

Impaired Hierarchical Control Within the Lateral Prefrontal Cortex in Schizophrenia

Guillaume Barbalat, Valerian Chambon, Philippe J.D. Domenech, Chrystèle Ody, Etienne Koechlin, Nicolas Franck, and Chlöé Farrer

Background: In schizophrenia, disturbances of cognitive control have been associated with impaired functional specialization within the lateral prefrontal cortex (LPFC), but little is known about the functional interactions between specialized LPFC subregions. Here, we addressed this question with a recent model that describes the LPFC functioning as a cascade of control processes along a rostrocaudal axis, whereby anterior frontal regions influence the processing in posterior frontal regions to guide action selection on the basis of the temporal structure of information.

Methods: We assessed effective connectivity within the rostrocaudal axis of the LPFC by means of functional magnetic resonance imaging in 15 schizophrenic patients and 14 matched healthy control subjects with structural equation modeling and psychophysiological interactions.

Results: In healthy subjects, activity in the left caudal LPFC regions was under the influence of left rostral LPFC regions when controlling information conveyed by past events. By contrast, schizophrenic patients failed to demonstrate significant effective connectivity from rostral to caudal LPFC regions in both hemispheres.

Conclusions: The hierarchical control along the rostrocaudal axis of the LPFC is impaired in schizophrenia. This provides the first evidence of a top-down functional disconnection within the LPFC in this disorder. This disruption of top-down connectivity from rostral to caudal LPFC regions observed in patients might affect their ability to select the appropriate sets of stimulus-response associations in the caudal LPFC on the basis of information conveyed by past events. This impaired hierarchical control within the LPFC could result from poorly encoded contextual information due to abnormal computations in the caudal LPFC.

Key Words: Effective connectivity, functional magnetic resonance imaging, hierarchical control, lateral prefrontal cortex, rostrocaudal axis, schizophrenia

In schizophrenia, disturbances of cognitive control, the ability to coordinate thoughts and actions in relation to internal goals, have been robustly associated with impaired functional specialization within the lateral prefrontal cortex (LPFC) (1–6). Recent models suggest that cognitive control is constructed as a set of hierarchical modules that involve selecting and maintaining goals at multiple levels of abstraction, from general task goals at higher levels (such as watching a movie in the cinema) to concrete motor responses at the lowest levels (such as taking transport to go to the cinema, buying a ticket at the box office, or sitting comfortably in front of the screen) (7). Such a behavioral hierarchy has been shown to be subserved by a hierarchical organization along the rostrocaudal axis of the LPFC, where more anterior regions are associated with progressively more abstract action control, whereas more posterior regions process more concrete information about action (i.e., action that is closer to the actual motor output) (8). Furthermore, there seems to be a dominance relationship whereby more anterior regions that process abstract, superordinate, domain-general rules, modulate domain-specific, subordinate, posterior regions (9).

From the Centre de Neurosciences Cognitives, (GB, VC, PD, NF), UMR 5229 CNRS, Université Claude Bernard Lyon1, Lyon, France; Centre Hospitalier le Vinatier (NF), Lyon; Institut National de la Santé Et de la Recherche Médicale (CO, EK), Université Pierre et Marie Curie and École Normale Supérieure, Paris; and Université de Toulouse (CF), CerCo, UPS and UMR5549 CNRS, Faculté de Médecine de Rangueil, Toulouse, France.

Authors VC and PJDD contributed equally to this work.

Address correspondence to Guillaume Barbalat, M.D., Ph.D. Centre de Neurosciences Cognitives Université Claude Bernard Lyon, 67, bd Pinel, 69 675 BRON, Cedex, France; E-mail: gbarbalat@isc.cnrs.fr.

Received Dec 30, 2009; revised Jan 31, 2011; accepted Feb 1, 2011.

0006-3223/\$36.00
doi:10.1016/j.biopsych.2011.02.009

We previously investigated the overall organization of cognitive control within the LPFC in schizophrenia with an influential model (10) that describes the architecture of cognitive control as a cascade of executive modules ranging from premotor to more anterior LPFC regions (3,11). This model includes a sensory control level involved in selecting the motor responses that are the most appropriate to stimuli that occur and subserved by the lateral premotor regions (typically, Brodmann Area [BA] 6). A contextual control level is then involved in selecting premotor representations (i.e., stimulus-response associations) according to contextual signals that accompany the occurrence of stimuli. This control is subserved by the caudal part of the LPFC (typically, BAs 9/44/45). Finally, the episodic control level is involved in selecting caudal LPFC representations (task-sets or consistent sets of stimulus-response associations evoked in the same immediate, perceptual context) according to the temporal episode in which stimuli occur. This control is subserved by the rostral part of the LPFC (typically, BAs 46/10).

We demonstrated that, although the lower-order, less abstract, sensory level of cognitive control was spared in schizophrenia, contextual control was significantly impaired (11), which was related to hypoactivation in the caudal LPFC regions (3). With regard to episodic control, we found mixed but consistent findings. When no contextual signals were involved in the task, there was no behavioral disturbance of episodic control in schizophrenia (11). By contrast, adding contextual signals in the task reduced this level of cognitive control. In other words, this impaired episodic control process refers in fact to a dysfunctional interaction between the “episodic” and the “contextual” modules (3,11).

At the neural level, this disturbed episodic control process in schizophrenic patients was not reflected by any hypoactivation in the rostral LPFC. By contrast, we found a hyperactivation in this region, which we interpreted as a consequence of the added effort that patients might expend to retrieve the poorly integrated contextual information (2,3,12,13). However, the neural substrates underlying this dysfunctional control of episodic signals remain unknown.

