Impaired Hierarchical Control Within the Lateral Prefrontal Cortex in Schizophrenia

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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).

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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.

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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 proceeding 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 ± SD, unless otherwise indicated.

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

[a]Sum of the scores for hallucinations and delusions from the SAPS.

[b]Sum of the scores for poverty of speech, flat affect, anhedonia/asociality, and amotivation from the SANS.

[c]Sum of the scores for formal thought disorder and bizarre behavior from the SAPS and the score for attention from the SANS.

[d]Depot doses of and daily-oral atypical antipsychotics at the time of the examination (risperidone in 6 patients, olanzapine in 3 patients, amilsupride 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.

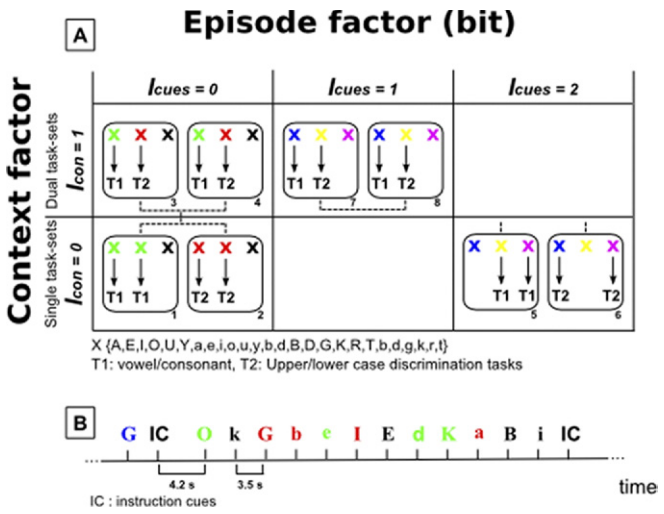

Figure 1. Experimental design. **(A)** Rounded boxes represent behavioral episodes (numbered from no. 1 to no. 8) with related stimuli (letters) and instructions. Episodes formed four distinct experimental conditions crossing the episodic factor with the context factor. According to the color of the 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

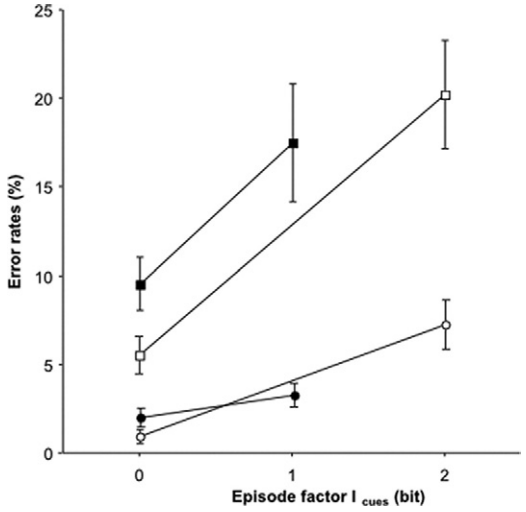

Figure 2. Behavioral results. Error rates (%, mean ± SE across participants) across experimental conditions. Open circles and squares indicate single task-set episodes in control subjects and schizophrenic patients, respectively. Solid circles and squares indicate dual task-sets episodes in control subjects 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] x	y	z	Analysis t[b]	Volume[c]	FDR p
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.

[a]Coordinates from the stereotaxic atlas of Talairach and Tournoux (52).

[b]Regional 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.

[c]Values are mm^3.

[d]These 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.

