 3C), lesions affected a more rostral portion of the prefrontal cortex including Brodmann areas 46 and/or 47 (n = 6) and could extend to frontopolar or medial areas, but spared the lateral premotor cortex and the caudal lateral prefrontal cortex. Six patients with frontal lesions who could not be categorized according to the above divisions, because of frontal lesions that did not affect the above regions of interest, were not included in the group study, but they were included in the lesion–behavior mapping study. In the lateral premotor group, the etiology of lesions was stroke (n = 8) or removal of a low-grade glioma (n = 3). In this group, 4 patients had a right frontal lesion and 7 patients had a left frontal lesion. In the caudal lateral prefrontal group, the etiology of the lesions was stroke (n = 7), removal of a low-grade glioma (n = 1) or focal traumatic brain injury (n = 1). In this group, 7 patients had a right frontal lesion and 2 patients had a left frontal lesion. In the rostral lateral prefrontal group, the etiology of lesions was stroke (n = 2), removal of a low-grade glioma (n = 2) or focal traumatic brain injury (n = 2). In this group, 3 patients had a right frontal lesion and 3 patients had a left frontal lesion. These three groups had no significant difference in terms of gender (Kruskal–Wallis ANOVA K = 1.56, $p = 0.46$), of age (K = 5.15,

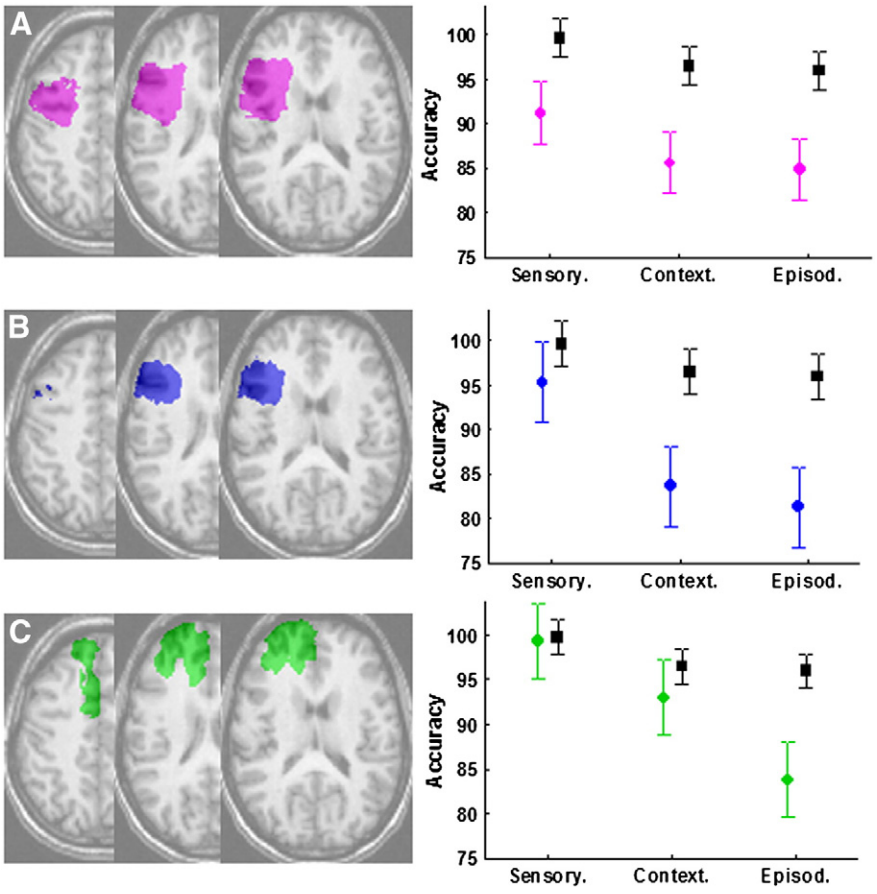

Fig. 3. Results of the group approach. (Left) Patients' lesions superimposed on a normal brain (axial sections) for each group. (Right) Task accuracy (mean accuracy of patients compared to mean accuracy of controls) for each patient group and for each condition (Sensory., Context. and Episod. for *sensory*, *contextual* and *episodic* conditions). Vertical bars represent the 0.95 confidence intervals. (A) Lesions and performance of the lateral premotor cortex group (n = 11). Patients appear in pink, controls appear in black. Note that this group showed significant deficits in the three conditions. (B) Lesions and performance of the caudal prefrontal group (n = 9). Patients appear in blue, controls appear in black. Note that this group showed significant deficits in both *contextual* and *episodic* conditions. (C) Lesions and performance of the rostral prefrontal group (n = 6). Patients appear in green, controls appear in black. Note that this group showed an isolated significant deficit in the *episodic* condition.

$p = 0.08$), of years of formal education ($K = 1.02$, $p = 0.59$) and of lesion size ($K = 0.49$, $p = 0.78$).