BIOL PSYCHIATRY 2011;70:73–80
© 2011 Society of Biological Psychiatry

According to the functional disconnection hypothesis proposed by Friston (14), such a dysfunctional interaction between two cognitive processes should result from dysfunctional interaction in the dynamics of the brain regions subserving these processes rather than dysfunctional specialization within a specific region. The framing of the cascade model further predicts that this impairment in episodic control would depend on the way rostral LPFC exerts its influence on the caudal LPFC regions (9). However, until now, studies that have investigated the interaction between specialized neural systems related to executive dysfunctions in schizophrenia have demonstrated altered LPFC connectivity with other cortical structures such as the inferior parietal lobule (5), the hippocampus (15), or the anterior cingulate cortex (16) but have not directly studied the functional integration of the different cognitive control modules within the LPFC itself.

The goal of this follow-up study was to test whether the perturbed control of temporal episodic signals in patients reflects a dysfunction in the top-down selection of caudal LPFC representations by rostral LPFC. For this purpose, we based our analysis on data collected in our previously published study (3) and measured effective connectivity between LPFC regions involved in controlling episodic and contextual signals in both groups with structural equation modeling (SEM) and psychophysiological interactions (PPIs).

Methods and Materials

Subjects

This analysis initially involved 15 schizophrenic patients ($n = 15$) and 15 matched healthy control subjects, 1 of whom was excluded because of excessive motion in the scanner ($n = 14$) (3). For more details about the description of the participants, please refer to Supplement 1 (see also Table 1).

Experimental Paradigm

The experiment included eight scanning sessions, each consisting of eight separate blocks presented in a counterbalanced order. Each block comprised a series of 12 successive stimuli (colored letters; duration: 500 msec; onset asynchrony: 3500 msec) preceded by an instruction cue lasting 4200 msec (Figure 1). Each instruction

informed the subjects to make speeded responses to stimuli by pressing left or right hand-held response buttons or to withhold a response to a no-go stimulus. Instructions were prelearned by the subjects before running the experiment to avoid possible biases due to learning effects during the test session.

In each scanning session, the eight blocks formed four distinct experimental conditions crossing the demands of contextual and episodic control varied by manipulating the context (I_{con}) and the episode (I_{epi}) factors, respectively. These variations were quantified according to the computational model from Koechlin *et al.* (10), on the basis of Shannon's information theory (17).

The color of the letter was the contextual signal within each block. According to the contextual signal, subjects had to perform one of three tasks: 1) ignore the letters; 2) a vowel/consonant discrimination task (T1: if the letter is a vowel, press the right response button; if the letter is a consonant, press left); or 3) a lower/uppercase discrimination task (T2: if the letter is uppercase, press right; if the letter is lowercase, press left). Where contextual control was low, the task remained the same across the entire block (T1 or T2, single-task-set blocks, $I_{con} = 0$ bit; block no. 1,2,5,6 in Figure 1). In high contextual control blocks, the task changed from trial to trial (T1 and T2, dual task-set blocks, $I_{con} = 1$ bit; blocks no. 3,4,7,8 in Figure 1).

The episodic signal was by definition the instruction cue preceding each block. Episodic signals conveyed information about the contingencies linking contextual signals (i.e., the color of the letter) and task-sets (i.e., T1 or T2) that occurred in the preceding sequence of letters and were chosen to parametrically vary the amount of episodic information across blocks. Therefore, the episode factor was the covariate of interest that contrasted episodes according to the episodic information I_{epi} conveyed by instruction cues that were required for subsequently selecting appropriate task-sets with respect to contextual signals ($I_{epi} = 0$ to 1 and 2 bits). For example, in Block No. 1, the instruction cue indicated that, if the letter is white, no response should be given, whereas if the letter is green, the subjects should perform task T1 (Figure 1). Then, with information theory, we computed different values for the episodic control demand, such that the more frequent the crosstemporal

Table 1. Clinical and Demographic Characteristics

| Characteristic | Patients ($n = 15$) | Comparison Subjects ($n = 14$) | p |
|---|-----------------------|----------------------------------|-----|
| Male Gender, n (%) | 8 (53) | 8 (57) | .68 |
| Age, yrs | 35 (10.5) | 36 (10.6) | .79 |
| Education, yrs | 11 (1.3) | 11 (1.9) | .82 |
| Handedness | .86 (.09) | .84 (.11) | .50 |
| Duration of Illness, yrs | 10 (9) | — | — |
| SANS Score | 43 (19) | — | — |
| SAPS Score | 23 (21) | — | — |
| Reality Distortion Score ^a | 8 (10) | — | — |
| Poverty Score ^b | 34 (18) | — | — |
| Disorganization Score ^c | 23 (13) | — | — |
| Chlorpromazine-Equivalent ^d , mg/day | 247 (190) | — | — |

Values are mean \pm SD, unless otherwise indicated.

SANS, Scale for the Assessment for Negative Symptoms (50). SAPS, Scale for the Assessment of Positive Symptoms (51).

^aSum of the scores for hallucinations and delusions from the SAPS.

^bSum of the scores for poverty of speech, flat affect, anhedonia/asociality, and amotivation from the SANS.

^cSum of the scores for formal thought disorder and bizarre behavior from the SAPS and the score for attention from the SANS.

^dDepot doses of and daily-oral atypical antipsychotics at the time of the examination (risperidone in 6 patients, olanzapine in 3 patients, amisulpride in 3 patients, and aripiprazole in 2 patients) were converted to average daily chlorpromazine-equivalent doses. None of the patients received a concurrent typical antipsychotic, anticholinergic agent, sedative treatment, mood stabilizer, antidepressant, or other psychotropic agent.