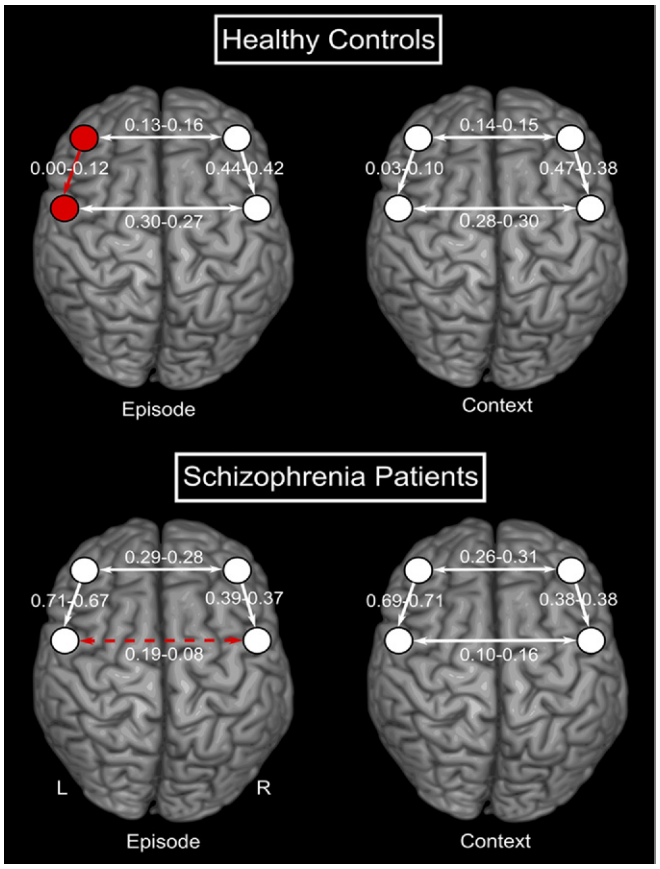

Figure 3. Diagram of path coefficients between lateral prefrontal regions involved in episodic and contextual control subjects for healthy subjects and schizophrenic patients. The structural equation model included the paths (lines, arrows indicate oriented structural paths) connecting prefrontal regions 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 × 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-naive 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