All patients and controls performed the three cognitive control tasks. Accuracy (percentage of correct responses) and Reaction Times (RTs) were recorded (see Supplementary Table) and analyzed using STATISTICA 6.0 software (Statsoft, Tulsa, USA). Demographic characteristics (effects of age, sex and level of education on accuracy) were analyzed using multiple regression analysis. To maximize statistical power, we analyzed the performance of patients according to the location of their frontal lesion (premotor cortex, caudal PFC or rostral PFC) regardless of their hemispheric lateralization. This analysis was rendered possible because a 3-way ANOVA on accuracy with factors group (premotor cortex, caudal PFC vs. rostral PFC), lesion side (right vs. left) and condition (*sensory*, *contextual* vs. *episodic*), showed an effect of condition ($F = 20.8$, $p = 0.0001$) but no significant interaction effects between condition, lateralization and group (all interactions with factor lateralization: $F < 1.8$, $p > 0.15$). This indicates that behavioral impairments were independent of lesion side, irrespective of patient groups and conditions.

Performance were analyzed using a repeated measures 4-by-3 ANOVA with group (premotor cortex, caudal PFC, rostral PFC, control subjects) as a between-subjects and condition (*sensory*, *contextual* vs. *episodic*) as a within-subjects factor. Due to the small sample group size, an additional non-parametric Kruskal–Wallis ANOVA was also performed to support the parametric study. We a priori hypothesized that an impaired performance in any given task should appear either as a decreased accuracy (i.e., a decrease in the number of correct responses) with normal or longer RTs, or as a normal accuracy but longer RTs.

Results

Demographic characteristics

Preliminary analyses were performed to insure that the main results could not be interpreted according to any other factor than the topography of lesions within the LFC. First, a multiple regression analysis was performed with accuracy as the dependent variable and group (patients or controls), condition (*sensory*, *contextual* or *episodic*), age, sex and years of education as independent variables. This analysis revealed a significant effect of age ($F = 13.4$, $p = 0.0001$) and education ($F = 3.93$, $p = 0.049$) on accuracy. However, neither the "condition * group * age" interaction ($F = 0.53$, $p = 0.589$) nor the "condition * group * education" interaction ($F = 0.32$, $p = 0.730$) had a significant effect on accuracy. These results indicate that age and educational level have a global effect on the experimental paradigm without affecting one group of subjects or one given task more than others. Neither the effect of sex ($F = 1.49$, $p = 0.223$) nor the "condition * group * sex" interaction ($F = 0.58$, $p = 0.559$) were significant. Second, in order to study the effect of lesion etiology on task accuracy, we performed a repeated measures 3-by-3 ANOVA with lesion etiology (stroke, tumor or trauma) as a between-subjects and condition (*sensory*, *contextual* vs. *episodic*) as a within-subjects factor. There was a significant effect of condition ($F = 7.71$, $p = 0.0012$), but there was

no effect of lesion etiology ($p = 0.22$) or interaction between lesion etiology and condition ($p = 0.57$), showing that behavioral impairments were independent of the etiology of lesions.