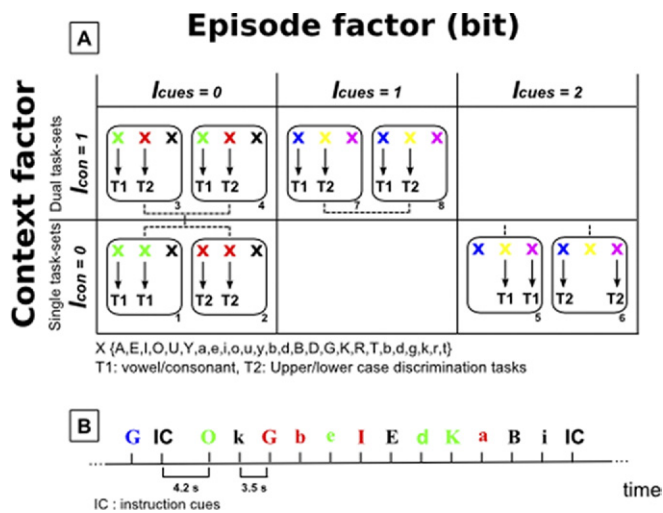


Figure 1. Experimental design. **(A)** Rounded boxes represent behavioral episodes (numbered from no. 1 to no. 8) with related stimuli (letters) and instructions. Episodes formed four distinct experimental conditions crossing the episodic factor with the context factor. According to the color of the letter (contextual signal), subjects either ignored the letter or performed a vowel/consonant (T1) or lower/uppercase (T2) discrimination task on the letters. Block no. 1: contextual signals were either green or white. White signals indicated that subjects should ignore the letter. Green signals indicated that subjects should perform task T1 (single task-set episode). Block no. 2: contextual signals were either red or white. White signals indicated that subjects should ignore the letter. Red signals indicated that subjects should perform task T2 (single task-set episode). Blocks no. 3 and no. 4: contextual signals were green, red, or white. Subjects responded to letters as described for blocks no. 1 and no. 2 (dual task-set episode). Blocks no. 5: contextual signals were yellow, blue, or purple. Blue signals instructed subjects to ignore the letters. Yellow and purple signals instructed subjects to perform task T1 (single task-set episode). Block no. 6: contextual signals were yellow, blue, or purple. Yellow signals instructed subjects to ignore the letters. Blue and purple signals instructed subjects to perform task T2 (single task-set episode). Blocks no. 7 and no. 8: contextual signals were yellow, blue, or purple. Purple signals instructed subjects to ignore the letters. Blue and yellow signals instructed subjects to perform tasks T1 and T2, respectively (dual task-set episode). Dashed lines connect episodes involving congruent associations between contextual signals and task-sets. **(B)** Typical episode.

contingencies between contextual signals and task-sets, the lower the amount of episodic information—thus the lower the demand of episodic control. More specifically, the episodic control demand depended on the proportion f of episodes involving congruent associations between contextual signals and task-sets over the whole experiment. When this proportion was maximal ($f = 1$, such as in blocks no. 1,2,3,4 where green always denoted “T1,” red always denoted “T2,” and white was always “no-go”), the demand of episodic control was low ($I_{epi} = 0$ bit). By contrast, the decrease of this frequency ($f < 1$, such as in blocks no. 5,6,7,8 where blue, purple, and yellow could all denote “T1,” “T2,” or “no-go”) led to an increase in the episodic control demand ($I_{epi} > 0$ bit). Because the same crosstemporal contingencies were involved in blocks no.7 and no. 8, these two blocks had a lower episodic control demand ($I_{epi} = 1$ bit) than that in blocks no. 5 or no. 6, which contained different crosstemporal contingencies ($I_{epi} = 2$ bits).

In each block, the proportion of letters to be ignored was 33%. In dual task-set blocks, the ratio of trials associated with task-set T1 versus task-set T2 was equal to 1. Finally, in each block, the ratio of left versus right responses was equal to 1, and the ratio of congruent versus incongruent letters (same vs. different responses for T1

and T2) was equal to 1. Accordingly, sensorimotor control was constant across the experiment.

The methods for the behavioral analyses, magnetic resonance imaging (MRI) procedures and preprocessing, delimitation of the regions of interest, and regions of interest analyses are reported in Supplement 1.

Effective Connectivity Analyses

We investigated, on the basis of anatomical and functional connections in the frontal lobes described previously (10,18), the existence of a top-down control system from rostral to caudal LPFC regions (identified by the exploratory analyses in each of the two groups, see Supplement 1).

Structural Equation Modeling

The structural equation model included top-down paths from rostral to caudal regions as well as additional reciprocal paths linking the same regions located in the left and right hemispheres to account for callosal interhemispheric connections. The functional model was therefore reformulated as a model of structural linear equations with path coefficients quantifying effective connectivity as partial temporal correlations between related regional activations.

We sought to test the prediction of the cascade model that path coefficients from rostral to caudal LPFC regions significantly increase with the demand of episodic control rather than contextual control (10). Subject-specific time series of functional MRI signals were obtained at activation peaks, averaged over subjects, and standardized in each condition (mean and variance were equated across conditions). The resulting time series were then used for structural model estimation and statistical inference on the basis of maximum-likelihood statistics. We assessed significant variations of path coefficients within each group with a nested model approach (19) (see also Supplement 1). Variations of path coefficients related to the episode and context factors were estimated from variations in interregional correlation matrices observed between all episodes with $I_{epi} = 0$ versus $I_{epi} > 0$ and $I_{con} = 0$ versus $I_{con} = 1$, respectively.

PPIs

To account for between-subject variability and to make a statistical inference about group differences in effective connectivity within the LPFC, we computed pair-wise PPI between LPFC regions (20).

Here, we specifically sought to test whether substantial variations from rostral to caudal LPFC activity resulted from underlying neuronal interactions with the episodic factor in both hemispheres (i.e., from the condition where the episodic control demand was low— $I_{epi} = 0$ bit—to the condition where the episodic control demand was high— $I_{epi} = 2$ bits—with $I_{con} = 0$ bit). For each of the regions identified by the exploratory voxel-wise contrasts, individual time-series were extracted at the peak voxel and standardized in each condition. Then, treating intersubject variability as a random factor, we tested whether the slopes (β) of the regression of caudal LPFC activity against rostral LPFC activity significantly increased as a function of the episodic factor within each group and between groups (from β_{low} , the slope when $I_{epi} = 0$, to β_{high} , the slope when $I_{epi} = 2$ bits) (see Supplement 1 for more details). Note that these PPI analyses are orthogonal with the ones issued from our previous report (3).