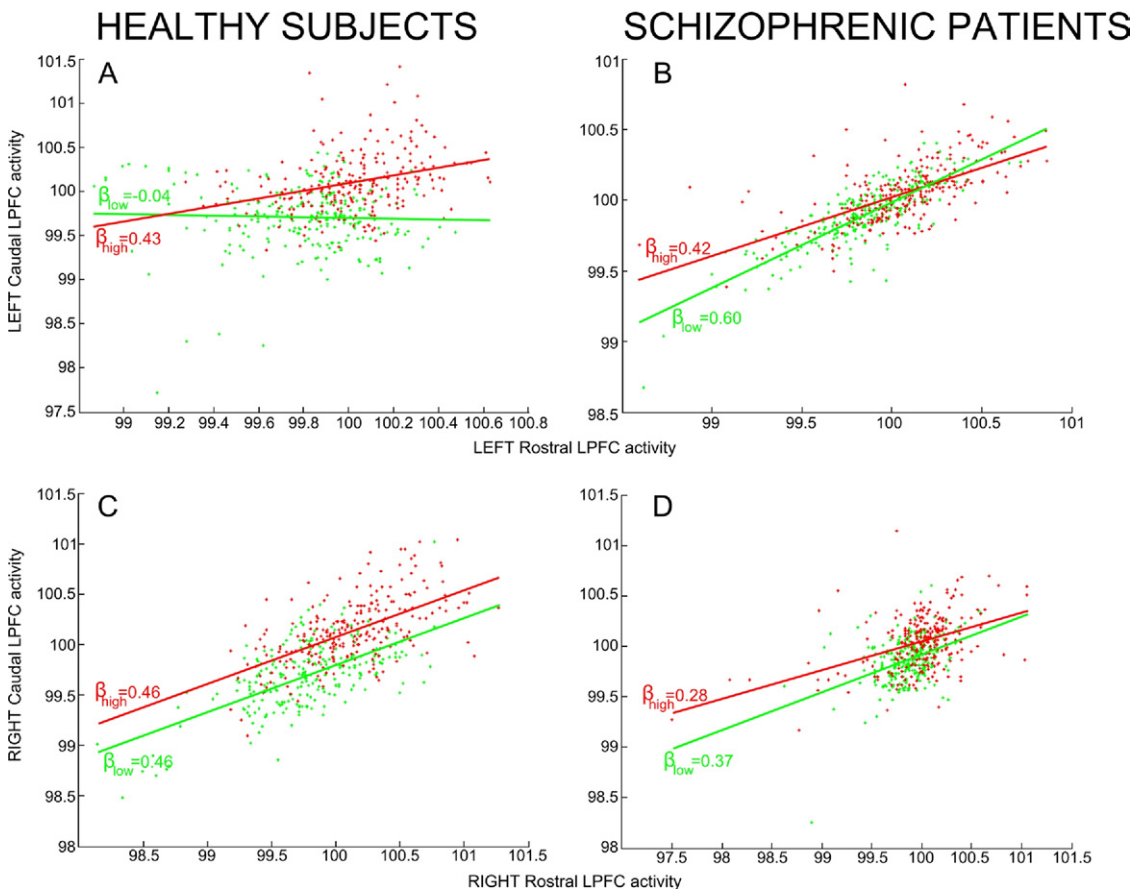

Figure 4. Psychophysiological interaction (PPI) between rostral and caudal lateral prefrontal cortex (LPFC) in healthy subjects and schizophrenic patients. Measurements when the demand of episodic control is low ($I_{epi} = 0$ bit), green crosses; measurements when the demand of episodic control is high ($I_{epi} = 2$ bits), red crosses. Condition-specific regression slopes, β_{low} (i.e., when $I_{epi} = 0$ bit) and β_{high} (i.e., when $I_{epi} = 2$ 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 reinstantiation 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.

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Supplemental Information

Subjects

Fifteen schizophrenic patients and 15 healthy controls, who were all right-handed (Edinburgh Handedness Survey (1)) and matched for age, sex, and years of education, were recruited to participate in the fMRI experiment (see the Clinical and Demographic Characteristics of the participants in Table 1 from the main article). Other results from this sample have been published elsewhere (2). After the study was completely described to the participants, written informed consent was obtained, as approved by the local ethics committee. All of the participants were paid for their time. Diagnosis was confirmed for each patient by an MD- and PhD-level clinical psychiatrist (masked to task performance) based on the Structured Clinical Interview of the DSM-IV-TR (3).

None of the participants had a history of brain trauma, seizure disorder, electroconvulsive therapy, mental retardation, affective disorder, substance abuse, or substance dependence within the past 6 months. In addition to these exclusion criteria, special exclusion criteria for the controls included having a history of an Axis I disorder, having a first-degree relative with a psychotic disorder, and receiving treatment with any psychotropic medication within the past 6 months. One control participant was excluded because of motion artifact in the scanner (> 2 voxels translation, > 2 degrees rotation) (4). No patients were excluded.

Training was done outside the scanner, in the three days preceding the scanning session. On average, healthy participants were trained one hour and schizophrenic patients, two hours. This procedure was critical to ensure that subjects correctly understood the task and to prevent any learning effects in the scanner (which might have recruited extra brain regions). In line with this point, we chose not to recruit participants who were clinically unstable or below a minimum level of education (8 years of education), because they would probably not have been able to perform the task properly. It is noteworthy that no patients from our sample were excluded because of not being able to follow the task rules.

Behavioral Analyses

Error rates and reaction times for correct trials acquired during scanning were analyzed using analyses of covariance with subject as a random factor, group as a between-subject factor,

context as a within-subject factor, and episode as a within-subject covariate. When significant, interactions were decomposed using *t* tests.

The analysis of covariance performed on reaction times showed significant effects of episode ($F(1,81) = 100.16$, $P < .001$) and context ($F(1,81) = 197.89$, $P < .001$), revealing slower reaction times as the demands of cognitive controls increased. Patients' reaction times, however, did not deteriorate in a manner that was distinct from the controls' as the demands of contextual and episodic controls increased (all interactions with group factor: $F(1,81) < 0.67$, $P > .05$), indicating that varying the amount of information conveyed by contextual and episodic signals did not increase patients' reaction times more than it did in the control group.

Participants' error percentages were found to significantly increase with the contextual ($F(1,81) = 4.16$, $P < .05$) and episodic ($F(1,81) = 66.23$, $P < .001$) factors. Significant interactions between group and cognitive factors were observed in both the contextual ($F(1,81) = 4.58$, $P < .05$) and the episodic ($F(1,81) = 13.26$, $P < .001$) factors. These effects were due to a greater decrement in performance among patients than controls regarding both the episodic and contextual factors. Patients performed worse than controls for I_{con}=0 and 1 bit and for I_{epi}=0, 1, and 2 bits (all $t > 3.50$, $P < .002$) (Figure 2 from the main article).