Voxel-based lesion–behavior mapping

We used a cluster-by-cluster lesion–behavior mapping technique described previously (Kinkingnehun et al., 2007) to identify specific damaged areas associated with behavioral deficits for each level of cognitive control. This technique, based on the superposition of patients' lesions (see Fig. 2A) allows the construction of statistical maps to detect clusters of voxels that significantly contribute to the alteration of performance observed in each condition (Fig. 2B).

A first whole-brain analysis (significance threshold $p = 0.05$, corrected for multiple comparisons) revealed a single area located in the lateral premotor cortex and extending to the surrounding white matter (BA 6, middle frontal gyrus; Talairach coordinates of epicenter: $x = -20$; $y = 14$; $z = 51$, $p = 0.0018$, Fig. 2B) that was significantly associated with a deficit in the *sensory* condition. In the *sensory* condition, accuracy associated with this cluster of lesioned voxels was lower than that of non-lesioned controls (82.6% vs. 99.7%).

A second whole-brain analysis (significance threshold $p = 0.05$, corrected for multiple comparisons) revealed a single cluster of lesioned voxels in the inferior frontal gyrus (*pars triangularis*, BA 45; Talairach coordinates of the epicenter: $x = -40$; $y = 35$; $z = 11$, $p = 6.1 \times 10^{-5}$, Fig. 2B) that was significantly associated with a deficit in the *contextual* condition. In the *contextual* condition, the accuracy associated with this cluster was significantly lower than that of non-lesioned controls (73.4% vs. 96.5%). Moreover, consistent with the cascade model, the lateral premotor region (BA 6) described above was also associated with significant deficits in the *contextual* condition ($p = 0.0013$).

A third whole-brain analysis (significance threshold $p = 0.05$, corrected for multiple comparisons) revealed only two areas specifically associated with a deficit in the *episodic* condition (Fig. 2B). The first area was located in the inferior frontal gyrus (BA 46; Talairach coordinates of the epicenter: $x = -46$; $y = 45$; $z = 4$, $p = 0.0004$), while the second was also located in the inferior frontal gyrus, in the ventrolateral part (BA 47; Talairach coordinates of the epicenter: $x = -35$; $y = 33$; $z = -12$, $p = 0.0001$). In the *episodic* condition, accuracy associated with both clusters of lesioned voxels was significantly lower than that of non-lesioned controls (70.3% for BA 46 and 68.8% for BA 47 vs. 95.9%). Moreover, consistent with the cascade model, the lateral premotor (BA 6) and inferior frontal regions (*pars triangularis*, BA 45) described above were also associated with significant deficits in the *episodic* condition ($p = 0.0018$ in both cases).

RTs were not used for building ANACOM maps because no significant result was obtained in nonparametric tests (see Supplementary Fig. 2).

Group study

Behavioral deficits (Fig. 3) were analyzed using a repeated measures 4-by-3 ANOVA with group (premotor cortex, caudal PFC, rostral PFC, control subjects) as a between-subjects and condition (*sensory*, *contextual* vs. *episodic*) as a within-subjects factor. These analyses showed an effect of condition ($F = 36.9$, $p = 0.0001$), an effect of group ($F = 9.97$, $p = 0.0001$), and a group-by-condition interaction ($F = 3.68$, $p = 0.002$). Post-hoc analyses showed that premotor cortex group was significantly impaired in *sensory* ($p = 0.04$), in *contextual* ($p = 0.009$), and in *episodic* conditions ($p = 0.008$) compared to controls. These analyses also showed that caudal PFC group was not impaired in *sensory* condition ($p = 0.32$), but was significantly impaired in *contextual* ($p = 0.005$) and in *episodic* conditions ($p = 0.002$) compared to controls. Post hoc analyses also showed that rostral PFC group was not impaired in *sensory* ($p = 0.92$) and in *contextual* conditions ($p = 0.35$) but was significantly impaired in *episodic* condition ($p = 0.04$). Moreover, *contextual* control was significantly worse than *sensory* control in the caudal PFC group ($p < 0.0001$) and *episodic* control was significantly worse than *contextual* control in the rostral PFC group ($p = 0.04$).