Results

Patients made significantly more errors than control subjects with regard to both the context and the episode factors (Figure 2). Because this poor performance in patients might confound

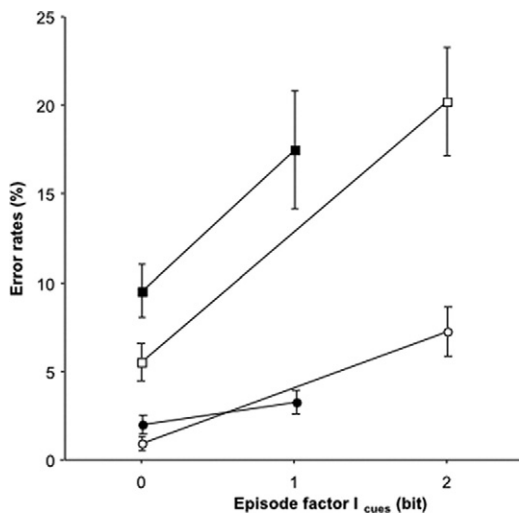


Figure 2. Behavioral results. Error rates (%; mean ± SE across participants) across experimental conditions. Open circles and squares indicate single task-set episodes in control subjects and schizophrenic patients, respectively. Solid circles and squares indicate dual task-sets episodes in control subjects and schizophrenic patients, respectively.

changes in functional brain activation, we matched groups for accuracy by removing from the analyses blocks in which performance was unsatisfactory (i.e., accuracy < .65) (see Tan *et al.* [4] for the use of a similar threshold) (see also Supplement 1 for more details). After applying this criterion, there were no behavioral differences between the two groups with regard to both the episode and the context factors [$F(1,81) < .21, p > .05$].

In each of the two groups, we first identified rostral and caudal LPFC as the LPFC regions involved in controlling episodic and contextual signals, respectively (Table 2). Caudal LPFC regions demonstrated a group × context interaction [$F(1,81) = 3.76, p = .05$], with patients showing no modulation of activation related to the contextual factor in these regions (Figure S1 in Supplement 1). By

contrast, caudal LPFC regions demonstrated neither a main effect of group nor an interaction between group and episode [$F(1,81) < 1.15, p > .05$]. Finally, we found a group effect in rostral LPFC regions [$F(1,81) = 6.97, p < .05$], with patients activating this region more than control subjects.

Structural Equation Modeling Analyses

The cascade model predicts that contextual control involves no top-down control from anterior to more posterior LPFC regions (10,18). Indeed, when the demand of contextual control increased, no path coefficients were found to significantly increase from rostral to caudal LPFC regions with the context factor in both groups [all $\chi^2(1) < 3.36, p > .05$; Figure 3].

By contrast, the model predicts that path coefficients from rostral to caudal LPFC regions will significantly increase with the demand of episodic control (10,18). Indeed, when the demand of episodic control increased, a significant increase of path coefficients was found in healthy subjects from rostral to caudal left LPFC regions [$\chi^2(1) = 4.44, p < .05$; in the right hemisphere: $\chi^2(1) = .23, p > .05$; Figure 3]. This left lateralization might result from the exclusive use of verbal material (letter stimuli), which is preferentially processed in the left hemisphere (21). In patients, however, no path coefficients significantly increased with the episodic factor from rostral to caudal LPFC regions in either hemisphere [$\chi^2(1) < 1.96, p > .05$; Figure 3].

PPI Analyses

In control subjects, the significant variations of path coefficients from rostral to caudal LPFC regions reported in the SEM analysis corresponded to a significant PPI between activity in rostral and caudal LPFC regions related to the episodic factor (Figure 4). In other words, the strength of the regression between activity in caudal and rostral LPFC regions depended on the episodic factor (from $I_{epi} = 0$ to $I_{epi} = 2$ bits). Indeed, we found a significant increase in the regression slopes (β) of left caudal LPFC activity against left rostral LPFC activity as a function of the episodic factor [$F(1,459) = 8.9, p < .005$; $\beta_{low} = -.04$; $\beta_{high} = .43$; Figure 4A]. In patients,

Table 2. Within-Group Localization of the LPFC Regions Displaying Episode and Context Effects Used for the Effective Connectivity Analyses

| Group, Effect, and Lateral Frontal Cortex Region | Estimated BA | Coordinates ^a | | | Analysis t^b | Volume ^c | FDR p |
|--|--------------|--------------------------|----|----|----------------|---------------------|---------|
| | | x | y | z | | | |
| Healthy Subjects | | | | | | | |
| Context effect ^d | | | | | | | |
| Left middle frontal gyrus, caudal PFC | BA 9 | -42 | 39 | 36 | 6.27 | 37,084 | .038 |
| Right middle frontal gyrus, caudal PFC | BA 9 | 42 | 33 | 39 | 5.21 | 8277 | .038 |
| Episode effect (excluding context effect) | | | | | | | |
| Left superior frontal gyrus, rostral PFC | BA 10 | -27 | 54 | -3 | 4.23 | 185 | .037 |
| Right middle frontal gyrus, rostral PFC | BA 10 | 33 | 63 | 9 | 3.49 | 139 | .037 |
| Schizophrenia Patients | | | | | | | |
| Context effect ^d | | | | | | | |
| Left middle frontal gyrus, caudal PFC | BA 9 | -33 | 42 | 12 | 4.92 | 2867 | .087 |
| Right middle frontal gyrus, caudal PFC | BA 9 | 33 | 36 | 27 | 4.41 | 786 | .087 |
| Episode effect (excluding context effect) | | | | | | | |
| Right middle frontal gyrus, rostral cortex | BA 10 | 27 | 51 | 0 | 4.77 | 8046 | .026 |
| Left middle frontal gyrus, rostral cortex | BA 46 | -36 | 48 | 9 | 4.02 | 1295 | .026 |

LPFC, lateral prefrontal cortex; BA, Brodmann’s Area; FDR, false discovery rate; PFC, prefrontal cortex.