MRI Procedures and Preprocessing

Images were collected using the 1.5T MRI system (Siemens Sonata Maestro Class; Siemens, Erlangen, Germany) of the CERMEP Imagerie du vivant in Lyon, France. The fMRI blood oxygenation level dependent (BOLD) signal was measured using a T2*-weighted echo-planar sequence (TR = 2500 msec, flip angle = 90°, TE = 60 msec). Twenty-six axial slices (thickness: 4 mm, gap: 0.4 mm, field of view: 220 mm, matrix size: 64 x 64, in-plane resolution: 3.4 x 3.4 mm^2) were acquired per volume. Following functional image acquisition, a high-resolution T1-weighted anatomical image (TR = 1970 msec, TE = 3.93 msec, 256 x 256 matrix, resolution: 1 x 1 x 1 mm^3) was collected for each subject.

Image preprocessing was performed using SPM5 (Wellcome Department of Imaging Neuroscience, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/). For each subject, each of the eight scanning sessions contained 155 functional volumes after the first five scans were rejected to eliminate the nonequilibrium effects of magnetization. All functional volumes were realigned to the first volume to correct for inter-scan movement. Functional and

structural images were coregistered and transformed into a standardized, stereotaxic space (MNI template) (5). Functional data were then smoothed with a 10 mm FWHM, isotropic Gaussian kernel and temporally high-pass filtered with a frequency cutoff period of 128 s. Serial correlations were accounted for by use of an autoregressive model of the first order. To control for possible noise artifacts in the data, we used a weighted least-squares approach, in which we down-weighted images with high noise variance (6).

A potential criticism of fMRI studies in schizophrenia is that increased movement among patients creates artifacts that impair detection of cortical activation. We evaluated this possibility by analyzing each of the 6 estimated movement measures in scan-to-scan incremental movements and in absolute movement from the reference scan, collapsed across conditions. Results of the *t* tests indicate no significant group differences for any of the parameters (all $t(27) < 1.18$, $P > 0.05$), suggesting that group-related activation differences cannot be attributed to differential movement in the scanner.

Delimitation of the Regions of Interest – Exploratory Analyses

For the fMRI data, we first conducted voxel-wise exploratory analyses of frontal regions subserving each level of cognitive control (context and episode), in both the schizophrenia and the healthy groups. As in previous studies based on a similar paradigm, we designed the present study as a block-design experiment and followed identical analysis procedures (7-8).

Using SPM5, statistical parametric t-maps (SPM{t}) were computed from local fMRI signals using a linear multiple regression analysis with conditions (modeled as box-car functions convolved by the canonical hemodynamic response function) and scanning series as covariates (9). For all conditions, we defined the preparation phase as the time interval between the instruction cue and the presentation of the first stimulus, and the execution phase was defined as the period from the first stimulus until the end of the series of stimuli. In the current study, we analyzed the frontal regions engaged in cognitive control exertion during the execution phase. Specifically, the context effect was computed as larger activations in the dual- (I_{con}=1 bit) than in the single- (I_{con}=0 bit) task-set episodes with I_{epi}=0 bit (contrast weights assigned as follows: [1] for blocks #3,4 i.e. conditions in which I_{con}=1 bit and I_{epi}=0 bit; [-1] for blocks #1,2 i.e. conditions in which I_{con}=0 bit and I_{epi}=0 bit), and the episode effect as activations that

parametrically varied as the episodic factor I_{epi} (i.e. from I_{epi}=0, to I_{epi}=1 and I_{epi}=2 bits). For the episode effect, the contrast weights were assigned as follows:

- [-3] for conditions in which I_{epi}=0 bit (that is, conditions in which I_{epi}=0 & I_{con}=1 and I_{epi}=0 & I_{con}=0 – i.e. 2 different regressors per run);
- [1] for conditions in which I_{epi}=1 bit (that is, conditions in which I_{epi}=1 & I_{con}=1 – i.e. 1 single regressor per run);
- [5] for conditions in which I_{epi}=2 bit (that is, conditions in which I_{epi}=2 & I_{con}=0 – i.e. 1 single regressor per run).