This parametric analysis was confirmed using a non-parametric Kruskal–Wallis ANOVA, also performed because of the small sample group. This non-parametric Kruskal–Wallis ANOVA was performed with 4 subject groups (lateral premotor cortex, caudal prefrontal cortex, rostral prefrontal cortex and controls) as independent variables and 3 conditions (*sensory*, *contextual*, *episodic*) as dependent variables. As expected, for every condition, we found an effect of group ($Ks > 17.7$, $ps < 0.0001$) on accuracy. Post hoc analyses revealed that the lateral premotor group showed significant deficits in the three conditions ($zs > 3.4$, $ps < 0.003$), that the caudal prefrontal group showed no deficit in the *sensory* condition ($z = 1.53$, $p = 0.74$) but showed significant deficits in both *contextual* and *episodic* conditions ($z = 3.7$, $p = 0.001$ and $z = 3.11$, $p = 0.01$, respectively), and finally, that rostral prefrontal cortex patients showed no deficit in *sensory* and *contextual* conditions ($z = 0.57$, $p = 1$, and $z = 2.1$, $p = 0.18$, respectively) but showed a significant deficit in the *episodic* condition ($z = 2.6$, $p = 0.05$).

RTs were also analyzed using a repeated measures 4-by-3 ANOVA with group (premotor cortex, caudal PFC, rostral PFC, control subjects) as between-subjects and condition (*sensory*, *contextual* vs. *episodic*) as within-subjects factors. These analyses showed a main effect of condition ($F = 106.2$, $p = 0.0001$) and group ($F = 6.5$, $p = 0.001$) with no significant group-by-condition interaction ($F = 1.6$, $p = 0.15$). Although these results did not resist to non-parametric analyses (non-parametric Kruskal–Wallis ANOVA performed with 4 subject groups – lateral premotor cortex, caudal prefrontal cortex, rostral prefrontal cortex and controls – as independent variables and 3 conditions – *sensory*, *contextual*, *episodic* – as dependent variables), they showed that RTs tended to vary in the same direction as error rates. Consequently, differential effects reported above on accuracy could not be ascribed to speed-accuracy trade-off across groups and conditions (see Supplementary Fig. 2).

Discussion

The differential role of distinct lateral frontal regions in cognitive control

Voxel-based lesion–behavior mapping showed that: i) deficits in the *sensory* condition were associated with damage to the lateral premotor cortex (BA 6), ii) deficits in the *contextual* condition were associated with damage to the inferior frontal gyrus (BA 45) or to the lateral premotor cortex (BA 6), and iii) deficits in the *episodic* condition were associated with damage to the anterior prefrontal cortex (BA 46 and BA 47), to the inferior frontal gyrus (BA 45), or to the lateral premotor cortex (BA 6). These results, based on statistical parametric lesion–behavior mapping, are consistent with previous neuroimaging studies using the same experimental cognitive paradigm (Koechlin et al., 2003). The present results show that three lateral frontal sectors from the premotor, to posterior and anterior prefrontal regions are associated with three distinct control levels, namely *sensory*, *contextual* and *episodic* control.

Thus, these three frontal regions are critical for cognitive control. Damage to the lateral and dorsal premotor region significantly contributed to impairments in *sensory* control. Consistent with the present results, previous studies in human and non-human primates using conditional associative tasks have demonstrated that the lateral premotor cortex is crucial for sensorimotor associative learning but not for motor execution per se (Halsband and Freund, 1990; Halsband and Passingham, 1982, 1985; Passingham, 1985; Petrides, 1982; Wise et al., 1983). Further studies have also shown that sensorimotor associative learning involves the dorsal rather than the ventral portion of the lateral premotor cortex (Boussaoud and Wise, 1993; Kurata, 1994; Kurata and Hoffman, 1994). Interestingly, the coordinates of

the damaged premotor area associated with the deficit in the *sensory* task in our study corresponded with those of a functional imaging study showing that the dorsal premotor area is activated by sensorimotor associative learning (Grafton et al., 1998). Taken together, these data suggest that the deficit observed in the *sensory* task in patients with a lateral premotor lesion is due to the inability to perform the sensorimotor association of the task rather than some form of motor impairment.