^aCoordinates from the stereotaxic atlas of Talairach and Tournoux (52).

^bRegional peak activation representing blood oxygen-level dependent signal change that reached a threshold of $p < .05$ (corrected for the false discovery rate) in a random-effect analysis.

^cValues are mm³.

^dThese peaks are nonsignificant but are reported because we do not want to give the impression that the activations are absent in schizophrenia patients regarding the context effect.

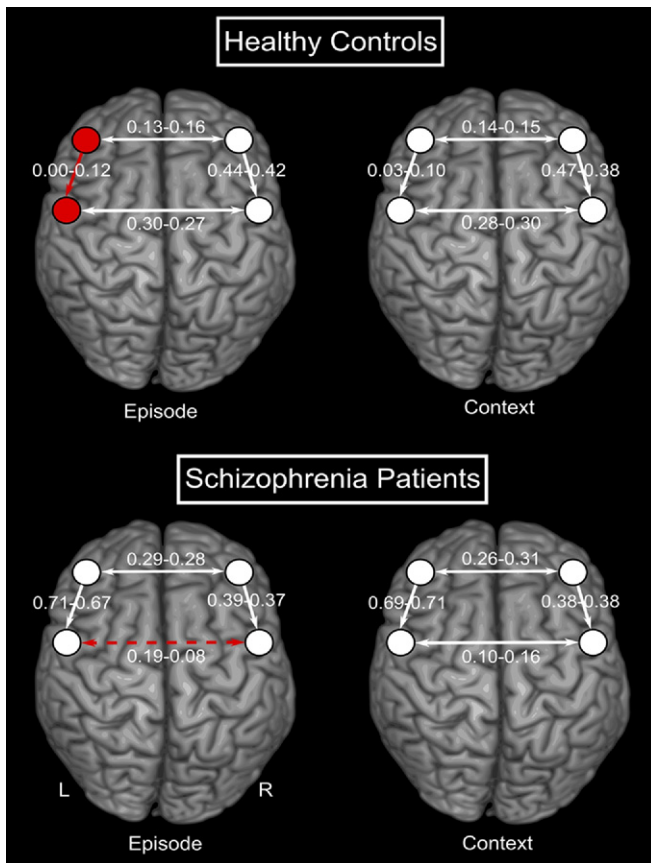


Figure 3. Diagram of path coefficients between lateral prefrontal regions involved in episodic and contextual control subjects for healthy subjects and schizophrenic patients. The structural equation model included the paths (lines, arrows indicate oriented structural paths) connecting prefrontal regions described in the text (circles, neurological convention, approximate locations). Variations of path coefficients in healthy subjects (upper panels) and in schizophrenic patients (lower panels) are shown. **(Left)** Path coefficients in episodes associated with $I_{epi} = 0$ (left number) and $I_{epi} > 0$ (right number). **(Right)** Path coefficients in single-task-set (left number) and dual-task-sets (right number) episodes. Path coefficients that significantly increased with the episodic factor are shown in red. No path coefficients were found to significantly increase with the context factor. The red dashed arrow in the left lower panel indicates a path coefficient that significantly decreased with the episode factor in patients [$\chi^2(1) = 15.78, p < .001$].

however, we found a significant decrease in the regression slopes of left caudal LPFC activity against left rostral LPFC activity as a function of the episodic factor [$F(1,492) = 8.9, p < .01; \beta_{low} = .60; \beta_{high} = .42$; Figure 4B]. We observed no significant PPI between rostral and caudal LPFC regions related to the episodic factor in the right hemisphere in either group ($F < 1.8, p > .05$; Figures 4C and 4D). Finally, we observed no significant PPI between rostral and caudal LPFC regions related to the contextual factor in both hemispheres, in either group ($F < 3.0, p > .05$), which confirmed the results of our SEM analysis.

We observed stronger effective connectivity from rostral to caudal LPFC regions related to the episodic factor in control subjects than in patients in the left hemisphere [left hemisphere: interaction among rostral LPFC activity, the episodic factor and the group factor: $F(1,951) = 16.6, p < .001$; right hemisphere: no interaction, $F(1,951) = .8, p > .05$]. The β value was significantly greater in the low-episodic control condition in patients than in control subjects [interaction between rostral LPFC activity and the group factor:

$F(1,462) = 14, p < .001$]. In contrast, the β values were nonsignificantly different between the two groups in the high-episodic control condition [rostral LPFC activity \times Group interaction: $F(1,462) = .01, p > .05$].

Finally, one could argue that the reduced rostrocaudal connectivity in patients could result from a bias in the analyses, because we excluded blocks in which accuracy was $< .65$ to prevent a performance bias. This manipulation could indeed have reduced the power of the analysis of the schizophrenia dataset relative to the control subjects. However, when rerunning the analysis with the whole dataset in both groups, we still found significantly less modulation of the caudal LPFC by the rostral LPFC in patients relative to control subjects with regard to the episodic factor in the left hemisphere [left hemisphere: interaction among rostral LPFC activity, the episodic factor, and the group factor, $F(1,951) = 10, p < .005$; right hemisphere: no interaction, $F(1,951) = .04, p > .05$].

Discussion

Our analyses support the idea that, in healthy subjects, the LPFC is hierarchically organized from rostral to caudal LPFC regions, where anterior regions integrate temporally dispersed information for selecting the appropriate action at each time from posterior LPFC regions (8–10,18,22). By contrast, we found impaired hierarchical control along the rostrocaudal axis of the LPFC in individuals with schizophrenia.