Therefore, the sum of the contrast weights per run was:

Σ = [-3]*2 regressors + [1] + [5] = 0.

In a second level of analysis, contrasts were performed using a random-effect model. According to the cascade model, rostral LPFC regions subserve episodic control, while caudal LPFC regions subserve contextual control. Another important feature of the model is that rostral LPFC regions select caudal LPFC representations according to the temporal episode in which stimuli occur. Consequently, rostral and caudal LPFC regions are both activated in the episodic control condition, whereas only caudal LPFC regions are activated in the contextual control condition. Therefore, we identified caudal and rostral LPFC as the regions showing an effect of context and an effect of episode but no context effect (computed by masking each region related to the episode effect with the context effect, using an uncorrected voxel-wise threshold $p < 0.05$), respectively (7-8). Those regions were localized within each group to avoid localization bias (i.e. the possibility that significant differences in activation result from the delimitations of the regions of interest in only one of the groups).

MNI coordinates were transformed to the standard space of Talairach and Tournoux (10) and reported as T-scores. In accordance with our a priori hypothesis and on the basis of the known distributed functional and structural anatomy of cognitive control (11-12), our analyses were restricted to the lateral prefrontal cortex by masking through use of WFU PickAtlas software (13) (dilatation parameter = 3 voxels, bilateral mask including Brodman areas [BAs] BA8, BA9, BA10, BA44, BA45 & BA46 from the built-in atlas). The significance voxel-wise threshold was chosen at $p < 0.05$ (corrected for the false discovery rate). Note that at this threshold, we did not find any activation in the caudal LPFC in patients, which suggested that caudal LPFC regions were more activated in controls than in patients during contextual control.

However, this region showed activation at a lowered FDR-corrected threshold of $p < 0.09$. We therefore used this more liberal threshold to find caudal LPFC activations in patients because we did not want to make the impression that the caudal LPFC was not activated in schizophrenia.

According to the seminal study of Koechlin et al. (2003), we defined a cluster as being part of the caudal LPFC region if its peak of activation was located in BAs 9/44/45 (posteriorly) while a cluster would belong to the rostral portion of the LPFC if its peak of activation was located in BAs 46/10 (anteriorly) (Table 2 from the main article) (14).

Regions of Interest Analyses

In a second step of analysis, we tested the prediction that caudal LPFC regions would be more activated in controls than in patients during contextual control. However, the caudal LPFC voxels subserving contextual control did not share the same coordinates in healthy subjects and in patients. Therefore, a usual between-group analysis on a voxel-by-voxel basis with SPM would have resulted in a bias towards hypoactivation in caudal LPFC voxels being activated in controls but not in patients. We therefore tested the above-mentioned assumption by running a region of interest analysis on the caudal LPFC activations whose localizations were different in each group (2). That is, peak-voxel activations for each subject in the healthy group were extracted from the caudal LPFC regions that were specifically identified by the contextual contrast in this group. Conversely, peak-voxel activations for each subject in the schizophrenic group were extracted from the caudal LPFC regions that were specifically identified by the contextual contrast in this latter group ($p < .09$, FDR corrected).

Peak voxel activations (i.e. the signal from the voxel that was the most activated at the group level) in the rostral and caudal LPFC regions identified by the exploratory analyses in each of the two groups were then separately entered into univariate repeated-measure analyses of covariance, with subject as a random factor, hemisphere (left vs. right) and number of alternatives (single vs. dual task set) as within-subject factors, episode (I_{epi}=0, 1, or 2 bits) as a within-subject covariate, and group (patients vs. controls) as a between-subject factor. When significant, interactions were further assessed using *t* tests. To conduct these analyses, we used STATISTICA8. Note that to prevent performance bias (i.e. the possibility that the differences in activations arise from patients' poor engagement in the task, rather than from a specific cognitive deficit), we matched groups for accuracy by removing from the analyses blocks in which

performance was unsatisfactory (i.e. accuracy < 0.65, see (15) for the use of a similar threshold). Using this threshold, a mean of 0.75 (SD = 1.06) blocks per run were considered to be performed near chance for the patients, compared to a mean of 0.12 (SD = 0.32) for the comparison participants ($p < 0.05$). Running the analysis considering only blocks where the accuracy was acceptable (i.e. accuracy > 0.65), there were no behavioral differences between the two groups regarding both the episode and the context factors ($F(1,81) < 0.21$ and $p > 0.05$).