Damage to a caudal portion of the lateral prefrontal cortex, namely the *pars triangularis* of the inferior frontal gyrus (BA 45) contributed to deficits in the *contextual* task. These deficits are unlikely to result from the verbal material used in this task. Indeed, consistent with previous results (Koechlin et al., 2003), there was no significant difference between the performances of patients with right as opposed to left frontal lesions. Moreover, Broca's area (which includes the left *pars triangularis*) and its homolog on the right hemisphere process hierarchically structured action plans and behaviors, regardless of their verbal component (Koechlin and Jubault, 2006). It is also important to note that the "verbal component" of the *contextual* task consisted of single letters associated with specific motor responses and required no language production. Altogether, these data suggest that the deficit observed in the *contextual* task reflects a deficit in processing contextual information for action selection rather than letter stimuli.

Consistent with previous fMRI results (Koechlin et al., 2003), damage to a more rostral portion of the prefrontal cortex (BA 46 and BA 47) contributed to impairment in the *episodic* task. In addition, converging data from anatomical (Barbas, 1988; Carmichael and Price, 1995; Petrides and Pandya, 2002) and functional imaging (Badre et al., 2005; Wagner et al., 2001) studies have shown that the very same region is involved in functions related to *episodic* control such as the retrieval of relevant information from posterior regions, particularly when the available cues are insufficient to activate relevant knowledge through bottom-up processes. These findings are also consistent with lesion studies in monkeys showing that this rostral portion of the prefrontal cortex is critical for cognitive and attention set switching (Dias et al., 1996; Owen et al., 1991).

Although this voxel-based lesion–behavior mapping provides important information about the respective roles of LFC areas in cognitive control, it is important to take into account that these results can only be interpreted for the prefrontal areas covered by the superimposition of lesions. The results provide no indications about the role of non-covered regions including especially retro-rolandic associative cortical areas and caudal medial prefrontal regions, which are also involved in these tasks (Jubault et al., 2007; Kouneiher et al., 2009). Moreover, frontal lesions were unilateral in this study, leaving the possibility that bilateral lesions may cause more intense deficit. Such a hypothesis is unfortunately very difficult to demonstrate, because very small bilateral lesions affecting separately one of the nodes identified by the present study are extremely rare. Altogether, the fact that lesions were unilateral and did not involve retro-rolandic associative cortices may explain the moderate impairment observed in these frontal patients. Finally, it should be noted that ceiling effects in the performance of controls (especially in *sensory* condition) were present and could therefore limit conclusions regarding lack of differences.

The nature of the frontal organization of cognitive control

Both brain-lesion mapping and the group approach (Fig. 4) show that damage to lateral premotor regions affect all three levels of control (*sensory*, *contextual*, *episodic*), while damage to caudal prefrontal regions affect only *contextual* and *episodic* control and damage to more rostral prefrontal regions affect only *episodic* control. Stated differently, *episodic* task requires *sensory*, *contextual* and *episodic* levels of cognitive control, *contextual* task requires *sensory* and *contextual* levels of cognitive control and the *sensory* task only requires the sensorimotor level of control. Thus, higher control processes involving more anterior prefrontal regions rely on the integrity of lower control processes in more posterior regions, whereas lower control processes can operate irrespective of the integrity of higher control processes. This asymmetry suggests a cascade of cognitive control where the more caudal posterior frontal regions are necessary nodes for ascending processing to prefrontal more rostral areas and/or for descending processing from the more rostral frontal regions. These data are also in accordance with the principle of "functional subsidiarity" (Koechlin, 2007): higher-level controls implemented in more anterior prefrontal regions are engaged only when lower-level controls cannot achieve action selection. Overall, our results agree with anatomical data in non-human primates showing asymmetrical cortico-cortical connections between rostral and caudal frontal regions (Barbas and Pandya, 1987; Petrides and Pandya, 2007), and with effective connectivity data from the human frontal cortex (Koechlin et al., 2003).