It is worth noting that our sample of patients was treated with atypical antipsychotics, which could potentially perturb the effective connectivity through the frontal cortex in schizophrenic patients. However, impaired effective connectivity within the frontal lobes has been observed in drug-naïve as well as in medicated patients, making this potential confound a less likely explanation of our findings (23,24). Another potential limitation of our findings pertains to the difficulty of the task itself. Because the task was relatively complicated, it is likely that the patients who participated in the study performed much better than other patients with lower levels of education or more florid positive or negative symptoms would. That being said, we are quite confident that our results are reproducible, provided that they involve clinically stable patients with a minimum level of education, as in the current experiment. Indeed, a previous study from our group found the same pattern of behavioral results (i.e., contextual and episodic control impairments in patients) with a different sample of subjects (11). Moreover, although our functional MRI findings are novel, they support other studies showing hypoactivation in the caudal LPFC in schizophrenia (1,2,4,5,13,25–27) and are consistent with our initial hypotheses.

According to the cascade model, rostral LPFC regions are involved in selecting caudal LPFC representations to monitor the appropriate selection of task-sets evoked in the same context, a process referred to as episodic control (10). More specifically, the episodic control demand depends on the proportion f of episodes involving congruent associations between contextual signals and task-sets. When this proportion is maximal ($f = 1$, such as in blocks no. 1, 2, 3, and 4 in our task), the demands on episodic control are low, which is paralleled by a decrease in top-down connectivity from rostral to caudal LPFC regions. By contrast, the decrease in this frequency ($f < 1$, such as in blocks no. 5, 6, 7, and 8) leads to an increase in episodic control demands and in rostrocaudal connectivity within the LPFC. In the current study, we demonstrated that this modulation of top-down LPFC connectivity by the demands of episodic control was impaired in schizophrenia. Crucially, this might have affected the ability of patients to select the appropriate

Figure 4. Psychophysiological interaction (PPI) between rostral and caudal lateral prefrontal cortex (LPFC) in healthy subjects and schizophrenic patients. Measurements when the demand of episodic control is low ($I_{\text{epi}} = 0$ bit), green crosses; measurements when the demand of episodic control is high ($I_{\text{epi}} = 2$ bits), red crosses. Condition-specific regression slopes, β_{low} (i.e., when $I_{\text{epi}} = 0$ bit) and β_{high} (i.e., when $I_{\text{epi}} = 2$ bits). All subjects are plotted together. The difference between regression slopes constitutes the PPIs. **(A and B)** Mean-corrected blood oxygen-level dependent (BOLD) activity (in arbitrary units) in left caudal LPFC is displayed as a function of the mean-corrected BOLD activity in left rostral LPFC. **(C and D)** Mean-corrected BOLD activity in the right caudal LPFC is displayed as a function of mean-corrected BOLD activity in right rostral LPFC.

sets of stimulus-response associations in the caudal LPFC on the basis of the information conveyed by past events.

Previous findings from our group demonstrated that this impaired episodic control process was specifically observed when patients had to control information conveyed by episodic and contextual (vs. sensory) signals (11). This result suggests that episodic control disturbances could arise from inappropriate contextual control, which is itself related to abnormal activation of the caudal LPFC (3). Other findings from the schizophrenia literature have also proposed that a context processing impairment could be at the core of the cognitive control disturbances in schizophrenic patients, related to specific disturbances in the dorso-caudal LPFC (1,2,26–30). In other terms, the disruption of top-down connectivity from rostral to caudal LPFC regions in patients could primarily be the consequence of poorly encoded contextual information, which might be due to abnormal computations in the caudal LPFC. In turn, hyperactivation in rostral LPFC regions might serve as a compensatory function to maintain a minimum level of performance during episodic control (i.e., to retrieve the poorly integrated contextual information) (12,13).

At a more distal level, our results suggest that this impaired effective connectivity within the LPFC in patients is related to abnormally high levels of connectivity between rostral and caudal LPFC regions in the low-episodic control condition (the regression

coefficient between rostral and caudal LPFC activities was significantly greater in patients than in control subjects in the low-episodic control condition, whereas the groups did not significantly differ in the high-episodic control condition). It is interesting to note that such an increase in connectivity in low-level conditions, together with a relative decrease in higher-level conditions of cognitive control, is conceptually analogous to findings from previous studies that also investigated cognitive control in schizophrenia, with computational models of context processing (31). Specifically, it was suggested that increased noise in the subcortical dopamine system at rest (32,33) leads to abnormal “gating” of context information into prefrontal cortex (34–35). Although these findings deal with distinct types of information (contextual vs. episodic signals), one cannot exclude that these two phenomena both rely on the same neurobiological mechanism responsible for “gating” different classes of information into specialized subregions within the prefrontal cortex.

Other hypotheses closely related to the concept of episodic control have been proposed to better characterize the impaired processes involved in episodic task performances in schizophrenia. One hypothesis highlights the importance of cognitive control and related LPFC functioning in episodic memory disturbances in schizophrenia (25,36). The cascade model claims that episodic control monitors the flexible and temporary reinstatement of episodic

information (e.g., past events, rules, or task instructions) to modulate action selection across a behavioral episode (9). As such, episodic control can be understood as the process that supervises the retrieval of information from episodic memory (37–39). Consistently, other studies have found that rostral LPFC activations were observed in episodic memory paradigms in retrieval phases, when subjects selected actions on the basis of the occurrence of previous events (40–43). Therefore, our finding of an impaired episodic control process related to a perturbed rostrocaudal hierarchy within the LPFC could represent a potential cause for the episodic memory retrieval disturbances in schizophrenia—a hypothesis that should be further investigated in the future.