We found a group effect in rostral LPFC regions ($F(1,81) = 6.97$, $p < 0.05$), with patients activating more this region than controls. By contrast, caudal LPFC regions demonstrated a group*context interaction ($F(1,81) = 3.76$, $p = 0.05$), with patients showing no modulation of activation related to the context factor in these regions (we provided a proper activation map to illustrate this between-group analysis on contextual control in Figure S1). Caudal LPFC regions did not demonstrate any main effect of group, nor an interaction between group and episode ($F(1,81) < 1.15$, $p > .05$). Note that these caudal LPFC hypoactivation and rostral LPFC hyperactivation in patients persisted after having re-run the analysis with the whole data set in both groups (2).

Effective Connectivity Analyses

The concept of effective connectivity between brain areas involves model-based assumptions about the effect that a defined neural system exerts over another (16). By contrast, functional connectivity is defined as the correlation of regional brain activity over time. Therefore, with effective connectivity, it is possible to detect increases or decreases in the information flow between regional brain activities with a defined direction (causality), whereas functional connectivity does not account for such directional effects or for an underlying structural model. Another important difference is that effective connectivity, rather than depending simply on the correlation of time courses across conditions, provides additional explanatory power by incorporating a psychological context (or experimental condition) in the analyses.

Here, we conducted hypothesis-driven effective connectivity analyses in the different regions identified by the exploratory analyses in each of the two groups (bilateral rostral and caudal LPFC regions). We used structural equation modeling (SEM) and psycho-physiological interaction (PPI) as effective connectivity measures (17).

→ Structural Equation Modeling

We first performed SEM within each group to assess the effective connectivity between LPFC subregions (18). We followed the same procedure as in previous studies that used an identical paradigm (7-8).

The structural equation modeling technique differs from other (parametrical) statistical approaches such as multiple regression or ANOVA because, instead of considering individual observations for the analyses, in SEM, the *covariance structure* between regional activations is emphasized. Indeed, SEM is a multivariate technique used to analyze the covariance of observations between regional activation – i.e. how much the neural activities of the brain regions involved in the model are related to each other (19). The values for effective connectivity between brain areas – i.e. connection strengths – are known as the path coefficients (i.e. similar to partial correlation or regression coefficients).

Our structural equation model included top-down paths from rostral to caudal LPFC regions, as well as additional reciprocal paths linking the same regions located in the left and right hemispheres to account for callosal interhemispheric connections.

We hypothesized that the connection strength from the rostral to the caudal LPFC would increase with the episodic but not the contextual factor, as demonstrated in (7-8). Crucially, to assess changes in connection strength between two conditions (e.g. from $I_{epi}=0$ vs. $I_{epi}>0$), we used the nested (or stacked) model approach (20-21). Specifically, we first defined the restricted null model, in which all of the path coefficients were forced to be equal between conditions. The second set of models comprised the corresponding alternate free models, in which all of the path coefficients were constrained to be equal between conditions except one that was allowed to vary between conditions. We defined as many free models as there were different pathways in the structural model, each different free model being defined as the free model *for that particular pathway* (4 different free models were therefore defined in our structural equation modeling system).

For each model, the path coefficients were estimated by minimizing the difference between the observed covariances between regional activations and the covariances predicted by the anatomical structural model (using a maximum likelihood fit function). A χ^2 test was used to measure the goodness of fit of each model. This χ^2 test summarized the discrepancy between observed values and values expected under the model in question. χ^2 values were computed for

all models (i.e. the null model and the free models) with corresponding degrees of freedom. Then, the χ^2 value for each free model was compared with the χ^2 value for the constrained null model. This was done by simply subtracting those χ^2 values – then this χ^2 difference was tested with degrees of freedom being equal to the difference of the degrees of freedom for the null vs. the free model.