Our study, by providing evidence for an asymmetric cascade of cognitive control based on functional subsidiarity, allows replicating findings shown in a previous lesion study (Badre et al., 2009). However, the present study appears to extend these anterior findings, most notably by providing evidence for three distinct levels of control whereas only two levels ("feature" and "dimension" levels) were demonstrated in the previous study. Furthermore, the present study is more accurate for the location of critical frontal regions, supported by the relatively large sample of patients and the voxel-lesion mapping method. Moreover, lesion studies provide convincing evidence for the critical and specific role of a brain region whereas functional imaging studies only show the involvement of a region in the specific studied process.

Taken together, our findings complement results of a previous lesion study as well as functional imaging data by showing both "criticality"

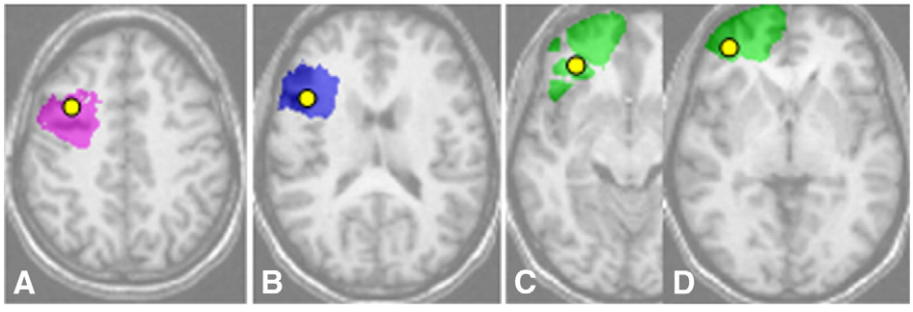

Fig. 4. Converging results of the two approaches. Lesions of the three patient groups (from the group approach) and significant damaged areas (from the lesion–behavior statistical mapping) superimposed in a normal brain (axial sections). (A) In pink, superimposed lesions of the lateral premotor group. The yellow point shows the damaged area significantly associated with a deficit in the *sensory* condition (BA 6, $x = -20$; $y = 14$; $z = 51$). (B) In blue, superimposed lesions of the caudal prefrontal group. The yellow point shows the damaged area significantly associated with a deficit in the *contextual* condition (BA 45, $x = -40$; $y = 35$; $z = 11$). (C and D) In green, superimposed lesions of the rostral prefrontal group. The yellow points show damaged areas significantly associated with deficits in the *episodic* condition (C: BA 47, $x = -35$; $y = 33$; $z = -12$, D: BA 46, $x = -46$; $y = 45$; $z = 4$). Note that the results of the two different approaches converge.

and "interdependency" of three distinct LFC regions for the three levels of cognitive control.

Temporal vs. complexity gradient in cognitive control

The nature of the cascade of cognitive control is still a matter of debate. Indeed, different hypotheses are being discussed. Some authors have proposed that progressively more anterior regions are recruited when the relational complexity of behavioral rules increases, i.e. hypotheses of "relational abstraction" (Badre and D'Esposito, 2007) or "integration demand" (Nee et al., 2013). Others have proposed that the lateral prefrontal cortex is organized along a caudo-rostral axis according to a temporal dimension, i.e. the temporal structure of events involved in action selection named "*episodic* control" (Koechlin and Summerfield, 2007; Koechlin et al., 2003) or an "active maintenance of working memory" (Reynolds et al., 2012).

Our lesion study was not designed to test these main hypotheses because manipulation of entropy was made difficult by the deficit of patients. However, data from the initial study testing decision-making in fMRI with a close but full paradigm (Koechlin et al., 2003) have provided further evidence for a temporal organization of cognitive control than for a complexity gradient. Further works are thus useful to address this issue in patients with frontal lesions.

Conclusion

To summarize, our study found that the impairment of each cognitive control level was associated with damage to distinct areas of the lateral frontal cortex along the caudo-rostral axis, as previously observed in neuroimaging studies. Second, this study showed that higher control processes implemented in more anterior prefrontal regions were disrupted following damage to posterior prefrontal regions, while the converse was not observed. Altogether, these findings support the idea that cognitive control is organized as a cascade of executive processes from premotor to anterior prefrontal regions.

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Conflict of Interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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