Another well-known concept intimately related to episodic control, as defined by the cascade model, is the so-called “episodic buffer,” a new component included in the former working memory model (44). Indeed, the cascade model generalizes the classical theory of executive control on the basis of a central executive system controlling multiple slave systems, inspired from the working memory framework (45). In those two models, each stage maintains active representations that are controlled by higher stages and that exert control on representations at lower stages. Recently, the episodic buffer has been defined as a new temporary system, thought to be biologically implemented by the frontal areas (44). Crucially, the episodic buffer is important for integrating representations of information bound in a multimodal code being entered into or retrieved from long-term episodic memory (44). Executive processes engaged in the episodic domain (i.e., episodic control) could thus be conceptualized as mechanisms that monitor the binding between different temporal features of information into a temporary, unitary, and coherent representation of events (i.e., within the episodic buffer). Our findings therefore suggest a core impairment in control processes devoted to building a new, consistent, multi-featured representation of temporally dispersed contextual signals, which might account for the perturbations of the episodic buffer observed by others in schizophrenia (46,47).

This impaired functional connectivity between rostral and caudal LPFC regions supports the functional disconnection hypothesis in schizophrenia initially proposed by Friston (14). We also provide, to the best of our knowledge, the first evidence of a top-down disconnection within the LPFC in this disorder. Because the anatomical connectivity within the LPFC was not found to be disrupted in schizophrenia (48,49), we suggest that our result reflects something more dynamic in the way those areas function as a whole to produce cognitive control (e.g., via impaired synaptic transmission) (14).

Finally, in addition to its clinical implications with regard to the pathophysiology of cognitive disturbances of schizophrenic patients, we believe that this result has more general theoretical implications. Indeed, there has recently been a growing interest in the study of the hierarchical organization of cognitive control within the rostrocaudal axis of the frontal lobes, either in healthy subjects (18) or in patients with frontal lobe damage (22). The present study provides additional support confirming that this hierarchy might be a fruitful framework in which to investigate frontal lobe architecture and its pathology.

This research was supported by a grant of the Conseil Scientifique de la Recherche, Le Vinatier (CSRA 05). The author GB was supported by a grant from the Fondation pour la Recherche Médicale (DEA20050904971). We wish to thank S.J. Blakemore and S. White for their assistance in proofreading this report.

The authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

1. Barch DM, Carter CS, Braver TS, Sabb FW, MacDonald A III, Noll DC, Cohen JD (2001): Selective deficits in prefrontal cortex function in medication-naïve patients with schizophrenia. *Arch Gen Psychiatry* 58:280–288.
2. MacDonald AW III, Carter CS, Kerns JG, Ursu S, Barch DM, Holmes AJ, *et al.* (2005): Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. *Am J Psychiatry* 162:475–484.
3. Barbalat G, Chambon V, Franck N, Koechlin E, Farrer C (2009): Organization of cognitive control within the lateral prefrontal cortex in schizophrenia. *Arch Gen Psychiatry* 66:377–386.
4. Tan H, Choo W, Fones CSL, Chee MWL (2005): fMRI study of maintenance and manipulation processes within working memory in first-episode schizophrenia. *Am J Psychiatry* 162:1849–1858.
5. Tan H, Sust S, Buckholtz JW, Mattay VS, Meyer-Lindenberg A, Egan MF, *et al.* (2006): Dysfunctional prefrontal regional specialization and compensation in schizophrenia. *Am J Psychiatry* 163:1969–1977.
6. Cannon TD, Glahn DC, Kim J, Van Erp TGM, Karlsgodt K, Cohen MS, *et al.* (2005): Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia. *Arch Gen Psychiatry* 62:1071–1080.
7. Badre D (2008): Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends Cogn Sci* 12:193–200.
8. Badre D, D'Esposito M (2009): Is the rostro-caudal axis of the frontal lobe hierarchical? *Nat Rev Neurosci* 10:659–669.
9. Koechlin E, Summerfield C (2007): An information theoretical approach to prefrontal executive function. *Trends Cogn Sci* 11:229–235.
10. Koechlin E, Ody C, Kouneiher F (2003): The architecture of cognitive control in the human prefrontal cortex. *Science* 302:1181–1185.
11. Chambon V, Franck N, Koechlin E, Fakra E, Ciuperca G, Azorin J, Farrer C (2008): The architecture of cognitive control in schizophrenia. *Brain* 131:962–970.
12. Weiss AP, Schacter DL, Goff DC, Rauch SL, Alpert NM, Fischman AJ, Heckers S (2003): Impaired hippocampal recruitment during normal modulation of memory performance in schizophrenia. *Biol Psychiatry* 53:48–55.
13. Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, Alpert NM (1998): Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nat Neurosci* 1:318–323.
14. Friston KJ (1998): The disconnection hypothesis. *Schizophr Res* 30:115–125.
15. Meyer-Lindenberg AS, Olsen RK, Kohn PD, Brown T, Egan MF, Weinberger DR, Berman KF (2005): Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. *Arch Gen Psychiatry* 62:379–386.
16. Honey GD, Pomarol-Clotet E, Corlett PR, Honey RAE, McKenna PJ, Bullmore ET, Fletcher PC (2005): Functional dysconnectivity in schizophrenia associated with attentional modulation of motor function. *Brain* 128:2597–2611.
17. Shannon C (1948): A mathematical theory of communication. *Bell Syst Tech J* 27:379–423,623–656.
18. Kouneiher F, Charron S, Koechlin E (2009): Motivation and cognitive control in the human prefrontal cortex. *Nat Neurosci* 12:939–945.
19. Mueller RO (1996): *Basic Principles of Structural Equation Modeling*. New York: Springer Texts in Statistics, Springer-Verlag.
20. Gitelman DR, Penny WD, Ashburner J, Friston KJ (2003): Modeling regional and psychophysiological interactions in fMRI: The importance of hemodynamic deconvolution. *Neuroimage* 19:200–207.
21. Stephan KE, Marshall JC, Friston KJ, Rowe JB, Ritzl A, Zilles K, Fink GR (2003): Lateralized cognitive processes and lateralized task control in the human brain. *Science* 301:384–386.
22. Badre D, Hoffman J, Cooney JW, D'Esposito M (2009): Hierarchical cognitive control deficits following damage to the human frontal lobe. *Nat Neurosci* 12:515–522.
23. Schlösser R, Gesierich T, Kaufmann B, Vucurevic G, Hunsche S, Gawehn J, Stoeter P (2003): Altered effective connectivity during working memory performance in schizophrenia: A study with fMRI and structural equation modeling. *Neuroimage* 19:751–763.
24. Schlösser R, Gesierich T, Kaufmann B, Vucurevic G, Stoeter P (2003): Altered effective connectivity in drug free schizophrenic patients. *Neuroreport* 14:2233–2237.

25. Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC (2009): Prefrontal activation deficits during episodic memory in schizophrenia. *Am J Psychiatry* 166:863–874.
26. MacDonald AW III, Carter CS (2003): Event-related fMRI study of context processing in dorsolateral prefrontal cortex of patients with schizophrenia. *J Abnorm Psychol* 112:689–697.
27. Barch DM (2005): The cognitive neuroscience of schizophrenia. *Annu Rev Clin Psychol* 1:321–353.
28. Holmes AJ, MacDonald A III, Carter CS, Barch DM, Andrew Stenger V, Cohen JD (2005): Prefrontal functioning during context processing in schizophrenia and major depression: An event-related fMRI study. *Schizophr Res* 76:199–206.
29. MacDonald AW III, Pogue-Geile MF, Johnson MK, Carter CS (2003): A specific deficit in context processing in the unaffected siblings of patients with schizophrenia. *Arch Gen Psychiatry* 60:57–65.
30. Delawalla Z, Csernansky JG, Barch DM (2008): Prefrontal cortex function in nonpsychotic siblings of individuals with schizophrenia. *Biol Psychiatry* 63:490–497.
31. Braver TS, Barch DM, Cohen JD (1999): Cognition and control in schizophrenia: A computational model of dopamine and prefrontal function. *Biol Psychiatry* 46:312–328.
32. Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, *et al.* (2002): Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat Neurosci* 5:267–271.
33. Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, *et al.* (2002): Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J Neurosci* 22:3708–3719.
34. Braver TS, Cohen JD (1999): Dopamine, cognitive control, and schizophrenia: The gating model. *Prog Brain Res* 121:327–349.
35. Swerdlow NR, Geyer MA (1998): Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. *Schizophr Bull* 24:285–301.
36. Ranganath C, Minzenberg MJ, Ragland JD (2008): The cognitive neuroscience of memory function and dysfunction in schizophrenia. *Biol Psychiatry* 64:18–25.
37. Henson RN, Rugg MD, Shallice T, Josephs O, Dolan RJ (1999): Recollection and familiarity in recognition memory: An event-related functional magnetic resonance imaging study. *J Neurosci* 19:3962–3972.
38. Henson RN, Rugg MD, Shallice T, Dolan RJ (2000): Confidence in recognition memory for words: Dissociating right prefrontal roles in episodic retrieval. *J Cogn Neurosci* 12:913–923.
39. Bunge SA, Burrows B, Wagner AD (2004): Prefrontal and hippocampal contributions to visual associative recognition: Interactions between cognitive control and episodic retrieval. *Brain Cogn* 56:141–152.
40. Velanova K, Jacoby LL, Wheeler ME, McAvoy MP, Petersen SE, Buckner RL (2003): Functional-anatomic correlates of sustained and transient processing components engaged during controlled retrieval. *J Neurosci* 23:8460–8470.
41. Sakai K, Passingham RE (2003): Prefrontal interactions reflect future task operations. *Nat Neurosci* 6:75–81.
42. Sakai K, Rowe JB, Passingham RE (2002): Active maintenance in prefrontal area 46 creates distractor-resistant memory. *Nat Neurosci* 5:479–484.
43. Fletcher PC, Henson RN (2001): Frontal lobes and human memory: Insights from functional neuroimaging. *Brain* 124:849–881.
44. Baddeley A (2000): The episodic buffer: A new component of working memory? *Trends Cogn Sci* 4:417–423.
45. Baddeley A, Della Sala S (1996): Working memory and executive control. *Philos Trans R Soc Lond B Biol Sci* 351:1397–1403; discussion:1403–1404.
46. Burglen F, Marczewski P, Mitchell KJ, van der Linden M, Johnson MK, Danion J, Salamé P (2004): Impaired performance in a working memory binding task in patients with schizophrenia. *Psychiatry Res* 125:247–255.
47. Rizzo L, Danion JM, van der Linden M, Grangé D (1996): Patients with schizophrenia remember that an event has occurred, but not when. *Br J Psychiatry* 168:427–431.
48. Jensen JE, Miller J, Williamson PC, Neufeld RWJ, Menon RS, Malla A, *et al.* (2006): Grey and white matter differences in brain energy metabolism in first episode schizophrenia: 31P-MRS chemical shift imaging at 4 Tesla. *Psychiatry Res* 146:127–135.
49. Highley JR, Walker MA, Esiri MM, McDonald B, Harrison PJ, Crow TJ (2001): Schizophrenia and the frontal lobes: Post-mortem stereological study of tissue volume. *Br J Psychiatry* 178:337–343.
50. Andreasen NC (1984): *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, Iowa: University of Iowa Press.
51. Andreasen NC (1983): *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, Iowa: University of Iowa Press.
52. Talairach J, Tournoux P (1988): *Co-Planar Stereotaxic Atlas of the Human Brain*. New York, New York: Thieme Medical Publishers.