For a particular pathway, if the χ^2 value for the null model was significantly larger than the one for the free model, the null model was refuted and the free model for that particular pathway was assumed to provide a better fit. In other words, for that particular pathway, there was a statistically significant global difference in path coefficients between the conditions (i.e. from $I_{epi}=0$ vs. $I_{epi}>0$). Such a significant difference in the absolute magnitude of the path coefficients was interpreted as a change in the strength of the influences conveyed through that particular pathway, related to that particular factor (i.e. episodic control).

The overall model fit was assessed by computing standard goodness of fit indices, including normed fit, centrality and relative non-centrality indexes (all indexes > 0.9 indicating an appropriate fit) (22).

SEM was processed using the MX software package (http://www.vcu.edu/mx/).

→ Psycho-Physiological Interactions

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).

PPI can be understood as the influence that one cerebral region exerts over another in a specific experimental condition. In other terms, PPI looks at how brain activity can be explained by the interaction between 2 variables: an experimental variable and activity in another particular brain area. Such a modulation is reflected by the variation in the slopes of the regression of one region's activity (here, caudal LPFC activity) against another's (here, rostral LPFC activity) as a function of an experimental cognitive factor (here, the episodic control demand) (17).

To demonstrate that the slopes were significantly different across conditions, we tested whether caudal LPFC activity was significantly influenced by the interaction between rostral LPFC activity (a continuous variable) and the episodic factor (a discrete factor with two levels).

When significant, we determined the direction of the psycho-physiological interaction (i.e. whether there is an increase or a decrease in connectivity from rostral to caudal LPFC regarding the episodic factor) by comparing the group level slopes between the low and the high levels of the episode factor.

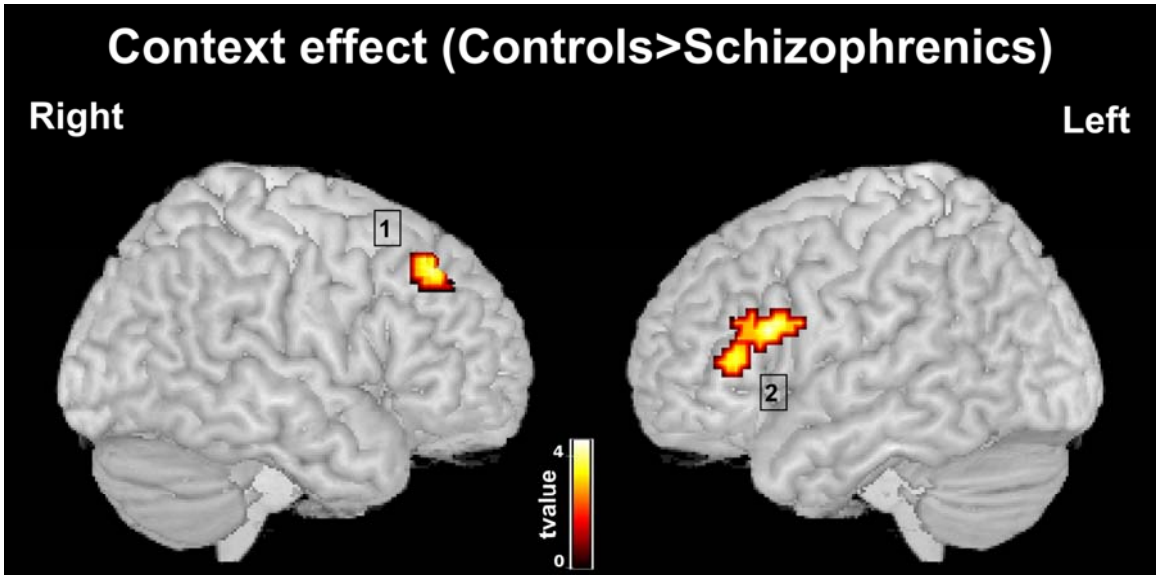

Figure S1. Caudal lateral prefrontal cortex regions demonstrating contextual effects that were significantly greater in healthy control participants than in participants with schizophrenia. 1 indicates dorsocaudal LPFC; 2, ventrocaudal LPFC. For display purposes, the regions of interest have thresholds of $p < .005$ and 15 contiguous voxels.

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